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Neuroscientific protocols for exploring the mental lexicon: Evidence from aphasia

Abstract: Research over the past 30 years has developed several protocols to investigate the anatomo-functional architecture of the mental lexicon. The first is the neuropsychological approach, based on anatomo-clinical correlations in selected groups of brain-damaged patients and on single case studies, in which association and/or dissociation between a damaged brain area and a specific linguistic ability is deeply investigated: this approach has produced relevant insight in the organization of the semantic system. The instrumental approaches studying perfusion and metabolism, such as PET scan and fMRI, have supported these data extending our knowledge on the neural substrates of word comprehension and production. Results from studies using non invasive brain stimulation techniques, have contributed to confirm and refine previous data. Very recently, intraoperative direct electrical stimulation in patients with brain tumours has been proposed in order to make critical surgical decisions on which area can not be removed due to its crucial role in language processing. Right now, the most promising innovative approach suggests to combine different neuroimaging methods in order to overcome the limitations of each technique.

In the present chapter, we will present the main achievements obtained through these different approaches.


Keywords: neural correlates of word processing, word retrieval deficits, aphasia, neuroimaging methods, neuromodulation

1 Introduction

Disorders of language are a frequent consequence of stroke, and aphasia is one of the most socially disabling consequences (Rhode, Worrall, and Le Dorze 2013). Aphasia is an acquired language disorder, which occurs, in general, after a left hemispheric lesion (Basso, Forbes, and Boller 2013). The aphasic symptoms vary

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in terms of severity and degree of involvement across the modalities of language processing, including production and comprehension of speech, reading and writing. For example, a production deficit can range from the occasional inability to select the correct word to telegraphic and very limited speech output (Basso 2005).

The impact of this disorder on the person and its frequency of occurrence have led many researchers to explore the anatomical basis of the different aphasic symptoms in order to identify the neural mechanisms which support specific language functions.

It is well known that in aphasia word-finding difficulties are the most pervasive symptom of language breakdown and that naming disorders lead to a variety of errors because of damage to different stages of word processing. Generally, anomic difficulties arise from an inability to retrieve either the semantic word representation or the phonological word form (Levelt 1989; Levelt and Meyer 2000). Semantic impairments lead to difficulties in both word comprehension and production, whereas lexical phonological disturbances result in spoken word retrieval impairments with preserved word comprehension (Caramazza 1997; Lambon Ralph, Moriarty, and Sage 2002; Wilshire and Coslett 2000). Due to the frequency of anomic deficits, most of the research on the neural correlates of language has been focused in exploring how words are processed in the mental lexicon.

In this chapter, we will review the main neuroscientific approaches that have been applied for investigating the neural correlates of word processing. The first approach ever used is the anatomo-clinical correlation, first, in selected groups of brain-damaged patients and then on single case studies, in which associations but especially dissociations between symptoms and the damaged brain region were investigated. This approach has produced relevant insights in defining the architecture of the mental lexicon and the internal organization of its components. The instrumental approaches studying perfusion and metabolism, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have supported these data, extending our knowledge on the neural substrates of word comprehension and production. Moreover, event-related brain potentials (ERPs) have further contributed to our understanding of the neural mechanisms underlying language processing. Recently, studies using neuromodulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have confirmed and refined previous data. In addition, among the neurostimulation techniques, intraoperative direct electrical stimulation (DES) in patients with brain tumors has become a common clinical practice in order to assess the functional role of restricted brain regions, in order to maximize the extent of resection without provoking cognitive impairment, particularly of language.

Right now, the most promising innovative approach suggests combining different methods in order to overcome the limitations of each technique.

In the following pages, we will present the main results obtained in the study of the mental lexicon applying different methodological approaches.

2 The anatomo-clinical correlation approach and the group studies

Since Broca's discovery in 1861 and 1865, it has been established that damage to the foot of the left third frontal gyrus causes a dramatic deficit of speech production. Some years later, Wernicke (1874) pointed out that the areas of the brain anterior to the central sulcus are motor regions involved in speech production, while the posterior parts are sensory areas crucial for language comprehension. Indeed, lesions to Wernicke's area, corresponding to the third posterior part of the left superior temporal gyrus, impair comprehension (see Figure 1).

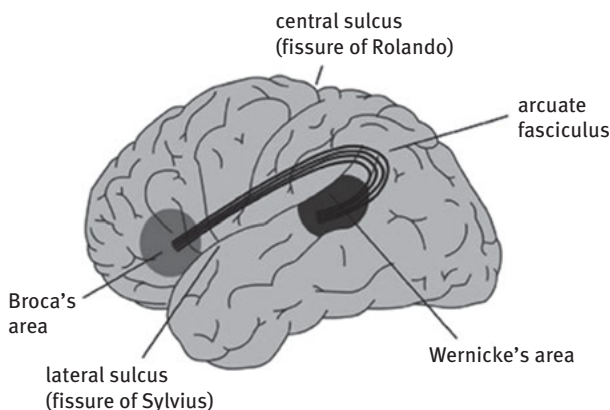


Figure 1: Localization of Broca's and Wernicke's area.

Wernicke assumed that since language is learned by imitating heard language, it is necessary for production to transfer information from the auditory receptive area to the anterior language motor area. Accordingly, patients with Wernicke's aphasia are impaired in understanding spoken or written language, and even though they can speak with an (almost) normal grammar, syntax, rate, and intonation, they do not produce a meaningful speech. Some years later in 1885, Wernicke suggested the existence of a third form of aphasia, namely conduction

aphasia, due to the interruption of the white matter tracts connecting Wernicke's and Broca's areas, namely the arcuate fasciculus (Anderson et al. 1999). In conduction aphasia, a disconnection syndrome, the two language areas are preserved, but damage involves the association fibers causing a disorder of speech, which affects mainly repetition, with phonological errors, because the preserved Wernicke's area cannot control for phoneme selection. The patient, however, is aware of his/her errors and comprehension is preserved.

As Wernicke, many neurologists in the second half of the 19th century, took the view that language was a multi-componential function. The most influential was Lichtheim (1885), who added to the Wernicke's model the "concept center", where concepts are stored, and the center for the visual images of words and for the images of motor sequences involved in writing. In Lichtheim's view, the main language functions (speaking, understanding, reading and writing) are discrete entities, each related to a specific site in the brain. He argued that the concept area is not, in a strict sense, a center, but it is distributed in the brain. However, although Lichtheim's model still retained some anatomical basis, the anatomical site of its centers was mostly ignored. At that time there were three types of models: those based on the brain, where every center and connection pathway was localized in a definite cerebral structure (e.g., Wernicke's model); models not based on the brain in which there was no correspondence between centers and connections and brain structures (Kussmaul 1887, who assumed two centers for the images of words under the control of the concept center) and, finally, mixed models, such as the Lichtheim's one, in which parts of the model were psychological, but other maintained an anatomical basis. With respect to reading words, some years later, Dejerine (1891) distinguished two forms of alexic syndromes, alexia with agraphia and alexia without agraphia. Meanwhile, he clarified the neuroanatomical basis of reading and writing. Patients suffering alexia with agraphia had an acquired deficit in reading (alexia) and writing (agraphia) and this was associated with damage to the left angular gyrus. The left angular gyrus was, therefore, the center for the visual images of words. In contrast, alexia without agraphia, associated with lesions to the left occipital lobe and the posterior part of the corpus callosum, the splenium,¹ followed the disconnection of the left angular gyrus from the visual cortex (Dejerine 1891).

Although in the 19th century single case reports provided the main source of evidence on dissociated patterns of impairment due to different anatomical lesions, the qualitatively and non-systematic psychological analysis of the patient's pathological behavior, mostly confined to clinical observation, revealed

¹ The corpus callosum is the white matter bundle connecting the two cerebral hemispheres.

the weakness of this approach. An important source of data came from patients suffering traumatic injuries after World War II. Relying on the information acquired examining these subjects, Luria (1947, revised in 1970) published his relevant book *Traumatic Aphasia*, in which he attempted to accommodate the localizationist approach with the idea of a functional system (an approach that, in some way, was later applied by the cognitive neuropsychologists, see Section 3). Many neuropsychologists from North America (Benton 1988; Geschwind 1965) took the view that standardized and quantitative methods had to be applied on groups of patients, in order to better define and classify the aphasic symptoms and their corresponding lesions and to replicate the results found on single cases. In describing the neoassociationist taxonomy of aphasic syndromes, which is very close to the Broca-Wernicke's classification, Geschwind (1965) used a neuroradiological approach. The typical procedure was to group neurological patients on the basis of the lesion side (left, right) and intra-hemispheric localization (anterior-frontal, posterior-temporal, etc). The performances on a standardized language examination of the different groups of patients were then compared with those of a group of normal controls, matched for demographic variables (i.e., age, educational level, time post-onset) and the corresponding patients' lesions were well-defined through validated methods. Indeed, the recent discovery of computerized tomography (CT) and of magnetic resonance imaging (MRI) allowed researchers to deeply investigate the neural correlates of the observed clinical symptoms. The aim was to establish anatomo-clinical correlations between damage to a specific left hemispheric area and the corresponding aphasic symptoms in the different modalities of language (i.e., production, reading, writing and/or comprehension) referring to the classic neurological models (e.g., Wernicke's model). Indeed, Geschwind (1965) resurrected the Wernicke-Lichtheim notion that certain areas of the left hemisphere have a strictly specialized function in language processing, and added a new form of aphasia, namely Anomic aphasia, characterized by word finding difficulties (i.e., anomia) in spontaneous speech and confrontation naming tasks in the context of preserved comprehension, repetition, reading and writing. As we will see in Section 3, this form of aphasia was the most thoroughly investigated type in the study of the mental lexicon.

Geschwind (1965)'s neoassociationist approach dominated aphasiology from the 1960s until the 1980s, and still has a significant influence. Wernicke's classification was repackaged as the Boston classification and became internationally known. Brain imaging was in its infancy, the main approaches being two: to collect patients on the basis of their symptoms and then assess the site of their lesion or, vice versa, to collect patients on the basis of their lesion and assess their language profile (e.g., Cappa et al. 1983). However, it was soon clear that patients

with the same aphasic symptoms (e.g., anomia) can suffer an impairment at different levels of word production. Therefore, the advent of the cognitive approach and of new neuroimaging methods (see Section 3 and 4 below) gave new insights into language processing.

3 The cognitive approach: Single case studies

Although the classic anatomo-clinical approach provided knowledge about the relationships between a specific brain area and its function, during the 1970s, researchers began to investigate the nature of the cognitive mechanisms underlying language processing with less interest on brain localization. A novel neuropsychological approach to aphasia developed: the cognitive neuropsychological approach. The aim of this approach was to explore the functional architecture of normal language processes, through the investigation of brain-damaged patients' behavior (Caramazza 1984; 1986). According to the cognitive approach, the mental faculties, and language in particular, require a number of connected components with specific functional properties. The mind being a multi-component system with specific features and connections, a sub-component of the system (or the connections between two of them) can be selectively affected by a brain lesion. Brain-damaged patients, therefore, can be investigated with two objectives: (1) interpreting their impairment in terms of the defective function of one or more components or connections of the system; (2) increasing knowledge about the functional architecture of the language system (Caramazza 1986; Caramazza and Hillis 1993).

Indeed, in contrast with the classic anatomo-clinical method, cognitive neuropsychologists argued for a functional approach to the study of the mind explicitly independent from the study of the brain. The group study approach was strongly criticized and refused, since diagnostic criteria referring to classic aphasia categories would be too generic (Caramazza and McCloskey 1988).

In order to study the functional architecture of the language system, one type of neuropsychological finding, dissociation, was considered to have a special status (Caramazza 1986). A dissociation occurs when a group of patients (or a single patient) performs poorly on one task and at a normal level (or significantly better) on another task. This is a simple dissociation. One interpretation of the dissociation is that the two tasks are sub-served by two different functions, which explain why they are differently impaired. However, it might be possible that the two tasks are sub-served by the same mechanism but differ in the level of difficulty and the more difficult task shows greater

impairment than the easier one, when the single sub-serving mechanism is impaired. According to Shallice (1988), the major attainment of single case studies has been the demonstration of the independence of specific subsystems by means of the double dissociation paradigm. A double dissociation occurs when patient A is impaired in task X and (nearly) unimpaired in task Y while patient B shows the reverse pattern.

By means of this approach, in the 1980s, the structure of the lexicon and how lexical representations interact was one of the most thoroughly investigated topics in cognitive neuropsychology.

The performance of brain-damaged patients with selective lexical-semantic disorders led researchers to decompose the normal language system into many interacting subcomponents and information processing models made up of boxes and arrows. A classic example is the word processing model proposed by Patterson & Shewell (1987), involving four different lexicons – the auditory input lexicon (corresponding to the auditory images of words), the orthographic input lexicon (corresponding to the visual images of words), the phonological output lexicon (corresponding to the motor images of words), and the orthographic output lexicon (corresponding to the motor images for writing) – plus a cognitive system, later identified as the semantic system.

This approach has provided several important insights in the lexicon architecture, thanks to the demonstration of selective deficits, such as the selective impairment of the semantic system, the dissociation between written and oral naming, the dissociation between nouns and verbs, the dissociation between abstract and concrete words and, inside concrete entities, the selective impairment of semantic categories.

For example, Caramazza and Hillis (1990) reported patient KE, who made semantically-related errors in reading, writing, naming and comprehension. The word *tiger*, for instance, was read “lion” and when the patient was presented with the picture of the tiger, he said “lion” and wrote <elephant>. In auditory- and written-word-picture matching tasks, he also made frequent semantic errors. The pervasiveness of the semantic errors and their similarity of occurrence across all modalities of input and output led the authors to hypothesize that the patient suffered damage to the semantic system.

Concerning the existence of two independent output lexicons, traditionally, it was proposed that successful writing requires a person to say the word to him/herself, translate the internally generated sounds into a string of letters, and finally write those letters (“phonic mediation theory” of writing) (Ellis and Young 1988). Recent advances in cognitive neuropsychology have, however, falsified this theory. First, patients have been reported who can still spell words whose spoken forms they were unable to retrieve from the phonological output

lexicon (e.g., Bub and Kertesz 1982; Ellis, Miller, and Sin 1983). Secondly, single-case studies were provided with the opposite pattern: patients were reported who made errors in writing to dictation and written naming, but could still retrieve the phonological word forms in oral naming, reading and spontaneous speech (e.g., Hillis, Rapp, and Caramazza 1999).

One deeply investigated organization parameter of the lexicon was the grammatical category of words. Indeed, several studies were reported on patients showing word production deficits restricted to the noun or verb category suggesting that words belonging to different grammatical classes are independently represented in the lexicon (Shapiro, Shelton, and Caramazza 2000). Selective sparing of nouns relative to verbs has been frequently reported, usually in Broca's aphasia patients (Baxter, Dooren, and Warrington 1985; McCarthy, Rosaleen, and Warrington 1985; Miceli et al. 1984; 1988), while the opposite dissociation, namely, verbs relatively better preserved than nouns, has been less frequently documented but is not rare and is generally found in anomia patients (Miceli et al. 1984; 1988; Rapp and Caramazza 1998; Silveri and Betta 1997; Zingeser and Berndt 1990) and in semantic dementia (Papagno, Capasso, and Miceli 2009a). All these reports of selective dysfunction of nouns and verbs suggested that a dimension of lexical organization is the grammatical class of words.

The noun-verb dissociation observed in aphasic patients has been explained in several ways. According to Caramazza and colleagues (e.g., Rapp and Caramazza 2002), dissociated impairments may be caused by damage that selectively affects verbs or nouns at a late lexical stage (phonological or orthographic output lexicons); this is suggested by the fact that patients have been described with modality-specific deficits restricted principally (the first patient) or only (the second) to verbs either in oral or written production, respectively (Caramazza and Hillis 1991). Alternatively, Berndt et al. (1997) have claimed the existence of a lexical-syntactic representation of grammatical class at a more central lexical level (the lemma, see Levelt et al., 2000). Bird, Howard, and Franklin (2000), on the other hand, argued that noun-verb dissociation might be a semantic, rather than a lexical, phenomenon, and they also suggested that many dissociations might be generated by the fact that aphasic patients are more affected by imageability, which is lower for verbs (Paivio 1971).

Lexical representations specify more than information about the grammatical categories of words: they also include their possible morphological transformations. Disorders of morphological processing have been systematically observed in so-called agrammatic aphasia (e.g., Goodglass 1976). Indeed, difficulties with nominal, adjectival and verbal inflections are a common feature of agrammatic speech across different languages (e.g., Menn and Obler 1990). The reverse picture, apparent sparing of morphological endings associated with the

production of neologistic root morphemes, has been reported in jargonaphasia (e.g., Buckingham and Kertesz 1976; Luzzatti, Mondini, and Semenza 2001; Marshall and Newcombe 1973; Semenza et al. 1990), but can be observed also in repetition (Kohn and Melvold 2000; Miceli, Capasso, and Caramazza 2004) and writing tasks (Badecker, Hillis, and Caramazza 1990). The errors made by these patients have led many authors to suggest that lexical information is represented in a morphologically decomposed form (Caramazza et al. 1985; Coltheart 1985), although not all authors agree with this view.

Further single case reports gave some suggestions regarding the internal organization of the semantic system. In an influential series of papers, Warrington and co-workers described patients with disorders that selectively affected abstract and concrete words (Warrington 1975, 1981), common and proper names (McKenna and Warrington 1978) and within the concrete entities, living and non-living things (McCarthy and Warrington 1990; Warrington and McCarthy 1983, 1987; Warrington and Shallice 1984).

Concerning the first issue, namely the double dissociation between concrete and abstract words, an advantage for concrete words as compared to abstract words was demonstrated in several psycholinguistic studies (see Paivio 1991 for a review). Neurologically unimpaired subjects fare better on concrete than on abstract words in free recall, cued recall, paired-associate learning and recognition memory; they are also faster at making lexical decisions to visually presented concrete than abstract words (James, 1975). This advantage is known as the concreteness effect. Aphasics frequently show an increased concreteness effect, since their performance is much better on concrete than abstract words in spontaneous speech (Howes and Geschwind 1964), reading (e.g., Coltheart, Patterson, and Marshall 1980), writing (e.g., Bub and Kertesz 1982), repetition (e.g., Martin and Saffran 1992), naming (e.g., Franklin, Howard, and Patterson 1995) and comprehension (e.g., Franklin, Howard, and Patterson 1994). Various hypotheses have been suggested to explain the concreteness effect, one possibility being that abstract words are represented entirely verbally, in the left hemisphere, whereas the representation of concrete words involves both verbal components in the left hemisphere and visuo-perceptual components in the right hemisphere (the so-called “dual-coding” theory; Paivio 1986). Alternatively, the concreteness effect has been attributed to a larger contextual support for concrete words (“context-availability” theory; Schwanenflugel and Shoben 1983). According to this account, concrete nouns are recognized faster because they activate richer associative information than abstract terms. Finally, an additional suggestion is that the concreteness effect stems from “ease-of-predication” (Jones 1985), as concrete words are supported by a larger number of semantic features than abstract words (see also Plaut and Shallice, 1991, 1993).

However, a reversal of the concreteness effect has been documented in a number of brain-damaged subjects (Bachoud-Lévy and Dupoux 2003; Breedin, Saffran, and Coslett 1994; Cipolotti and Warrington 1995; Macoir 2008; Marshall et al. 1996; Papagno, Capasso, and Miceli 2009a; Sirigu, Duhamel, and Poncet 1991; Warrington 1975, 1981; Warrington and Shallice 1984; Yi, Moore, and Grossman 2007), who demonstrate better performance on abstract as compared to concrete words. A reversed concreteness effect is incompatible with the three theories mentioned above, as these can accommodate the concreteness effect, but not its reversal. To explain the reversed concreteness effect, it has been proposed that abstract and concrete concepts are distinguished because they are acquired in a different way, and because of the relative weight of sensory-perceptual features in their representation (Breedin, Saffran, and Coslett 1994). Sensory experience would be crucial for the acquisition of concrete concepts, whereas abstract ones are acquired in the context of language, through exposure to multiple sentence contexts but without direct perceptual input. Since concrete words rely on visual/perceptual features more than abstract ones, loss of perceptual features would disproportionately impair concrete entities, producing a reversed concreteness effect. Crutch and Warrington (2005) have provided a different account: the primary organization of concrete concepts is categorical, whereas abstract concepts are predominantly represented by association to other items. In this framework, a reversed concreteness effect might result from selective damage to categorical information (which would selectively affect conceptual representations of concrete words).

A second repeatedly reported dissociation that has shed light on the architecture of the semantic system is the specific impairment of semantic categories. Warrington and Shallice (1984) proposed that the living/non-living distinction could be the by-product of a dichotomy, concerning the different weighting that visuo-perceptual and functional attributes have in the identification of members of living and non-living things, respectively. Identification of a given exemplar of a living category would rely upon visual features, such as color, size, shape, etc., whereas identification of a member of a non-living category (particularly of man-made artefacts) would crucially depend upon the different function of that object. Warrington and Shallice (1984) provided evidence from four patients (and not just one single case), but this dissociation has been repeatedly confirmed in additional single case reports, with the same pathology (herpes simplex encephalitis), or a form of dementia, called semantic dementia, in which there is a progressive impairment of the semantic system (Hodges et al. 1992).

Warrington and Shallice's (1984) 'differential weighting' account of the living/non-living distinction has been challenged by alternative models of category-specific disorders. On one hand, Caramazza and Shelton (1998) have argued

that the dissociation between living and non-living entities does not depend on the sensory/functional dimension, but rather reflects the discrete organization in the brain of different ‘domains of knowledge’. They suggest that evolutionary pressure may have resulted in the elaboration of dedicated neural mechanisms for the domains of ‘animals’ (potential predators), of ‘plant life’ (possible source of food and medicine or poison) and of man-made artefacts. Finally, some authors argued against this organization into modality-specific subsystems in favor of a unitary, amodal system of conceptual organization, one proposal being the Organized-Unitary-Content Hypothesis (OUCH; Caramazza et al., 1990). Extending this model, Gonnerman et al. (1997), Garrard et al. (1998, 2001), and Moss et al. (1998) have proposed that the dissociation between living and non-living things is more related to the different level of interconnections existing between sensory and functional attributes in these two categories than to the differential weighting of these attributes. According to this model, the semantic representations of living things are characterized by the congruity of perceptual and functional shared properties. For instance, the perceptual properties “having eyes” and “having ears” regularly co-occur with the functional attributes “can see” and “can hear”, whereas artefacts have a greater proportion of distinctive properties that are less densely interconnected. This would explain why the number of patients with the opposite dissociation, namely a selective impairment of non-living things with sparing of living categories (Behrmann and Lieberthal 1989; Sacchett and Humphreys 1992; Warrington and McCarthy 1983, 1987) is limited.

Cognitive neuropsychologists were interested in functional processes involved in these dissociations, and not in the anatomical localizations of lesions. However, it was soon evident that these selective impairments were related to lesions in specific and different regions of the brain, giving therefore a new input to the study of the neural correlates of language and, in particular, of the mental lexicon.

4 Neuroimaging methods

As previously introduced, in the nineteenth and twentieth centuries, our understanding on how the human brain analyses and produces language was shaped by aphasiology. This approach helped to define a model of language architecture, in which Broca’s and Wernicke’s area were assigned the leading roles in language production and comprehension, respectively (Damasio and Geschwind 1980).

In the 1980s, the introduction of non-invasive functional brain imaging techniques, such as positron emission tomography (PET) and fMRI, causes a renewed interest for the study of the neural basis of language (Perani et al. 1999). The

logic underlying this approach is complementary to that of the anatomic-clinical correlation method. In this case, the relevant correlation is between the localization of the variation (usually the increase) in the regional cerebral blood flow (rCBF) and the task performed by the subject, rather than between a defective performance and the site of the lesion. Practically, what is measured is the clearance of the tracer from different cerebral areas, which depends strictly on rCBF.

With both functional methods, the conclusion that a given task is associated with the activation of one or more cerebral areas is based on the comparison between the experimental condition and an appropriate control condition, which differs from the former only in the process or task under investigation. For example, the cerebral areas activated during listening to words may be revealed by subtracting from the rCBF activation values of this condition the activation pattern of the control condition in which subjects do not perform any task, but just look at a fixation point. Since the two conditions differ only in the auditory-verbal stimulation, their difference provides the activation pattern that is specific to word listening. However, one important limitation of these techniques is that they only suggest that a specific area is active when a given task is performed, but do not imply that this area is essential for the execution of the task (Menon and Kim 1999).

PET and fMRI have allowed the investigation of specific components of the mental lexicon (for example phonological vs. semantic) and its neural organization by means of specific experimental neurolinguistic paradigms. Phonological processing has been investigated in a number of fMRI studies using different tasks, which required the subjects to repeat syllables (Bookheimer et al. 2000; Wildgruber, Ackermann, and Grodd 2001); to read, listen, or attend to syllables or letters (Joanisse and Gati 2003; Paulesu et al. 2000; Poeppel et al. 2004); to read a pseudoword (constructed upon the orthographic rules of a given language but without meaning) or count the number of syllables it encompassed (Kotz et al. 2002; Meyer et al. 2002); to count the number of syllables in a word (Heim and Friederici 2003) or to discriminate whether a word ended with the same sound (Heim and Friederici 2003; Zatorre et al. 1996). A meta-analysis performed on these studies (Vigneau et al. 2006) revealed two main foci of activity: one mainly localized in the posterior part of the frontal lobe along the precentral gyrus and the second one in the temporal lobe along the superior temporal gyrus and the supramarginal gyrus. The authors proposed that these areas are organized into two neural components dedicated to speech sound perception and production: a frontotemporal auditory-motor network and a frontoparietal loop for phonological working memory (Vigneau et al. 2006) (see Figure 2).

With regard to semantic processing, the meta-analysis (Vigneau et al. 2006) included fMRI studies using different semantic tasks such as semantic retrieval

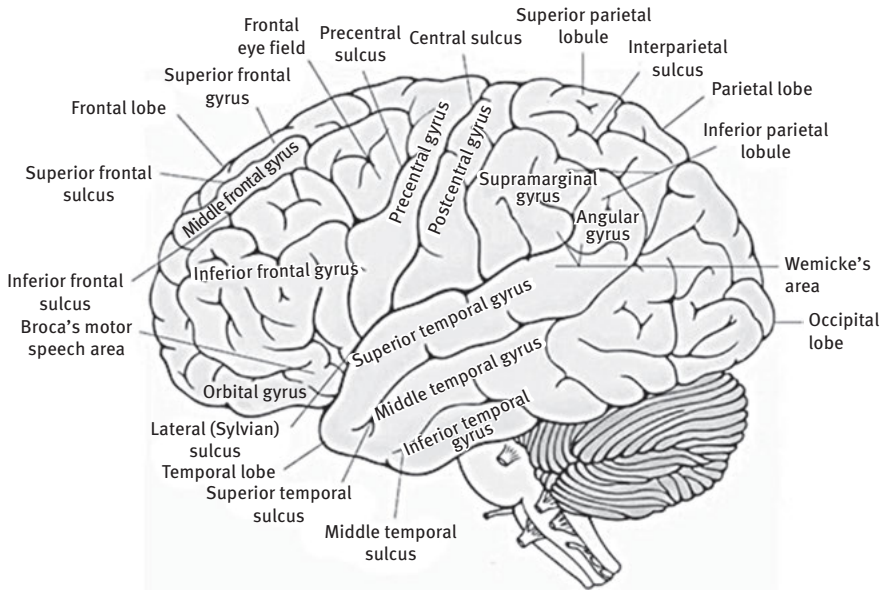


Figure 2: Representation of human cortical lobes and gyri on brain surface.

(James and Gauthier 2004; Heun et al. 2000); semantic selection (where semantic association activations with high or low competitors are compared) (Noppeney and Price 2004; Wise et al. 2001); or semantic priming tasks (Kotz et al. 2002; Wagner et al. 2000). Results showed that activations corresponding to semantic contrasts were mainly segregated into frontal and temporal regions distinct from the phonological network. The frontal operculum appeared to host semantic areas, while sub-parts of the pars triangularis of the inferior frontal gyrus (IFG) were differentially recruited: the dorsal part by the working memory component of phonology and the ventral part by semantic processing. These observations suggested a functional parcellation of the IFG for phonological and semantic processing (Vigneau et al. 2006). Another focus of activation was located in the orbital part of the IFG, a region that Demb et al. (1995) have proposed to be involved in online retrieval of semantic information. Indeed, this area is activated also during categorization tasks (Adams and Janata 2002; Binder et al. 2003; Braver and Bongiolatti 2002; Bright, Moss, and Tyler 2004; Jennings et al. 1998; Noesselt, Shah, and Jancke 2003; Noppeney and Price 2004; Perani et al. 1999; Poldrack et al. 1999), association (Booth et al. 2002; Damasio et al. 2001), and word generation tasks (Gurd et al. 2002; Martin et al. 1995). The analysis of the semantic contrasts that elicit activation peaks in the temporal lobe revealed a clear functional organization, including a modality-

specific verbal area in the superior temporal gyrus, a modality-independent verbal area in the middle temporal gyrus, and amodal conceptual areas in the angular and fusiform gyri. The superior temporal gyrus cluster was activated by semantic contrasts based on written words, such as reading words versus pseudowords (Fiebach et al. 2002; Fiez et al. 1999; Howard et al. 1992; Moore and Price 1999; Small et al., 1996), and categorization of written words (Chee et al. 2000; Heim, Opitz, and Friederici 2002; Jennings et al. 1998; Perani et al. 1999), leading to the hypothesis that the superior temporal area processes the graphemes converted into syllable sounds and maintained in working memory by means of the phonological networks that operate during reading; this processing makes them accessible in a verbal format for further syntactic (in the temporal lobe) or conceptual (in the angular gyrus and in the fusiform area) processing (Vigneau et al. 2006). Finally, the angular gyrus activation was considered involved in conceptual knowledge retrieval. This region, a high-order heteromodal association cortex, can be seen as a gateway, which coordinates reciprocal interactions between the sensory representation of words or objects and their meaning (Mesulam 2000; Vigneau et al. 2006). The fusiform area was supposed to be implicated in semantic processing of words and pictures (Binder et al. 1996, 1999; Bright, Moss, and Tyler 2004; Davis, Meunier, and Marslen-Wilson 2004; Vandenberghe et al. 1996). Vigneau et al. (2006) suggested that the angular and the fusiform gyri – the two amodal conceptual temporal areas devoted to meaning– and the temporal pole together with the inferior orbital frontal cluster constitute a temporo-frontal semantic network. This semantic network can be considered to construct an overall meaning on the basis of the association of integrated knowledge issued from the main domain of external (audition, vision) and internal (long-term memory, emotion) messages (Vigneau et al. 2006).

We have reported that the available evidence so far on single case studies suggests that different neural circuits are responsible for processing nouns and verbs, concrete and abstract concepts and different semantic categories.

In the case of verb-noun dissociation, neuroimaging studies in normal subjects, however, have provided only limited support to the lesion-based hypothesis. The discrepancies among studies were attributed to a number of factors, among which the fact that earlier studies investigating differences in noun and verb processing used nouns referring to objects and verbs referring to actions, therefore introducing a confound between the grammatical and the semantic class. In the imaging literature, this is the case not only in earlier studies using verb generation (Petersen et al. 1988, 1989; Martin et al. 1995; Warburton et al. 1996) but also in more recent ones using picture naming (Tranel et al. 2005).

Studies that attempted to lessen the semantic confound factor by using both concrete and abstract nouns and verbs provided mixed results. In an

Italian lexical decision study by Perani et al. (1999) using concrete and abstract nouns and verbs, verb-specific activations were reported in the left IFG but no noun-specific activations were observed. This finding was replicated in English in a semantic decision study using inflected nouns and verbs (Tyler et al. 2004) but not in a lexical decision study using uninflected words (Tyler et al. 2001). It was argued that greater left IFG activation for verbs than nouns in previous studies was not due to grammatical class differences but likely to morphosyntactic processes that may be more demanding for verbs than nouns (see Binder et al. 2004; Thompson-Schill et al. 1997; Vigliocco et al. 2006). It was also noted that most languages have more morphologically inflected verb than noun forms, so task performance on verbs may place greater demands on selection and decision processes attributed to the left IFG (Binder et al. 2004; Gold and Buckner 2002; Thompson-Schill et al. 1997). Accordingly, verb-specific activation may result from an interaction between grammatical class and task demands. Indeed, support to this hypothesis comes from a study by Longe et al. (2007), in which greater activations of the left IFG for verbs than nouns were observed when English speakers made semantic judgments on inflected words but not when they made judgments on the same uninflected words.

In an attempt to control for the semantic correlates of noun-verb differences, Shapiro, Moo, and Caramazza (2006) considered only areas of significant fMRI activations emerging both when speakers were producing phrases in response to real words (including abstract nouns and verbs) and when they were producing phrases in response to pseudowords. Moreover, in order to control for morphophonological correlates of grammatical class differences, only areas of significant activation when speakers were producing both regularly and irregularly inflected nouns and verbs were considered. Across three experiments, participants were presented with words (either a noun or a verb) or pseudowords (to be used in either a noun or verb context) and their task was to produce short phrases such as *many doors* or *he sweeps*. Significant greater activations for nouns across experiments were observed within the left fusiform gyrus, while significant greater activations for verbs were found in the left prefrontal cortex and left superior parietal cortex, suggesting that nouns and verbs were independently processed by different brain regions. In a PET study by Vigliocco et al. (2006) in Italian, only words referring to events, either nouns or inflected verbs, and referring to either sensation or motion were used. Participants were presented auditorily with blocks of sensory or motor nouns or verbs and asked to simply listen to the words. Whereas significant activation differences between sensory and motion words were found, no specific activations for nouns or verbs were observed.

More recently, Siri et al. (2008) performed an fMRI study presenting Italian speakers with pictures of events and asked participants to name them as (1)

infinitive verb (e.g., *mangiare* ‘to eat’); (2) inflected verb (e.g., *mangia* ‘she/he eats’); and (3) action noun (e.g., *mangiata* ‘the eating’). The authors did not find any verb-specific activation. However, reliable left IFG activations were found when contrasting the action noun with the infinitive verb condition. A second-level analysis indicated then that activation in the left IFG was the greatest for action nouns, intermediate for inflected verbs, and the least for infinitive verbs. The authors concluded that when all other factors are controlled (i.e., semantics, grammatical class), nouns and verbs are processed by a common neural system. Differences in the left IFG activation emerge only as a consequence of increased linguistic and/or general processing demands (Siri et al. 2008).

A similar result was obtained in a recent meta-analysis (Crepaldi et al. 2013) on the neuroimaging evidence concerning noun and verb processing: the results did not support the notion that verb processing is predominantly based in the left frontal cortex and noun processing on temporal regions, or that verb lexical-semantic representations rely on embodied information. Instead, this meta-analysis showed that the cerebral circuits for noun and verb processing are spatially close, relying on a wide network including frontal, parietal, and temporal regions (see also Piras and Marangolo 2007 for similar conclusions).

In conclusion, from the literature discussed above it seems likely that words belonging to different grammatical classes (nouns and verbs) are not actually represented in segregated neural networks. Rather, neural segregation emerges as the result of other differences between nouns and verbs. First, in previous patient and imaging studies, differences between nouns and verbs may have come about as a semantic difference between objects and actions. Indeed, in previous studies that did not suffer from this confound, and in which morphological processes were not highly engaged, no verb-specific activations in left IFG were found (Vigliocco et al. 2006). Moreover, as one controls for semantic differences (asking participants to name only events and more specifically the same events as either noun or verb) and manipulates the extent of morphological processing across the grammatical class of verbs and nouns, left IFG activations appear to be modulated by the complexity of the morphological processes rather than being associated to verb-specific processing (Siri et al. 2008). Thus, all of these results do call into question the view that grammatical class *per se* drives neural segregation, suggesting that both categories might rely on a common anatomical substrate, providing evidence for a more interactive system between the two classes of words.

Evidence from neuroimaging studies concerning the abstract-concrete dissociation is also controversial. The single case approach suggests that this dissociation appears in people with a pathology involving the anterior part of the left temporal lobe (such as in herpes simplex encephalitis or semantic dementia). Neuroimaging studies are sometimes difficult to evaluate, due to the

extreme variability of the experimental paradigms, ranging from explicit semantic judgments to (auditory and/or visual) lexical decision tasks. In some cases, activations for concrete nouns were observed in left temporal regions usually affected as first areas by semantic dementia (Binder et al. 2005; Noppeney and Price 2004; Sabsevitz et al. 2005), but in other cases they occurred in regions not affected in earlier stages of semantic dementia, such as the left posterolateral temporal and prefrontal regions (Grossman et al. 2002b; Mellet et al. 1998) and the left superior temporal and inferior frontal regions (Sabsevitz et al. 2005). Interestingly, some investigations demonstrate significantly greater hemodynamic response to abstract than to concrete words in the right temporal pole (e.g., Kiehl et al. 1999; Perani et al. 1999), while no reports of greater activation for concrete than abstract words in the same region are described. In another study, activation to abstract terms was greater in the right than in the left temporal lobe (Whatmough et al. 2004). Finally, at least one study shows greater activation for concrete than abstract words in left temporal regions (Mellet et al. 1998).

As reported in the single case approach, one of the most studied topics in the neuroimaging literature is the dissociation between semantic categories. The single case approach suggested a correlation between the locus of lesion and the patterns of categorical impairment, which Gainotti (2000) summarized as it follows: (a) a bilateral injury to the antero-mesial and inferior parts of the temporal lobes in patients with a category-specific semantic impairment for living things; (b) a lesion of the infero-mesial parts of the temporo-occipital areas of the left hemisphere in patients showing a specific lexical impairment for members of the 'plants' category; (c) an extensive lesion of the areas lying on the dorso-lateral convexity of the left hemisphere in patients with a category specific semantic impairment for man-made artefacts. Taken together, these results seem to show that the category-specific disorder is crucially related to the kind of semantic information processed by the damaged areas, supporting the Warrington and Shallice's (1984) and Warrington and McCarthy's model (1987). Similarly, PET and fMRI studies have investigated whether there is evidence that different areas of the brain are differentially involved in processing/storing information corresponding to different categories of stimuli.

Chao, Haxby, and Martin (1999) observed that the medial aspect of the fusiform gyri differentially responded to pictures and/or words referring to tools (e.g., *hammer, saw*), whereas the lateral aspect of the fusiform gyri differentially responded to pictures of animals (e.g., *dog, horse*). Comparable segregation of activation has been observed in the lateral temporal cortex: items corresponding to animate categories (i.e., animals) differentially activated the superior temporal sulcus, whereas activation associated with inanimate categories (e.g., tools)

activated more inferior regions on the left middle temporal gyrus. Furthermore, it has been observed that the superior temporal sulcus responds differentially to moving of animate entity (e.g., dog), whereas the left middle temporal gyrus differentially responds to moving of inanimate object. (e.g., a dot). This study seems to suggest that there is a neural differentiation by semantic category, at least between animate vs. inanimate categories.

In contrast, Devlin et al. (2002) in three different experiments failed to find functional segregation between animate vs. inanimate categories, suggesting that conceptual knowledge is represented in a unitary, distributed system undifferentiated by categories of knowledge.

5 Event-Related Potentials (ERPs)

The results of the neuroimaging studies described so far have revealed important correlation evidence for the involvement of several brain regions in word processing. However, neuroimaging methods do not provide the best temporal resolution available for studying cognitive functions. Indeed, fMRI does not directly measure neural activity, but instead relies on indirect changes in blood flow and volume triggered by modulation in neural activity (Kaan 2007). fMRI signals are much slower than neuronal activity, as the time course of hemodynamic signals is in the order of five seconds. As neurons work ten times faster (we can recognize an image in about 200 ms), the dynamics of fMRI signals are too slow to understand how the brain computes in real time (Kaan 2007). Since language processing occurs at an extremely fast rate to allow fully understanding of the stages involved and their timing, we need to apply a method with very good temporal resolution. Recording event-related brain potentials (ERPs) is such a technique. Electrical brain activity can be recorded by placing electrodes on a person's scalp. ERPs are obtained by presenting the participant with a given stimulus and recording the electrical potentials (brain waves) from the start of the stimulus or other events of interest. These potentials are then averaged over a large number of trials of the same type. Averaging will enhance the brain potentials that are related to the onset of the event and will reduce brain potentials that are not tied to the onset of the event and are assumed to be random (Kaan 2007). Several waveforms, such as the N1, P2, and N400, have been distinguished on the basis of their polarity, timing (latency) of the onset or the peak, their duration, and/ or distribution across the scalp, that is, at which position on the scalp a waveform is smallest or largest. Usually, the experiments

include two or more conditions and investigate how ERP waveforms change as a function of the experimental manipulation.

ERPs provide several advantages for the study of language processing. First, ERPs allow researchers to collect a continuous stream of data with a temporal accuracy of a few milliseconds: the sampling rate is typically between 250 and 512 Hz (samples per second) in language-related experiments. This matches the fast rate of language comprehension, and, hence, represents an attractive feature for researchers wanting to track continuous online processing. A second, strong advantage of ERPs is that recording of ERPs is one of the few techniques that allow researchers to investigate online processing of spoken words and sentences (Kaan 2007).

In a seminal paper on ERPs and language, Kutas and Hillyard (1980) reported a negative component for words that are semantically anomalous given the preceding context (*he spread the warm bread with socks*), which they labelled the “N400” component. Since then, hundreds of experiments have replicated this result and investigated the cognitive and neural mechanisms underlying this component. The N400 is a negative component, peaking between 300 and 500 ms after onset of the critical stimulus (word or picture). The term “N400” is often used to refer to the component itself (all content words elicit an N400); the term “N400 effect” is used to refer to the difference in N400 amplitude in two conditions (e.g., semantically anomalous words vs. plausible words; or words preceded by an unrelated vs. a related word). Several neural sources have been proposed for the N400, among which are locations in the anterior temporal lobe (Nobre and McCarthy 1995; for more details see Van Petten and Luka 2006). The prevailing view of the N400 is that it reflects difficulty in semantically integrating the stimulus into the preceding context. This context can be a single word, sentence, discourse (Van Berkum, Hagoort, and Brown 1999), or a non-linguistic one, such as a picture sequence (West and Holcomb 2002). One argument in favor of the view that the N400 reflects semantic integration is that the N400 amplitude to content words (nouns, verbs and adjectives) decreases with each increasing linear word position in the sentence, that is, with a more strongly established semantic context (Van Petten 1993; Van Petten and Kutas 1990). Second, the N400 amplitude is affected by the expectancy of the word given the preceding context: if a word is highly expected given a preceding context, as in *the bill was due at the end of the month*, the N400 amplitude is smaller than when a word is unexpected, but still plausible, as in *the bill was due at the end of the hour* (Kutas and Hillyard 1984). The N400 has also been found to be sensitive to lexical properties, although this is somewhat controversial. Indeed, highly frequent content words elicit a smaller N400 than lower frequency words suggesting that the N400 might reflect the

signature of lexical retrieval/access as well as word meaning integration in the learning of novel words (Van Petten 1993; Van Petten and Kutas 1990, 1991).

Studying overt language production with ERPs is difficult because mouth movements cause severe artifacts in the ERP signal. For this reason, researchers have used an indirect way to study production, namely by associating a particular (semantic, syntactic, phonological) aspect of the to-be-produced word to a particular manual response. Using the left and right scalp electrodes above the motor strip, one can record the activity related to hand movement preparation. The potential will be more negative at the electrode in the contralateral hemisphere to the response hand than in the hemisphere, ipsilaterally to the response hand. These recordings are time-locked to the onset of either the stimulus or the actual response. The potentials at the ipsilateral electrode are then subtracted from the potentials at the contralateral electrode and averaged over left and right response hand trials to cancel out activity not related to response hand selection. The resulting ERP is called “lateralized readiness potential”, or LRP, which indexes response hand preparation. Word production paradigms using the LRP typically employ a two-choice go/no-go task. In such a task, the participant sees a series of pictures and is asked to respond with the right hand if, for example, a living object is depicted and with the left if an inanimate object is presented, but to respond only if, for example, the name of the object starts with an /s/ (go), and to withhold the response if the name starts with a /b/ (no-go) (Kaan 2007). Using such paradigms, investigators have tested in which order distinct sorts of information are accessed during word production (Levelt 1999) and the relative timing of these production stages. For instance, using a paradigm as the above and varying the type of information, the go/no-go decision based on semantic information was shown to precede the phonological information by 120 ms in production (Van Turennout, Hagoort, and Brown 1997), and the gender information to precede the phonological information by 40 ms (Van Turennout, Hagoort, and Brown 1998).

Although the use of ERPs is attractive to researchers investigating language processing, this technique also has limitations. First, many trials are needed to obtain ERPs with a good stimulus-to noise ratio. The number of trials depends on many factors, including the size of the effect and the number of participants. Typically, an experiment investigating word processing with 20 participants would require at least 40 stimulus tokens per condition, especially when the effect one is looking for is rather small. Presenting 40 or more items per condition (i.e., ambiguous vs. unambiguous word) in an experiment may lead to fatigue and processing strategies that are not intended by the investigator. A large number of items per condition is also required, because many trials will be lost due to artifacts. ERPs are sensitive to muscle tension and eye movements, which may

confound the actual brain response. When dealing with healthy adult participants, trials with such artifacts are often rejected from the analysis. Participants are instructed to remain still and not to blink during designated times to minimize the number of artifacts. Such instructions, however, may affect the participant's attention to the stimuli. More importantly, although ERPs have a good temporal resolution, the pattern of activation recorded at the scalp is not very informative as to where in the brain the activity occurs (Kaan 2007).

6 Neuromodulation approach

In addition to the temporal limitation described so far regarding the fMRI technique, which might in part be overcome using ERPs, it should be noted that, although fMRI has been widely used for studying the neural correlates of language, it has a limited spatial resolution of about a cubic millimeter. In such a volume one can find 100,000 neurons. In other words, the 'fMRI microphone' cannot listen to individual cells, but to a whole stadium full of them. Therefore, this technique cannot unequivocally determine whether an active area is essential for a particular function or behavior (Price and Friston 1999).

In these last years, the progress of new technologies has made additional tools available. In the field of aphasia, the application of non-invasive stimulation methods, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), has contributed to better define possible correlations between a specific brain region and its language function (Miniussi et al. 2008). In particular, TMS can be used to investigate the neural activity in a specific brain region avoiding the aforementioned criticism regarding the fMRI and ERPs methods. Indeed, the TMS-induced activity in the subpopulation of neurons located under the stimulating coil interacts effectively with any pattern of activity that is occurring at the time of stimulation (Walsh and Pascual-Leone 2003). In other words, unlike neuroimaging methods, which only indicate correlations between brain and behavior, TMS can be used to demonstrate causal brain-behavior relations.

More recent studies have also suggested to apply these techniques as adjunct tools for planning new therapeutic interventions for language rehabilitation (Marangolo and Caltagirone 2014), and direct electrical stimulation (DES) in language areas has been used during intraoperative mapping to guide brain tumor surgery (see Papagno 2017).

In Section 6.1, the most recent neuroscientific evidence on the use of these stimulation techniques in investigating the neural correlates of word processing will be presented.

6.1 Transcranial magnetic stimulation (TMS)

The major potential contribution of TMS to our understanding of the lexicon organization consists in the transient disruption of focal cortical activity to establish the causal role and the timing of the contribution of a given cortical region in behavior. This effect allows empirically testing specific neuropsychological models and constructs. TMS produces either transient or enduring focal changes in patterns of brain activity (Miniussi et al. 2008). It employs the principle of electromagnetic induction and involves the generation of a rapid time-varying magnetic field in a coil of wire. When this coil is applied to the head of a subject, the magnetic field penetrates the scalp and skull and induces a small current parallel to the plane of the coil in the brain that is sufficient to depolarize neuronal membranes and generate action potentials.

There are several possible paradigms to study language by means of TMS. The first distinction is between offline and online paradigms: interference with cognitive processing when TMS is applied during performance of a task is called online TMS (Pascual-Leone, Walsh, and Rothwell 2000). In contrast, in the case of offline stimulation, TMS is applied for several minutes before the subject performs a given task.

The online approach transiently disrupts ongoing neural processing in the stimulated cortex while subjects perform a language task. This permits to infer causal relations with respect to the contribution of the stimulated area to a specific brain function (Hartwigsen 2015). Online TMS protocols consist in the application of single pulses, paired pulses and short high-frequency bursts of repetitive TMS (rTMS). While the majority of studies targeting language areas used rTMS to interfere with a specific language function (e.g., Papagno et al. 2009b, Sliwinska, Vitello, and Devlin 2014), some language studies also applied single, double, or triple pulse protocols in a chronometric fashion (e.g., Devlin, Matthews, and Rushworth 2003; Schuhmann et al. 2009, Sliwinska et al. 2012). This consists in delivering TMS at distinct time-points during a task to perturb intrinsic neural activity in the stimulated area. As a single TMS pulse interferes with ongoing neural activity for several tens of milliseconds, this approach provides high temporal resolution to identify the time period during which the stimulated region makes a critical contribution to that task. The effects of rTMS are often referred to as “virtual lesion” (Pascual-Leone, Walsh, and Rothwell

2000; Walsh and Cowey 2000). Generally, the experimental protocols in TMS studies have employed two different stimulation conditions: a real condition which allows to explore the effect of stimulation over the targeted area (i.e., Broca's area) on language processing and a "placebo" control condition (i.e., sham condition) in which the stimulator is turned- off after few seconds. This is performed in order to ensure that the behavioral changes are specifically attributable to stimulation (Marangolo and Caltagirone 2014).

Offline TMS is given continuously as long trains at a constant rate (i.e., continuous rTMS, often applied at a frequency of 1 Hz) or intermittently as repetitive bursts (i.e., intermittent or burst-like rTMS) to induce lasting functional effects in the stimulated area and connected sites (Siebner and Rothwell 2003). These protocols can modulate brain activation for a longer time period of about 30–45 min after the end of stimulation thus allowing for the induction of rapid functional reorganization in the stimulated area and in connected brain regions (Rossi and Rossini 2004). These "remote" effects may occur over large distances at interconnected sites. Usually, the applied rTMS protocol is "inhibitory" on motor cortical excitability, but the effects on cognitive functions may depend on the context.

A number of studies reported behavioral facilitation when single pulse TMS or high-frequency rTMS was given immediately before picture naming over left-hemispheric language areas (offline TMS) (e.g., Mottaghy et al. 1999; Mottaghy, Sparing, and Töpper 2006; Sparing et al. 2001; Töpper et al. 1998; Wassermann et al. 1999). For instance, in Töpper et al. (1998)'s study, TMS of the left motor cortex had no effect, while stimulation of Wernicke's area significantly decreased picture naming latencies. These data suggest that focal TMS facilitates lexical processes, likely inducing a general pre-activation of linguistic neural networks.

rTMS has been also used to investigate different classes of words (nouns and verbs). Response times following real stimulation over the left prefrontal cortex increased for verbs and pseudoverbs but were unaffected in the case of nouns and pseudonouns (Shapiro et al. 2001). Also, the issue concerning abstract/concrete nouns has been investigated using rTMS with a lexical decision paradigm (Papagno et al. 2009b). Interference with accuracy was found for abstract words when rTMS was applied over the left superior temporal gyrus, while for concrete words accuracy decreased when rTMS was applied over the right contralateral homologous site. Moreover, accuracy for abstract words, but not for concrete words, decreased after left IFG stimulation. These results suggest that abstract lexical entries are stored in the posterior part of the left temporal and possibly in the left frontal sites, while the regions involved in storing concrete items include the right temporal cortex. In contrast, other studies

reported decreased behavioral accuracy when online rTMS bursts were applied during picture naming over frontal or temporal language areas (Flitman et al. 1998, Wassermann et al. 1999). These studies suggest that the type of task and the stimulation protocol strongly affect the results.

In sum, online and offline TMS represent complementary approaches that enable the researcher to investigate the functional relevance of the targeted brain area within a language network. The changes in neural activity evoked by TMS are generally measured as changes in reaction times and/or error rates. Effects of TMS on electrophysiological parameters or neural activation, on the other hand, can be assessed with ERPs or neuroimaging read-outs. However, risk of rTMS use should be assessed carefully and its dosage should generally be limited according to published safety guidelines (Wassermann 1998).

6.2 Transcranial Direct Current Stimulation (tDCS)

In more recent years, a new stimulation technique, namely transcranial direct current stimulation (tDCS), has been applied to the study of language. However, in comparison with TMS, whose focal activity allows inferring causal brain-behavior relation, tDCS, due to its large stimulation electrodes, is considerably less focal. Hence, tDCS is less suitable to investigate functional-anatomic subdivisions within the language system but it is mainly used for therapeutic purposes (e.g., in post-stroke rehabilitation, see Marangolo and Caltagirone 2014; Monti et al. 2013). Indeed, an important advantage of tDCS is the apparent absence of any significant unpleasant effects when using standard protocols. Specifically, tDCS has not been reported to provoke seizures, which is a frequent undesirable effect in brain-damaged subjects, since the delivered electrical current is well below the threshold of eliciting action potentials (Nitsche and Paulus 2011). Therefore, compared with the research on TMS discussed earlier, to date tDCS studies have not been performed for investigating possible correlations between a language task and its underlying neural representation but to understand whether this technique is a viable option for the recovery of language after stroke (Miniussi et al. 2008).

tDCS involves the application of small electrical currents (typically 1–2 mA) to the scalp through a pair of surface electrodes (5 x 7 cm large) over a long period, usually minutes (5–30 minutes), to achieve changes in cortical excitability by influencing spontaneous neural activity. Unlike TMS, which induces currents of sufficient magnitude to produce action potentials, the weak electrical currents employed in tDCS are thought to modulate the resting membrane potentials of neurons (Monte-Silva et al. 2013; Nitsche and Paulus

2011). The effect of tDCS depends on which electrode is applied to the scalp. Generally, the anode increases cortical excitability when applied over the region of interest, whereas the cathode decreases it limiting the resting membrane potential. These effects may last for minutes to hours depending on the intensity, polarity and duration of stimulation (Nitsche and Paulus, 2011). As TMS studies, tDCS experimental protocols make use of a crossover design, whereby each participant receives two different stimulation conditions: a real condition which allows researchers to explore the effect of stimulation over the targeted area (i.e., Broca's area) on the investigated function and a "placebo" control condition (i.e., sham condition) in which the stimulator is turned-off after a few seconds. This design has been implemented to ensure that the subject's behavioral changes are specifically attributable to the stimulation condition.

Like rTMS, most of the tDCS studies started with its application in the healthy population in order to investigate whether stimulation over the left language areas (i.e., Broca's or Wernicke's area) might facilitate language learning (Flöel et al. 2008), verbal fluency (Cattaneo, Pisoni, and Papagno 2011) and/or picture naming (Sparing et al. 2008). The results showed that it is possible to produce interaction between task execution and stimulation, thereby reducing or improving subject performance depending on the type of stimulation applied (anodal vs. cathodal). For instance, in a study by Flöel et al. (2008), tDCS was applied over the left Wernicke's area of 19 healthy individuals while they acquired 30 novel object names (nonwords). Each subject underwent one session of anodic tDCS, one session of cathodic tDCS, and one session of sham stimulation. The second electrode (reference electrode) was positioned over the contralateral supraorbital region. During stimulation, subjects were presented with a pair of stimuli (an auditory nonword matched with an object picture) they had to remember. In a subsequent phase, they had to judge whether the picture of the object and the novel word were the same as in the previously presented pair. Outcome measures were learning speed and learning success in acquiring the novel words. Results showed significant effects for both measures only during anodic stimulation of the left Wernicke's area. Similar results were obtained by Sparing et al. (2008) in a group of 15 healthy subjects who performed a picture naming task before and after stimulation of Wernicke's area. In their study, all subjects underwent four sessions of different stimulations: anodic, cathodic, and sham stimulation over the left Wernicke's area and anodic stimulation over the homologous right Wernicke's area. In all conditions the reference electrode was fixed contralaterally over the orbit. The authors found that the subjects responded significantly faster only following anodic tDCS over the left Wernicke's area. In a multimodal approach, Holland et al. (2011) investigated the effects of

anodal tDCS over the left IFG (i.e., Broca's area) on behavioral performance and neural activity. Relative to sham tDCS, 2 mA of anodal tDCS significantly facilitated picture naming latencies. Behavioral improvements were accompanied by decreased task-related activity in the stimulated area during concurrent fMRI. Correlational analysis showed that faster naming responses were associated with decreased neural activity in the IFG. The decreased neural activation in this area was suggested to parallel effects of neural priming reported in previous behavioral studies. Accordingly, it was suggested that anodal tDCS during picture naming can facilitate behavioral responses via a regionally specific neural adaptation mechanism in the left IFG.

Given the facilitatory effects on language learning in the healthy population, as previously stated, most of current research in this area is devoted to assess whether tDCS might be used as an adjuvant strategy to language therapy in order to speed up language recovery in post-stroke aphasia. Indeed, a growing body of evidence has indicated that tDCS enhances language functions (Marangolo and Caltagirone 2014) and its use might be extended even in domains other than the treatment of word-finding difficulties (Baker, Rorden, and Fridrikson et al. 2010; Fiori et al. 2011; 2013), such as the recovery of articulatory deficits (Marangolo et al. 2011; 2013a) and speech production (Marangolo et al. 2013b; 2014).

To summarize, several possible mechanisms can account for the effects of TMS and tDCS on language performance. Both methods have given novel insights into the mechanisms of adaptive short/long term reorganization and plasticity in the undamaged and damaged language system.

6.3 Direct electrical stimulation (DES)

During brain surgery for tumor resection it is a common clinical practice to awaken patients in order to assess the functional role of restricted brain regions, so that the surgeon can maximize the extent of the exeresis without provoking cognitive impairment, particularly of language. This technique allows for localization of extremely small (1 cm²) brain areas (Ojemann et al. 1989). Patients may be asked to perform a picture naming task while the surgeon inactivates restricted regions around the tumor by means of electrical stimulation. If the patient is unable to produce a response or produces an incorrect one, the surgeon refrains from removing the stimulated region. By cumulating performance over the areas stimulated and across subjects, a map can be constructed of the functional role of different brain regions (Papagno 2017). This neurophysiological procedure has allowed assessing the contribution of both cortical and

subcortical structures, for example, in naming animate and inanimate objects (Papagno et al. 2011), nouns and verbs (Lubrano et al. 2014) and abstract and concrete words (Orena et al. 2019).

7 Conclusions and future directions

Over the past two decades, functional neuroimaging has dramatically increased our understanding of human brain functions and in particular of language. In earlier times, language could be studied only indirectly via neuropsychological tests administered to brain-damaged patients. Today, functional neuroimaging allows mostly non-invasive *in vivo* visualization of cerebral activity, although several limitations must be considered.

With regard to the study of the neural correlates of the mental lexicon, the findings summarized above might lead to the conclusion that there is considerable evidence that distinct cerebral areas process different classes of words (i.e., noun vs. verb; concrete vs. abstract; living vs. non-living stimuli). However, before drawing any definite conclusion it is necessary to consider that in language, more than in other cognitive domains, several uncontrolled variables could produce a misinterpretation of results. As previously discussed, the proposal that the difference between nouns and verbs cannot be reduced to a single factor but is actually based on a continuum of differences at the semantic, syntactic and phonological level has important implications. If we just think of the role of morphological factors, the presence of verb-specific suffixes in languages such as Italian might have played a role in the different experiments in which a verb-specific region was identified in Broca's area. Indeed, this area is also active during the detection of syntactic anomalies, suggesting that in some reported studies, the activation was related to grammatical specificity of the verb and not to the verb category *per se*. This fact underlines the need for a careful evaluation of all the variables before establishing a causal relationship between a language task and the activation of a specific brain region.

Moreover, when inferring brain functions using neuroimaging methods, it is important to recognize their limitations. The main limitation of fMRI is that it detects neural activity indirectly, through the associated hemodynamic variations. On the contrary, ERPs recordings can directly detect neural activity with optimal temporal resolution. Therefore, to date, there is a growing interest in combining the different techniques (i.e., simultaneous ERPs-fMRI recordings) for a better understanding of the brain dynamics involved in language processing.

Recently, there have been successful efforts to combine TMS with simultaneous ERP recording, in order to study the temporal and functional impact of TMS interference on cognitive processes (Fuggetta et al. 2009; Taylor, Nobre, and Rushworth 2007). The value of this combination lies in the fact that the fine temporal resolution of EEG allows one to make an on-line measure of the effects of TMS at different stages of processing (e.g., sensory and post-perceptual), within brain regions, which are anatomically remote from the area impaired by the TMS (Fuggetta et al. 2009). This technique has been used to gain insight into the neural basis of semantic systems and in particular to study the temporal and functional organization of object categorization processing.

The picture emerging from all these experiments that we have described suggests that word production is achieved by a network of regions which vary in their computational specificity. The challenge is connecting the brain science of language to formal models of linguistic representation. As underlined by Poeppel et al. (2012: 14130), “in the new neurobiology of language, the field is moving from coarse characterizations of language and largely correlational insights to fine-grained cognitive analyses”.

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