REFRACTORINESS WITHIN THE SEMANTIC SYSTEM: INVESTIGATIONS ON THE ACCESS AND THE CONTENT OF SEMANTIC MEMORY

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“Geniali dilettanti
In selvaggia parata,
Ragioni personali
Una questione privata”

“Gifted dabblers
In wild parade,
Personal reasons
A private matter”

Giovanni Lindo Ferretti

Summary:

Abstract:

The starting purpose of this project was to investigate some issues related to the mechanisms underlying the efficient access to concepts within the semantic memory systems. These issues were mainly related to the role of refractoriness in explaining the comprehension deficits underlying semantic access. The insights derived from this first approach were then used to formulate and test hypotheses about the organization of the contents of the semantic system itself.

The first part of the thesis presents an investigation of the semantic abilities of an unselected case-series of patients affected by tumours to either the left or right temporal lobes in order to detect possible semantic access difficulties. Semantic access deficits are typically attributed to the semantic system becoming temporarily refractory to repeated activation. Previous investigations on the topic were mainly based on single case reports, mainly on stroke patients. The rare examples of group studies suggested moreover the possibility that the syndrome might not be functionally unitary. The tasks used in the study were two word-to-picture matching tasks aimed to control for the typical variables held to be able to distinguish semantic access from degradation syndromes (consistency of access, semantic relatedness, word frequency, presentation rate and serial position).

In the group of tumour patients tested access deficits were consistently found in patients with high grade tumours in the left posterior superior temporal lobe. However, the patients were overall only weakly affected by the typical temporal factors (presentation rate and serial position) characterizing an access syndrome as refractory. The pattern of deficit, together with the localization data, suggested that the deficit described is qualitatively different from typical semantic access syndromes and possibly caused by the disconnection of posterior temporal lexical input areas from the semantic system.

In the second study we tried to answer the question whether semantic access deficits are caused by the co-occurrence of two causes (refractoriness *and* a lexical-semantic disconnection) or whether the presence of refractoriness in itself is sufficient to induce all the behavioural effects described in access syndromes. A second aim of the study was moreover to investigate the precise locus of refractory behaviour, since

refractory effects have also been reported in naming tasks in which the possibility exists that the interference might be located at a post-semantic lexical stage of processing. To address these issues a series of three behavioural experiments on healthy subjects was conducted. The tasks used were speeded versions of the same word-to picture matching tasks used in the previous study. A speeded paradigm was adopted in order to induce a mild refractory state also in healthy participants. The results showed that it was possible to induce, in the group of subjects tested, a performance similar to that of refractory semantic access patients. Since no post-semantic stage of processing is assumed to be necessary to perform these tasks it was argued that refractoriness arises due to interference occurring between representations *within* the semantic system itself.

In the second part of the project, the finding that refractoriness arises due to interference involving semantic representations themselves, was used to investigate issues related to the organization of the content within the semantic memory. In particular, a second series of behavioural experiments was performed to investigate whether the way an object is manipulated is indeed a feature that defines manipulable objects at a semantic level. The tasks used were speeded word-to-picture matching tasks similar to those previously described. A significantly greater interference was found in the recognition of objects sharing similar manipulation than in the recognition of objects sharing only visual similarity. Moreover the repeated presentation of objects with similar manipulation created a 'negative' serial position effect (with error increasing over presentations), while the repeated presentation of objects sharing only visual similarity created an opposite 'positive' serial position effect (learning).

The role of manipulability in the semantic representation of manipulable objects was further investigated in the last study of this work. In a second unselected group of brain tumour patients the ability to name living things and artifacts was investigated. Artifacts were manipulable objects, varying in the degree of their manipulability. Results from both behavioural and Voxel-based Lesion Symptom Mapping (VLSM) analyses showed that the only patients showing a selective deficit in naming artifacts (particularly highly manipulable objects) were patients with lesions in the posterior middle and superior portions of the left temporal lobe, an area lying within the basin of those regions involved in processing object-directed actions and previously linked to the processing of

manipulable objects in a wide range of studies. The results of these last two studies support 'property-based networks' accounts of semantic knowledge rather than 'undifferentiated network' accounts.

Overall this series of studies represents an attempt to better understand the mechanisms that underlie the access to semantic representations and, indirectly, the structure of representations stored within semantic networks. The insights obtained about the mechanisms of access to stored semantic representations were used as a tool to investigate the structures of the same semantic representations. A combination of different approaches was used (from behavioural speeded interference paradigms on healthy subjects, to neuropsychological case series investigations, as well as Voxel-based Lesion Symptom Mapping technique), to 'cross-validate' the results obtained at any level of analysis.

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Now the sky could be blue, I don't mind….Without you it's a waste of time.

Some of the experiments reported in the thesis have also been submitted elsewhere. Specifically, the data relative to the first neuropsychological study on semantic access have been described in a paper recently published in *Brain* [Authors: Campanella, F, Mondani, M Skrap, M, Shallice, T (2009). *Brain, 132,* 87-102]; the data from the first behavioural study on refractoriness will soon be resubmitted after a first revision to *Cognition* [Authors: Campanella, F, Shallice, T]; the data from the second neuropsychological group study have been be resubmitted after a first revision to *Neuropsychologia* [Authors: Campanella, F, D'Agostini, S, Skrap, M, Shallice, T]; finally, the data from the second behavioural study on manipulability are currently under revision after submission to *Experimental Brain Research* [Authors: Campanella, F, Shallice, T].

CHAPTER 1:

1.1 SEMANTIC MEMORY: AN INTRODUCTION

1.1.1 Historical overview

In one of the first systematic investigations on semantic memory disorders, Warrington (Warrington, 1975) described the semantic system as "that system which stores, processes and retrieves information about the meaning of words, concepts and facts" and therefore the system that allows us to give meaning to what we see and interact with in our everyday life. However, as pointed out by Humphreys and Forde (2001), "despite the general use of the term, or perhaps because of it, there has been little attempt to provide a more rigorous definition […]. It is perhaps symbolic that semantic memory is represented as an under-specified cloud in many standard models of cognition".

One of the most influential positions, in the field of long term memory studies, regarding the organization of the content of the long term memory store, was put forward by Endel Tulving in 1972 (Tulving, 1972). Tulving distinguished two parallel and partially overlapping information-processing systems within the long term memory store organised on the basis of the type of stored knowledge. The first memory system, named *episodic memory*, refers to memory for personal events and the temporal-spatial relations among these events, whereas the second one, named *semantic memory*, represents organized knowledge that a person possesses about words and other verbal symbols, their meaning and referents, about relations among them, and about rules and algorithms for the manipulation of symbols, concepts, and relations (Tulving, 1972).

Although the term "semantic" was first "officially" used in 1972 (borrowed, however, from the PhD dissertation of Quillian, 1966) the debate on the organization of the content of this system devoted to the storage of concepts and meaning of words, was already open[1].

One of the first formal theories on the organization and structure of semantic memory in the field of modern cognitive neuroscience, is the one proposed by Collins and Quillian (1969), who conceived of the semantic system as a network in which conceptual nodes are hierarchically structured into different levels, with subordinate nodes at the base of the hierarchy and superordinate nodes at the

[1] Questions related to the processes of conceptualizations were already debated by neurologists during the 19th century (see e.g. Wernicke or especially the concepts centre in Lichtheim's "house model").

top. The properties of each concept are linked to their respective nodes at each level of the hierarchy, and the process of semantic determination was thought to go from the bottom to the top of the hierarchy. The logical consequence of this is that damage to some of the subordinate nodes should impair also superordinate concept determination. However early literature on semantic deficits showed that there was, on the contrary, a selective advantage for superordinate concepts compared to subordinate ones (e.g. Warrington, 1975).

Collins and Loftus (1975) proposed therefore a model of semantic system organized according to a spreading activation principle. When an exemplar of a category is activated, the activation also spreads to other exemplars of the same category and part of this activation also spreads from each of these concepts to the relative superordinate, which therefore receives the highest activation level, coming from many different sources, making it more resistant to possible damage. The organization of concepts within the semantic system in their model follows therefore a semantic distance metric, with nodes that are related (e.g. those referring to exemplars of the same category) being more clustered together with respect to more unrelated nodes. When two concepts are stimulated, the time it takes for the activation to spread between the two nodes depends on the distance between them.

A different set of theories (mainly connectionist models) conceived semantic memory representations as constituted by an unstructured set of distributed features variously linked to the concept (e.g. Rieger, 1978; McClelland and Rumelhart, 1985). In this view, superordinate representations just conflate features common to many exemplars. Exemplars are, according to this view, not to be conceived as 'units of knowledge' but rather as a complex network of activation states of single features. When a concept is activated, the system tends to move towards a stable state of activation achieved by means of subsequent activations of configurations of single features (which become to an 'on' state). Access to concepts is, thus, obtained by subsequent approximations to the 'correct' (stable) state.

In about the same period, a different but somewhat related debate which still remains an open issue also nowadays, concerned whether the semantic system should be conceived as a single amodal system or whether separate systems exist that store concrete, abstract, visual, verbal or also information from other modalities. One of the first amodal semantic system models was proposed by Seymour (Seymour, 1976) who claimed that the storage within the semantic memory depends on a prepositional code, with access to memory being feasible via two re-coding systems, responsible for the 'translation' of the code in either pictorial or verbal format. A contrasting position has been

however held for example by the 'dual code' theory proposed by Paivio (e.g. Paivio, 1978) who claimed that when concrete, perceptual properties of concepts are concerned, a pictorial code is engaged in storing this information, while a verbal code is used to store abstract, linguistic features of the concepts.

The possibility of the existence of separate semantic systems devoted to store information in different formats for different modalities seems rather counterintuitive, but comes from the observation of a series of peculiar neuropsychological phenomena described in some brain damaged patients. For example Warrington (1975) described two patients who showed greater semantic difficulties in the verbal than the visual modality (patient EM) and the reverse pattern (patient AB) respectively. Also the case of modality-specific aphasias speaks in favour of this hypothesis. Patients have been indeed described with strong naming deficits but restricted only to one modality of presentation. This is the case of optic aphasic patients, who are selectively impaired in naming visually presented objects (in absence however of agnosia) but are quite good in naming the same objects if presented in, say, the tactile modality (e.g. Beauvois, 1982; Coslett and Saffran, 1989; Plaut and Shallice, 1993a) or to indicate its use. These phenomena have been explained in terms of separable verbal and modality-specific non-verbal separable semantic systems. The communication between the verbal semantic system and the modality specific systems should in these pathologies be impaired (e.g. Beauvois, 1982).

Other models however exist which tried to account for the same deficits without the need for separate semantic stores. Indeed following for example Riddoch and colleagues (1986), the existence of a pre-semantic perceptual classification system (which, following Marr, they called 'structural description system') directly linked to the 'action' system, bypassing the (unitary) semantic store, would easily explain the behaviour of optic aphasic patients, who are able to indicate the use of objects they cannot name, without identifying them at a truly semantic level.

The double dissociation between verbal and visual modalities has been questioned also by other authors (Rapp and Caramazza, 1993; Lambon Ralph et al., 1999). The difficulty of naming objects when presented in the visual modality might be accounted for in terms of more general and peripheric visual perceptual impairment. On the other hand, the selective difficulties of some patients to comprehend and produce the names of objects in spite of a good ability to access semantic information from the visual modality (pictures) would simply be explained by assuming that spoken and written words gain access to the (unitary) semantic system after accessing a pre-semantic "word

form" lexicon (which would be damaged in these patients). On the contrary Pictures access the semantic system directly (e.g. Lambon Ralph and Howard, 2000).

Some support for both positions comes also from another important line of neuropsychological investigations, that of category-specific semantic deficits, which will be introduced later in this chapter.

1.1.2 Mechanisms of semantic access

Among the studies of the structure and mechanisms of functioning of the semantic memory store(s), a particular place should be reserved to the studies of the mechanisms of accessing the meaning of concepts. Regardless of the theoretical approach to the structure of the semantic memory (like those briefly outlined in the previous section), from the late seventies of the past century a series of studies clearly highlighted that not all the semantic memory deficits were qualitatively the same.

In the same seminal work of 1975 (already outlined in the previous section), the patients described by Warrington (1975), who were suffering from cerebral atrophy (probable semantic dementia), were showing selective progressive difficulties in comprehending the meaning of words and the significance of objects in spite of a fluent and generally syntactically correct speech. Those patients were highly consistent in their likelihood of retrieving a given concept and were strongly affected by the frequency of the target word. They behaved as if the semantic representations underlying concepts had been degraded.

In contrast to this pattern of performance, Warrington and Shallice, (1979) and later Warrington and McCarthy (1983; Warrington and McCarthy, 1987), described patients whom they argued have problems in accessing the semantic representations they still retained; they were inconsistent in whether a concept could be activated and were at most only weakly affected by word frequency. Moreover, Warrington and McCarthy (1983; Warrington and McCarthy, 1987) showed that the probability of correctly recognizing a target stimulus was influenced by the semantic distance between the target word and distractors and by the rate at which the items were presented. They argued that these problems in accessing concepts were due to a temporary unavailability of the stored representations due to abnormal refractoriness within the semantic system. Refractoriness was defined as 'the reduction of the ability to utilize the system for a certain period of time following activation' (Warrington and McCarthy, 1983 p.874).

The apparent complementarity of the pattern of impairment of the patients presented in those studies configured the semantic access syndrome (which was however only described pre-theoretically in the terms of a set of clinical criteria) as a 'phenomenon in search for an explanation', but, nevertheless in the following years, little effort was put into the attempt to fully account for this phenomenon from the theoretical point of view.

Given this lack of theoretical background Rapp and Caramazza (1993) challenged the usefulness of distinction on both theoretical and empirical grounds. From the theoretical point of view, the distinction was, in their opinion, not derived from any 'fully worked-out' theoretical model, with specific predictions to be tested by putatively relevant evidence. On the other hand, from a more practical point of view, their main concerns were especially referring to the fact that the criteria outlined to contrast access from degradation deficits were never tested together and more importantly, never in the same group of patients with the same tests and materials.

In partial answer to these concerns however, Warrington and Cipolotti (1996) published an important study on the topic. In their investigation, the authors tested and contrasted the performance of 6 patients. 4 of the patients were affected by 'probable Pick's disease' (the main pathology involved in semantic dementia) and therefore they were held to show possible degradation of semantic representations. The other two patients were suffering from Stroke (patient A1) and a brain tumour affecting the left temporal lobe (patient A2). With the same series of word-picture matching tasks, the authors were able to show complementary patterns of performance in the two groups of patients. While semantic dementia patients were sensitive to word frequency and were consistent in the likelihood of achieving the correct answer across subsequent re-presentations of items, they were not influenced by the semantic distance between the target word and the distractors, and did not benefit from slow presentation rates. On the contrary, patients A1 and A2 were very inconsistent across trials in identifying target stimuli, and were strongly influenced by semantic distance and by the rate of presentation of stimuli (patient A1 showed also a serial position effect, i.e. his performance deteriorated across subsequent re-presentations of the same items), while word frequency had little effect on them.

But how could the 'refractoriness' explanation (Warrington and McCarthy, 1983; 1987) account for the contrasting pattern of performance showed by the two groups of patients? If, as postulated by Warrington and McCarthy, in access patients the semantic representations undergo a pathologically prolonged refractory state after a first effective activation, then, of course, their

likelihood of accessing a concept would become inconsistent and unpredictable, while a degraded representation would never be accessed. Moreover, access patients would benefit from prolonged inter-trial intervals, but if the semantic representations are degraded, then giving more time to the patient would not increase the chances of retrieving a concept which is no longer available. Subsequent representations of the same target item in a narrow time window (serial position) would impair a semantic system under a refractory condition; on the contrary, again, if some concepts are degraded, then the chance of accessing them would be constant. Semantic distance effects are expected from access patients if we postulate that the activation of semantic representations follows a 'spreading activation' principle: indeed if the activation of a concepts spreads partially to neighbouring concept, then also refractoriness is expected to partially spread to neighbouring concepts. On the contrary, in degradation patients generally semantic distance effects are sometimes present only when broad category boundaries are crossed. In this case semantic distance effect would be secondary to the loss of subordinate categories of concepts (see for example Crutch and Warrington, 2005 for a deeper investigation on this topic) [2].

More difficult is the account for the absence of word frequency effects (which are traditionally ubiquitously linked to semantic memory problems); however as correctly pointed out by Warrington and Cipolotti (1996), high frequency concepts, though being the easiest to access, they also receive, because of their richer and stronger networks of links, the highest activation and therefore, they also undergo the highest level of refractoriness, which would, in the end, counterbalance the frequency effect.

Although the work by Warrington and Cipolotti (1996) answered many of the criticisms raised by Rapp and Caramazza (1993), the attempt to theoretically account for access syndromes was not that strong, and, in particular, after this work very little effort has been put into the modelling of the

[2] The influence of semantic distance in the two types of patients is not as clear-cut as it might appear. Indeed, effects of semantic distance are also found in degradation patients, particularly in semantic dementia (e.g. Rogers et al., 2004). However, the effects of semantic distance in these two populations of patients might be qualitatively different since access patients tend to show semantic distance effects both with low and high frequency concepts, (Crutch and Warrington, 2005; see also Chapter 2 of this thesis, supplementary table J) and at within-category level of analysis. By contrast the effect of semantic distance for degradation patients seems to emerge only with low frequency items. However, in general, what changes in the two types of syndromes is the general pattern of influence of the variables: in semantic access patients word frequency has a milder effect than would be expected from a semantic impairment while semantic distance has a stronger role. In contrast, in degradation patients the opposite often happens: word frequency has a very strong effect while semantic distance effects are less consistent. In general, indeed, they sometimes emerge when major category boundaries are crossed, suggesting the preservation of superordinate knowledge instead of a genuine semantic distance effect (but see Rogers et al., 2004 for examples of degradation patients in which within-category semantic distance effects have been reported) or they are found in presence of also significant word frequency effects.

properties empirically claimed to hold for semantic access dysphasia. In 2002, however, Gotts and Plaut put forward a comprehensive computational model of access to the semantic system in order to account for the different types of syndromes on the access/degradation spectrum.

Gotts and Plaut (2002) proposed that the key for understanding semantic access deficits lies in the concept of *synaptic depression*. When a presynaptic neuron in the cortex fires repeatedly the rate of firing of the postsynaptic neuron decreases (Abbot et al., 1997). Recovery from synaptic depression typically takes 3-4s but complete recovery can take a minute or even more (Finlayson and Cynader, 1995; Varela et al., 1999). Two very common neurotransmitters, acetylcholine and norepinephrin, have the effect of reducing neurotransmitter release at the synapse (e.g. Vidal and Changeux, 1993; Hasselmo, 1995 for a review); reducing the effects of synaptic depression. A large set of cholinergic fibres comes from the basal forebrain nuclei of Meynart (nbM-Ch4), which spreads throughout the neocortex including the temporal lobes (Selden et al., 1998).

The authors tried to reproduce the contrasting pattern of performance of degradation and access patients through the implementation of a simple feed-forward neural network. This neuromodulation effect was simulated by Gotts and Plaut by changing a 'neuromodulation parameter' (*M*). By reducing its value the authors aimed to simulate access condition. On the other hand degradation pattern of performance was simulated by partially lesioning the hidden → semantic units pathway.

Under the appropriate conditions of damage to neuromodulatory or hidden units, the network effectively mimicked the contrasting pattern of performance of the patients of Warrington and Cipolotti. Also, under certain combinations of the two types of damage, the network could reproduce also some of the mixed patterns of performance showed by some patients reported by Rapp and Caramazza (1993), which were difficult to explain in terms of the classical refractory account.

A somewhat different account for semantic access dysphasia was more recently proposed by Jefferies, Baker, Doran and Lambon Ralph (2007). They assessed the semantic abilities of a group of left hemisphere stroke patients and found an overall refractory behaviour in those patients whose lesion involved the left inferior prefrontal cortex as well as the temporal lobes. Jefferies and colleagues argued that lesions in this area may lead to a failure in control processes, which are held to be required to assure adequate and flexible semantic access especially when dealing with highly demanding tasks such as naming when stimuli are presented quickly (see also Schnur et al., 2006 for a similar account). Control processes were argued to come into play in these situations.

1.1.3 Organization of semantic content and category specific semantic deficits

As already anticipated in section 1.1.1, the possibility of the selective loss of one or more categories of knowledge, gave strong interesting insights in the investigations on the organization of the information within the semantic memory store, especially regarding the possibility of the semantic system being a highly structured multi-modal system.

Indeed, in the past 30 years, many patients have been described and studied in detail, reporting the most disparate selective losses or preservations of the most disparate categories of semantic content. Dissociations have been found between abstract and concrete concepts (e.g. Warrington, 1975; Warrington and Shallice, 1984; Breedin et al., 1994), words vs. pictures (McCarthy and Warrington, 1988), objects and actions (McCarthy and Warrington, 1985), proper vs. common names (e.g. Semenza and Zettin, 1988), selective loss and preservation of knowledge for countries (Incisa Della Rocchetta et al., 1998), or body parts (e.g. Sacchett and Humphreys, 1992; or Shelton et al., 1998) or also selective loss (Beauvois, 1982) or preservation (Yamadori and Albert, 1973) of colours knowledge.

However, perhaps the most intensively studied and reported dissociation is the one observed between the selective loss or preservation of Living vs. Nonliving entities. The first reports of this selective dissociation in semantic knowledge, was found in Nielsen (Nielsen, 1946) and Hecaen and De Ajuriaguerra (Nielsen, 1946; Hecaen and De Ajuriaguerra, 1956), both reporting patients with selective difficulties with inanimate objects. However the first formal investigation of such dissociation comes from the works of Warrington and Shallice (Warrington and Shallice, 1984), reporting four patients with selective loss of knowledge about living entities, and Warrington and McCarthy (Warrington and McCarthy, 1983; Warrington and McCarthy, 1987) reporting the opposite dissociation. By 2003, 61 patients had been described showing the selective loss of knowledge about living entities and many fewer (18, about 1/3) were described showing the opposite pattern of loss (Capitani et al., 2003).

Category specific semantic deficit for living entities is usually linked to a rare pathological condition called herpes simplex virus encephalitis (HSVE). HSVE usually produces widespread damage to the anterior medial portions of both temporal lobes (generally more prominent on the left side however) (see e.g.Gitelman et al., 2001; Noppeney et al., 2007 for morphometric studies on 5 and 4 subjects respectively).

Since the type of deficit could appear quite strange and counterintuitive, in the beginning it was treated skeptically and many attempts were made to account for it in terms of the hidden effect of some more basic variable. Systematic differences in familiarity or visual complexity or word frequency of the members of the two categories (Funnell and Sheridan, 1992; Stewart et al., 1992) were claimed to be able to explain the general category specificity effect, as well as the relative density of the concepts in the semantic space (Gaffan and Heywood, 1993). More recently, different accounts tried to explain the effect in terms of premorbid individual differences. On one hand, Laws (2005) stressed the importance of controlling the performance of the control group on the same tasks used with patients, showing that small category-specific effects might be present also in healthy subjects. On the other (Albanese et al., 2000; Barbarotto et al., 2002), it has been shown that while men tend to be more familiar with tools, woman seem to possess a higher familiarity for living things.

Notwithstanding these concerns, it is now well accepted (see e.g. Sartori et al., 1993; Caramazza and Shelton, 1998), that even controlling for all these possible confounds, the category specific loss of knowledge for living things is a genuine phenomenon. This is especially true because, even if these variables could account for living things deficit, they can hardly account for the reverse dissociation (i.e. the selective loss of the category of artifacts), in which putatively easier material is involved[3].

As we said, up to 2003 the selective semantic deficit for artifacts was reported in only 18 cases (Capitani et al., 2003). This peculiar, less frequent (and less studied) dissociation in the preservation of semantic material, can be very interesting and open new insights for theories about the organization of semantic content within semantic memory store, as we will see in the next section.

Theories of category specificity:

Many different theoretical approaches have been proposed to extract insights on the organization of the semantic system from the study of category specific semantic deficits. The most influential positions in the field were illustrated by three main theoretical approaches to the problem.

The first theoretical account (traditionally known as Sensory-Functional Theory) for category specific semantic deficit is the one proposed in the first investigations on the topic by Warrington and Shallice (1984) and Warrington and McCarthy (1983; 1987). According to this first account, category

[3] Note however that not all the psycholonguistic variables have been found to favour the category of nonliving with respect to living entities. For example imageability and age of acquisition of words referring to those categories seem to favour living things with respect to artifacts (see e.g. Howard et al., 1995)

specific semantic loss would be due to the damage to separate relevant semantic subsystems localized in different parts of the brain. These separate subsystems would be devoted to processing and storing semantic information of different types which have different importance in building the semantic representations of different classes of concrete concepts, with some types of information being more important than others in defining a given category. For example, the key attributes to distinguish among living entities would be those related to perceptual properties of these concepts (such as colour, texture, shape, the sound they make and so on). On the other hand, to distinguish among artifacts, the most important type of information to be retained is the one related to its 'functional properties' (i.e. what is for, how it is used and so on), while specific perceptual attributes such as colour or texture might be irrelevant. These different core attributes would be stored in separate parts of the brain and can be therefore selectively damaged or spared in case of brain damage. In this view, therefore, category specific loss would just be a 'byproduct' of this differential weighting, rather than reflecting the genuine loss of the category, which would not be therefore represented in the brain as segregated entities. A direct prediction of this account is that category specificity effects should involve more than one category and, for example, living things deficits should not involve living things alone but also categories sharing the same type of relevant defining properties (see e.g. Borgo and Shallice, 2001; 2003).

A completely different, simple and fascinating account for this puzzling deficit was the one proposed by Caramazza and colleagues (known as Domain-Specific account) in the nineties of the past century (Caramazza et al., 1990; Caramazza and Shelton, 1998). On this position, segregated semantic domains have been developed under evolutionary pressures to distinguish among evolutionary critical domains for the human being. These systems (which are the most often selectively damaged or spared) comprise a semantic store for living entities, one for plant life, one for conspecifics and one for artifacts. Following this position, categories are separately represented in the brain in segregated cortical areas which would be responsible for the processing of all the types of information relative to the concepts belonging to it. Caramazza and colleagues, therefore, reject the possibility of separate attribute-specific areas and predict that the loss of a category of knowledge should involve all types of attributes and information relative to those concepts. The main criticism Caramazza and colleagues make with respect to the position of Warrington and colleagues is that patients exist showing a genuine category specific deficit, but without a concomitant disproportionate loss of perceptual rather than functional knowledge (e.g. Basso et al., 1988; Sartori and Job, 1988; Silveri and Gainotti, 1988).

Moreover, patients exist in which the selectivity of the deficit is even narrower than the general living-nonliving distinction, involving very precise sub-categories such as the only plant life category (Caramazza and Shelton, 1998), which is difficult to account in terms of the general predictions made by the sensory-functional account. Regardless of the theoretical account, both these theories predict that category specific semantic deficits arise from lesions in different regions of the brain, because they are either devoted to categorical processing, or to the processing of relevant features.

A completely different approach to the same problem, is the one proposed by a different set of researchers (Devlin et al., 1998; Tyler et al., 2000; Tyler and Moss, 2001). In this view (also known as Conceptual Structure account), categories of concepts have different sets of connections with different strengths with each other. The core idea is that categories of knowledge can be conceived as an emergent property of the structure of semantic memory based on the distinctiveness and correlation between features. This approach develops an original idea of DeRenzi and Lucchelli (1994), that the internal organization of living and nonliving entities is different. For artefacts, functional information is strongly linked to perceptual attributes (a strong form-function link), and both these attributes are distinctive. On the other hand the same link exists also for living things, but the attributes to which functional information is linked are shared among many different exemplars (e.g. that legs are for moving).

The idea at the base of Tyler and colleague's approach is that the robustness to damage of concepts from a given category depends on three factors.

First, the more features are shared by the members of a category, the more robust the category is. When a feature is damaged, its retrieval is still supported by the presence of many other correlated features.

Second, the higher the number of distinctive features in a category, the more damage is necessary to make the category undistinguishable.

Third, a category is more robust if the distinctive properties are also the ones that are more correlated, giving the higher protection to the category (as for example happens with artefacts)[4].

The crucial difference between this approach and the previous ones is that in this view semantic memory is conceived as an anatomically undifferentiated network in which the representations of

[4] Note however that a series of studies exist showing that the predictions made by Tyler and colleagues are not confirmed when analyzing the features composing large samples of concrete concepts (Garrard et al., 2001a;Garrard et al., 2001b;Garrard et al., 2005)

concepts are widely distributed and concepts are characterized simply by different patterns of connection within this distributed network.

A direct prediction coming from this approach is that no systematic anatomical segregation in the representations of either living or nonliving entities should be found. On the contrary, for both the previously outlined approaches, anatomical differences are clearly predicted.

More recently, a possible integration of all the three accounts has been proposed by Simmons and Barsalou with the so-called Similarity-In-Topography theory (Simmons and Barsalou, 2003). The authors claim that all three main approaches to category specificity phenomenon highlight a different important aspect of the functioning of the semantic memory store and propose that the three principles of organization proposed (categorical, feature-specific and distinctiveness-correlation) are true at different levels of the organization of the semantic system.

Simmons and Barsalou propose that semantic system could be indeed organized, at more peripheral stages, in modality-specific stores, devoted to the storage of elementary sensory-motor features congruent with the modality of the channel. However at higher stages of information processing these features are linked in complex 'convergence zones' (e.g. Damasio and Damasio, 1994) in which the semantic space becomes 'lumpy' and features are store at different distances and differently correlated following principles similar to those of the Conceptual Structure theory. At the highest levels of abstraction, semantic information is then stored also following a purely categorical (Domain-Specific) principle and the authors propose that the different patterns of patients performance supporting one or the other of the previous accounts were due to patients with lesions involving one or more of these different stages.

A final theoretical framework has been recently proposed by Rogers, Patterson and colleagues: the so-called "distributed-plus-hub" account (Rogers et al., 2004; Patterson et al., 2007). According to this approach which can be considered as a halfway-house between the sensory/functional and the categorical accounts, sensory-motor aspects of conceptual knowledge are a necessary aspect but not a sufficient one to explain the organization of semantic memory. Since an important role of semantic memory is that of categorizing and abstracting across concepts that have similar semantic significance (but not necessarily similar specific attributes), the authors argue that sensory-functional attributes alone are not a sufficient basis for these kind of operations and that a 'semantic hub' needs to be postulated. The role of this 'hub' is that of connecting all the modality-specific sensory-motor representations into a general amodal semantic representation. To support their view, the authors take

the example of semantic dementia, characterized by the selective bilateral atrophy of temporal poles, but more prominently on the left (e.g. Hodges et al., 1992; Mummery et al., 2000).

1.1.4 Structures and anatomy of semantic memory

The relationship between temporal lobes and language comprehension has been widely investigated in cognitive neuroscience since Wernicke's seminal work (Wernicke, 1874). It is now well accepted that different clinical syndromes affecting temporal areas in the human brain produce deterioration of conceptual knowledge with subsequent difficulties in comprehending language. In particular, language comprehension difficulties often follow after left hemisphere stroke (especially in the territory of the middle cerebral artery) (Forde and Humphreys, 1995; Warrington and Crutch, 2004), or as a consequence of semantic dementia (SD) (Snowden et al., 1989; Hodges et al., 1992) or Alzheimer disease (AD) (Chertkow and Bub, 1990; Lambon Ralph et al., 1997; Grossmann et al., 2001) or herpes simplex virus encephalitis (HSVE) (Kapur et al., 1994; Gitelman et al., 2001).

However, language comprehension is a complex process consisting of different stages, ranging from acoustic perception and decoding of speech signal, to the access of lexical (word form) representations, to the access to word meaning (semantic memory). This latter stage involves directly the access to conceptual-semantic representation of words. There is now a widespread debate on whether these stages of word comprehension are limited to the left hemisphere temporal lobe and whether different portions of left temporal lobe play different roles in the different stages of speech decoding.

Hickok and Poeppel (2004) for example, reviewing the literature on speech comprehension, argue that the early stages of acoustic speech perception are carried out bilaterally by acoustic sensory areas and both superior temporal gyri (STG). These systems interface then with the conceptual system via a more left lateralized network in the posterior-inferior temporal regions (MTG and ITG). The authors suggest that the processing stages devoted to the analysis of pre-semantic information about the images of words (lexical stages, Levelt et al., 1999) might be implemented in the lateral inferior parts of the left temporal lobe (see also Luders et al., 1991; Foundas et al., 1998). On the other hand Ullman (2001) and Miozzo and Gordon (2005) attribute a more prominent role to the posterior superior portions (including also inferior parietal regions) of the left temporal lobe in lexical stages, with more inferior parts of the posterior temporal lobes involved in semantic processing. Posterior areas of the left temporal lobe are also thought to be critical in semantic memory according to different

studies on AD patients (for example the left posterolateral temporal-inferior parietal cortex: Grossman et al., 2003).

On the other hand, according to a different line of studies (based mostly on HSVE and SD patients performance), semantic memory processes should be locate more anteriorly in the temporal lobes. Semantic dementia causes typically the deterioration of semantic representations and it is linked to a degeneration process involving selectively the temporal lobes bilaterally (even if sometimes asymmetrically), with the damage involving particularly the temporo-polar regions and the inferior temporal cortex (see Mummery et al., 1999; Mummery et al., 2000). According to this line of evidence anterior areas are likely to be more linked to semantic processing with posterior ones more devoted to lexical processes. Even if a lack of activity is also found in posterior areas in SD patients, this might be due to the strong links these areas have with the anterior temporal regions which are atrophic. Also the HSVE literature tends to attribute semantic deficits associated with this pathology to damage to the anterior portions of the temporal lobes, bilaterally but more lateralized to the left hemisphere (see Gainotti, 2000; Capitani et al., 2003; Noppeney et al., 2007).

An interesting issue related to the location of semantic representations within the anterior portion of the temporal lobes, relates to the apparent conflict in the observation that the most commonly reported aetiologies causing bilateral anterior temporal damage (SD and HSVE) tend to produce very different types of semantic impairments. Indeed while in a considerable number of cases (more than half) HSVE tends to produce category specific semantic impairment for living things (Capitani et al., 2003), SD (which tends to damage pretty much the same areas) very rarely leads to category specific impairments (Lambon Ralph et al., 2003). To explain this apparent contradiction, Lambon Ralph and colleagues (Lambon Ralph et al., 2007) suggested that the two aetiologies produce a different type of damage within the same areas. While semantic representations in SD are “dimmed” or degraded, due to neural loss and thinning of the white matter, HSVE would tend to produce a damage that mainly “distorts” semantic representations, due to full-thickness necrosis of both the cortex and the white matter.

Together with these contributions in the localization of the semantic store coming from patients study, neuroimaging evidence has also been accumulating over the past 15 years indicating that many different areas distributed within the temporal lobes are active during tasks involving semantic memory at different levels. Semantic judgment tasks revealed (e.g. Vandenberghe et al., 1996; Price et al., 1997; Price, 2000) that both anterior and posterior regions are indeed active during tasks involving

the use of semantic memory; these areas include the left temporal pole as well as the left angular gyrus and left occipito-temporo-parietal junction. However, when tasks more specific than simple semantic judgment are used, more delimited regions are found to be active. For example Tyler and colleagues (2004) found that naming objects at progressively higher levels of categorical specificity activates areas that are progressively more anterior within the temporal lobes. Subordinate level naming specifically was found to activate left entorhinal and perirhinal cortices. The same anterior temporal regions have been suggested to act as a 'Semantic Hub' by Patterson (2007) integrating semantic information that may be stored also in sensory-motor congruent channels (such as those proposed by the Sensory-Functional theory of Warrington and Shallice) to build complete semantic representations of different classes of concrete concepts such as living things and artifacts.

Indeed many lines of evidence coming mainly from fMRI studies, have been converging in recent years suggesting that there are brain areas that selectively respond to either living things or artefacts in tasks in which the recognition or semantic processing is required. In a study combining lesion data from almost 100 patients with evidence coming from fMRI, Damasio and colleagues (Damasio et al., 1996) found that naming animals activated particularly left inferior temporal cortex and left temporal pole, and the same area was most commonly damaged in the group of patients showing deficit in naming living things, while naming tools (and the associated naming deficit) involved more postero-lateral left temporal areas.

In a rigorous review and meta-analysis of 7 previous neuroimaging studies on the topic, Devlin and colleagues (Devlin et al., 2002) found instead that regions consistently activated in many different tasks involving living things are left and right medial anterior temporal areas, while naming tools activated the left posterior middle temporal gyrus.

Therefore, there are suggestions that living things and artefacts might be stored in segregated brain areas, supporting both the Sensory-Functional approach and the Domain Specific approach. However focusing the attention on the studies involving semantic processing of artefacts, some specific support to the Sensory-Functional approach is found.

Many of these fMRI studies indeed highlighted (as outlined above) a series of posterior left lateralized brain structures as critically active in a wide variety of tasks involving artefacts (especially tools) (Chao and Martin, 2000; Kellenbach et al., 2003; Martin, 2007; Weisberg et al., 2007; Canessa et al., 2008). These areas constitute a complex left hemisphere lateralized network involving middle temporal and premotor areas, as well as the intraparietal sulcus (IPS) and the inferior parietal lobe

(IPL). Many of these areas are indeed part of that cortical circuit which is responsible for the processing of action related information and for visuomotor interaction: the so called “dorsal” or “where” pathway (Goodale et al., 1991; Goodale and Milner, 1992; Culham and Valyear, 2006). The partial overlapping of the areas involved in processing tools with those involved in processing movement-related information suggests that the category of tools might be relying especially on this type of information, as suggested by the Sensory-Functional approach to category specificity.

1.2 THE NEUROPSYCHOLOGICAL METHOD IN COGNITIVE NEUROSCIENCE

As already outlined in the previous sections, the debate on the structures and organization of semantic memory received relevant contributions and insights form the study of brain damaged patients. Cognitive neuropsychology is in general a powerful tool for investigating the organization of cognitive system. The power of inferences from patients’ studies lies in the possibility of highlighting dramatic dissociations in the behaviour of brain damaged patients which might, in turn, confirm or falsify theories on the organization of cognitive modules. Compared with standard cognitive investigations on healthy participants, the effects found in brain damaged patients might be much clearer, dramatic and unequivocally present even in a single subject avoiding therefore possible averaging artifacts coming from the analysis of the performance of a group as a whole (we will come back to this point later).

The contribution to of neuropsychology to cognitive neuroscience comes from the two traditional approaches to the study of patients and from a third approach that is, in recent years, becoming more and more popular. The first two approaches are those of single case and group studies, both giving important contributions but showing also potential risks and limits. The case-series approach, finally, tries to take the advantages of both the previous approaches, trying at the same time to limit the risks. We will briefly discuss each of them in turn in the next sections.

1.2.1 Single Case studies

The most traditional approach to cognitive neuropsychology comes from the study of single cases of neurological patients. For many years, this type of studies has been considered the best (and sometimes the only) methodological approach to make theoretically relevant inferences from brain damage to the structure of cognitive processes (see e.g. Caramazza, 1986; Caramazza and McCloskey, 1988).

The assumption upon which, according for example to Caramazza, single case neuropsychological investigations should be based are that one should have a model of how the cognitive system is organised in a given domain; that a hypothesis is available about how the model is modified by brain damage; finally that the underlying cognitive systems are assumed to be organised in a similar fashion across all individuals. Following these assumptions, inferences drawn from the analysis of the behaviour of single patients are considered to be sufficient for theorizing about the cognitive architecture and even more reliable than those obtained from group studies.

An obvious advantage of studying cognitive architecture from single case studies is that a single patient might be available many times for subsequent testing, allowing deep investigation of a given deficit. This would moreover allow a researcher to adapt experimental paradigms flexibly over time, according to further evidence emerging as the study proceeds.

If the deficit shown by the patient is 'pure' enough, then reliable inferences might be drawn on the organization of the function of a given cognitive module. In the most extreme formulations of the single case study approach, the correlation between the behaviour and the anatomical localization of the damage is seen as conceptually irrelevant.

On the other hand, an obvious limit of relying on single patients' data to draw inferences about the organization of the cognitive system is the possibility of idiosyncratic behaviour or cognitive organization of a particular patient, which obviously limits the possibility to generalize any given result. The replicability of any result is indeed a key factor to take into account to generalize any result to the functioning of the cognitive system in general.

1.2.2 Group studies

The interest in studying large samples of brain damaged patients comes from the need to generalize and to validate the results and insights obtained from single case studies. Of course, if a given effect or dissociation is found in many patients, this constitutes a much more solid finding. Indeed, the possibility of studying multiple patients with the same paradigm increases the reliability of the finding reducing the possibility that any effect could be due to the effects of specific material on a specific individual.

Moreover, group studies stress one of the factors that in single case studies is usually underestimated, if not explicitly distrusted, i.e. the effort to localize in a given brain region a specific cognitive function.

As we pointed out in the previous section, a more extreme approach to cognitive neuropsychology, conceives the efforts to localize deficits in particular parts of the brain as conceptually irrelevant, since a given cognitive syndrome might be found in patients with very different brain lesions, and moreover sometimes lesions in brain damaged patients are very widespread.

Another relevant limit of group studies is that, as cleverly pointed out by Caramazza (1986), the data theses studies provide are nothing more than an 'average' of behaviour, and this formally prevents any theoretical inference from those data. Indeed, if the group is not functionally homogeneous, then there could be subgroups of individual behaving in different ways under the same test conditions. This would make any inference, at best, irrelevant, if not clearly misleading. The only way to know that a group is functionally homogeneous would be to analyze data from single patients separately, but this would make the group study nothing more than a series of individual cases, which therefore are the only logical approach to cognitive neuropsychology.

On the other hand, however, as pointed out by Shallice (1988), the same problems of averaging of behaviour is ubiquitously present in any investigation on cognitive psychology, even in normal experimental psychology, nevertheless inferences from those studies are commonly considered as valid.

A series of practical problems are nevertheless linked to group studies, which make them very costly and difficult to perform. First of all, they take very long time to be performed; to collect a reasonably large sample of patients usually takes more than one year. The only way to speed up the study is to widen the criteria for inclusion of patients in the group, making however the study more prone to show heterogeneous behaviour (as pointed out by Caramazza). On the other hand narrowing the selection criteria might produce selection biases, which might also be produced by the availability of certain populations of patients rather than others. Finally, the long time needed to set-up and conduct a group study, leads to a very high cost of any error in building experimental tasks (a problem which is very limited in single case studies), and is reflected in the low level of flexibility of group studies.

On the other hand an important advantage of group studies over single-case investigations is that testing many patients only once, avoids the possibility of learning effects which are possible even in brain damaged patients with repeated testing and are a relevant drawback of the flexibility of these studies. Moreover the possibility to generalize results and to provide brain-behaviour correlation is, in

modern cognitive neuroscience, an invaluable resource which makes group studies particularly important, even with all these limitations.

1.2.3 The Case-series approach

Trying to take into account all the limitations of the previously presented approaches to neuropsychological investigations, case series investigations (e.g. Lambon Ralph et al., 2002; 2003; 2007; Woollams et al., 2007) have recently become more popular, being a promising way to (using the words of Shallice, 1988) "steer very well clear of the Scylla of sole reliance on a standard reductionist approach that relies solely on group studies, but also [to avoid] the Carybdis of ultra-cognitive neuropsychology".

In the so-called case series approach, each patient's results are considered individually and not pooled in an overall average, as they would be in a more standard group study. This avoids the problem of individual differences that might account for any possible dissociation found. Consideration of the performance of a large series of patients enables one to identify whether a typical profile exists for the group considered and, most critically allows one to potentially identify any patients who deviate from this profile (Lambon Ralph et al., 2002; 2003; 2007; Woollams et al., 2007). This is the reason why this approach is particularly suitable for investigations in those cognitive domains in which individual differences might be expected, such as in the domain of semantic knowledge.

Concerning the 'group study' aspect, case-series investigations critically rely on the fact that patients are 'unselected', meaning that they are not selected *because* of the presence of a given phenomenon of interest, as it was common practice in traditional neuropsychological group studies. Therefore, data from case-series investigations can be more reliably generalized and give important insights in localizing anatomically a given syndrome (as group studies do). However the possibility of double checking any group result with the performance of every single subject belonging to the group, allows one to highlight the presence of possible sub-groups of heterogeneous behaviour within the main series, and to possibly even give the proper importance and space to any single patient showing a peculiar behaviour of interest. A further possibility allowed by case-series investigation is the one offered by "comparative case-series" which compare groups of patients affected by different aetiologies to assess whether each individual within each case-series shows an effect that is similar or contrasting to that shown by the other group.

On the other hand, unfortunately, case-series investigations tend to suffer from some of the same practical problems which are present in group studies, i.e. the length of the study and the limited flexibility of the experimental paradigms to be used, making these investigations less rich, from a functional point of view.

1.3 BRAIN TUMOURS:

Different criteria of selection of patients might be considered in group studies and case series investigations. Especially in case series investigations, the two main selection criteria for patients are generally the anatomical location of the lesion or, more generally, the etiology.

With respect to other etiologies (such as stroke for example), brain tumours have received a limited amount of attention from the point of view of the effects they have on the cognitive system, probably because of the complexity of the effects produced by these expansive lesions which still remain largely unclear.

Brain tumours are expansive lesions growing within the brain, causing continuous changes in the brain tissue during the progression of the illness. Moreover, different types of tumours have different dynamics and therefore different impacts on the cognitive system.

Yet, in the last decade, a growing amount of interest was directed toward the effects of brain tumours, probably for two main reasons: the first is that, compared to other types of lesions, brain tumours tend to produce more circumscribed lesions on the brain tissue, and secondly because the study of brain tumours might give new interesting insights on the topic of cognitive plasticity and reorganization (see for example Desmurget et al., 2007 for extensive review).

Therefore in this section some general information about brain tumour's physiology will be briefly summarized and more specifically a brief review about the cognitive impact of brain tumours will be added.

1.3.1 Features and classification of main types of brain tumours[5]

Brain tumours are expansive lesions growing within the skull. Many different types of brain tumours exist and their classification is based on their normal cell of origin, with the tumour being named by the predominant cell type. Despite the progress in histological techniques, the origin of some

[5] Most of the unreferenced information used in this section was taken from Greenberg et al (1999), when not otherwise stated.

of these tumours still remains a mystery. The degree of malignancy depends on its histopathological features; in the years many classification systems have been developed and the most used are now the ones based on the biologic behaviour of the tumour (e.g. Kernohan and Sayre, 1950; revised in Daumas-Duport et al., 1988).

The most common system of classification of brain tumours divides tumours in four main classes basing on the degree of malignancy: grade I ('benign'), grade II ('semibenign'), grade III (relatively malignant), grade IV (highly malignant)..

The main types of tumours having possible cognitive sequelae are Meningiomas but especially Astrocytomas. Meningiomas are tumours mainly composed of neoplastic arachnoidal cells and most of them have a 'benign' grade I biological behaviour. They do not invade or infiltrate the brain but tend to displace the surrounding brain tissue, possibly causing edema in case of a large mass being present. Very rare are meningiomas showing a grade III (anaplastic) or IV (malignant) behaviour. In any case meningiomas are most often treated by surgical resection.

The most common neuroepithelial tumour is however the astrocytoma, composed predominantly by neoplastic astrocytes. They are well differentiated tumours that infiltrate the surrounding brain tissue, spreading along the white matter tracts. While grade I and II astrocytomas are considered as low-grade gliomas, grade III and IV are considered as high-grade gliomas (named as anaplastic astrocytoma and glioblastoma respectively).

Type I Astrocytomas are solid and do not infiltrate the surrounding brain (they therefore tend to displace and compress). On the other hand type II tumours have solid portions and in addition individual cells infiltrate the surrounding tissue. Grade III (anaplastic) astrocytomas are composed of only infiltrative cells without a solid mass; they progress rapidly and may transform into glioblastoma. Finally, grade IV (mainly glioblastoma) astrocytomas, the most malignant gliomas, have a clear infiltrative behaviour and show either vascular proliferation or necrosis. They often produce hemorrhages. Other, less frequent, types of tumour are oligodendroglioma and oligoastorcytoma and other mixed types of tumours. They usually show a grade II or III biologic behaviour.

Finally, special classes of brain tumours are the metastases. Metastatic brain tumours spread to the brain from a primary site elsewhere in the body, spreading through the arterial circulation, and they can form single but also (in approximately half of the cases) multiple contemporary lesions. They show the behaviour of the tumour type of origin. Brain metastases develop vasculature, the disruption of which in the end causes vast edema in this type of tumour.

1.3.2 The impact of brain tumours on the cognitive system

Low grade (I and II) and high grade (III and IV) brain tumours tend to differ substantially in the type and extent of cognitive effects they produce on the brain. It is well known that fast/aggressive high grade tumours (glioblastoma) are associated with reduced cognitive abilities and that cognitive level tend to deteriorate during the progression of the illness (see for example Scheibel et al., 1996; Kayl and Meyers, 2003; Brown et al., 2006; Bosma et al., 2007). On the other hand low grade tumours tend not to produce cognitive deficits for many years during progression of the illness (Walker and Kaye, 2003). In fact in 80% of the cases the presence of the tumour is revealed not by the onset of cognitive deficit, but rather by the onset of seizures (DeAngelis, 2001). Moreover the resection of low-grade tumours tends to produce only (if any) mild cognitive sequelae, which are largely recovered within one year (see Desmurget et al, 2007 for an extensive review on the contrasting effects of slowly growing tumours and sudden destructive stroke lesions on the cognitive system).

Numerous pre-operative neurofunctional imaging studies have shown that tumour invasions trigger major neural reorganizations. This effect seems however to be more linked to slowly growing low grade tumours. These reorganizations explain why most low-grade patients appear either normal or only slightly impaired under standard neurological assessments (e.g. Duffau et al., 2005).

The neurobiology of the two kinds of tumours is very different in many respects: both high and low grade tumours infiltrate the surrounding brain (Daumas-Duport, 1994); however, while high grade tumours tend to be destructive (leading to the necrosis of the tissue they infiltrate), low grade tumours can 'coexist' with the healthy tissue even for many years. Unfortunately, also low grade tumours are destined to change their biological behaviour in the end turning into a high-grade aggressive tumour. Haemorrhage is another factor commonly observed in the presence of high grade tumour, while it is not very commonly observed in low grade lesions. This, together with the common observation that high grade tumours produce higher levels of oedema (generated by the presence of cytokines which are also produced by both types of tumours), could explain the difference in the cognitive impact of two types of tumours. Low grade tumours on the other hand tend to be more epileptogen than high grade lesions. Even though antiepileptic drugs tend to have a cognitive impact, this nevertheless leads to only mild effects in the cognitive level of these patients (see again Desmurget et al. 2007 for a review).

Finally, both types of tumours however tend to modify the metabolism and have neuromodulation effects on the brain, also in areas which are distant from the ones involved. Of course

the impact of such effects must be carefully taken into account when evaluating the performance of brain tumour patients.

1.4 THE PRESENT PROJECT

The aim of this project was to investigate different aspects of the organization and functioning mechanisms of the semantic memory. Many issues and questions are still open regarding especially the mechanisms of access to semantic content.

The main questions we will try to answer with this set of studies are: is the clinical characterization of semantic access syndrome sufficiently solidly based, meaning it being characterized by a set of clinical features consistently present in all semantic access syndromes? Is refractoriness the only mechanism involved in semantic access difficulties? Is, moreover, refractoriness a phenomenon acting on the representations and features *within* the semantic system? What counts as a *semantic* feature? Finally: are semantic categories built around different relevant semantic features which are stored in separate anatomical regions?

To try to answer these questions we ran four studies using different methodologies to investigate both the structure and the access mechanisms of semantic memory.

In the first study (Chapter 2) we investigated the performance of an unselected case series of left and right temporal lobes tumour patients on two tasks aimed to investigate the semantic access abilities of the patients. The results showed that left hemisphere high grade tumours reliably produced semantic access difficulties in the sample of patients we tested. The syndrome we describe, however, shows only weak signs of refractoriness and appears more plausibly explainable as a consequence of a disconnection of lexical input from semantic memory, as also suggested by the areas indicated by the overlapping of the lesions of patients showing access difficulties, which highlight a posterior-superior temporal area of maximum overlap.

Then, the issue whether refractory semantic access syndrome can be a unitary syndrome was investigated, meaning that, in conditions in which refractoriness is supposed to occur, all the behavioural effects typical of refractoriness should be present. We therefore tested whether we could obtain a mild refractory state in a group of healthy subjects by means of a speeded version of the same tasks we used with patients. In this second study (Chapter 3) three behavioural experiments were performed using a series of simple word-picture matching tasks at a fast stimulus presentation rate. The results showed that healthy subjects too show a pattern of performance clearly mimicking that of

typical refractory semantic access patients. Having obtained a refractory behaviour in a comprehension task, however, suggests that refractoriness effects occur *within* the semantic system itself and not (as proposed for example by Howard et al., 2006) at a later post-semantic stage of processing.

If observing refractory behaviour in a comprehension task is the sign of a process occurring within the semantic system, then this information might be used to infer whether a given feature is indeed a semantic feature and whether it plays an important role in defining a concept. Starting from these considerations, in the third study (Chapter 4) we ran a second behavioural investigation on another group of healthy participants. The aim of this study was to test whether the manipulability of an object is an important defining semantic feature for manipulable objects. Two experiments were performed in which manipulability was shown to interfere with object recognition and, most critically, repeated presentation of pairs of objects sharing the same manipulation movement causes an increasing amount of errors in recognition, a clear sign of refractoriness taking place.

The possibility of manipulability being an important semantic feature for manipulable objects was then further investigated in the fourth study (Chapter 5). In this study a large series of patients suffering from tumours in the temporal lobes was asked to perform a naming task involving both living things and artifacts, with the latter category being composed of only manipulable objects differing in the degree of their manipulability. Results from both behavioural and Voxel-based Lesion Symptom Mapping (VLSM) analyses clearly showed that the only patients showing a selective deficit in naming artifacts (and highly manipulable objects in particular) were left posterior superior temporal patients.

In the final chapter (Chapter 6) we draw the main conclusions from all the studies trying to analyze the main theoretical and methodological implications coming from these studies.

CHAPTER 2:

2.1 INTRODUCTION:

2.1.1 Theoretical accounts of Semantic Access Dysphasia:

After the first formal distinction made by Tulving (1972) between episodic and semantic memory, the first selective impairment of semantic knowledge was reported by Warrington in 1975. Warrington described three patients with cerebral atrophy (probable semantic dementia) and selective progressive difficulties in comprehending the meaning of words and the significance of objects in spite of a fluent and generally syntactically correct speech. Those patients were highly consistent in their likelihood of retrieving a given concept and were strongly affected by the frequency of the target word. They behaved as if the semantic representations underlying concepts had been degraded.

Since this first report, degradation of semantic memory has almost always been associated with widespread damage to the neocortex of the temporal lobes as, for example, that produced by Alzheimer disease (Chertkow and Bub, 1990; Lambon Ralph et al., 1997) or herpes simplex virus encephalitis (Warrington and Shallice, 1984; Gitelman et al., 2001), or semantic dementia (Snowden et al., 1989; Hodges et al., 1992), a subtype of the fronto-temporal lobar degeneration (FTLD), typically involving anterior portions of the neocortex of the temporal lobes, mainly on the left (Mummery et al., 1999; 2000; Noppeney et al., 2007).

In contrast to these disorders held to cause the degradation of semantic memory representations, Warrington and Shallice, (1979) and then Warrington and McCarthy (1983; Warrington and McCarthy, 1987), described patients whom they argued have problems in accessing the semantic representations they still retained; they were inconsistent in whether a concept could be activated and were at most only weakly affected by word frequency. Moreover, Warrington and McCarthy (1983, 1987) showed that the probability of correctly recognizing a target stimulus was influenced by the semantic distance between the target word and distractors and by the rate at which the items were presented. They re-defined access conditions as due to a temporary unavailability of the stored representations due to abnormal refractoriness within the semantic system. Refractoriness was defined as ‘the reduction of the ability to utilize the system for a certain period of time following activation’ (Warrington and McCarthy, 1987 p. 874).

Since these first reports, however, the appropriateness of the distinction between deficits of semantic access and semantic degradation has been questioned on both theoretical and empirical grounds. Rapp and Caramazza (1993) pointed out that the criteria proposed to distinguish the two syndromes had never been assessed in the same fashion on both groups of patients. In fact patients of the two types had been studied with different procedures and materials. They also argued from a theoretical point of view, that there was no theoretical account available to explain the phenomena putatively held to co-occur in the semantic access syndrome.

In an attempt to respond to the first of these concerns, Warrington and Cipolotti (1996) using the same tests and materials, contrasted the performance obtained by a group of patients with a putative semantic degradation syndrome (4 patients with probable semantic dementia), and that of 2 patients putatively affected by semantic access syndrome (1 stroke and 1 left temporal high grade tumour). In the word-to-picture matching tasks administered, "degradation" patients performed consistently on whether they could access concepts and were also sensitive to the lexical frequency of the target item but not to the semantic distance between the target and the distractors. Moreover, they were not affected by changes in the response-stimulus-interval (RSI). By contrast, "semantic access" patients were very inconsistent in whether they could access concepts and were strongly influenced by semantic distance, while word frequency had only a very weak effect. Manipulation of the rate of presentation had a dramatic effect on their performance with "access" patient A2 who showed a serial position effect. The sensitivity of the patient to the rate of presentation variable was then held to be a crucial factor in the definition of a "refractory" syndrome: in addition the performance of the patients should deteriorate progressively when the same stimulus is subsequently re-presented (a serial position effect) (Warrington and McCarthy, 1983; 1987).

Since 1996, the only group study conducted to assess the proposed distinction between access and degradation deficits, is that of Jefferies and Lambon Ralph (2006). This study confirmed (although with different tasks[6]) the complementarity of the performances between a group of 10 patients affected by semantic dementia (who showed degradation of semantic representations) and a group of 10 fronto-temporal or temporo-parietal stroke patients (who showing access difficulties). However, later individual case studies showed that not all patients held to be of access type are sensitive to temporal factors and so cannot be characterised as being of a refractory type. Thus Warrington and Leff (2000)

[6] The use of different tasks was due to the fact that the patients they studied were less severely impaired with respect to those tested by Warrington and Cipolotti

failed to find rate effects in the reading aloud performance of a jargon dyslexic patient; similarly, Gotts and colleagues (2002) did not find rate effects in the naming performance of their patient. However, in these patients the locus of the impairment could be attributed to a post-semantic (lexical selection) stage of processing.

Few formal attempts have been made to model the properties empirically claimed to hold for semantic access dysphasia. In 2002, however, Gotts and Plaut put forward a comprehensive computational model of access to the semantic system in order to account for the different types of syndromes on the access/degradation spectrum. Their basic idea was that while degradation of semantic representations could be due to damage involving cortical neurons within the semantic system itself (encoding information itself), access deficits could be due to damage involving neuromodulatory white matter fibres system implicated in the efficient regulation of normal refractory processes within the cortical semantic network (Gotts and Plaut, 2002).

Their model has, as a central concept, that of synaptic depression, the typical reduction in the activity of synapses after repetitive firing (see for example Varela et al., 1999). To reduce the effects of synaptic depression and so ensure efficiency in repeatedly stimulated synapses, neuromodulatory systems, in particular cholinergic, play a key role in reducing the probability of transmitter release in the pre-synaptic neurons (e.g. Hasselmo and Bower, 1992; Hasselmo, 1995 for a review) and so reducing the adaptation of the firing-rate. The largest set of cholinergic fibres comes from the basal forebrain nuclei of Meynart (nbM-Ch4), which spreads throughout the neocortex including the temporal lobes (Selden et al., 1998). They can in principle be selectively damaged by different pathologies. In their model, Gotts and Plaut (2002) hypothesize that vascular accidents in the territory of the middle cerebral artery could in principle cause a large neuromodulatory breakdown within the temporal lobes, causing abnormal levels of synaptic depression that would lead to refractoriness in the semantic system.

More recently, Jefferies, Baker, Doran and Lambon Ralph (2007) proposed a somewhat different account of refractory semantic access disorders. They assessed the semantic abilities of a group of left hemisphere stroke patients (the same patients as in the 2006 study) and found an overall refractory behaviour in those patients whose lesion involved the left inferior prefrontal cortex as well as the temporal lobes. This was a more consistent effect in naming than in matching tasks and quite variable in magnitude across the different patients. Jefferies and colleagues argue that lesions in this area may lead to a failure in control processes, which are held to be required to assure adequate and

flexible semantic access especially when dealing with highly demanding tasks such as naming when stimuli are quickly presented. When several semantically related competitors are repeatedly activated at a fast rate, activation will spread among them without having time to fully decay between trials, leading to summation effects worsening the performance over time (see also Schnur et al., 2006 for a similar account). Control processes were argued to come into play in these situations. An interesting additional finding was that two of the patients reported by Jefferies and colleagues, who had left posterior temporo-parietal lesions, did not show any sign of refractoriness at all.

2.1.2 Aim of the study:

Rapp and Caramazza (1993) criticised the early empirical characterisations of the claimed functional syndromes of semantic access disorders as insufficiently solidly based. With the exception of the study of Jefferies et al (2006) both the earlier and later characterisations of the functional syndrome have relied on individual case studies of patients selected for their pattern of performance, the standard methodology of cognitive neuropsychology. However, the study of Woollams et al (2007) on the preservation of word reading in semantic dementia has shown that the methodology is subject to the potential danger of selection artefacts. The alternative methodology these authors propose is the case series in which non-behavioural criteria are used to select the patients whose performance, though, can be assessed individually. The one application of this methodology to the semantic access set of disorders – that of Jefferies et al on stroke patients – suggests that the patients so characterised may not all present with the same functional syndrome.

Individual patients who have been held to manifest semantic access disorders have included patients with temporal tumours as well as stroke patients. However, while stroke patients have been extensively investigated on semantic access, tumours patients have very rarely been studied. Brain tumours tend indeed to induce lesions that are more circumscribed and restricted to the white matter. Therefore tumours can give better chances to localize a pathological behaviour both functionally and anatomically. We have therefore investigated the behaviour of a series of patients with temporal lobe tumours on tasks derived from those used initially by Warrington and McCarthy using a case series methodology. The principal aim was to confront the critique made by Rapp and Caramazza of the empirical adequacy of semantic access disorder as a unitary functional syndrome. The secondary aim was to assess the theoretical accounts of the disorder presented by Warrington and McCarthy, Gotts and Plaut, and Jefferies et al. Our study involved the five main variables thought to distinguish

semantic access from degradation disorders. The patients were, though, not selected on the basis of the presence of semantic difficulties. The only inclusion criteria were the presence of a glioma of either high or low grade within the left or right temporal lobe.

2.2 EXPERIMENTAL INVESTIGATION:

2.2.1 Subjects:

Tumour patients' group:

This study involved a consecutive series of 20 patients with a glioma located within the temporal lobes. The selection of the patients followed a clinical criterion: regardless of their cognitive level or neuropsychological picture, patients were selected on the basis the presence of a glioma either exclusively or mainly within the left or the right temporal lobe. All patients gave their consent to participate in the study; the study was approved by the ethical committee of SISSA-ISAS (International School for Advanced Studies, Trieste). 10 of the patients were affected by high grade malignant gliomas (glioblastoma) and 10 by low grade gliomas. 13 patients had a left and 7 a right hemisphere lesion. Basic demographic information is summarized in Table 1. All the patients were tested prior to the surgical removal of the mass, 15 of them being also available for re-testing post-operatively. All of the patients underwent the complete resection of the tumour except for patient LL5. No cases were treated differently from a medication point of view.

Patients were usually tested the day before and from 3 to 6 days after the operation, in a session lasting about 2 hours. Due to the strictly limited time available, in addition to tests assessing their semantic abilities, the patients were administered with brief baseline neuropsychological tasks, in order to monitor their basic visuo-perceptive, semantic and attentive/executive skills. The results of the baseline screening as well as neurological data are reported in Table 1.

Control patients:

To check whether the tasks developed could potentially provide evidence on semantic degradation effects as well as semantic access ones and to test the procedures developed also on a patient affected by the aetiology traditionally associated with refractory semantic access disorders, we administered both experiments to three control patients. The first two patients should in theory show degradation effects as they had sustained primary damage to the cortex. Patient MU is a herpes encephalitis patient (see Borgo and Shallice, 2001) whose semantic memory skills were gravely degraded after his illness. Patient MG is a 78 right-handed retired metalworker showing signs of cortical atrophy on CT scan.

The third patient, SV, suffered from a stroke involving the left basal ganglia and the left anterior frontal-temporal Areas. Patient SV was tested with the same battery of tasks on two separate occasions.

Control patients: Neuropsychological profile

MU: is a 42 years old plumber with 13 years of schooling which in September 1994 suffered from herpetic encephalitis. The EEG performed after his recovering from vigil coma, in April 1995, was characterized by signs of severe diffuse cerebral damage. Both CT and MRI scans showed severe cortical damage involving bilaterally the temporal lobes (with larger involvement of the right hemisphere), the medial part of the frontal lobes and the medial part of the right occipital cortex (see Borgo and Shallice, 2001 for a more detailed case description). His semantic memory skills were gravely degraded after his illness (Borgo and Shallice, 2001, 2003). His neuropsychological clinical picture is now overall constant and stable. Between 2003 and 2004 he was tested with a wide and complete neuropsychological assessment. On B.A.D.A. (Batteria per l'Analisi dei Deficit Afasici, Miceli et al. 1994) test he showed evident naming difficulties both for names and verbs. Moreover mildly impaired were also his auditory visual comprehension abilities (for nouns and verbs). His short memory abilities were within the limits of the norms (digit span forward=5). On the other hand long term memory functions were severely impaired: short story recall (Spinnler and Tognoni, 1987): 4.4/16. Also his face recognition skills were gravely impaired: Benton test: short version 7/13; long version corrected score: 0). Attentive skills as measured by Visual search test, were within the limits of the norms: 52/60. Substantially preserved were his logical abilities: Raven coloured matrices=29/36. On the perceptual screening he performed completely within the normal range: Screening test: 20/20; Object decision: 17/20.

MG: is a 78 retired metalworker, former carpenter, with 4 years of schooling. He was admitted to the Cattinara hospital in Trieste due to onset of aphasia and right hemi-paresis. An EEG run the day after revealed discreetly marked sign of left hemisphere sufferance. Although angiography revealed signs of bilateral carotid stenosis, a CT scan performed the same day did not reveal ischemic signs. The scan however revealed signs of cortical atrophy. A complete neuropsychological assessment was performed 2 months later. At the testing, he showed some language difficulties: he appeared to be mildly dysarthric with difficulties both in production (AAT: Aachen Aphasia Test: Naming: 94/120) and in comprehension (AAT: Aachen Aphasia Test: Oral comprehension: 48/60; written comprehension: 43/60) of the language. Also his memory skills appeared to be somehow impaired:

while his Short term memory appeared substantially intact (Digit span forward: 4; Corsi's spatial memory span: 5), he appeared to have difficulties in Long term memory storing abilities (Short story recall (Novelli et al., 1986): 5.5; Short recognition memory for faces (Warrington, 1996) 15/25; Rey complex Figure: 4.5). Also his attentive and logical analytical skills were somehow reduced (Visual search: 33/60) even if still within the lower limits of the norms. Borderline was also considered his praxic skills (Ideomotor Apraxia test (DeRenzi): 54/72). On the other hand his perceptive skills were considered to be intact (VOSP screening test: 19/20; Object decision: 16/20). Substantially preserved moreover were his logical abilities (Raven's progressive matrices: 25/30).

SV: is a 66 years old housewife with 8 years of education who suffered in 2006 from a left hemisphere ischemic episode. The stroke involved the left basal ganglia and the left fronto-temporal cortex and was largely subcortical. Her lesion was reconstructed as ROI with MRIcro software and is showed in appendix B: Fig.2. Lesion volume was equal to 78cc. Between May and June 2006, she underwent a complete neuropsychological assessment. The general diagnosis was that of moderate-severe Broca's aphasia. On the AAT (Aachen Aphasia Test, Luzzatti et al, 1995) she showed significant comprehension (Token Test: 36/50; Oral comprehension: 28/60; Written comprehension: 18/60) as well as naming (29/120) difficulties. Written language skills were also impaired (AAT: Reading: 16/30; Dictation: 3/30; Writing: 0/30). Memory skills were overall preserved (Corsi spatial span: 6; Warrington face recognition: 21/25). However semantic memory difficulties emerged in the testing (Pyramids and palm trees: 39/52). Importantly, she showed mild attentive deficits: on the rail Making test (Giovagnoli et al 1996) she performed very poorly at the part A and was unable to perform the part B (implying task switching abilities). However she showed normal categorization abilities in the Weigl sorting test (Spinnler and Tognoni, 1987). Her logical abilities were found to be normal (Raven progressive matrices: 26/36), while some mild difficulty emerged in the visuo-perceptive skills (V.O.S.P.: Screening test: 20/20; Object decision: 13/20). Her praxic skills were within the limits of the norms (Ideomotor apraxia: 55/72; Ideative Apraxia: 14/14).

Healthy controls sample:

The performance of the patients in the experimental tasks was compared with that of a group of 20 control subjects divided into two age groups (below and above 50 years of age) and two education groups (below and above 10 years of schooling). Age and education cut-offs were determined on the basis of demographic characteristics of a group of similar patients (Vallesi et al., 2007). Thus, the performance of four subgroups of five subjects each could be compared with that of each tumour

patient matched for age and education at the single case level of analysis. At the group level however, all control subjects were collapsed into an overall group of 20 subjects. The control subjects, performed virtually at ceiling in both tasks. In Experiment 2 however, they showed a very small advantage for distant arrays (Wilcoxon matched pairs test: z= 3.72; p=0.0002) (see figures 1 and 2), but no effect of word frequency (Wilcoxon matched pairs test: z= 0.71; p=0.47).

2.2.2 General experimental procedures:

Unlike the previous studies on semantic access disorders, which employed a single task for testing all the variables of interest at the same time, we were forced to split the assessment of semantic access skills of the tumour patients into two separate tasks because of the time constraints in testing the patients. When possible, all the patients were tested with both tasks on the two separate occasions. Both tasks used a spoken-word-to-picture matching technique and were implemented for computer presentation using E-prime software (Psychology Software Tools). After hearing the target item from the computer loudspeakers the patient was required to identify and touch the appropriate picture among the four simultaneously presented on a touch-screen. The Response Stimulus Interval (RSI) was controlled by the software. The tasks were designed to control for the typical variables thought to be critical in the definition of semantic access deficits and to distinguish them from degradation deficits: semantic distance, word frequency (experiment1), rate of presentation and consistency of response (and possible serial position effects) (experiment2). The general procedures were basically the same as used in previous works on this topic (see for example Cipolotti and Warrington, 1995;Warrington and Cipolotti, 1996).

Table 1: Baseline assessment and neurological data of the group of tumour patients

Patient	Age	Edu	TUMOUR TYPE	TUMOUR LOCATION	SEMANTIC FLUENCIES (1min)						BORB(a) (n/25)				VOSP(b) (n/20)				VISUAL SEARCH©	
					Animals		Objects		Proper Names		Minimal Features		Forshort. Views		Incomplete Letters		Object Decision			
					pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
1. LH1	61	8	Glioblastoma	Left Temporal	3^	4^	2^	0^	8^	9^	23	24	23	23	16	10*	15	15	26*	26*
2. LH2	66	5	Glioblastoma	Left Temp.-Insular	0^	--	0^	--	0^	--	0*	--	NA	--	0*	--	9*	--	NA	--
3. LH3	63	7	Glioblastoma	Left Temporal	17	19	8	11	18	19	22	22	22	24	6*	5*	12*	13*	41	42
4. LH4	70	5	Glioblastoma	Left Sup-Post Temp.	16	5^	10	2^	NA	NA	22	22	23	22	19	17	15	10	NA	NA
5. LH5	81	5	Glioblastoma	Left Post.Temp-Par.	3^	3^	2^	2^	10	10	18*	18*	12*	15*	2*	0	11*	6*	32	29
6. LH6	48	13	Glioblastoma	Left Post. Temporal	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
7. LH7	69	17	Glioblastoma	Left Temporal	NA	--	NA	--	NA	--	NA	--	NA	--	NA	--	NA	--	NA	--
8. LL1	45	13	Anapl Astrocyt	Left Sup-Post Temp.	19	NA	23	NA	25	NA	25	NA	24	NA	19	NA	16	NA	57	NA
9. LL2	36	17	Grd II Astrocyt	Left Inf.-Post. Temp.	23	23	21	22	25	15^	24	24	25	25	19	19	16	15	53	NA
10. LL3	38	17	Grd II Astrocyt	Left Ant. Med. Temp.	29	21	16^	21	23	20	25	25	24	25	18	18	18	18	57	56
11. LL4	38	9	Grd II Astrocyt	Left Frontal-Temp.	18	6	21	16	27	8^	25	21	24	22	19	14	12*	15	48	NA
12. LL5	25	17	Grd II Astrocyt	Left Frontal-Temp.	26	--	21^	--	12^	--	24	--	25	--	20	--	17	--	58	--
13. LL6	46	17	Grd II Astrocyt	Left Ant. Med .Temp.	25	21	23	16^	21	22	25	25	25	25	19	19	18	19	54	60
14. RH1	65	5	Glioblastoma	Right Temp.-Insular	15	11	16	15	16	NA	24	NA	19	NA	6*	0	12*	14	NA	NA
15. RH2	71	5	Glioblastoma	Right Temp.-Insular	12	12	10	9	15	21	19	NA	NA	NA	NA	NA	NA	NA	26*	NA
16. RH3	72	8	Glioblastoma	Right Ant. Temporal	16	12	12	9	19	21	22	22	19	22	14*	11*	12*	11*	37	40
17. RL1	68	5	Grd II Astrocyt	Right Frontal-Temp.	16	--	10	--	NA	--	24	--	23	--	NA	--	NA	--	NA	--
18. RL2	30	13	Grd II Astrocyt	Right Anterior Temp.	12^	--	12^	--	16^	--	25	--	25	--	19	--	14*	--	50	--
19. RL3	57	13	Grd II Astrocyt	Right Temp.-Polar	21	29	24	30	28	32	25	23	25	23	17	18	13*	14	58	58
20. RL4	63	13	Grd II Astrocyt	Right Post. Temp.	20	17	21	24	23	22	25	24	24	24	19	18	10*	13*	56	54

(a)BORB= British Object Recognition Battery (Riddoch and Humpreys, 1993);
(b)VOSP= Visual Object and Space Perception (Warrington and James, 1991); (c) Spinnler and Tognoni (1987)
*= below normal range; ^= below age/education matched sample (5 subjects) range; NA= not administered;

2.2.3 Experiment 1: Rate-Consistency Matching task

This first task was designed in order to control the consistency of patients' responses and to investigate whether possible serial position effects occurred. The rate of presentation was strictly controlled.

Materials:

Stimuli for this task consisted of 16 coloured digital pictures of manipulable objects. Each picture was sized to a resolution of 400x300 pixels and arranged in 4 arrays of 4 items on a 1024x768-pixel touch screen display. Each array was built with the following properties: (I) low frequency: to produce the higher level of difficulty possible (Word frequency ratings were obtained from *Dizionario di frequenza della lingua italiana*, CNR, Unpublished: mean frequency: 3.94); (II) closely related distance: to produce a higher level of semantic interference. Semantic distance ratings were obtained from the same group of 20 healthy participants (10m, 10f, mean age: 29.75; education: >17), who were asked to judge the 'conceptual' distance of the objects in each array on a 7-point scale (mean semantic distance: 2.28).

Procedure:

The task consisted of a fast and a slow presentation rate conditions. In the Fast condition, the name of the target stimulus was first acoustically presented from the computer to the patient together with a fixation point in the centre of the screen for 1500 msec. After the auditory presentation, an array of four items was presented on the screen and lasted until the response was made by touching the screen. After response was collected, the *same* array was pseudo-randomly rearranged after a Response Stimulus Interval (RSI) of 1000 msec, and a second target from the same array was presented. The order of presentation was pseudo-random, the position of the target and other stimuli in each array being constantly varied. Target position was balanced across each of the four possible screen positions This procedure was repeated until all 4 stimuli were presented as targets and until each target was presented 3 times. Then the array was replaced by another composed of four other objects. The fast and slow conditions therefore involved a total amount of 48 presentations each (4 stimuli x 4 arrays x 3 times). The same order of presentation was used across subjects. The slow condition was identical to the fast one with the exception of the adoption of 10 sec. of interval between the stimuli (RSI). The two conditions were administered in separate blocks.

Patients LH1 and LH2:

These first two patients were administered with a slightly different version of Experiment 1. The differences were limited to the different number of stimuli (20 instead of 16, meaning 5 instead of 4 arrays of 4 stimuli) and the fact that the number of repetitions for each stimulus was 2 instead of 3. The stimuli (except for 1 extra array in this version of the task) as well as the procedure were the same in both tasks. The reason why this Experiment was substituted by the actual Experiment 1 was that patients LH1 and LH2 were not showing signs of refractory behaviour in this task, not being influenced by presentation rate or showing serial position effects (only patient LH1 after the surgery presented the effect but in absence of any trace of rate effect). The results are reported in appendix A (Table D) and tables 4 and 5 in the main text. Also one of the degradation patients (MG) was administered with this task. Due to this difference their data are reported at the single-case level of analysis but at the group level their data were not included.

2.2.4 Experiment 2: Frequency-Distance Matching task

In this second task the word frequency of the target stimuli and the semantic distance between them were manipulated in order to assess their possible effects on the performance of the patients.

Materials:

The stimuli consisted of 80 coloured digital pictures of manipulable objects divided into 4 sessions of 20 items each. Each picture had a resolution of 400x300 pixels and was arranged in a 4-items array. There were 5 blocks for each session. Arrays were presented on a 1024x768 touch screen display. Each block was built in order to fit the following criteria:

a) Low frequency, closely related (20 stimuli)
b) Low frequency, distant (20 stimuli)
c) High frequency, closely related (20 stimuli)
d) High frequency, distant (20 stimuli)

Unlike previous investigations, in this task stimuli differed between close and distant and low and high frequency conditions. This was done to avoid excessive stimuli repetitions in the same session of testing. Given the use of different stimuli in the close and distant conditions, also other possible confounding variables were taken into account and carefully controlled.

Word frequency ratings were obtained from *Dizionario di frequenza della lingua italiana* (CNR, Unpublished). Mean frequencies were: 2.03 for low frequency items; 32.55 for high frequency ones. Frequency differed significantly between the 2 categories (Mann-Whitney U test: U=13; $p<0.0001$). Semantic distance ratings were obtained from a group of 20 healthy participants who were asked to judge the overall 'conceptual' distance between the objects of each array on a 7-point scale. mean semantic distance was: 2.67 for Close items, 5.88 for Distant items. Semantic distance differed significantly between the 2 groups (Wilcoxon matched pairs test: $z=3.85$; $p<0.0001$). Given the use of different stimuli in the close and distant conditions, also other possible confounding variables were taken into account and carefully controlled. The visual complexity of the stimuli belonging to each of the 2 levels of frequency and distance was completely matched (Kruskal-Wallis ANOVA: p=0,39): no differences in visual complexity were therefore reported. Also the familiarity of the item used was controlled: coherently with its close link to the frequency of the corresponding word a significant difference in familiarity was reported when confronting high Vs. low frequency stimuli (Mann-Whitney U test: $p<0.0001$) but critically no difference whatsoever was found between close and distant arrays (Mann-Whitney U test: $p=0.72$).

Procedure:

The general procedure for each trial was as follows: the name of the target stimulus was first acoustically presented by the computer together with a fixation point in the centre of the screen for 1500 msec. Then an array of 4 items was presented until the patient responded. After the response, the procedure started again with a different array belonging to the same frequency/distance block. Each stimulus was presented only once in a pseudo random order. The position of stimuli belonging to each array was changed across trials, as was target position. Target position was moreover balanced across each of the four possible screen positions. The same order of presentation was maintained across subjects. A standard 1-second Response Stimulus Interval (RSI) timing was adopted. The target stimuli were presented only once, without stimulus repetition.

2.2.5 General procedures for the analysis of the results:

We analysed the performance of the patients both at a single case (appendix A: tables C, D, E, F) and at a group level (Tables 3, 5, 6).

Group analysis procedure:

As a dependent variable the differences between the mean scores obtained by each patient was used on each of the 2 levels of the 3 independent variables: semantic distance (Distant-Close: i.e. subtracting accuracy on close from accuracy on distant arrays), word frequency (high-low) and presentation rate (slow-fast). Kruskal-Wallis non-parametric ANOVAs were then carried out to investigate group differences between patients and controls together with the attendant post-hoc comparisons (see Siegel and Castellan, 1988 for details). We were interested in investigating two main types of effect, namely the location (left or right hemisphere) and histology (high or low proliferation grade) of the tumour, together with possible interactions between these two variables. Since non-parametric ANOVAs do not allow the direct determination of interactions, the following logic was adopted in the analysis of the data: Kruskal-Wallis ANOVAs were carried out on the results of the patients after being separately grouped in parallel according to both the location and the histology of the lesion. As two parallel statistical analyses were carried out, a Bonferroni correction was adopted: the p-level threshold was set at 0.025 (i.e. 0.05/2). If a significant effect was detected in either parallel confrontation, then the effect was further investigated in terms of whichever variable had been significant, location or histology, using post-hoc comparisons, to assess which of the groups was significantly different from the others (see tables 2-6-7). For instance, if in the comparison of controls vs. high vs. low grade patients, the Kruskal-Wallis ANOVA gave a significant effect of histology, and post-hoc comparisons highlighted high grade patients as the source of this effect, then another ANOVA was carried out comparing controls vs. left high grade vs. right high grade patients to assess the effect of laterality given the critical histology.

Single case procedure:

The Fisher exact chi square test was adopted when analyzing accuracy scores for each patient.

Table 2: Mean accuracy raw scores across all the sub-groups of patients, in each of the tasks.

		BEFORE SURGERY											
		PRESENTATION RATE				SEMANTIC DISTANCE				WORD FREQUENCY			
		FAST		SLOW		CLOSE		DISTANT		LOW		HIGH	
GROUP	N. of subj.	MEAN (n/48)	SD	MEAN (n/48)	SD	MEAN (n/40)	SD	MEAN (n/40)	SD	MEAN (n/40)	SD	MEAN (n/40)	SD
CONTROLS	20	47.6	0.6	47.3	0.8	39.2	0.9	39.9	0.2	39.7	0.6	39.5	0.8
HIGH GRADE	10	36.9	10.1	39.6	7.7	29.0	8.5	35.5	4.5	31.6	5.5	32.9	6.9
LOW GRADE	10	46.8	2.1	47.3	2.2	39.3	1.3	39.9	0.3	39.6	0.7	39.6	1.0
LEFT HEM	13	40.9	10.3	42.8	8.0	32.5	9.4	37.3	4.4	34.7	6.6	35.2	7.0
RIGHT HEM	7	44.7	3.4	45.6	2.9	37.1	2.5	38.4	2.4	37.3	2.8	38.3	1.9
LEFT HIGH GR.	7	33.0	11.0	36.6	8.4	26.4	9.1	35.0	5.1	30.3	6.2	31.1	7.6
LEFT LOW GR.	6	47.5	0.8	48.0	0.0	39.7	0.8	40.0	0.0	39.8	0.4	39.4	1.3
RIGHT HIGH GR.	3	43.3	3.8	44.7	2.3	35.0	1.0	36.7	3.1	34.7	2.1	35.3	2.1
RIGHT LOW GR.	4	45.8	3.2	46.3	3.5	38.8	1.9	39.8	0.5	39.3	1.0	39.3	1.5

		AFTER SURGERY											
		PRESENTATION RATE				SEMANTIC DISTANCE				WORD FREQUENCY			
		FAST		SLOW		CLOSE		DISTANT		LOW		HIGH	
GROUP	N. of subj.	MEAN (n/48)	SD	MEAN (n/48)	SD	MEAN (n/40)	SD	MEAN (n/40)	SD	MEAN (n/40)	SD	MEAN (n/40)	SD
CONTROLS	20	47.6	0.6	47.3	0.8	39.2	0.9	39.9	0.2	39.7	0.6	39.5	0.8
HIGH GRADE	8	39.4	6.8	43.1	4.7	32.0	4.4	36.9	2.0	35.0	1.7	34.5	3.7
LOW GRADE	7	47.7	0.5	47.9	0.4	39.1	1.2	40.0	0.0	39.4	1.1	39.7	0.5
LEFT HEM	10	42.8	7.6	44.8	4.8	34.6	5.7	38.3	2.2	37.1	2.8	36.3	4.2
RIGHT HEM	5	45.0	3.0	46.8	1.6	36.8	2.1	38.4	2.2	37.0	2.5	38.2	2.4
LEFT HIGH GR.	5	36.5	7.6	41.0	5.2	30.0	4.4	36.6	1.9	34.8	1.6	32.8	3.1
LEFT LOW GR.	5	47.8	0.4	47.8	0.4	39.2	1.3	40.0	0.0	39.8	0.4	39.8	0.4
RIGHT HIGH GR.	3	43.3	3.2	46.0	1.7	35.3	1.2	37.3	2.3	37.0	1.7	37.3	2.9
RIGHT LOW GR.	2	47.5	0.7	48.0	0.0	39.0	1.4	40.0	0.0	39.5	0.7	39.5	0.7

Consistency analysis:

The consistency of responding was computed by analyzing the performance obtained by patients in the 'fast' presentation rate condition of Experiment 1. We used the same procedure as Warrington and Cipolotti (1996).

A binomial test was used to compute the probability of a chance response (inconsistent behaviour) on the triplets of stimuli on which at least one error occurred. The overall probabilities of success (p) and failure (q) in each of the three (independent) trials vary across subjects depending on the overall comprehension abilities of different patients. This probability was therefore separately calculated for each patient (p=n.corr/48; q=1-p). Using these assessments of the probabilities, the expected number of consistent (0 or 3 failures out of 3 trials: q3 and p3 respectively) and inconsistent (three combinations of 1 or 2 failures: 3(q2*p) and 3(q*p2)) triplets was computed. Finally, a chi-square test was used to compare whether the numbers of consistent and inconsistent triplets produced by the patient significantly differed from the expected ones. If $p<0.05$, then the pattern of performance exhibited was considered to be significantly more consistent than the chance response expectation (see also Warrington and Cipolotti 1995, 1996). The results of the consistency analyses are reported in Table 4. With $p<0.05$, the pattern of performance exhibited was considered to be significantly more consistent than the chance response expectation. The results of the consistency analyses are reported in Table 4. In addition with this procedure we also analyzed consistency by means of consistency coefficient φ calculation and logistic regression (Jefferies and Lambon Ralph, 2006; Jefferies et al., 2007); results are provided in appendix A (tables K and L).

Serial Position effects:

To examine whether serial position effects occur in Experiment 1, the number of times that the first probe was correct and either the second or the second and the third were missed by the patients, was contrasted with the number of times the complementary pattern of responding was found. A binomial test was performed in order to assess the significance of this difference. The results of this analysis are reported in Table 5.

Table 3: accuracy group analysis: Experiment 1: Kruskal-Wallis ANOVA and post hoc comparisons: presentation rate (slow-fast condition)

PRESENTATION RATE: ACCURACY

BEFORE SURGERY

Contrast	Main Effect:	p-level	Contrast	Post Hoc:	p-level
Ctrls (n=20) Vs.			**Ctrls Vs. High Gr**	**Z=2.92**	***0.010°***
High Gr. (n=8) Vs.	**$H_{(2,38)}$=9.89**	***0.007****	Ctrls Vs. Low Gr	Z=1.64	0.302
Low Gr (n=10)			High Gr Vs. Low Gr	Z=1.26	0.617
Ctrls (n=20) Vs.			Ctrls Vs. Left High	Z=2.32	0.061
Left High (n=5) Vs.	$H_{(2,28)}$=7.05	***0.029***	Ctrls Vs. Right High	Z=1.54	0.372
Right High (n=3)			Left High Vs. Right High	Z=0.29	1
Ctrls (n=20) Vs.			**Ctrls Vs. Left Hem**	**Z=2.45**	***0.042°***
Left Hem (n=11)Vs.	**$H_{(2,38)}$=8.16**	***0.017****	Ctrls Vs. RightHem	Z=1.95	0.152
Right Hem (n=7)			Left Hem Vs. Right Hem	Z=0.14	1
Ctrls (n=20) Vs.			**Ctrls Vs. Left High**	**Z=2.51**	***0.037°***
Left High (n=5) Vs.	$H_{(2,31)}$=6.76	***0.03***	Ctrls Vs. Left Low	Z=0.52	1
Left Low (n=6)			Left High Vs. Left Low	Z=1.68	0.27

AFTER SURGERY

Contrast	Main Effect:	p-level	Contrast	Post Hoc:	p-level
Ctrls Vs. (n=20)			**Ctrls Vs. High Gr**	**Z=3.43**	***0.002°***
High Gr. (n=7) Vs.	**$H_{(2,33)}$=12.88**	***0.002****	Ctrls Vs. Low Gr	Z=0.84	1
Low Gr (n=7)			High Gr Vs. Low Gr	Z=2.17	0.088
Ctrls (n=20) Vs.			**Ctrls Vs. Left High**	**Z=2.67**	***0.023°***
Left High (n=4) Vs.	**$H_{(2,26)}$=11.17**	***0.004***	Ctrls Vs. Right High	Z=2.25	0.071
Right High (n=3)			Left High Vs. Right High	Z=0.09	1
Ctrls (n=20) Vs.			Ctrls Vs. Left Hem	Z=1.97	*0.146*
Left Hem (n=9) Vs.	**$H_{(2,33)}$=8.31**	***0.016****	**Ctrls Vs. Right Hem**	**Z=2.41**	**0.048°**
Right Hem (n=5)			Left Hem Vs. Right Hem	Z=0.74	1
Ctrls (n=20) Vs.			**Ctrls Vs. Right High**	**Z=2.64**	***0.025°***
Right High (n=3) Vs.	**$H_{(2,24)}$=8.13**	***0.017***	Ctrls Vs. Right Low	Z=1.01	0.93
Right Low (n=2)			Right High Vs. Right Low	Z=0.89	0.97

*= Bonferroni correction: p= 0.025; °= significant corrected post-hoc contrast

2.3 RESULTS:

2.3.1 Presentation rate effects (exp. 1: slow-fast condition):

Grouping the patients initially on the basis of the histology (high vs. low grade tumours vs. controls) (Table 3), led to significant effect of presentation rate on group (Kruskal-Wallis ANOVA: p=0.007 before and p=0.002 after the surgery). The performance of high grade patients, in particular, was significantly more influenced by presentation rate, with respect to controls both before (p=0.01) and after (p=0.002) surgery. On the other hand, performance of low grade patients (see Fig. 1 and 2) did not, meaning that high grade patients, as a group, were significantly worse in identifying target stimuli when presented at a faster presentation rate low grade patients on the other hand did not differ significantly from the controls.

To examine this finding in further detail left high grade patients were compared with right high grade ones and controls. An effect of lateralization was found (Kruskal-Wallis ANOVA: p=0.029 before and p=0.004 after the surgery). Post hoc comparisons showed that the effects of presentation rate tended to be higher for left high grade patients (see Fig.3 and 4) with respect to controls especially after the surgery (p=0.061 before and p=0.023 after surgery), while for right high grade patients the difference was never significant. No significant difference was however found in the direct comparison of left and right high grade patients.

When patients were initially grouped on the basis of lateralization of the lesion alone, a significant main effect of presentation rate was found both before (Kruskal-Wallis ANOVA: p=0.017) and after the surgery (p=0.016). Post hoc comparisons however showed that before surgery the performance of left hemisphere patients was significantly more influenced by presentation rate (p=0.042) than the controls, while that of right hemisphere patients was not. To examine this finding in further detail left high grade patients were compared with left low grade ones and controls. An effect of lateralization was found (Kruskal-Wallis ANOVA: p=0.030 before and p=0.017 after surgery). Post hoc comparisons showed that the effects of presentation rate were significant for left high grade patients (p=0.037) with respect to controls while left low grade patients completely overlapped to controls. After surgery however, post hoc comparisons investigating the source of the group effect showed that presentation rate had a significant effect for right hemisphere patients (p=0.048) with respect to controls. Comparing right high and right low grade tumour patients with controls, an overall

rate of presentation effect was again found (Kruskal-Wallis ANOVA: p=0.017). Post hoc comparison showed that the effect was attributable to right high grade patients being more affected by presentation rate with respect to controls (p=0.025).

2.3.2 Single case analysis (exp.1): rate, consistency and serial position

In Experiment 1 high grade patients had great difficulties, being constantly below the range of controls (Table D suppl. mat.). Considering the findings at a single case level of analysis however, the effects of presentation rate are also weak. Although almost all patients showed better performance with slower presentation rates, the effect did never reach significance in any patient except for patient LH5 who showed a marginally significant effect before surgery. On the other hand, low grade tumour patients constantly performed at ceiling level with respect to accuracy.

However, with only one exception (patient RH3 after surgery), all high grade tumour patients who had difficulties in the task (7/8) showed an inconsistent pattern of responding (p>0.05), suggesting they have difficulties in accessing the concept rather than in storage per se (see Table 4.). Once again, nearly all low grade patients (9/10) almost always scored at ceiling. Finally, only for patient LH6 was there a significant serial position effect, in his case, both before and after surgery (Table D).

2.3.3 Semantic distance and word frequency effects (exp. 2: distant-close; high-low frequency):

When the performance of the tumour patients group was compared initially on the basis of the histology of the gliomas (high grade Vs. low grade vs. controls) (Fig. 1 and 2), a significant main effect of semantic distance was found both before (Kruskal-Wallis ANOVA p=0.002) and after the surgery (Kruskal-Wallis ANOVA p=0.004) (see Table 5). These significant effects were attributable to the high grade patients being both significantly different from the controls (p=0.01 before and p=0.0006 after) and from low grade patients (p=0.008 before and p=0.041 after). On the other hand low grade patients did not differ significantly from controls. To investigate semantic distance effects for high grade patients further, a Kruskal-Wallis ANOVA (Left high grade Vs. Right high grade Vs. Controls) was performed to assess whether, within high grade patients, semantic distance had a larger effect on Left rather than Right hemisphere patients (Fig. 3 and 4). A significant main effect of hemisphere was found both before (p=0.025) and after (p=0.002) surgery. Once again the source of this effect was due to the worse performance of Left hemisphere high grade patients (p=0.001 before

and p=0.002 after surgery) with respect to controls. Right hemisphere high grade patients did not significantly differ from either controls or Left hemisphere high-grade patients.

Regardless of the histology, a parallel grouping by tumour location was then carried out. No main effect either of semantic distance (tab. 5) or word frequency (tab. 6) were found for any of the variables either before (p=0.17) or after the surgery (p=0.083). This may have been due to the increase in variability resulting from the combining of high and low grade patients who showed very different patterns of behaviour.

In contrast with all these effects of semantic relatedness, no effect whatsoever was obtained for word frequency (tab. 6) in any of the contrasts.

2.3.4 Single case analysis (exp.2)

The semantic relatedness effect is even clearer when results are examined on the single case level of analysis: many (7/10) of the high grade patients (especially left hemisphere ones: 6/7) were significantly affected by semantic relatedness (tab. E suppl. mat.) at a single case level. On the other hand word frequency (tab. F suppl. mat.) did not show a significant effect for any of the patients (with the exception of patient RH2 after the surgery). Almost all (8/10) low grade patients again performed at ceiling.

2.3.5 Effects of surgery:

A direct comparison of the performance of the patients before and after the surgical removal of the tumour was carried out in order to assess the effects of the operation on the patients. Again, as dependent variables we used the differences between the mean scores obtained on each of the 2 levels of the 3 independent variables (semantic distance, word frequency and presentation rate) by each patient (for example the difference between the score obtained in the distant versus the close condition). The obtained scores were then compared with the ones obtained after surgery by the same patients using the Wilcoxon matched pairs test. The analysis did not reveal any significant difference between the two testing sessions in the effects of semantic distance, word frequency or presentation rate for any of the groups considered, nor where there any significant differences when comparing accuracy in each of the individual conditions before and after surgery. Low grade patients tended to show ceiling performance in each condition both before and after surgery. Roughly the same number of high grade patients improved and worsened (see also appendix A: tables C, E, F).

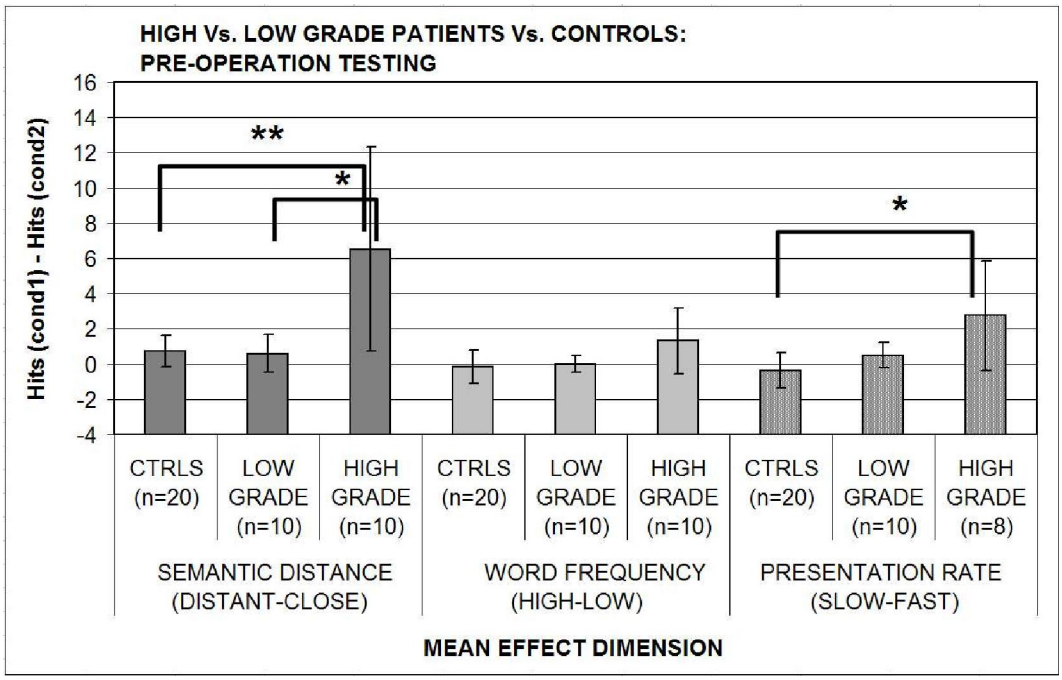


FIG.1: effects of semantic distance, word frequency and presentation rate on high vs. low grade tumour patients before the surgery: asterisks indicate presence of effects in post-hoc comparisons after significant main effect: *=p<0.05 **=p<0.01

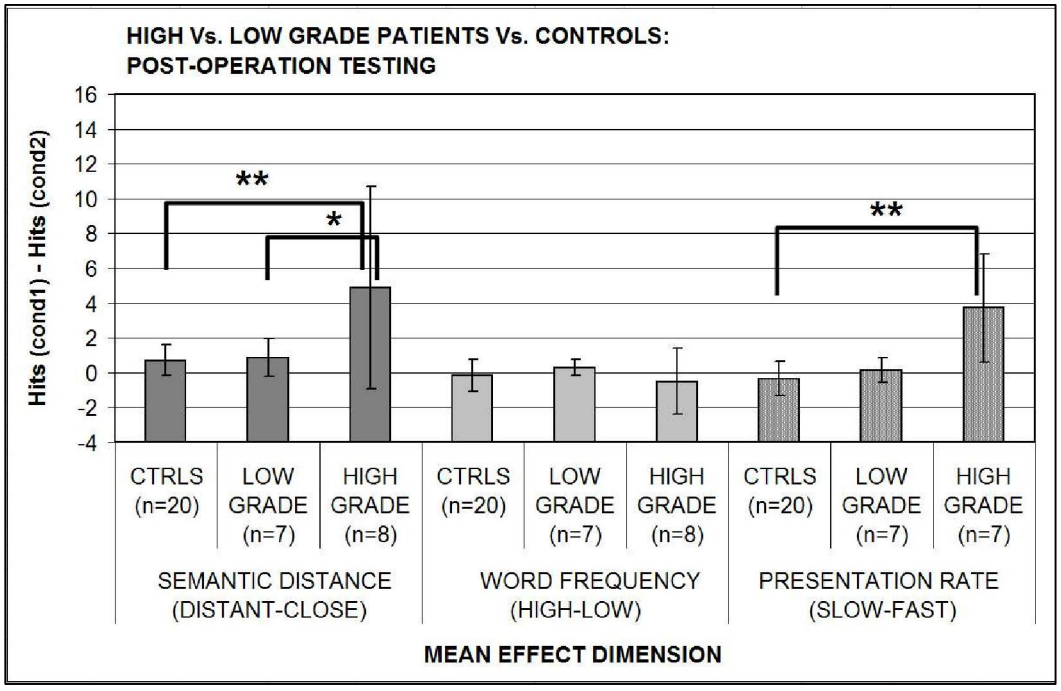


FIG.2: effects of semantic distance, word frequency and presentation rate on high vs. low grade tumour patients after the surgery: asterisks indicate presence of effects in post-hoc comparisons after significant main effect: *=p<0.05 **=p<0.01

Table 4: Experiment 1: consistency calculation by patient: left high, low grade and right hemisphere tumors.

Before surgery						After surgery					
Tumor Type	**Pat.**		**Consistent** (vvv/xxx)	**Inconsistent** (vvx/vxx)	**Signif.** ($\chi^2_{(1)}$)	**Tumor Type**	**Patient**		**Consistent** (vvv/xxx)	**Inconsistent** (vvx/vxx)	**Signif.** ($\chi^2_{(1)}$)
Left High Gr.	*LH1*[1]	*expected* *observed*	*10* *9*	*10* *11*	*n.s.*	*Left High Gr.*	*LH1*	*expected* *observed*	*10* *14*	*10* *6*	*n.s.*
Left High Gr.	*LH2*[1]	*expected* *observed*	*10* *8*	*10* *12*	*n.s.*	*Left High Gr.*	*LH2*	*N.T.*	*N.T.*	*N.T.*	*N.T.*
Left High Gr.	LH3	expected observed	13 12	3 4	n.s.*	Left High Gr.	LH3	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left High Gr.	LH4	expected observed	13 12	3 4	n.s.	Left High Gr.	LH4	expected observed	9 9	7 7	n.s.
Left High Gr.	LH5	expected observed	6 7	10 9	n.s.	Left High Gr.	LH5	expected observed	5 7	11 9	n.s.
Left High Gr.	LH6	expected observed	4 5	12 11	n.s.	Left High Gr.	LH6	expected observed	5 3	11 13	n.s.
Left High Gr.	LH7	expected observed	4 3	12 13	n.s.	Left High Gr.	LH7	N.T.	N.T.	N.T.	N.T.
Left Low Gr.	LL1	***n.c.***	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL1	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL2	***n.c.***	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL2	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL3	***n.c.***	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL3	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL4	***n.c.***	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL4	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL5	***n.c.***	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL5	N.T.	N.T.	N.T.	N.T.
Left Low Gr.	LL6	***n.c.***	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL6	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Right High Gr.	RH1	***n.c.***	***n.c.***	***n.c.***	***n.c.***	Right High Gr.	RH1	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Right High Gr.	RH2	expected observed	9 11	7 5	n.s.	Right High Gr.	RH2	expected observed	11 12	5 4	n.s.
Right High Gr.	RH3	expected observed	13 14	3 2	n.s.	Right High Gr.	RH3	expected observed	10 14	6 2	p<0.05
Right Low Gr.	RL1	expected observed	10 15	6 1	p<0.05	Right Low Gr.	RL1	N.T.	N.T.	N.T.	N.T.
Right Low Gr.	RL2	***n.c.***	***n.c.***	***n.c.***	***n.c.***	Right Low Gr.	RL2	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Right Low Gr.	RL3	***n.c.***	***n.c.***	***n.c.***	***n.c.***	Right Low Gr.	RL3	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Right Low Gr.	RL4	***n.c.***	***n.c.***	***n.c.***	***n.c.***	Right Low Gr.	RL4	***n.c.***	***n.c.***	***n.c.***	***n.c.***

*Significant results indicate a performance more consistent than the expected

N.T. = not tested. N.c. = not computed (≤ 3 errors in the condition)

[1] Patients lh1 and lh2 were administered with a different version of exp1 (see section 2.2.3.3 for further details)

Table 5: accuracy group analysis: Experiment 2: Kruskal-Wallis ANOVA and post hoc comparisons: semantic distance (distant-close condition)

SEMANTIC DISTANCE: ACCURACY

BEFORE SURGERY

Contrast	Main Effect:	p-level	Contrast	Post Hoc:	p-level
Ctrls (n=20) Vs. High Gr. (n=10) Vs. Low Gr (n=10)	**$H_{(2,40)}$=12.25**	***0.002****	**Ctrls Vs. High Gr**	**Z=2.93**	***0.010°***
			Ctrls Vs. Low Gr	Z=0.47	1
			High Gr Vs. Low Gr	**Z=2.99**	**0.008°**
Ctrls (n=20) Vs. Left High (n=7) Vs. Right High (n=3)	**$H_{(2,30)}$=13.08**	***0.001***	**Ctrls Vs. Left High**	**Z=3.52**	***0.001°***
			Ctrls Vs. Right High	Z=0.59	1
			Left High Vs. Right High	Z=1.73	0.24
Ctrls (n=20) Vs. Left Hem (n=13)Vs. Right Hem (n=7)	$H_{(2,40)}$=3.44	0.178*	--		

AFTER SURGERY

Contrast	Main Effect:	p-level	Contrast	Post Hoc:	p-level
Ctrls Vs. (n=20) High Gr. (n=8) Vs. Low Gr (n=7)	**$H_{(2,35)}$=11.19**	***0.004****	**Ctrls Vs. High Gr**	**Z=3.07**	***0.006°***
			Ctrls Vs. Low Gr	Z=0.06	1
			High Gr Vs. Low Gr	**Z=2.47**	***0.041°***
Ctrls (n=20) Vs. Left High (n=5) Vs. Right High (n=3)	***$H_{(2,28)}$=12.38***	***0.002***	**Ctrls Vs. Left High**	**Z=3.35**	***0.002°***
			Ctrls Vs. Right High	Z=1.06	0.85
			Left High Vs. Right High	Z=1.41	0.47
Ctrls (n=20) Vs. Left Hem (n=10) Vs. Right Hem (n=5)	$H_{(2,35)}$=4.97	0.083*	--		

*= Bonferroni correction: p= 0.025; °= significant corrected post-hoc contrast

Table 6: accuracy group analysis: Experiment 2: Kruskal-Wallis ANOVA and post hoc comparisons: word frequency (low-high condition)

WORD FREQUENCY: ACCURACY

BEFORE SURGERY

Contrast	Main Effect:	p-level	Contrast	Post Hoc:	p-level
Ctrls (n=20) Vs. High Gr. (n=10) Vs. Low Gr (n=10)	$H_{(2,40)}$=6.36	0.041*	--	--	--
Ctrls (n=20) Vs. Left Hem (n=13)Vs. Right Hem (n=7)	$H_{(2,40)}$=4.19	0.12*	--	--	--

AFTER SURGERY

Contrast	Main Effect:	p-level	Contrast	Post Hoc:	p-level
Ctrls Vs. (n=20) High Gr. (n=8) Vs. Low Gr (n=7)	$H_{(2,35)}$=1.89	0.38*	--	--	--
Ctrls (n=20) Vs. Left Hem (n=10) Vs. Right Hem (n=5)	$H_{(2,35)}$=2.35	0.31*	--	--	--

*= Bonferroni correction: p= 0.025; °= significant corrected post-hoc contrast

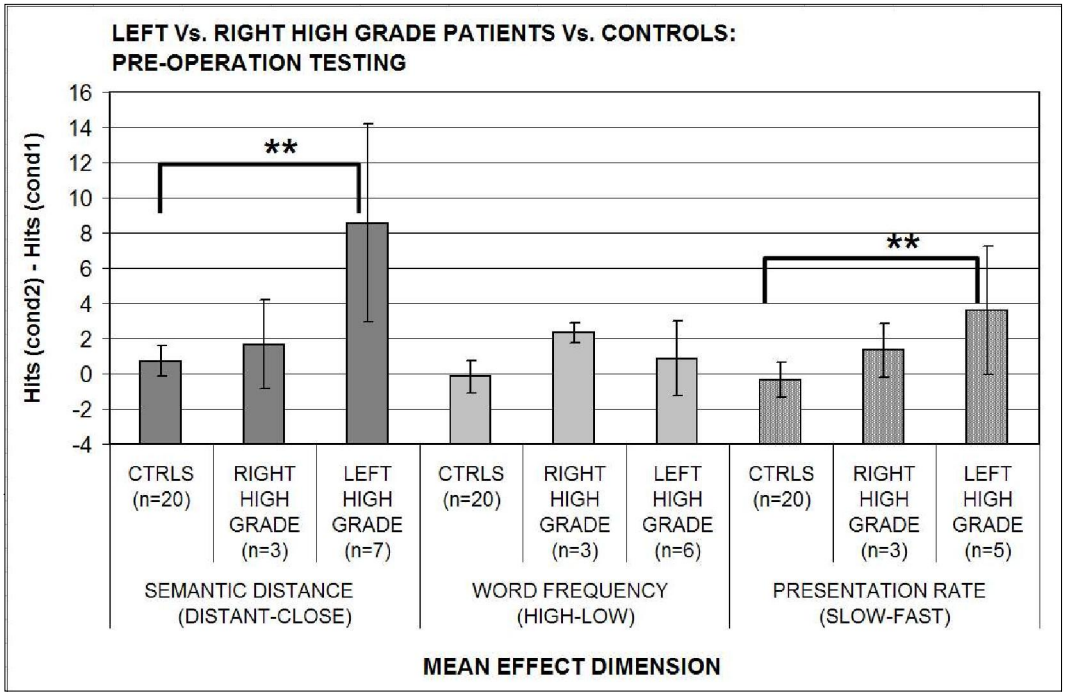


FIG.3: effects of semantic distance, word frequency and presentation rate on left vs. Right high grade tumour patients before the surgery: asterisks indicate presence of effects in post-hoc comparisons after significant main effect: *=p<0.05 **=p<0.01

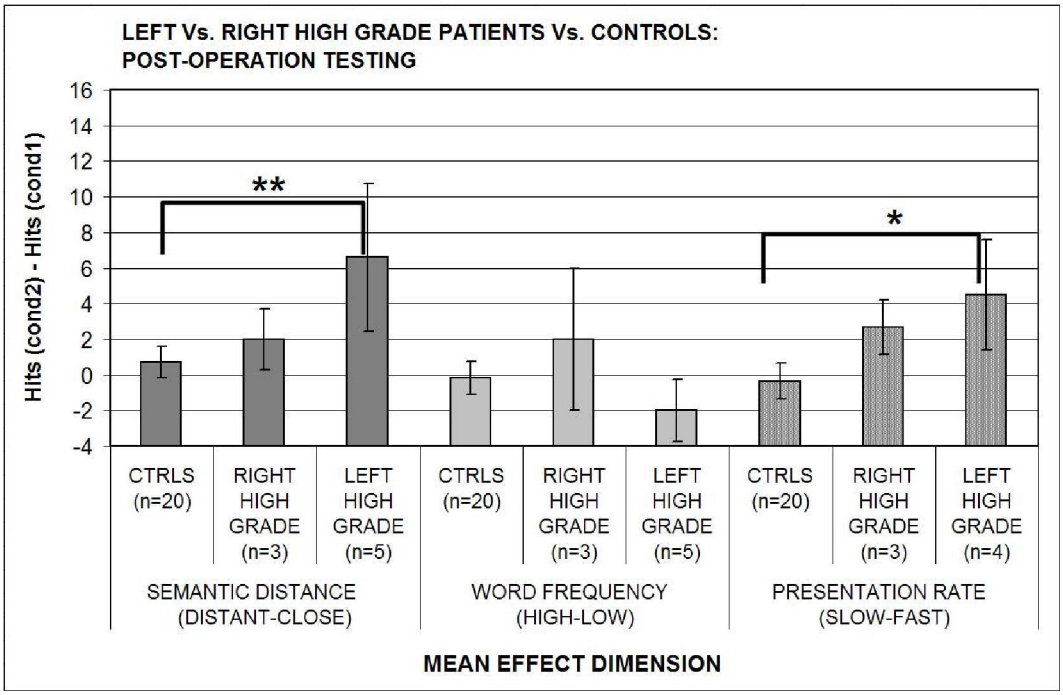


FIG.4: effects of semantic distance, word frequency and presentation rate on left vs. Right high grade tumour patients after the surgery: asterisks indicate presence of effects in post-hoc comparisons after significant main effect: *=p<0.05 **=p<0.01

2.3.6 Control Patients:

Patients MU and MG:

In Experiment 2, neither of the cortical damaged patients showed an effect of semantic distance on accuracy (see appendix A: Table G), but they had significantly worse scores on low frequency compared to high frequency arrays (MU: $p=0.05$; MG: $p<0.05$). In Experiment 1 MU unlike nearly all the tumour patients performed significantly more consistently than chance (see appendix A: Table H) suggesting that items not recognized had degraded semantic representations. MG was tested with the same version of Experiment 1 as tumour patients LH1 and LH2. In this version of the task, MG also performed significantly more consistently than chance ($p<0.01$; see appendix A: Table H) and was not influenced by presentation rate being even better with fast than with slow presentation rates. These results indicate that the particular experimental paradigms used were potentially sensitive to effects associated with semantic degradation effects (i.e. word frequency,)

Patient SV:

Stroke patient SV (see appendix A: Table I), in Experiment 1 behaved as a typical refractory semantic access patient, showing inconsistency of response and being significantly influenced by presentation rate in both testing occasions. Moreover, she showed the classical serial position effect in the first testing session ($p<0.01$). In Experiment 2, SV again behaved as expected from a refractory semantic access patient, being influenced by semantic distance more than by word frequency. However, this time semantic distance effects were milder than the effects of temporal factors and were significant only in the first testing session (being however always larger than word frequency effects). These results clearly suggest that the task procedures were sensitive also to temporal variables, and that, therefore, the non-refractory behaviour shown by tumour patients was genuine.

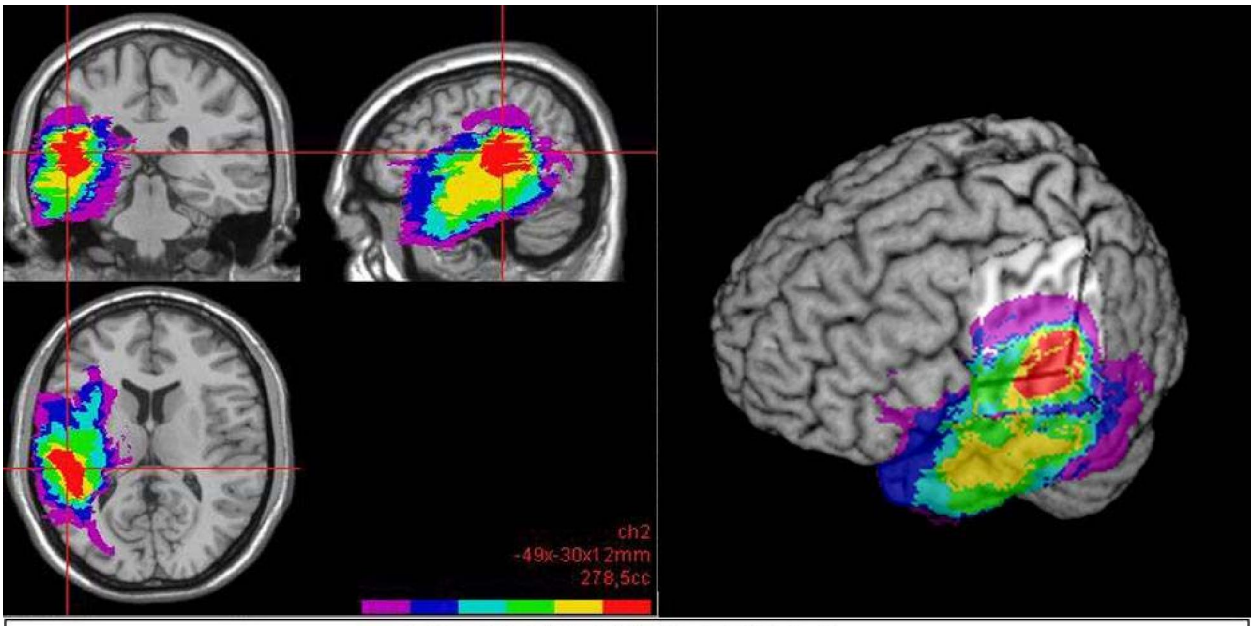
2.3.7 Lesion mapping:

Mapping of lesion sites was carried out to investigate which brain areas were responsible for the pattern of results obtained. Lesion reconstruction was performed on the scans of the patients who showed a clear semantic access pattern of performance, namely 6

out of 7 of the left hemisphere high grade tumour patients. The seventh patient (LH3) was excluded, because of his clinical history and because he did not have any apparent semantic deficit on the tasks. He had suffered a left temporal lobe glioblastoma, but this was in the same area in which he had been operated some years before for the removal of an AVM (Arterio Venous Malformation). It is in principle possible that the AVM could have influenced the organization of his semantic memory, as they have sometimes been reported to induce a shifting in the cortical organization of the underlying cognitive functions (see for example Duffau et al., 2000).

The pre-operative location of the tumour was determined using digital format T1-weighted MRI scans. Only pre-operative MRI scans were used for reconstruction purposes, as in post-operative scans, lesion locus is usually at least partially replaced by healthy neighbouring tissue. The 3D reconstruction of lesions were drawn as regions of interest (ROI) using each slice of the MRI scan of each patient on the horizontal plane, using MRIcro software (Rorden and Brett, 2000). ROIs included both the lesion boundaries and oedema (given that oedema has been found to commonly cause cognitive deficits). Each patient's MRI scan underwent spatial normalization using SPM2 software, in order to match and align images on a common Talairach space (Talairach and Tournoux, 1988). Normalized 3D reconstructed lesions were then overlapped on a common Montreal Neurological Institute (MNI) template.

Fig.5 shows a common region of involvement shared by all the left high grade patients reporting semantic access difficulties. This region is confined to the posterior superior portion of the left temporal lobe. Superimposing these data on an AAL (Automated Anatomical Labeling) template (Tzourio-Mazoyer et al., 2002), which shows a macroscopic anatomical parcellation of the MNI template, the region of maximum overlap was found to mainly involve posterior portions of the superior and middle temporal gyri (area 21 and 22) and also the transverse temporal cortex (area 41 and 42). The largest region of lesion overlap (reported in detail in Fig. 5) however involves area 48 (retrosubicular cortex) which cytoarchitectonically also includes the Insula.
It is worth noting, as shown in Fig.5, that this area is largely subcortical.



BRODMANN AREAS		
NUMBER	NAME	N. OF VOXELS
48	Retrosubicular	3611
41	Anterior transverse temporal	1821
21	Middle temporal	1475
22	Posterior transverse temporal	843
42	Superior temporal	707
37	Occipito-temporal	106

FIG.5: 3-D lesion reconstruction highlights a subcortical common area of involvement in the posterior part of the left superior and middle temporal gyri, for patients showing semantic access difficulties. The red colour indicates the area of maximum overlap (6/6 subjects). the table reports the proportions of the Brodmann areas involved in this region.

2.4 GENERAL DISCUSSION:

While there is now widespread agreement on the disease processes and cognitive mechanisms underlying the degradation of semantic representations, many questions still remain open in the field of the semantic access disorders. It still remains unclear whether semantic access disorders constitute a functionally unitary syndrome or not. Moreover no consensus has been found on the functional locus of damage, whether it lies within the semantic system itself (Warrington and Cipolotti, 1996), or in the failure of neuromodulatory mechanisms acting on semantic memory (Gotts and Plaut, 2002), or in the failure of selection mechanisms (Jefferies et al., 2007), or, finally, a simple disconnection between lexical input and semantic representation areas.

In this study we have developed two spoken word-to-picture matching tasks which were aimed to assess consistency, rate of presentation and serial position effects (Experiment 1) and semantic distance and word frequency (Experiment 2), in a series of patients selected only by aetiology and general localization of the lesions (temporal lobes). We analysed the findings both at a single case and at a group level of analysis. Single case comparisons were carried out by directly comparing the performance of each patient with an appropriate small group of age and education matched control subjects. Group analysis was carried out by means of a series of hierarchically organized comparisons between the patients (grouped in parallel according to lateralization or histology of the tumour) and the overall collapsed control group.

Our findings show that in brain tumour patients, who had lesions affecting the temporal lobes, semantic impairments emerged in a considerable number of cases. We have shown that the performance of high grade tumour patients was, with the sole exception of patient RH1 after surgery in Experiment 1 always outside the accuracy cut-off scores of control subjects. Deficits were especially severe in left hemisphere patients. Low grade temporal tumours, either of the left or the right hemisphere, on the other hand did not produce semantic deficits on our tests (with occasional exceptions such as patients RL1 in both experiments and LL2 in Experiment 1 before surgery and patient LL6 in Experiment 2 after surgery; these patients however performed only slightly below the normal range).

Whenever semantic deficits emerged in the current series of patients, they were qualitatively of a clear "access" type. Patients having difficulties in performing the comprehension tasks (all high grade tumour patients) were found indeed to be inconsistent in whether they were correct or not (Experiment 1). The only exceptions were patients RL1 before and RH3 after operation, which were consistent. In addition all left hemisphere high grade tumour patients, in at least one of the two testing sessions and normally in both (except for patient LH3) were affected by the semantic distance between the target and distractors (Experiment 2). At a group level, both before and after surgery, high grade tumour patients were significantly more affected by semantic distance than both the low grade tumour patients and the controls with the latter two groups giving similar types of performance. Left high grade tumour patients were the source of this effect, being significantly more influenced by semantic relatedness than either the right high grade tumour patients or control subjects. By contrast, word frequency effects never reached significance in any of the patients, either at a single case or a group level of analysis, with the one exception of patient RH2 after surgery. Semantic relatedness effects have been reported also in cases of degraded semantic representations (e.g. Rogers et al., 2004; Crutch and Warrington, 2005). However, in these cases either they were found in presence of significant effects of also word frequency, or they emerged when semantic distance crossed major category boundaries (i.e. they suggested the preservation of superordinate knowledge).

Surprisingly in Experiment 1, only two patients showed a significant serial position effect in the whole series of patients tested (patient LH6 both before and after surgery and patient LH1 but only after surgery). In addition, the rate of presentation variable had a much milder effect than would be expected from a refractory access disorder. None of the individual high or low grade tumour patients tested, either left or right, showed a significant rate of presentation effect. However, at a group level of analysis this effect was found to be significant for high grade tumour patients. In particular the effect was attributable to left high grade tumour patients who were significantly more influenced by rate of presentation than the right high grade tumour group or the controls before surgery. After surgery however right high grade tumour patients seemed to be more prone to presentation rate effects.

2.4.1 Tumour Histology and cognitive impact:

The difference in the cognitive impact of fast versus slow tumours is widely acknowledged. It is well known that fast/aggressive high grade tumours (glioblastoma) are associated with reduced cognitive abilities and that cognitive level tend to deteriorate during the progression of the illness (see for example Brown, Jensen et al, 2006, 1996; Bosma, Vos et al, 2006; Kayl and Meyers, 2003; Sheibel, Meyers and Levin). On the other hand low grade tumours have been found not to show cognitive deficits for many years during progression of the illness (Walker and Kaye, 2003). In fact in 80% of the cases the presence of the tumour is revealed not by cognitive deficit onset, but rather by the onset of seizures (DeAngelis, 2001). Moreover the resection of low-grade tumours tends to produce only (if any) mild cognitive sequelae, which are largely recovered within one year (see Desmurget et al, 2007 for an extensive review on the contrasting effects of slowly growing tumours and sudden destructive stroke lesions on the cognitive system). The neurobiology of the two kinds of tumours is very different under many aspects: both high and low grade tumours infiltrate the surrounding brain (Daumas-Duport, 1994); however, while high grade tumours tend to be destructive (leading to the necrosis of the tissue they infiltrate), low grade tumours can 'coexist' with the healthy tissue until the fatal transition to the high grade. Haemorrhage is another factor commonly observed in the presence of high grade tumour, while it is not very commonly observed in low grade lesions. This, together with the common observation that high grade tumours produce higher levels of oedema (generated by the presence of cytokines which are also produced by both types of tumours), could explain the difference in the cognitive impact of two types of tumours. Low grade tumours on the other hand tend to be more prone to epileptic seizures than high grade lesions. Even if antiepileptic drugs tend to have a cognitive impact, this however leads nevertheless to only to mild effects in the cognitive level of these patients (see again Desmurget et al. 2007 for a review). Regarding our patients, all of them (either high or low grade, left or right) were treated with antiepileptic drugs the therapy is typically maintained constant both before and after the operation. Therefore it is unlikely that the putative effect of anti-epileptics could account for the significant differences found between left high grade tumour patients with respect to the other groups, shaping such a consistent set of concomitant effects. Finally, both types of tumours however tend to modify the metabolism

and have neuromodulation effects on the brain, also in areas which are distant from the ones involved. Given however the presence of focal effects in our patients which are compatible with the locus of the lesion (comprehension deficits in presence of a lesion in Wernicke's territory), and given the absence of effects in low grade tumour patients, we are led to believe that these effects may not be relevant at least in the patients we tested.

Our results are in accord with the findings on the different cognitive impact of high and low grade tumour lesions: indeed not all types of temporal lobe tumour regularly produced semantic memory impairments on these tests. In this study, high grade aggressive tumours (such as glioblastomas) regularly impaired access to the semantic representations, but low grade tumours did not. The performance of low grade patients was always in the range of the controls in both tasks. An obvious explanation of the difference is in terms of the different developmental dynamics of high and low malignancy rate tumours. The slow rate of growth of low grade tumours (typically grade I or II astrocytomas) means that the compressed areas could well have time to adapt to the presence of an abnormal mass by reorganizing the underlying functions in neighbouring vicarious areas (see Desmurget et al., 2007 for review).

On the other hand instead, the presence of a high grade glioma (if left-sided) almost invariably leads to semantic deficits that bore the hallmarks of the access syndrome. Highly aggressive tumours such as glioblastoma could indeed produce a sudden damage to the white matter fibres leaving no time for reorganization of function to occur.

2.4.2 Refractoriness and Brain Tumors:

In the introduction we defined refractory access deficits as a subtype of access deficits characterised by sensitivity of the patients to *temporal factors* (presentation rate). Indeed, within the cases characterised as *semantic access* deficits, most of the patients previously described, have been sensitive to this variable, and therefore the main theoretical accounts for this type of deficit have involved refractoriness. A striking feature of the performance of the current group of patients was, instead, that at a single case level of analysis, none was significantly influenced by the rate of presentation of the stimuli. Over the left high grade tumour patients group as a whole there was an advantage for the more slowly presented stimuli that resulted in a significant effect. However, the effect was

weaker than would have been expected on the traditional refractory account. It is conceivable that this lack of effect is due to the minor changes we made in procedure compared to previous studies and that the patients showed some degree of refractoriness which resolved after a very short period. However given that a deficit still exists at a 10s interval the pattern of performance is more plausibly attributable to a qualitative difference from previously described refractory patients. These results do not fit with the predictions of Gotts and Plaut's neural network simulation: their model gave rise to strong effects of rate of presentation even with mild neuromodulatory damage, while in general, semantic distance effects were milder at each level of neuromodulatory damage (see their Fig.8). The performance of the left high grade tumour patients on the contrary shows a different pattern of effects.

The weakness of any observed rate effect in the context of strong semantic distance effects suggests that the semantic problems showed by the glioblastoma patients could be qualitatively different from those of most of the previously studied patients. In fact, our stroke patient SV showed a clearly significant rate effect. Critically, the lack of significant rate effects does not mean that the comprehension problems shown by these tumour patients are not of an access type because all were highly inconsistent in retrieving semantic information. It seems likely then, that left temporal high grade tumours can give rise to a specific different type of semantic access syndrome in which temporal factors play a secondary role by comparison with the stronger semantic relatedness effects.

Overall, the syndrome we are describing shows features similar to those reported by Jefferies and colleagues (2007) in two of the stroke patients they described. While the group of anterior fronto-temporal stroke patients described by the authors showed refractory behaviour, two of their patients were not sensitive to temporal factors at all. Moreover these patients were sensitive to semantic relatedness, but not word frequency. They also had a more posterior lesion, compatible in lesion location with that obtained in the current tumour patients. Although no detailed anatomical report was provided, lesion location seems to be much more similar to the one we found in our tumour patients.

Jefferies and colleagues (2007), however, suggest that the differences in behaviour between anterior and posterior patients may not be critical and that the failure of cognitive selection mechanisms may account for both behaviours. According to Jefferies and

colleagues, prefrontal cortex together with temporo-parietal attentional areas, may constitute a complex cognitive control network with an important role in tasks with high level of selection demands, the higher the competition, the higher the demands, the more critical the role of selection mechanisms (see also Peers et al., 2005). With repetitive presentations of the same 'high-demand' array of objects (semantically close arrays), failure of such mechanisms would lead to summation effects and progressive deterioration of performance (serial position effects). However this is clearly not happening to posterior patients. If, as suggested by Jefferies and colleagues, (but also by Peers et al., 2005) this high level function is supported by a complex network of separate but interconnected areas such as lateral inferior prefrontal cortex (LIPFC) and temporo-parietal junction (TPJ) (see also tractography studies: Parker et al., 2005; Powell et al., 2006), then damage to either of these areas should produce a similar behavioural failure with increasing difficulties with increased task demands. This is however not the case in our current group of patients.

Another possibility could be that the onset of a fully refractory behaviour might be linked to the overall level of severity of the damage, with milder patients showing some but not all the hallmarks of a refractory access syndrome. Indeed, the posterior "non-refractory" patients tested in Jefferies et al study had a milder overall cognitive picture than anterior ones. However, controlling the overall level of accuracy obtained by the patients we tested, it is evident that the overall level of accuracy obtained by the left high grade tumour patients in the tasks was completely comparable to that obtained by patient SV, who showed a clearly refractory behaviour. Moreover left high grade tumour patients showed a broad range of severity of word comprehension impairments; nevertheless, even the most impaired patients failed to show fully refractory behaviour (see supplementary tables C, E and F).

The patients described here seem therefore to present a slightly different syndrome: the left high grade patients (as well as the Jefferies et al posterior patients) show weaker refractory behaviour. This suggests that the origin of such behaviour may differ between the two syndromes.

2.4.3 An alternative account for tumour-induced semantic access syndrome:

As shown by the lesion mapping results, the common region of maximum overlap in the patients with semantic access effects mainly involves a subcortical white matter area located in the posterior superior part of the left temporal lobe. This area, which is located in the territory of Wernicke's region, has traditionally been associated with word comprehension, both as a possible seat for semantic processing itself (see e.g. Binder et al., 2009 for a very recent review and metaanalysis on this topic) but also linked to lexical pre-semantic components of this process (see for example Friederici and Kots, 2003; Miozzo and Gordon, 2005). Semantic processing has been, on the other hand also linked to more ventral anterior parts of the temporal lobes (see for example Mummery et al., 1999; 2000; Devlin et al., 2002; Thompson-Schill, 2003; Bright et al., 2004; Moss et al., 2005; Patterson et al., 2007).

One possibility is that functionally the critical damage could be to the connections linking lexical processing regions in the superior posterior left temporal area to the semantic processing areas, (Scott and Johnsrude, 2003), regardless of whether they are associated with Wernicke's area or with more ventral temporal areas. Anatomical evidence discussed by Scott and colleagues (2003) suggest that pathways involved in auditory comprehension may run from both rostral and caudal parabelt auditory cortices anteriorly towards STS, but also to more posteriorly to the inferior temporal areas. Indeed the white matter tracts underlying the left posterior parabelt areas are involved in the region of maximum overlap of lesions founding this study, and their location is therefore compatible with the functional hypothesis of a (possibly partial) disconnection of lexical processing regions (or phonological-to-semantic hidden units) from semantic units.

An important issue to deal with, with respect to this hypothesis is whether semantic distance effects could arise due to disconnections at this level of processing. The current functional syndrome can be thought of as the auditory verbal correspondence of the semantic access dyslexia syndrome originally described by Warrington and Shallice (1979) in the acquired dyslexic patient AR or of the form of pure alexia with partially spared comprehension (Shallice and Saffran, 1986; Coslett and Saffran, 1989; 1993). Thus for AR, word frequency effects were weak as in the left hemisphere high grade tumour patients reported here. Semantic distance effects were not directly addressed in the original

investigation of AR; however, he often produced semantic errors in word reading, which represented confusions between closely related word pairs (e.g. 'peach' for 'apricot'). Moreover, AR was still able to categorize stimuli, which suggests a preserved ability to discriminate between semantically distant stimuli. These two complementary phenomena suggest the presence of a semantic distance effect in AR.

Hinton and Shallice (1991) put forward a multi-layer neural network model to implement the mapping of written words onto semantic representations (see also Plaut and Shallice, 1993a). After training, the network was able to produce a final correct target semantic pattern given a particular pattern of activation of input units (letters). The trajectory of semantic access in the space state of the network was realised through attractor basins. For the correct semantic target to be reached, the initial semantic representation produced by the input had to fall roughly within the correct basin. The operation of part of the network then enabled it to 'clean–up' initially somewhat distorted patterns of semantic activation in order to allow them to activate the correct target semantic representation. Lesioning the connections between the graphemic level and hidden units or between hidden and semantic units led to the occurrence of semantic errors. Moreover, the network was able to correctly select the superordinate category an item was in, when it could not identify it explicitly. This implies a semantic distance effect. Noise in a network where an intact clean-up system is partially disconnected from its input would produce inconsistency of responding

Caramazza and Hillis (1990; but see also Morton and Patterson, 1980) had independently made somewhat analogous proposals about the output system, namely that semantic errors could occur as a result of damage to the lexical level as well as within the semantic system itself. That lesions subsequent to the semantic system on the output side could also lead to "access-type" deficits which are less sensitive to temporal factors, would fit the behaviour of certain other patients (Warrington and Leff, 2000; Gotts et al., 2002).

As far as the current patients are concerned, the possible influence of impairments to temporo-parietal junction attentional systems in the pattern of performance of the left temporal high-grade tumour patients cannot be excluded. Indeed some cannot solely have input problems as they had low scores in fluency tasks. Our theoretical account relates specifically to their word-picture matching performance.

2.4.4 Conclusions:

Overall, we would suggest that patients described as having a semantic access disorder are not functionally unitary. Refractoriness is clearly a major factor in many such patients, possibly due to a failure of control mechanisms or possibly through inappropriate regulation of cholinergic neuromodualtory mechanisms. However in certain of the patients described here, the relative weakness of refractory effects in the presence of effects of semantic distance but not frequency suggests an alternative cause. To conclude, we believe that our study, together with the works by Jefferies and colleagues (2006; 2007) provide complementary evidence for the better understanding of brain bases of semantic access syndromes.

CHAPTER 3:

3.1 INTRODUCTION:

What can be argued from the study presented in chapter 2 is that the patients who are typically defined as suffering from semantic access syndrome might not necessarily suffer from a unitary disorder from a functional point of view. Taking together the evidence coming from neuropsychology of patients, both in production (Warrington and Leff, 2000;Gotts et al., 2002) and in comprehension (see Chapter 2), it is evident that cases exist of access syndromes in which semantic distance effects are found in absence of sensitivity of the patients to those temporal factors (such as rate and serial position effects), critically defining an access syndrome as 'refractory' (e.g. Crutch and Warrington, 2005).

This result left the question open as to whether the presence of refractoriness in itself could be a factor sufficient to generate all the behavioural effects described in refractory semantic access patients, or if, in those patients, a disconnection syndrome (responsible for the semantic distance effect) co-occurs together with the presence of refractoriness (responsible for the sensitivity to temporal factors) within the semantic system. Furthermore, if semantic distance effect can be found in non-refractory access syndromes in which the locus of impairment may lie outside the semantic system itself (as for example in the links between lexical and semantic stores), what is the exact cognitive locus of the refractory behaviour? These questions drove the building of the series of experiments that will be presented in the present chapter.

3.1.1 Refractory effects in healthy subjects and patients populations:

As already discussed in chapter 2, the cause of a specific "semantic access" deficit has been held to be linked to abnormal refractoriness within the semantic system. In this context, refractoriness is defined as 'the reduction of the ability to utilize the system for a certain period of time following activation' (Warrington and McCarthy, 1983 p.874). In this formulation, refractoriness is assumed to be a normal neural state which is abnormally prolonged in these patients and this could potentially explain all the effects linked to the typical semantic access pattern of impairment. If, following an initial successful accessing

of the meaning, the target representation falls into an abnormally prolonged refractory state, the faster the presentation rate of the stimuli, the higher should be the probability of dysfunctional access (presentation rate effect). Moreover, if the duration of refractoriness exceeds the interval between two of the same stimuli of a set in a series, further attempts to access the same concept will lead to a decrease in the probability that that concept will be correctly accessed (serial position effect). Furthermore, on many computational models of the lexical system it is assumed that when a given target is activated, some activation spreads to representations of neighbouring concepts. If this also happens in the context of the abnormal refractoriness of the system, then concepts that are semantically related to the previously accessed one will be more difficult to access, while unrelated concepts will still be relatively easily accessed (semantic distance effects). Finally, the weakness of the word frequency effect could be explained by the high frequency concepts being assumed to have richer and more interrelated representations in which more synapses are involved. In this situation, refractoriness would affect the synapses of high frequency concepts more than those of low frequency ones. This effect would therefore work against the normal frequency effect (Crutch and Warrington, 2005).

Genuinely refractory behaviour is however indicated by sensitivity to temporal factors such as the rate of presentation and especially the serial position effect. Indeed semantic distance effects have also been reported in the absence of a clearly refractory symptom pattern (e.g. Warrington and Cipolotti, 1996; Crutch and Warrington, 2005 in the context of degradation syndromes; Warrington and Leff, 2000; Gotts et al., 2002 in the context of disorders of lexical access; see also Chapter 2 for evidence in the context of semantic access)

However in these cases the problem is generally attributed to a deficit occurring outside the semantic system itself. By contrast, in all refractory semantic access syndromes reported in the neuropsychological literature, the semantic system itself has been presumed to be the locus of the refractory behaviour. For example in Warrington and Cipolotti (1996) and in Forde and Humphreys (1997) the locus of damage was held to be directly within the semantic system, since the performance of the patients was unimpaired in all presemantic tasks such as visuoperceptive matching tasks. In other studies, the semantic system was held to be indirectly influenced through the failure of a hypothetical selection mechanism

(Wilshire and McCarthy, 2002; Schnur et al., 2006; Jefferies et al., 2007) or through the putative breakdown of neuromodulatory systems controlling physiological synaptic depression dynamics (Gotts and Plaut, 2002).

According to the 'selection' account of Jefferies et al (2006), refractory behaviour in semantic access difficulties is explained by inadequate functioning of a selection mechanism ,held to be in the lateral inferior prefrontal cortex, which is used by the cognitive system to resolve the competition between coactivated semantic competitors during highly demanding tasks (see e.g. Badre and Wagner, 2007). Therefore the competition could arise within the semantic system itself, but be modulated by the action of an external system (LIPFC), which acts as an active selection mechanism.

On the other hand, a more 'automatic' account of the resolution of semantic access conflict is given by the 'neuromodulation' account (Gotts and Plaut, 2002). According to this position, efficient access to concepts is supported by a number of neuromodulatory systems acting to minimize the effects of physiological refractory processes which are also operating in the healthy brain. In particular it has been suggested that acetylcholine reduces the probability of transmitter release in presynaptic neurons while, at the same time, it blocks the adaptation of post synaptic cells to the repetitive firing (firing rate adaptation) which occurs after repeated stimulation of the same synapse, so making the synapse more efficient and functional for a longer time (Hasselmo and Bower, 1992; Tsodyks and Markram, 1997). These neuromodulatory systems can therefore be implicated in processing, learning and in particular in the efficient recall of information (Hasselmo, 1995), helping the cortical network to efficiently discriminate, for example, between stimuli that share overlapping features. As far as semantic memory is concerned, however, it has been found that a selective bundle of fibers of the acetylcholine system spreads within the temporal lobes, potentially providing modulation for temporary refractory conditions ('synaptic depression') in the semantic system (Selden et al., 1998).

In normal subjects, refractory behaviour has been explored but always being investigated by means of tasks involving the explicit naming of semantically blocked stimuli. In these tasks the items were to be named either once (Kroll and Stewart, 1994; (Hodgson and Lambon Ralph, 2008) or in multiple consecutive cycles (e.g. Maess et al., 2002; Damian and Bowers, 2003; Belke et al., 2005). In Belke, Meyer and Damian (2005),

for example, mild refractoriness was found with a semantic blocking paradigm in the naming latencies of the subjects. Refractoriness was detected in terms of a reduction in the amount of the repetition priming effect: basically the performance of the subjects improved with repetition of the stimuli, but the amplitude of this beneficial effect decreased with subsequent re presentations.

However, the systems involved during naming tasks include not only the semantic system but also other stages required in name retrieval, such as those related to the phonological output lexicon. Indeed theories of speech production are in agreement that semantic and lexical forms constitute distinct levels of representation (see for example Caramazza and Hillis, 1990 for neuropsychological evidence for a double dissociation between selective deficits at the semantic vs. the lexical level). The main view is moreover that the lexical level of representation can further be fractionated into two different types of intermediate representations: the Lemma (semantically and syntactically specified lexical representation) and the Lexeme (lexical/phonological representation) (Roelofs, 1992; Levelt et al., 1999) (but see Caramazza, 1997 for a criticism of this theory).

All these systems may be implicated in the interference which leads to a refractory behaviour both in patients and healthy subjects. Indeed a post semantic locus for the refractory effects in naming tasks was suggested by Howard, Nickels, Coltheart and ColeVirtue (2006). In their Experiment subjects had to name five exemplars from 24 different categories separated by intervening trials so as to create different lags between each item and the next one from the same category (from 2 to 8 intervening trials). Their results showed that there was a cumulative linear slowing in naming each successive exemplar of each category with respect to the previous one. In a simulation of the same conditions in the same naming task, clear signs of refractory setting up across trials were observed and the network also showed a clear serial position effect. Howard and colleagues claim that any model able to account for these results should possess three necessary properties: 1) competition: they argue that the presence of lateral inhibitory connections amongst the lemma level units is necessary; 2) priming: strong bidirectional connections between each lemma and its respective semantic units is also needed; 3) shared activation: they implement this feature in terms of stronger activation for the target semantic unit, with some minor activation to neighbouring units. The simulation did not produce refractory

effects if any one of the three properties was absent. The critical point concerning the position of Howard and colleagues is that two of the three mechanisms (priming of the lemma level representations and competition) occur outside the semantic system. This account would not though explain the evidence from the study of patients with semantic access dysphasia where verbal production is not required.

3.1.2 Aim of the study: what is the locus of refractory behaviour?

All the evidence supporting a semantic locus for the refractory effects comes from the study of patients (e.g. Warrington and McCarthy, 1983; 1987; Cipolotti and Warrington, 1995; Forde and Humphreys, 1995, 1997; Warrington and Cipolotti, 1996;Crutch and Warrington, 2005). On the other hand all the behavioural studies on refractoriness have been conducted by means of naming tasks.

The aim of the study was therefore to investigate the possibility of finding some sign of refractoriness with a task which did not involve language production and in particular to assess whether, in healthy subjects too, a related phenomenon occurs to the effects obtained by patients suffering from "refractory semantic access dysphasia". The same types of task (word to picture matching tasks) were used, but with very fast presentation rates and a deadline response paradigm. Indeed, studies on the time course of physiological refractory states in cortical neurons, suggest that synapses in the healthy brain usually recover from refractory states within 3, 4 seconds from the stimulation (e.g. Finlayson and Cynader, 1995; Tsodyks and Markram, 1997; Varela et al., 1999). It could be speculated that, if stimuli are repeated within this time window, even mild residual refractory effects could sum in the healthy brain. If these residual activations spread within the semantic network so as to involve neighboring concepts, that share a number of common features, then the summation of these effects could also lead to healthy subjects making errors when carrying out a task such as word to picture matching which is usually very easy. We therefore carried out a series of 3 experiments using a speeded word to picture matching paradigm, to determine whether related phenomena to the semantic refractoriness effects found in patients also occur in healthy subjects.

Since we wanted to assess whether a parallel existed between the effects obtained in patients and potentially similar effects in the healthy brain, this study employed a speeded

version of the same tasks used in Chapter 2. In Experiment 1 the role of semantic distance and word frequency in the recognition of quickly presented target stimuli was assessed. This experiment was the equivalent speeded version of task 2 described in Chapter 2. To obtain an exacerbation of any possible mild refractoriness in the process of stimuli recognition, the stimuli had to be processed at a very fast rate. This was obtained by the use of a deadline procedure and by removing the interval between consecutive trials (the Response Stimulus Interval (RSI) was set to '0'). A sign of refractoriness present would be the presence of semantic distance effects being greater than those of word frequency.

It might be argued that, in principle, it is not appropriate to provide a direct comparison of the effects of two variables (such as semantic distance and word frequency) which are measured on different scales and which are different by definition. However, the stimuli used in this experiment were the same as employed in Experiment 2 in Chapter 2 in which it was shown that the frequency of the words used had a small effect on the semantic access patients studied but a large, significant effect on a semantic degradation patient. On the other hand, in the same task with the same stimuli, semantic distance had complementary contrasting effects in the semantic access patients and in the semantic degradation patient. Nevertheless, in analysing the data from this experiment we avoided any direct comparison of the overall effect of the two variables and we instead have analysed these effects separately.

In Experiments 2 and 3 we directly investigate the effects of different presentation rates on matching abilities, specifically to determine whether serial position effects occur. These experiments were the equivalent speeded version of task 1 described in Chapter2. The presence of the effects in a word to picture matching paradigm is a critical test of the key assumption that competition amongst different candidates takes place within (and not necessarily outside) the semantic system. In fact, while semantic distance effects have been found to occur also from lesions prior to the semantic system (see Plaut and Shallice, 1993a;Plaut and Shallice, 1993b; see also Chapter 2), rate and serial position effects are intrinsically linked to the definition of a refractory behaviour which, in the neuropsychological literature, is assumed to occur due to abnormally prolonged activation of the semantic representations themselves (Forde and Humphreys, 1995; 1997; Warrington and Cipolotti, 1996). Therefore a clear sign of refractory dynamics would be indicated by

the presence of both presentation rate and serial position effects. A presentation rate effect would imply a better performance with slowly presented items. A serial position effect would be shown if, following good performance on the first presentation of an item, there was a decrease in performance in later presentations. We manipulated presentation rate by using a zero RSI in the fast condition and an RSI of one second in the slow condition.

3.2 EXPERIMENTAL INVESTIGATION:

3.2.1 Experiment 1

Participants:

20 participants took part in this experiment (12 female and 8 male). All subjects had normal or corrected to normal vision. The mean age was 23 (range of 19 to 38). All participants were university or graduate students.

Materials:

Stimuli and normative data for this experiment were the same as those used in Chapter 2 (task 2). The set of stimuli consisted of 80 digital coloured pictures depicting common objects. Pictures were in '.bmp' format and had a resolution of 400x300 pixels in order to be presented in arrays of four on a 1024x768 17" CRT computer monitor. The monitor was positioned at approximately 50 cm from subjects.

Design and procedure:

The 80 stimuli were divided into 4 blocks of 20 items each. Each 20 item block comprised 5 arrays of 4 stimuli sharing similar levels of word frequency and semantic distance between the target stimulus and the distractors. The four combinations were: low frequency/closely related; low frequency/distant; high frequency/closely related; high frequency/distant. Word frequency ratings were obtained from *Dizionario di frequenza della lingua italiana* (CNR, Unpublished). Mean frequencies were: 2.03 for low frequency items; 32.55 for high frequency ones. Frequency differed significantly between the 2 categories (Mann Whitney U test: $U=13$; $p<0.0001$). Semantic distance ratings were obtained from a group of 20 healthy participants (10m, 10f, mean age: 29.7; education:

university or graduate students), who were asked to judge the overall 'conceptual' distance between the objects of each array on a 7 point scale. Mean semantic distance was: 2.67 for "close" items (on a 7 point scale) and 5.88 for distant items. Semantic distance differed significantly between the 2 groups (Wilcoxon matched pairs test: $z=3.85$; $p<0.0001$). The complete list of stimuli used with frequency and semantic distance values is reported in the supplementary material section.

Each stimulus was presented only once as a target. Within each block, the order of presentation of stimuli was pseudorandom and was kept constant across subjects. The position of foils in each array was changed across trials, as was the position of the target. Target position was also equally balanced across each of the four possible screen positions. There was no Response Stimulus Interval (RSI) between the end of a trial and the beginning of the subsequent trial. The four different blocks were separated by brief rest pauses. The experimental session was preceded by a brief 4 trial practice session to familiarize the subjects with the task.

Subjects were divided into in 4 groups of 5. Each subgroup was given a different frequency/distance block arrangement in a Latin Square design. Figure 1 illustrates the sequence of events. Unless otherwise stated, the same sequence of events was used across all the three experiments.

The general procedure for each trial of the four blocks was as follows: the name of the target stimulus to be recognized appeared briefly in the centre of the screen for 300 ms. Immediately after presentation, the word was replaced by an array of 4 items on the screen numbered from 1 to 4 in a counterclockwise order starting from the top left edge, corresponding to an equivalent arrangement of keys on a PC keyboard (numbered from 1 to 4). These stimuli remained on the screen for a maximum time of 1500 ms, in which the participants were allowed to answer by pressing the key corresponding to the position of the item on the screen. After the response (or after 1500 ms.), the procedure started again with a different stimulus from the same array. The same array was used until all four stimuli had been presented, and then it was replaced by another array belonging to the same frequency/distance block. A deadline was used to put subjects under time pressure. The deadline of 1500 ms. Provided sufficient time for subjects to provide an answer on the large majority of the trials.

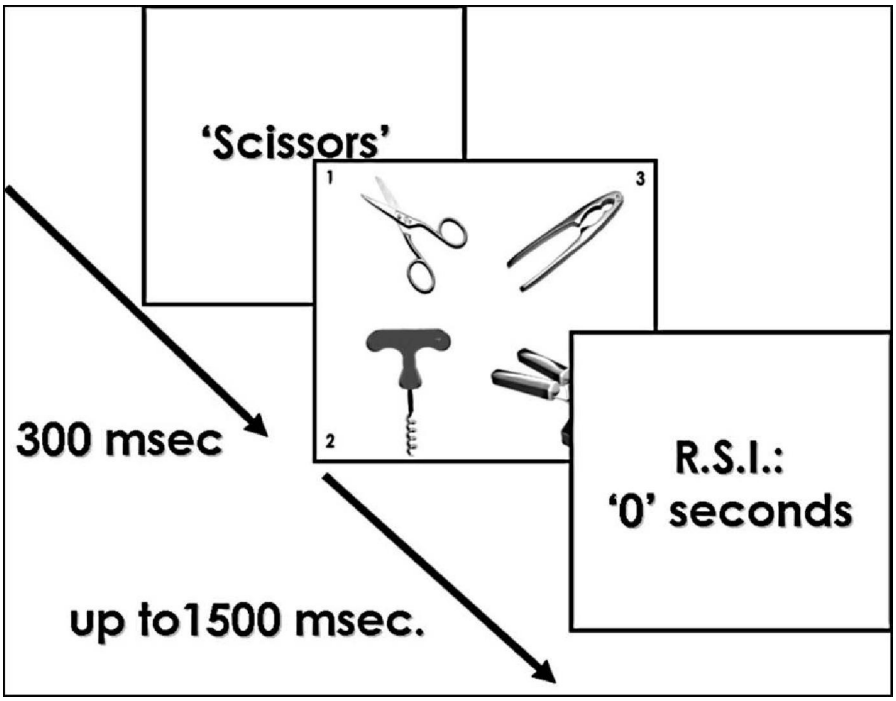


Fig.1: Event sequence for all the three experiments. In experiments 2 and 3 a RSI of 1 second was also used. In this case a fixation point appeared in the centre of the screen during the interval

Results:

The mean accuracy level across subjects in this task was 86.2 % (sd= 8.1%). No subjects were excluded from the analysis. Only 3.7/80 answers per subject (4.7%) on the average were provided after the deadline. These answers were scored as wrong responses assuming that the time provided was not sufficient to complete the semantic decision.

Considering the performance of the participants on the four frequency/distance blocks separately (Fig.2a), a significant main effect of block type was found (Friedman ANOVA: chi square= 31.79; $p<0.0001$). Te results of subsequent post hoc non parametric paired comparisons show interesting interactions between the effects of word frequency and those of semantic distance. Since there were 6 possible confrontations among the different blocks, Bonferroni correction threshold for multiple comparisons was set at 0.05/6 = 0.008.

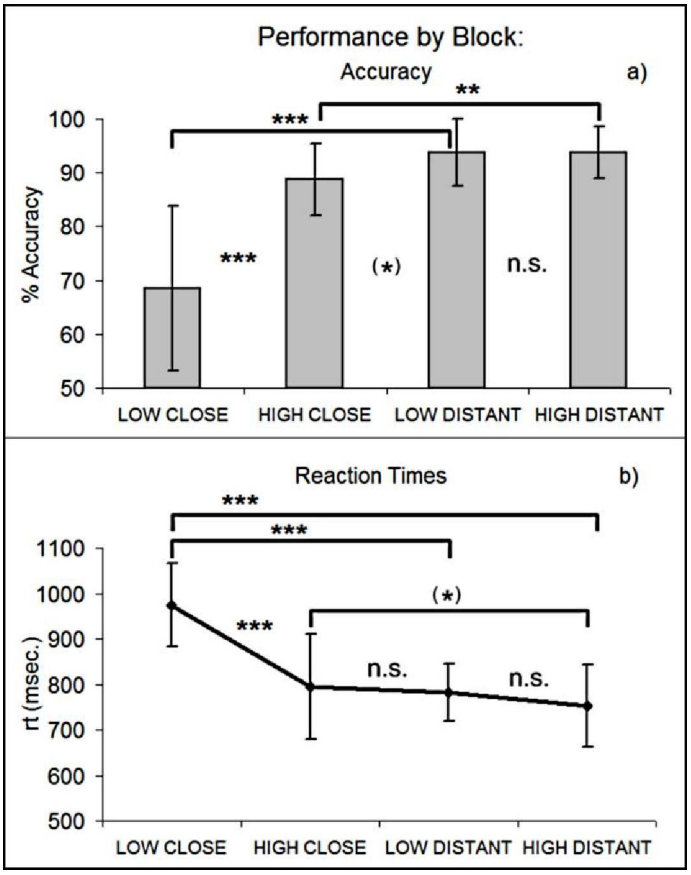


Fig.2: Experiment 1: Performance of the subjects in each of the four blocks of trials (low frequency closely related/ distant; high frequency closely related/distant). Panel a) reports accuracy results; panel b) reports reaction times.
Error bars represent Standard Deviations. Bonferroni correction threshold was set at p=0.05/6=0.008. Asterisks indicate significant results surviving Bonferroni correction

When semantic relatedness was equal, comparing the performance in low vs. high frequency blocks, a significant frequency effect was found only in the semantically closely related blocks (Wilcoxon matched pairs test: low close vs. high close blocks: z=3.762, p=0.0002), while in the semantically distant arrays no frequency effect was observed (Wilcoxon matched pairs test: low distant vs. high distant: z=0.094, p=0.924). By contrast, when word frequency was equal, the direct comparison between the accuracy obtained in the low close block and that in the low distant block gave a significant effect of semantic relatedness (Wilcoxon matched pairs test: z=3.662 p=0.0002); and the same held for the comparison between the high close and high distant blocks (Wilcoxon matched pairs test:

z=2.691 p=0.007). These results show that, whereas word frequency effects are present only when interacting with the effect of semantic distance (i.e. when the semantic distance is low as in the close condition), in this experimental condition the effects of semantic distance are also present in the easier condition of high frequency concepts. This suggests that semantic distance effects are more consistent than those of word frequency.

When analyzing the Reaction Times of the participants on the four frequency/distance blocks separately (Fig.4b), a significant main effect of block was again found (Friedman ANOVA: chi square= 30.3; $p<0.0001$). Subsequent post hoc non parametric paired comparisons (Wilcoxon test: Bonferroni correction threshold for multiple comparisons set at 0.05/6 = 0.008) however revealed that the main effect was due to the performance of subjects only in the low/close condition. Indeed subjects were significantly slower only in this condition with respect to all the others (low/close vs. high/close: z=3.695; p=0.0002; low/close vs. low/distant: z=3.919; $p<0.0001$; low/close vs. high/distant: z=3.845; p=0.0001). No other significant difference in speed was found in any of the other comparisons (low/distant vs. high/distant: z=1.605; p=0.1084; high/close vs. low/distant: z=0; p=1; high/close vs. high/distant: z=2.352; p=0.0187).

Discussion:

The results from this first experiment show that, by using a deadline procedure and by simply removing the RSI between the presentation of stimuli an evident error rate occurred in a word to picture matching, in this group of healthy participants. An effect of semantic distance was evident in both word frequency conditions (low close vs. low distant and high close vs. high distant). However, word frequency effects only occurred in the semantically related conditions (low close vs. high close but not low distant vs. high distant). These findings indicate that word frequency has no effect when stimuli are unrelated. Indeed in the distant condition accuracy levels for high and low frequency target concepts did not differ.

Drawing a parallel with the literature on semantic access deficits in brain damaged patients, a common finding is that patients are more sensitive to semantic distance than to word frequency, a fact that is counterintuitive, since word frequency effects are common in other types of semantic memory impairments. Patients with access problems, instead, show

reduced frequency effects with respect to patients showing degradation of semantic representations (Warrington and McCarthy, 1983; 1987; Warrington and Cipolotti, 1996;Crutch and Warrington, 2005). More specifically the fact that frequency effects were found only between semantically related items is another feature that has been reported in semantic access patients (see patient AZ in Crutch and Warrington, 2005 experiment 1). As we outlined in the introduction, traditional accounts of refractory semantic access dysphasia assume that the origin of semantic distance effects in access patients lies in the fact that refractoriness spreads from the target concept partially also to neighbouring concepts sharing links and synapses in the semantic space, while semantically distant concepts are less prone to refractoriness due to the fewer links between them. The results from this experiment seem to suggest that word frequency has an effect on target recognition only when some amount of refractoriness was induced by the close semantic relatedness of the stimuli.

However, the reaction time results leave open the possibility that the effects may simply be explicable by the use of a deadline. Moreover, the presence of semantic relatedness effects is not always unequivocally attributable to interference *within* the semantic system itself but may also be linked to problems occurring in the input from the lexical to the semantic systems (see Chapter 2). Therefore further evidence is needed to confirm the semantic nature of the interference produced by the procedure adopted and that the effects could not be simply attributable to the presence of a deadline. In particular the effects of rate of presentation and the serial position effect were not investigated in this first experiment. Both these effects represent clearer signs of refractoriness taking place and have never been reported in non refractory contexts.

In experiments 2 and 3 we wanted to test the presence of such effects in a paradigm similar to that used in Experiment 1, and similar to task 1 described in Chapter 2.

3.2.2 Experiment 2:

Participants:

20 participants took part in this experiment (13 females, 7 males). All subjects had normal or corrected to normal vision. The mean age was 23.4 (range of 19 to 33). All participants were university or graduate students.

Materials:

The stimuli and normative data for this experiment were the same as those used in Chapter 2 (task 2). The set of stimuli consisted of 16 digital coloured pictures depicting common objects. The pictures were in '.bmp' format and had a resolution of 400x300 pixels in order to be presented in arrays of four on a 1024x768 17" CRT computer monitor. The monitor was positioned approximately 50 cm from subjects.

Design and Procedure:

This task was designed to investigate the only effects of presentation rate and serial position (see task 1 in Chapter 2). Each array was composed by low frequency and semantically closely related stimuli only. Word frequency ratings were obtained from *Dizionario di frequenza della lingua italiana,* (CNR, Unpublished). Mean frequency was 3.94. Semantic distance ratings were obtained from the same group of 20 healthy participants as in Experiment 1. Subjects were asked to judge the 'conceptual' distance of the objects in each array on a 7 point scale. Mean semantic distance for stimuli of Experiment 2 was 2.28. The complete list of stimuli with frequency and semantic distance ratings is reported in the supplementary material. The stimuli were arranged in 4 arrays of 4 pictures each.

The general event sequence in this task was the same as that used in Experiment 1 (see Fig.1). In line with the previous experiment, the array of stimuli remained on the screen for a maximum of 1500 ms. (see exp.1), in which participants were allowed to provide an answer by pressing the key corresponding to the position of the item on the screen. After the response (or after 1500 ms.), the *same* array of four stimuli was pseudo randomly rearranged and a second target word from the same array was presented. This procedure was repeated until all 4 stimuli were presented as targets and until each target

was presented 3 times. The order of presentation was pseudo-random, the position of the target and other stimuli in each array being constantly varied. Target position was balanced across each of the four possible screen positions. After these 12 trials, a brief pause was provided to the participants. After the pause, the previous array of stimuli was replaced by another one composed of four other objects, presented with identical procedure. Each complete block of trials therefore involved a total of 48 presentations (4 arrays x 4 stimuli x 3 times). The same presentation order was used across subjects. The experimental block was presented four times: two at a Fast and two at a Slow presentation rate. In the Fast condition blocks, as in Experiment 1, no RSI was provided and so the next trial followed *immediately* after the response. In the Slow condition blocks, however, an RSI of 1000 ms. was provided. In both cases, though, the deadline remained at 1500 ms.

Subjects were divided into two groups of 10 participants. Each group had a different block order. For the first group of 10 subjects the order of blocks was Slow/Fast/Fast/Slow (SFFS); for the second group it was Fast/Slow/Slow/Fast (FSSF). As in Experiment 1, the experimental session was preceded by a brief 4 trial practice session in order to familiarize the participants with the speed of the task.

Results:

The average level of accuracy across subjects was 90.4% (sd= 4.7%). Two subjects were excluded from the analysis and replaced by 2 other subjects because of an excessively low accuracy rate (<3 SD below the mean accuracy of other subjects). Responses outside the deadline of 1500 ms were only sporadic. An average number of 5.9/192 answers per subject (3.1%) occurred after the deadline. Overall there were 4.2/96 (4.4%) of the answers that were provided outside the deadline in the Fast condition and only 1.7/96 (1.8%) in the Slow condition. The distribution of the responses outline the deadline across groups and conditions was as follows: for the FSSF group 5.9/96 (6.15%) of the answers was provided outside the deadline in the Fast condition and 2/96 (2.08%) in the Slow condition. For the SFFS group 2.5/96 (2.6%) of the answers was provided outside the deadline in the Fast condition and 1.4/96 (1.46%) in the Slow condition. Answers provided outside the deadline were scored as incorrect answers on the assumption that the time provided was not sufficient to complete the semantic decision.

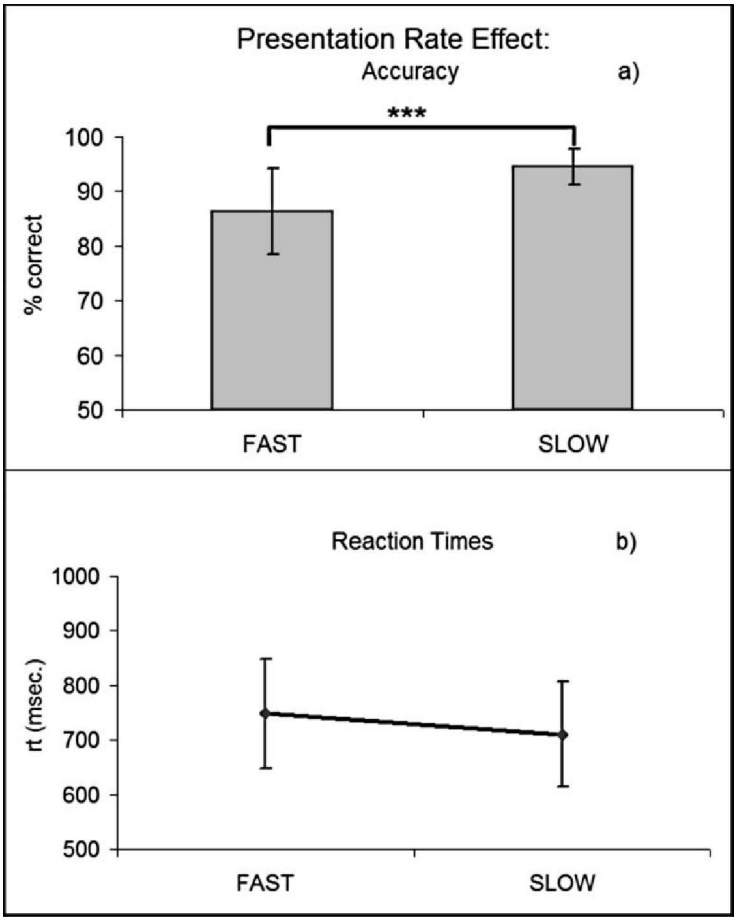


Fig.3: Experiment 2: Presentation rate effects on the accuracy (panel 'a') and reaction times (panel 'b') of the subjects. Error bars represent Standard Deviations. Asterisks indicate significant differences: *p<0.05; **p<0.01; ***p<0.001

Presentation Rate:

Eighteen out of twenty subjects performed worse in the 'Fast' condition than in the 'Slow' condition. As shown in Figure 3a, this consistency was reflected in a strongly significant effect of presentation rate (Wilcoxon matched pairs test: z=3.547; p=0.0004) on accuracy. There was no significant effect of presentation rate on reaction times (Fig. 3b) (Wilcoxon matched pairs test: z=1.61; p=0.11).

Serial Position:

We used the Page's test for ordered alternatives (see Siegel and Castellan, 1988 for details on the procedure), to assess whether there were possible serial position effects.

Page's test is used to test the hypothesis of an ordered increasing (or decreasing) effect of the influence of a variable in a series of 3 or more samplings of an event (or a behaviour as in this case). We used this test in order to test whether the number of errors of the subjects tended to increase with subsequent representations of the items. Given the presence of ceiling effects in the Slow condition, we analysed the performance of the participants in the Fast condition only, in which a higher degree of refractoriness is assumed to occur. However as far as accuracy was concerned (see Fig.4a) no serial position effect was apparent (Page's test: n=20: L=248, $p>0.05$).

The lack of serial position effect in accuracy concealed however a major difference in the behaviour of the two groups of subjects (the SFFS group and the FSSF group) (see Fig. 5a). The two groups behaved in clearly different ways with respect to the first item. Participants in the SFFS group showed a clear serial position effect in their fast blocks of trials, performing better with the first than the other two presentations (Page's test: n=10; L=132.5, $p<0.01$) (Bonferroni correction threshold was set at $p=0.05/2=0.025$). By contrast, participants belonging to the FSSF group showed the opposite pattern in that they performed slightly but insignificantly worse when identifying the target stimulus the first time they saw it, showing an opposite trend (Page's test: n=10; L=115.5, $p>0.05$)

Comparing directly the performance of the two subgroups of subjects, with different orders of blocks, for the 1^{st}, the 2^{nd} and the 3^{rd} presentations of the stimuli (Fig.5a), the difference in accuracy on the first stimulus was significant across the two groups (Mann Whitney U test: 1^{st} presentation: U=15.5, $p=0.007$) (Bonferroni correction threshold set at $p=0.05/3=0.017$). There was no difference between the groups on the second or the third presentation (Mann Whitney U test: 2^{nd} presentation: U=49.5, $p=0.971$; 3^{rd} presentation: U=50, $p=1$).

This suggests that a lack of familiarity with the stimuli in the subjects who were presented first with a fast block might have played a role in the failure to obtain a serial position effect in this experiment. To investigate this possibility further, a more detailed analysis was performed across blocks for the FSSF group of subjects. If this was the case, then in the fourth block (i.e. the second Fast block), when participants were already well familiarized with the material, a serial position effect should be present. By contrast, in the first block (fast block) a learning effect with bad performance on the first trial is expected.

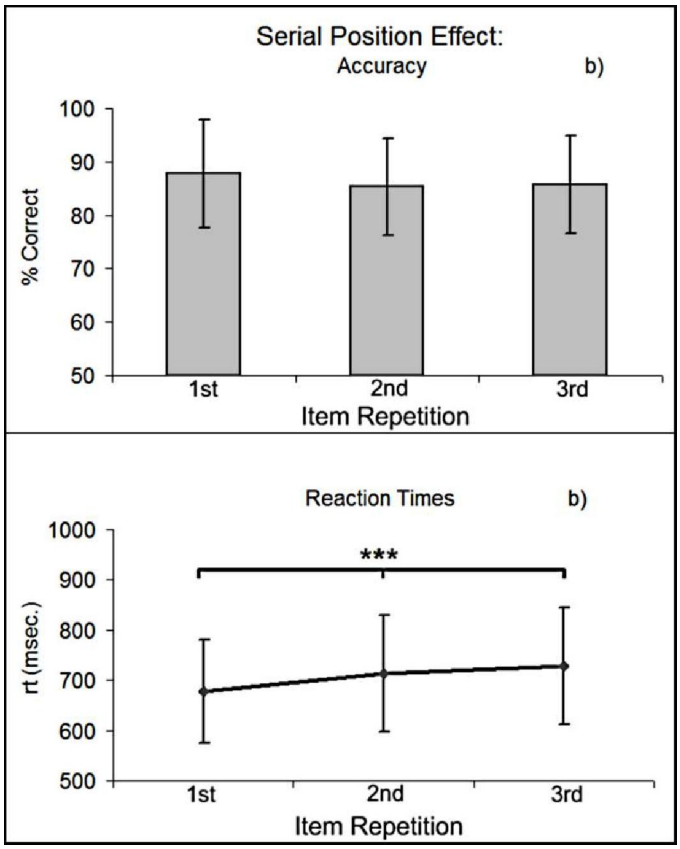


Fig.4: Experiment 2: Serial position effects on the accuracy (panel 'a') and reaction times (panel 'b') of the subjects. Error bars represent Standard Deviations.
Asterisks indicate significant differences: *p<0.05; **p<0.01; ***p<0.001

This was indeed the case. The distribution of the responses between the first and the fourth block was similar to that found between the SFFS and FSSF groups of participants (see Fig.5b). A significant difference in accuracy was found between the first and the fourth block, on the first presentation of the items (Wilcoxon matched pairs test: z=2.803; p=0.005), while the same difference was not significant for the second or the third presentation of the items (Wilcoxon matched pairs test: 2^{nd} and 3^{rd} presentation: z=1.478; p=0.139 in both cases) (see Fig.5b). These results again show that on the fourth block, in which subjects were already largely familiar with the stimuli presented, participants tend to perform better with the first presentation of the items than with the second or third, suggesting some refractoriness to take place.

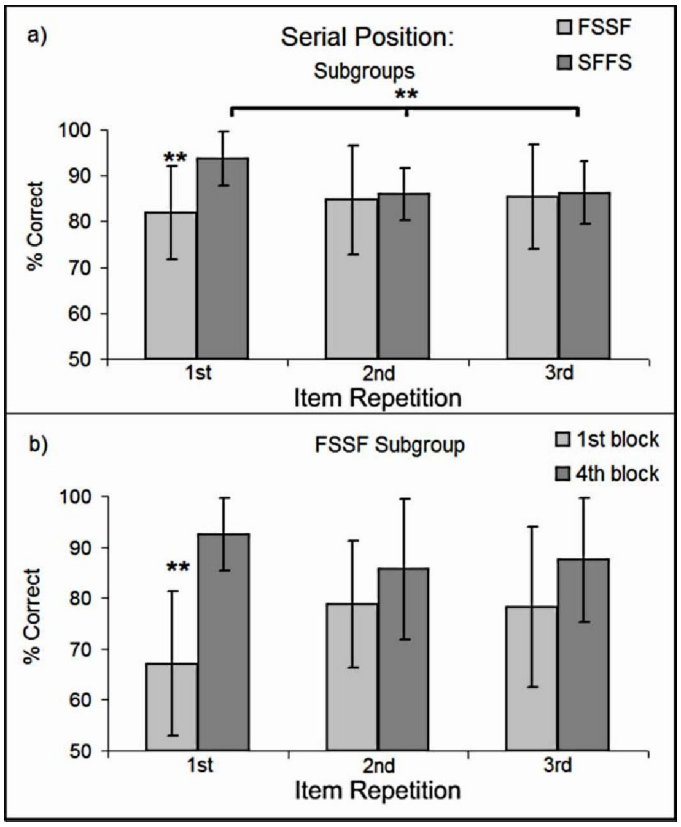


Fig.5: Experiment 2 (Fast condition): Panel a) Accuracy of the two subgroups of subjects administered with the two block order presentations (FSSF group: Fast/Slow/Slow/Fast and SFFS group: Slow/Fast/Fast/Slow). The subgroup of subjects administered with the slow block first (SFFS) shows the serial position effect. Panel b): Accuracy of the FSSF subgroup of subjects in the first and the fourth blocks of trials (both at a Fast rate). Performance with the first presentation is significantly different among the two blocks.
Error bars represent Standard Deviations. Asterisks indicate significant differences: *p<0.05; **p<0.01; ***p<0.001

The analysis of reaction times, on the other hand, (Fig. 4b) showed that, regardless of group, participants tended to be faster in responding when presented with the target item for the first time as compared to both the second and the third presentation (Page's test: n=20; L=161, p<0.001) showing a clear serial position effect.

Discussion:

In the Fast condition subjects had an RSI of 0 sec. This led the participants to make a fairly high rate of errors. These errors were almost completely absent in the Slow condition where an RSI of 1s is used: only 1.8% of responses over the deadline vs. 4.4% in the Fast condition. The results from this experiment therefore show a clear effect of presentation rate on accuracy. The fact that a similar rate effect was not found for reaction times, counts against the possibility that the effects found in accuracy were just due to a greater percentage of answers simply exceeding the deadline in the Fast condition, due to a general slowing of responding in that condition.

As far as the serial position effect is concerned, while this effect was present in reaction times, no such effect was found for accuracy. However a deeper analysis revealed that there were two different patterns of behaviour if the participants were divided into two subgroups according to the order in which the different types of block were presented. When subjects were presented with a Slow block first, they had the opportunity to familiarize themselves with the stimuli in the easier condition. When subsequently they were presented with a fast block (SFFS group) the presence of serial position effects was then evident. When, on the other hand, a Fast block was presented first (FSSF group) subjects tended to fail on the first trial, in which they were not familiar with the stimuli. This difference in the performance on the first trial across subgroups was significant.

To check that this was a plausible explanation for the lack of a serial position effect in this experiment, a within block analysis in the FSSF group was performed. The analysis showed that while in the first (fast) block subjects tended to show worse performance on the first than in subsequent trials, in the fourth block (the second fast one), they produced better performance in the first presentation of a stimulus. Also, in this case the difference in the level of performance across subgroups on the first trial was significant. In Experiment 3 therefore, we modified the paradigm to assure that the subjects were familiar with the stimuli and thus assessing whether serial position effects could be found.

3.2.3 Experiment 3:

In order to formally assess whether the lack of familiarization with the test material was responsible for the absence of the serial position effect, in Experiment 3, a familiarization block was added at a slow presentation rate before carrying out the 4 experimental blocks.

Participants:

20 participants took part in the experiment (13 females, 7 males). All subjects had normal or corrected to normal vision. The mean age was 24.1 (range of 19 to 27). All participants were university or graduate students.

Materials:

The stimuli used were the same as in Experiment 2.

Design and Procedure:

The experimental design was generally the same as in Experiment 2, as was the general procedure. The difference was that after the short 4 trial practice session an extra block was added before the 4 experimental blocks. This block was considered as a 'familiarization block' and the results were not included in the analysis. The familiarization block was presented at a Slow presentation rate (1s RSI given) and its only purpose was that of familiarizing the participants with the stimuli.

Results:

The average level of accuracy was: 91.35% (sd= 7.02%). No subjects were excluded from the analysis. Responses outside the deadline of 1500 ms were only sporadic. An average number of 4.7/192 answers per subject (2.45%) occurred after the deadline. The distribution of the responses outline the deadline across groups and conditions was as follows: for the FSSF group 2.4/96 (2.5%) of the answers was provided outside the deadline in the Fast condition and 1.8/96 (1.9%) in the Slow condition. For the SFFS group 3.6/96 (3.7%) of the answers was provided outside the deadline in the Fast condition and 1.6/96 (1.7%) in the Slow condition. Overall there were 3 (3.13%) the answers that were

provided outside the deadline in the Fast condition and only 1.7 (1.77%) in the Slow condition. Answers provided outside the deadline were scored as incorrect on the assumption that the time provided was not sufficient to complete the semantic decision.

Presentation rate:

Sixteen out of the twenty subjects performed more poorly in the 'Fast' than in the 'Slow' condition. This was reflected in a significant effect of presentation rate on accuracy (Wilcoxon matched pairs test: $z=3.53$; $p<0.001$) which reliably replicated that obtained in Experiment 2 (see Fig. 6a). There was not a significant effect of presentation rate for reaction times (Fig. 6b) (Wilcoxon matched pairs test: $z=1.04$; $p=0.269$).

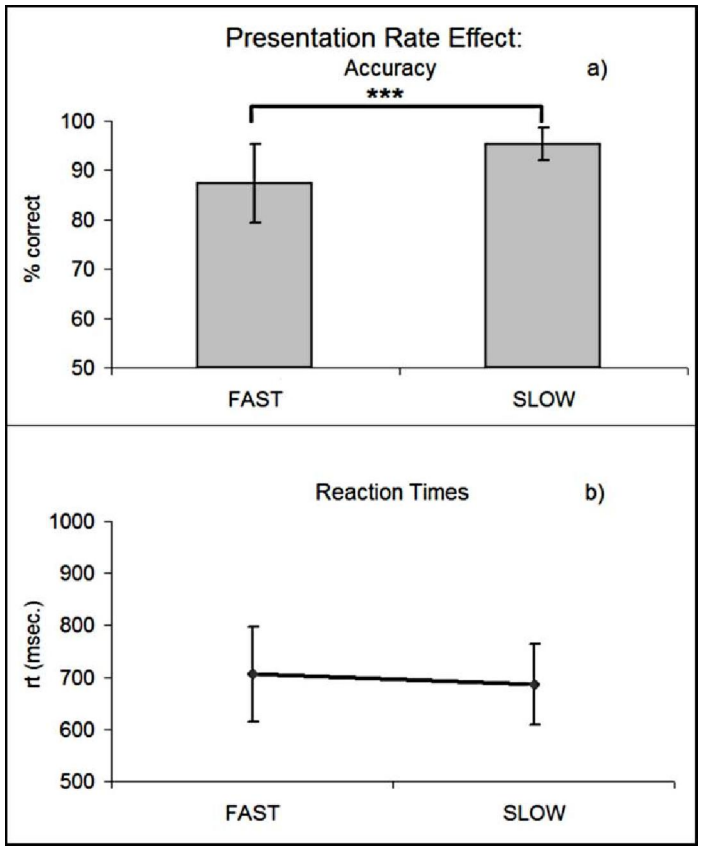


Fig.6: Experiment 3: Presentation rate effects on the accuracy (panel 'a') and reaction times (panel 'b') of the subjects. Error bars represent Standard Deviations. Asterisks indicate significant differences: *p<0.05; **p<0.01; ***p<0.001

Serial Position:

Comparing the performance of participants across the three presentations of each item (Fig.7a), a clear serial position effect emerged. In the Fast presentation rate blocks, participants were significantly less accurate with subsequent representations of stimuli after better performance on the first presentation (Page's test: n=20; L=256.5, p<0.01). The same effect was also found in reaction times. A clear serial position effect was again present: participants (Fig. 7b) were faster in recognizing each item the first time they saw it than the second or third time (Page's test: n=20; L=253, p<0.05).

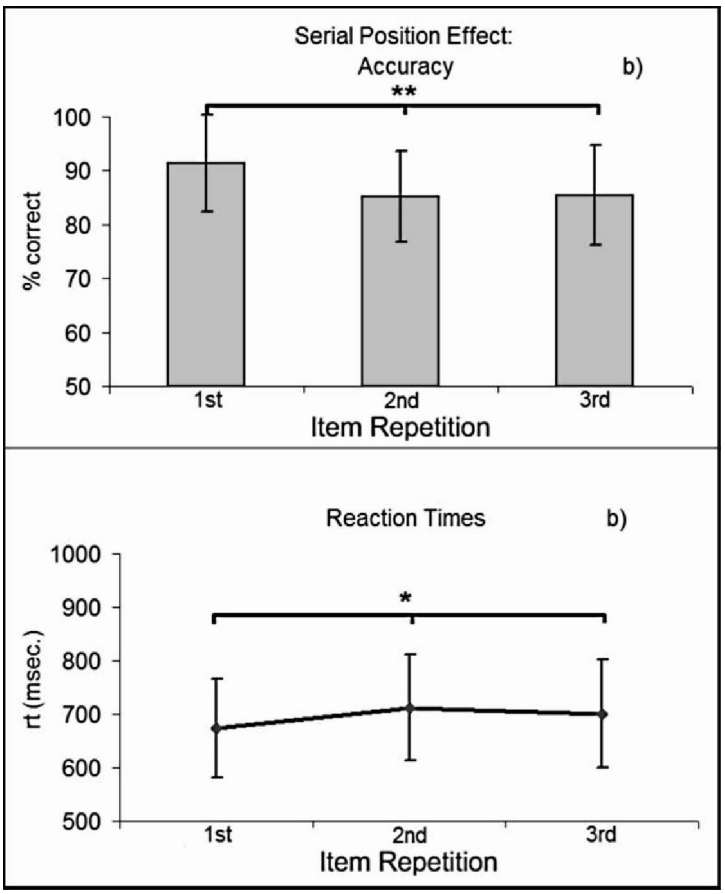


Fig.7: Experiment 3: Serial position effects on the accuracy (panel 'a') and reaction times (panel 'b') of the subjects in the Fast condition. A clear serial position effect was reported both in accuracy and in reaction times. Error bars represent Standard Deviations.
Asterisks indicate significant differences: *p<0.05; **p<0.01; ***p<0.001

Discussion:

This third experiment was a replication of Experiment 2 but with the addition of an initial familiarization block. As in Experiment 2, an effect of rate of presentation was again found. A clear serial position effect was moreover found when the stimuli were repeated. This finding suggests that the failure to find an overall serial position effect in Experiment 2 was indeed due to a lack of familiarity with the stimuli. Thus in this experiment even when familiar with the experimental material, participants were more accurate with the first presentation of each stimulus than they were with the second or the third.

3.3 GENERAL DISCUSSION:

3.3.1 Refractoriness arising within the semantic system

The results from the experiments of this study reproduce all the hallmark effects of a refractory semantic access syndrome in a set of healthy participants. Refractory semantic access dysphasic patients have difficulties in accessing semantic representations they still retain (Forde and Humphreys, 1995;Warrington and Shallice, 1979; Warrington and McCarthy, 1983; Warrington and Cipolotti, 1996;Crutch and Warrington, 2005). The access to the concept is influenced by different variables playing a role to a different degree in their performance. These patients show a reduced effect of word frequency by comparison, say, with semantic dementia patients. However they are heavily influenced by the semantic distance between the target concept to be accessed and the distractors: the higher the distance, the easier the access. Critically, moreover, they are strongly influenced by the rate of presentation of the stimuli: if the interval between a stimulus and the next (Response Stimulus Interval or RSI) is short, their performance is gravely impaired; on the other hand longer RSIs lead to a sensible improvement. These patients also show a serial position effect: subsequent presentations of the same target stimulus reduce the probability of the stimulus to be recognized.

In the experiments we presented we were able to induce in healthy participants a pattern of performance which was analogous to that of semantic access dysphasia patients. In Experiment 1 an effect of semantic distance was found both with high and low frequency

concepts. However, word frequency effects only occurred when target stimuli were semantically related. A clear effect of presentation rate was found in both Experiments 2 and 3: subjects were consistently more accurate with slow rates of stimuli presentation than with faster. In the Fast condition, which involved an RSI of 0 seconds, participants made a significantly greater number of errors in the task. However adding an RSI of just one second was sufficient for the subjects to perform at ceiling in the task. More importantly, however, a serial position effect was found in Experiment 2 (but in one condition only), and more critically in Experiment 3, when familiarization of the participants with the stimuli preceded the experimental blocks. This finding gave further strength to the claim that efficient access to simple, familiar concepts was becoming more and more difficult in time for subjects.

The main results obtained in accuracy were also in general reflected in terms of the speed of processing of the subjects (Reaction Times). The most salient result regarding reaction times was that in Experiments 2 and 3 subjects produced a clear serial position effect, being slower in recognizing the target concepts after the initial fast (and effective) access.

The results cannot be explained just as a simple byproduct of the use of an excessively strict deadline procedure, since the deadline is the same in the two conditions. Moreover, in both experiments 2 and 3 no significant slowing of reaction times is found in the fast with respect to the slow condition. Moreover this possibility could not account for the serial position effects found.

Instead the results obtained can be explained if one assumes that the semantic system itself undergoes some degree of refractoriness. An effect of semantic distance was found in both the frequency conditions of Experiment1, while word frequency effects only occurred with semantically related concepts, when one can presume that refractoriness is higher. No word frequency effect was found with unrelated stimuli (see also Crutch and Warrington, 2005; experiment 1). Most importantly however, the presence of clear serial position effects gives strong support to the claim that the semantic system is becoming refractory over time with repeated presentations of semantically related stimuli.

An important result from this study is that, whereas possible refractory effects in accessing word meaning have been studied in the past by means of naming tasks, the

refractory effects we found in this set of tasks were obtained with a word to picture matching procedure. This difference, as we will see, is of critical importance for assessing the precise locus of refractory effects.

The amount of refractoriness induced by the paradigm was strong enough to impair the identification ability of the subjects. This is different from what was obtained for example in the study by Belke and colleagues (2005), in which refractoriness occurred only in terms of a reduction in the amount of facilitation in recognizing repeatedly presented stimuli.

In the 'Slow' condition of experiments 2 and 3 the use of an RSI of just 1 s. was sufficient to enable participants to produce accurate performance, close to ceiling. All effects discussed above were obtained, in the context of a deadline procedure, by simply reducing the Response Stimulus Interval (RSI) to '0'. This finding is compatible with the idea that stimulus repetition in the time window of a normal mild refractory neural state (Finlayson and Cynader, 1995; Tsodyks and Markram, 1997; Galarreta and Hestrin, 1998; Varela et al., 1999) may lead to the accumulation of some amount of residual neural refractoriness eventually leading to representations becoming more difficult to access for a very brief time period.

In neurological patients, the cause of refractory behaviour in tasks similar to ours has been held to be within the semantic system itself, since patients were usually found to be unimpaired in presemantic perceptual matching tasks (Warrington and Cipolotti, 1996; Forde and Humphreys, 1997). Since the error pattern that we found was analogous to that occurring in patients and moreover this behaviour showed unequivocally refractory traits, it is proposed that the conditions necessary and sufficient for producing this type of behaviour in normal subjects also, relate to processes within the semantic system itself.

In a number of respects these results are similar to those found by Schnur et al (2006), Belke et al (2005) and others on semantic blocking effects. However, the present findings relate to a different level of language processing. All previous refractoriness effects were obtained in naming tasks, which involve a number of output stages in which selection among competing candidates may potentially occur. By contrast, no activation of postsemantic lexical representations is needed in order to perform the word to picture matching tasks used here. In these tasks, the competition among different candidates can

only occur at the time when the four concepts are elicited by the pictures. This difference is critical in order to consider whether models of word production such as that of Howard and colleagues (2006) can account for these findings.

According to the model developed by Howard and colleagues, refractory behaviour in word retrieval occurs as a consequence of the concomitant contribution of three cognitive mechanisms: shared activation (spreading within the semantic system between the target representation and the semantic neighbors); priming (strengthening of the output connections between the target semantic representation and its correspondent lexical representation) and competition (lateral inhibition process occurring at the output lexicon level between the target representation and the semantically related lexical candidates). The critical point, with regards to our results, is that both the priming and the competition mechanisms in the model of Howard and colleagues are located after the semantic system at a later stage of processing (the 'Lemma' stage). The design of our experiments excludes this stage as a potential locus of the mechanisms causing refractoriness, since in our task only one lexical entry is activated (the one corresponding to the auditory word in input) and moreover the only output needed is the pressing of the key corresponding to the correct picture.

An alternative possibility could be however, that the activation from the semantic system units could partially spread back to hypothetical lemma units at input. They would then receive residual activations even if not directly activated. In this case the competition might still occur at an equivalent level as that postulated by Howard. Nevertheless, to accept this possibility we should need to make one of two supplementary alternative assumptions on the model. The first is that the lemma stage at the input level is either a separate but completely isomorphic module to the one at the output stage (and therefore with the same architecture), or that there is only one lemma stage which processes the information both in input and output from the semantic system (as hypothesized for example by Levelt et al., 1999). In both cases, to account for the results we found, bidirectional connections would need to be present at each stage of processing both from and to the semantic system. However, the network model designed by Howard and colleagues implies only feedforward connections between the subsequent stages of

processing, excluding any possibility of backpropagation from the activated competing semantic nodes to the preceding competing lemmas.

Such bidirectional connections are present in another model of word production: that of Levelt and colleagues (Levelt et al., 1999). Levelt et al hypothesize, as also do Howard et al, that there is a 1:1 mapping between each 'lexical concept' (semantic unit) and the corresponding lemma unit. These connections are bidirectional and the model assumes the processing of information at input and output is carried out by the same module. However, unlike the Howard et al architecture, this model involves interactions between adjacent units *at a semantic level only*; no direct interaction is assumed to occur between lemma units, as assumed by Howard and colleagues. Therefore an architecture (such as that of Levelt et al.) which assumes that the competition occurs within the semantic system seems to be able to better account for the current findings. While the model of Howard and colleagues (2006) seems entirely appropriate in accounting for refractoriness in production, it would need further refinements in order to explain the findings of this study.

As stated in the Introduction, while there has been an extensive effort made over cognitive and computational modeling of word production processes, less effort has been put into modeling word comprehension processes in the absence of spoken or written output. The only relevant model simulating the stages composing the word comprehension pathway, is that proposed by Gotts and Plaut (2002) which is designed with the specific aim of modeling the refractory behaviour of neurological patients in semantic access tasks, similar to the ones we used. The network proposed by Gotts and Plaut is a very simple three layer feedforward network comprising a phonological layer of units, unidirectionally connected to a layer of hidden units, which are, in turn, connected to a set of semantic units. Each semantic unit is not intended to be representative of a single concept. Concepts are defined by a 'semantic pattern' of activation over subsets of semantic units, half of the patterns representing semantically closely related and half distant concepts.

Gotts and Plaut's model is mainly focused on the modeling of neuromodulatory mechanisms which assure an effective and reliable access to target representations. This neuromodulation efficacy was implemented in the model by Gotts and Plaut (2002), in terms of an abstract *'M'* value representing the amount of neuromodulator present in the

synapses and modulating the operation of the connections between the layers of the network. In their simulation, lower levels of neuromodulation led to abnormal synaptic depression, causing enhanced refractoriness in the semantic network in time. The refractoriness became higher and higher in subsequent trials, generating an increasing number of errors particularly in the presence of a small set of semantically related inputs. This led the network, in the end, to produce refractory behaviour. As a result, the simulation by Gotts and Plaut reproduced elegantly the pattern of performance provided by semantic access dysphasic patients.

As far as these results are concerned, the elimination of interstimulus intervals and the fast presentation rate would act against neuromodulatory efficacy on the model, leading to the accumulation of residual refractoriness in the semantic network. This lowered neuromodulatory efficacy would lead to greater difficulty in identifying stimuli at a fast presentation rate, where no interstimulus interval is provided, and lead to the accumulation of residual mild synaptic depression effects over time, which would produce a tendency for a serial position effect such as that found in both experiments 2 and 3 to occur. Moreover the residual synaptic depression would spread from the target representation to semantically close stimuli, so explaining the semantic distance effects found in Experiment 1. Since, finally, high frequency concepts have also richer and more interconnected neural representations, they would be more prone to refractoriness and this would partially counterbalance the frequency effects.

Gotts and Plaut's model is however considered by its authors to be very simple and does not specify in detail the composition of each level of processing, focusing attention instead more on the implementation of dynamic factors that generate possibly refractory states. The authors, though, agree that a full instantiation of the model would require feedback connections between each level and the preceding. In any case, in the form they implemented it, the model contains only feedforward connections and therefore the competition between semantically related representations can only occur at the semantic level. A major strength of this model is that, though being simple, it gives a neurally plausible explanation for the phenomenon of refractoriness and the results we found in this group of healthy subjects fit well with the predictions made by this model. Whether alternative neuropsychological accounts of the refractoriness effects in patients, such as that

proposed by Jefferies and colleagues (2007) could also explain the findings, remains however to be further investigated.

In conclusion, in this series of behavioural experiments healthy participants showed a performance profile which reproduced the pattern of performance of semantic access dysphasia patients. Under strong time pressure healthy subjects also show problems in recognizing common objects in a written word to picture matching task. The analysis of the error profile suggests that subjects were undergoing some degree of refractoriness in their ability to recognize the presented stimuli. Most importantly, for the first time, a refractory pattern of performance is reported in comprehension (matching) tasks, while previously it was reported only in production (naming) tasks.

CHAPTER 4:

4.1 INTRODUCTION:

In Chapter 3 we showed how the presence of refractoriness can be a factor sufficient to generate all the behavioural effects described in refractory semantic access patients, suggesting therefore that the syndrome described in Chapter 2 was a qualitatively different one. However, an important result of the studies conducted in Chapter 3 was also that refractoriness was found to arise in a series of *comprehension* tasks in healthy subjects. This suggested that, since no post-semantic lexical level of processing is assumed be necessary to produce an answer in similar tasks, the only level at which the refractoriness could have taken place was that of the semantic representations themselves. From a computational point of view, the model proposed by Gotts and Plaut (2002) seemed to nicely fit and explain the refractory effects found in the series of experiments proposed. In the model proposed by the authors concepts are, however, not conceived as unitary 'nodes' in a network (cfr. e.g. Collins and Loftus, 1975), but rather, in accordance with many recent accounts of semantic memory structure (e.g. Tyler et al., 2000; Simmons and Barsalou, 2003) as configurations of activation of set of semantic features, some of which are shared between concepts.

If refractoriness can arise as a consequence of interference occurring among the features shared between concepts which are, by virtue of this, closely related in the semantic space, then the presence of refractoriness might indicate that two concepts share a particular semantic feature in common. Following this rationale we designed the study described in the present chapter, which was aimed at investigating whether manipulability is indeed a relevant *semantic* feature for manipulable objects.

4.1.1 Possible interactions between 'What' and 'Where':

Models of object perception postulate a distinction between the neural paths devoted to object recognition and those devoted to the processing of the appropriate actions to interact with the object (Ungerleider and Mishkin, 1982; Goodale et al., 1991; Goodale and Milner, 1992; Culham and Valyear, 2006). While object identification relies on the processes occurring in the so-called 'ventral' or 'what' pathway (occipito-temporal), on-

line object-directed actions are controlled by the so-called ‘dorsal’ or ‘where’ pathway (occipito-parietal). It has been proposed (Goodale et al., 1991; Jeannerod et al., 1994) that these two distinct streams of information processing might be carrying out different processes, suggesting a separation between the processes of identification and action. Indeed neuropsychological evidence has been provided that, for example, a patient can be unable to efficiently discriminate the size of a perceived object, while being efficiently able to grasp the same object in the appropriate way (Goodale et al., 1991). By contrast, optic ataxic patients, who typically suffer from superior posterior parietal lobe lesions, correctly recognize objects but may fail in guiding actions toward the same objects (e.g. Jeannerod et al., 1994).

This classical view suggests that the two systems might be somewhat independent with no interaction between them. However in the past ten years several different lines of research have indicated that interactions might exist between the systems devoted to object recognition and those devoted to process the appropriate actions to manipulate visual objects correctly, suggesting that the action appropriate to use an object might influence its recognition.

Suggestions of a link between object-directed actions and the recognition of the same objects come for example from behavioural studies on the role of ‘affordances’ on object recognition. The term “affordance” was first used by Gibson (1979), who defined them as all "action possibilities" latent in the environment, independent of the individual's ability to recognize them. Later, the term shifted its meaning referring more specifically to just those action possibilities (on objects) which are readily perceivable by an actor (Norman, 1988).

In a seminal work on the implicit processing of object affordances, Tucker and Ellis (1998) showed that when asked to respond whether an object was upright or inverted by pressing a left or right button, subjects are faster if the hand of the answer is compatible with how one grasps the seen object, showing that “visual objects potentiate actions even in absence of an explicit intention to act” (p.830). In another somewhat related study, Creem and Proffitt (2001), used a dual task paradigm to interfere with cognitive or visuomotor processing. They showed that a semantic task can interfere with grasping objects by their handles in the appropriate way showing that the visuomotor system alone can direct the

effective grasping of an object, but this grasping is *inappropriate* for its use. By contrast with a concurrent spatial interfering task the objects were grasped appropriately. The *semantic* interfering task consisted in producing the word associated with a presented word, after a training-learning phase; the *spatial* interfering task consisted in judging the location (yes= top or bottom; no= anywhere else) of the edges of a series of block letters. With this study, for the first time it is suggested that the action appropriate to use an object correctly is something *more* than the result of a pure on-line visual-perceptual interaction.

A further step has been made more recently by Helbig, Graf and Kiefer (2006). They showed that the action appropriate to use an object can also facilitate the *recognition* of that object. The authors found that the accuracy in naming a manipulable object is higher when the object (for example a frying pan) is primed by the brief (masked) presentation of an object which is acted upon in the same way (for example a dustpan), suggesting that the processing of object-directed actions can indeed influence the recognition of objects.

A second line of evidence in favour of a link between object-directed actions and recognition of small manipulable objects comes moreover from several neuroimaging studies. These studies (e.g. Chao and Martin, 2000; Kellenbach et al., 2003; Creem-Regehr and Lee, 2005; Martin, 2007; Weisberg et al., 2007; Canessa et al., 2008) indicate that a complex left lateralized network of areas, including left posterior middle temporal and left inferior parietal as well as premotor areas, is active when performing tasks requiring the recognition of small manipulable objects. Many of these areas lie within the 'dorsal stream'. Of particular interest is the study of Weisberg and colleagues (2007) in which subjects had to identify pictures of novel objects before and after extensive training in their use. After training, neural activity emerged, in those areas associated with motion perception (middle temporal) and manipulation (intraparietal and premotor). These areas overlap to those previously found to be active when retrieving information about tools.

Evidence coming from neuropsychology moreover suggests the possibility that the way an object is manipulated might play an important role in representing the meaning of the same object. Indeed within the field of the so-called "category specific semantic deficits" the selective loss of categories of meaning has been found in patients with damage to particular brain regions. While the most studied category specific deficit involves the selective loss of knowledge about living entities with selective sparing of artifacts (mainly

tools) (e.g. Warrington and Shallice, 1984), some cases of the reverse dissociation (selective loss of knowledge about artifacts) have also been reported (e.g. Warrington and McCarthy, 1983; Warrington and McCarthy, 1987; see Gainotti, 2000; Capitani et al., 2003 for reviews). In particular there have been reports (e.g. Damasio et al., 1996; and, more recently, Brambati et al., 2006; see also chapter 5) of selective loss of the ability to name manipulable objects in patients with damage to the left posterior lateral temporal cortex, in particular the left posterior middle temporal gyrus. The location of the lesion sites overlaps the areas that, in neuroimaging studies have been linked to the representation of manipulable objects.

Indeed, similar anatomical regions were also involved in the lesions reported by the first two patients described as suffering from a category specific loss of knowledge about artifacts. Patients VER (Warrington and McCarthy, 1983) and YOT (Warrington and McCarthy, 1987), both suffered from left middle cerebral artery strokes which produced damage in the left fronto-parietal and temporo-parietal regions respectively. Both these patients however, in addition to a category specific semantic deficit for artifacts, were described as having a previously unreported disorder concerning accessing semantic representations. The pattern of performance of these patients in a series of word-to-picture matching tasks suggested that the semantic representations of the patients were still intact, but that the access to them was impaired. As extensively discussed in Chapter 2, also the group of left posterior-superior temporal tumour patients described, showed the presence of semantic access difficulties in a series of word-to-picture matching tasks involving small manipulable objects only.

Performance on semantic tasks of patients suffering from disorders involving semantic representations has been found to be influenced by a number of variables. These variables have been held to be useful in distinguishing problems in the access from problems to the storage of semantic material in memory (see e.g. Warrington and McCarthy, 1983; Warrington and McCarthy, 1987; Warrington and Cipolotti, 1996). Patients suffering from access disorders have indeed been found to be:

a) Inconsistent in their performance on individual items (suggesting that the concept is being accessed only on some trials)

b) Very sensitive to the semantic distance between the target and the distractors presented, showing a better performance with unrelated stimuli (semantic distance effect).
c) Only weakly affected by the frequency of the target word to be retrieved (word frequency effect).
d) Strongly influenced by the rate of presentation of the stimuli: patients perform better when the interval between presentations is longer (presentation rate effect).
e) Influenced by the serial position of the stimulus presented: repeated presentations of the same set of target stimuli leads to a progressive deterioration in their performance (negative serial position effect).

The complementary pattern of performance is found in patients suffering from degradation of the semantic representations (e.g. Warrington and Cipolotti, 1996 see also Chapter 2).

Within the field of neuropsychology, difficulties in accessing concepts have been traditionally explained in terms of the semantic system itself undergoing an abnormally prolonged refractory state (e.g. Warrington and McCarthy, 1983; Warrington and McCarthy, 1987; Forde and Humphreys, 1995; 1997; Gotts and Plaut, 2002). For instance, following the model proposed by Gotts and Plaut (2002), the semantic system temporarily undergoes an abnormally prolonged refractory state. This is caused by an abnormal persistence of a synaptic depression phenomenon, a physiological neural refractory state occurring after repeated activation of the same synapse (Hasselmo and Bower, 1992; Tsodyks and Markram, 1997). In this abnormal neural state the following phenomena are expected to occur:

a) The access to the concept should become sometimes difficult (Inconsistency of access)
b) The refractoriness affecting a concept will spread partially also to those synapses shared between that concept and the semantically related ones (semantic distance effect)
c) A higher level of refractoriness is expected to affect those concepts which are more frequent, since high frequency concepts have richer and more inter-related representations, reducing the dimension of frequency effects which are otherwise very common in semantic deficits (lack of frequency effect).
d) Stimuli presented at a slow pace should have better chances to be recognized since the effects of abnormal refractoriness should be attenuated (presentation rate effect).

e) If stimuli are repeatedly presented within the time window of the refractory state, residual refractoriness is likely to accumulate, leading to a decrement in the chance of accessing the concept in repeated attempts (a negative serial position effect).

Of particular interest, as far as this study is concerned, are however the effects of semantic distance and the negative serial position effects. Both types of effect have been reported in refractory semantic access syndromes. However, semantic distance effects have also been reported in patients showing access difficulties but not refractoriness (e.g. Warrington and Leff, 2000; Gotts et al., 2002 in the context of naming tasks; see Chapter 2 for evidence in the context of matching tasks); these patients were indeed insensitive to 'temporal factors' such as presentation rate and serial position, showing however inconsistent access to concepts and being sensitive to semantic distance. In these patients the deficit was attributed to interference occurring outside the semantic system itself (pre- or post-semantically). By contrast, all the *refractory* semantic access syndromes (i.e. those in which patients show the rate of presentation and especially a negative serial position effect) have been attributed to interference occurring among the semantic representations themselves (e.g. Warrington and Cipolotti, 1996; Forde and Humphreys, 1997).

Behavioural refractory effects, such as serial position, have also been reported in healthy subjects under specific circumstances (see Belke et al., 2005; Howard et al., 2006; Schnur et al., 2006; see also Chapter 3), suggesting that also healthy subjects can undergo some degree of refractoriness under the appropriate conditions. In particular, as extensively discussed in Chapter 3, it was possible to induce in healthy subjects a pattern of performance similar to that of refractory semantic access patients in comprehension tasks similar to those used with patients. From the results it was argued that the pattern of performance can be explained only by assuming that the locus of refractoriness lies within the semantic system itself.

4.1.2 Is manipulability a *semantic* feature?

The aim of the present work was first to confirm the existence of the link between object-directed actions and object recognition, but also, more specifically, to investigate whether the way an object is manipulated is a *semantic* dimension critical in building the representation of the meaning of the object. A deadline response word-to-picture matching

paradigm was therefore used in two experiments, with the aim of creating interference in the recognition of different pairs of objects sharing a common manipulation movement or not.

These experiments show how the shared manipulation movement of pairs of objects interferes with their identification more than their visual similarity does (Experiment 1), causing an interference which resembles the classical semantic distance effect. Moreover, in Experiment 2, we show that the repeated presentation of stimuli sharing different types of features leads to different patterns of performance in the subjects. In particular the repeated presentation of pairs of stimuli sharing no particular relation produced few, if any, interference and a performance close to ceiling was found. However, the repeated presentation of pairs of stimuli sharing only visual similarity led to an increase in accuracy after an initial perceptual interference (learning effect). By contrast, the repeated presentation of stimuli sharing a common manipulation movement generated the typical negative serial position effects shown also by semantic access patients, indicating some amount of refractoriness arising between the pairs of stimuli and therefore suggesting that the interference occurring among these stimuli is of a semantic nature.

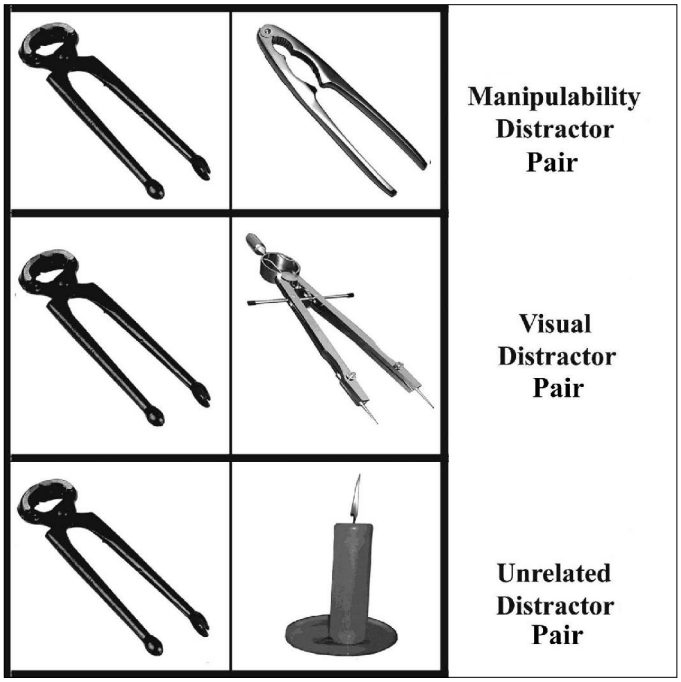


Fig.1: Examples of stimuli pairs. The Target stimulus (Pincers) is alternatively paired with a Manipulability distractor (Nutcracker), a Visual distractor (Compasses) or an Unrelated distractor (Candle).

4.2 EXPERIMENTAL INVESTIGATION:

4.2.1 Experiment 1

Participants:

20 participants took part in this experiment (13 females, 7 males). All subjects had normal or corrected to normal vision. The mean age was 26.85 (range of 21 to 34). All participants were university or graduate students.

Materials and procedure:

Stimuli consisted of pairs of black and white coloured pictures of manipulable objects taken from arrays of 4 manipulable objects each. There were 12 arrays for a total of 48 stimuli. Each array comprised: a Target Stimulus (*TR*) a Manipulability Distractor (*MD*: an object which is manipulated in the same way), or a Visual Distractor (*VD*: an object which is visually similar to the target stimulus but is manipulated in a completely different way) and an Unrelated Distractor (*UD*: a manipulable object which is completely unrelated to the target stimulus). Examples of stimulus couples are given in Fig.1; a complete list of the stimuli and arrays used is given in appendix C.

Each stimulus from an array was paired with every other stimulus from the same array in all the possible combinations. Therefore there were 6 possible combinations for each of the arrays, the total number of stimulus pairs being 12x6=72. Each pair was presented twice during the experiment (once for each of the 2 stimuli of the pair to be requested): therefore there was a global amount of 144 trials in the task. The order of presentation of the stimuli was randomized across subjects.

However, only in half (72/144) of the trials, were *TR* stimuli present, either as a target or as a distractor. Since no predictions were formulated about the possible relations among the other types of stimuli (e.g. *VD* stimuli with *UD*, or *MD* with *VD*), the trials in which *TR* stimuli were not directly involved were considered as 'fillers'. The performance of the participants in these trials was not analyzed.

Stimulus pairs were presented in a dark room on a 19" PC screen placed at 50cm from the participants. The sequence of the events (illustrated in Fig.2) was as following: a cross was presented briefly in the middle of a blank screen for 500 ms and then the stimulus word was presented for 200 ms, immediately followed by the pair of stimuli to choose between. The

stimulus display was presented for 400 ms, followed by a 500 ms blank screen. Subjects had to identify the target stimulus in the display by pressing one of two appropriately labeled keys on the keyboard of the computer within the time window defined by the stimulus display presentation and the following blank screen, for a total maximum response time of 900 ms. The stimulus display was presented for 400 ms, followed by a 500 ms blank screen. Subjects had to identify the target stimulus in the display by pressing one of two appropriately labelled keys on the keyboard of the computer within the time window defined by the stimulus display presentation and the following blank screen, for a total maximum response time of 900 ms. The time window was therefore very short and much shorter than that used in the experiments presented in Chapter 3.

The choice of such a quick deadline was dictated by the fact that, differently from the experiments in Chapter 3, just 2 alternatives were provided instead of 4 and therefore further time pressure needed to be put on subjects in order to force them to make some error in such an easy task. Even if very short, however, the overall time provided for answering was 900 msec, which should be sufficient to assure semantic access. Indeed, it is standardly assumed from ERP studies, that the initial retrieval of semantic information occurs after 300 msec from stimulus onset (linked to the so-called N300 wave) (see e.g. Barrett and Rugg, 1990 for ERP evindence on the timing of access to semantic memory)

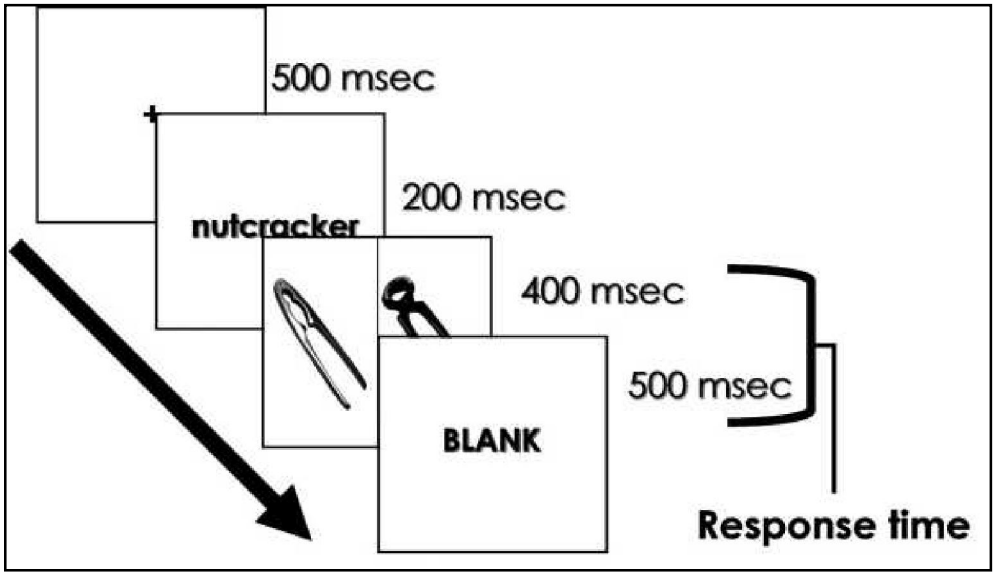


Fig.2: Event Sequence

Results:

The overall level of accuracy was high (86.74 +/- 6.13), confirming that the timing of the presentation and the time allowed for responding was sufficient to recognize the stimuli in the large majority of the cases. The average accuracy with Filler arrays was 90.07% (sd=6.50%) while for arrays in which the Target (*TR*) stimulus was present it was 83.40% (sd=6.55%); in the displays in which the target stimulus was present, subjects were significantly lower in accuracy than in the filler displays (Wilcoxon matched pairs test: $z=3.92$; $p<0.0001$).

To check whether there were differences in accuracy in the arrays in which different distractors were paired with the Target stimuli *(TR)*, a Friedman ANOVA was performed. Then a series of Wilcoxon matched pairs test was used to perform post-hoc comparisons and compare the accuracy obtained by the subjects when the target stimulus was paired with the three types of distractors. Therefore the accuracy obtained with Manipulability Distractor pairs was compared with that obtained with Visual Distractor and Unrelated Distractor pairs. Bonferroni corrections for multiple comparisons were used, setting the significance threshold at $p=0.05/3=0.017$. The Friedman ANOVA showed highly significant differences in the accuracy of subjects in the three conditions (Chi Square $_{(n=20,\ df=2)} = 34.78$; $p<0.0001$). Post hoc comparisons moreover revealed that for Unrelated Distractor pairs, the accuracy level (which was almost at ceiling: 94.79%; sd=6.32%), was significantly higher than for either Manipulability Distractor or Visual Distractor pairs (Wilcoxon matched pairs test: $z=3.92$; $p<0.0001$ and $z=3.72$; $p<0.001$ respectively). Critically, however, for Manipulability Distractor pairs the accuracy of the subjects was much lower (72.5%; sd=7.58), than for Visual Distractor pairs (82.92%; sd=10.37%) (see Fig.3). This difference was significant (Wilcoxon matched pairs test: $z=2.94$; $p<0.01$).

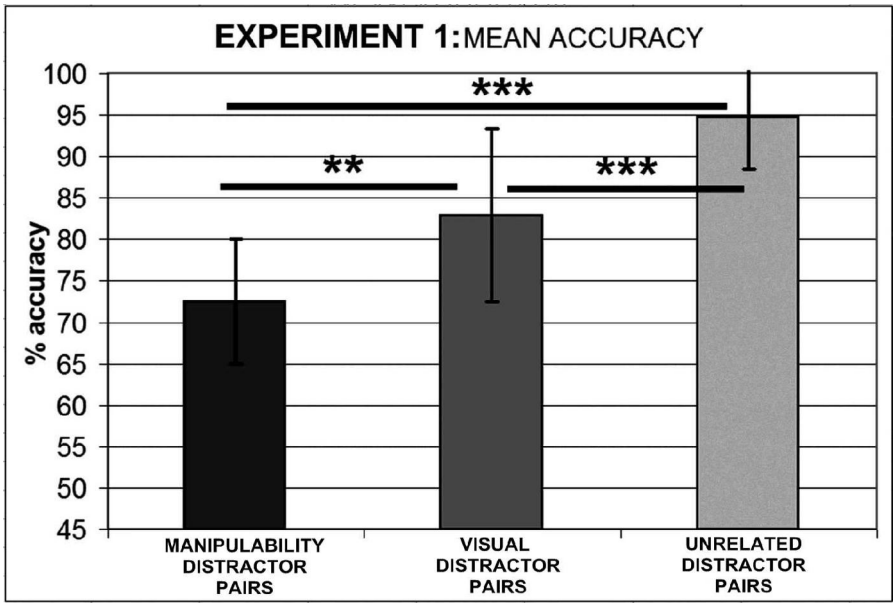


Fig.3: In the presence of a Manipulability Distractor (MD), the accuracy with the Target stimulus (TR) is significantly lower than in the presence of either a Visual (VD) or Unrelated (UD) Distractor. **= $p<0.01$; ***= $p<0.001$

Responses outside the deadline of 900 ms were rare. An average number of 1.60/72 answers per subject (2.22%) occurred after the deadline. The distribution of the responses outside the deadline across conditions was as follows: for Manipulability Distractor pairs there was an average of 0.95/24 (3.96%) of answers outside the deadline. For Visual Distractor pairs these were 0.60/24 (2.50%), while only 0.05/24 (0.21%) of the answers were provided outside the deadline in the Unrelated Distractor condition. A Friedman ANOVA revealed that the number of responses outside the deadline differed across the three conditions (Chi Square $_{(n=20,\ df=2)}$ = 15.51; $p<0.001$). However, the number of responses outside the deadline did not differ between Manipulability Distractor and Visual Distractor pairs (Wilcoxon matched pairs test: $z=1.60$; $p=0.11$), while this difference was significant for both condition only if compared to the Unrelated Distractor condition (Wilcoxon matched pairs test: Manipulability Distractor/Unrelated Distractor $z=3.06$; $p=0.002$; Visual Distractor/Unrelated Distractor $z=2.52$; $p=0.011$). Bonferroni corrections for multiple comparisons were adopted, setting the significance threshold at $p=0.05/3=0.017$.

Significant differences were found also in general in the speed of responding across the three types of pair (Friedman ANOVA: Chi Square $_{(n=20,\ df=2)}$ = 30.40; $p<0.0001$).

Reaction times did not however differ between Manipulability Distractor and Unrelated Distractor conditions (Wilcoxon matched pairs test: $z=1.19$; $p=0.232$), showing that subjects were equally fast in reaching a decision in both conditions. Again in both conditions subjects were slower with respect to the easier Unrelated Distractor condition (Wilcoxon matched pairs test: $z=3.91$; $p<0.0001$ for both comparisons. Bonferroni correction threshold set at $p=0.017$).

Further Analyses:

These results seem to suggest that the way an object is manipulated might influence its recognition. However, in order to exclude possible alternative explanations of the results obtained, a series of control analyses was performed.

Semantic distance effects: A first control was made to check whether a general effect of semantic distance could account for the greater difficulty in identifying Manipulability Distractor pairs. Indeed the possibility exists that objects that are manipulated in similar ways are also used in the same context. In this case an additional semantic similarity effect may have increased the difficulty of recognition of these stimuli with respect to the other two types of pair. In the 12 arrays used, 6 of the Manipulability Distractor pairs involved objects used in similar contexts (e.g. Hammer and Axe) and 6 did not (e.g. Racket and Carpet-beater) (See appendix C). Comparing the accuracy obtained by subjects in the closely related pairs (Average accuracy=72.81%, sd=12.99%) with that obtained in the distant ones (Average accuracy=72.50%, sd=10.85%), no difference of any sort was detected (Wilcoxon matched pairs test: $z=0.043$; $p=0.965$).

Visual similarity effects: Objects that are manipulated in the same way tend also to be visually similar. It is therefore in principle possible that the visual similarity of Manipulability Distractor pairs of objects was higher than that of Visual Distractor pairs making Manipulability Distractor pairs more difficult to discriminate. To control for this possibility a group of 15 extra subjects was asked to judge the visual similarity of the pairs of objects involved in the experiment on a 7-points scale (values are reported in appendix C). Only Manipulability Distractor and Visual Distractor pairs were then considered for the analysis in order to control whether significant visual similarity differences could be found. While the difference between the two types of pairs was not significant (Wilcoxon matched

pairs test: p=0.064), there was nevertheless a strong trend. Therefore it was considered appropriate to directly check whether a significant relation could be detected between the accuracy and the visual similarity of the pairs, regardless of the type of pair. A nonparametric correlation was computed, but no significant relation was found between the two variables (Spearman Rank Order Correlation: r=-0.109; p>0.05).

Word frequency effects: The stimuli used in building the arrays were also controlled for word frequency, in order to asses whether possible systematic frequency biases could account for the difference in accuracy found between Manipulability and Visual Distractors conditions. Frequency ratings were obtained from the ColFis frequency database for Italian words (Bertinetto et al., 2005). A Friedman ANOVA was conducted to compare the frequency of the Target (TR) words with that of Manipulability (MD), Visual (VD) and Unrelated (UD) distractor words. A general effect of frequency was found at this level of analysis (Friedman Anova: Chi Square $_{(n=12,\ df=3)}$ = 8.5; p=0.037). However, post hoc direct contrasts (using Wilcoxon matched pairs test) revealed that no difference in frequency was present when confronting either Target (TR) and Manipulability (MD) distractor words (z=0.561; p=0.575) or Target (TR) and Visual (VD) distractor words (z=0; p=1). The only significant difference found was between Target (TR) and Unrelated (UD) distractor words which were found to be higher in frequency (z=2.222; p=0.026).

Even if no difference in frequency was associated with either Manipulability (MD) or Visual (VD) distractor words, the possibility still exists that subjects tended to perform worse in those arrays in which the mean frequency of the words used was lower. To control for this possibility, the average frequency of each pair of stimuli (Target words + Manipulability or Visual Distractors) was computed and correlated with the average accuracy for that pair, regardless of the type of pair. No significant correlation was found (Spearman Rank Order Correlation: r=0.29, p=0.185), suggesting that any potential difference in frequency cannot account for the results found.

Discussion:

The results of this experiment show that under strong time pressure, subjects showed some degree of difficulty in recognizing target stimuli when they were paired with distractors sharing some similarity with them (Manipulability Distractors *MD* or Visual

Distractors *VD*). The degree of accuracy achieved by subjects in the easier condition (when the target stimulus was paired with the Unrelated Distractor, *UD*), was the same as that obtained by subjects in the easier condition of the experiments presented in Chapter 3, suggesting therefore that, even with a very strict deadline, subjects had enough time to achieve full semantic access in the easier condition.

On the other hand, the number of errors was significantly higher in the presence of a Manipulability Distractor (*MD*) than it was in the presence of a Visual Distractor. Different control analyses showed that neither contextual interference nor differences in the degree of visual similarity between pairs of stimuli, or possible differences in the frequency of the words used for each pair of stimuli could account for the results obtained.

The results suggest therefore that the way an object is manipulated plays an important role in the recognition of the object. What still remains unclear at this stage is, however, the *nature* of this interference: is it occurring at a pre-semantic level (e.g. a more perceptual level such as that of structural description) or is the manipulability of an object a feature linked to the meaning of the object itself being therefore a semantic dimension of the object?

The effect found resembles the typical semantic distance effect found in refractory semantic access impaired patients, suggesting therefore that the way an object is manipulated might be a semantic dimension. However, as already anticipated in the introduction, the semantic distance effects have also been found in patients showing access problems but without clear signs of refractoriness (Warrington and Leff, 2000; Gotts et al., 2002 see also Chapter 2). In these cases the deficit was attributed to an interference occurring at a pre- or post-semantic stage, but in any case *outside* the semantic system, while all the semantic access syndromes consistently attributed to a deficit *within* the semantic system itself have been found to show refractory characteristics (sensitivity to 'temporal factors').

As was said in the Introduction, one characteristic of refractory semantic access disorders is the deterioration of the performance over time in word-to-picture matching tasks in which repeated presentation of the same stimulus using the same set of semantically related items (negative serial position effect) occurs. In Experiment 2 we

investigated if the manipulability effect found could be replicated and also if this effect shows refractory characteristics under the appropriate circumstances.

4.2.2 Experiment 2:

Participants:

20 participants took part in this experiment (13 females, 7 males). All subjects had normal or corrected to normal vision. The mean age was 24.5 (range of 20 to 29). All participants were university or graduate students.

Materials and procedure:

The same stimuli as in Experiment 1 were also used in this second experiment. Stimuli consisted of pairs of black and white coloured pictures of manipulable objects, presented in a dark room on a 19" PC screen placed at about 50cm from the participants. The same 12 arrays (see appendix C) of 4 manipulable objects used in experiment1 (48 stimuli in total) were used in this second experiment: a Target Stimulus (*TR*) was paired with either a Manipulability Distractor (*MD***)** or a Visual Distractor (*VD***)**, or an Unrelated Distractor (*UD***)** (see appendix C). Stimuli were arranged according to same criteria used in experiment1: each stimulus from an array was paired with every other from the same array in all the possible combinations for a total amount of 144 trials. However, in this second experiment each stimulus was presented three times to assess possible serial position effects. Hence, the total amount of trials in the experiment was: 144x3=432**.** As in experiment1, only in half (216) of the trials however, *TR* stimuli were present, either as a target or as a distractor. Since no predictions were formulated about the possible relations among the other types of stimuli (e.g. *VD* stimuli with *UD*, or *MD* with *VD*), the trials in which *TR* stimuli were not directly involved were considered as 'fillers'. The performance of the participants in these trials was not analyzed.

Stimuli were presented in a pseudo-random order with the following criteria: the same array of four stimuli was presented to the subjects coupling every stimulus with every other from the same array in all the possible combinations of pair displays. After every trial was presented once, the same stimuli within the same array were represented (in the same order), until each stimulus was presented 3 times. After 3 presentations, the array of stimuli

was changed with the following one. The same randomization criteria were applied to all the 12 arrays.

The sequence and timing of the events for each trial were the same as in the previous experiment (see Fig.2). Subjects were therefore asked to identify the briefly presented word among the two stimuli presented on the computer screen by pressing one of two keys on the keyboard.

Serial Position effect computation:

To assess whether there were possible serial position effects, Page's test (1963) for ordered alternatives was adopted (see Siegel and Castellan, 1988) in order to test whether the number of errors tends to increase with repeated presentations of the items. We therefore compared for each subject, the average accuracy obtained in the first presentation of the items with the second and the third, for each type of pair display. Predictions about the trends in the accuracy of subjects across trials differed in the two critical conditions. If, as has been argued, the manipulability effect arises from interference at the semantic level, then refractoriness would be expected to arise with repeated presentations of the same pair of stimuli and so accuracy should decrease across presentations. If any interference effect is due to extra non-semantic perceptual effect, as for the visual distractors, then there is no reason for accuracy to decline and instead it is likely to increase across trial following a learning curve.

Results:

The overall level of accuracy (target + filler displays) was high (85.86%; sd=6.05%). Average accuracy with the filler displays was 89.65% (sd=5.92%), while average accuracy in the displays in which the target stimulus was present was 82.08% (sd=6.51%). In the displays in which the target was present, subjects were significantly less accurate than in the filler displays (Wilcoxon matched pairs test: $z=3.92$; $p<0.0001$).

As in Experiment 1, to check whether differences in accuracy could be found in the arrays in which a Target (*TR*) stimulus was present and paired with different distractors, a Friedman ANOVA was performed first and then, a series of Wilcoxon matched pairs test was used to perform post-hoc comparisons on the accuracy obtained by the subjects in the arrays in which a Target stimulus was paired with a Manipulability Distractor (Manipulability Distractor pairs), with the accuracy obtained in the arrays in which a Target

stimulus was paired with a either a Visual Distractor (Visual Distractor pairs) or an Unrelated Distractor (Unrelated Distractor pairs). Bonferroni correction for multiple comparisons was adopted, setting the significance threshold at p=0.05/3=0.017.

The Friedman ANOVA revealed largely significant differences in the accuracy of subjects in the three conditions (Chi Square $_{(n=20,\ df=2)}$ = 32.5; p<0.0001). Post hoc comparisons moreover confirmed that in this second experiment a clear replication of the main manipulability interference effect was obtained (see Fig.4). For *Unrelated Distractor* pairs, the accuracy was close to ceiling (93.40%; sd= 4.39%). In both the other conditions, instead, the accuracy of the subjects was significantly lower (Wilcoxon matched pairs test: z=3.92; p<0.0001 for *Manipulability Distractor* pairs and z=3.92; p<0.0001 for *Visual Distractor* pairs). Critically however, the accuracy of subjects for *Manipulability Distractor* pairs was also significantly lower (73.32%; sd= 9.40%) than that for *Visual Distractor* pairs (79.44%; sd=9.10%), (Wilcoxon matched pairs test: z=3.06; p<0.01).

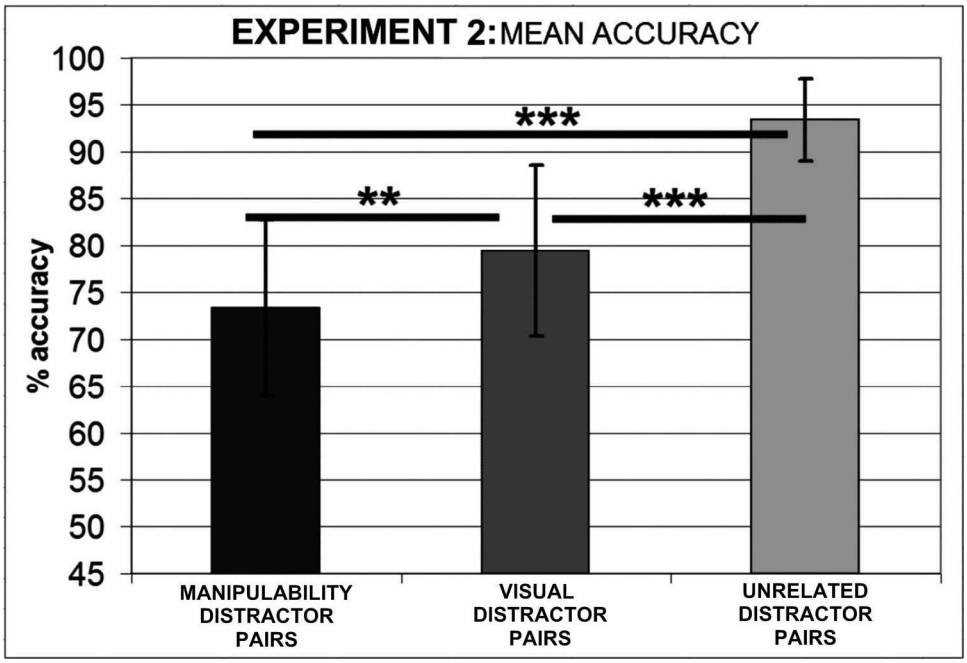


Fig.4: The main manipulability interference effect is clearly also replicated in Experiment 2. **= p<0.01; ***= p<0.001

In the reaction times analysis, responses outside the deadline of 900 msec were rare. An average number of 5.55/216 answers per subject (2.57%) occurred after the deadline. The distribution of the responses outside the deadline across conditions was as follows: for

Manipulability Distractor pairs there was an average of 2.40/72 (3.33%) of answers provided outside the deadline For *Visual Distractor* pairs these answers were 2.55/72 (3.54%), while only 0.60/72 (0.83%) of the answers were provided outside the deadline in the *Unrelated Distractor* condition. The number of responses outside the deadline did not differ between *Manipulability Distractor* and *Visual Distractor* pairs (Wilcoxon matched pairs test: $z=0.42$; $p=0.67$), while this difference was significant for both condition compared to the *Unrelated Distractor* condition (Wilcoxon matched pairs test: *Manipulability Distractor*/*Unrelated Distractor* $z=2.98$; $p=0.003$; *Visual Distractor*/*Unrelated Distractor* $z=3.29$; $p=0.0009$). Bonferroni correction for multiple comparisons was adopted, setting the significance threshold at $p=0.05/3=0.017$. Reaction times did not differ between *Manipulability Distractor* and *Unrelated Distractor* conditions (Wilcoxon matched pairs test: $z=0.93$; $p=0.35$), showing that subjects were equally fast in reaching a decision in both conditions. Again in both conditions subjects were slower with respect to the easier *Unrelated Distractor* condition (Wilcoxon matched pairs test: $z=3.91$; $p<0.0001$ for both comparisons. Bonferroni correction threshold set at $p=0.017$).

Serial Position effect:

As predicted by the 'refractory hypothesis', with *Manipulability Distractor* pairs, subjects made an increasing number of errors (see Fig.5a) across the three presentations (Page's test: $n=20$: $L=254$; $p<0.05$) following good performance on the first trial; they showed therefore a negative serial position effect, characteristic of refractory semantic access disorders. With Visual Distractor pairs instead, the performance of the subjects showed a clear learning effect (see Fig.5b) with the number of errors decreasing across the three presentations (Page's test: $n=20$: $L=251.5$; $p<0.05$).

The two types of distractors, therefore, seem to exert an opposite influence on the accuracy of the subjects. Indeed, for the first presentation of each stimulus, the accuracy in the two conditions is at comparable levels with no significant difference (Wilcoxon matched pairs test: $z=1.370$; $p>0.05$). However for the second and third presentations of the stimulus, while the accuracy with *Visual Distractor* pairs increases, that with *Manipulability Distractor* pairs it decreases. The difference in accuracy between the two conditions is significant both for the second (Wilcoxon matched pairs test: $z=2.939$;

p<0.01) and the third (Wilcoxon matched pairs test: z=2.873; p<0.01) presentations (Bonferroni correction threshold for multiple comparisons: p=0.05/3=0.017).

For *Unrelated Distractor* pairs, as expected, the performance was close to ceiling. No particular influence was therefore expected on the recognition of the target from the presence of the unrelated distractor. No significant serial position or learning effect was found in this condition (Page's test: n=20: L=248.5; p>0.05)

As regards reaction times, subjects were found to become quicker over time in reaching a decision across the three presentations of the same stimulus in all three the conditions (Page's test: n=20: *Manipulability Distractor*: L=270; p<0.001; *Visual Distractor*: L=261; p<0.001; *Unrelated Distractor*: L=263; p<0.001).

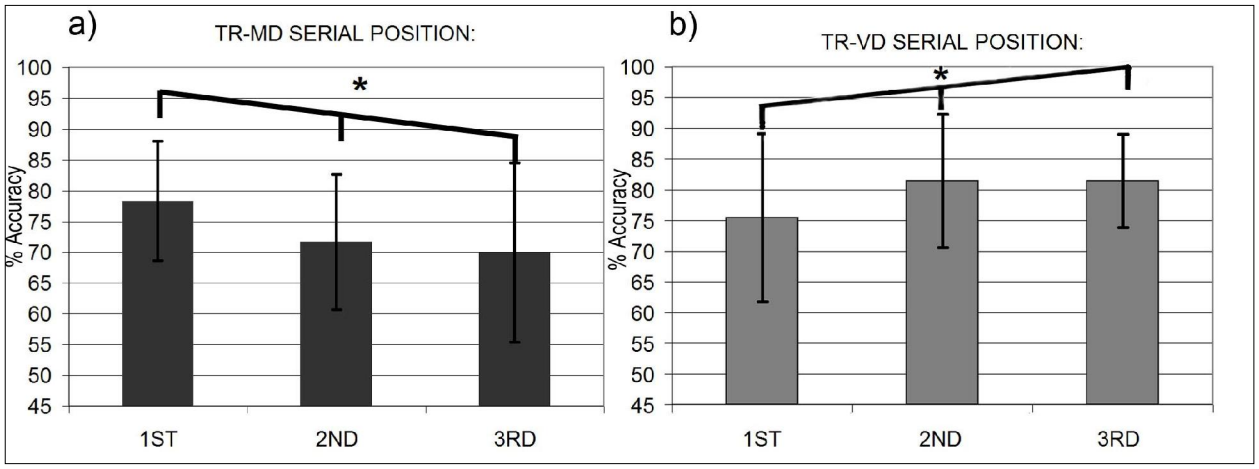


Fig.5: Experiment 2: serial position effects: a) With Manipulability Distractor pairs subjects show a clear negative serial position effect, with accuracy decreasing across trials. b) With Visual Distractor pairs the opposite effect (learning) is found, with increasing accuracy across trials. *= p<0.05

Discussion:

In this second experiment a clear replication of the general manipulability interference effect was found. Moreover we were able to show that different types of distractors have different effects over time on the accuracy in recognizing the target stimulus with repeated presentations. A distractor which is visually similar to the target tends to cause a certain amount of interference on the first trial. However, with repeated presentations of the same pair of stimuli, the visual interference decreases and the subjects learn to perform an efficient visual discrimination. Similar amounts of interference on the first trial were also

found in the presence of a manipulability distractor. However, unlike what happens with visually similar stimuli, the subjects are not only unable to learn to efficiently discriminate between the pairs over trials, but, on the contrary, they become increasingly inefficient, showing an increase in the interference effect. In the neuropsychological literature, this negative serial position effect is typically explained in terms of an interference occurring at the semantic stage. According to some classical models of semantic memory (e.g. Collins and Loftus, 1975), semantic representations are represented as semantic nodes in a network. Activation in such networks spreads partially also from the target conceptual node to neighbouring ones with an intensity which is proportional to the conceptual distance between the nodes. However, according to more recent models of semantic memory (e.g. Smith and Medin, 1981; Rumelhart et al., 1986; but also Tyler et al., 2000; Simmons and Barsalou, 2003; Rogers et al., 2004) semantic representations would be better conceived as a distributed pattern of activation of different semantic features, some of which are shared among concepts. When a concept is activated, all of its features become active and, as a consequence, concepts sharing some of those features would also be partially activated. If the resting time between repeated activations of the same pool of features is not sufficient to allow the full decay of the activation, then some degree of activation may persist in following trials for the target stimulus but also for a distractor sharing some of these features at the semantic level, causing a higher level of interference in recognition. Since the material in Experiment 2 was exactly the same used in Experiment 1, all the same possible confounding variables (contextual interference, word frequency and visual similarity) do not seem to be able to explain the current data (see Experiment1).

4.3 GENERAL DISCUSSION

4.3.1 Contrasting serial position effects for semantic and non-semantic features:

Although the neural pathways devoted to object recognition (occipito-temporal or "ventral") and those devoted to the processing of object-directed actions (occipito-parietal or "dorsal") have traditionally been separated (Goodale et al., 1991; Goodale and Milner, 1992), a number of different lines of research have suggested an interaction between the two systems (e.g. Tucker and Ellis, 1998; Creem and Proffitt, 2001). In particular a number

of studies suggest that the way an object is actually manipulated influences its recognition (e.g. Helbig et al., 2006) and some suggest that this information is part of the semantic representation of the object per se (Warrington and McCarthy, 1983; 1987; Warrington and Shallice, 1984; Saffran and Schwartz, 1994).

The aim of the present study was to investigate, at a behavioural level, if such an interaction exists by assessing whether the manipulability of an object could influence the identification of the object itself but to assess also whether manipulability is a feature which is part of the semantic representation of the object. The neuropsychological literature suggested a number of variables which are useful to detect deficits involving concepts and features within the semantic system and to distinguish between access and degradation problems (e.g. Warrington and Cipolotti, 1996). Of particular interest for the aims of this study were the semantic distance and the serial position effects. Patients with problems in accessing semantic representations are very sensitive to the semantic distance between the target stimulus and the distractors presented, showing a better performance with unrelated stimuli. Critically, repeated presentations of the same set of target stimuli leads to a progressive deterioration in their performance. These effects are commonly explained in terms of abnormal refractoriness persisting between repeatedly activated representations sharing semantic features (e.g. Gotts and Plaut, 2002). These two variables seem therefore to tap processes involving semantic representations and features directly (see also Chapter 3).

Both experiments 1 and 2 involved a word-to-picture matching task conducted by means of a speeded deadline response procedure. In Experiment 1 it was found that the presence of objects sharing a common manipulation with a target object interfere significantly with its identification. This interference is stronger than that produced by two objects that only share visual similarity. A series of control analyses ruled out the possibility that the visual similarity or the frequency of the words used could have any significant effect on the accuracy of the subjects.

The one described resembles the classical semantic distance effect found in semantic access dysphasic patients (but also in healthy subjects: see e.g. Chapter 3), which suggests that manipulability is a semantic relatedness dimension. However, a general 'contextual' semantic distance effect seems insufficient to explain the results found, since

the accuracy of the subjects was also comparably low with those pairs of stimuli in which the Target stimulus and the Manipulability Distractor are used in different contexts. The 'semantic distance' effect described here seems therefore to be caused by the influence of a more specific type of semantic feature: the shared manipulation.

However, as already discussed in the Introduction, semantic relatedness effects have also been found to occur as a result of damage occurring outside the semantic system (Warrington and Leff, 2000; Gotts et al., 2002; Crutch and Warrington, 2005; see also Chapter 2). Since, however, negative serial position effects have been consistently found in patients showing refractory semantic access disorders, in which the interference is held to occur *within* the semantic system itself (e.g. Warrington and Cipolotti, 1996; Gotts and Plaut, 2002), it was investigated in Experiment 2 whether a negative serial position effects also emerges with repeated presentations of the pairs of stimuli sharing a similar manipulation. The results of the experiment were that, while the repeated presentation of objects sharing only visual similarity creates a 'positive' serial position effect (learning effect), the repeated presentation of objects sharing a similar manipulation creates a clear opposite negative serial position effect.

Taken together these results suggest something more than a simple interaction between the action-related and the recognition systems. Such interaction has already been proposed both in the direction of an influence of the recognition in directing an action toward the object (e.g. Tucker and Ellis, 1998; Ellis and Tucker, 2000) but also in the opposite direction of an influence of the manipulation information on the recognition of an object (e.g. Creem and Proffitt, 2001; Helbig et al., 2006).

These results not only confirm this link but may shed further light on the nature of such interplay. Indeed, it has been suggested that the presence of a serial position effect in a word-to-picture matching task is sign of a refractory process taking place between features that are shared by semantically related concepts (cfr. Warrington and McCarthy, 1983; Forde and Humphreys, 1995; Jefferies and Lambon Ralph, 2006; Schnur et al., 2006). In all refractory semantic access syndromes reported in the neuropsychological literature, the semantic system itself appears indeed to be the locus of the refractory behaviour (Warrington and Cipolotti, 1996; Gotts and Plaut, 2002). Refractory phenomena in accessing concepts have been explained in terms of a failure of semantic selection

mechanisms, which are unable to resolve the competition arising between semantically related co-activated representations (e.g. Jefferies et al., 2007). On the other hand, according to Gotts and Plaut (2002) the phenomenon is explained in terms of an abnormal persistence of physiological neural refractory states (synaptic depression) which occurs after repeated activation of the same pool of synapses (Hasselmo and Bower, 1992; Tsodyks and Markram, 1997). Some of this abnormal synaptic depression is held to spread from the target concept also to semantically neighbouring concepts sharing some of its features, which then have temporarily raised activation thresholds. In healthy subjects too, if stimuli are repeated in a very narrow time window, refractory effects can be found in tasks similar to those used with patients (e.g. Chapter 3).

Regardless of the account, refractory states in neuropsychological literature are always thought to occur at the semantic level, involving semantic representations themselves. What is suggested here therefore is that the way an object is manipulated is indeed a semantic feature, and that this feature is important for identifying manipulable objects. The fact that the classical serial position effect was not found with objects that are just visually similar supports the idea that a 'negative' serial position effect is the sign of a semantic effect, as far as manipulable objects are concerned. It seems therefore from these findings that, for manipulable objects, the sharing of visual properties does not produce a major degree of proximity in semantic space, as it has been proposed to do for example for living things (e.g. Warrington and Shallice, 1984; Borgo and Shallice, 2001). The interference found in recognizing manipulable objects that are only visually similar fits with the similarity being at a pre-semantic perceptual level. On the other hand, it seems that an important feature in defining manipulable objects at a *semantic level* might be the way these objects are manipulated.

4.3.2 Manipulability: a re-definition

Our definition of manipulability combines two different aspects of the physical interaction with the object: the 'affordances' and the 'utilization movement' *associated with the proper use* of the object, which is something that has to be learned.

Affordances, in the original definition made by Gibson (1979) are all "action possibilities" latent in the environment, independent of the individual's ability to recognize them. In the following years the term shifted its meaning referring more specifically to just those action possibilities which are readily perceivable and made available to an actor (Norman, 1988). Gibson was later criticized for grounding his theory of affordances only on perception and neglecting the process of cognition. For instance, Lakoff (1987 p.216) claims that "the Gibsonian environment is not the kind of world-as-experienced that is needed in order to account for the facts of categorization".

The concept of manipulability we propose is more linked to this later "experience-related" definition of affordances. Indeed, if it is true that an object automatically affords a certain number of actions on it, these action possibilities that are readily perceivable by the actor are not always necessarily linked to the *proper* use of the same object (see the work by Creem and Proffitt, 2001 described in the Introduction to this chapter). This means that, while the concept of affordance grasps of course an important 'perceptual' aspect of the properties of an object, it is not sufficient to explain, alone, how we build the knowledge of the appropriate manipulation of an object. We think this difference is critically linked to the building of a *semantic* representation of manipulable objects.

From this perspective, the affordances would of course be important in building the representation of the object, however also (and maybe more) crucial is the role of the *movement associated with the proper use* of the object, and this latter aspect is not necessarily triggered by the affordances alone; it is rather more likely to be built with experience. A crucial example to explain the distinction between affordance and this *'utilisation movement'* is that of the *syringe*. A syringe affords a type of grasping movement that is similar to that of grasping a stick. However, the action which is most appropriate to use it (and which therefore has to be learned) is very different. This action appears to be unique, not being shared with any other similar object. The more distinctive the movement, the easier is the identification of the object will be, since fewer objects will be manipulated in the same way.

Hence, our definition of manipulability of an object comprises both aspects of the physical interaction with the object (perceptual affordances and utilization movement) with

the latter, however, being more crucially linked to the building of a *semantic* representation of the object in that it is learned by experience.

It has been proposed (Allport, 1985) that knowledge about concepts might be distributed across the brain areas that are active at the time of encoding. In the case of manipulable objects, these cortical regions should be the ones that are dedicated to encode the movement needed to interact in the appropriate way with the object. In this perspective, during the first interactions with a new object, the affordances of the object might be critical, triggering automatic motor approaches to grasp the object. However these automatic grasping schemas are not always necessarily inked to the *proper use* of the object (cfr also Creem and Proffitt, 2001).

Thus, at a semantic level of definition, the manipulability of an object could be conceived as the semantic counterpart of the concept of "affordance". Thus, when we see a manipulable object, the precise way an object is manipulated is something that is more related to processes of learning with experience. These results seem therefore to favour those models of semantic memory conceiving the semantic system as organized at least partially around features that are differentially relevant for different concepts (e.g. Warrington and Shallice, 1984; Warrington and McCarthy, 1987; De Renzi and Lucchelli, 1994; Tyler and Moss, 2001; Mahon et al., 2007); for manipulable objects a very relevant type of semantic information (or feature) seems indeed to be the way the object is manipulated. This information is built in time through repetitive interactions between the action-related neural systems and the memory systems.

This account is not in principle in contradiction with some other distributed models of semantic memory such as those of Tyler and colleagues (Tyler et al., 2000; Tyler and Moss, 2001) or Caramazza and colleagues (Caramazza et al., 1990). These models conceive the semantic system as internally structured: the semantic space becomes 'lumpy' because of 'privileged' correlation between particular features for different classes of concepts (such as 'form' and 'function' for manipulable objects; see also De Renzi and Lucchelli, 1994). The main difference between these latter accounts and the earlier Sensory-Functional account (Warrington and McCarthy, 1983; 1987; Warrington and Shallice, 1984) is that the former do not postulate any anatomical differentiation within sub-systems in the semantic memory, while the Sensory-Functional account hypothesize that the regions

processing different semantic features are not just functionally specialized but also anatomically segregated. However these data do not speak directly in favour of either of these accounts with respect of this particular issue and further investigation would of course be needed.

CHAPTER 5:

5.1 INTRODUCTION:

In the first part of last chapter (Chapter 4), we drove the attention on a peculiar 'coincidence': among the first patients described as suffering from a semantic access deficit, patients VER and YOT (Warrington and McCarthy, 1983; 1987) were also the first patients described as reporting a category-specific impairment of their semantic representations. These patients were found to be selectively impaired with regards to the only category of nonliving things. Both VER and YOT were moreover suffering from vascular accidents causing damage to the left temporo-parietal and fronto-parietal areas.

The second part of this 'coincidence' was that in the unselected group of tumour patients we described in Chapter 2 showing clear semantic access difficulties, the anatomical region of maximum overlap of the lesions was restricted to the posterior-superior portions of the left temporal lobe. Moreover, the material used in preparing the semantic access tasks was restricted to the only category of small manipulable objects.

It is in principle possible, however, that this was a mere coincidence, since the behaviour of the same patients with other categories of concepts was not tested and moreover the Temporo-Parietal Junction (TPJ) is an heteromodal association area whose functions have been associated with a wide range of cognitive processes rangin from semantics (e.g. Binder et al., 2009) to lexical speech processing (e.g. Scott and Johnsrude, 2003) to attentional processing (e.g. Parker et al., 2005; Peers et al., 2005).

However, in Chapter 4 we showed how the way an object is manipulated might really be a defining semantic feature for manipulable objects, since the repeated, speeded presentation of pairs of stimuli sharing similar manipulation, produces a refractory behaviour in healthy subjects leading to a declining serial position effect which is typical also of the behaviour of semantic access patients. While these findings supported a series of semantic memory models assuming semantic representations to be better conceived as a distributed pattern of activation of semantic features differentially weighted according to the relevance and distinctiveness for the concept (e.g. Warrington and McCarthy, 1983; 1987; Warrington and Shallice, 1984; Tyler et al., 2000; Simmons and Barsalou, 2003), the data, however, did not disentangle the question as to whether these features should be

conceived as homogeneously distributed into an undifferentiated semantic space or, if they are, on the contrary, organised at least partially according to modality-specific segregated anatomical regions.

Starting form these suggestions, in Chapter 5 we aimed to formally investigate the link between manipulability and semantic deficits for nonliving things. We aimed to investigate, moreover, the anatomical underpinnings of the more rarely reported phenomenon of the category specific semantic deficit for nonliving things. We investigated these issues in a second, unselected group of patients with tumours involving the left or right temporal lobes, by means of a naming task assessing the ability of the patients to name living things as well as manipulable objects selected on the basis of their degree of manipulability.

5.1.1 Category specificity and representation of manipulable objects in the brain:

The debate in cognitive neuroscience on the organisation and anatomical underpinnings of the semantic memory is still open. Semantic memory impairments have been widely associated with damage to the temporal lobes bilaterally but more prominently with respect to the left hemisphere (see e.g. Gainotti, 2000; Mummery et al., 2000; Noppeney et al., 2007). Several aetiologies have moreover been found to be likely to produce semantic impairments (see Patterson et al., 2007 for a review), ranging from degenerative syndromes such as semantic dementia (e.g. Snowden et al., 1989; Hodges et al., 1992) or Alzheimer disease (e.g. Giffard et al., 2001;Grossman et al., 2003), to herpes simplex encephalitis (e.g. Warrington and Shallice, 1984; Noppeney et al., 2007), stroke (e.g. Jefferies and Lambon Ralph, 2006) or, as in this context, brain tumours (Chapter 2).

In Chapter 2, it has been shown that tumours in the posterior portion of the left temporal lobe consistently produce difficulties in accessing concepts from verbal input. These difficulties have been interpreted as resulting from the disconnection of the lexical input from the more inferior temporal semantic areas, caused by the presence of gliomas (tumours involving the subcortical white matter). Interestingly, the material used in the study comprised stimuli belonging only to the category of small manipulable objects.

A similar type of deficit and a similar anatomical localization are found in one of the first seminal investigations about category specific semantic memory impairments.

Warrington and McCarthy (Warrington and McCarthy, 1987) described a patient (YOT) who suffered a left posterior temporal-parietal lesion following a left middle cerebral artery occlusion. As for the tumour patients described in Chapter 2, this patient also had a semantic deficit of an access rather than degradation type. YOT was also one of the first patients described as having a selective semantic deficit affecting the category of nonliving things. A similar deficit had been previously reported in only one occasion but in a patient with a different aetiology: like YOT, patient VER (Warrington and McCarthy, 1983) suffered from a semantic access impairment which selectively affected nonliving things. Her lesion involved the left frontal and parietal areas.

The selective loss of knowledge specific to one (or a few) categories of knowledge has been extensively investigated in the last 30 years but from a theoretical point of view this phenomenon still remains an open issue. The most investigated category specific effect involves the double dissociation between the selective loss of knowledge about living entities with respect to artefacts (Warrington and Shallice, 1984) and the complementary syndrome (Warrington and McCarthy, 1983; 1987). From a clinical point of view, many more cases of deficit for living things than nonliving entities have been reported in the literature (see Gainotti, 2000; Capitani et al., 2003 for reviews), in a ratio of approximately 3:1. However, in a recent investigation on the naming ability of a very large sample of patients suffering from different neurodegenerative diseases, Brambati and colleagues (2006) found a brain area which was more clearly associated with a deficit in naming nonliving things. This area was restricted to a portion of the posterior and superior parts of the left temporal lobe which was close to that reported in the study described in Chapter 2.

From a theoretical point of view, the original account proposed to explain category specific deficits (later called the Sensory Functional Theory or SFT) was that knowledge could be stored in modality congruent ‘channels’, with the relative weight of information contained in these channels varying across different concepts. The knowledge which is crucial in order to distinguish between living entities is held to rely mainly on sensory quality features (mainly visual ‘channels’: shape, colour, texture) and therefore could be primarily retained in bilateral ventral temporal brain areas (Gainotti, 2000) which process visual aspects of percepts (Goodale and Milner, 1992). On the other hand, knowledge about artefacts was originally held to rely more on functional attributes (what it is for, how it is

used) and more recently (e.g. Saffran and Schwartz, 1994) to rely more specifically upon a system controlling action, with a different anatomical substrate. This means that one's knowledge of a concrete entity would comprise both visual and functional/action attributes, but not in equal proportions for all categories of entities. Therefore the categorical dissociation effect would be a byproduct of this differential weighting of features.

In recent years, a considerable amount of evidence, coming mainly from fMRI studies, has been accumulated suggesting that there are brain areas that selectively respond to a variety of tasks in which the recognition or semantic processing of manipulable objects is required (Chao and Martin, 2000; Kellenbach et al., 2003; Martin, 2007; Weisberg et al., 2007; Canessa et al., 2008). These areas constitute a complex left hemisphere lateralized network including the middle temporal areas, the inferior parietal lobe (IPL) and the intraparietal sulcus (IPS), as well as premotor areas. Many of these areas are indeed part of the cortical circuit which is responsible for the processing of action related information and for visuomotor interaction: the so called "dorsal" or "where" pathway (Goodale et al., 1991; Goodale and Milner, 1992; Culham and Valyear, 2006). The dorsal pathway comprises several cortical areas, including the medial temporal area (MT or V5), the medial superior temporal area (MST), and the ventral and lateral intraparietal areas (VIP and LIP). It has, however, been suggested that the activation of at least some the areas involved in this 'manipulable object processing' complex left hemisphere circuit (in particular pre-motor areas) may also reflect a post-semantic activation more linked to explicit imagery processes, rather than reflecting access to stored knowledge about the concept (e.g. Harris et al., 2008; Papeo et al., 2009).

The main argument against the sensory/functional account has been that some patients exhibiting category specific losses of knowledge did not show a concomitant selective loss of perceptual or functional knowledge, the loss of the two types of knowledge being comparable (Caramazza and Shelton, 1998; Lambon Ralph et al., 1998). However, while there has been overall agreement on how to define "perceptual" features, the common definition of a "functional feature" has been much broader and less well defined. It has even ranged from strictly functional and motor related aspects (how it is manipulated) to more contextual aspects (where it is found). Indeed, Caramazza and Shelton (1998), when testing the semantic competence of their patient EW, just divided the features to be tested

into Visual/Perceptual and Associative/Functional, conflating action and function-related information with more encyclopaedic information. Moreover they conflated all inanimate entities together as 'nonliving things'. This conflation in the criteria for functional features can lead to the use of a category of "nonliving things" which, from the perspective of the Sensory Functional Theory, encompasses too many heterogeneous categories of inanimate objects such as manipulable as well as non-manipulable objects as well as buildings, vehicles and so on.

A second theoretical account which has been proposed to explain the phenomenon is that knowledge could actually be organized in the brain on a purely categorical base (Caramazza and Shelton, 1998): categories of knowledge developed under evolutionary pressure so as to represent animals, artifacts and plant life separately for adaptive reasons. A problem with this account is that very few patients have been reported showing animal-specific deficits and no clear anatomical localization of the deficit has been provided.

In more recent years, an alternative to the categorical and to the feature-related organization positions has become popular, namely that categories of knowledge can be conceived as an emergent property of the structure of semantic memory based on the distinctiveness and correlation between features. The features defining a concept are conceived as distributed in a semantic network which is undifferentiated from the point of view of different features within the temporal lobes (Tyler and Moss, 2001) rather than emerging from a semantic system organized architectonically in terms of categories or type of features. The only anatomical differentiation is held to occur following a postero-anterior gradient within the temporal lobes when processing objects at different levels of specificity (Tyler et al., 2004), with anterior regions responsible for the processing of basic-level exemplars and posterior regions devoted to process concepts at a more general categorical level. A key prediction from this account is that no anatomical difference should be related to the different types of category specific semantic deficits.

5.1.2 Specifying the concept of manipulability

Taking into account also the more recent findings from neuropsychology and neuroimaging and the consideration that the stimuli used in the study described in Chapter 2 in which semantic problems have been consistently found in posterior temporal tumour

patients, were manipulable objects, we aimed to shed further light on the organization of the semantic system by testing the naming abilities of a group of patients affected by tumours in the left or right temporal lobes. A naming task was used, as naming tasks are relatively quick and easy to administer and more importantly they are sufficiently difficult to be sensitive to even small semantic difficulties and so are more likely to allow a proper comparison with a control group since this will be less prone to perform at ceiling.

The naming task we designed consisted of both living and nonliving things. However, we restricted the category of nonliving things to manipulable objects only and graded the stimuli according to their degree of manipulability. We have given an extensive definition of Manipulability in the General Discussion of Chapter 4. To briefly summarize it, our definition of manipulability combines two different aspects of the physical interaction with the object: the 'affordances' and the 'utilization movement' *associated with the proper use* of the object, which is something that has to be learned.

A crucial example to explain the distinction between affordance and this *'utilisation movement'* is that of the *syringe*. A syringe affords a type of grasping movement that is similar to that of grasping a stick. However, the action which is most appropriate to use it (and which therefore has to be learned) is very different. This action appears to be unique, not being shared with any other similar object. The more distinctive the movement, the easier is the identification of the object will be, since fewer objects will be manipulated in the same way: these objects are, in our definition, *highly manipulable objects.* Hence, our definition of manipulability of an object comprises both aspects of the physical interaction with the object (perceptual affordances and utilization movement) with the latter, however, being more crucially linked to the building of a *semantic* representation of the object in that it is learned by experience. This definition of manipulability is similar to that given in a paper by Magnie and colleagues: 'the capacity of an object to evoke an action that *unambiguously allows it [the object] to be recognized'* (Magnie et al., 2003, p.524) .

It has indeed been proposed (Allport, 1985) that knowledge about concepts might be distributed across all the areas that are active at the time of encoding. In the case of manipulable objects, these areas should include the ones that are dedicated to encode the movement needed to interact with it in the appropriate way. In this perspective, the

semantic representation of highly manipulable objects might rely more on features processed in action-related areas in the "dorsal pathway".

When the manipulability of the object is, on the contrary, *weak*, the object will not have a specific, distinctive way of being manipulated and may afford different grasping, none of them being distinctive. It is therefore possible that such weakly manipulable objects will rely more on perceptual properties for identification than highly manipulable objects do and be processed more in bilateral inferior temporal areas (following the ventral pathway) together with most of the living entities which heavily rely on these features.

If categories within the semantic system are an emergent property of the differential weighting of sensory and motor attributes, then we predict that possible category specific deficits for nonliving entities should be more likely to occur to patients with lesions involving action-related areas in the "dorsal pathway", such as the left posterior middle temporal as well as inferior parietal areas. Category specific deficits for living things would instead be linked to damage to bilateral inferior temporal areas. A second prediction is that patients showing selective difficulties with nonliving entities should experience particular difficulty with the more highly manipulable objects. In contrast, patients with category specific deficits for living things should also experience some difficulty with some nonliving objects, but *only* with weakly manipulable ones.

We tested these predictions in an unselected series of 30 patients suffering from brain tumours involving either the left or the right temporal (or temporo-parietal) areas. Since all the patients were tested in the days around the operation for the removal of the tumour, the time available for testing the patients was restricted. Patients were available for one testing session of two hours before the surgery and one such session after. Therefore, the assessment of their semantic skills was limited to the only naming task developed. Their performance was compared with that of a control group of 20 healthy subjects matched for age and education. In addition, the task was also administered to a patient with widespread bilateral inferior temporal cortical damage (MU) who suffered from herpes simplex encephalitis (HSE), and who in previous investigations (Borgo and Shallice, 2001; 2003) showed clear category specific semantic impairment for living entities. From our predictions, we expect MU also to show some difficulty in naming weakly manipulable objects.

To try to localize which areas of the brain might then be more likely to be linked to any possible category specific effect, a Voxel-Based Lesion-Symptom Mapping (VLSM) procedure (Bates et al., 2003; Rorden et al., 2007) was also adopted to relate the behavioural finding to a more specific lesion site. With this technique, it is possible to correlate the score obtained in a given neuropsychological test to each voxel of the reconstructed lesion of a patient and, by means of a statistical voxel by voxel confrontation of the lesions of each patient, it is possible to test which voxels are correlated with a larger effect on the relevant cognitive dimension. The importance of the VLSM analysis lies in the fact that no a-priori anatomical assumption is made in grouping the patients.

5.2 METHODS:

5.2.1 Subjects:

Tumour patients group:

This study involved a consecutive series of 30 patients with a tumour located within the temporal lobes. Most of the tumours (n=24) were either high (n=10) or low (n=14) grade gliomas. The selection of the patients followed a clinical criterion: regardless of their cognitive level or neuropsychological picture, patients were selected on the basis the presence of a tumour within the left or the right temporal lobe. The study was approved by the ethical committee of SISSA-ISAS (International School for Advanced Studies, Trieste). 20 patients had a left and 10 a right hemisphere lesion. Left hemisphere patients were further subdivided into an anterior and a posterior temporal group. A patient was considered as ‘posterior’, if his/her lesion directly involved the posterior portions of the left temporal lobe or also the inferior parietal lobe. All other left temporal patients were considered as ‘anterior’. There were 11 left anterior temporal and 9 left posterior temporal patients (see supplementary Fig.1 for the overlap of lesion sites of the three groups).

Patients were available for testing in two sessions, one usually the day before the surgery and the second from 3 to 6 days after the operation. Due to the strict time constrains for testing patients only a brief neuropsychological assessment was administered in order to monitor the broad perceptual, linguistic and attentive skills. Some of the patients, especially after the operation, had limited availability and were able to sustain only brief testing

sessions. Therefore, for a few of the patients only the experimental naming task was administered.

Demographic as well as baseline neuropsychological information is summarized in Table 1. All the patients (with the exception of patient LA5) were tested prior to the surgical removal of the mass, 26 of them being also available for retesting after surgery (except patients LA4, RH3, RH4, RH5).

Control patient MU:

To check whether the naming tasks developed could potentially provide evidence also on the presence of category specific deficits in naming living entities, we also administered the naming task to a patient who in previous investigations found a stable category specific semantic deficit for living things. Patient MU suffered form herpes simplex encephalitis. His semantic memory skills were gravely degraded after his illness. For further details on his neuropsychological profile see Borgo and Shallice (2001; 2003)

Healthy control sample:

The performance of the patients in the experimental tasks was compared with that of a group of 20 control subjects divided into two age groups (below and above 50 years of age) and two education groups (below and above 12 years of schooling). Age and education cut-offs were determined on the basis of the demographic characteristics of the group of patients described in Chapter 2. Thus, the performance of four subgroups of five subjects each could be compared with that of each tumour patient matched for age and education at the single case level of analysis. At the group level however, all control subjects were collapsed into a group of 20 subjects.

The mean age for the patient group was 46.42 (+/- 12.1 SD) and for the control group it was 45.65 (+/- 19.40 SD). The mean age for the right temporal group was 51.20 (+/- 10.56 SD), for the left anterior temporal group it was 42.55 (+/- 11.76 SD) and for the left posterior temporal group was 50 (+/- 14.35 SD).No significant age difference was found between the three groups of patients and the controls (Kruskal-Wallis ANOVA $_{(H=3, N=50)}$=2.22; p=0.53). The mean years of education for the patient groups was 10.9 years (+/- 4.11 SD); for control group it was 12.94 (+/- 4.52 SD). The mean education for the right temporal group was 11.20 (+/- 4.32 SD), for the left anterior temporal group it was 11.73 (+/- 3.98 SD) and for the left posterior temporal group was 8.78 (+/- 3.80 SD). No

significant education difference was found between the three groups of patients and the controls (Kruskal-Wallis ANOVA $_{(H=3, N=50)}$=3.92; p=0.27).

The distribution of accuracy scores for the control group did not differ from normal (Shapiro-Wilks test: W=0.974; p=0.836). The average naming level of the control sample was 92.62% (SD= +/- 3.60%). Scores were considered to be pathological when below 1.96 SD from the mean (α=0.05 2-tailed). Cut-off accuracy score was therefore set at 85.56%.

5.2.2 Experimental Procedure:

The task used was a computer presented naming task. The stimuli consisted of a set of 120 digital coloured pictures of real objects and animals. 60 pictures represented living things and 60 represented manipulable objects. The living things were further divided into 30 animals (both mammals and birds) and 30 vegetables (both fruit and vegetables). The nonliving things (all artefacts) were divided into 30 highly manipulable objects and 30 weakly manipulable objects.

The procedure was as following: a cross was presented in the centre of the screen for 500 ms immediately followed by the picture of the stimulus to name. The picture remained on the screen until an answer was provided or until the patient claimed he/she could not name the target stimulus. The subsequent stimulus was then presented by the experimenter (FC) pressing the spacebar on the keyboard. The same pseudo-random order of administration was used across subjects. The whole procedure was divided into two sub-sessions separated by a pause.

Picture stimuli were collected from the web. All pictures were processed with Adobe Photoshop 7.0 in order to eliminate all the background and contextual information, and were therefore presented on a white background. Pictures were sized to a dimension of 500 x 400 pixels and presented in the centre of the screen. Experimental stimuli were selected from a larger corpus of 219 pictures that later underwent selection to obtain the best balancing possible for the most common semantic confounding dimensions.

Table 1 **:** Baseline assessment and neurological data of the group of tumour patients

Patient	Age	Edu	TUMOUR TYPE	TUMOUR LOCATION	SEMANTIC FLUENCIES (1min)						BORB[(a)]						VISUAL SEARCH[(b)]	
					Animals		Objects		Proper Names		Size Match (n/30)		Foreshorten. Views (n/25)		Object Decision Easy (n/32)			
					pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
1. RH1	33	13	Meningioma	Right Ant. Tempor	21	--	**13^**	--	**22^**	--	NA	--	24	--	NA	--	49	--
2. RH2	48	17	Grd II Astrocyt	Right Frontal-Temp	32	36	26	30	29	20	26	NA	24	NA	30	NA	47	NA
3. RH3	44	8	Glioblastoma	Right Ant. Tempor	24	--	14	--	18	--	28	--	24	--	31	--	58	--
4. RH4	65	5	Glioblastoma	Right Ant. Tempor	12	--	12	--	21	--	27	--	22	--	NA	--	46	--
5. RH5	53	8	Grd II Astrocyt	Right Frontal-Temp	16	NA	13	NA	19	NA	27	27	24	23	**24***	**20***	51	42
6. RH6	65	8	Glioblastoma	Right Ant. Tempor	12	17	16	**6^**	13	13	23	24	24	25	**27***	**27***	NA	45
7. RH7	41	17	Grd II Astrocyt	Right Frontal-Temp	23	29	35	19	37	26	24	22	25	23	28	29	41	40
8. RH8	52	13	Grd II Astrocyt	Right Inf-Post Temp	17	17	16	23	**10^**	**15^**	27	25	23	23	21	21	50	NA
9. RH9	49	15	Glioblastoma	Right Post Med Tmp	24	24	17	17	24	20	22	NA	24	24	31	32	43	NA
10.RH10	62	8	Glioblastoma	Right Post Tmp-Par	29	26	21	13	22	14	26	25	25	23	**25***	30	42	NA
11.LA1	38	9	Grd II Astrocyt	Left Frontal-Temp	18	**14^**	21	**14^**	27	**15^**	NA	NA	24	25	NA	NA	40	NA
12.LA2	25	17	Grd II Astrocyt	Left Frontal-Temp	26	21	**21^**	23	**12^**	17	20	NA	17	NA	25	NA	46	NA
13.LA3	46	17	Grd II Astrocyt	Left Ant Med Temp	23	21	21	**16^**	25	22	NA	NA	25	25	NA	NA	42	48
14.LA4	48	13	Metastasys	Left Temp-Polar	19	--	21	--	28	--	29	--	23	--	29	--	NA	
15.LA5	36	17	Glioblastoma	Left Ant Med Temp	19	23	18	24	21	23	26	23	24	24	30	31	46	48
16.LA6	42	8	Dysembryogen	Left Hippocampus	24	31	20	18	33	29	27	27	24	24	30	29	46	NA
17.LA7	62	12	Grd II Astrocyt	Left Temp-Polar	22	15	32	16	45	31	28	26	21	23	31	29	53	NA
18.LA8	29	13	Grd II Astrocyt	Left Sup-Ant Temp	30	18	25	25	26	**22^**	28	28	25	24	30	32	43	44
19.LA9	34	8	Grd II Astrocyt	Left Temp-Polar	25	17	18	15	24	20	29	28	23	22	29	31	50	51
20.LA10	60	8	Gliosarcoma	Left Frontal-Temp	12	**5**	9	**2**	19	10	28	30	25	24	30	28	NA	**29***
21.LA11	48	7	Glioblastoma	Left Temp-Polar	**11^**	**4^**	**12^**	**5^**	18	**13^**	28	28	25	24	32	**27***	48	53
22.LP1	51	12	Glioblastoma	Left Sup-Post Tmp	**7^**	**10^**	**7^**	**11^**	**13^**	**14^**	30	27	25	25	29	NA	54	51
23.LP2	44	15	Meningioma	Left Post. Tempor	--	--	--	--	--	--	--	--	--	--	--	--	--	--
24.LP3	55	2	Metastasys	Left Tmp-Par+Front	--	--	--	--	--	--	--	--	--	--	--	--	--	--
25.LP4	18	12	Ependymoma	Left Occip-Temp	**14^**	--	14	--	23	--	25	--	24	--	31	--	59	57
26.LP5	64	8	Metastasys	Left Post Temp-Par	--	--	--	--	--	--	--	--	--	--	--	--	--	--
27.LP6	41	8	Grd II Astrocyt	Left Parieto-Temp	28	**8^**	23	**6^**	28	**7^**	25	26	22	25	28	31	50	40
28.LP7	58	8	Glioblastoma	Left Parieto-Temp	19	17	16	15	26	24	28	27	24	23	30	30	54	56
29.LP8	55	8	Glioblastoma	Left Sup-Post Temp	18	**4^**	NA	8	NA	12	NA	NA	23	NA	NA	NA	NA	NA
30.LP9	64	6	Grd II Astrocyt	Left Post-Tmp Insul	**4^**	**4^**	9	**2^**	14	**7^**	**21***	**22***	20	21	**18***	**16***	NA	NA

[(a)]BORB= Birmingham Object Recognition Battery (Riddoch and Humphreys, 1993); [(b)] Spinnler and Tognoni (1987)
*= below normal range; ^= below age/education matched sample (5 subjects) range; NA= not administered;

5.2.3 Balancing of the experimental material:

In order to exclude the possibility that any effect found could be explainable in terms of spurious nonsemantic variables, experimental material was balanced for the standard nonsemantic lexical and perceptual variables that can influence the naming of a stimulus (Funnell and Sheridan, 1992; Stewart et al., 1992; Albanese et al., 2000). The variables considered were word frequency, number of syllables, familiarity and visual complexity. A summary of the average values for these variables in each of the categories of interest s given in Table 2.

Word frequency: Norms for word frequency were obtained from the CoLFIS Italian corpus of word frequency (CNR, Unpublished). No significant difference was found either between Living and Nonliving things (Mann-Whitney U test: U=1635.5 p=0.39) or between highly and weakly manipulable objects (Mann-Whitney U test: U=421 p=0.67) (see Table2)

Number of syllables: No significant difference was found either between living and nonliving things (Mann-Whitney U test: U=1708, p=0.63) or between highly and weakly manipulable objects (Mann-Whitney U test: U=405 p=0.66).

Familiarity and Visual complexity: Norms for familiarity and visual complexity were obtained from a group of 20 control subjects. Stimuli were presented on a computer screen one at the time and subjects were asked to rate them on both dimensions on a 7 point scale using the keys from 1 to 7 on the keyboard.

Regarding the familiarity, no significant difference was found either between living and nonliving things (Mann-Whitney U test: U=1647.5; p=0.42) or between highly and weakly manipulable objects (Mann-Whitney U test: U=403; p=0.49). Also for visual complexity, no significant difference was found either between Living and Nonliving things (Mann-Whitney U test: U=1484.5; p=0.10) or between highly and weakly manipulable objects (Mann-Whitney U test: U=404.5; p=0.50).

Since differences have been found between male and female subjects in judging the familiarity of different categories of semantic material (Albanese et al., 2000), a further control was performed in order to assess the possible presence of such biases. For each comparison (male Vs female in living Vs. nonliving) a Bonferroni corrected threshold p-value of 0.05/4=0.0125 was adopted. Neither male (Mann-Whitney U test: U=1570;

p=0.23) nor female subjects (Mann-Whitney U test: U=1632; p=0.38) found living things more familiar than nonliving. Moreover male or female subjects did not rate living (Mann-Whitney U test: U=1355, p=0.019) or nonliving (Mann-Whitney U test: U=1460, p=0.07) differently with respect to familiarity. As far as the nonliving things category is concerned, no statistical difference of any kind was found across sex in rating high vs. low manipulability items. This was probably due to the fact that the manipulable objects we chose were not only tools in general, which are more prone to gender biases (e.g. microphone, tennis racket, ashtray, basket, hourglass).

Manipulability ratings: A group of 20 subjects was asked to rate the level of manipulability of each object picture from al large set of 147 manipulable object pictures. The rating procedure was similar to that adopted in the study by Magnie and colleagues (2003) (see introduction). Subjects were asked to judge how easy it was for them to mime the action commonly associated to the presented object so that anyone seeing that action could understand which object is associated to that action. The scale ranged from 1 to 5, with '5' meaning that the action was easily 'mimeable' and was unique for that object, and '1' meaning that there is not a specific action that could identify the object. Manipulability ratings were significantly higher for highly than for weakly manipulable objects (Mann-Whitney U test: z=6.652 p<0.0001). Highly manipulable objects ratings ranged from 3.50 to 4.88 (mean rating= 4.20 +/- 0.37 SD); weakly manipulable objects' ratings ranged from 1.30 to 2.90 (mean rating= 2.06 +/- 0.46 SD).

Table 2: Experimental material balancing: Average values for the main extra-semantic variables for each of the categories involved in the experimental task.

Word Freq.			Familiarity			Visual Compl.			N.of Syllables			Manipulability		
Aver°	SD	p=*	Aver°	SD	p=*	Aver°	SD	p=*	Aver°	SD	p=*	Aver°	SD	p=*
2.53	1.18		1.58	0.22		1.31	0.27		1.03	0.25		-	-	
2.83	1.62	0.39	1.6	0.24	0.42	1.25	0.25	0.1	1.03	0.36	0.3	-	-	-
2.87	1.59		1.58	0.26		1.24	0.22		1.07	0.38		1.43	0.09	
2.79	1.68	0.67	1.63	0.23	0.49	1.25	0.29	0.5	0.98	0.33	0.96	0.7	0.24	<0.0001

°=All the values reported refer to the NatLog of the original raw values obtained from control subjects. NatLog transformation was performed in order to make the values more homogeneous across variables and the distributions closer to normal.
*=Mann-Whitney U-test

5.2.4 General procedures for behavioural data analysis:

Accuracy scoring:

All responses from each subject were tape-recorded in order to allow a more adequate analysis of the answers of the patients in the case of ambiguous responses. For an answer to be considered as correct, the lexical form had to be either clearly correct or the word had to be entirely pronounced, with the first phoneme and 2/3 of the word being correctly pronounced. Since what was important was not the word per se, but rather the concept behind the word, 'conduit d'approche' were allowed if the target word (or an appropriate synonym) was produced in the end. Dialect forms of the target word were also treated as correct,

Cross-subject analysis:

In analyzing the behavioural data a twofold statistical approach was adopted. Accuracy data from the patients were indeed analysed both at a single case and at a group level of analysis. Since not all the patients could be tested both before and after surgery, for the patients that were tested twice the main analyses were performed on the average score obtained in both testing sessions for each of the variables considered. For the patients that were tested only once the tests were performed on the actual score obtained in the testing session they performed. The scores for each session were however kept separated at the group level of analysis when assessing the effects of surgery.

Single case level:

The naming performance of each patient in the task was compared, at a single case level of analysis, with that of an appropriate age and education matched subgroup of control subjects. Statistical analysis was performed by means of Crawford t-test (Crawford and Garthwaite, 2002) in order to assess the abnormality of possible test scores differences when compared with small size control samples. In addition to the scores obtained by the patient in the two conditions of interest, this statistic takes into account the mean scores and standard deviation obtained by the control sample in the same two conditions as well as the correlation between the scores of the controls in the two conditions.

For each patient two statistical tests were performed: the first one assessed the presence of category specific deficits in naming living or nonliving things in general. The

second one assessed the presence of possible selective naming difficulties for high or low manipulability objects within the category of nonliving entities.

Group level:

Since the data obtained from the performance of the patients (especially for left hemisphere) was not normally distributed, only nonparametric tests were used to assess the presence of any effect at a group level of analysis. A series of nonparametric tests were used to compare the performance of the group of patients with respect to that of the controls. The presence of within-group significant category specific effects was also directly assessed by means of series of Wilcoxon matched-pairs tests.

The size of any possible effect of category or manipulability was then computed by subtracting the accuracy score obtained by each patient (and control subject) with the first category of interest (Nonliving things and highly manipulable objects respectively) from that obtained with the other category (Living things and weakly manipulable objects respectively). The presence of any significant difference in these effects between groups was thus directly assessed by means of Kruskal Wallis ANOVA with the attendant post-hoc corrected comparisons (Siegel and Castellan, 1988)

Cross Stimulus analysis:

In addition to a 'cross-subject' analysis, a 'cross-stimulus' analysis was also conducted in order to double-check the generalizability of the results (see Clark, 1973). A series of ANCOVAs was conducted on the average accuracy obtained by each group of subjects for each stimulus, co-varying it with the average level of each of the variables (familiarity, visual complexity, frequency, number of syllables) for each stimulus. The category of interest (living/nonliving or high/low manipulability) was used as a categorical predictor, to check whether possible categorical effect would survive.

5.3 RESULTS:

5.3.1 Cross-subject analysis:

General naming skills:

8/20 left hemisphere patients performed below the accuracy cut-off score of 85.56% obtained from control subjects, while only 1/10 of the right hemisphere patients did. A series of chi-square tests were used to assess whether these proportions were significant

when compared with control subjects. As two groups were being compared with contrasts, Bonferroni correction for multiple comparisons was set to a threshold of 0.05/2=0.025.

A significant number of left hemisphere patients (Fisher exact χ^2: p=0.002) scored below the cut-off value. The proportion of right hemisphere patients scoring below the cut-off value was not significant (Fisher exact χ^2: p=0.310). Within the left hemisphere group itself however, only 1/11 of the left anterior temporal patients performed below the cut-off naming score, while 7/9 of the left posterior temporal patients did. This difference was again highly significant (Fisher exact χ^2: p=0.003) indicating that not only are left hemisphere patients the only ones to show naming problems but that in our sample these difficulties were restricted almost exclusively to left posterior temporal patients, as left anterior temporal patients did not differ significantly from controls (Fisher exact χ^2: p=0.355).

Group level analysis:

Categories x Hemisphere interactions: A first assessment of the possible presence of category specificity or manipulability effects was conducted by separating the group of patients on the basis of the hemisphere of interest. A series of Wilcoxon matched pairs test was conducted on the performance of (i) controls, (ii) left hemisphere and (iii) right hemisphere patients to test whether significant within-group differences could be detected in naming living and nonliving items. For both series of comparisons, Bonferroni threshold for multiple comparisons was set to 0.05/3=0.017. To look for possible interactions in the size of the potential effects detected between the groups, a series of Kruskal-Wallis nonparametric ANOVAs was then conducted, with the attendant post-hoc corrected comparisons (Siegel and Castellan, 1988).

The within-group comparison revealed that left hemisphere patients showed a significant category specific naming difficulty for nonliving things compared with living things (Wilcoxon matched pairs test: z=3.808; p<0.001) (see Fig.1). No category specificity effect was found either in the control subjects (Wilcoxon matched pairs test: z=0.491; p=0.623) or the right hemisphere patients (Wilcoxon matched pairs test: z=1.481; p=0.139).

Since, however, the size of this left hemisphere effect (though significant) might not be larger than that of right hemisphere patients or that of control subjects, the presence of possible interactions was assessed by comparing the size of the category effect (nonliving-

living) between controls, right and left hemisphere patients. A significant main effect of group was found (Kruskal-Wallis ANOVA: $H_{(2, N= 50)}$=16.650; p<0.001). Post hoc analysis revealed that the category effect was larger in left hemisphere patients than in either controls (z=3.812; p<0.001) or right hemisphere patients (z=2.873; p=0.012).

Manipulability x Hemisphere interactions: No significant effect of manipulability was found at the group level of analysis. The lack of effect, however, may be due to the heterogeneity of behaviour within subgroups of left hemisphere patients, as will be seen in the next section.

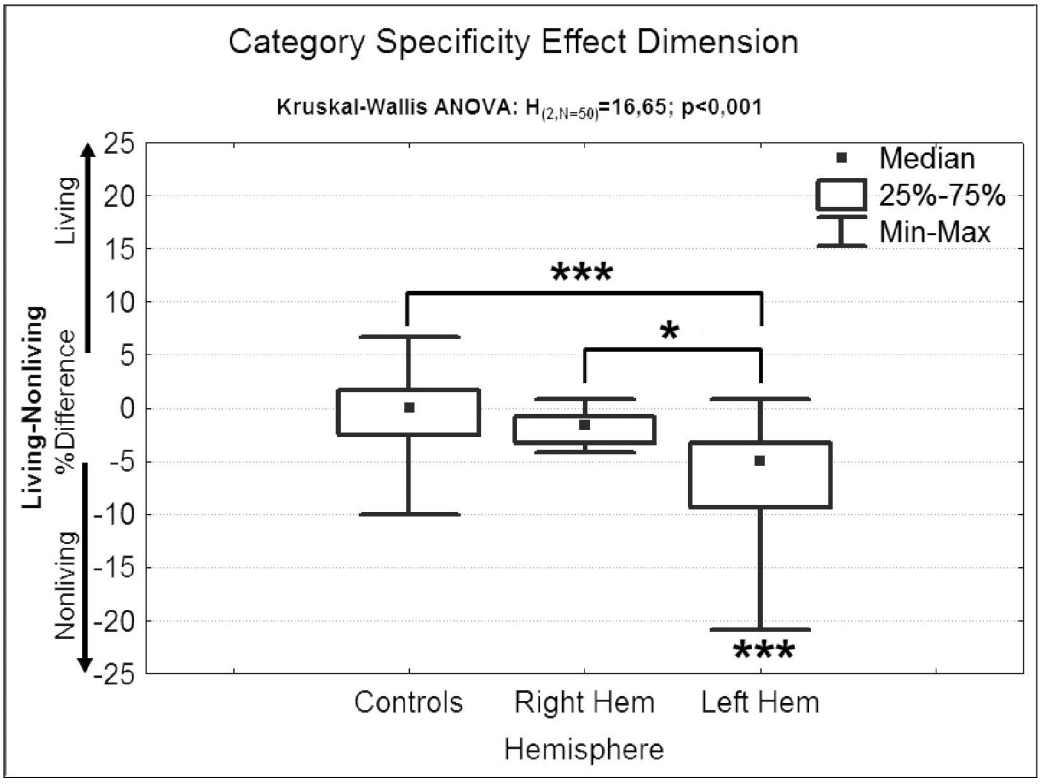


Fig.1: Category specific effect dimension between controls, left and right hemisphere patients. Left hemisphere patients show a clear category specific naming difficulty for nonliving items. *=p<0.05; **=p<0.01; ***=p<0.001

Left Hemisphere patients: Category effects: Since right hemisphere patients did not show any apparent naming deficit at all, a further analysis compared possible category or manipulability effects in left hemisphere patients with respect to controls. The analysis was performed on controls, left anterior temporal and left posterior temporal patients: therefore a Bonferroni correction threshold was set at: 0.05/3=0.017. At a within group level of

analysis, both left posterior and anterior temporal patients showed a significant category specific naming deficit for nonliving things compared to living things (Wilcoxon matched pairs test: z=2.666; p=0.008 for both groups). In addition, when comparing the size of the effect between the controls, the left anterior and the left posterior temporal patients, a significant main effect of group was found (Kruskal-Wallis ANOVA: $H_{(2,\ N=40)}$=17.045; p=0.002) (Fig.2). Subsequent post hoc analysis revealed that only the category effect of left posterior temporal patients was larger than that of controls (z=4.068; p<0.001), the performance of left anterior temporal patients being no different from that of the controls (Kruskal-Wallis ANOVA post hoc test: z=1.992; p=0.138).

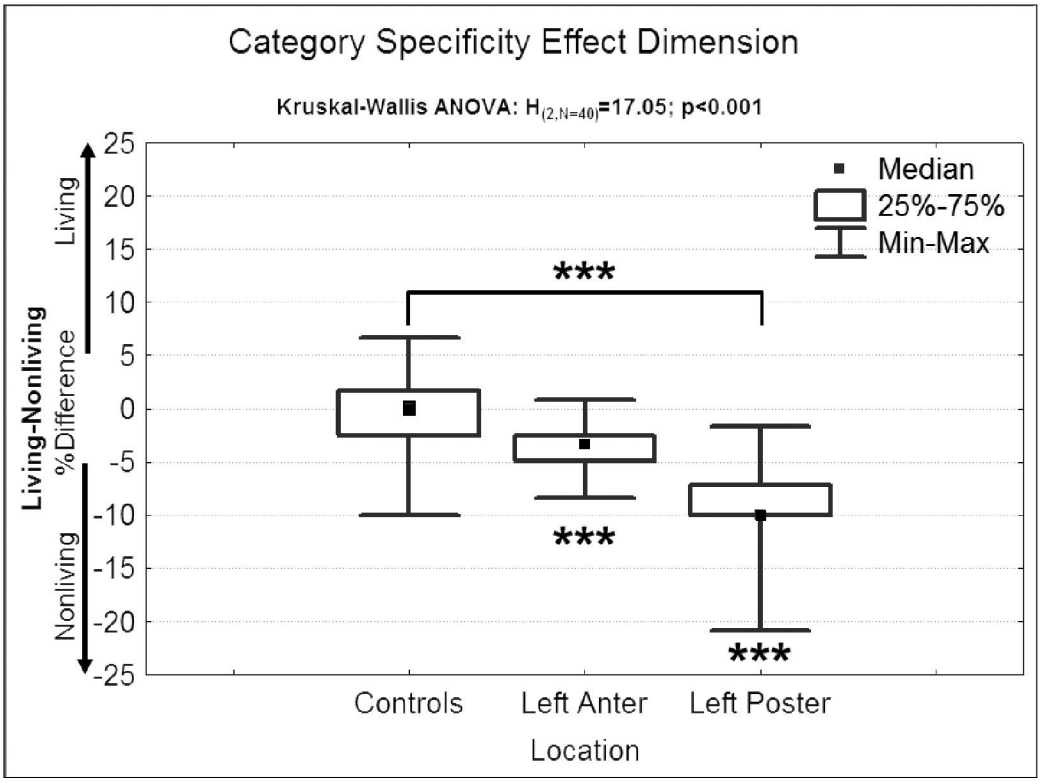


Fig.2: Within the left hemisphere, left posterior temporal patients showed a larger category specificity effect with respect to controls. Left anterior temporal did not. *=p<0.05; **=p<0.01; ***=p<0.001

Left Hemisphere patients: Manipulability effects: To assess for possible manipulability effects, the performance of the left hemisphere patients (anterior and posterior temporal) and that of controls subjects within the category of nonliving things only were directly compared (Fig.3). The within-group analysis, comparing directly controls, left anterior temporal and left posterior temporal patients (Bonferroni correction threshold: 0.05/3=0.017) revealed that the manipulability influenced the patient groups in opposite ways: thus left posterior temporal patients had significantly greater difficulties in naming highly manipulable objects (Wilcoxon matched pairs test: z=2.521; p=0.012), while left anterior temporal patients tended to perform worse, but not significantly (Wilcoxon matched pairs test: z=2.191; p=0.028) with weakly manipulable objects. The between-group analysis of the effects of manipulability comparing controls, left anterior and left posterior temporal patients, gave a main effect of group (Kruskal-Wallis ANOVA: $H_{(2, N=40)}$=14.362; p=0.008). Post hoc analysis revealed that the manipulability effect was significantly greater for left posterior patients than it was for both controls (z=2.878; p=0.012) and left anterior temporal patients (z=3.669; p<0.001).

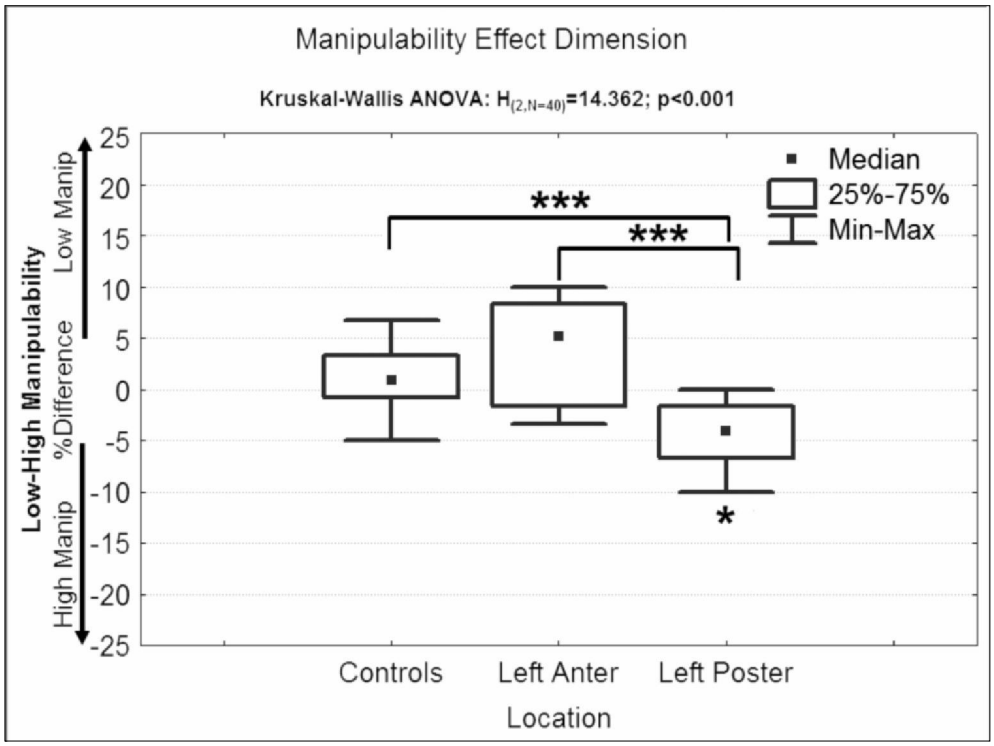


Fig.3: Manipulability effect dimension: Left posterior temporal patients performed worse with highly manipulable objects. *=p<0.05; **=p<0.01; ***=p<0.001

Effects of surgery:

A final group analysis was performed in order to assess possible effects of the surgery on the naming skills of the patients. Only patients who were tested both before and after the surgery (25/30) were included. Effects of surgery were directly investigated by comparing the performance obtained before and after the surgery for each patient with a series of Wilcoxon matched pairs tests. Patients were sorted first in terms of the hemisphere of the lesion. If a significant effect was found for either hemisphere, then the group was further subdivided according to the location (anterior vs. posterior temporal) of the lesion. The dimension of the effect was also assessed to investigate for a possible interaction between groups with logic similar to that adopted for investigating category effects. The measure was obtained by subtracting the performance obtained by the patients before the surgery from that obtained after. A series of Mann-Whitney U tests was conducted to compute these effects.

Considering the effects of surgery on both left and right hemisphere patients (Fig. 4a) it was evident that left hemisphere patients were more impaired by surgery than were right hemisphere patients (Mann-Whitney U test: $U=26$; $p=0.025$). Thus, left hemisphere patients showed a significant decline in their post-operative performance (Wilcoxon matched pairs test: $z=2.887$; $p=0.003$), but right hemisphere patients did not do so (Wilcoxon matched pairs test: $z=0.929$; $p=0.352$). Again, when comparing the left anterior and the left posterior temporal patients (Fig.4b), it was only the left posterior temporal patients who showed a significant reduction in performance after surgery (Wilcoxon matched pairs test: $z=2.310$; $p=0.021$). However the effect of surgery was only marginally higher for these patients than for the left anterior temporal patients (Mann-Whitney U test: $U=21.5$; $p= 0.093$).

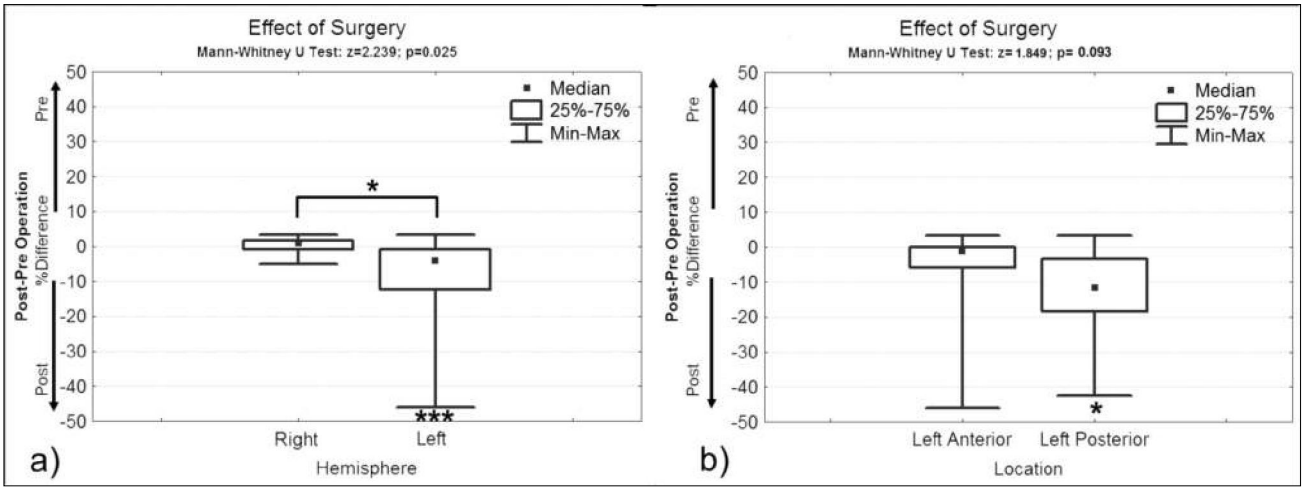


Fig.4: a) The naming abilities of left hemisphere patients were impaired following the surgery. Right hemisphere patients did not show any impairment. B) Left anterior temporal patients did not suffer significantly form surgery, while left posterior temporal patients did. *=p<0.05; **=p<0.01; ***=p<0.001

5.3.2 Cross-stimulus analysis:

The effects of category and especially of manipulability, while significant, were small. It was therefore thought appropriate to examine the robustness of the effects by assessing their generalizability across stimulus items as well as across subjects (Clark, 1973). The performance of all subjects in a group was averaged for each stimulus item, and this average performance was used as the dependent variable. The performance of left anterior and posterior temporal patients was separately analyzed with this method.

Analyzing the results obtained by left posterior temporal patients, category membership (living-nonliving) still exerted a highly significant effect on the naming performance of this group (ANCOVA: effect of category: $F_{(1,114)}=27.75$, $p<0.0001$). Many of the baseline lexical variables also had a significant influence on the naming abilities of the patients: familiarity ($F_{(1,114)}=25.50$, $p<0.0001$); word frequency ($F_{(1,114)}=23.12$, $p<0.0001$); number of syllables ($F_{(1,114)}=15.85$, $p=0.0001$). Visual complexity did not influence performance ($F_{(1,114)}=0.68$, $p=0.41$). Somewhat similar results were obtained for the left anterior temporal patients. Category membership had still a significant (even if smaller) effect: $F_{(1,114)}=6.68$, $p=0.011$). Frequency ($F_{(1,114)}=22.89$, $p<0.0001$) and number of syllables ($F_{(1,114)}=4.19$, $p=0.042$) also had a significant effect. Familiarity and visual

complexity did not influence the performance (visual complexity: $F_{(1,114)}$=0.121, p=0.728; familiarity: $F_{(1,114)}$=0.842, p=0.361).

However, when the same type of analysis was performed on the manipulability effect within the category of nonliving things, a more complex pattern of results was obtained. For the left posterior temporal patients a significant effect of many of the extra-semantic variables was found (familiarity: $F_{(1,114)}$=33.73, p<0.0001; frequency: $F_{(1,114)}$=10.92, p=0.002; number of syllables: $F_{(1,114)}$=8.46, p=0.005), while visual complexity did not influence performance ($F_{(1,114)}$=0.00, p=0.97). However the effect of manipulability in this case was far from significant ($F_{(1,114)}$=0.00, p=0.92). By contrast, a significant effect of manipulability was found for the performance of left anterior temporal patients; patients in this group had more difficulty in naming weakly manipulable than highly manipulable objects. Thus, in addition to familiarity ($F_{(1,114)}$=5.25, p=0.025) and frequency ($F_{(1,114)}$=8.66, p=0.005), manipulability *also* influenced naming performance ($F_{(1,114)}$=4.75, p=0.033).

5.3.3 Single case level analysis:

The analysis of the results at a single case level provides further support for the group level results. Table 2 shows that significant category specificity naming deficits were only present in left posterior temporal patients. While none of the right hemisphere or even left anterior temporal patients showed significant category effects, 6/9 of the left posterior temporal patients had a category specific naming deficit for nonliving entities, using the Crawford procedure. Moreover, 4 of those 6 patients *also* showed a category specific naming deficit for highly manipulable objects.

Table 3: Single case level results: The only group showing category specific naming deficits for artefacts is that of left posterior temporal patients.

CATEGORY

Pat.	Lesion type	BEFORE SURG. LIV.	BEFORE SURG. NLIV.	AFTER SURG. LIV.	AFTER SURG. NLIV.	*AVERAGE CAT. LIV.*	*AVERAGE CAT. NLIV.*	Crawford t-test:
RA1	Meningioma	100,00	93,33	100,00	98,33	100,00	95,83	p=0.190
RA2	Grd II Astrocyt	98,33	95,00	100,00	96,67	99,17	95,84	p=0.250
RA3	Glioblastoma	96,67	95,00	95,46	93,80	96,07	94,40	p=0.400
RA4	Glioblastoma	83,33	80,00	81,50	82,16	82,42	81,08	p=0.470
RA5	Grd II Astrocyt	93,33	95,00	98,68	92,95	96,01	93,98	p=0.370
RA6	Glioblastoma	98,33	100,00	100,00	100,00	99,17	100,00	p=0.370
RP1	Grd II Astrocyt	98,33	95,00	93,33	90,00	95,83	92,50	p=0.260
RP2	Grd II Astrocyt	96,67	96,67	100,00	100,00	98,34	98,34	p=0.440
RP3	Glioblastoma	96,67	100,00	100,00	95,00	98,34	97,50	p=0.470
	MEAN	**95,74**	**94,44**	**96,55**	**94,32**	**96,15**	**94,38**	
	SD	**5,01**	**5,89**	**6,15**	**5,65**	**5,38**	**5,50**	
LA1	Grd II Astrocyt	98,33	93,33	95,00	86,67	96,67	90,00	p=0.080
LA2	Grd II Astrocyt	100,00	96,67	100,00	96,67	100,00	96,67	p=0.253
LA3	Grd II Astrocyt	96,67	93,33	95,00	93,33	95,84	93,33	p=0.061
LA4	Metastasys	96,67	90,00	84,65	82,09	90,66	86,05	p=0.330
LA5	Glioblastoma	96,21	94,63	98,33	90,00	97,27	92,32	p=0.153
LA6	Dysembryogen	95,00	90,00	96,67	95,00	95,84	92,50	p=0.262
LA7	Grd II Astrocyt	91,67	93,33	93,33	85,00	92,50	89,17	p=0.271
LA8	Grd II Astrocyt	95,00	98,33	98,33	96,67	96,67	97,50	p=0.363
LA9	Grd II Astrocyt	95,00	93,33	91,67	95,00	93,34	94,17	p=0.354
LA10	Gliosarcoma	91,67	95,00	93,33	81,67	92,50	88,34	p=0.211
LA11	Glioblastoma	85,00	64,41	26,67	30,51	55,84	47,46	p=0.067
	MEAN	**94,66**	**91,12**	**88,45**	**84,78**	**91,55**	**87,95**	
	SD	**4,05**	**9,20**	**20,91**	**18,86**	**12,14**	**13,87**	
LP1	Glioblastoma	85,00	71,67	83,33	55,00	84,17	63,34	***p<0.001***
LP2	Meningioma	96,67	96,67	95,00	91,67	95,84	94,17	p=0.405
LP3	Metastasys	70,00	43,33	18,33	10,00	44,17	26,67	***p=0.001***
LP4	Ependymoma	75,00	66,10	76,67	71,19	75,84	68,65	p=0.084
LP5	Metastasys	56,67	43,33	40,00	33,33	48,34	38,33	***p=0.036***
LP6	Grd II Astrocyt	98,33	98,31	70,00	52,54	84,17	75,43	***p=0.039***
LP7	Glioblastoma	100,00	94,92	98,33	91,53	99,17	93,23	p=0.104
LP8	Glioblastoma	95,00	85,00	83,33	73,33	89,17	79,17	***p=0.020***
LP9	Low Grade	56,67	53,33	45,00	28,33	50,83	40,83	***p=0.035***
	MEAN	**81,48**	**72,52**	**67,78**	**56,32**	**74,63**	**64,42**	
	SD	**17,53**	**22,42**	**27,34**	**28,45**	**21,31**	**24,33**	

MANIPULABILITY

BEFORE SURG. HI-MAN	BEFORE SURG. LO-MAN	AFTER SURG HI-MAN	AFTER SURG LO-MAN	*AVERAGE MANIP. HI-MAN*	*AVERAGE MANIP. LO-MAN*	Crawford t-test:
86,67	90,00	93,33	100,00	90,00	95,00	p=0.111
100,00	90,00	100,00	93,33	100,00	91,67	p=0.136
96,67	93,33	94,27	93,29	95,47	93,31	p=0.490
83,33	76,67	82,87	81,41	83,10	79,04	p=0.419
93,33	96,67	92,65	93,24	92,99	94,96	p=0.243
100,00	100,00	100,00	100,00	100,00	100,00	p=0.386
96,67	93,33	90,00	90,00	93,34	91,67	p=0.467
96,67	96,67	100,00	100,00	98,34	98,34	p=0.379
100,00	100,00	93,33	96,67	96,67	98,34	p=0.272
94,82	**92,96**	**94,05**	**94,22**	**94,43**	**93,59**	
6,04	**7,16**	**5,60**	**6,03**	**5,42**	**6,22**	
96,67	90,00	93,33	80,00	95,00	85,00	p=0.095
96,67	96,67	93,33	100,00	95,00	98,34	p=0.180
96,67	90,00	96,67	90,00	96,67	90,00	p=0.210
93,33	86,67	83,86	80,31	88,60	83,49	p=0.320
94,57	94,47	90,00	90,00	92,29	92,24	p=0.357
96,67	83,33	96,67	93,33	96,67	88,33	p=0.140
96,67	90,00	90,00	80,00	93,34	85,00	p=0.150
96,67	100,00	96,67	96,67	96,67	98,34	p=0.272
93,33	93,33	93,33	96,67	93,33	95,00	p=0.250
93,33	96,67	90,00	73,33	91,67	85,00	p=0.230
63,33	65,52	36,67	24,14	50,00	44,83	p=0.494
92,54	**89,70**	**87,32**	**82,22**	**89,93**	**85,96**	
9,81	**9,35**	**17,23**	**21,08**	**13,47**	**14,66**	
60,00	83,33	60,00	50,00	60,00	66,67	***p=0.037***
96,67	96,67	90,00	93,33	93,34	95,00	p=0.261
33,33	53,33	10,00	10,00	21,67	31,67	***p=0.005***
63,33	68,97	70,00	72,41	66,67	70,69	p=0.094
43,33	43,33	33,33	33,33	38,33	38,33	p=0.164
96,67	100,00	46,67	58,62	71,67	79,31	***p=0.034***
96,67	93,10	90,00	93,10	93,34	93,10	p=0.373
83,33	86,67	73,33	73,33	78,33	80,00	p=0.209
50,00	56,67	26,67	30,00	38,33	43,33	***p=0.039***
69,26	**75,79**	**55,56**	**57,12**	**62,41**	**66,45**	
24,77	**20,82**	**28,28**	**28,89**	**25,24**	**23,53**	

5.3.4 VLSM analysis:

Using the VLSM approach to lesion analysis (Bates et al., 2003) we aimed to localize which areas of the temporal lobes were involved with respect to the category specific naming difficulty. Original T1 and (when available) T2 weighted scans of each patients were obtained for all the patients (except for patient RH6) in 'analyze' digital format to determine the preoperative location of the tumour. Only preoperative MRI scans were used for reconstruction purposes, as in postoperative scans, the region of the surgical lesion is usually at least partially replaced by healthy neighbouring tissue. The 3D reconstruction of lesions were drawn as Regions Of Interest (ROI) by one of the researchers (FC) using each slice of the MRI scan of each patient on the horizontal plane, using MRIcro software (Rorden and Brett, 2000). ROIs included both the lesion boundaries and oedema (since oedema is found to commonly cause cognitive deficits).

All the ROIs where then double-checked and, if necessary, corrected by an expert neuroradiologist (SDA) who was blind to the aims of the study and to the performance of each patient on the task. Each patient's MRI scan underwent spatial normalization using SPM2 software, in order to match and align images on a common Talairach (Talairach and Tournoux, 1988) space.

Initially, whether the severity of any deficit observed in naming could merely be linked to lesion volume was checked. The volume of the reconstructed lesions of three subgroups of patients (right vs. left anterior vs. left posterior temporal) was therefore compared. No significant differences were found between groups (Kruskal-Wallis ANOVA: $H_{(2,\ n=29)}=1.051$; $p=0.591$).

Voxel by voxel statistical analyses were performed by means of NPM software (www.MRIcro.com). Since manipulability results were considered as not being completely reliable after cross-stimulus analysis, only data coming from the general category contrast (living vs. nonliving) underwent VLSM analysis. The behavioural measure used to compute the statistic was obtained by subtracting the scores obtained in naming living things from the score obtained in naming nonliving objects for each patient. The statistical test used to compute for the presence of any effect was a T-test. A threshold of $p<0.001$ (with False Discovery Rate correction applied) was used to consider a result as significant. To minimize the effects of

observation of possible outliers the analyses were conducted only on those voxels that were damaged in at least 3 patients.

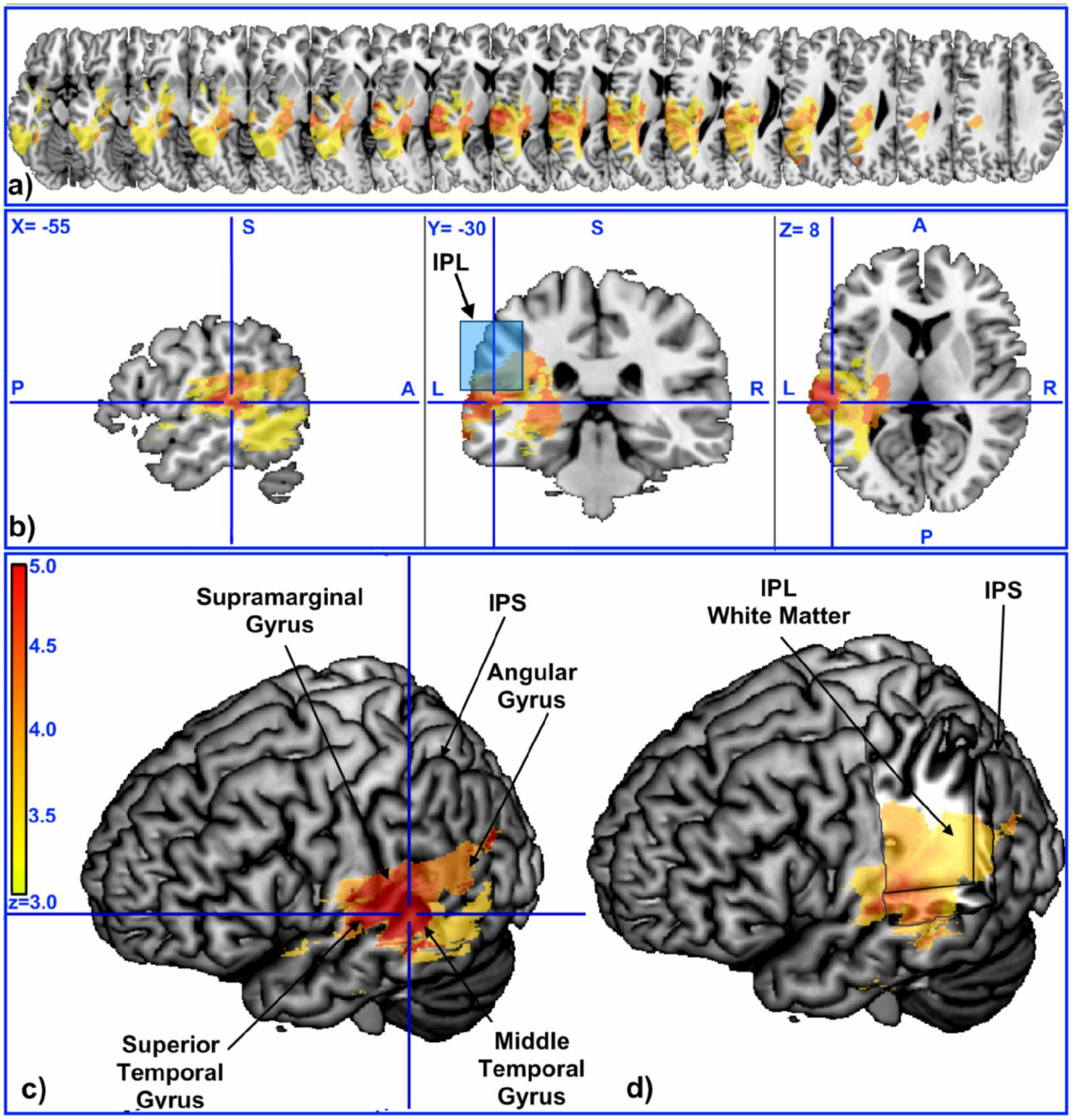


Fig. 5: VLSM analysis. The areas associated with a significant naming deficit for nonliving things ($p<0.001$) involve a large part of the posterior temporal lobe. The cortical area associated with the largest category specific deficit in naming artefacts is the posterior portion of the left middle temporal gyrus. (a) multi-slice coronal view, (b) anatomical centre of mass (x=-55; y=-30; z=-8) and (c) 3-D anatomical reconstruction of the areas involved.

Fig.5 shows the areas associated with a significant naming deficit for nonliving things ($p<0.001$). These areas involve a large part of the posterior temporal lobe. The cortical area associated with the largest category specific deficit in naming artefacts is the posterior portion of the left middle temporal gyrus (centre of mass: x=-55; y=-30; z=8) (Fig.6: panels b and c). In addition, posterior portions of the left superior and inferior temporal gyri were involved as well as a small portion of the inferior parietal cortical areas and part of the hippocampus. However, the largest number of voxels involved in category specific naming deficit was found in the subcortical white matter underlying the left posterior temporal lobe. Of particular interest is that a part of this white matter lesion disconnects large portions of the left inferior parietal lobe from the temporal lobe (see Fig.6, panels b and d).

5.3.5 Patient MU:

Patient MU, who had previously been found to have a stable category specific loss of knowledge for living entities (Borgo and Shallice, 2001; Borgo and Shallice, 2003), was also tested on the same task. The pattern of performance was as would be predicted (see Fig.5): he named living things worse than nonliving things (40% and 58.33% respectively; Crawford t-test: t=-2.63, p=0.029) and low manipulability objects worse than high manipulability ones (43.33% and 73.33% respectively; Crawford t-test: t=-2.99, p=0.020). The performance of patient MU thus provides a double dissociation with respect to the performance of posterior temporal patients.

Cross-stimulus analysis confirmed the robustness of these results. as the analysis involved the results of a single subject only with just dichotomic (0 or 1) responses, a logistic regression was used. Category per se had a significant influence on the performance (Wald Statistic $_{(df=1)}$=3.99, p=0.045); there was also an influence of visual complexity and word frequency of the target item (Wald Statistic $_{(df=1)}$=4.34, p=0.037 and Wald Statistic $_{(df=1)}$=7.72, p=0.005 respectively). In addition, regarding manipulable objects only, the manipulability of the stimulus (high or low) significantly influenced the probability of MU finding the correct name (Wald Statistic $_{(df=1)}$=7.54, p=0.006). Among the extra-semantic variables, only familiarity was found to exert an influence on his naming ability ($F_{(1,114)}$=7.74, p=0.007) at this level of analysis.

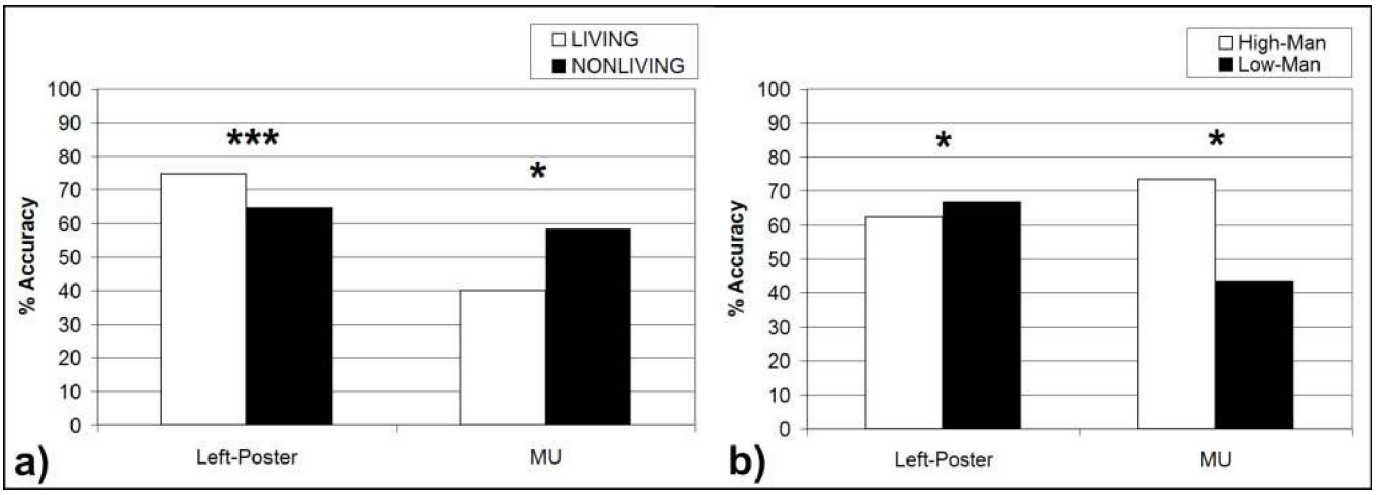


Fig.6: Performance of patient MU compared with that of left posterior patients. MU shows the complementary pattern of naming, experiencing difficulties in naming living things (panel a) and also weakly manipulable objects (panel b). *=p<0.05; **=p<0.01; ***=p<0.001

5.4 DISCUSSION

5.4.1 Summary of the results

The aim of this study was to try to shed further light on the organization of concepts within the semantic memory. More specifically, we wanted to assess whether semantic information about concrete concepts is stored in more than one brain region organised. This could be according to the dominant type of feature necessary for their identification (sensory rather than motor/function related) on the one hand (Warrington and McCarthy, 1983; 1987; Warrington and Shallice, 1984; Farah and McClelland, 1991; Saffran and Schwartz, 1994), or by category (Caramazza and Shelton, 1998), or could involve a hub and spoke structure (Rogers et al., 2004; Patterson et al., 2007). The alternative possibility, on the other hand, is that it is stored in an undifferentiated semantic network within the temporal lobes with preservation of categories arising from underlying differences in distinctiveness and correlation structure (Tyler and Moss, 2001). These different accounts have been developed to explain the puzzling neuropsychological phenomenon of the selective loss of semantic information for one or more categories of knowledge shown by some brain-damaged patients. Of particular interest is the well known dissociation between the category specific loss of knowledge about living with respect to nonliving entities.

This study focused on the reverse pattern of loss (about nonliving things) which has been less frequently reported. By restricting this category only to manipulable objects, we tested two predictions. First, we investigated if there was a specific cortical region which is involved in the storing of information relevant specifically to nonliving things, as the literature about living things suggests. Second, if manipulability information (held to be a dimension related to motor knowledge) is a crucial feature in characterizing manipulable objects semantically, then patients showing a category specific deficit for nonliving things should experience more problems with highly manipulable objects, while patients with specific deficit for living things should have more difficulties with weakly manipulable objects (more defined in terms of their perceptual properties).

We tested these predictions in a consecutive series of 30 patients affected by brain tumours located in either the right or left temporal lobes using a naming task involving both living and nonliving items with nonliving things divided into high and low manipulability objects. The performance of the patients was compared with that of a patient showing a stable category specific semantic deficit for living things and with that of a group of 20 control subjects. We analyzed the findings at a behavioural level both at a single case and group level of analysis, and also by means of Voxel-based Lesion Symptom Mapping (VLSM) technique in order to localise the brain areas in which category or manipulability effects occurred.

Only left hemisphere patients had any naming deficit on our task. This effect was however entirely attributable to left posterior temporal patients, since the performance of left anterior temporal patients was generally similar to controls (with the one exception of patient LA11). Moreover left hemisphere patients in general showed a category specific deficit for nonliving things, but only for left posterior temporal patients was the category effect larger than that shown by controls.

The left posterior temporal patients *also* showed difficulties in naming highly manipulable objects more than weakly manipulable ones. These results were not just the outcome of a group effect as they were also present in many of the patients at a single case level of analysis. However, while the category specific deficit in naming manipulable objects in general was very robust, being confirmed both at a cross-subject level and also at a cross-stimulus level of analysis, the effect of manipulability was not consistent across the two types of analysis. Indeed, for left posterior temporal patients it was significant only at a cross-subject

level of analysis, while at a cross-stimulus level of analysis left anterior temporal patients only showed an effect of manipulability being worse in naming weakly manipulable objects.

Giving however further support for a role of manipulability in influencing the naming of artefacts, patient MU who consistently showed in past investigations a category specific semantic deficit for living entities (Borgo and Shallice, 2001; 2003), on the same task named living things worse than manipulable objects and consistently with our predictions *also* had more difficulties in naming weakly than highly manipulable objects. This effect was also significant at a cross-stimulus level of analysis.

From an anatomical point of view, VLSM analysis showed that category specific naming deficit for manipulable objects was associated with lesions in the left posterior middle and superior temporal gyri. Interestingly, a large portion of the subcortical white matter underlying the inferior parietal cortex was also significantly involved in those patients showing the larger category specific naming deficit for manipulable objects, supporting the possibility of a disconnection between the inferior parietal cortex and the left temporal lobe.

The lack of category specificity deficits for living things found in the sample of tumour patients we tested may appear surprising. However it has been suggested (Gainotti, 2000) that knowledge about living things may be distributed more bilaterally in the temporal lobes than that of nonliving entities. Brain tumours only sporadically produce bilateral lesions and none of our patients showed bilateral temporal involvement. However, the performance of patient MU in this task supports the idea that patients affected by a selective loss of knowledge of living things, name the living stimuli used in this task more poorly than they do nonliving items. In addition, he experienced more difficulties with weakly manipulable objects, which lack a clearly unique manipulation.

Taken together, these data shed further light on the organization of content within semantic memory. It is difficult to account for these results in terms of any non-semantic explanation. The material we used was completely balanced to control for all the usual extra-semantic interfering variables. The cross-stimulus control analysis shows that the effect persists across stimuli indicating that the result cannot be explained by the possibility of a failure to balance the stimuli in a particular part of the range in one or the other stimulus dimension.

More problematic is the more fine-grained effect of the level of manipulability on the naming abilities of the patients. On one hand, the performance of MU gives support to the

prediction that patients showing a category specific semantic deficit for living things will also have difficulties in dealing with weakly manipulable objects. However, the performance of the tumour patients was less clear-cut, since the selective difficulty of left posterior temporal tumour patients in naming highly manipulable objects found in the between-subject analysis was not confirmed in a between-stimulus analysis. However the possibility that manipulability does have a real effect in these patients is suggested by the performance of left anterior temporal patients who showed a significant difficulty in naming weakly manipulable objects, an effect that fits with the prediction that more ventral areas might process more perceptual kinds of information. That this effect, in left anterior temporal patients, was not coupled with a deficit in naming living entities too, might be explained by the fact that this latter deficit is usually associated with bilateral temporal lesions (as in the case of MU) (e.g. Gainotti, 2000; Capitani et al., 2003).

An important result of this experiment was that by carefully controlling the material used and the definition of what counts as a nonliving item (i.e. in this case an artefact), we were able to find a high density of patients with category specific naming difficulties for nonliving items. The adoption of the case series methodology (Woollams et al., 2007) gives further strength to the findings since the results of the group analyses were deriving from effects that were largely present and significant already at the single case level of analysis.

The VLSM analysis we performed showed that the cortical areas mostly involved also included areas that are situated within the Wernicke territory (especially the posterior portion of left superior temporal sulcus and the temporo-parietal junction) which have been linked to both speech comprehension and production (Wise et al., 2001; Blank et al., 2002). This could explain the presence of a general naming deficit in this group of patients. However together with these regions, the left middle temporal gyrus and the white matter underlying the inferior parietal cortex (see Fig.6) were also specifically involved. These areas have been extensively linked to object use and identification in many studies (Devlin et al., 2002; Spatt et al., 2002; Lewis, 2006; Weisberg et al., 2007) in recent years and have been moreover directly linked to tool naming (Martin et al., 1996; Chao et al., 1999). These results are in agreement with the recent claims, coming from fMRI studies (Chao and Martin, 2000; Kellenbach et al., 2003; Martin, 2007; Canessa et al., 2008) but also from neuropsychological investigations (Goodale et al., 1991; Hodges et al., 1999; Spatt et al., 2002), about the important role of left parietal areas in the sensorimotor transformations underlying action organization and object use, with perception

of a manipulable object affording the action towards it (Grezes and Decety, 2002; Rumiati et al., 2004; Johnson-Frey et al., 2005).

5.4.2 Category specificity following temporal lobes tumours:

As previously outlined, a category specific deficit for nonliving things has been more rarely reported than that for living entities (Gainotti, 2000; Capitani et al., 2003) and more importantly such evidence has come almost exclusively from single case investigations. Such studies are rarely able to assess individual differences in the relative strength of living things and artefacts deficits premorbidly, which could potentially produce selection biases (see e.g. Laws, 2005). Evidence for segregated cortical regions associated with naming deficits for artefacts have however been reported in some group studies. For example Damasio and colleagues (Damasio et al., 1996) found, in a large sample of patients with different aetiologies (but mainly stroke), that naming deficits for artefacts were especially associated with damage to left posterior inferolateral temporal cortex damage, particularly to the posterior portion of the left middle temporal and angular gyri. More recently, in a voxel-based morphometry study, conducted by Brambati and colleagues (Brambati et al., 2006), the cortical volume preserved in the left posterior middle temporal gyrus was positively correlated with the ability to name familiarity-matched nonliving items. The study was conducted on a large sample of patients suffering from different types of neurodegenerative diseases (see also Garrard et al, 1998, for related findings).

The results we report constitute a further confirmation that left posterior middle temporal regions are associated with a deficit in naming artefacts. This is especially important because our results come from a completely different population of brain-damaged patients, i.e. brain tumours, who consistently showed greater naming deficits for artefacts when the lesion involved left posterior middle temporal regions. Particularly striking, moreover, is the overlap between the sites of the lesions found in the study by Brambati and colleagues (Brambati et al., 2006), and the lesion site found in the sample of patients we investigated. The region of maximum overlap we found is clearly included and perfectly matches the region included in the peaks of maximum cortical volume reduction found by Brambati and colleagues.

5.4.3 Conclusions:

To conclude, the idea of a semantic system organized in a (both anatomically and functionally) undifferentiated network would seem to have great difficulty in accounting for these results. These finding rather supports the idea that semantic system may be organized in modality congruent 'channels', with the relative weight of information contained in these channels varying across different concepts (Warrington and McCarthy, 1983; Warrington and Shallice, 1984). However the specific prediction on the role of manipulability gradients in the knowledge of manipulable objects was only partially confirmed. Thus, the topic deserves deeper investigation.

CHAPTER 6:

6.1 A BRIEF SUMMARY

As already outlined in the introduction to this work, notwithstanding the great amount of attention dedicated in the past 30 years to the study of semantic memory, the mechanisms and structure of the semantic store still remain largely underspecified and not clearly explained. Symbolic of this situation is the representation of semantic memory "as an under-specified cloud in many standard models of cognition" (Humphreys and Forde, 2001).

The main aim of the present project was then to try "dissipating" at least partially this cloud and shed some light on the mechanisms that regulate the access to concepts, which has unfortunately been a largely neglected aspect of the study of semantic memory in the past years. As we said in chapter one, the first purpose of this project was that of investigating which are the mechanisms regulating the access to concepts and better specify their role. We then tried to show how, by better defining the mechanisms of access, it is possible to extract also useful information on the organization of the content of the semantic store, trying also to provide some anatomical evidence on the localization of these structures in the brain. To this aim, we used a combination of neuropsychological investigations and behavioural studies on healthy subjects, each of which provided cross-validation of the results found at the previous step.

In this chapter, the results of this project will be discussed and reviewed. First we will discuss the results of the first neuropsychological study (Chapter 2) in which we investigated the semantic access abilities of an unselected case series of left and right temporal lobes tumour patients, consistently showing a weakly refractory access syndrome. We then compared the results of the tumour patients with those of a group of healthy subjects on a speeded version of the same tasks (Chapter 3) trying to localize, from a cognitive point of view, the locus of refractory behaviour. We then investigated (Chapter 4) the presence of refractory effects in the recognition of objects sharing the same manipulation in another group of healthy subjects with another series of speeded matching tasks. Finally, in Chapter 5 we used the suggestion of manipulability being indeed a semantic feature to investigate its role in the rarely reported category specificity deficit for nonliving things, in a second unselected series of brain tumour patients.

The last section of this chapter will then deal with the limits of this project and will try to suggest possible future lines of development for the discussed topics.

6.2 DISCUSSION OF THE RESULTS OF THE PROJECT

6.2.1 Disconnecting the auditory input from the semantic system: a non-refractory access syndrome in left high grade brain tumours

The first aim of this project was that of investigating the semantic access abilities of brain tumour patients. The choice of brain tumours as the referring population of patients was dictated by two main considerations: the first was that one of the two access patients reported by Warrington and Cipolotti (1996) in their seminal work on the clinical characterization of refractory semantic access syndromes was indeed a tumour patient and no one has ever investigated the relationship between brain tumours and semantic access deficits. Investigating the effects of brain tumours on the semantic skills provides secondarily a further opportunity: stroke-induced lesions (traditionally linked to semantic access deficits) tend to be large, often involving extensive portions of the hemisphere, making it difficult to formulate specific anatomo-functional hypotheses. Brain tumours, instead, tend to induce lesions, on the average, which are more circumscribed, selective and restricted to the white matter.

From a theoretical point of view, the aim of the study was to try to answer some of the many questions still open on the mechanisms that regulate the access to concepts, in spite of a widespread agreement on the cognitive mechanisms underlying the degradation of semantic representations. In chapter 2 therefore we reported the results of a neuropsychological investigation of a series of unselected patients affected by brain tumours within the temporal lobes, on two spoken word-to-picture matching tasks which were aimed to assess consistency, rate of presentation and serial position effects (Experiment 1) and semantic distance and word frequency (Experiment 2).

Our findings show that in brain tumour patients, who had lesions affecting the temporal lobes, semantic impairments emerged in a considerable number of cases. These deficits were limited however to the only high-grade group. Left high grade patients, in particular, consistently showed a clear semantic access pattern, being inconsistent in whether they were correct or not (Experiment 1), and being dramatically influenced by the semantic distance

between the target and the distractors, but not at all by word frequency (experiment2). Surprisingly, however, none of the left high-grade tumour patients showed a significant rate of presentation effect (experiment1), the effect being significant only at a group level, due to a homogeneous weak tendency of the patients to benefit, to a certain degree, from slower presentation rates. Also serial position effects (experiment1) were almost absent in our sample of patients; the tendency of the patients to increase the number of errors with repeated presentations of the same target was present in only two of the left high grade tumour patients. Taken together, these results suggest the presence, in these patients, of semantic difficulties of a clear access type, but, since the influence of 'temporal factors' such as presentation rate and serial position were at most weak, the syndrome we found in these patients can hardly be defined as refractory (Warrington and McCarthy, 1987; Warrington and Cipolotti, 1996). On the other hand, patient SV, suffering form a left anterior fronto-temporal stroke and separately tested on the same tasks, showed clear refractory behaviour with evident rate of presentation and serial position effects.

The overlapping of lesion sites in the left high-grade tumour patients showed that the region of maximum overlap of lesions was located in the posterior superior portion of the left temporal lobe. This region is compatible with that reported in two of the patients described in Jefferies et al. (2007), who also behaved similarly with respect to left high grade tumour patients, showing semantic access difficulties with no signs of refractoriness, unlike the group of left anterior fronto-temporal patients they tested.

However Jefferies and colleagues believe that the differences between the behaviour of their anterior and posterior patients are not critical and that both lateral inferior prefrontal cortex and the temporo-parietal junction constitute a complex cognitive control network with an important role in tasks with high levels of selection demands (such as in the semantically close condition of a matching task). The failure of this control system prevents the competing activation of repeatedly activated representations to decay completely, particularly if they are semantically related. This leads in the end to summation effects over time. Unlike Jefferies and colleagues however, we think that the behaviour of our sample of left posterior temporal patients (but also that of the two posterior patients they tested) speaks against the claim that the differences in performance between anterior and posterior temporal patients are only minor, and on the contrary highlight two qualitatively different syndromes. It is indeed true that lateral

inferior prefrontal cortex (LIPFC) and temporo-parietal junction (TPJ) constitute a complex network of separate but interconnected areas (Parker et al., 2005; Powell et al., 2006). However, stroke patient SV, suffering from an the anterior left fronto-temporal lesion showed unequivocally refractory behaviour, as did the anterior patients in Jefferies et al (2007), while left posterior high grade tumour patients showed a clearly different non-refractory pattern of behaviour.

From the behavioural pattern provided by our patients and from the localisation of the lesion sites, we were led to argue that, functionally, the critical damage could be to the connections linking lexical processing regions in the superior posterior left temporal area (see e.g. Scott and Johnsrude, 2003) to the semantic processing areas, located more ventrally in the temporal lobes (e.g. Mummery et al., 1999; Devlin et al., 2002). Indeed the region of maximum lesion overlap is largely subcortical, suggesting the possibility of a disconnection syndrome. From a cognitive point of view, we suggested that the current syndrome could be conceived as the auditory verbal correspondence of the semantic access dyslexia syndrome originally described by Warrington and Shallice (1979) in the acquired dyslexic patient AR. Similarly to our patients, word frequency had only weak effects on AR. Moreover, AR produced semantic paraphasias in reading (substituting a target word with another one, semantically close) being able to efficiently categorise (semantically distant words were correctly identified). Therefore, this pattern suggests the presence of semantic distance effects in patient AR, though it was not directly investigated.

In 1991, Hinton and Shallice (1991; see also Plaut and Shallice, 1993b), built a multi-layer neural network simulation of the mapping of written words onto semantic representations. The network, through the operation of attractor basins and a series of clean-up units, with the function of 'cleaning' somewhat distorted patterns of input, was able to produce a correct target semantic pattern given a particular input of letters. By lesioning the network between the graphemic and the semantic levels, semantic errors occurred, as in AR, with categorizing ability intact. If we turn moreover to the output of the semantic system, patients have been described showing access patterns in production but without clear signs of refractoriness (Warrington and Leff, 2000; Gotts et al., 2002) and, in a similar context, Caramazza and Hillis (1990) also proposed that semantic errors could also occur after damage to lexical level. In these cases, the damage was supposed to occur outside the semantic system itself.

From a more clinical-neurological point of view, this study gave also useful insights on the cognitive impact of brain tumours in general. From this perspective, the main result from this study is the difference in the cognitive impact of high vs. low grade lesions. While high grade lesions, especially if left-sided, consistently produced semantic difficulties in the sample of patients we tested, low grade lesions had little, if any, impact on their semantic abilities.

The difference in the cognitive impact of fast versus slow tumours is widely acknowledged. It is well known that fast/aggressive high grade tumours (glioblastoma) are associated with reduced cognitive abilities and that cognitive level tend to deteriorate during the progression of the illness (e.g. Scheibel et al., 1996; Kayl and Meyers, 2003; Brown et al., 2006; Bosma et al., 2007). On the other hand low grade tumours have been found not to show cognitive deficits for many years during progression of the illness (see Desmurget et al., 2007 for review).

This fits well we the behaviour found in this sample of brain tumour patients. It is likely that sudden aggressive lesions within the temporal lobes such as those produced by glioblastoma may damage the semantic system leaving no time for the brain to compensate or re-organize the function. On the other hand, slowly-growing low grade lesions might develop in years in the brain leaving the time for the cognitive system to adapt to it and shift either in neighbouring brain structures or in the other hemisphere.

6.2.2 Looking for the locus of refractory behaviour

At the end of chapter 2 we concluded by saying that patients described generally as having a semantic access disorder might not be functionally unitary. Refractoriness is surely a major factor in explaining their performance, but cases have been reported, mostly in production (Warrington and Leff, 2000; Gotts et al., 2002), but, in our case, also in comprehension (see Chapter 2) in which semantic distance effects are reported in absence of a clear refractory pattern. A question that still remained open concerned whether refractory access dysphasia is a syndrome in which a disconnection between lexical and semantic stores (responsible for the semantic distance effect) and refractoriness (responsible for the sensitivity to temporal factors), simply co-occur or, on the contrary, refractory semantic access dysphasia is a unitary syndrome in which abnormal refractoriness is sufficient to produce all the critical effects. In this case, the one we described would simply be a different access syndrome from the refractory one.

Some of the results from the previous study suggested that the second possibility might be the most likely since the stroke patients SV we reported as a control patient was showing clearly refractory behaviour with a lesion which was fairly distant and more anterior (fronto-temporal) with respect to the one found in the tumour patients. Still, semantic distance effects in her performance were somewhat reduced with respect to the ones consistently found in the tumour patients.

The second study we performed (Chapter 3) was carried out in order to try to answer this as well as another important question: what is the cognitive locus of refractory behaviour? According to some models of word retrieval and production (Howard et al., 2006) refractory behaviour in word retrieval occurs as a consequence of the concomitant contribution of three cognitive mechanisms: shared activation (spreading within the semantic system between the target representation and the semantic neighbors); priming (strengthening of the output connections between the target semantic representation and its correspondent lexical representation) and competition (lateral inhibition process occurring at the output lexicon level between the target representation and the semantically related lexical candidates). Both the priming and the competition mechanisms in the model of Howard and colleagues are assumed to occur at a later stage of processing (the phonological output lexicon), after the processing at the semantic level has been completed. On the other hand, the literature on semantic access disorders, which mainly investigates these difficulties by means of comprehension tasks, suggests that the locus of the refractory behaviour might be within the semantic system itself (e.g. Warrington and Cipolotti, 1996; Forde and Humphreys, 1997).

Trying to answer these questions, in chapter 3 we presented the results of a behavioural study on a group of healthy subjects in which we aimed to reproduce a refractory semantic access pattern of performance in a healthy subjects with an appropriately modified version of the same comprehension tasks used with patients.

Experiment 1 was a speeded version of Experiment 2 of the first study, a word-to-picture matching task in which semantic distance and word frequency effects were investigated. The response-stimulus interval was reduced to zero in order to induce a mild refractory state also in healthy subjects. Results showed that an effect of semantic distance was found both with high and low frequency concepts. However, word frequency effects only occurred when target stimuli were semantically related when one could presume the refractoriness was higher,

suggesting word frequency having no effect when stimuli are unrelated and refractoriness is absent (see also Crutch and Warrington, 2005 experiment 1). This result might suggest a refractory state to take place in the healthy subjects, but since the semantic distance effect might be attributed also to disruption at a pre-semantic level of processing (see chapter 2) this evidence was not sufficient to localize the locus of refractory behaviour.

Therefore we reported the results of experiments 2 and 3 in which serial position and presentation rate effects were investigated in a task similar to Experiment one of chapter 2 but using a 'zero' seconds response-stimulus interval in the fast condition and 1 second in the slow condition. In both experiments we were able to find a clear presentation rate effect and in Experiment 3 also a clear serial position effect in a condition moreover in which subjects were largely familiarized with the stimuli presented. These results clearly suggested some amount of refractoriness taking place in the subjects and, since no activation of post semantic lexical representations is needed in order to perform the word to picture matching tasks used here, we were led to conclude that the locus of refractoriness taking place was within the semantic system itself.

Overall, these results are similar to those found by Schnur et al (2006), Belke et al (2005) and others on semantic blocking effects. However, differently from what obtained for example in the study by Belke and colleagues (2005), in which the presence of refractoriness was inferred form the observation of a reduction in the amount of facilitation in recognizing repeatedly presented stimuli, the amount of refractoriness we were able to induce in our paradigm was strong enough to impair the recognition ability of the subjects. It was possible to obtain such amount of refractoriness by removing any Response Stimulus Interval and this is compatible with the idea that stimulus repetition in the time window of a normal mild refractory neural state, as suggested by neurophysiological investigations (Tsodyks and Markram, 1997; Galarreta and Hestrin, 1998; Varela et al., 1999) might lead to summation of residual activation over time, generating some amount of refractoriness.

If, on the one hand, these data clearly suggest that the locus of origin of the refractoriness is within the semantic system itself, it is difficult, on the other hand, to model the exact mechanisms and cognitive structures giving rise to it.

As stated both in the introduction and the discussion of chapter 3, while there has been an extensive effort made over cognitive and computational modeling of word production

processes, less effort has been put into modeling word comprehension processes in the absence of spoken or written output. The only relevant model simulating the stages composing the word comprehension pathway, in tasks similar to the used in this study, is that proposed by Gotts and Plaut (2002) which, however, focused attention on the modeling of neuromodulation mechanisms (assuring efficient access to concepts) more than on the specification of the different processing stages. The neuromodualtion efficacy was implemented in the model, in terms of a scalar *'M'* value representing neuromodulatory levels in the synapses. This value influenced the activity of both the 'pre-synaptic' input layer units and the 'post-synaptic' semantic layer units.

Lower values of *'M'* simulated abnormal synaptic depression, causing enhanced refractoriness in the semantic network over time. The simulation by Gotts and Plaut reproduced nicely the pattern of performance provided by semantic access dysphasic patients. The only effect that was however not perfectly reproduced was the semantic distance effect, which, though mimicking the appropriate pattern, resulted somewhat small.

A possible explanation of this reduced semantic distance effect might be the lacking of interactivity within the network. Indeed in the simulation concepts correspond to patterns of activations of 'feature-like' units. The amount of 'neuromodulator' (implemented by the 'M' value) is equally distributed across the different 'features' in the network. Since more features are shared by concepts which were designed to be 'closely related', the amount of refractoriness was higher in the case of a reduced *'M'* value for these concepts. However, no direct interaction is assumed to occur between the 'feature-units' themselves, a factor which could add further influence to their activation states.

Interactivity, in a neural network, is usually achieved when units can mutually constrain each others in settling on the most consistent interpretation of the output (Plaut et al., 1996) and this is typically made possible by allowing feedback or recurrent connections among units. This is the classical principle which is adopted in *attractor* networks. In an attractor network the units interact with each others repeatedly updating their states in such a way that the activity of the input gradually settles into a stable state, within the correct basin. The cleaning up of the input is made possible by the direct interaction among the semantic units and feedback interactions with the input units. The network designed by Gotts and Plaut, by contrast, is a simple feed-forward network with no recurrent feedback connection between the stages and with no direct

connection between the units within the semantic layer (working in a more 'deterministic' way) and is therefore unable to build attractor basins. The authors indeed agreed (p.195) that a full instantiation of the model would need the addition of interactivity in the model, which was 'overlooked' for the sake of simplicity.

Some of the details lacking in their simulation can however be found in some earlier connectionist models developed in the past to account for naming errors in optic aphasic patients (Plaut and Shallice, 1993a), who have a selective deficit in naming visually presented objects. The network developed was isomorphic (with the exception of the presence of short-terms weights in the connections developed to account for perseverative errors) to the networks used to model the occurrence of semantic errors in the reading of deep dyslexic patients (Hinton and Shallice, 1991; McLeod et al., 2000; Plaut and Shallice, 1993b; see also the discussion of chapter 2).

Plaut and Shallice's (1993a) simulation for optic aphasia focuses mainly on the modeling of processing levels in the input stages to the semantic system. After training, the neural network was able to produce a final correct target semantic pattern given a particular pattern of activation of input units. The network operated by means of attractor basins. For the correct semantic target to be reached, the initial semantic representation produced by the input had to fall roughly within the correct basin. By the operation of a set of 'clean–up' units, a somewhat incorrect initial pattern of semantic activation is refined to later activate the correct target semantic representation (by gradient descent towards the 'minimum' of the correct basin). Another relevant point in this network was the existence of direct connections between sememe units which allowed the network to develop lateral inhibitory interactions between the activation of rival sememe units, and therefore implementing the 'competition' factor directly *within* the semantic system itself.

By damaging the network at a variety of points, Plaut and Shallice were able to reproduce the type of errors produced by optic aphasic patients. In particular, a high rate of semantic errors (which conceptually relate to semantic distance effects) was obtained when the damage involved the connections between the semantic and the clean-up layers. The result of this damage was an abnormal cleaning-up of the input which tended to increase its probability of falling within the wrong basin.

The drawback of this model is that it lacks any possible explanation of the cumulative effects which are typical of a refractory pattern of behaviour and which are, on the other hand, nicely implemented in Gotts and Plaut's (2002) model, which is also more biologically plausible. Therefore a model which could implement both principles (schematically outlined in Fig.1) would be important to test the validity of the outlined architecture for word comprehension mechanisms. The main question in conceiving such a model is whether, in conditions similar to those described by Gotts and Plaut, an attractor network would produce a larger semantic distance effect with respect to a more deterministic feed-forward network.

In the same conditions of enhanced synaptic depression, a main difference exists in principle between the dynamics of activation of the two types of networks. When in the non-interactive network a semantic pattern is activated in response to an input word some residual synaptic depression will persist in those units which are shared also by semantically related concepts. However such residual refractoriness will not, by definition, influence those units which are not shared by the two concepts, since no interaction is assumed and therefore the activity of one unit would not influence the activity of others. On the contrary, in an attractor network, residual refractoriness would partially spread in principle also to those units which were not directly shared between the concepts, since all the units of that concept would be connected with each other. This would in principle allow the speculation that at comparable levels of neuromodulatory damage, an attractor network would probably show higher levels of refractoriness and therefore commit a higher rate of errors.

Whatever the computational implementation, at this stage it is however impossible to assess whether the accumulation of refractoriness over time could be due to the failure of more 'deterministic' neuromodulatory mechanisms, or rather can be better accounted by the assumption of a failure in the action of cognitive selection structures, such as LIPFC (Jefferies and Lambon Ralph, 2006; Jefferies et al., 2007). A further possibility could moreover be that the cognitive control structures regulate the efficient access to concepts by modulating the action of neuromodulatory systems.

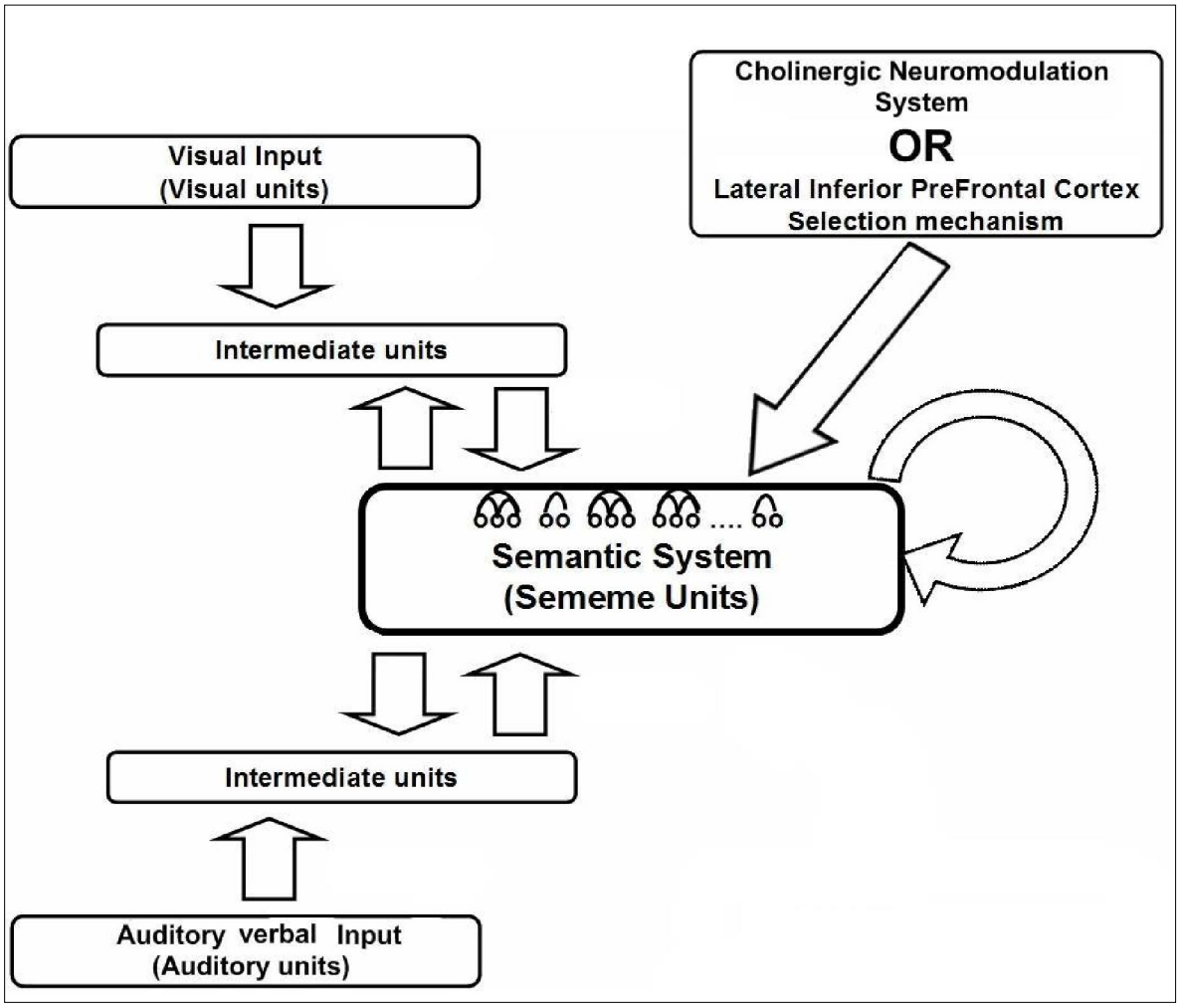


Fig.10: A tentative integration of the models of Plaut and Shallice (1993a) on access to semantics from a visual input and the neuromodulation mechanism responsible for the suppression of refractoriness within the semantic system proposed by Gotts and Plaut (2002).

6.2.3 Refractoriness reveals semantic features: the role of manipulability in object recognition

The presence of a clear refractory behaviour in a group of healthy subjects in tasks similar to those used to investigate semantic access disorders in patients and in which no post-semantic lexical stage of processing is needed in order to perform the tasks, led us to conclude that, apart from the specific cognitive or physiological mechanism generating it, the locus of a refractory behaviour should be within the semantic system itself. As we already said in other sections of this work (e.g. Chapter 4), according to some computational models of semantic

memory (e.g. Rumelhart et al., 1986; but also Damasio and Damasio, 1994; Tyler et al., 2000; Gotts and Plaut, 2002; Simmons and Barsalou, 2003) semantic representations are better conceived as a distributed pattern of activation of different 'neuron-like' semantic features. These semantic features differentially contribute to the characterization of the semantic representation. Some of these features are shared between concepts, partially defining the 'semantic' distance among them: the higher the number of features shared, the lower the semantic distance. In the light of this definition of semantic representations, refractoriness is held to arise as a consequence of accumulated residual synaptic depression among semantic features that are shared between concepts which are semantically related.

But if refractoriness is a process that involves only features that are part of the semantic representation of a concept, then its presence can in principle also be used as a tool to investigate whether a feature of a given concept is part of the semantic representation of a concept or not. This hypothesis drove the behavioural study we carried out and reported in chapter 4. In this second study on healthy participants, we built two speeded word to picture matching tasks to investigate whether the information about how an object is manipulated influences its recognition and specifically whether this information is indeed a semantic feature.

Although the neural pathways devoted to object recognition (occipito-temporal or "ventral") and those held to process the appropriate actions to manipulate visual objects correctly, (occipito-parietal or "dorsal") have been traditionally conceived as completely separated (Goodale et al., 1991; Goodale and Milner, 1992), converging lines of research have suggested in the recent years an interaction between the two systems at a behavioural level (e.g. Tucker and Ellis, 1998; Creem and Proffitt, 2001), as well as in fMRI investigations (e.g. Weisberg et al., 2007; Canessa et al., 2008). In particular a number of researches suggest that the way an object is actually manipulated influences the likelihood of it being recognized (e.g. Helbig et al., 2006) and some suggest that this information is part of the semantic representation of the object per se (e.g. Warrington and McCarthy, 1987).

The two experiments described in chapter 4 showed that, in a speeded forced-choice matching tasks (Experiment1), an object which is manipulated in the same way as a target one interferes with the recognition of the target object more than a visually similar one does. Moreover and most critically, in Experiment2 it is shown how the repeated presentation of the same couple of objects which are manipulated in similar ways, leads to an increasing degree of

interference in target recognition, causing a declining serial position effect which is one of the key phenomena suggesting refractoriness taking place. On the contrary the repeated presentation of objects sharing only visual similarity leads to a progressive improvement in the recognition of the target stimulus, highlighting the presence of a learning effect.

These results suggests not only that the action-related 'where' network and the recognition 'what' network might interact and influence each other (see e.g. Tucker and Ellis, 1998; Helbig et al., 2006; but also Creem and Proffitt, 2001) but also that the way an object is manipulated is indeed a semantic feature. Most critically, in identifying manipulable objects this feature is more important than the visual appearance. Indeed, the fact that the repeated presentation of stimuli sharing only visual similarity leads to a 'positive' serial position effect (learning), suggests indeed that these objects might be, semantically speaking, "distant" and that visual similarity therefore does not constitute a main proximity criterion within the semantic space for manipulable objects. The interference found between these types of objects seems therefore to be relegated at a pre-semantic perceptual level of processing.

To explain how the information about how the manipulation of an object becomes actually an important semantic feature for that object we suggested that, as proposed for example by Allport (1985), the knowledge about concepts might be distributed across all the areas that are active at the time of encoding. In the case of manipulable objects, these areas might largely involve the ones dedicated to encode the movement needed to interact in the appropriate way with the object. During the first approaches with the object a crucial role is played by the affordances, those perceptual "properties in the environment that are relevant for an animal's goals" (Gibson, 1979). If we refer to the manipulable objects domain, they can be defined as those physical properties of the objects which define the way in which it can be grasped. However, as elegantly shown by Creem and Proffitt (2001) these automatic grasping schemas are not always necessarily inked to a *proper use* of the object. The way an object must be handled for an appropriate use of it has to be learned with experience and subsequent interaction with the object. It is at this level that the motor interaction channel becomes critical in building a semantic definition and categorization of the object, being the favourite modality of interaction together with the visual. This type of information makes it possible to categorize the object basing on the uniqueness and distinctiveness of its manipulation movement. The more unique and distinctive the manipulation is, the easier will become the distinction between the

object and similar ones (see also Caramazza et al., 1990; De Renzi and Lucchelli, 1994; Tyler and Moss, 2001; Simmons and Barsalou, 2003 for discussion on the role of feature distinctiveness in building semantic representations).

6.2.4 Anatomical correlates of category specific naming deficits for manipulable objects

In the fifth chapter, we dealt with the last experimental investigation of this project. The idea behind the last study was triggered by some aspects of the results coming from the studies described in chapters 2 and 4. In chapter 2 we showed how tumours in the posterior portion of the left temporal lobe consistently produced semantic access deficits as indicated by the performance of the patients in the matching tasks we developed. The material used in those tasks comprised stimuli belonging only to the category of small manipulable objects. Moreover, anatomically, the region of maximum lesion overlap indicated in the lesion analysis of chapter 2 is compatible with those indicated by neuropsychological (e.g. Warrington and McCarthy, 1983; 1987; Brambati et al., 2006) as well as neuroimaging (e.g. Kellenbach et al., 2003; Mahon et al., 2007; Weisberg et al., 2007; Canessa et al., 2008) studies on the organization of the semantic content of the category of artefacts (specifically small manipulable objects). These areas often lie within the basin of those brain regions implicated in the processing of aspects of the motor interaction with the object (the so-called 'Dorsal Pathway). These areas include the left middle temporal, inferior and superior parietal areas of the left hemisphere, as well as pre-motor areas (Goodale et al., 1991; Goodale and Milner, 1992; Culham and Valyear, 2006).

However many of the neuroimaging studies on the topic have recently been questioned on the ground of the level at which the presumed semantic processing is occurring. In particular it has been proposed that the activation of at least some of the areas involved in this complex left hemisphere circuit (in particular pre-motor areas, but also potentially parietal) might also reflect a post-semantic activation more linked to explicit imagery processes, rather than reflecting access to stored knowledge about the concept (e.g. Harris et al., 2008; Papeo et al., 2009). However, in chapter 4 we showed that the way an object is manipulated can interfere with whether it is recognized and that repeated presentation of objects manipulated in similar ways, may induce refractoriness, suggesting manipulability being indeed be an important role in building the representation of manipulable objects *at a semantic level*.

From these findings and suggestions, we argued that if the degree of manipulability contributes heavily in building the representation of the nonliving category of manipulable objects, then the degree of manipulability of an object might be the key factor explaining the less frequently reported category specific semantic deficit for artefacts. In the final study we reported in chapter 5, we therefore described the performance of a second unselected series of brain tumour patients in a naming task involving both living and nonliving (artefacts) items, but with the latter category comprising only small manipulable objects divided, moreover, in high and low manipulability objects, basing on the degree of their manipulability. The key predictions for this study were that restricting the category of artefacts to the only manipulable objects a higher number of category specific naming deficits for artefacts than in previous studies would be detected. Secondarily, we predicted that if manipulability plays a critical role in defining manipulable objects at a semantic level, then patients showing deficits for artefacts would have greatest difficulties with objects having a higher degree of manipulability. On the other hand, objects having a low degree of manipulability would probably rely on different types of information in building their semantic representations, such as their physical sensory properties. If this was the case, then patients having difficulties with living things (which are more critically defined in terms of their sensory properties) should experience some difficulties also with some artefacts, but only those with low manipulability. Finally, we predicted that the patients showing category specific deficits for manipulable objects would have lesions involving those areas which lie within the basin of the so-called 'where' pathway.

In the study we reported, we were able to confirm many of these predictions: indeed a high number of patients showing significant category specific deficits for artefacts were reported both at a single case and at a group level of analysis. The anatomical lesion site associated with the larger category specific effect dimension was found in the left posterior middle and superior temporal areas with large part of the white matter underlying the left inferior parietal lobe also involved. These areas nicely fit with previous evidence reported on the topic (e.g. Chao and Martin, 2000; Martin, 2007; Weisberg et al., 2007; Canessa et al., 2008), but most strikingly perfectly matched with those indicated in a voxel-based morphometry similar naming study reported by Brambati and colleagues (2006).

On the other hand, the prediction we made on the performance of patients showing category specific deficit for living things was completely confirmed by the behaviour of patient

MU, who suffered form herpes simplex encephalitis. Together with a deficit in naming living things, he, consistently with our predictions, showed also a significant difficulty in naming weakly manipulable objects. However the parallel prediction that patients showing category specific naming deficit for artefacts should show also a greater difficulty in naming highly manipulable objects was only partially confirmed. Even though the effect was found both at a single case and at a group level of analysis, it was smaller than expected and, contrary to the results found at the broader category level, significant only at a cross subject level of analysis but not at a cross-stimulus level.

Although these results provide strong evidence in favour of a property based organization of the semantic content (e.g. Warrington and Shallice, 1984; Warrington and McCarthy, 1987; Damasio and Damasio, 1994; Simmons and Barsalou, 2003; Martin, 2007), they, however did not give the final conclusive answer to the question, leaving room for improvement of the paradigms as well as the hypotheses. Still the evidence we provided in this study (especially if integrated with those coming from the previous study presented in chapter 4) gives strong support to the claim that semantic information for manipulable objects might be determined by similarity metrics which are largely dependent on the motor-relevant attributes of these objects (Warrington and Shallice, 1984; Damasio and Damasio, 1994; Simmons and Barsalou, 2003;Mahon et al., 2007; Martin, 2007).

This claim, is only partially compatible with those theories of semantic organization of concrete concepts which claim (e.g. Tyler and Moss, 2001; Tyler et al., 2004) for an important role of the similarity metrics in organizing the distinctive features defining a concept, but do not postulate an anatomical specialization and segregation for these different features in separated "dedicated" brain regions (such as the left middle temporal and inferior parietal lobule).

On the other hand the fact that we indicated separate brain areas to be selectively involved in naming manipulable objects do not either support any "domain specific" hypothesis (Caramazza et al., 1990; Caramazza and Shelton, 1998) of semantic content organization. Indeed, we found that within the even very restricted domain of small manipulable objects, differences are found in the naming abilities of our patients depending on a "domain-independent" and instead "property-based" feature defining the stimuli we used, i.e. a motor-relevant attribute. What we claimed in chapter 5 is that the "domain" is just a behavioural by-product of the fact that very generally the category of artefacts is commonly assessed by using

often a large number of tools, and that many of these tools are generally highly manipulable objects, i.e. objects whose motor-relevant attributes critically distinguish them from among other similar objects. Hence, (see chapter 4) it seems that these motor-relevant attributes constitute the similarity metric that binds manipulable objects close in the semantic space, making manipulable objects prone to some refractoriness but only when these motor-relevant aspects (but not the visual ones) are "over-elicited".

The results we presented in the last two chapters of this thesis about the organization of the content of semantic memory store, were critically derived from hypotheses and findings obtained in the first part of this work in which the mechanisms regulating the access to concepts were investigated. In chapters 2 and 3 we found that the presence of refractory dynamics in the recognition of repeatedly presented stimuli seems to be the hallmark of a process occurring within, and not outside, the semantic system itself among features that are shared by semantically clustered concepts.

In chapter 4 we used this finding to investigate which of the features defining manipulable objects (visual or motor-related) is indeed a semantic feature, finding that only objects sharing the same manipulation undergo refractoriness over repeated presentations, while the repeated presentation of visually similar objects leads, on the contrary, to an improved recognition of those items. Finally, in chapter 5 we found that the brain areas which are damaged in patients showing difficulties in naming manipulable objects nicely match the areas previously indicated as being part of the complex left-lateralized network responsible of the processing of tools and motor-related tools information (e.g. Brambati et al., 2006; Canessa et al., 2008;Mahon et al., 2007; Martin, 2007; Weisberg et al., 2007). Critically however we were able to show that a patient showing category specific deficit for living things (MU) has also difficulties in naming weakly manipulable objects, for which motor-related semantic information is not critically linked to recognition, making this effect difficult to account for any "domain-specific" explanation of category specificity semantic deficits.

6.2.5. On the structure of semantic memory and semantic representations:

What is, then, our idea about the organization of the semantic system? What is semantic memory? And what is a semantic representation?

According to different approaches, semantic memory has been defined as a memory system able to memorize facts but also solving problems, make logical deductions (Rumelhart et al., 1972); or as an internal lexicon representing a person's knowledge of language (Kintsch, 1972); or a highly structured network of concepts, words and images, able to make inferences and comprehending language (Collins and Loftus, 1975). As we said in the introduction Warrington (1975) defined it as "that system which stores, processes and retrieves information about the meaning of words, concepts and facts" and therefore that system that allows us to give meaning to what we see and interact with in our everyday life. It is important to specify that the semantic representations that were investigated in the present work are only those referring to concepts that have a concrete referent, i.e. a referent in the physical world.

According to Tulving's classical view (Tulving, 1972) semantic memory does not register perceptible properties of inputs, but rather the 'cognitive referents' of input signals. According to this view, then, semantic representations appear to be 'disembodied' from their input, meaning that they are detached from any direct 'bodily interaction with the world'.

However, following Tulving's definition, semantic memory has only two types of input: 'perception' on the one hand, and 'thought' on the other. As far as the testing situations in this thesis are concerned, only the 'perception' input modality was investigated. According to Tulving, when input is perceptual, perceptual attributes are important only to the extent they permit unequivocal identification of the semantic referents. However, even if these properties themselves are *not* recorded in semantic memory, still they have always some cognitive referent (i.e. a 'link' to what they 'signify' at a cognitive level) (Tulving, 1972). This latter point is quite important since it introduces the so-called 'symbol grounding' problem (see e.g. Glenberg, 1997). If internal semantic representations are, in a sense, 'meaningless symbols', how can these symbols take on meaning? According to Glenberg, these symbols have to be grounded by the perceptual system: what a symbol means is what it refers to in the 'outside' world. Therefore semantic memory cannot be a set of representations which are just meaningless propositions and these representations cannot even be simply referring to a general 'lexicon', because words in a

lexicon are by definition also arbitrary symbols and need to be grounded themselves. According to Glenberg, then, symbols 'carry meaning' only when they are mapped into the world.

The consequence of this view is that there has to be a strong link between internal semantic representations and the processes of perception and interaction with the outside world. Both perception and interaction with the outside world can only happen through sensory or motor systems, but these systems might not provide equally important information for different classes of 'objects', since the perceptual/motor systems that will be more important for an object would be only those that would, using the words of Tulving, 'permit unequivocal identification of the semantic referents'.

But how would the semantic system, 'select' which sensory/motor channel would be more relevant to identify an object? And how should the semantic system be organized according to these premises? A simple computational principle is that the more frequently two components of a network are activated together, the stronger the connection between the components will become. According to Shallice (1988; 1993) it may be useful to think of the semantic system as a "a giant distributed net in which regions tend to be more specialized for different types of processes. This specialization could arise because of the pattern of connections -outside the semantic system itself-, used by each particular process. The basis on which differentiation between processing regions within the semantic system would develop would include *the most favoured modality of input* for that process" (cfr. Shallice, 1993, p.254). Is it reasonable to think that the most favoured modality of input would be the one that most easily (or critically) allows the identification of the concept and that, because of this, becomes *favoured.* If any kind of interference affects directly these "favoured" input modalities (because of the experimental paradigm used, as in chapter 4, or following brain damage, as in chapter 5) the processing within these 'specialized regions' will become difficult and therefore also the activation or identification of the target concept will be defective.

However, depending also on the task, different semantic metrics might become important in organizing the semantic representations at different levels. We are not claiming, for example, that manipulability is the only dimension important in defining the semantic representation of manipulable objects. The similarity metrics within the same concepts can be different depending on the level of analysis. As we have seen in Chapters 2 and 3 for example, it is also possible to obtain refractory effects by tapping a 'contextual' level of organization of the

concepts involved (which were however, always manipulable objects). Therefore, our conception of semantic representations is that of composite representations hierarchically organized and clustered in the neural space with different metrics depending on the different levels of organization.

6.3 LIMITS OF THE RESEARCH AND FURTHER DIRECTIONS

In this thesis we used a combination of neuropsychological and behavioural methods for investigating the access mechanisms as well as the content of semantic memory store. Each step provided evidence and drove a series of hypotheses which guided the building of the next step and both methods were used to cross-validate the findings obtained at the previous step, as well as formulating further questions to be investigated in the next. Though a series of answers were provided during the course of the work, still many questions remained unanswered and would deserve further investigation in order to better clarify the instances raised by these experiments.

First of all, if, as suggested in chapter 2, patients described as having a semantic access disorder may not be functionally unitary, it still remains unclear whether the major refractory component described in the majority of the semantic access dysphasic patients is due to a to a failure of frontal (or parietal) control mechanisms (Jefferies et al., 2007) or possibly through inappropriate regulation of cholinergic neuromodulatory mechanisms (Gotts and Plaut, 2002). In the sample of patients we tested, fronto-temporal lesions were largely under-represented, making it impossible to directly assess the role of frontal lesions in generating refractory behaviour. It would therefore be useful to directly contrast the performance of an anterior fronto-temporal and a posterior temporo-parietal group of patients on the same tasks we used in chapter 2 in order both to directly investigate this issue and also to evaluate whether the role of posterior temporo-parietal attentive areas is comparable to that of anterior frontal areas in generating potential refractory effects. It would moreover be useful to investigate better the performance of low-grade tumour patients in order to assess whether semantic access difficulties which were invisible at an accuracy level of analysis could emerge in reaction times using more refined paradigms.

Regarding the second study on the behavioural locus of refractory dynamics, we suggested a possible architecture of the cognitive modules which might be implicated in the

efficient access to stored representations. Of course it would be critical to test the appropriateness of the speculations formulated by developing a computational simulation of a semantic network implementing both principles of attractor architecture as well as a neurally plausible neuromodulation mechanisms simulation.

Some questions also remain open as regards the study presented in chapter 4. Indeed, while the effect of refractory interference found in the recognition of only those objects sharing the same manipulation, appears to be cognitively evident, any clue about the anatomical correlates of these effects were lacking in the study. The same stimuli and general paradigm might be used to investigate whether selective difficulties in identifying objects sharing similar manipulation are found by disrupting the processes occurring in different brain areas using repetitive trains of TMS pulses. Potential interference might be found when interfering with the neural activity in the left middle temporal or inferior parietal areas, as suggested by many other converging lines of evidence (Mahon et al., 2007; Martin, 2007; Weisberg et al., 2007; Canessa et al., 2008).

Another intriguing question is whether manipulation constitutes the *only* similarity metrics around which manipulable objects are organized. We already showed in chapters 2 and 3 that also manipulable objects sharing a similar context of use may undergo some degree of refractoriness in the appropriate conditions. It would be useful to investigate what is the role of the more "contextual" "functional" information about those types of artifacts (e.g. Canessa et al., 2008). It might be plausible to hypothesize that objects with the same "function" but not necessarily the same manipulation, might also undergo refractoriness with repeated presentations. And it would also be useful to test whether the different anatomical correlates suggested in the study by Canessa et al (2008) for the two types of information, are confirmed in terms of enhanced refractoriness following repeated TMS stimulation.

A complementary set of questions is related to the study presented in chapter 5. Indeed in this study anatomical correlates relating to deficits in naming highly manipulable objects were suggested. However, the task used was a naming task and it would be critical to know whether similar deficits are found also in a comprehension task. However an appropriate matching task should be used in which the distractors should be not only manipulable objects in general but also objects sharing the *same* manipulation; an appropriately modified version of the tasks used in chapter 4 would be possible to use. It seems moreover that the definition of highly

manipulable objects should be refined since the effects reported on this more fine grained level of analysis were not clear-cut and unequivocal.

A final suggestion might be proposed to investigate the features that build the representations of semantic categories. If manipulability, but not visual similarity has been shown to produce refractoriness in manipulable objects recognition, on the contrary the sharing of more perceptual, visual properties might induce refractoriness in recognizing living things in paradigms similar to those used in chapters 3 and 4. We might find that, in this case, the visual similarity of the item couples would predict the degree of refractoriness and therefore the amount of errors in recognition.

6.4 CONCLUSION

The aim of this project was to investigate both the mechanisms that regulate the access to stored semantic representation and the content of semantic representations themselves. A series of behavioural as well as neuropsychological studies were conducted showing that refractoriness is a major (but not the only) feature of the dysfunctional access to stored knowledge and that it is occurring among the representations stored within the semantic system itself. It was moreover shown that refractoriness occurs only among *semantic* features and this finding has been used to show that the content of semantic memory is built on similarity metrics which are derived from the semantic features which most critically define the concept and allow the distinction among concepts.

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Appendices:

Appendix A: Supplementary tables from Chapter 2:

Table A: Experiment 1: norms for stimuli used in the experiment.

Array	Target Stimulus	Frequency Ratings	Mean Semantic Distance Rating
1	1 Expresso pot	1	2.75
	2 Saucepan	3	
	3 Frying pan	3	
	4 Colander	1	
2	1 Wing mirror	2	2.15
	2 (Front) Seat	20	
	3 Steering wheel	19	
	4 Headlamp	2	
3	1 Stapler	1	2.00
	2 Clip	1	
	3 Ruler	1	
	4 Pencil-sharpener	1	
4	1 Grater	1	2.20
	2 Chopping knife	1	
	3 Whisk	5	
	4 Potato masher	1	
	MEAN	**3.94**	**2.28**

Table B: Experiment 2: norms for stimuli used in the experiment

Low-Freq Close	Frequency Ratings	Mean Sem. Dist. Rating	High-Freq Close	Frequency Ratings	Mean Sem. Dist. Rating
Strainer	2		Dish	61	
Funnel	3	2.80	Fork	6	2.30
Ladle	1		Spoon	8	
Bottle opener	1		Knife	41	
Scissors	5		Envelope	22	
Corkscrew	2	3.30	Pencil	9	2.25
Nutcracker	1		Pen	14	
Can opener	1		Eraser	26	
Shovel	1		Microphone	11	
Rake	1	2.35	Record	27	2.75
Pitchfork	1		Radio	51	
Pick	4		TV	50	
Screwdriver	2		Lamp	21	
Spanner	4	1.80	Frame	16	3.70
Pincers	1		Vase	18	
Pliers	2		Ashtray	5	
Trowel	1		Pitcher	3	
Drill	1	3.15	Cup	25	2.30
Saw	4		Glass	63	
Axe	1		Bottle	30	
MEAN	**1.95**	**2.68**	**MEAN**	**25.35**	**2.66**

Low-Freq Distant	Frequency Ratings	Mean Sem. Dist. Rating	High-Freq Distant	Frequency Ratings	Mean Sem. Dist. Rating
Chopping Board	1		Chain	68	
Garbage-can	4	6.10	Bracelett	10	5.70
Brush	2		Hoe	13	
Rolling pin	1		Cigarette	49	
Toaster	1		Suitcase	40	
RecordPlayer	4	5.75	Hammer	18	6.20
Tweezers	3		Lightbulb	9	
Scotch	2		Watch	47	
Sandglass	1		Alarm Clock	55	
Lighter	2	5.95	Candle	20	5.80
Boxing Gloves	3		Pipe	12	
Watercan	1		Ladder	101	
Rocksack	2		Phone	125	
Cork	3	6.15	Compass	12	5.25
Dustpan	1		Plug	20	
Cigar	3		Battery	11	
Sewing machine	1		Chair	51	
Compasses	2	5.95	Book	109	5.90
Syringe	3		Necklace	12	
TennisRacket	2		Matches	13	
MEAN	**2.10**	**5.98**	**MEAN**	**39.75**	**5.77**

Table C: Experiment 1: presentation rate effects in accuracy of left high, low grade and right hemisphere tumors.

Before surgery					After surgery				
Tumor Type	**Patient**	**Fast**	**Slow**	**Wilcoxon Match. Pairs**	**Tumor Type**	**Patient**	**Fast**	**Slow**	**Wilcoxon Match. Pairs**
Left High Gr.	*LH1*[1]	*21/40 (53%)*	*25/40 (63%)*	*p=0.26*	*Left High Gr.*	*LH1*	*22/40 (55%)*	*23/40 (57%)*	*p=0.82*
Left High Gr.	*LH2*[1]	*17/40 (43%)*	*17/40 (43%)*	*p=1*	*Left High Gr.*	*LH2*	*N.T.*	*N.T.*	*N.T.*
Left High Gr.	LH3	44/48 (92%)*	46/48 (96%)*	p=0,46	Left High Gr.	LH3	46/48 (96%)*	46/48 (96%)*	p=1
Left High Gr.	LH4	44/48 (92%)*	42/48 (88%)*	p=0,46	Left High Gr.	LH4	39/48 (81%)*	45/48 (94%)*	p=0.09
Left High Gr.	LH5	33/48 (69%)*	39/48 (81%)*	p=0,058	Left High Gr.	LH5	32/48 (67%)*	37/48 (77%)*	p=0.22
Left High Gr.	LH6	23/48 (48%)*	30/48 (63%)*	p=0,18	Left High Gr.	LH6	29/48 (60%)*	36/48 (75%)*	p=0,16
Left High Gr.	LH7	21/48 (44%)*	26/48 (54%)*	p=0,34	Left High Gr.	LH7	N.T.	N.T.	N.T.
Left Low Gr.	LL1	48/48 (100%)	48/48 (100%)	p=1	Left Low Gr.	LL1	48/48 (100%)	48/48 (100%)	p=1
Left Low Gr.	LL2	46/48 (96%)*	48/48 (100%)	p=1	Left Low Gr.	LL2	47/48 (98%)	48/48 (100%)	p=1
Left Low Gr.	LL3	48/48 (100%)	48/48 (100%)	p=1	Left Low Gr.	LL3	48/48 (100%)	47/48 (98%)	p=1
Left Low Gr.	LL4	47/48 (98%)	48/48 (100%)	p=1	Left Low Gr.	LL4	48/48 (100%)	48/48 (100%)	p=1
Left Low Gr.	LL5	48/48 (100%)	48/48 (100%)	p=1	Left Low Gr.	LL5	N.T.	N.T.	N.T.
Left Low Gr.	LL6	48/48 (100%)	48/48 (100%)	p=1	Left Low Gr.	LL6	48/48 (100%)	48/48 (100%)	p=1
Right High Gr.	RH1	46/48 (96%)*	46/48 (96%)*	p=1	Right High Gr.	RH1	47/48 (98%)	48/48 (100%)	p=1
Right High Gr.	RH2	39/48 (81%)*	42/48 (88%)*	p=0,31	Right High Gr.	RH2	42/48 (88%)*	45/48 (94%)*	p=0.31
Right High Gr.	RH3	45/48 (94%)*	46/48 (96%)*	p=0,68	Right High Gr.	RH3	41/48 (85%)*	45/48 (94%)*	p=0.20
Right Low Gr.	RL1	41/48 (85%)*	41/48 (85%)*	p=1	Right Low Gr.	RL1	N.T.	N.T.	N.T.
Right Low Gr.	RL2	47/48 (98%)	48/48 (100%)	p=1	Right Low Gr.	RL2	N.T.	N.T.	N.T.
Right Low Gr.	RL3	48/48 (100%)	48/48 (100%)	p=1	Right Low Gr.	RL3	48/48 (100%)	48/48 (100%)	p=1
Right Low Gr.	RL4	47/48 (98%)	48/48 (100%)	p=1	Right Low Gr.	RL4	47/48 (98%)	48/48 (100%)	p=1

* Scores considered to be pathological (cutoff= less or equal to the score obtained by the worst of the control subjects: fast: ≤96%; slow: ≤96%)

N.t. = not tested.

[1] patients lh1 and lh2 were administered with a different version of exp1 (see pag.1 of this section for further details)

Table D: Experiment 1: serial position effect analysis by patient: left high, low grade and right hemisphere tumors.

Before surgery					After surgery				
Tumor Type	**Pat.**	vvx/vxx	xvv/xxv	**Binomial Test P level**	**Tumor Type**	**Pat.**	vvx/vxx	xvv/xxv	**Binomial Test P level**
Left High Gr.	*LH1*[1]	*6*	*5*	*0.12*	*Left High Gr.*	*LH1*	*5*	*1*	*0.017*
Left High Gr.	*LH2*[1]	*6*	*6*	*0.17*	*Left High Gr.*	*LH2*	*N.T.*	*N.T.*	*N.T.*
Left High Gr.	LH3	0	4	***n.c.***	Left High Gr.	LH3	***n.c.***	***n.c.***	***n.c.***
Left High Gr.	LH4	1	3	0.75	Left High Gr.	LH4	1	6	0.91
Left High Gr.	LH5	4	5	0.27	Left High Gr.	LH5	3	6	0.53
Left High Gr.	LH6	8	3	0.004	Left High Gr.	LH6	9	4	0.004
Left High Gr.	LH7	5	8	0.34	Left High Gr.	LH7	N.T.	N.T.	N.T.
Left Low Gr.	LL1	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL1	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL2	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL2	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL3	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL3	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL4	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL4	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL5	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL5	N.T.	N.T.	N.T.
Left Low Gr.	LL6	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL6	***n.c.***	***n.c.***	***n.c.***
Right High Gr.	RH1	***n.c.***	***n.c.***	***n.c.***	Right High Gr.	RH1	***n.c.***	***n.c.***	***n.c.***
Right High Gr.	RH2	2	3	0.47	Right High Gr.	RH2	1	3	0.76
Right High Gr.	RH3	0	2	***n.c.***	Right High Gr.	RH3	1	1	0.51
Right Low Gr.	RL1	0	1	***n.c.***	Right Low Gr.	RL1	N.T.	N.T.	N.T.
Right Low Gr.	RL2	***n.c.***	***n.c.***	***n.c.***	Right Low Gr.	RL2	N.T.	N.T.	N.T.
Right Low Gr.	RL3	***n.c.***	***n.c.***	***n.c.***	Right Low Gr.	RL3	***n.c.***	***n.c.***	***n.c.***
Right Low Gr.	RL4	***n.c.***	***n.c.***	***n.c.***	Right Low Gr.	RL4	***n.c.***	***n.c.***	***n.c.***

N.T. = not tested. n.c. = not computed (≤ 3 errors in the condition or impossible to compute)

[1] patients lh1 and lh2 were administered with a different version of exp1 (see pag.1 of the supplementary material for further details)

Table E: Experiment 2: semantic distance effects in accuracy. Left high, low grade and right hemisphere tumors.

Before surgery					After surgery				
Tumor Type	**Patient**	**Close**	**Distant**	**Signif. ($\chi^2_{(1)}$)**	**Tumor Type**	**Patient**	**Close**	**Distant**	**Signif. ($\chi^2_{(1)}$)**
Left High Gr.	LH1	23/40 (56%)*	39/40 (98%)*	p<0.0001	Left High Gr.	LH1	24/40 (68%)*	36/40 (90%)*	p<0.05
Left High Gr.	LH2	12/40 (30%)*	28/40 (70%)*	p<0.001	Left High Gr.	LH2	N.T.	N.T.	N.T.
Left High Gr.	LH3	38/40 (95%)	39/40 (98%)*	n.s.	Left High Gr.	LH3	36/40 (90%)*	39/40 (98%)*	n.s.
Left High Gr.	LH4	34/40 (85%)*	39/40 (98%)*	p=0.05	Left High Gr.	LH4	31/40 (78%)*	34/40 (85%)*	n.s.
Left High Gr.	LH5	32/40 (80%)*	38/40 (95%)*	p<0.05	Left High Gr.	LH5	28/40 (70%)*	38/40 (95%)*	p<0.01
Left High Gr.	LH6	27/40 (68%)*	34/40 (85%)*	p=0.05	Left High Gr.	LH6	31/40 (78%)*	36/40 (90%)*	p<0.01
Left High Gr.	LH7	19/40 (46%)*	28/40 (70%)*	p<0.05	Left High Gr.	LH7	N.T.	N.T.	N.T.
Left Low Gr.	LL1	40/40 (100%)	40/40 (100%)	n.s.	Left Low Gr.	LL1	40/40 (100%)	40/40 (100%)	n.s.
Left Low Gr.	LL2	40/40 (100%)	40/40 (100%)	n.s.	Left Low Gr.	LL2	40/40 (100%)	40/40 (100%)	n.s.
Left Low Gr.	LL3	40/40 (100%)	40/40 (100%)	n.s.	Left Low Gr.	LL3	40/40 (100%)	40/40 (100%)	n.s.
Left Low Gr.	LL4	38/40 (95%)	40/40 (100%)	n.s.	Left Low Gr.	LL4	39/40 (98%)	40/40 (100%)	n.s.
Left Low Gr.	LL5	40/40 (100%)	40/40 (100%)	n.s.	Left Low Gr.	LL5	N.T.	N.T.	N.T.
Left Low Gr.	LL6	40/40 (100%)	40/40 (100%)	n.s.	Left Low Gr.	LL6	37/40 (93%)*	40/40 (100%)	n.s.
Right High Gr	RH1	36/40 (90%)*	40/40 (100%)	p=0.05	Right High Gr	RH1	36/40 (90%)*	40/40 (100%)	p=0.05
Right High Gr	RH2	35/40 (86%)*	34/40 (85%)*	n.s.	Right High Gr	RH2	36/40 (90%)*	36/40 (90%)*	n.s.
Right High Gr	RH3	34/40 (85%)*	36/40 (90%)*	n.s.	Right High Gr	RH3	34/40 (85%)*	36/40 (90%)*	n.s.
Right Low Gr.	RL1	36/40 (90%)*	39/40 (98%)*	n.s.	Right Low Gr.	RL1	N.T.	N.T.	N.T.
Right Low Gr.	RL2	40/40 (100%)	40/40 (100%)	n.s.	Right Low Gr.	RL2	N.T.	N.T.	N.T.
Right Low Gr.	RL3	39/40 (98%)	40/40 (100%)	n.s.	Right Low Gr.	RL3	38/40 (95%)	40/40 (100%)	n.s.
Right Low Gr.	RL4	40/40 (100%)	40/40 (100%)	n.s.	Right Low Gr.	RL4	40/40 (100%)	40/40 (100%)	n.s.

*scores considered to be pathological (cutoff= less or equal to the score obtained by the worst of the control subjects: close: ≤ 93; distant: ≤ 98; low freq: ≤ 95; high freq: ≤ 95)
N.t.: not tested

Table F: Experiment 2: word frequency effects in accuracy. Left high, low grade and right hemisphere tumors.

Before surgery					After surgery				
Tumor Type	**Patient**	**Low Freq.**	**High Freq.**	**Signif. ($\chi^2_{(1)}$)**	**Tumor Type**	**Patient**	**Low Freq.**	**High Freq.**	**Signif. ($\chi^2_{(1)}$)**
Left High Gr.	LH1	29/40 (72%)*	33/40 (83%)*	n.s.	Left High Gr.	LH1	33/40 (83%)*	30/40 (75%)*	n.s.
Left High Gr.	LH2	21/40 (53%)*	19/40 (48%)*	n.s.	Left High Gr.	LH2	N.T.	N.T.	N.T.
Left High Gr.	LH3	37/40 (93%)*	40/40 (100%)	n.s.	Left High Gr.	LH3	37/40 (93%)*	38/40 (95%)*	n.s.
Left High Gr.	LH4	36/40 (90%)*	37/40 (93%)*	n.s.	Left High Gr.	LH4	34/40 (85%)*	31/40 (78%)*	n.s.
Left High Gr.	LH5	35/40 (88%)*	35/40 (88%)*	n.s.	Left High Gr.	LH5	34/40 (85%)*	32/40 (80%)*	n.s.
Left High Gr.	LH6	30/40 (75%)*	31/40 (78%)*	n.s.	Left High Gr.	LH6	36/40 (90%)*	33/40 (83%)*	n.s.
Left High Gr.	LH7	24/40 (60%)*	23/40 (56%)*	n.s.	Left High Gr.	LH7	N.T.	N.T.	N.T.
Left Low Gr.	LL1	40/40 (100%)	40/40 (100%)	n.s.	Left Low Gr.	LL1	40/40 (100%)	40/40 (100%)	n.s.
Left Low Gr.	LL2	40/40 (100%)	40/40 (100%)	n.s.	Left Low Gr.	LL2	40/40 (100%)	40/40 (100%)	n.s.
Left Low Gr.	LL3	40/40 (100%)	40/40 (100%)	n.s.	Left Low Gr.	LL3	40/40 (100%)	40/40 (100%)	n.s.
Left Low Gr.	LL4	39/40 (98%)	39/40 (98%)	n.s.	Left Low Gr.	LL4	40/40 (100%)	39/40 (98%)	n.s.
Left Low Gr.	LL5	40/40 (100%)	40/40 (100%)	n.s.	Left Low Gr.	LL5	N.T.	N.T.	N.T.
Left Low Gr.	LL6	40/40 (100%)	40/40 (100%)	n.s.	Left Low Gr.	LL6	37/40 (93%)*	40/40 (100%)	n.s.
Right High Gr.	RH1	37/40 (93%)*	39/40 (98%)	n.s.	Right High Gr	RH1	37/40 (93%)*	39/40 (98%)	n.s.
Right High Gr.	RH2	33/40 (83%)*	36/40 (90%)*	n.s.	Right High Gr	RH2	33/40 (83%)*	39/40 (98%)	$p<0.05$
Right High Gr.	RH3	34/40 (85%)*	36/40 (90%)*	n.s.	Right High Gr	RH3	36/40 (90%)*	34/40 (85%)*	n.s.
Right Low Gr.	RL1	38/40 (95%)*	37/40 (93%)*	n.s.	Right Low Gr.	RL1	N.T.	N.T.	N.T.
Right Low Gr.	RL2	40/40 (100%)	40/40 (100%)	n.s.	Right Low Gr.	RL2	N.T.	N.T.	N.T.
Right Low Gr.	RL3	39/40 (98%)	40/40 (100%)	n.s.	Right Low Gr.	RL3	39/40 (98%)	39/40 (98%)	n.s.
Right Low Gr.	RL4	40/40 (100%)	40/40 (100%)	n.s.	Right Low Gr.	RL4	40/40 (100%)	40/40 (100%)	n.s.

*scores considered to be pathological (cutoff= less or equal to the score obtained by the worse of the control subjects: close: ≤ 93; distant: ≤ 98; low freq: ≤ 95; high freq: ≤ 95)
N.t.: not tested

Table G: Experiment 1: cortical damaged patients: semantic distance and word frequency effects

	ACCURACY				
	Lesion Type	**Patient**	**Close**	**Distant**	**Signif. ($\chi^2_{(1)}$)**
SEM DIST	HSE	MU	36/40 (90%)*	37/40 (93%)*	n.s.
	Atrophy	MG	33/40 (83%)*	37/40 (93%)*	n.s.
WORD FREQ	HSE	MU	34/40 (85%)*	39/40 (98%)*	p=0.05
	Atrophy	MG	32/40 (80%)*	38/40 (95%)*	p<0.05

*scores considered to be pathological

Table H: Experiment 2: cortical damaged patients: consistency and presentation rate effects

CONSISTENCY					
Lesion Type	**Patient**		**Consistent** (vvv/xxx)	**Inconsitent** (vvvx/vxx)	**Signif. ($\chi^2_{(1)}$)**
HSE	MU	expected	10	6	p<0.05^
		observed	14	2	
Atrophy[1]	*MG*	*expected*	*13*	*7*	*p<0.01^*
		observed	*19*	*1*	
PRESENTATION RATE					
Lesion Type	**Patient**		**Fast**	**Slow**	**Wilcoxon Match. Pairs**
HSE	MU		42/48 (88%)*	42/48 (88%)*	p=1
Atrophy[1]	*MG*		*31/40 (78%)**	*29/40 (73%)**	*p=0.6*

^Significant results indicate a performance more consistent than the expected
[1] patients MG was administered with a different version of exp1
* scores considered being pathological

Table I: Stroke Patient SV: performance on experiments 1 and 2.

CONSISTENCY				
Testing session		**Consistent** (vvv/xxx)	**Inconsitent** (vvvx/vxx)	**Signif.** ($\chi^2_{(1)}$)
1st	expected	5	11	n.s.
	observed	4	12	
2nd	expected	4	12	n.s.
	observed	6	10	
SERIAL POSITION				
Testing session		vvx/vxx	xvv/xxv	**Binomial test p-level**
1st		8	4	p<0.01^
2nd		3	7	n.s.
PRESENTATION RATE				
Testing session		**Fast**	**Slow**	**Wilcoxon Match. Pairs**
1st		19/48 (37%)*	29/48 (60%)*	p<0.05
2nd		23/48 (48%)*	37/48 (77%)*	p<0.01
SEMANTIC DISTANCE				
Testing session		**Close**	**Distant**	**Signif.** ($\chi^2_{(1)}$)
1st		25/40 (62%)*	37/40 (92%)*	p<0.0001
2nd		26/40 (65%)*	32/40 (80%)*	n.s.
WORD FREQUENCY				
Testing session		**Low**	**High**	**Signif.** ($\chi^2_{(1)}$)
1st		29/40 (72%)*	33/40 (82%)*	n.s.
2nd		29/40 (72%)*	29/40 (72%)*	n.s.

Table J: Accuracy levels for each of the patients in the 4 different distance/frequency blocks.

	BEFORE SURGERY				AFTER SURGERY			
PATIENT	**LOW CLOSE**	**HIGH CLOSE**	**LOW DISTANT**	**HIGH DISTANT**	**LOW CLOSE**	**HIGH CLOSE**	**LOW DISTANT**	**HIGH DISTANT**
LH1	9	14	20	18	15	12	19	18
LH2	6	6	15	13	N.T.	N.T.	N.T.	N.T.
LH3	18	20	19	20	17	19	20	19
LH4	16	18	20	19	18	13	16	18
LH5	16	16	19	19	14	14	20	18
LH6	13	14	17	17	16	15	20	18
LH7	7	12	17	11	N.T.	N.T.	N.T.	N.T.
MEAN: (n/20)	**12.14**	**14.29**	**18.14**	**16.71**	**16.00**	**14.60**	**19.00**	**18.20**
SD	**4.81**	**4.54**	**1.86**	**3.40**	**1.58**	**2.70**	**1.73**	**0.45**
LL1	20	20	20	20	20	20	20	20
LL2	20	20	20	20	20	20	20	20
LL3	20	20	20	20	20	20	20	20
LL4	19	19	20	20	19	20	20	20
LL5	20	20	20	20	N.T.	N.T.	N.T.	N.T.
LL6	20	20	20	20	17	20	20	20
MEAN: (n/20)	**19.83**	**19.83**	**20.00**	**20.00**	**19.20**	**20.00**	**20.00**	**20.00**
SD	**0.41**	**0.41**	**0.00**	**0.00**	**1.30**	**0.00**	**0.00**	**0.00**
RH1	17	19	20	20	17	19	20	20
RH2	17	18	16	18	16	20	17	19
RH3	16	18	19	17	19	15	17	19
MEAN: (n/20)	**16.67**	**18.33**	**18.33**	**18.33**	**17.33**	**18.00**	**18.00**	**19.33**
SD	**0.58**	**0.58**	**2.08**	**1.53**	**1.53**	**2.65**	**1.73**	**0.58**
RL1	18	18	20	19	N.T.	N.T.	N.T.	N.T.
RL2	20	20	20	20	N.T.	N.T.	N.T.	N.T.
RL3	19	20	20	20	19	19	20	20
RL4	20	20	20	20	20	20	20	20
MEAN: (n/20)	**19.25**	**19.50**	**20.00**	**19.75**	**19.50**	**19.50**	**20.00**	**20.00**
SD	**0.96**	**1.00**	**0.00**	**0.50**	**0.71**	**0.71**	**0.00**	**0.00**

Table K: Consistency calculation: BEFORE SURGERY: Bonferroni correction threshold on φ test and logistic regression: p=0.025

Before surgery									
Tumor Type	**Pat.**		**Consistent (VVV/XXX)**	**Inconsitent (VVX/VXX)**	**$\chi^2_{(1)}$**	**$\varphi_{(1)}$ (1st-2nd)**	**$\varphi_{(1)}$ (2nd-3rd)**	**Logistic regression (1st-2nd)**	**Logistic regression (2nd-3rd)**
Left High Gr.	LH1	expected	10	10	n.s.*	n.s.		n.s.	
		observed	7	13					
Left High Gr.	LH2	expected	10	10	n.s.	n.s.		n.s.	
		observed	7	13					
Left High Gr.	LH3	expected	13	3	n.s.	n.s.	***n.c.***	n.s.	***n.c.***
		observed	12	4					
Left High Gr.	LH4	expected	13	3	n.s.	n.s.	n.s.	n.s.	n.s.
		observed	12	4					
Left High Gr.	LH5	expected	6	10	n.s.	n.s.	n.s.	n.s.	n.s.
		observed	7	9					
Left High Gr.	LH6	expected	4	12	n.s.	n.s.	n.s.	p<0.01	n.s.
		observed	5	11					
Left High Gr.	LH7	expected	4	12	n.s.	n.s.	n.s.	n.s.	n.s.
		observed	3	13					
Left Low Gr.	LL1	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL2	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL3	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL4	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL5	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL6	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Right High Gr.	RH1	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Right High Gr.	RH2	expected	9	7	n.s.	n.s.	n.s.	n.s.	n.s.
		observed	11	5					
Right High Gr.	RH3	expected	13	3	n.s.	***n.c.***	n.s.	n.s.	***n.c.***
		observed	14	2					
Right Low Gr.	RL1	expected	10	6	p<0.05	n.s.	p<0.01	p<0.01	p<0.001
		observed	15	1					
Right Low Gr.	RL2	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Right Low Gr.	RL3	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Right Low Gr.	RL4	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***

Table L (a): Consistency calculation: AFTER SURGERY: Bonferroni correction threshold on φ test and logistic regression: p=0.025

After surgery									
Tumor Type	**Pat.**		**Consistent (vvv/xxx)**	**Inconsitent (vvx/vxx)**	**χ^2 (1)**	**φ (1)**		**Logistic regression**	
						(1st-2nd)	**(2nd-3rd)**	**(1st-2nd)**	**(2nd-3rd)**
Left High Gr.	LH1	expected	10	10	n.s.	n.s.		n.s.	
		observed	13	7					
Left High Gr.	LH2	N.T.	N.T.	N.T.	N.T.	N.T.		N.T.	
Left High Gr.	LH3	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left High Gr.	LH4	expected	9	7	n.s.	n.s.	n.s.	n.s.	n.s.
		observed	9	7					
Left High Gr.	LH5	expected	5	11	n.s.	n.s.	n.s.	n.s.	n.s.
		observed	7	9					
Left High Gr.	LH6	expected	5	11	n.s.	n.s.	n.s.	n.s.	n.s.
		observed	3	13					
Left High Gr.	LH7	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.
Left Low Gr.	LL1	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL2	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL3	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL4	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL5	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.
Left Low Gr.	LL6	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Right High Gr.	RH1	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Right High Gr.	RH2	expected	11	5	n.s.	n.s.	n.s.	n.s.	n.s.
		observed	12	4					
Right High Gr.	RH3	expected	10	6	p<0.05	n.s.	p<0.01	n.s.	p<0.01
		observed	14	2					
Right Low Gr.	RL1	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.
Right Low Gr.	RL2	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Right Low Gr.	RL3	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***
Right Low Gr.	RL4	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***	***n.c.***

Table L (b): Consistency calculation: effects of familiarity in predicting accuracy on each presentation: Bonferroni correction threshold: p=0.017

Before surgery					After surgery				
Tumor Type	**Patient**	**Familiarity (Log. Regr.) 1st**	**2nd**	**3rd**	**Tumor Type**	**Patient**	**Familiarity (Log. Regr.) 1st**	**2nd**	**3rd**
Left High Gr.	LH1	n.s.	n.s.		Left High Gr.	LH1	n.s.	n.s.	
Left High Gr.	LH2	n.s.	n.s.		Left High Gr.	LH2	N.T.	N.T.	
Left High Gr.	LH3	n.s.	n.s.	n.s.	Left High Gr.	LH3	***n.c.***	***n.c.***	***n.c.***
Left High Gr.	LH4	n.s.	n.s.	n.s.	Left High Gr.	LH4	n.s.	n.s.	n.s.
Left High Gr.	LH5	n.s.	n.s.	n.s.	Left High Gr.	LH5	n.s.	n.s.	n.s.
Left High Gr.	LH6	n.s.	n.s.	n.s.	Left High Gr.	LH6	n.s.	n.s.	n.s.
Left High Gr.	LH7	n.s.	n.s.	n.s.	Left High Gr.	LH7	N.T.	N.T.	N.T.
Left Low Gr.	LL1	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL1	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL2	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL2	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL3	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL3	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL4	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL4	***n.c.***	***n.c.***	***n.c.***
Left Low Gr.	LL5	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL5	N.T.	N.T.	N.T.
Left Low Gr.	LL6	***n.c.***	***n.c.***	***n.c.***	Left Low Gr.	LL6	***n.c.***	***n.c.***	***n.c.***
Right High Gr.	RH1	***n.c.***	***n.c.***	***n.c.***	Right High Gr.	RH1	***n.c.***	***n.c.***	***n.c.***
Right High Gr.	RH2	n.s.	n.s.	n.s.	Right High Gr.	RH2	n.s.	n.s.	n.s.
Right High Gr.	RH3	n.s.	n.s.	***n.c.***	Right High Gr.	RH3	n.s.	n.s.	n.s.
Right Low Gr.	RL1	n.s.	n.s.	n.s.	Right Low Gr.	RL1	N.T.	N.T.	N.T.
Right Low Gr.	RL2	***n.c.***	***n.c.***	***n.c.***	Right Low Gr.	RL2	***n.c.***	***n.c.***	***n.c.***
Right Low Gr.	RL3	***n.c.***	***n.c.***	***n.c.***	Right Low Gr.	RL3	***n.c.***	***n.c.***	***n.c.***
Right Low Gr.	RL4	***n.c.***	***n.c.***	***n.c.***	Right Low Gr.	RL4	***n.c.***	***n.c.***	***n.c.***

Table M: EFFECT SIZE CALCULATION: PRESENTATION RATE

PRESENTATION RATE: EFFECT SIZE

BEFORE SURGERY

Contrast	Effect Size: Eta-Squared	Contrast	Cohen's '*d*' on Ctrls SD	Hedges 'g'
Ctrls Vs. High Gr. Vs. Low Gr	0.37	Ctrls Vs. HighGr	3.25	
		Ctrls Vs. LowGr	1.00	
		HiGr Vs. LowGr		1.01
Ctrls Vs. LeftHigh Vs. Right High	0,46	Ctrls Vs. LeftHigh	1.48	
		Ctrls Vs. RightHigh	1.83	
		LeftHigh Vs. RightHigh		0.85
Ctrls Vs. LeftHem Vs. RightHem	0,24	Ctrls Vs. LeftHem	2.41	
		Ctrls Vs. RightHem	1.36	
		LeftHem Vs. RightHem		0.42
Ctrls Vs. LeftHigh Vs. LeftLow	0,45	Ctrls Vs. LeftHigh	1.48	
		Ctrls Vs. LeftLow	-0.25	
		LeftHigh Vs. LeftLow		1.24

AFTER SURGERY

Contrast	Effect Size: Eta-Squared	Contrast	Cohen's '*d*' on Ctrls SD	Hedges 'g'
Ctrls Vs. High Gr. Vs. Low Gr	0,59	Ctrls Vs. HighGr	4.21	
		Ctrls Vs. LowGr	0.64	
		HiGr Vs. LowGr		5.18
Ctrls Vs. LeftHigh Vs. Right High	0,70	Ctrls Vs. LeftHigh	5.00	
		Ctrls Vs. RightHigh	3.17	
		LeftHigh Vs. RightHigh		0.59
Ctrls Vs. LeftHem Vs. RightHem	0,28	Ctrls Vs. LeftHem	2.41	
		Ctrls Vs. RightHem	2.30	
		LeftHem Vs. RightHem		0.07
Ctrls Vs. RightHigh Vs. RightLow	0,52	Ctrls Vs. RightHigh	1.83	
		Ctrls Vs. RightLow	-0.25	
		RightHigh Vs. RightLow		1.19

Table N: EFFECT SIZE CALCULATION: SEMANTIC DISTANCE

SEMANTIC DISTANCE : EFFECT SIZE

BEFORE SURGERY

Contrast	Effect Size: Eta-Squared	Contrast	Cohen's '*d*' on Ctrls SD	Hedges 'g'
Ctrls Vs. High Gr. Vs. Low Gr	0.43	Ctrls Vs. HighGr	6.46	
		Ctrls Vs. LowGr	-0.14	
		HiGr Vs. LowGr		5.51
Ctrls Vs. LeftHigh Vs. Right High	0,59	Ctrls Vs. LeftHigh	2.74	
		Ctrls Vs. RightHigh	1.06	
		LeftHigh Vs. RightHigh		8.07
Ctrls Vs. LeftHem Vs. RightHem	0,23	--		

AFTER SURGERY

Contrast	Effect Size: Eta-Squared	Contrast	Cohen's '*d*' on Ctrls SD	Hedges 'g'
Ctrls Vs. High Gr. Vs. Low Gr	0,42	Ctrls Vs. HighGr	4.64	
		Ctrls Vs. LowGr	0.15	
		HiGr Vs. LowGr		1.77
Ctrls Vs. LeftHigh Vs. Right High	0,60	Ctrls Vs. LeftHigh	6.57	
		Ctrls Vs. RightHigh	1.43	
		LeftHigh Vs. RightHigh		2.30
Ctrls Vs. LeftHem Vs. RightHem	0,23	--		

Table O: EFFECT SIZE CALCULATION: WORD FREQUENCY:

WORD FREQUENCY : EFFECT SIZE

BEFORE SURGERY

Contrast	Effect Size: Eta-Squared	Contrast	Cohen's '*d*' on Ctrls SD	Hedges 'g'
Ctrls Vs. High Gr. Vs. Low Gr	0.23	Ctrls Vs. HighGr	1.59	
		Ctrls Vs. LowGr	0.18	
		HiGr Vs. LowGr		0.90
Ctrls Vs. LeftHigh Vs. Right High	0,12	Ctrls Vs. LeftHigh	-2.54	
		Ctrls Vs. RightHigh	2.70	
		LeftHigh Vs. RightHigh		-0.33
Ctrls Vs. LeftHem Vs. RightHem	0,30	--		

AFTER SURGERY

Contrast	Effect Size: Eta-Squared	Contrast	Cohen's '*d*' on Ctrls SD	Hedges 'g'
Ctrls Vs. High Gr. Vs. Low Gr	0,02	Ctrls Vs. HighGr	-0.36	
		Ctrls Vs. LowGr	0.49	
		HiGr Vs. LowGr		-0.29
Ctrls Vs. LeftHigh Vs. Right High	0,13	Ctrls Vs. LeftHigh	-1.99	
		Ctrls Vs. RightHigh	2.35	
		LeftHigh Vs. RightHigh		-1.00
Ctrls Vs. LeftHem Vs. RightHem	0,34	--		

APPENDIX B: Supplementary Figures from Chapter 2

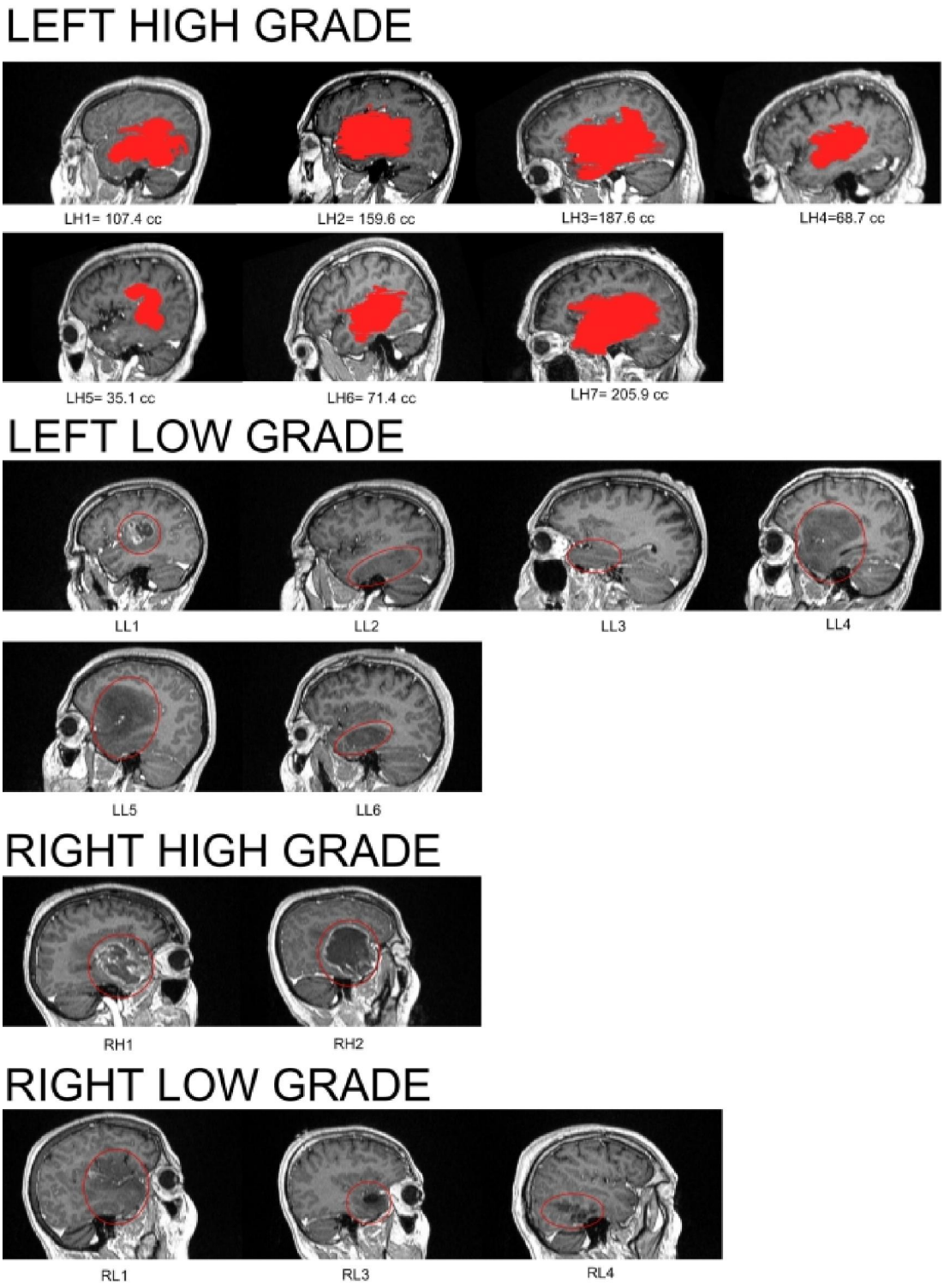


Fig.1: Sagittal sections of the MRI scans of each of the tumour patients. Scans from patients RH3 and RL2 were not available. Lesion reconstruction and lesion volume were obtained from the only left high grade patients.

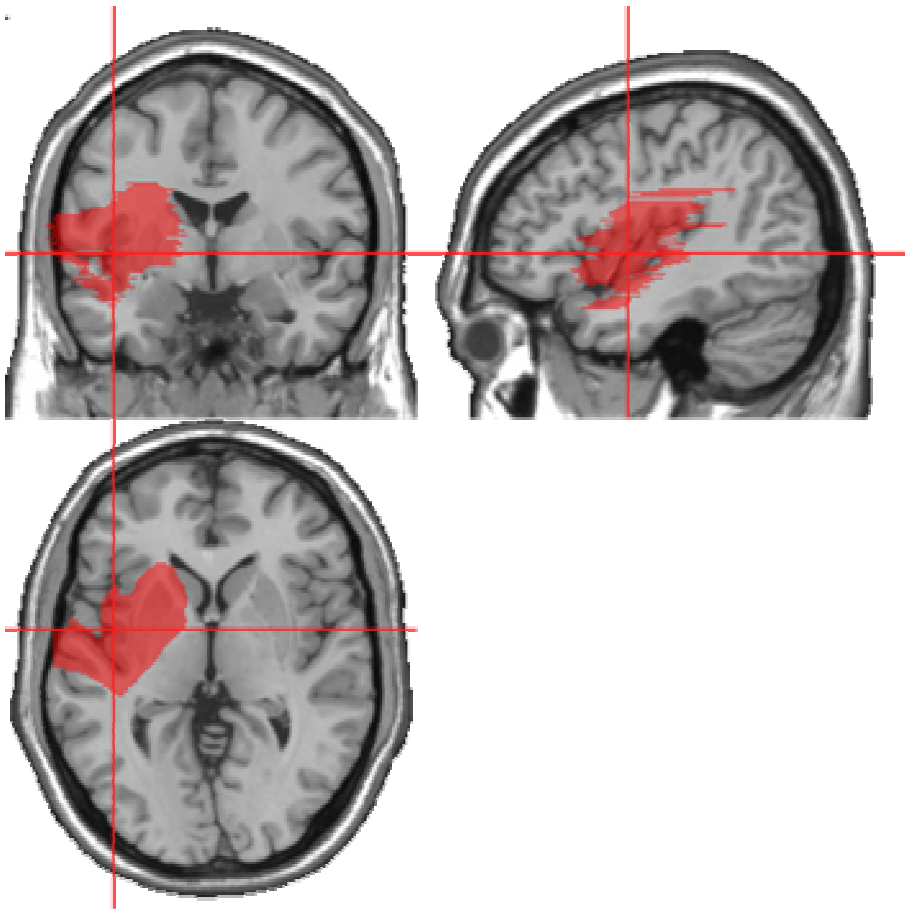


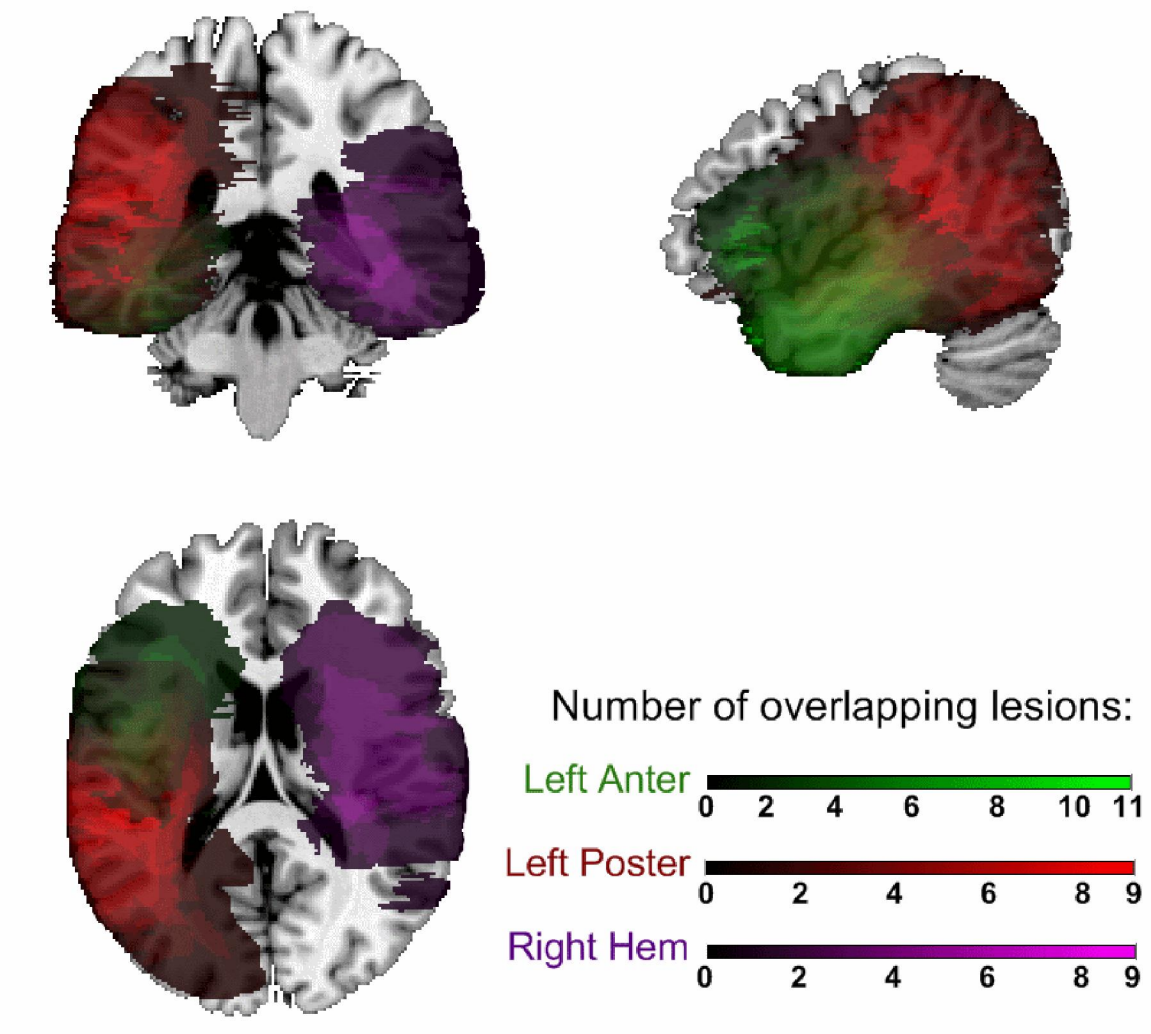
Fig.2: Lesion reconstruction from stroke patient SV, showing the involvement of fronto-temporal regions and basal ganglia. Lesion Volume was 78 cc

APPENDIX C: Supplementary Table from Chapter 4

Array n.	Stim Type	Stimulus Name	TR-MD SemDist	VisSim with TR	Word Freq	Array n.	Stim Type	Stimulus Name	TR-MD SemDist	VisSim with TR	Word Freq
1	TR	Racket	Distant	-	15	7	TR	Hammer	Close	-	18
	MD	Carpet beater		5,08	1		MD	Axe		5,69	1
	VD	Brush		4,92	2		VD	Razor		4,69	16
	UD	Vase		1,62	53		UD	Watch		1,00	102
2	TR	Pincers	Distant	-	65	8	TR	Screwdriver	Close	-	2
	MD	Nutcracker		4,85	1		MD	Screw		4,38	40
	VD	Compasses		5,31	2		VD	Syringe		5,08	19
	UD	Candle		1,69	36		UD	Steering Wheel		1,46	106
3	TR	Pitchfork	Close	-	1	9	TR	Drill	Distant	-	8
	MD	Shovel		4,85	1		MD	Gun		6,15	32
	VD	Fork		5,38	6		VD	Corkscrew		3,85	2
	UD	Pin		1,00	1		UD	Chair		1,62	83
4	TR	Frying pan	Close	-	3	10	TR	Microphone	Distant	-	35
	MD	Strainer		5,38	2		MD	Baby bottle		3,85	3
	VD	Magnifier		5,54	4		VD	Torch		5,92	53
	UD	Scissors		1,62	18		UD	Dice		1,15	6
5	TR	Remote control	Distant	-	1	11	TR	Pencil	Close	-	19
	MD	Mobile phone		5,62	3		MD	Pen		6,23	14
	VD	Calculator		5,46	3		VD	Rolling-pin		5,23	1
	UD	Pipe		2,00	16		UD	Fan		1,00	4
6	TR	Broom	Distant	-	6	12	TR	Cigarette	Close	-	49
	MD	Rake		5,62	18		MD	Cigar		5,46	3
	VD	Pickaxe		4,69	22		VD	Paintbrush		5,23	7
	UD	Light bulb		1,77	12		UD	Glass		1,15	111

Supplementary Table 1: Stimuli used in Experiments 1 and 2. Control data about semantic distance, visual similarity (on a scale from 1 to 7) and word frequency are also provided. TR=Target stimulus; MD=Manipulability Distractor; VD=Visual Distractor; UD=Unrelated Distractor

APPENDIX D: Supplementary Figure from Chapter 5



Supplementary Figure 1: overlapping of the lesion sites of all the patients tested. Green= left anterior temporal patients. Red= left posterior temporal patients. Purple= right hemisphere patients