Verbs and nouns in awake neurosurgery

needs and answers

by

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To my dearest wife

Chapter 1
General introduction

Awake neurosurgery (henceforth, awake surgery) is a medical procedure recommended for patients with brain tumors or pharmacologically intractable epilepsy. It borrows its name from the intraoperative stage in which patients are awake, so that neuropsychological and/or language tasks can be administered (e.g., Berger 1996; Duffau et al. 1999; Huncke, Van de Wiele, Itzhak, & Rubinstein, 1998; Kilbride, 2013; Ojemann & Mateer, 1979; Penfield & Boldrey, 1937). Awake surgery has gained popularity over the last years, because in more classical approaches - where patients are not awake and language tests cannot be administered - less tumor tissue may be removed and worse cognitive outcomes may be obtained (see, for a meta-analysis, De Witt Hamer, Gil-Robles, Zwinderman, Duffau, & Berger, 2012). Language testing is usually also performed shortly before and after surgery (the so-called "perioperative stages"). Awake surgery finds its way within a multidisciplinary field that includes a range of specialists – radiologist, anesthesiologist, neurosurgeon, neuropathologist, neurophysiologist and neuropsychologist (or speech/language therapist or clinical linguist). All these professionals have a specific role in the assessment and treatment of each individual patient. As researchers, we should strive to understand the needs of these professionals, and provide answers that help them reach their goals, while enabling us to gain knowledge on language and the brain, and to improve current standards of patient care.

A recurrent topic throughout this dissertation is that the language capacities of patients with brain tumors have been traditionally assessed with few tasks, and sometimes with non-standardized materials (e.g., Finch & Copland, 2014; Rofes & Miceli, 2014). Object naming tasks have been a key component of these assessments (for a review see De Witte & Mariën, 2013). Object naming has much to commend it, as seeing a picture and producing a noun (“apple”) or a determiner phrase (“the apple”) engages lexico-semantic input and output processes that are indispensable for everyday communication (Goodglass & Wingfield, 1997). For example, perioperative processing speed on object naming has been shown to correlate with postsurgical chances of return to work in patients undergoing this type of surgery (Moritz-Gasser, Herbet, Maldonado, & Duffau, 2012). Furthermore, object naming tasks were introduced by pioneers in the field and have maintained their role as a gold standard in the identification of areas relevant for language processing during surgery (Hamberger & Tamny, 1999; Ojemann & Mateer, 1979; Ojemann, Ojemann, & Lettich, 2002; Sanai & Berger, 2009).

Despite these positive results, having object naming as the main component of assessment in awake surgery may not be always sufficient. This is because (1) the language capacities required for object naming may be relatively spared in spite of damage to other language abilities such as reading, writing, comprehension, or naming of actions (Santini, Talacchi, Squintani, Casagrande, Capasso, & Miceli, 2012; Satoer et al., 2014); (2) there are language processes typically used in everyday language (e.g., for sentence formulation, to refer to actions, or to moments in time) that cannot be assessed with object naming (e.g., Rofes & Miceli, 2014; for a review); and (3) the neural correlates of object naming may be partially segregated from those of other processes such as action-naming (e.g., Mätzig, Druks, Masterson, & Vigliocco, 2009; Vigliocco, Vinson, Druks, Barber, & Cappa, 2011; for reviews). These are important issues in aphasiology, neurolinguistics, and cognitive neuroscience, which we revisited to work on critical improvements for awake surgery: the use of standardized tasks for language mapping, more specifically, the use of verbs as isolated words and finite verbs in sentences.

Verbs differ from nouns in a number of ways: they typically refer to actions (Gentner, 1982), and may weigh differently on psycholinguistic variables that affect performance in individuals with aphasia and non-brain-damaged people (e.g., Whitworth, Webster, & Howard, 2005; Vigliocco, Vinson, Druks, Barber, & Cappa, 2011). Verbs also entail a predicate-argument and a thematic structure (Carlson & Tanenhaus, 1989), and when they are used in the context of a sentence they require that agreement relations between the subject and the verb be fulfilled (Hale & Keyser, 1998). Verbs also allow the positioning of events in time and reference to events within a specific time frame (Bastiaanse, Bamyaci, Hsu, Lee, Yarbay Duman, & Thompson, 2011). Furthermore, they may be processed in different brain regions compared to nouns. It has been shown that verb processing elicits activation in the frontal and inferior-parietal lobe, whereas nouns trigger more activation in the temporal lobe (e.g., subjects KJ-1360, AN-1033 and Boswell in Damasio & Tranel, 1993; Lubrano, Filleron, Démonet, & Roux, 2014; Miceli, Silveri, Noncentini, & Caramazza, 1988).

Overall, earlier research suggests that the current assessments in awake surgery are pertinent but not sufficient. In this dissertation, we contribute to the efforts that are underway to meet the needs of awake surgery, both in terms of behavioral and anatomical knowledge. We approach the issue from the perspective of aphasiology, neurolinguistics and cognitive neuroscience (e.g., Coltheart 2011; Withworth et al., 2005). The chapters of this thesis each correspond to an article published in an international peer-reviewed journal or to a final draft that is (or will be) submitted for publication.

The thesis begins with a review of language mapping with tests that use verbs and sentences (Chapter 2). This chapter serves as a critical introduction to some of the needs that neurosurgeons and people responsible for the assessment of language skills in individuals with brain gliomas face in everyday practice. More specifically, it talks about renewing the consideration of tasks that use verbs, an approach already tackled in classical papers such as Ojemann and Mateer (1979). After this introduction, we deal with the design and development of an object naming task and a task with finite verbs in sentences, specifically designed to assess Italian-speakers undergoing awake surgery (Chapter 3). Such tools did not exist for the Italian language. The standardization of the tasks is described so that both the task methodology and the standardization of the tasks can be easily adopted by other research or awake surgery teams.

In Chapter 4, the validity of the noun and verb picture-naming tasks are assessed, as well as two other tasks typically used to assess language deficits in communicative contexts. By evaluating the performance of people suffering from post-stroke aphasia, we assess how well these naming tasks correlate with the ability to use language in an everyday context. The next two chapters describe the implementation of these tasks in surgical rooms and report the neurofunctional results of perioperative tests, their relation to the current neuroscience of language literature, and a critical review of the advantages and disadvantages that language mapping tasks may entail for awake surgery (Chapter 5 and Chapter 6).

We finish the dissertation with a general discussion, aimed at describing theoretical and clinical reasons way a rigorous approach may improve awake surgery procedures. We also discuss some future implications of this line of work (Chapter 7).

Chapter 2
Language mapping with verbs and sentences in awake surgery: A Review[1]

Abstract

Introduction: Intraoperative language mapping in awake surgery is typically conducted by asking the patient to produce automatic speech and to name objects. These tasks might not map language with sufficient accuracy, as some linguistic processes can only be triggered by tasks that use verbs and sentences. Verb and sentence processing tasks are currently used during surgery, albeit sparsely.

Methods: Medline, PubMed, and Web of Science records were searched to retrieve studies focused on language mapping with verbs/sentences in awake surgery. We review the tasks reported in the published literature, spell out the language processes assessed by each task, list the cortical and subcortical regions whose stimulation inhibited language processing, and consider the types of errors elicited by stimulation in each region.

Results: Eight types of tasks that use verbs and sentences were found in 20 studies. These are action naming, producing a finite verb in sentence context, sentence comprehension, sentence completion, verb generation, naming objects to oral description, reading sentences aloud, and translating paragraphs.

Discussion: We argue that using verb tasks allows a more thorough evaluation of language functions. We also argue that verb tasks are preferable to object naming tasks in the case of frontal lesions, as lesion and neuroimaging data demonstrate that these regions play a critical role in verb and sentence processing. We discuss the clinical value of these tasks and the current limitations of the procedure, and provide some guidelines for their development. Future research should aim toward a differentiated approach to language mapping – one that includes the administration of standardized and customizable tests and the use of longitudinal neurocognitive follow-up studies. Further work will allow researchers and clinicians to understand brain and language correlates and to improve the current surgical practice.

Keywords: awake surgery; language mapping; sentence processing tasks; verb processing tasks; review.

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2.1. Introduction

Awake surgery is a procedure administered to patients with brain tumors or intractable epilepsy in functionally relevant areas (Berger, 1996; Duffau et al., 1999; Hunke, Van de Wiele, Itzhak, & Rubbinstein, 1998; Ojemann & Mateer, 1979). The procedure requires the patient to be awake and cooperative, in order to perform relevant cognitive tasks during electrical stimulation of cortical and subcortical structures (Bello et al., 2007; Benzagmout, Gatignol, & Duffau, 2007; Duffau et al. 2003; Ojemann, Ojemann, Lettich, & Berger, 1989; Skirboll, Ojemann, Berger, Lettich, & Winn, 1996). This approach permits an accurate resection of pathological tissue, while at the same time allowing surgical teams to avoid iatrogenic language injury and to improve or at least preserve (in the case of surgery for brain tumors) the patient"s quality of life (De Witt Hammer, Gil-Robles, Zwinderman, Duffau, & Berger, 2012; Sanai, Mirzadeh, & Berger, 2008).

Over the past 20 years, the interest of the scientific and clinical community for the procedure has steadily increased. A Google search shows that between 1994 and 2013 publications dealing with awake surgery both for brain tumors and epilepsy have increased more than 5 times (from 3070 to 17500 publications per year). The interest for the cognitive outcome of the procedure has grown even more, as in the same time span publications investigating cognitive deficits in general have shown an eightfold increase (from 385 to 3720 publications per year), and studies dealing with language functions have increased by 15 times (from 152 to 1810 publications per year).

The characterizing feature of awake surgery is the electrical stimulation of cortical and subcortical structures during the performance of cognitive/linguistic tasks. The assumption underlying the approach is that, since electrical stimulation disrupts neurocognitive functions, the procedure allows surgical teams to identify and spare brain structures involved in critical cognitive (e.g., language) processes (Desmurget, Song, Mottolese, & Sirigu, 2013).

Even though this rationale is firmly established in the current practice (Kayama, 2012), a debate exists on whether electrical stimulation should be considered as the gold standard for language mapping in awake surgery. For one thing, it is still unclear whether the effects triggered by electrical stimulation of a specific area are the same to those that would emerge after resection of the same brain area. Borchers, Himmelbach, Logothetis, & Karnath (2011) suggested that the deviant behavioral responses triggered during surgery do not necessarily reflect a causal relation between electrical stimulation and the function(s) of the stimulated area. As an example, the fact that a patient shows an anomic state or produces a paraphasia after cortico-subcortical stimulation may be related to a temporary and reversible imbalance in the language network, of which the stimulated area may or may not be a necessary component.

In an attempt to overcome this limitation, fMRI protocols have been designed to pre-surgically assess language laterality and to predict and minimize post-surgical language deficits. Foki, Gartus, Geissler, & Beisteiner (2008) asked patients to read sentences aloud in an intraoperative task similar to some of those reviewed later in this manuscript. Other studies investigated neurobehavioral fMRI measures such as resting state, verb generation, semantic/tone decision, and passive listening to words or tones for the same purpose (Binder, Swanson, Hammeke, & Sabsevitz, 2008; Mehdorn, Giebel, & Nabavi, 2013). These studies mostly focused on surgery for epilepsy, and were used as an alternative to Wada testing (e.g., Sabsevitz et al., 2003).

Despite the excellent contribution of these studies, fMRI measures are still regarded as insufficiently sensitive and specific for an accurate mapping of language functions in patients undergoing awake surgery, when compared to electrical stimulation. For example, FitzGerald et al. (1997) indicated a sensitivity of 83% and a specificity of only 53% when comparing areas showing preoperative BOLD responses to those showing interference during surgery. Giussani, Roux, Ojemann, Sganzerla, Pirillo, and Papagno (2010) provided similar results in a recent review of the literature. Navigated transcranial magnetic stimulation (nTMS) has also been used for similar purposes and compared with findings during intraoperative stimulation. Picht et al. (2013) showed a sensitivity of 90% but a specificity of just 24% for this technique, compared with electrical stimulation.

On the whole, electrical stimulation is still the technique that allows the most reliable localization of language functions. In a recent meta-analysis, De Witt Hammer, Moritz-Gasser, Gatignol, and Duffau (2012) showed that, when compared to surgeries where it is not used, electrical stimulation leads to maximal tumor resection and to better preservation of cognitive functions – hence, of quality of life. For these reasons, electrical stimulation is recommended over other methods to detect function in the brain during surgery and therefore to guide surgical decisions (Kayama, 2012).

Another grey area is provided by the undefined role played by the subject"s profile (e.g., age, education, language spoken, preoperative language problems, etc.) and pathology (e.g., type of tumor, volume, cortico-subcortical extension, brain plasticity phenomena, associated psychological problems, etc.). Bizzi et al. (2008) indicated that patients with gliomas in the left ventral precentral sulcus are more likely to present preoperative language deficits than patients with gliomas in the inferior frontal gyrus. Santini, Talacchi, Squintani, Casagrande, Capasso, & Miceli (2012), Satoer, Vincent, Dirven, Smits, and Visch-Brink (2011) and Satoer, Work, Visch-Brink, Smits, Dirven, and Vincent (2012) recently showed that tumor histology, but not the extent or resection or demographic variables, correlates with cognitive outcome after surgery in language areas. Santini et al. (2012) documented anxiety and depression in almost half of the patients. In a bilingual patient, Roux and Trémoulet (2002) documented a language-specific disturbance after surgery, resulting in the recommendation that multilingual patients be intraoperatively assessed in all languages they normally speak.

Even though numerous outstanding questions still surround the awake surgery procedure, the present review wishes to draw attention on issues that concern the evaluation of the neurocognitive status of the patient (with a brain tumor or epilepsy). Neuropsychological testing is part and parcel of awake surgery, pre-, intra- and post-operatively. Therefore, one way to contribute to improving the procedure is to develop increasingly sensitive and dedicated tasks. We first briefly discuss the language tasks typically used in awake surgery, to then concentrate on intraoperative tasks that tap verb and sentence processing. We review the tasks reported on in the literature, the brain areas shown to be involved in these tasks, and the types of errors observed during electrical stimulation. We then examine the relationships between intraoperative testing, and pre- and post-operative language evaluations with a focus on their clinical value. We provide theoretical considerations and empirical evidence from the neuroscience of language that justify a more systematic use of verb and sentence processing tasks as tools for intraoperative language mapping. Finally, we propose a rationale that might improve, enhance and constrain the use of language (especially verb) tasks in awake surgery.

2.1.1. Language mapping tasks in awake surgery

The tasks traditionally used to map language during awake surgery are automated speech and object naming (Hamberger & Tamny, 1999; Ojemann & Mateer, 1979; Ojemann, Ojemann, & Lettich, 2002; Sanai et al., 2008; for a review see De Witte & Mariën, 2013). Automated speech tasks such as counting or reciting the days of the week are administered to assess articulation, as they pose little demands on semantic and lexical knowledge (Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 2000). Object naming tasks are used to assess also semantic and lexical retrieval, as they require patients to produce nouns in response to pictures. Good performance on these latter tasks is positively correlated with quality of life and return to work (Moritz-Gasser, Herbet, Maldonado, & Duffau, 2012).

These tasks were introduced by the pioneers of awake surgery procedures, and have deservedly maintained their role, as they are simple, fast, and accurate in detecting speech arrest and object naming impairments. There is a vast literature on these tasks, showing that they are sensitive to electrical stimulation of many different brain loci (e.g., Benzagmout et al., 2007 and Sanai et al. 2008 for Broca”s area, the inferior frontal gyrus, and related subcortical areas; Ojemann et al., 1989 for the superior temporal gyrus, the middle temporal gyrus, postcentral gyrus, and inferior parietal lobe; Leclercq et al., 2010 and Papagno et al., 2011 for recent studies on long association fiber pathways). However, the everyday use of language poses greater demands on the cognitive system (e.g., an ecological use of language requires the ability to produce sentences). If the goal of an intraoperative task is to detect subtle language deficits during electrical stimulation, automated speech and object naming may not be the most sensitive tools. To mention but one issue, object naming can be spared in the face of damage to action naming or to grammatical processing (e.g., Miceli, Silvieri, Villa, & Caramazza, 1984; Hillis, Tuffiash, & Caramazza, 2002; see Pillon & D”Honinchthun, 2009 for a review), and production of nominal morphology can remain intact in the presence of severe difficulty producing verbal morphology (e.g., Shapiro, Shelton, & Caramazza, 2000; Tsapkini, Jarema, & Kehayia, 2002). Other tasks, just as simple and fast as automated speech or object naming, could be administered during surgery, to assess a broader range of linguistic abilities and to better prevent their disruption. Thoughtful consideration should be given to tasks that use verbs and sentences.

2.1.2. Why use verbs in intraoperative language mapping?

Verbs and nouns engage distinct types of knowledge and play distinct roles in connected speech. Nouns typically provide a written or spoken label to physical characteristics and functions of objects. For instance, the word “table” refers to a discrete entity with a rectangular, round or oval shape, four or more legs, made of wood or other robust material and with specific uses (eating, studying, playing, etc.). Verbs, on the other hand, both as isolated words and as predicates in sentences, refer to actions and project their properties (e.g., argument structure, thematic roles, reference of time and person) to other word categories, such as nouns. As an example, when we want to say that “someone” (John) completed the action of making “something” (the table) clean in the past, we do so by producing the sentence “John cleaned the table”. In the sentence, the verb “cleaned” glues together the different words and indicates what happened, when, and to whom (or to what).

Even though the precise nature of the differences between nouns and verbs is still a matter of debate (for contrasting views, see Shapiro & Caramazza, 2003; Vigliocco, Vinson, Druks, Barber, & Cappa, 2011), there is agreement that the two word types differ at the semantic, lexical and lexical-grammatical level. From the semantic standpoint, verbs are on average less referential, more abstract and less imageable than nouns. They also differ at the lexical-grammatical level (e.g., they take different sets of inflections). In many languages, differences at this latter level typically result in greater processing demands for verbs than for nouns. For example, English verbs have four possible inflections and nouns have two. In Italian, verbs have about 46 inflected forms, and nouns only two or, in very rare cases, four (e.g., *ragazzo, ragazzi, ragazza*, *ragazze*, boy, boys, girl, girls). In other languages, like Chinese, the reverse is the case, as nominal morphology is more complex than verb morphology (Bastiaanse, Bamyaci, Hsu, Lee, Yarbay Duman, & Thompson, 2011).

Lesion studies have also repeatedly shown that verbs and nouns are processed by at least partly separable neural substrates, and that left prefrontal structures are critical for verb processing (Bastiaanse & Jonkers, 1988; Damasio & Tranel, 1993; Miceli, Silvieri, Nocentini, & Caramazza, 1988; Pillon & d"Honincthun, 2011; Shapiro & Caramazza, 2003; Woods, Carey, Tröster, & Grant, 2005; Zingeser & Berndt, 1990; for review see Mätzig, Druks, Masterson, & Vigliocco, 2009). Similar data were obtained in neuroimaging studies that revealed stronger activation of left inferior frontal sources during EEG for unambiguous verbs (Federmeier, Segal, Lombrozo, & Kutas, 2000), during MEG for inflectional verb affixes (Pulvermüller & Shtyrov, 2009; Tsigka, Papadelis, Braun, & Miceli, 2014), and greater and more widespread BOLD activation in the left Inferior Frontal Gyrus (IFG) for inflected verbs than for inflected nouns (Davis, Meunier, & Marslen-Wilson, 2004; Den Ouden, Fix, Parrish, Thompson, 2009; Den Ouden, Hoogduin, Sowe, & Bastiaanse, 2008; Finocchiaro, Basso, Giovenzana, & Caramazza, 2010; Tyler, Bright, Fletcher, Stamatakis, 2004; Yokoyama et al. 2006). In a recent study on a large stroke population, six verb processing tasks were administered (Kemmerer, Rudrauf, Manzel, & Tranel, 2012). The poorest performance was observed in participants suffering from damage to the left inferior frontal gyrus or to prefrontal areas (Figure 2.1).

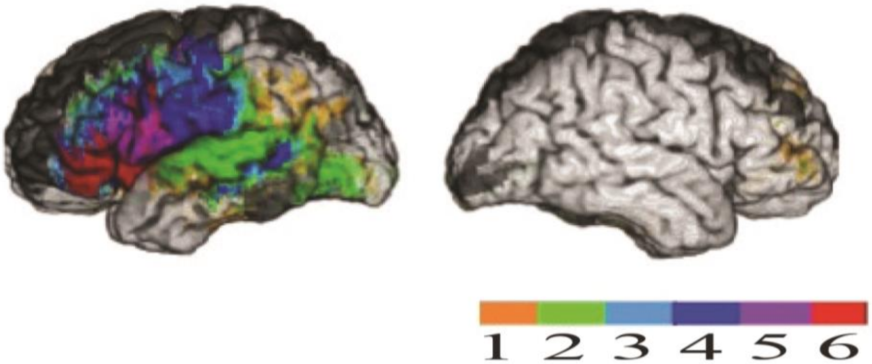

Figure 2.1. Kemmerer et al. (2012). Greater implication of the left inferior frontal regions in verb processing. The scale indicates the number of impaired tasks from 1 (orange) to 6 (red). Reproduced with permission.

The message we wish to convey is clear: in the context of intraoperative language mapping, verb processing tasks would tap articulation, just like automatic speech and object naming. They would also engage semantics and lexical retrieval like object naming, but would do so by recruiting neural and cognitive mechanisms at least partially different to those involved in noun processing. In addition, and also differently to object naming, they would tackle the grammatical processes that allow the speaker to combine words into sentences, to indicate when the action happened, to make reference to the person performing the action, etc. For this reason, tasks that use verbs would increase the sensitivity, specificity and predictive values of intraoperative language mapping procedures. This would be particularly evident in the case of surgery on the frontal lobe, as very processing is typically impaired following damage to this region.

2.2. Methods

MEDLINE, PubMed, and Web of Science records were searched for studies of language mapping with verbs and sentences in awake surgery. The following search terms were used:

actions, action naming, awake surgery, auditory naming, comprehension, (direct) electrical stimulation, language, language mapping, neurosurgery, production, reading, sentences and verbs. The reference section of each study was examined to identify further relevant research. For each study, the following aspects were considered: type of task, standardization, type of stimuli, task design, number of stimulations, error categorization, number of participants, type of electrical stimulation, sites of electrical stimulation, areas that inhibited language processing (cortical and subcortical), etiology, tumor grade and methods used for language localization.

Studies in which verb and sentence processing tasks had not been administered were excluded. In these studies, patients either were operated under general anesthesia, or completed other cognitive tasks (e.g., object naming, calculation, naming famous people, semantic decision or line bisection) during awake surgery procedures.

2.3. Results

2.3.1. Tasks with verbs and sentences

Eight types of tasks using verbs and sentences during surgery were found in 20 studies. We describe each task separately:

Action naming (Bello, Acerbi, Giussani, Baratta, Taccone, & Songa, 2006; Bello et al., 2007; 2008). Patients see the black-and-white drawing of an action. They are asked to produce the infinitival form of the verb depicted in the drawing. For instance, for a picture of “a man running”, English-speaking patients are expected to say the verb “run” or “to run”, and Italian-speaking patients the verb “*correre*”.

Producing a finite verb in sentence context (Lubrano, Filleron, Démonet, & Roux, 2014). Patients see a black-and-white drawing of an action. They are asked to produce the verb in the correct inflected form, preceded by the subject of the sentence. For example, for a drawing of a man cutting, patients have to say “he cuts”.

Sentence comprehension (Bello et al., 2007). Patients are shown two black-and-white drawings and then hear a sentence that corresponds to one of them. Their task is to indicate which of the two images correctly represents the stimulus sentence. For example, a subject sees the drawing of “a boy pushing a girl” and another one of “a girl pushing a boy”. Then he hears the sentence “the boy is pushing the girl” and must point to the corresponding drawing. A correct interpretation of the verb and its arguments is necessary for the correct response.

Sentence completion (Ojemann & Mateer, 1979). Patients read incomplete sentences of 8 to 10 words. They are required to complete each sentence with the appropriately inflected verb form. For example, for the sentence “If it”s sunny next Saturday she ... beach”, the target is the future form “will go”.

Verb generation (Bizzi et al., 2008; Herholz et al., 1997; Ojemann et al., 2002; Papagno et al., 2011; Roux, Boulanouar, Lotteri, Mejdoubi, LeSage, & Berry, 2003). Patients see black-and-white drawings of objects (Papagno et al., 2011; Roux et al., 2003) or written names of objects (Herholz et al.,1997; Ojemann et al., 2002). They are expected to say an action that can be performed with these objects, using a verb in the infinitival form. For example, for a drawing of an apple or for the written word “apple”, patients are expected to say “eat” or “to eat”, in English; and “*mangiare*”, in Italian.

Naming objects to oral description (Hamberger, McClelland, McKhann, Williams, & Goodman, 2007; Hamberger, Seidel, Goodman, Perrine, McKhann, 2003; Hamberger, Seidel, McKhann, Perrine, & Goodman, 2005). Patients hear a sentence describing an object, and are asked to produce the name of the object. For a sentence like “an instrument you beat with sticks”, the expected answer is “drum”. Even though this task does not exclusively (or mainly) tap verb processing, correct responses require comprehension of the stimulus sentence, which includes a lexical verb relevant to access the representation of the target noun (cf. “It is used to *make* coffee” and “It is used to *drink* coffee”).

Reading sentences aloud (Ojemann et al., 1989; Roux & Trémoulet, 2002; Roux, Lubrano, Lauwers-Cances, Trémoulet, Mascott, & Démonet, 2004; Sacko, Lawers-Cances, Brauge, Sesay, Brenner, & Roux, 2011). Patients are asked to read sentences presented on screen (e.g., “The chair is beautiful”; “Take the book and read it!”). As in the previous task, verbs are not the only target words, as they appear in sentence context. However, correct responses require that the verb in the sentence be read accurately.

Translating paragraphs (Borius, Giussani, Draper, & Roux, 2012). This task is applicable to bilingual patients only. Patients are given short paragraphs, written in their second language, from newspapers. They are required to translate the paragraphs into their first language. Also in this case, verbs are not the only target, but they must be processed correctly in order to produce the correct response.

Administration and design of these tasks share some features. The typical subject to whom they are administered is a right-hander with a lesion in the left (dominant) hemisphere. The types of lesions operated upon are low-grade or high-grade gliomas of the frontal, temporal or parietal lobe. Studies with patients suffering from intractable epilepsy are also reported (Hamberger et al., 2003, 2005, 2007; Ojemann et al., 1998; Ojemann et al., 2002). Patients affected by meningiomas, vascular malformations, mesial temporal sclerosis and dysembryoplastic neuroepithelial tumors in the left hemisphere also completed these procedures (Hamberger et al., 2003; Ojemann et al. ,1998, Ojemann et al., 2002; Roux et al., 2004; Sacko, Lawers-Cances, Brauge, Sesay, Brenner, & Roux, 2011). Across studies, stimulation parameters and number of stimulations per brain site are roughly the same. A bipolar dipole that uses rectangular pulses and a biphasic current and allows the exact delimitation of an area is used. Electrical stimulation does not exceed 4 seconds, to make sure that the behavioral disruption is caused by electrical stimulation and not by language impairment. Electrical stimulation is applied before stimulus onset, 2 to 4 times per brain site, never consecutively to the same site and with a control test without stimulation between two stimulations. The number of stimuli in each task ranges from 22 to 80. These details do not differ from those reported in the guidelines for awake surgery (Kayama, 2012).

2.3.2. Language processes assessed by each task

The discussion we present here is based on the cognitive neuropsychological approach (Coltheart 2001, Whitworth, Webster, & Howard, 2005). The language components putatively addressed by each task and sketched here are largely agreed upon scholars who described speech processing models (i.e., box-and-arrow diagrams that are used to operationalize a theory and test its viability) within this approach (Caramazza, 1997; Levelt, 1989). Models agree that linguistic information about a word is represented at three independent levels: a semantic, a lexical, and a lexical-grammatical or syntactic level. Regardless of the specific functional architecture of the system (for contrasting views see Caramazza, 1997 and Levelt, 1989) these components are thought of as long-term memory stores.

Models typically include a central semantic level where word meaning is stored and accessed. An intact semantic level is necessary both to understand a word and to select it for production. Its assessment during surgery is crucial, as damage to meaning representations interferes with word comprehension and production, and has a negative effect not only on language skills but also on quality of life (Goodglass & Wingfield, 1997).

Peripheral to the semantic level, the lexical system is a multi-component representational level with input and output subcomponents. It is critical for recognizing spoken (phonological lexicon, input) or written words (orthographic lexicon, input), thus allowing access to their meaning, and for retrieving words from semantics in speech (phonological lexicon, output) or writing (orthographic lexicon, output).

The syntactic level is needed to process grammatical features of words. These are necessary to produce and comprehend articulated discourse (Bastiaanse & Jonkers, 1998). This level must be assessed during surgery, as its damage may disrupt the ability to understand and/or produce the action corresponding to the verb, as well as the time and person of the action. Further description of these processes can be found in single-word processing models (Patterson & Shewell, 1987; Whitworth et al., 2005). In Table 2.1 we provide a list of the language processes assessed by each task. The list is not exhaustive and does not necessarily correspond to the order in which language processes occur.

Table 2.1

Language processes assessed by each task

	ACTN	VSC	NOOD	RSEN	SCOMPL	SCOMPR	TRANSLP	VGEN
Phonological lexicon (Input)			✓					
Structural description (Input)	✓	✓				✓		✓
Orthographic lexicon (Input)				✓	✓		✓	
Semantic level	✓	✓	✓	*	✓	✓	✓	✓
Phonological lexicon (Ouput)	✓	✓	✓	*	✓		✓	✓
Orthortographic lexicon (Ouput)				*	✓		✓	
Syntactic level (morphosyntactic features)		✓	✓	*	✓	✓	✓	

Notes. ACTN = Action naming; VSC = Producing a finite verb in sentence context; NOOD = Naming objects to oral description; RSEN = Reading sentence aloud; SCOMPL = Sentence completion; SCOMPR = Sentence Comprehension; TRANSLP = Translating Paragraphs; VGEN = Verb Generation. Check marks (✓) indicate that the process is assessed in the task. Asterisks (*) indicate that the process may be assessed in the task. A blank space indicates that the process is not assessed by the task. Phonological lexicon (input/output), Structural stimulus description (input), Orthographic lexicon (input/output) are independent components, whose engagement depends on the type of task administered. For instance, naming objects to oral description uses oral input. Hence, it involves the Phonological lexicon (input) but not the retrieval of visual-structural stimulus descriptions, which is needed when the stimulus is a drawing, or the Orthographic lexicon, that is used when the stimulus is a written word/text. The list is not exhaustive and does not necessarily correspond to the order in which language processes occur. However, it provides an overview of the components engaged by each task.

Each task in the list poses a unique computational problem and taps several components of the language system. These should be regarded in terms of the language processes assessed, the modalities tested (i.e., written vs. oral), the time necessary to perform the task, and the patient's profile.

2.3.3. Areas where cortico-subcortical stimulation inhibited language processing, and types of errors elicited by stimulation

In Figure 2.2 (upper half) we indicate the cortical and subcortical areas of the language-dominant hemisphere in which language processing was detected by each task during intraoperative stimulation. Detailed information is reported in Tables A1 and A2, in the Appendix. In most reviewed studies sample size is small, and subject-specific factors and stimulation parameters are addressed only inconsistently. Consequently, the data represented in Figure 2.2 are suggestive and therefore warrant replication.

Each task elicited speech errors in a wide range of left frontal, temporal, and parietal cortical areas. Only two studies (Bello et al., 2006; 2007) carried out subcortical mapping. These indicate that verb processing involves different portions of long association fiber pathways (i.e., Superior Longitudinal Fasciculus, the Arcuate Fasciculus, Uncinate Fasciculus, Inferior fronto-occipital fasciculus, etc.). We did not report on the results of stimulation of right hemisphere areas, as these were hardly ever assessed. Bello et al. (2007) and Sacko et al. (2010) operated on patients with right hemisphere tumors, but did not discuss data from individual participants.

Figure 2.2 (lower half) shows the types of errors elicited by stimulation during each task. Purely perceptual (visual or auditory) or purely motor (articulatory) errors were disregarded.

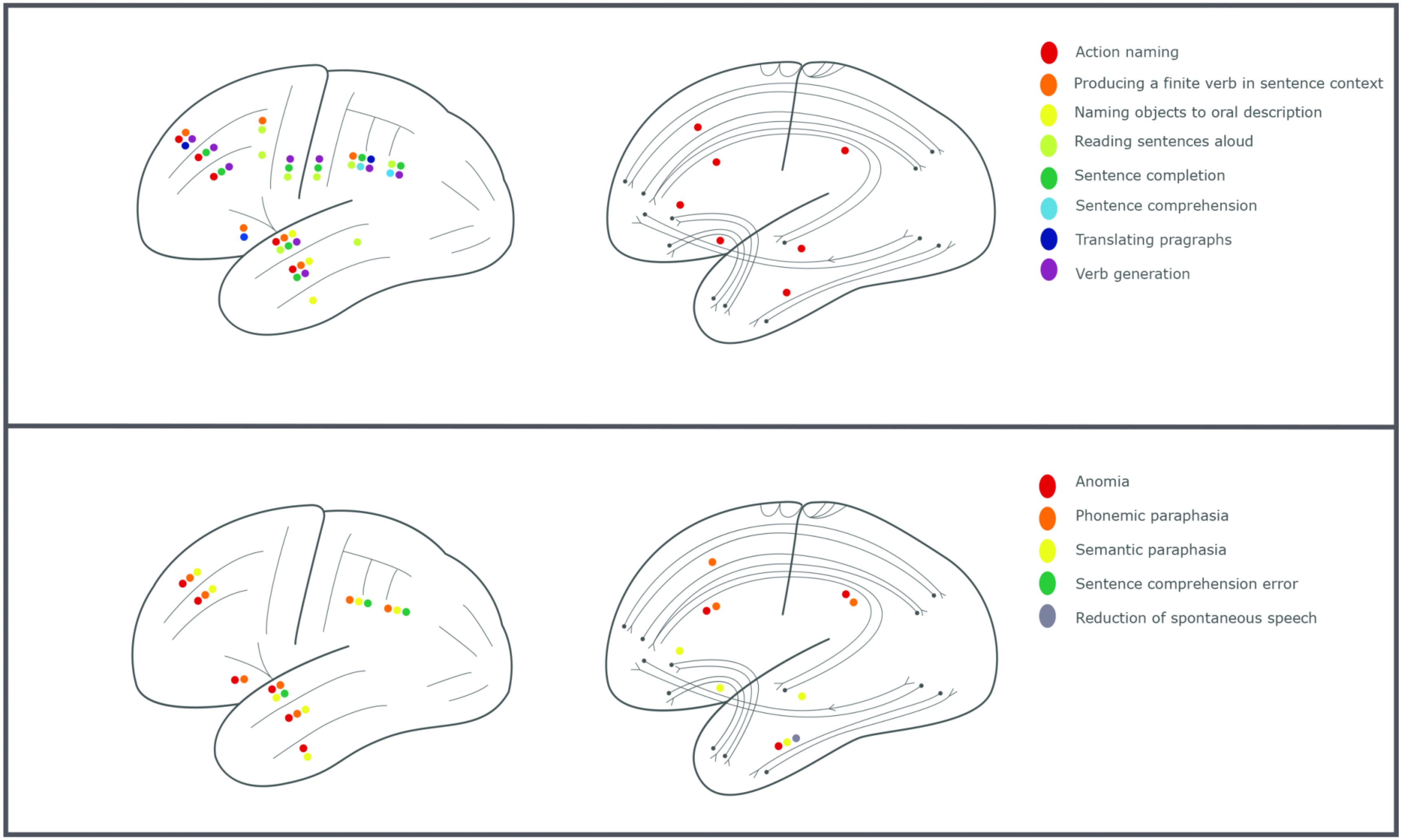

Figure 2.2. Cortical (right) and subcortical (left) structures in which intraoperative stimulation interfered with language processing (upper half), and types of errors elicited by stimulation of each area during each task (lower half). Colored dots indicate involvement of a gross anatomical structure (e.g., Superior Frontal Gyrus, Arcuate Fasciculus) and not a specific location within it. The absence of dots of a given color means that the area/error was not reported or unaffected during stimulation. See also Tables A1 and A2.

The focus is on incorrect responses due to linguistic impairment, such as anomias, semantic and phonemic paraphasias, and syntactic errors (see also Tables A1 and A2 in the Appendix).

The term anomia indicates the failure to produce a response, in the absence of damage to perceptual or articulatory mechanisms. Errors of this type arise at the semantic and/or lexical level. Some authors distinguish anomia that persists after the end of stimulation from anomia that only occurs during stimulation (Hamberger et al., 2003; 2007). An example of anomia in a reading task is the sudden arrest when reading a sentence like “the car is blue and…”. It should be stressed that a speech arrest is scored as an anomia only if it does not result from a peripheral motor impairment – during stimulation no face or tongue contraction is visible and the patient succeeds in reading the sentence as soon as stimulation is interrupted (Roux et al., 2004). Another issue is controlling for effects in motor programming (e.g., apraxia of speech) which nobody has reported up-to-date. Anomias are the most frequent error in aphasic speakers (Williams & Canter, 1987), and have limited localization value (Kertesz & McCabe, 1977). Data from awake surgery make no exception: failures to name were reported in all the tasks reviewed here, and in association to the stimulation of a variety of cortical and subcortical structures (Figure 2.2).

The term paraphasia denotes erroneous responses to words, resulting from incorrect production of their segments (phonemic paraphasia – e.g., “sunny” > “sucky”; Ojemann & Matter, 1979) or from uttering a word related in meaning to the target (semantic paraphasia – e.g., “chair” > “table”; Marshall & Newcombe, 1996). Paraphasias were elicited by stimulation during action naming, reading sentences aloud, sentence completion and verb generation tasks. Interestingly, subcortical stimulation yielded only phonemic paraphasias in dorsal associative pathways such as the Arcuate Fasciculus, the Superior Longitudinal Fasciculus, and the Subcallosal Fasciculus, whereas semantic paraphasias were elicited during stimulation of more ventral pathways such as the Inferior Frontal-Occipital Fasciculus, the Inferior Longitudinal Fasciculus, and the Uncinate Fasciculus. These observations suggest that these two sets of fasciculi (and the structures they connect) have a different impact on processes involving phonology as opposed to semantics.

Incorrect responses of the syntactic type result from errors or omissions that involve morphological and sentence-building elements. An example of a syntactic error is reading and completing the sentence "If my son is late for class again he… [will see] the principal" as "If my son will getting late today he'll see the principal". Errors of this type were elicited by stimulation during sentence completion tasks that overtly assess syntactic processes (Ojemann & Mateer, 1979). They were not reported when subjects were engaged in the production of finite verbs (Lubrano et al., 2014), which also requires syntactic processing. Ojemann and Mateer (1979) reported grammatical errors during stimulation in six scattered areas in the frontal and temporoparietal cortex.

2.4. Discussion

The clinical value of any intraoperative test is determined by its sensitivity, specificity, and predictive values. Evaluating these dimensions is relevant to decide which tasks are best suited to detect eloquent areas at risk during surgery, and to choose the items to be used intraoperatively. We reviewed eight different tasks with verbs and sentences that have been used during surgery, as reported in 20 studies. Both functional and anatomical considerations lead to expect that verb and sentence processing tasks would be a useful addition to the repertoire of testing tools for intraoperative language mapping. This could be true already if verb processing tasks are considered in isolation (i.e., as standalone tasks for intraoperative mapping). Verbs involve a broader range of cognitive/linguistic resources than nouns. They refer to events that project their properties into other words (noun typically refer to discrete entities), and the processing costs of time reference, argument structure and thematic role assignment pose demands at the grammatical level that do not apply to nouns (Bastiaanse & Van Zonneveld, 2004; Caramazza 1997; Kemmerer & Tranel, 2000; Levelt 1989; Whitworth et al. 2005). The mere fact that verb processing engages a larger number of language components makes verb tests a potentially more sensitive instrument for intraoperative language mapping than object naming tasks.

The relevance of verb processing tasks for accurate intraoperative language mapping is even more compelling if they are considered in combination with object naming tasks. Verb tasks are not simply more "complex", due to the involvement of a greater number of processing resources – they tap different abilities to those recruited by noun processing tasks, and involve at least partially distinct neural substrates. Therefore, combining object and verb processing tasks would ensure a more accurate and thorough mapping of language. Assessing a patient with these two tests is feasible as demonstrated by Lubrano et al. (2014). The risk for extending testing time was not reported by the authors as a problem. In our own group, this procedure increases testing time by about 5 minutes for cortical mapping and 5 minutes for subcortical mapping (total = 10 minutes) provided that we use our whole list of 70 items (70 items x4 seconds per item = 280 seconds = 4.7 minutes). So far this extension of time has not yet triggered any issue during surgery, as patients respond to the tasks normally.

2.4.1. Towards a differentiated approach to language mapping

In the current literature there is no clear indication for using specific tasks as a function of the affected brain region (see Fernández Coello, Moritz-Gasser, Martino, Martinoni, Matsuda, &

Duffau, 2013 for review). As a case in point, verb processing tasks may be particularly useful in the event of frontal lobe gliomas. Currently, the only criterion for using verb processing tasks is the presence of a lesion in the language-dominant hemisphere. Such an “undifferentiated” approach is reasonable: language localization is still an unresolved issue; patients have different language profiles and brain morphology; and plasticity may modify the neural underpinnings of language representations/processes (e.g., Borchers et al., 2011; Desmurget et al., 2007; Desmurguet, Bonnetblanc, & Duffau, 2013; Duffau, 2004).

Published results favor verb production over verb comprehension tasks for intraoperative mapping. Sentence comprehension and, partly, naming objects to description (that relies on verb comprehension) were mostly disrupted by temporal lobe stimulation (Bello et al., 2007; Hamberger et al., 2003; 2007). In contrast, production tasks such as action naming and verb generation were disrupted by both temporal and frontal lobe stimulation (Bello et al., 2006, 2007; Ojemann et al. 2002; Roux et al., 2003). This could be because production engages more anterior regions and comprehension more posterior regions, or because the two processes engage distinct language networks with different intensities (Hickok & Poeppel, 2007). Only a thorough understanding of the computational demands of each task will eventually provide firm theoretical motivations for preferring some tasks over others. However, production tasks have a clear advantage already. They require that the stimulus be analyzed at the perceptual and conceptual level, and that lexical forms (possibly inflected) be retrieved and produced. Therefore, they engage a larger number of cognitive and neural mechanisms. The need for overt spoken responses facilitates on-line monitoring and error detection during surgery; and online error classification allows surgical teams to identify the linguistic processes interfered with.

2.4.2. Design of intraoperative tasks

Considering that a goal of language mapping is to decide how far a successful resection can proceed without damaging relevant language processes (Berger, 1996; Fernández Coello et al., 2013; Miceli, Capasso, Monti, Santini, & Talacchi, 2012; Ojemann et al., 1989), the greatest care should be taken in designing intraoperative tasks. For example, all intraoperative tasks should be reasonably short, as time for language mapping is restricted and patients cannot be overwhelmed with tasks during surgery. Stimuli should be selected so as to ensure that in each case a response can be produced by a healthy individual in less than 4 seconds. (Duffau, 2004; Kayama, 2012). When administering and interpreting the task, the limitations of the stimulation procedure should be taken into account – e.g., the spatial resolution of the bipolar probe, the variation of sensitivity in relation to current intensity, inaccuracies in localizing an already stimulated area, time differences between electrical stimulation and stimulus onset, etc. Across-patient variability, possible effects of anesthetics (Adhikary, Thiruvenkatarajan, Babu, & Tharyan, 2011; Lotto & Schubert, 2008) and other intraoperative, non-surgical and non-neuropsychological monitoring procedures should also be considered (Borchers et al,. 2011; Talacchi et al., 2012)

Intraoperative tasks should also be sufficiently sensitive to pinpoint fine-grained deficits. To this end, the materials could be black-and-white line drawings as in many current tests (Bastiaanse, Edwards, Maas, & Rispens, 2003; Howard, Swinbum, & Porter, 2010; Metz-Lutz et al. 1991) or videos that require fewer inferences than drawings or pictures (Corina, Gibson, Martin, Poliakov, Brinkley, & Ojemann, 2005; Den Ouden et al., 2009). Also, the stimuli should be checked for visual complexity (i.e., the amount of visuo-perceptual processing they require) and name agreement (i.e., their capacity to elicit the expected word from all participants).

Careful analysis of the responses collected from healthy volunteers is needed to prevent significant response variability.

Intraoperative tasks should be based on current knowledge in the cognitive neuroscience of language. Relevant lexical variables to control for in selecting target verbs are frequency of usage (Whitworth et al., 2005), age of acquisition (Bell, Davies, Hermann, & Walters, 2000; Morrison, Ellis, & Quinlan, 1992), imageability (Berndt, Haendiges, Burton, & Mitchum, 2002; Luzzatti, Raggi, Zonca, Piastrini, Contardi, & Pinna, 2002), word length in phonemes (Nickels & Howard, 2004) and instrumentality (Jonkers & Bastiaanse, 2007). Grammatical variables to control for are transitivity (De Bleser & Kauschke, 2003; Luzzatti et al., 2002), actionality (Finocchiaro & Miceli, 2002), number of internal arguments (Bastiaanse & Van Zonneveld 2004; Thompson, Lange, Schneider, & Shapiro, 1997) and regularity (Morrison et al., 1992; Sach, Seitz, & Indefrey, 2004). These variables should be checked for, as they can affect response accuracy and reaction times (Bastiaanse & Van Zonneveld, 2004; Bell et al., 2002; Berndt et al. 2002; De Bleser & Kauschke, 2003; Finocchiaro & Miceli 2002; Jonkers & Bastiaanse, 2007; Luzzatti et al., 2002; Morrison et al., 1992; Sach et al., 2004; Thompson et al., 1997; Whitworth et al., 2005). In addition, tasks should be language-specific, as concepts may be expressed differently across languages (e.g., the same action is expressed in English by the verb "cycling" and in Italian by the object-based circomlocution "*andare in bicicletta*", literally, to go on bike). When using sentence items in tasks that are adapted to bilingual or multilingual populations, the sentences should be matched for morpho-syntactic complexity. Some languages, such as Dutch require extra syntactic operations that add further costs (e.g., Verb Second in main clauses), and that do not exist in others such as English or Italian (Den Ouden et al., 2008). Other languages, such as Chinese do not express tense through morphological inflection like Turkish, or English do (Bastiaanse et al., 2011).

2.4.3. Relevance of standardized and customizable tasks

Our strategy aims at building standardized and customized tasks with psycholinguistically controlled content, and at using these tasks as part of the longitudinal neurocognitive follow-up of each patient. So far, only few studies that mapped verb/sentence processing have used standardized stimuli (Bello et al., 2006; 2007; 2008; Hamberger et al., 2003; 2005; Santini et al. 2012). It may be still legitimate to administer non-standardized items, considering that during surgery patients are typically presented with stimuli they responded to correctly in preoperative baselines, and that therefore each subject acts as his/her own control case (Benzagmout et al., 2007; Duffau et al., 1999; Ojemann et al., 1989). However, administering stimuli that are not standardized (i.e., not fully controlled for psycholinguistic and stimulus-specific variables) is not satisfactory, for at least two reasons. In the first place, it prevents the careful diagnosis of intraoperative errors, beyond the mere statement that verb processing was affected by electrical stimulation. Secondly, it prevents the possibility to compare, contrast and generalize conclusions across studies – all critical steps to establishing the usefulness of specific materials (e.g., nouns, adjectives, verbs, sentences, etc.) during surgery.

With this respect, it cannot be stressed enough that intraoperative tasks are part of a longitudinal neurocognitive follow-up that includes preoperative, intraoperative and postoperative testing. Preoperative testing should identify the components of verb processing spared and impaired by the tumor, provide the baseline against which to compare data from follow-up evaluations, and constrain the selection of the stimuli to be presented during surgery.

A viable strategy would be to build a large dataset of standardized verb items. These stimuli should be administered preoperatively, in order to measure the variables (if any) that influence performance in each subject. Results should lead the neurosurgical team to set up for each subject the appropriate intraoperative task, that would consist of standardized stimuli. For example, in different subjects it may be relevant to include transitive rather than intransitive verbs, or one-argument rather than multiple-argument verbs, or regular rather than irregular verbs, etc. This is because in the face of disproportionate preoperative damage/sparing, a verb type may be excluded from (or selected for) intraoperative assessment, in order to reduce the probability of false positives during brain mapping. During surgery, such a custom-made task would lead to identify eloquent areas, thus allowing the largest possible resection while avoiding post-operative language deficits (other than those already present before surgery). At follow-up evaluations, exhaustive knowledge of preoperative deficits gathered from administering standardized materials permits careful longitudinal evaluations of the linguistic status of the patient that may support decisions on clinical management at each stage. Needless to say, such an approach would also provide the experimental data needed to establish whether verb and sentence processing, as opposed to object naming tasks, are more accurate predictors of better quality of life and communicative abilities in specific groups of subjects.

2.4.4. Other neurocognitive components of intraoperative language mapping

We recommended the intraoperative use of verb tasks in addition to noun tasks. Applying the suggested approach to the neurocognitive component of intraoperative language mapping would yield better data during surgery and would allow for more systematic and informative follow-up neuropsychological evaluations. Having said that, many issues related to intraoperative language mapping would still remain open. One such obvious issue concerns the relative weight of functional, oncological and radiological indices in surgical decisions. There is no recommended conduct in this case (De Benedictis & Duffau, 2011; Duffau, 2013). In the last instance, surgical decisions will have to rely on tumor location and classification, as well as on the neuropsychogical profile and intraoperative performance, based on each surgical team”s experience and individual patient”s needs. Another critical question is how to proceed when contrasting results emerge, during surgery. Intraoperative tests have dichotomous outcomes – an area is judged to be functional or not. Given the lack of explicit recommendations, at this stage, a conservative conduct is preferable – if a test indicates that a specific area is functional, and another that it is not, the area should be considered as functional, and therefore should not be removed.

Many other issues are still unsolved (see Talacchi et al., 2012 for review). For example, there are very few randomized clinical trials to show that awake surgery is preferable to fully-anesthetized surgery (e.g., Duffau et al., 2005). Little is known about which prognostic factors should lead to opt for a specific surgical goal (i.e., stereotactic biopsy; partial/subtotal/total tumor removal; e.g., Sanai & Berger, 2009). The electrical protocol to decide when an area is eloquent has not been fully discussed (how many stimuli should be delivered? how many of these should interfere with function to consider that area eloquent?). Similar considerations apply with regard to the factors to be considered when choosing stimulation modality (same or different intensity for cortical and subcortical mapping? how to establish a reliable threshold? how to select stimulation frequency? etc.). Needless to say, solutions to technical problems will impact on the neurocognitive component. Be this as it may, outstanding problems can only encourage further research in this area.

2.5. Conclusion

In established practice, patients undergoing awake surgery are still largely tested on nouns. We reviewed eight different tasks that use verbs and sentences during surgery, in 20 different studies. Theoretical considerations and empirical evidence suggest that tasks using verbs and sentences may be a useful addition to intraoperative testing in general, but particularly in patients with frontal lobe lesions. These tasks should fulfill general requirements (standardization, reasonable duration, ease of administration). They should be carefully controlled for the relevant psycholinguistic variables, as well as for stimulus-specific features. Their addition to the repertoire of neurosurgical teams would constitute a step toward a differentiated approach to intraoperative language mapping, and carefully controlled, neurocognitive follow-up studies – both primary goals for awake surgery procedures.

Ideally, for each case intraoperative testing should be based on tasks that use standardized items and that, based on lesion site, are most likely to be affected by surgery. Developments in the neurocognitive component of awake surgery should be marked by constant revisions and updates of available tools, driven by knowledge in the cognitive neuroscience of language. If possible, testing should not be restricted to just one language domain, and should be strategically devised so as to include as many at-risk functions as possible. This would provide each patient with the language mapping procedure most appropriate for his/her needs, including the needs of multilingual patients. It would also give clinicians and neuroscientists critical information on the neural underpinnings of language functions, which could complement those that can be obtained by neuroimaging studies or by the analysis of lesion cases.

Chapter 3

A minimal standardization setting for language mapping tests: An Italian example[2]

Abstract

Introduction: During awake surgery, picture-naming tests are administered to identify brain structures related to language function (language mapping), and to avoid iatrogenic damage. Before and after surgery, naming tests and other neuropsychological procedures aim at charting naming abilities, and at detecting which items the subject can respond to correctly. To achieve this goal, sufficiently large samples of normed and standardized stimuli must be available for preoperative and postoperative testing, and to prepare intraoperative tasks, the latter only including items named flawlessly preoperatively.

Methods: We discuss design, norming and presentation of stimuli, and describe the minimal standardization setting used to develop two sets of Italian stimuli, one for object naming and one for verb naming, respectively. The setting includes a naming study (to obtain picture-name agreement ratings), two on-line questionnaires (to acquire age-of-acquisition and imageability ratings for all test items), and the norming of other relevant language variables.

Results: The two sets of stimuli have >80% picture-name agreement, high levels of internal consistency and reliability for imageability and age of acquisition ratings. They are normed for psycholinguistic variables known to affect lexical access and retrieval, and are validated in a clinical population.

Discussion: This framework can be used to increase the probability of reliably detecting language impairments before and after surgery, to prepare intraoperative tests based on sufficient knowledge of pre-surgical language abilities in each patient, and to decrease the probability of false positives during surgery. Examples of data usage are provided. Normative data can be found in the Supplementary materials.

Keywords: norming, picture-naming, test, awake surgery, verbs, nouns

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3.1. Introduction

Neurosurgery teams administer picture-naming tests during awake surgery (Berger, 1996; Duffau et al., 1999; Ojemann & Mateer, 1979). The patient names items, while the neurosurgeon stimulates a specific cortical or subcortical structure to identify areas that play a role in language processing (e.g., Bello et al., 2007; Ojemann & Mateer, 1979) This procedure is called language mapping. Areas detected by electrical stimulation are usually not removed, in order to avoid postoperative language deficits (Miceli, Capasso, Monti, Santini, & Talacchi, 2012). This technique allows the resection of more neoplastic tissue and a better preservation of the patients" quality of life than surgeries that do not employ it (De Witt Hammer, Gil Robles, Zwinderman, Duffau, & Berger, 2012).

Object naming tests were successfully introduced to assess the lexical-semantic properties of nouns (Moritz-Gasser, Herbet, Maldonado, & Duffau, 2012; Ojemann & Mateer, 1979; Papagno, Casarotti, Comi, Gallucci, Riva, & Bello, 2012). Some neurosurgical teams introduced tests with verbs and sentences to assess the lexical-grammatical or syntactic levels of language (Rofes & Miceli, 2014). These tests could be more sensitive than nouns tasks, particularly in patients with frontal lesions, considering the role that anterior regions play in verb processing (Lubrano, Filleron, Démonet, & Roux, 2014).

Naming tasks are administered before surgery as part of a larger language evaluation, to decide if a patient is eligible for language mapping, and to identify spared items to be administered during surgery (Bello et al., 2007; Miceli et al., 2012). The intraoperative presentation of items that the patient named flawlessly is argued to reliably pinpoint eloquent areas and to prevent false positives during electrical stimulation (Berger, 1996; Duffau et al., 1999; Kayama, 2012; Ojemann & Mateer, 1979). Naming tasks are administered after surgery to monitor the patients" abilities and to recommend language therapy, if necessary. Postoperative results may indicate the overall quality of the surgical procedure, and provide insights into neuropsychological and methodological developments (Santini, Talacchi, Squintani, Casagrande, Capasso, & Miceli, 2012; Satoer, Work, Visch-Brink, Smits, Dirven, & Vincent, 2012). See Figure 3.1.

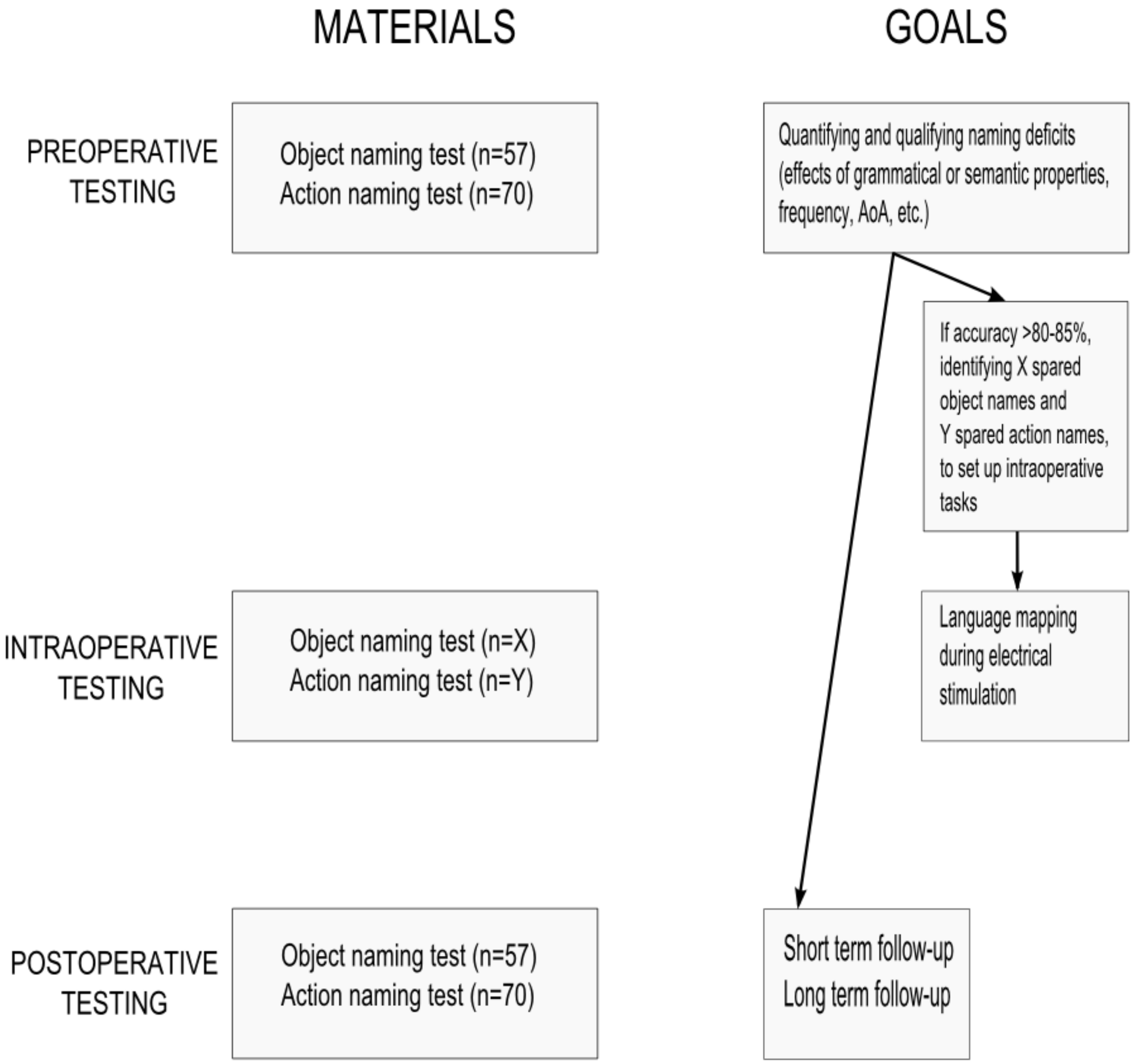

Figure 3.1. The use of picture naming tasks in awake surgery. Materials and goals are schematically represented. Only items that are correctly named during preoperative testing are used intraoperatively.

In clinical practice, home-made tasks are commonly used to detect preoperative language deficits (Kayama, 2012). Such tasks are not normed for language variables, and do not contain structured information on the performance of healthy subjects. This renders the results of the assessments difficult to interpret, impossible to compare with previous or ensuing evaluations and impedes a careful selection of the intraoperative items.

Much attention should be paid to the design of naming tasks for awake surgery. These tasks should be easy to answer and to score. Black-and-white line drawings, colored pictures, or simple videos can be used as stimuli (Catricalà, Della Rossa, Ginex, Mussetti, Plebani, & Cappa, 2013; Corina, Gibson, Martin, Poliakov, Brinkley, & Ojemann, 2005; Metz-Lutz et al., 1991; Snodgrass & Vanderwart, 1980). If text is required, a sans-serif font is preferable, as it easily readable (Moret-Tatay, & Perea, 2011). Stimulus presentation is reduced to 4 seconds (i.e., the duration of intraoperative electrical stimulation), as longer electrical stimulation may induce epileptic discharges (Bello et al., 2007; Ojemann & Mateer, 1979). A computer program with specialized software may be used to show each item preceded by a beep, to inform the patient that a new item is going to appear. See Figure 3.2.

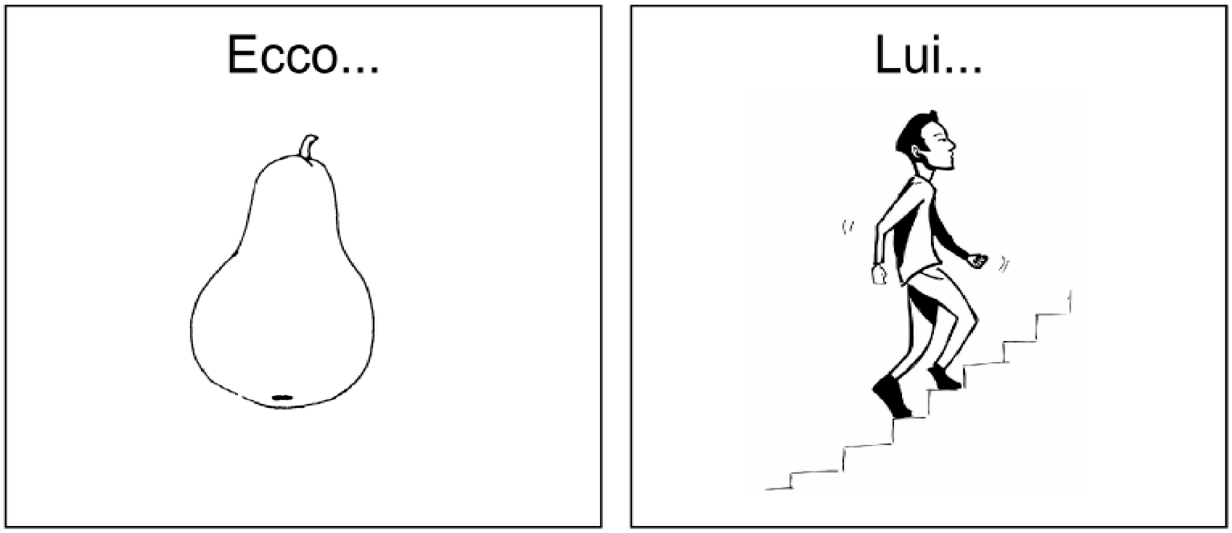

Figure 3.2. Examples of picture stimuli.

Tests should be controlled for lexical-grammatical and visual complexity variables, to permit fine-grained analyses of language deficits. The current neuroscience of language literature offers some guidelines as to the variables that may affect lexical access and retrieval, particularly in patients with language deficits (Whitworth, Webster, & Howard, 2005). Among other particularities, deficits may be of semantic nature as indicated by low scores on low Imageability items (Luzzatti, Raggi, Zonca, Piastrini, Contardi, & Pinna, 2002), Biological/Artifactual entities and Semantic category (Catricalà et al., 2013). Deficits may affect the lexical level as indicated by lower scores related to the H-statistic[3] (Snodgrass & Vanderwart, 1980), written word Frequency (Carrol & White, 1973) Age of acquisition (Carroll & White, 1973), word Length in phonemes/syllables (Nickels & Howard, 2004), Instrumentality and Name-relatedness to a noun (Jonkers & Bastiaanse, 2007) or affect sublexical processes as shown by effects of word Length (Nickels & Howard, 2004). Effects can also be grammatical as indicated by contrasts in Regularity (Howard et al., 1992), Transitivity (De Bleser, & Kauschke, 2003), Number of arguments (Thompson, Langue, Schneider, & Shapiro, 1997). Other variables to consider when mapping specific brain regions are Manipulation (Tranel, Kemmerer, Adolphs, Damasio, Damasio, 2003) and Action-related verbs (Hauk, Johnsrude, & Pulvermüller, 2004). Visual complexity variables may be used to match items within the same category (Transitive vs Intransitive verbs) or between categories (Objects vs Actions).

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[3] We provided a MATLAB script to calculate the H-Statistic (see Supplementary materials)

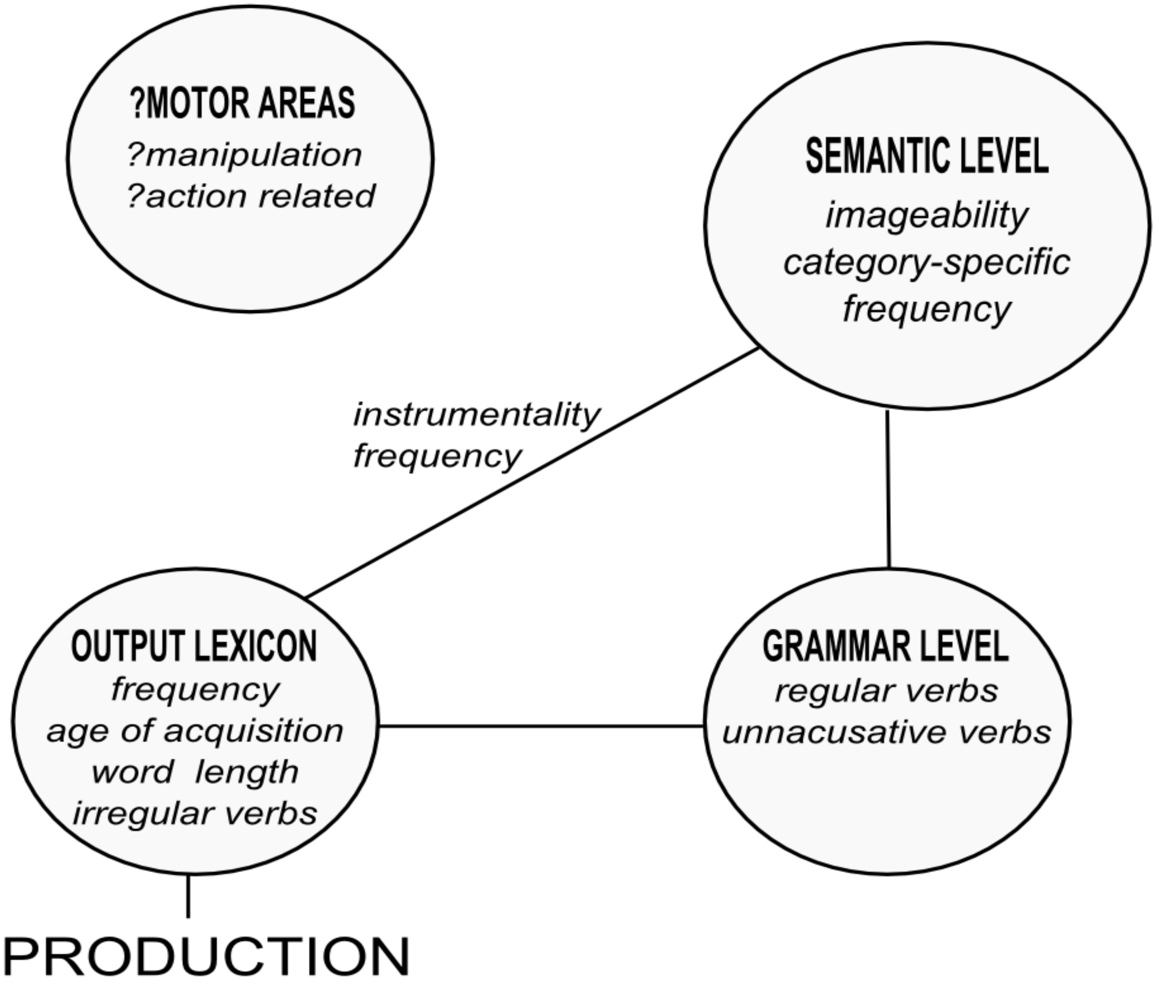

Figure 3.3. The indicative value of psycholinguistic variables detecting damage to language and the brain.

Here we present a minimal standardization setting for language mapping tests developed for Italian-speakers that should be easily adapted to other languages. We built two sets of stimuli: an object naming test and an action-naming test. The setting includes a 4-second picture-name agreement task, norming of relevant language variables including imageability and age of acquisition, and a validation in a clinical population. Norms for each test are reported in Supplementary materials.

3.2. VISC (verb production in sentence context)

This task includes 70 stimuli to which non-brain-damaged people can respond to in less than 4000msec. It is an adaptation to Italian of the original Dutch test developed by Rofes, De Witte, Mariën, & Bastiaanse (2012). Stimuli consist of black-and-white line drawings representing actions. A graphic designer created the drawings anew. Above the drawing, the subject of the sentence is provided in the pronominal form ("He/She…"; *Lui*/*Lei*…). The participant is asked to produce the verb in the correct inflected form. For example, for a picture of "a man eating", subjects are expected to say "He eats" (*Lui mangia*). All verbs are action verbs (i.e., they have an agent as the subject). Unaccusative or reflexive verbs were not included. Items are divided in 10 subsets to facilitate the study of Action relatedness, Frequency, Instrumentality, Length in phonemes (two subsets), Manipulation, Name-relatedness to a noun, Regularity, Transitivity, and to contrast the items of this test with those of the ECCO. It follows a description of the picture-name agreement, the cut-offs, and the norming of stimuli.

3.2.1. Picture-name agreement and cut-offs

Seventy-five people participated in this study. To assess picture quality, a first group of 10 university students (5 female) rated 68 pictures of actions without time constraints. A second group named the 60 pictures to which the first group had provided more than 80% of correct answers. This time, pictures were presented for 4 seconds, as specified in awake surgery procedures (Kayama, 2012). The second group included 65 subjects (30 female), ranging in age between 21 and 85 years (21-34 years: n=14; 35-54 years: n=14; 55-64 years: n=12; 65-74 years: n=17; 75-85 years: n=8). Education ranged between 5 and 18 years (5 years: n=7; 8 years: n=7; 13 years: n=26; 16-18 years: n=25). All participants scored within the norm on the Mini-Mental

State Examination (Measso et al., 1993), provided informed consent and were paid to participate. Seventy action drawings had a name agreement greater than 80% (mean=94.4, sd=5.23) and were responded to in less than 4000ms. Within the 70 drawings, we found a significant difference between age groups (X2=25,492; df=4; p=0.000). *Post-hoc* tests revealed significant differences between people 75-85 compared to all groups (p<0.05). We also encountered differences between people aged 21-34 and 35-54 compared to people 65-74 years (p<0.05). Significant differences were also found for education (X2=18,584; df=3; p=0.000). *Post-hoc* tests revealed significant differences between people who had received 5 years of education compared to 8 years, 13 years, and 16-18 years (p<0.05). Provided these results we calculated cut-off accuracy scores per age range (i.e., the first score below which a performance is significantly different from that of a control sample at p<.05, 2-tailed). We used modified t-tests (Crawford, Garthwaite, & Porter, 2010), as these reduce Type 1 error rates in the face of skewed control data. Cut-offs are reported in Table 3.1.

Table 3.1

Age-based cut-off scores VISC and ECCO

	21-34	35-54	55-64	65-74	75-85
VISC	64	53	59	49	29
ECCO	52	48	49	48	39

Note. People with 5-8 years of education may produce two items less than people with 16-18 years of education.

3.2.2. Norming of the stimuli

Norms for Imageability and Age-of-acquisition were obtained with two on-line questionnaires. Imageability was rated by 16 male and 34 female participants (N=50). Age ranged between 19 and 66 years (mean=27.8, sd=10.26), and education between 13 and 18 years (13 years=16; 16-18 years=34). A different group of subjects rated the items for Age-of-acquisition. Age-of-acquisition was rated by 16 male and 34 female subjects (N=50). Age ranged between 19 and 66 years (mean=28.9, sd=10.51) and education between 13 and 18 years (13 years=12; 16-18 years=38). All participants had normal or corrected-to-normal vision; none had neurological or neuropsychological problems or history of drug abuse. They all volunteered for the study. The number of participants is sufficient for measuring group differences based on current standards (Wilson VanVoorhis, & Morgan, 2007). Results indicate that internal consistency and inter-rater reliability were excellent: imageability (73 items, α=0.971; 50 raters, α=0.937); age-of-acquisition (73 items, α=0.967; 50 raters, α=0.975). Frequency norms were extracted from an Italian database (Bertinetto et al., 2005). H-statistic was calculated based on the formula from Snodgrass and Vanderwart (1980) and Visual complexity through a process of GIF lossless compression (Forsythe, Mulhern, & Sawey, 2008). Transitivity, Instrumentality, Name-relatedness to a noun, Action-relatedness, Manipulability and Regularity were discussed by the three authors until consensus was reached. A full set of norms, descriptions of the subsets, and further methodological details is reported in the Supplementary materials.

3.3. ECCO (object naming test)

It consists of 57 drawings of objects to which non-brain-damaged people can respond to in less than 4000msec. Subjects are asked to produce a noun phrase. For example, for the picture of a "pear", participants are expected to say "*Ecco la pera*" (Here [is] the pear). The ECCO is based on the current gold standard (Metz-Lutz et al., 1991). It includes pictures of the Snodgrass and Vanderwart battery (Snodgrass & Vanderwart, 1980). Items are divided in 5 subsets of items to facilitate control over biological/artifactual entities, Frequency, Length in phonemes (two subsets), and to contrast the items of this test with those of the VISC.

3.3.1. Picture-name agreement and cut-off scores

The same participants than in the VISC participated in this study. Fifty-seven drawings of objects showed >80% name agreement (mean=96.8, sd=4.31) and were responded to in less than 4000ms. Within the 57 drawings, we found a significant difference in accuracy between age groups (X2= 14,450; df=4; p=0.006). *Post-hoc* tests revealed significant differences between people +75 compared to all groups (p<0.05). Significant differences were also detected between education groups (X2= 24.183; df=3; p=0.000). People who had received 5 years of education fared worse compared to 8 years, 13 years, and 16-18 years (p<0.05). People who had received 8 years of education scored two items worse than people that had 16-18 years of education, differences were significant (p<0.05). We indicated age range cut-offs in Table 3.1.

3.3.2. Norming of the stimuli

The same procedure than in the VISC was followed. Imageability raters included 15 males and 35 females (N=50). Age ranged between 20 and 62 years (mean=27.7, sd=8.32), and education between 13 and 18 years (13 years=11; 16-18 years=39). A different group of Age-of-acquisition raters included 13 males and 37 females (N=50). Age ranged between 20 and 62 years (mean=27.9, sd=9.62) and education between 13 and 18 years (13 years=11; 16-18 years=39). All participants had normal or corrected-to-normal vision; none had neurological or neuropsychological problems or history of drug abuse. They all volunteered for the study. Internal consistency was excellent for both variables: imageability (57 items, α=0.968); age-of-acquisition (57 items, α=0.967). Inter-rater reliability was fair for imageability (50 raters, α=0.599) and excellent for age-of-acquisition (50 raters, α=0.985). Frequency, H-statistic, Visual complexity, Length in phonemes, Biological/Artifactual entities, and Semantic Category were calculated in the same way than in the VISC (see Supplementary materials)

3.4. Validation on a clinical population

3.4.1. Participants

Fourteen right-handed subjects (6 female) with post-stroke aphasia participated in this study. Six subjects were non-fluent, and 8 were fluent. Age ranged between 44 and 91 years (mean=62, sd=0.14), and education between 5 and 18 years (mean=11.43, sd=4.4). Ten subjects presented with a single lesion in the left hemisphere, four presented with two left-hemisphere lesions. All were at least 6 months post-onset (mean=39.71, sd=46.67). A population of stroke patients is typically chosen when evaluating the merits of similar tasks for analogous purposes, as language production deficits in these subjects are more severe than in subjects undergoing surgery for brain tumors (Anderson, Damasio, & Tranel, 1990)

3.4.2. Materials and procedure

Thirty items from the ECCO and thirty from the VISC were chosen, as they had at least 80% of picture-name agreement and were matched for Age-of-acquisition (p=0.424), Frequency (p=0.396), and Length in phonemes (p=0.171). We included two scores that potentially predict language abilities (language predictors) and one that focuses on cognitive functions other than language (non-language predictor). The language predictors are the Italian adaptation of the *The Communicative Abilities in Daily Living Two* (CADL2, Carlomagno et al., 2013), and the subset of reading, writing and calculation from the same test (CADL2_RWC). The *Attentive Matrices test* was used as a non-language predictor (Spinnler & Tognoni, 1987).

3.4.3. Analyses and results

Convergent validity measures were calculated by correlating the ECCO and the VISC with the CADL2 and CADL2_RWC subset score. ECCO scores did not significantly correlate with either predictor (p>0.05). VISC scores correlated with both CADL2 (R=0.0692, p=0.006) and CADL2_RWC (R=0.620; p=0.018). Divergent validity measures were calculated by correlating the ECCO and the VISC with the non-language predictor. No significant correlation was found between the Attentive Matrices and the two naming tasks (p>0.05). Finally, ECCO and VISC scores showed a significant correlation (R=0.718; p=0.018). Correlations between the language predictors and the non-language predictor failed to reach significance (p>0.05).

Table 3.2

Convergent and divergent validation: summary of results

	CADL2	CADL2_RWC	ECCO	VISC	AM
CADL2		R=0.911* p=0.000	R=0.181 p=0.535	R=0.692* p=0.006	R=0.231 p=0.427
CADL2_RWC	R=0.911* p=0.000		R=-0.006 p=0.984	R=0.620* p=0.018	R=0.280 p=0.331
ECCO	R=0.181 p=0.535	R=-0.006 p=0.984		R=0.718* p=0.004	R=-0.051 p=0.863
VISC	R=0.692* p=0.006	R=0.620* p=0.018	R=0.718* p=0.004		R=0.317 p=0.269
AM	R=0.231 p=0.427	R=0.280 p=0.331	R=-0.051 p=0.863	R=0.317 p=0.269	

Notes. AM=Attentive Matrices. Pearson's R and p-value. N=14 for all factors. The asterisk (*) indicates significant correlations.

3.4.4. Example of data usage in a single-case setting using hypothetical scenarios

Scenario 1. Scores within the normal range in the naming tasks, effects of one or more language variables. Preoperative assessments show that a 53-year-old patient performs within the normal range in both tests (ECCO=52/57, 91.3% correct, cut-off=49; VISC; N=63/70, 90% correct, cut-off=59). Analyses of specific subsets show significantly worse performance on transitive than intransitive verbs (transitive 7/23, intransitive 23/23; Fisher exact $p<0.001$). Regarding language performance alone (i.e., other non-linguistic factors may be considered), preoperative assessments indicate that the patient is eligible for awake surgery (naming accuracy>80%). For the intraoperative procedure, the ECCO stimuli that the patient failed to name are removed (N=5), but no further manipulation of intraoperative noun stimuli is necessary. As regards intraoperative verbs, all transitive stimuli are removed (N=23), because preoperatively they were named significantly less successfully than transitive verbs, and therefore may yield errors not related to the electrical stimulation. The whole set of verbs is administered postoperatively, to obtain as much information as possible on the subject"s language profile.

Scenario 2. Performance below non brain-damaged controls" values in one of the tests, confirmed by performance on the matched subsets of actions and objects (see Ob_balanced and Ac_balanced, in Supplementary materials), but no effects of language variables. Preoperatively, a 32-year-old patient might fare significantly worse than controls in object naming (N=41/57, 72%, cut-off=52). Further analyses might show that objects are significantly more impaired than actions (Ob_balanced=13/20, Ac_balanced=19/20; Fisher"s Exact $p=0.044$), and scrutiny of language variables might fail to demonstrate specific damage to language variables ($p>.05$ two-tailed). In this example, the verb test may be more suitable than the noun test for intraoperative use. In our routine, at this stage language mapping is performed by means of both tests, as noun tests are more commonly used and still better known. The final decision on whether a given area plays a specific functional role in noun vs verb naming becomes a clinical issue in which both language and surgical factors (extent of the resection, tumor type, surgical aim, etc.) are carefully pondered. All items of both tasks are used after surgery.

Scenario 3. Deficits in both tests, no effects of one or more language variables. On preoperative assessment, a 71-year-old patient might fare below normal in both tasks (ECCO=20/57, 35% correct, cut-off=49; VISC=30/70; 43% correct, cut-off=48). Further analyses might fail to reveal effects of measurable language variables ($p>.05$ two-tailed). Mapping language by electrical stimulation may not be profitable, as a large number of errors unrelated to stimulation is likely to occur. Further research should be devoted to the possibility of using non-linguistic tasks or tasks that may be useful to map other relevant cognitive domains.

3.5. Discussion

We presented a minimal standardization setting to develop language tests for language mapping. Two picture-naming tasks were purposely designed and standardized for language mapping. In preparing stimulus sets, we selected items with at least 80% picture-name agreement that could be named in less than 4 seconds by cognitively unimpaired participants. Items were also normed for relevant psycholinguistic variables (Whitworth, Webster, & Howard, 2005). The two sets of stimuli have excellent internal consistency and excellent inter-rater reliability for age-of-acquisition and imageability, with the exception of imageability ratings for the noun test (ECCO) which were only fair, in agreement with Cicchetti (1994). Cut-off scores for each test and a validation on a clinical population is included. People over 75 with 5-8 years of education may perform poor in both tasks compared to younger people (21-64) or people with more years of education (16-18).

We take these data to indicate that these two tasks (and particularly the VISC) are sensitive enough to be used to map language functions during awake surgery. We do not disregard their use for language mapping in people with epilepsy or post-stroke assessments. The VISC is the first of its kind in Italy. As regards object naming, the test by Catricalà et al. (2013) has proven beneficial in awake surgery, as it is carefully controlled for variables relevant for biological vs non-biological entities, and allows in-depth lexico-semantic analyses (Rofes & Miceli, 2014). The ECCO is based on the current gold standard and contains imageability ratings, which are key for noun-verb comparisons (Luzzatti et al., 2002). The novelty of the tests reported here relies on the fact that each stimulus is normed for psycholinguistic dimensions known to affect (aphasic) naming (see Supplementary materials), and specifically designed for awake surgery (e.g., all items can be produced in less than 4 seconds by non-brain-damaged speakers). As indicated in the three examples, when administered before surgery, the two tasks allow the identification of fine-grained preoperative language deficits, and the selection of items for intraoperative testing based not only on raw accuracy, but also on the effects of psycholinguistic variables. These tests should stimulate research onto what is the minimum possible number of items/subsets usable while avoiding false positives, and whether it possible to exert an exquisite item-control for people with low naming to undergo language mapping.

Chapter 4
Verb production tasks in the measurement of communicative abilities in aphasia[4]

Abstract

Background: The neurofunctional correlates of verbs and nouns have been the focus of many theoretically oriented studies. In clinical practice, however, more attention is typically paid to nouns, and the relative usefulness of tasks probing nouns and verbs is unclear. The routine administration of tasks that use verbs could be a relevant addition to current batteries. Evaluating performance on both noun and verb tasks may provide a more reliable account of everyday language abilities than an evaluation restricted to nouns.

Aims: To assess the benefits of administering verb tasks in addition to noun tasks, and their relation to three functional measures of language.

Method and procedure: Twenty-one subjects with poststroke language disorders completed four picture-naming tasks and a role-playing test (Communicative Abilities in Daily Living, Second Edition, CADL–2), commonly used as measure of everyday language abilities. Two questionnaires (Communicative Effectiveness Index, CETI, and Communicative Activity Log, CAL) were completed by caregivers. Picture-naming tasks were matched for psycholinguistic variables to avoid lexicosemantic and morphosyntactic confounds.

Results: No significant differences emerged across picture-naming tasks. Scores on the role-playing test and the two questionnaires differed; scores between the two questionnaires did not. The four naming tasks correlated significantly with CADL–2, CETI, and CAL. The strength of the correlation with CADL–2 was significantly greater for Producing a finite verb in sentence context than for Object Naming. Thirteen participants showed no differences in performance between tasks, 6 fared significantly worse on verb tasks than on Object Naming, 1 fared better at Producing a finite verb in sentence context though his performance was poor overall, and 1 was significantly more impaired on verbs.

Conclusions: Performance on tasks that use verbs, and especially Producing a finite verb in sentence context, may provide a more accurate estimate of language abilities in daily living than Object Naming alone. Administering both verb and noun tasks may be recommended in clinical practice.

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[4] Published manuscript. Rofes, A., Capasso, R., & Miceli, G. (in press). Verb production tasks in the measurement of communicative abilities in aphasia. *Journal of Clinical and Experimental Neuropsychology, 37*(5), 483-502. doi:10.1080/13803395.2015.1025709

4.1. Introduction

Aphasic disorders can affect the subject’s ability to communicate, to various extents and in various forms. A well-known phenomenon in aphasic speech is the separability of noun and verb processing (for reviews, see Black & Chiat, 2003; Damasio & Tranel, 1993; Kiefer & Pulvermüller, 2012; Mätzig, Druks, Masterson, & Vigliocco, 2009; Pulvermüller, 2005; Shapiro & Caramazza, 2003b; Vigliocco, Vinson, Druks, Barber, & Cappa, 2011). Such distinction is the object of a growing and controversial body of neuropsychological investigations, trying to establish the neurofunctional correlates of the two word types. Studies have reached contrasting conclusions, and the patterns of associations/dissociations documented in language-impaired individuals have been attributed to lexical variables (e.g., Shapiro & Caramazza, 2003b), to supramodal semantic variables (e.g., Bird, Howard, & Franklin, 2000), or to sensorimotor semantic properties (e.g., Pulvermüller, 2005). Regardless of where they locate the critical distinctions, however, these experimental studies have devoted comparable attention to nouns and verbs and have contributed to a better understanding of the representation/processing of nouns and verbs, and of their neural underpinnings (e.g., Damasio & Tranel, 1993).

By contrast, in clinical practice object naming is part-and-parcel of most aphasia screening tests (e.g., Goodglass & Kaplan, 1983; Huber, Poeck, & Willmes, 1983; Kertesz, 1982; Swinburn, Porter, & Howard, 2004; Riddoch & Humphreys, 1993) but relatively little attention has been devoted to verbs (Bastiaanse, Edwards, Maas, & Rispens, 2003; Conroy, Sage, & Lambon Ralph, 2009; de Aguiar, Paolazzi, & Miceli, 2015; Rofes & Miceli, 2014). As a consequence, to date information on the relative usefulness of noun and verb production tasks in assessing communicative abilities in everyday life is still scarce. To evaluate the benefits of systematically administering verb tasks in clinical evaluations, especially when measuring communicative difficulties in everyday life, we studied the performance of people with aphasia on four picture- naming tests that use verbs and nouns (Object Naming, Verb Generation, Producing a finite verb in sentence context, and Action Naming) and the relation of such tasks with three functional measures of language—a role-playing test administered to the patient, and two questionnaires filled by the caregiver.

4.1.1. Differences between verbs and nouns

Verbs and nouns contain many lexicosemantic variables that must be controlled to avoid unwanted confounds (Kemmerer & Tranel, 2000; Whitworth, Webster, & Howard, 2005; for a review). For example, verbs used in experimental designs typically refer to actions and are less referential than nouns, which refer to objects (Gentner, 1982). The different distributions of nouns and verbs as regards frequency and imageability values have also been the source of a recurrent argument in the neuropsychological literature (Bird et al., 2000; Luzzatti et al., 2002; for contrasting results see Berndt, Haendiges, Burton, & Mitchum, 2002; Black & Chiat, 2003). When nouns and verbs are studied in the context of language disorders, further problems may arise. In the case of nouns, an additional difficulty may stem from the overlap of deficits for the grammatical category "noun" with semantic category-specific effects, selectively affecting or sparing conspecifics, animals, plant life, or tools (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Hart, Berndt, & Caramazza, 1985; Warrington & McCarthy, 1983; Warrington & Shallice, 1984). In the case of verbs, difficulties may arise from diverse syntactic structure complexities (transitive vs. intransitive verbs) or from similarity to a noun (Jonkers & Bastiaanse, 2007; Thompson, 2003). Additional issues may arise with verbs denoting actions performed with specific body parts (Finocchiaro & Miceli, 2002; Pulvermüller, 2005), or with nouns referring to a manipulable object (Aggujaro, Crepaldi, Pistarini, Taricco, & Luzzatti, 2006; Bub & Masson, 2012; Rueschemeyer, van Rooij, Lindemann, Willems, & Bekkering, 2010). Number of phonemes, stress patterns (Black & Chiat, 2003; Nickels & Howard, 2004), and age of acquisition (Bell, Davies, Hermann, & Walters, 2000; Morrison, Ellis, & Quinlan, 1992) may also play a relevant role.

Verbs and nouns also differ along morphosyntactic dimensions. Verbs are the main component of the predicate: They entail a complex argument structure (Thompson, 2003), thematic role assignment (Carlson & Tanenhaus, 1989), subject–verb agreement (Hale & Keyser, 1998), and other processes relevant to communication, such as time reference (Berndt, Haendiges, Mitchum, & Sandson, 1997). By contrast, nouns typically function as arguments of the predicate: They complete its meaning by filling in the grammatical requirements of the verb (e.g., subject/agent, object/theme, locative/goal). For example, in order to convey that "someone" ("the boys") finished the action ofmaking "something" ("the car") clean, we may use the sentence "The boys have washed the car," where the verb "have washed" indicates what happened (verb meaning) and when it happened (time reference), and tells who performed the action and to whom or what (reference to person, number, argument structure, thematic roles). The nouns "boys" and "car" indicate the agent and theme of the action, as projected by the grammatical properties of the verb. Another potentially critical difference between nouns and verbs is that different languages may take very diverse sets of verbal and nominal inflections. For example, English verbs have four possible inflections, but English nouns only have two. Italian verbs have 46 inflected forms, and nouns two, or in rare cases four (e.g., bambino, bambini, bambina, bambine; boy, boys, girl, girls). The opposite is the case in Chinese, where verb morphology is less complex than noun morphology (Bastiaanse et al., 2011; Tsapkini, Jarema, &

Kehayia, 2002). Other morphosyntactic variables with potential impact on performance are the number of internal arguments (Bastiaanse & Van Zonneveld, 2004; Thompson, Lange, Schneider, & Shapiro, 1997), transitivity (De Bleser & Kauschke, 2003; Luzzatti et al., 2002), and regularity (Morrison et al., 1992; Pinker & Prince, 1994; Sach, Seitz, & Indefrey, 2004).

Verb and noun differences have behavioral, neuroanatomical, and neuroimaging correlates. Verbs are associated with longer reaction times than nouns in psycholinguistic paradigms, including picture naming (Arévalo, 2002; Székely et al., 2005; cf. Tsigka, Papadelis, Braun, & Miceli, 2014). People with aphasia frequently fare worse at production tasks that use verbs than at tasks that use nouns (Bastiaanse & Jonkers, 1998; Kemmerer, Rudrauf, Manzel & Tranel, 2012; Luzzatti et al., 2002; Mätzig et al., 2009; Tranel, Adolphs, Damasio, & Damasio, 2001; Vigliocco et al., 2011), although the opposite pattern has also been documented (e.g., Miceli, Silveri, Nocentini, & Caramazza, 1988; Miceli, Silveri, Villa, & Caramazza, 1984; Damasio & Tranel, 1993; Goldberg & Goldfarb, 2005). Dissociations between verbs and nouns raised the question of whether these word categories may be represented in at least partly separable neural networks. In neuroimaging studies, large sources of activity in the left inferior frontal gyrus have been detected in processing unambiguous verbs as compared to nouns (Federmeier, Segal, Lombrozo, & Kutas, 2000) and inflectional verb affixes as compared to noun affixes (Den Ouden, Fix, Parrish, & Thompson, 2009; Finocchiaro, Basso, Giovenzana, & Caramazza, 2010; Pulvermüller & Shtyrov, 2009; Tsigka et al., 2014; Tyler, Bright, Fletcher, & Stamatakis, 2004; Yokohama et al., 2006). A greater involvement of frontal regions for verbs than nouns has also been reported in several brain-damaged populations, including stroke, frontotemporal dementia, Alzheimer's disease, HIV-1 inflection, brain tumors, and epilepsy (Conner, Chen, Pieters, & Tandon, 2014; Corina et al., 2005; Damasio & Tranel, 1993; Hillis &

Caramazza, 1995; Kemmerer et al., 2012; Kemmerer & Tranel, 2000; Lubrano, Filleron, Démonet & Roux, 2014; Miceli, Silveri, Romani, & Caramazza, 1989; Shapiro & Caramazza, 2003a, 2003b; Tranel et al., 2001; Woods, Carey, Tröster, & Grant, 2005).

4.1.2. Language properties involved by picture-naming paradigms

Response accuracy on a given task can be differentially affected by many variables, including the types of knowledge (semantic vs. lexical) tapped by the stimuli, the lexicosemantic and morphosyntactic characteristics of the target words, and whether the target word appears in isolation or in sentence context (Nickels & Howard, 1995). The picture-naming tasks used in the present study require participants to respond to drawings of actions by producing the name of the action with a verb in the infinitive form (i.e., Action Naming), or with a finite verb in the third person singular (i.e., Producing a finite verb in sentence context). We also administered tasks that require participants to generate verbs in response to object drawings (i.e., Verb Generation), or by producing the article and the corresponding noun (i.e., Object Naming). Each of these tasks taps on related, yet distinguishable, language levels. The language processes assessed by each task are schematically represented in Table 4.1.

Table 4.1

Language processes assessed by each task

	ObNam	VGen	FinVerb	ActNam
Phonological lexicon (Input)				
Structural description (Input)	✓	✓	✓	✓
Orthographic lexicon (Input)				
Semantic level	✓	✓	✓	✓
Phonological lexicon (Ouput)	✓	✓	✓	✓
Orthortographic lexicon (Ouput)				
Syntactic level (morpho-syntactic features)	*		✓	

Notes. ActNam: Action Naming; ObNam: Object Naming; FinVerb: Producing a finite verb in sentence context; Vgen: Verb generation. Check marks (✓) indicate that the process is assessed in the task. Asterisks (*) indicate that the process may be assessed in the task. A blank space indicates that the process is not assessed by the task.

4.1.3. Impairment-level and functional-level measures

In brain-damaged individuals, language abilities may be measured with a focus on diagnosing the processing/representational level(s) affected by the lesion, or with emphasis on the subject's ability to use language to communicate. Picture-naming tasks are typically used to obtain impairment-level measures, since they provide objective quantitative (and sometimes qualitative) measures of specific linguistic processes (Katz et al., 2000), such as the ability to retrieve a target word in response to its visual portrayal. In aphasic patients, performance accuracy is usually higher on picture-naming tasks than on tasks that require linguistically more complex responses. For example, Barton, Maruszewksi, and Urrea (1969) showed that people with aphasia fare better in picture naming and sentence completion than in naming to verbal description.

Goodglass and Stuss (1979) reported that individuals with aphasia respond more accurately to picture naming than to naming to description.

Role-playing tests, rating scales, and questionnaires are functional-level measures, frequently administered to chronic outpatients. They provide the examiner with a broad picture of the subjects' ability to use language in everyday life (Katz et al., 2000). Role-playing tasks require participants to act out in several fictitious circumstances, mimicking everyday-life events. They may be used to assess how proficiently the patient looks up a number in an agenda, dials a phone number, reports a message, and so on, and how effectively the aphasic speaker uses language when responding to a threat, in a humorous situation, when making a doctor's appointment, or writing down a grocery list. A well-known example of these functional tests is the Communicative Abilities in Daily Living (CADL, Holland, 1980; Second Edition, CADL–2, Holland, Frattali, & Fromm, 1999), which has been shown to measure the severity of language impairment (Fromm & Holland, 1989) and its improvement following treatment (Aten, Caligiuri, & Holland, 1982; see the section Materials). Examples of questionnaires are the Communicative Effectiveness Index (CETI, Lomas et al., 1989) and the Communicative Activity Log (CAL, Pulvermüller et al., 2001). Functional-level measures are valuable tools for language assessment, as the context in which language is produced and the purpose of the communicative interaction affect the choice of words and syntactic structures (Williams & Canter, 1982). The use of synonyms and circumlocutions, or just knowing that responses can be provided without time constraints, may also ease language production or mask a specific deficit, while allowing successful communication (Williams, 1983, for review). Context effects are also reported when using picture-naming tests (Zingeser & Berndt, 1988) and in comparisons between picture naming and spontaneous speech (Herbert, Hickin, Howard, Osborne, & Best, 2008).

Some work has been directed to finding relations between impairment-level and functional-level measures. Aftonomos, Steele, Appelbaum, and Harris (2001) and Bakheit, Carrington, Griffiths, and Searle (2005) found a significant correlation between the patients' scores on the Western Aphasia Battery (WAB; Kertesz, 1982) and caregivers' opinion on their language abilities at different stages of speech and language therapy protocols, as measured by the CETI (Lomas et al., 1989). Best, Greenwood, Grassly, and Hickin (2008) argued for a relationship between the outcome of therapy targeting word retrieval and the patients' opinions on their communicative abilities. In subjects with acquired dysgraphia, Carlomagno, Pandolfi, Labruna, Colombo, and Razzano (2001) showed that improvement of writing performance after treatment correlated with better performance on the reading and writing subtest of the CADL (Holland, 1980). Fucetola et al. (2006) found a positive correlation between comprehension tasks that require semantic processing and the CADL–2 (Holland, Frattali & Fromm, 1998). In a less direct manner, other studies suggested that difficulties producing verbs significantly interfere with connected speech in aphasia (e.g., Bastiaanse & Jonkers, 1998; Crepaldi et al., 2011; Miceli et al., 1989; Saffran, Berndt & Schwartz, 1989; Zingeser & Berndt, 1990).

4.1.4. Questions and hypotheses

To evaluate the potential benefit of administering verb tasks, we asked (a) whether three commonly used verb tasks provide a sensitive account of (i.e., significantly correlate with) functional measures of language abilities in daily living; and (b) whether any of these tasks provide a more sensitive account of language abilities in daily living than an object naming task matched for difficulty (i.e., if the strength of the correlation between any of the verb tasks and communicative abilities is significantly different to the strength of the correlation between

Object Naming and communicative abilities). To verify that our subject sample was not biased by the inclusion of a greater than normal number of language-impaired individuals with noun- or verb-specific deficits, we compared each individual's accuracy on Object Naming to that on Verb Generation, Producing a finite verb in sentence context, and Action Naming. To ensure that findings could be attributed to the impairment of different processing levels and/or sources of information engaged by verbs and nouns, rather than to an imbalance between psycholinguistic variables shared by these two word categories, stimuli included in all tasks were matched for 12 lexicosemantic and morphosyntactic variables (see Table C4.1).

We predicted that verb tasks would provide a sensitive account of communicative difficulties, as measured by CADL–2 and by the two questionnaires. In addition, we expected that the task requiring the production of finite verb forms would measure language difficulty more reliably than Object Naming and other verb production tasks. This is because only Producing a finite verb in sentence context entails morphosyntactic operations (e.g., argument structure, thematic role assignment, time reference, verb inflection, etc.) in addition to lexicosemantic processes. Morphosyntactic operations are essential for sentence formation (e.g., Berndt et al., 1997; Carlson & Tanenhaus, 1989; Hale & Keyser, 1998; Thompson, 2003) and are frequently affected in aphasia (e.g., Bastiaanse & Jonkers, 1998; Mätzig et al., 2009; Rofes, Bastiaanse, & Martínez- Ferreiro, 2014; Vigliocco et al., 2011). Of course, we did not expect verb tasks to be systematically more impaired than Object Naming. Worse performance on objects than on actions has been reported in patients with temporal lobe lesions (e.g., subjects AN-1033 and Boswell, in A. R. Damasio & Tranel, 1993; see also Daniele, Giustolisi, Silveri, Colosimo, & Gainotti, 1994), while patients with prefrontal lesions frequently show greater difficulty with verb tasks (e.g., subject KJ-1360 in A. R. Damasio & Tranel, 1993; Finocchiaro et al., 2010; Kemmerer & Tranel, 2000; Lubrano et al., 2014; Rofes, De Witte, Mariën, & Bastiaanse, 2013; Tranel, Kemmerer, Adolphs, Damasio, & Damasio, 2003). This study reports the first attempt to correlate action and object picture-naming tasks, matched for lexicosemantic and morphosyntactic variables, with functional measures of language.

4.2. Methods

4.2.1. Participants

Twenty-one adult, right-handed Italian-speaking aphasic volunteers were recruited (10 female; mean age = 63 years, sd = 15; mean years of education = 13, sd = 4). They were all at least 6 months post onset of a left-hemisphere stroke (mean months = 40, sd = 47) and had moderate-to-severe naming impairment, as shown by performance on the naming subtests of the Battery for the Analysis of Aphasic Disorders (BADA; Miceli, Laudanna, Burani, & Capasso, 1994). Subjects were excluded if they were under age 18, completed fewer than 5 years of formal education, had psychiatric disorders, or were taking drugs that could affect cognitive performance. Participants were relatively heterogeneous as for age, education, lesion site, and time post onset. They were tested as outpatients. Table 4.2 provides information on the main demographic and neurological features of participants. This study was approved by the Ethics Committee of the University of Trento.

Table 4.2

Main demographic and neurological features of participants

	Gender	Age	Years of schooling	Etiology	MPO	Lesion site
AL	m	40	17	ICVA	20	LH FT
BL	m	75	18	ICVA	6	LH O
BS	f	43	18	CVST + HCVA	24	LH OT
CB	f	52	13	ICVA	19	LH FTI
CC	f	77	8	HCVA	12	LH P
CK	f	76	19	HCVA	46	LH NB
ES	f	72	8	ICVA	10	LH IC, RH F
FT	f	42	15	ICVA	153	LH FTP
GC	m	68	8	ICVA	30	LH FTPO
GM	f	62	10	ICVA	50	LH FTPB
LF	m	44	15	2 ICVA	40	LH FT, RH OC
OS	f	71	13	ICVA	42	LH TPI
OT	m	65	8	ICVA	7	LH FTI
PG	m	73	10	ICVA	176	LH FTPI
PI	f	51	8	HCVA	6	LH TP
PS	m	76	18	ICVA	15	LH TP
RA	m	57	14	ICVA	8	LH FTP
RG	m	76	14	HCVA	29	LH TP
RL	f	44	13	ICVA	100	LH TI
TG	m	91	11	ICVA	18	LH TPI CR
UA	m	58	13	HCVA	29	LH F, RH FP
m(sd)		63(15)	13(4)		40(47)	

Notes. MPO: Months post-onset. ICVA: ischemic cerebrovascular accident; HCVA: hemorrhagic cerebrovascular accident; CVST: Cerebral venous sinus thrombosis; LH: left-hemisphere; CR: Corona radiata; F: frontal; I: insular; NB: Nucleus basalis; O: occipital; P: parietal; T: temporal. m(sd): mean and standard deviation.

4.2.2. Materials

4.2.2.1. Picture-naming tasks

Each participant completed four picture-naming tasks:

Object Naming. Patients see a black-and-white drawing of an object or an animal. The introductory sentence “Here . . . ” (Ecco . . .) is written above the drawing. Participants are asked to respond by producing its corresponding noun, with the appropriate determiner. For the picture of an “apple,” participants are expected to say “Here the apple” (Ecco la mela). This structure is commonly used and fully grammatical in Italian. A Google search for the structure “Ecco la mela” resulted in 17,000 hits.

Verb Generation. Patients are shown the black-and-white drawing of an object and must name an action that can be performed with the object, using a verb in the infinitival form. For example, for a drawing of a book, patients are expected to say “to read” (leggere).

Producing a finite verb in sentence context. Patients are shown a black-and- white drawing of an action. The subject of the sentence “He/she . . . ” (Lui/lei . . .) is written above the drawing. Patients are asked to read the pronoun and finish the sentence with the verb in the correct inflected form. For the drawing of “a woman painting,” patients have to say “She paints” (Lei dipinge).

Action Naming. A black-and-white drawing of an action is presented. Patients are asked to produce the infinitival form of the verb represented in the drawing. For example, for a picture of “a man kicking a football,” patients are expected to say the verb “to kick” (calciare, in Italian).

Each task contained 20 items with more than 80% picture name agreement, as assessed by the responses of 30 Italian-speaking healthy adults (15 male, 15 female) matched to brain-damaged participants for age (mean = 53.43 years, sd = 15.2) and years of education (mean = 13.93, sd = 3.35). Across tasks, items were matched for lexicosemantic and morphosyntactic variables that affect language production (see Table C4.1 in the Appendices; and the section on the differences between verbs and nouns for a description). These variables may affect processing at the semantic level (imageability, frequency, whether or not objects correspond to biological vs. nonbiological entities, manipulability), at the lexical level (length in phonemes, age of acquisition, name relation to a noun), at the lexical–grammatical level (instrumentality, transitivity, regularity), and at other levels (e.g., actions performed with face, arm, or leg muscles).

4.2.2.2. Functional measures of language

Three functional measures of language were used:

Communicative Abilities in Daily Living, Second Edition (CADL–2; Carlomagno et al., 2013, Italian version). This role-playing test consists of 50 questions revolving around fictitious environments (e.g., going to the doctor's office, grocery shopping, making a phone call, looking for directions, driving a car). It is used to assess skills such as reading, writing, and calculation; social interactions; divergent communication; contextual communication; nonverbal communication; humor and metaphors; and sequential relations. For example, participants are asked to read a notice and complete a form, to write down three things they may need from a supermarket, and to buy a medicine with the change left after buying a drink.

Communicative Effectiveness Index (CETI; Lomas et al., 1989). This questionnaire is completed by the caregiver. It contains 16 questions that resulted from a study in which patients with aphasia and their spouses were asked which communicative situations were relevant in their everyday life. Caregivers rate whether "never, rarely, sometimes, often, or always the patient is able to" get somebody's attention, participate in conversations, communicate emotions, understand writing, describe or discuss something in depth, and so on.

Communicative Activity Log (CAL; Pulvermüller et al., 2001). This questionnaire is also completed by the caregiver. It contains 18 questions that revolve around how frequently the patient communicates with friends, in a group, and with one or more strangers; how frequently she or he uses the phone, listens to or watches the news, writes notes, does simple mathematical operations (e.g., getting change at the supermarket), asks/answers questions appropriately, etc.

4.2.3. Procedure and scoring

Test administration was balanced following a Latin square design. The assessment lasted one hour on average. The CADL–2 was administered and scored following recommendations (Carlomagno et al., 2013). The picture-naming tasks were administered on a laptop computer. To ensure consistent stimulus presentation across tasks, each item was shown for 4000-ms, preceded by a 500-ms beep. This paradigm is used in clinical practice (Brookshire, 1971; Kayama, 2012; Rofes & Miceli, 2014). See Figure 4.1.

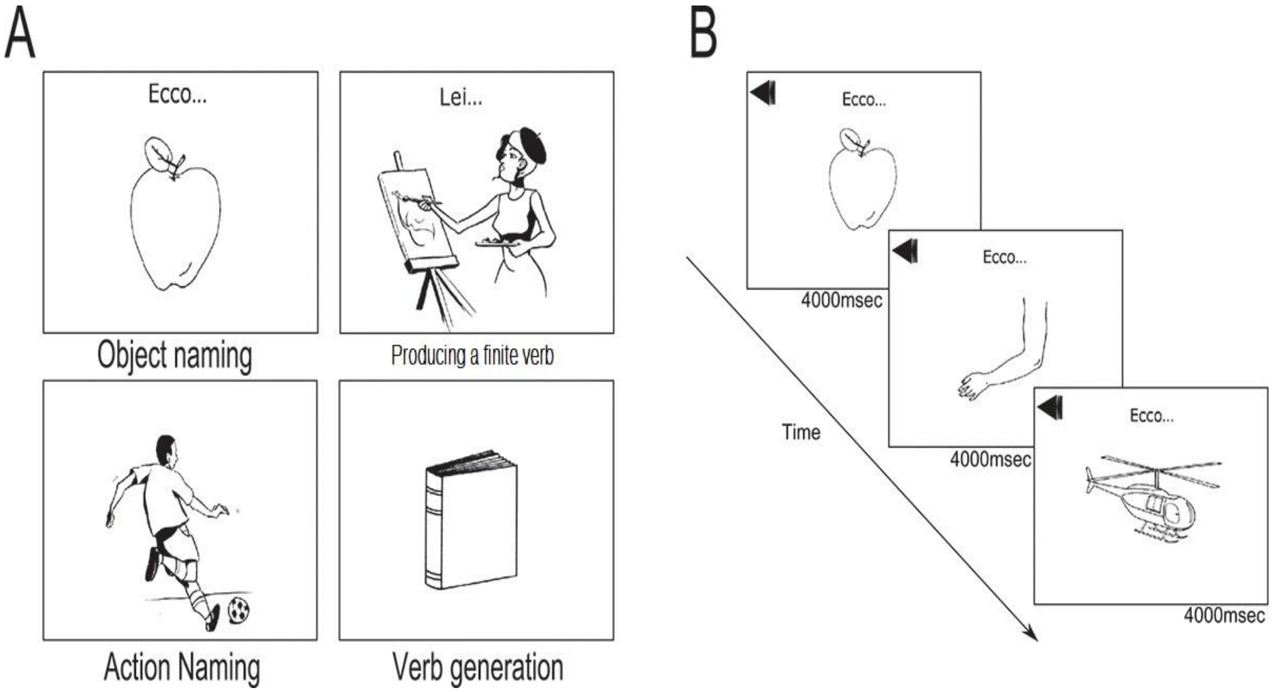

Figure 4.1. (a) Examples of items from each of the tasks (20 items per task). (b) Structure of an experimental trial: Each image is shown for 4000 ms; a beep is played 500 ms before picture presentation.

Four practice items were included at the beginning of each picture-naming task, to ensure that participants understood the procedure. Incorrect responses were classified as lexical errors (semantic paraphasias were included in this category), part/whole errors (patient says “wheel” instead of car), anomias, circumlocutions, and unrelated words. Formal errors included fragments (“medit… ” instead of “meditate”), phonemic paraphasias, and neologisms. Morphosyntactically incorrect responses included errors of time, person, and number, and morphologically decomposable, derivational neologisms (e.g., “*fooding” for “eating” where “*fooding” can be interpreted as being derived from “food”; *pietanzare for mangiare in Italian). Since subjects had been instructed to produce verbs in the infinitival form in Action Naming and Verb Generation, responses consisting of a verb in the third singular form were counted as errors in these tasks. Additional error types included incorrect responses produced outside the 4-s window. *Conduites d’approche* (effort to approximate to the target item) and hesitations were not scored as errors, as long as the target word was produced within the allotted response time.

Morphosyntactic errors with correct semantic andlexical information were counted as incorrect—for example, “*Lui mangiare” (*He to eat) where the verb is in the infinitive instead of the correct inflected form (i.e., Lui mangia, He eats), or *Ecco la$_{\text{f.sg.}}$ piede$_{\text{m. sg}}$. (This is thef.sg. foot$_{\text{m.sg.)}}$ where a feminine instead of a masculine determiner is used.

4.3. Results

Scores were normalized to 100. Nonparametric Friedman’s test $\chi 2$ was used to check for differences across conditions. Post hoc two-tailed Wilcoxon signed rank tests were also used, when needed. False discovery rate (FDR)-adjusted p-values were systematically calculated to correct for multiple comparisons (Benjamini & Hochberg, 1995). At the group level, correct response rates on the naming tasks were significantly different (50% for Object Naming, 41% for Verb Generation, 48% for Producing a finite verb in sentence context, and 37% for Action Naming), Friedman's test $\chi 2(3) = 8.18$, $p = .042$. However, post hoc tests revealed no significant differences between conditions ($p < .05$). Also at the group level, the patients' performance on CADL–2 was 81% (range = 49–100%)—where lower values denote diminished or poor communicative abilities. On the same scale, the caregiver's opinion of the communicative abilities of the patient's was 72% (range = 42.5–93.8%) for CETI and 71% (range 41.1–96.7%) for CAL. Significant differences were detected between CADL–2, CETI, and CAL, Friedman's test $\chi 2(2) = 12.10$, $p = .002$. Post hoc tests revealed significant differences between CADL–2 and CETI ($Z = 2.36$, $p = .036$) and between CADL–2 and CAL ($Z = 2.43$, $p = .036$), but not between CETI and CAL ($Z = 0.24$, $p = .808$). The four naming tasks correlated significantly with CADL–2, CETI, and CAL ($p \leq .05$). Spearman nonparametric correlations were used instead of multiple regression, due to sample size (VanVoorhis & Morgan, 2007; Wampold & Freund, 1987). Even though both Producing a finite verb in sentence context and Object Naming correlated significantly with CADL–2, the strength of the correlation was significantly different (Steiger's $Z = –2.34918$, $p = .028$), being greater for Producing a finite verb in sentence context. No other differences in correlation strength were detected ($p < .05$). Test scores and correlation values are reported in the Appendices (Tables A2 to A5).

Three main response patterns were detected at the individual level. In 13/21 participants (A.L., B.L., B. S., C.C., E.S., F.T., G.M., O.S., P.G., P.I., R.A., R. G., and R.L.), or 61.9% of the sample, performance across tasks was statistically indistinguishable. Subjects A.L., B.S., C.C., E.S., F.T., O.S., P.I., and R.L. performed with relatively high accuracy, and patients B.L., G.M., P.G., R.A., and R.G. fared rather poorly, in all picture-naming tests. Six out of 21 subjects (C.B., C.K., O.T., P.S., T.G., and U.A.), or 28.6% of the sample, scored significantly higher on Object Naming than on the verb-naming tasks. P.S. is a clear example of this pattern: He scored 13/20 correct in Object Naming, but scored below 4/20 correct for the three verb tasks. By contrast, one subject (G.C.) performed relatively better on verb tasks than on Object Naming. He provided 5 to 8/20 correct responses in the three verb tasks, but only 1/20 in Object Naming. A last subject (L.F.) performed relatively poorly in all tasks, although he scored significantly better in Producing a finite verb in sentence context than in Verb Generation. Significance tests for each participant are reported in the Appendices (Table C4.6).

Qualitative analysis reveal five major error types. Anomias are the most frequent error type across tasks. Phonemic and semantic paraphasias and responses produced after more than 4 s were also common. Category substitution errors (from verb to noun) were the second most common error type for the Verb Generation task. Error frequency varied slightly across tasks. The major error types per task and participant are reported in the Appendices (Table C4.7).

4.4. Discussion

The anatomical and behavioral correlates of verbs and nouns have been the focus of many studies in the neuroscience of language (e.g., Black & Chiat, 2003; Shapiro & Caramazza, 2003b; Damasio & Tranel, 1993; Daniele et al., 1994; Mätzig et al., 2009; Pulvermüller, 2005; Vigliocco et al., 2011). This knowledge has made its way in clinical practice only occasionally, and greater attention is still being paid to noun than to verb tasks (Bastiaanse et al., 2003; Conroy et al., 2009; de Aguiar, et al., 2015; Rofes & Miceli, 2014). In this study, we assessed the benefit of administering verb tasks in relation to three functional language measures: the CADL–2

(Carlomagno et al., 2013), the CETI (Lomas et al., 1989), and the CAL (Pülvermuller et al., 2001). Individual analyses were also carried out to check for noun- or verb-specific deficits.

All verb tasks (Verb Generation, Producing a finite verb in sentence context, and Action Naming) significantly correlated with CADL–2, CETI, and CAL ($p \leq .05$). Object Naming also correlated with the three functional level measures ($p \leq .05$). Thus, both verb and object picture-naming tasks would seem to provide reliable indices of language abilities in daily living. More specifically, the processes required to understand a structural description of a picture, to access the corresponding word meaning at the semantic level, and to retrieve its sound elements in the phonological lexicon are good predictors of communicative abilities in everyday life. These processes are shared by the four naming tasks, are commonly used in everyday language, and are typically damaged in people with aphasia (Damasio & Tranel, 1993; Miceli et al., 1988; Miceli et al., 1984; Nickels & Howard, 1995; Tsapkini et al., 2002).

4.4.1. An advantage for producing a finite verb in sentence context over other tasks?

Interesting differences emerge from the analysis of the relative sensitivity of verb tasks in measuring language difficulties. Producing a finite verb in sentence context strongly correlates with the CADL–2, while only a moderate correlation with CADL–2 is observed for Verb Generation, Action Naming, and Object Naming (see Figure 4.2). In light of the differences between verbs and nouns, it is worth enquiring whether the strength of the correlation between each task and the CADL–2 also differs. As expected, the strength of the correlation between CADL–2 and Producing a finite verb in sentence context is significantly greater than the strength of the correlation between CADL–2 and Object Naming. This indicates that the processes involved in Producing a finite verb in sentence context (i.e., verb retrieval and the morphosyntactic processes required by naming verbs in sentence context) are better predictors of functional communication skills than the language processes required by Object Naming (see Table 4.1). This is because producing an inflected verb requires lexicosemantic and overt morphosyntactic processes that are not required (at least, not overtly) by Object Naming. For example, producing “Lui mangia” (He eats) in the Producing a finite verb in sentence context task involves at least four steps that are not necessary for Object Naming. The participant must compute (a) a predicate- argument structure indicating which arguments the verb requires to bear out of its meaning (in the example, a subject and an implicit object); and (b) a thematic structure (Carlson & Tanenhaus, 1989) to indicate that the subject position is filled by the agent performing the action (e.g., “He” in “He eats”). Furthermore, the participant is required (c) to establish an agreement relation (Hale & Keyser, 1998) between subject and verb, which in Italian is overtly marked by the morpheme “–a” in “Lui mangia” (i.e., the “–s” in “He eats”); and (d) to locate the action in time by considering tense and time reference (e.g., Bastiaanse et al., 2011). In addition, all these steps also involve working memory processes (Hartsuiker & Barkhuysen, 2006).

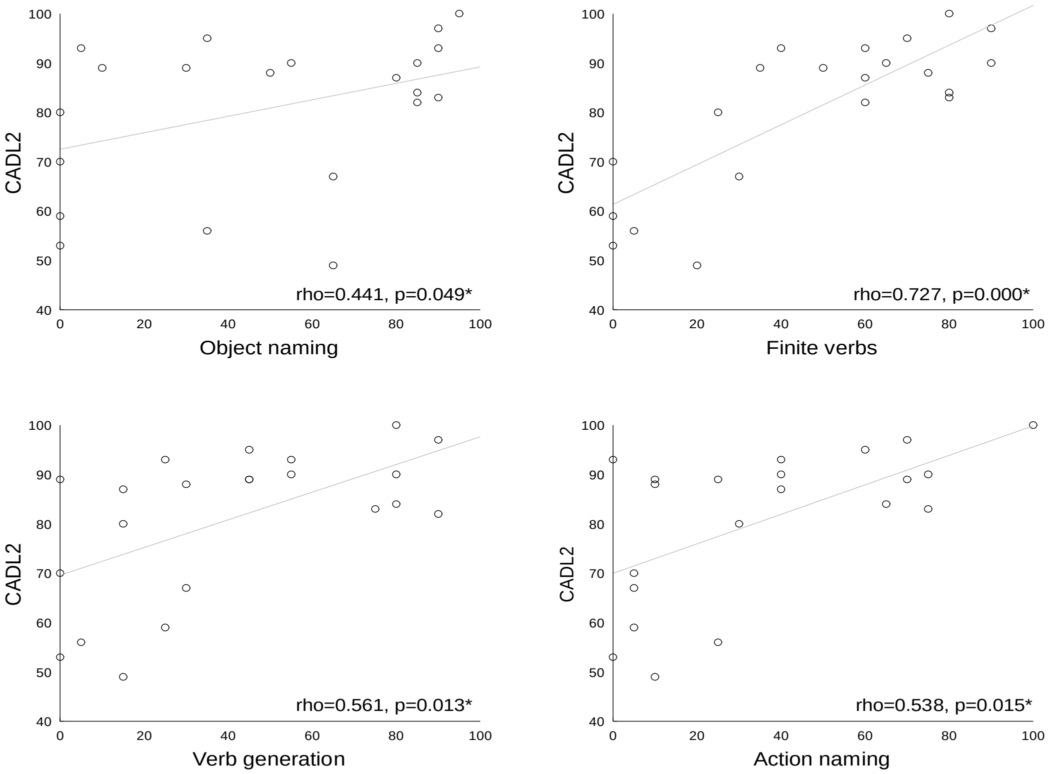

Figure 4.2. Spearman correlations between Communicative Abilities in Daily Living, Second Edition (CADL‑2) and picture-naming tasks. All tasks correlate with the CADL‑2. The correlation value of Producing a finite verb in sentence context and CADL‑2 is significantly different to that of Object Naming and CADL‑2 (p = .0324*).

On these premises, the need to use overt morphology could be a key factor in making Producing a finite verb in sentence context a better predictor of language abilities in daily living than Object Naming and the other verb production tasks. Finding a great number of subject–verb agreement errors in Producing a finite verb in sentence context would strengthen this hypothesis. However, qualitative analyses indicate that overt morphology per se may not be the main factor, as only 3/ 21 participants produced a maximum of two morphosyntactic errors in this task. Therefore, it is likely that the sensitivity of the Producing a finite verb in sentence context task stems from the need to carry out the complex set of computations listed above (retrieving predicate-argument structure, assigning thematic roles, encoding agreement relation, tense and time reference, while engaging working memory processes), rather than exclusively or mainly from difficulty with morphosyntactic processes.

However, the strength of the correlations between naming tasks and CADL–2 results from the specific nature of the processes engaged by each naming task, rather than merely from their number. This is suggested by the fact that the correlation between Verb Generation and CADL–2 is strong ($\rho = .649$) but not significantly different to that between Object Naming and CADL–2. If engaging a greater number of steps were sufficient to yield stronger correlation with the CADL–2, Verb Generation should be differentially linked with the CADL–2 as compared with Object Naming, since it requires not only processing of the portrayed object (just like Object Naming), but also the ability to retrieve an action related to the object.

4.4.2. Both object and action naming tasks may be relevant in clinical practice

Individual-level analyses indicate that the results obtained in our sample do not stem from recruiting a biased number of subjects with noun- or verb specific deficits. Overall, 13/21 participants (61.9%) failed to show significant differences across tasks. Of these, 8 fared relatively well, and 5 relatively poorly in all tasks. Of the participants showing across-task differences, only G.C. was particularly inaccurate in Object Naming (1/20) when compared to Producing a finite verb in sentence context (8/20) and Action Naming (8/20; see Figure 4.3). L.F. scored significantly better at Producing a finite verb in sentence context, although his performance was low overall. The remaining six subjects fared worse on at least one of the verb tasks than on Object Naming.

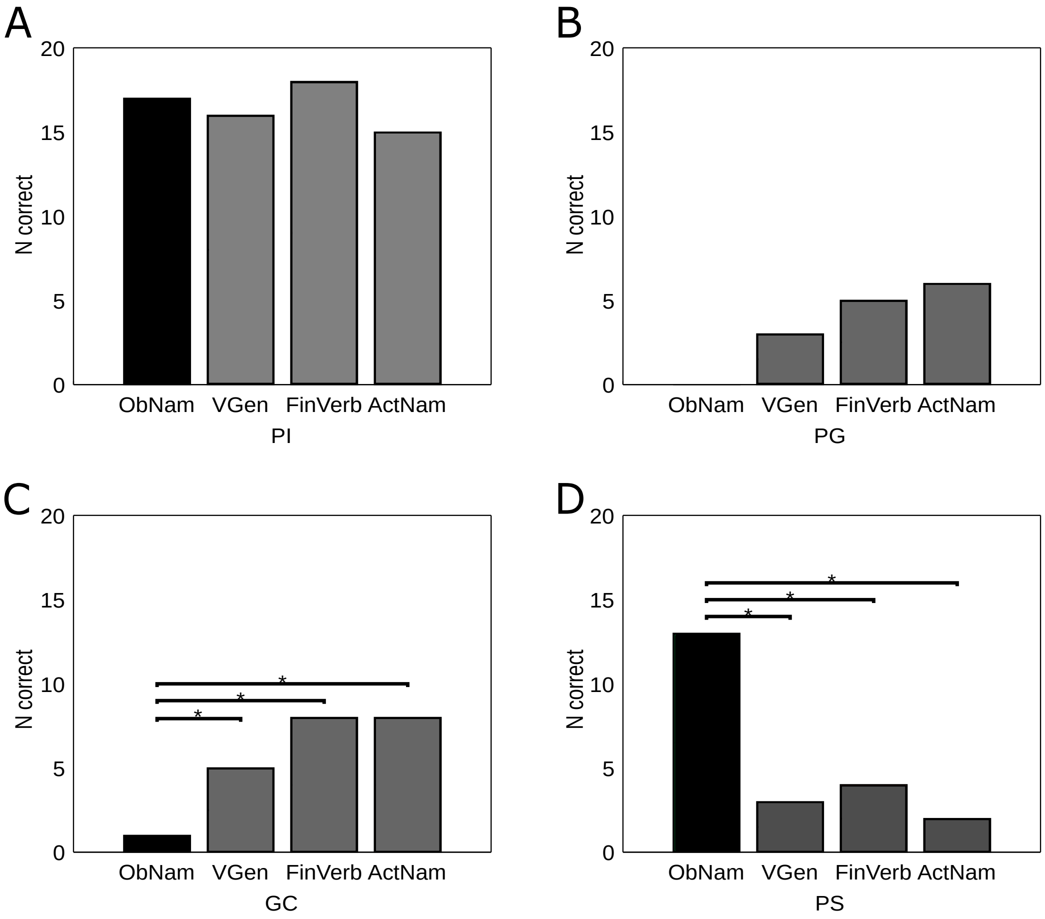

Figure 4.3. Performance patterns in individual participants. Subjects P.I. and P.G. present no difference across tasks (Figures 4.3a and 4.3b). G.C. fares worse in Object Naming than in the other three tasks (Figure 4.3c). P.S. fares worse in the three verb tasks than in Object Naming (Figure 4.3d). ObNam = Object Naming; VGen = Verb Generation; FinVerb = Producing a finite verb in sentence context; ActNam = Action Naming.

These findings alert us to the possibility that clinical language assessments restricted to noun or to verb tasks yield misleading results (e.g., Rofes et al., 2013), by failing to identify individuals whose impairments are limited to one word type, and/or by underestimating communicative problems in a sizeable proportion of aphasic individuals. More sensitive assessments of language functions may be granted by test batteries that tap both noun and verb processing. In the present study, production of finite verbs proved to be a particularly useful addition.

4.4.3. CADL–2, CETI, and CAL as measures of communicative abilities in aphasia

In the present study, all the functional measures (CADL–2, CETI, and CAL) significantly correlated with all the picture-naming tasks. CADL–2 scores differed from CETI and CAL scores, which in turn did not differ from each other. Furthermore, even though all the picture-naming tests significantly correlated with CADL–2, CETI, and CAL, differences in correlation strength between Producing a finite verb in sentence context and Object Naming reached significance only for CADL–2. Consideration of the structure of CADL–2 leads us to prefer this task to CETI and CAL as a functional measure of everyday communicative abilities. This is because the participant's score relies on an objective analysis of his or her linguistic/communicative skills as they emerge in a number of tasks that are not directly tied to performance in any specific cognitive area (e.g., reading, writing, speech, etc.). This is in contrast with the scores that can be obtained from CETI and CAL, which are based on the subjective opinion of an observer, emotionally involved in the subject's difficulties.

Contrary to our conclusions, other researchers argued that questionnaires such as CETI and CAL are better measures of functional impairment than CADL, because scores are provided by someone who is familiar with the patient's premorbid communicative style (Aftonomos et al., 2001; Bakheit et al., 2005). It could be argued that in our study there was an intrinsic bias for CADL–2 to provide a better fit than CETI and CAL. In the first place, naming accuracy and CADL–2 scores are often collected in the same testing session, and by an external observer who does not have prolonged experience with the subject's current (as opposed to premorbid) communicative difficulty. Secondly, 32/50 questions in CADL–2 use picture stimuli, just like object and action naming tasks. These two objections, however, fail to account for the significantly greater correlation between CADL–2 and Producing a finite verb in sentence context than between CADL–2 and Object Naming— both tasks are collected essentially simultaneously by an external observer and use picture stimuli. Different correlation strength is likely due to the different linguistic demands of the two naming tasks.

4.4.4. Relevance and limitations of the study

This investigation is open to questions related to task choice, especially considering that the relative value of the three functional measures used in this study is not established. For example, one might question whether CADL–2 or the two questionnaires provide the more adequate measure of communicative abilities in everyday life. Of course, CADL–2 is not the only objective functional measure of everyday language difficulties—although both CADL and CADL–2 have been frequently used for this purpose (see Fromm & Holland, 1989; Fucetola et al., 2006, for studies on CADL; and Carlomagno et al., 2001, for studies on CADL–2).

Measuring several variables that may influence the narratives elicited during picture description (e.g., Cookie Theft; Goodglass & Kaplan, 1972) could be a suitable alternative, as spontaneous speech would diminish the need for impersonation inherent in CADL–2 (the patient is required to pretend being at the doctor's office, at the supermarket, etc.). Different methods for collecting and analyzing spontaneous speech have been proposed (Craig et al., 1993; Miceli et al., 1989; Nicholas & Brookshire, 1993; Prins & Bastiaanse, 2004; Saffran et al., 1989; Yorkston & Beukelman, 1980), with heterogeneous conclusions. Yorkston and Beukelman (1980) probed the validity of different variables in the spontaneous speech of an aphasic individual, showing that the participant conveyed information informatively (as indicated by the total number of content units), but less efficiently than controls (as indicated by the number of syllables and content units per minute). Similarly, Nicholas and Brookshire (1993) showed that people with aphasia produce fewer words, words per minute, content units, and content units per minute than non-brain-damaged participants. Jacobs (2001) found a correlation between such measures and the ratings of naïve listeners on the informativeness, efficiency of communication, and listening comfort of spontaneous speech samples before and after specific language treatment. Herbert et al. (2008) found significant correlations between picture-naming accuracy and the proportion of content words as speech units. Berndt et al. (1997) found that people with verb deficits relied on simple sentence structures with light verbs (e.g., give, do, have, be, etc.) and on verbs that do not require inflections (or require zero inflection). Bastiaanse and Jonkers (1998) and Crepaldi et al. (2011) reported that people with nonfluent aphasia produce a lower proportion of verb types in spontaneous speech than non-braindamaged speakers. Goral and Kempler (2009) indicated that naïve listeners perceived a positive change (e.g., less stress, less awkwardness) in the communicative abilities of a person with chronic nonfluent aphasia after training of verb production.

Thus, CADL–2 and spontaneous speech analyses can be considered as good predictors of the patient's communicative abilities in daily life, as both rely on objective measures of the patient's behavior and therefore provide more reliable results than subjective rating scales, exposed to potential biases on the examiner's part. On the other hand, both are exposed to the same criticism— namely, that it is not yet completely understood whether they provide sufficient information on functional communicative abilities. Our (slight) preference for CADL–2 stems from the fact that scores on this task are obtained via a procedure shared by the users of this test. By contrast, further work is needed to establish which features of spontaneous speech provide the most sensitive measure of effective communication in daily life (e.g., content units, fluency, mean length of utterance, proportion or ratio of specific word categories, number of syllables, type–token ratio, proportion of inflected verbs, etc.).

Regarding impairment-level measures, we administered four picture-naming tasks that require the ability to produce nouns that refer to objects (e.g., apple, arm, trumpet) and verbs that refer to actions (e.g., to count, to moo, to squeeze). Further work could be directed towards finding correlations of functional-level measures with nouns that do not refer to objects (e.g., month, future, realm) or verbs that do not refer to actions (to love, to trust, to shine). Other tasks requiring spoken output, such as repetition and connected speech, or comprehension tasks could be administered in addition to picture-naming tasks.

As in any correlational study, results are indicative. The statistics employed were adequate in the light of sample size and number of items included in each task (Benjamini & Hochberg, 1995; VanVoorhis & Morgan, 2007; Wampold & Freund, 1987). Further work on a larger subject sample should correlate the patterns observed here with lesion site and with the underlying language deficit. Most participants in this study suffered from single focal lesions in the middle cerebral artery territory (e.g., middle and inferior frontal gyrus, insula, inferior parietal lobule, superior and middle temporal gyrus). Further insights on this issue may be gained by studying subjects who fare worse in Object Naming than in verb tasks (such as our case G.C.), whose lesions typically affect the posterior cerebral artery territory, thus damaging inferomesial temporo-occipital areas (cases B.L., B.S.), or subjects with etiologies other than stroke (e.g., degenerative or slowly growing lesions, in which brain plasticity may modify anatomo-behavioral correlates).

4.5. Conclusion

Verb tasks correlated with abilities in daily living, as measured by CADL–2. Producing a finite verb in sentence context and Object Naming differently correlated with CADL–2. More subjects fared worse on one or more verb tasks than on Object Naming, but the opposite pattern was also reported. These patterns should be further investigated by focusing on lesion site, etiology, and underlying language deficit. Results strongly encourage the use of both verb tasks and noun tasks in clinical practice, when evaluating subjects with language disorders.

Chapter 5

Advantages and disadvantages of intraoperative language tasks in awake surgery: a three-task approach for prefrontal tumors[5]

Abstract

Introduction: Multidisciplinary efforts are being made to provide surgical teams with sensitive and specific tasks for language mapping in awake surgery. Researchers and clinicians have elaborated different tasks over time. A fair amount of work has been directed to study the neurofunctional correlates of some of these tasks, and there is recent interest in their standardization. However, little discussion exists on the advantages and disadvantages that each task poses from the perspective of the cognitive neuroscience of language. Such an approach may be a relevant step to assess task validity, to avoid using tasks that tap onto similar processes, and to provide patients with a surgical treatment that ensures maximal tumor resection while avoiding postoperative language deficits. An understanding of the language components that each task entails may also be relevant to improve the current assessments and the ways in which tasks are administered, and to disentangle neurofunctional questions.

Methods: We review 17 language mapping tasks that have been used in awake surgery. We provide examples of a three-task approach we are administering to patients with prefrontal lesions.

Results: Overt production tasks have been a preferred choice over comprehension tasks. Tasks tapping lexico-semantic processes, particularly object naming, maintain their role as gold standards. Automated speech tasks are used to detect speech errors and to set the amplitude of the stimulator. Comprehension tasks, reading and writing tasks, and tasks that assess grammatical aspects of language may be regularly administered in the near future.

Conclusions: Future advances in this area are contingent upon reviewing gold standards and introducing new assessment tools. Our three-task approach is feasible and useful.

Keywords: brain mapping, language tests, semantics, quality of life

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5.1. Introduction

There is increasing interest in the neurocognitive components of language mapping in awake surgery: efforts are being directed towards providing surgical teams with appropriate assessment tasks (De Witte, Satoer, Robert, Colle, Verheyen, Visch-Brink et al., 2015; Połczyńska 2009; Rofes, de Aguiar, Miceli, 2015); literature exists regarding the selection of tasks based on lesion localisation and functional networks (e.g., Chang, Raygor, & Berger, 2014; Coello, Moritz-Gasser, Martino, Martinoni, Matsuda, & Duffau, 2013; Hamberger, 2015; Mesulam, 1990); and relevant work has been devoted to studying the neural correlates of language tests in relation to direct electrical stimulation (DES) and brain plasticity (e.g., Binder, Swanson, Hammeke, & Sabsevitz, 2008; Desmurget, Song, Mottolese, & Sirigu, 2013; Foki, Gartus, Geissler, & Beisteiner, 2008; Kristo, Raemaekers, Rutten, de Gelder, & Ramsey, 2015; Picht, Krieg, Sollmann, Rösler, Niraula, Neuvonen, et al., 2013; Zacà, Nickerson, Deib, & Pillai, 2012; Zacà, Jarso, & Pillai, 2013). The field is blooming with new and increasingly refined approaches, encouraged by the fact that language mapping in awake surgery provides better outcomes for the patient than fully-anesthetized surgeries (De Witt Hamer, Gil-Robles, Zwinderman, Duffau, & Berger, 2012). However, little discussion exists on the advantages and disadvantages that currently used tasks entail for the assessment of language during surgery.

Here we review 17 language mapping tasks commonly reported in the literature. This may help awake surgery teams to choose which task(s) may better suit their surgical needs, to avoid administering tests that assess too similar processes, and to preserve the patient's language abilities and quality of life. We discuss the language components assessed by each task from a cognitive neuropsychological perspective (Coltheart, 2001; Whitworth, Webster, & Howard, 2005). We take into account language components that are typically agreed-upon in language processing models (e.g., Caramazza 1997; Levelt 1989). We consider the semantic level as a central component, as its damage may affect production and comprehension processes, with consequent impact in the patient's quality of life (Goodglass & Wingfield, 1997; Weitzner, Meyers, & Byrne, 1996). We also discuss the order of administration of tasks and provide an overview of an intraoperative three-task approach we are successfully implementing. Finally, we point toward some future directions in this field.

Discussion over non-language factors such as type and timing of electrical stimulation, histological factors, lesion localisation, extent of tumor resection, patient's profile, variability, anxiety, responsiveness, etc. is outside the scope of this paper. Attention has been often paid to these issues (e.g. Borchers, Himmelbach, Logothetis & Karnath, 2011; Gil-Robles & Duffau, 2010; Hamberger 2015; Ojemann & Mateer, 1979; Ruis, Wajer, Robe, & van Zandvoort, 2014; Santini, Talacchi, Squintani, Casagrande, Capasso, & Miceli, 2012; Skirboll, Ojemann, Berger, Lettich, & Winn, 1996; Talacchi, Taphoorn, & Miceli, 2012). Similar work could be aimed at reviewing tasks that are used to assess memory (Feudio & Van Buren, 1975; Ojemann, 1978; Ojemann & Dodrill, 1985; Teixidor, Gatignol, Leroy, Masuet-Aumatell, Capelle, & Duffau, 2007), executive functions (Wager et al., 2013), visual processing (Duffau, Velut, Mitchel, Gatignol, & Capelle, 2004), mentalizing (Herbet, Lafargue, Moritz-Gasser, Bonnetblanc, & Duffau, 2014), numerosity and calculation (Roux, Boukhatem, Draper, Sacko, & Démonet, 2009), etc.

5.1.1. Language testing in awake surgery

Before being operated upon, patients undergoing awake surgery may be assessed with batteries that allow an evaluation of language in its different input and output components (e.g., reading, writing, speaking, and listening). Tasks prepared for intraoperative use are administered at this stage to decide which items or item-categories can be used during surgery. Only those items (or subsets of items) that patients can produce flawlessly before surgery are administered intraoperatively, as this is thought to minimize false positives (i.e., instances in which the patient is unable to answer in the absence of electrical stimulation) and to provide reliable language maps (Rofes, de Aguiar, & Miceli, 2015). During surgery, low-intensity electrical trains are directly applied to the cortex and subcortical areas, while the patient is asked to respond to each language stimulus (e.g., Ojemann & Mateer, 1979). The intraoperative occurrence of speech errors (i.e., anomia, paraphasias, latencies, etc.) during language mapping is taken as an indication that the stimulated region is a relevant part of the language network (see Borchers et al., 2011, Desmurget et al., 2013, for contrasting opinions). The types of errors that emerge during electrical stimulation of an area may reveal the role that area plays in the language network. For example, stimulation to the superficial layer of the inferior fronto-occipital fasciculus (IFOF) may trigger semantic errors in production (e.g., saying “tiger” in response to the picture of a lion) and in comprehension (e.g., stating that “pyramid” is related with “palm tree”, but not with “pine tree”), suggesting that this fiber bundle plays a role in semantic processing (Moritz-Gasser, Herbert, & Duffau, 2013).

5.1.2. Models of language processing

Models of language processing are the operationalization of theories of language production and comprehension. They are based on studies in healthy people and on behavioral dissociations documented in neurological populations (e.g., patient A is worse at writing nouns than producing nouns aloud, while patient B has the opposite profile). The articulation of these models may be schematically represented in box-and-arrow diagrams, where boxes represent separable memory/language components and arrows correspond to connections between these components. A schematic representation of one of such model can be found in Figure 5.1.

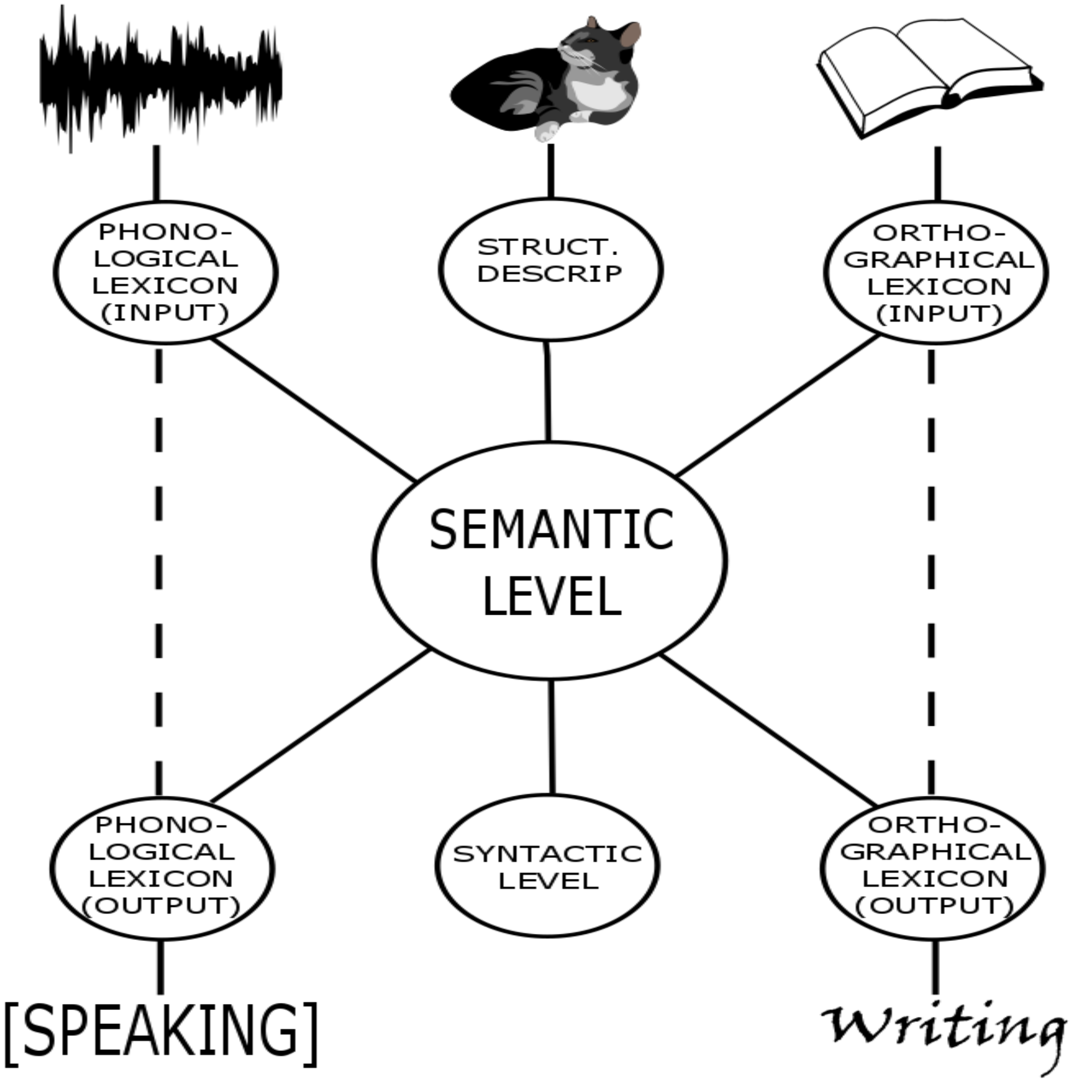

Figure 5.1. Schematic representation of language components. The schema includes input and output phonological and orthographic lexical components that revolve around a semantic level. It also includes a visuo-perceptual, and a (lexico-) syntactic component.

On a broad level, input lexical components ensure that the subject recognizes orthographic or phonological sequences as familiar (i.e., as words stored in orthographic/phonological long-term memory). The output lexicons provide access to orthographic or phonological sequences that are familiar to the subject. The semantic system represents meanings (i.e., the word /dog/ stands for a typically domesticated mammal that has a good sense of smell, howls and barks, has a long snout, etc.) and is accessed both for production and for comprehension. Syntactic processes allow us to glue words into sentences to express complex meanings, to refer to time and place, etc. (i.e., “My wife has two dogs”). Visuo-perceptual processes are needed for the interpretation of pictorial stimuli (e.g., Gibson, 2013). Finally, articulatory processes allow the production of speech sounds through the correct movement of the speech organs (e.g., tongue, lips, larynx, etc.).

5.1.3. Advantages and disadvantages of tests reported in the literature

The language processes and modalities tested, the time needed to perform the task (ideally, no more than 4 seconds per item), and the patient's pre-surgical profile (cognitive abilities, age, education, pathology, etc.) determine advantages and disadvantages of intraoperative tasks. We briefly describe each task, with a focus on the language processes and modalities tested. We comment on other factors and contrast various tasks, where necessary. We discuss the tasks in subgroups, according to whether they pose greater demands on non-semantic/sublexical, lexico-semantic, or grammatical processes. This does not imply that some tasks grouped among those tackling lexico-semantic processes, for example, may not be useful to assess also grammatical processes (e.g., action-naming). A summary of the language processes assessed by each task can be found in Table 5.1.

Table 5.1

Language processes assessed by each task.

	PhL (Input)	StrD (Input)	OrL (Input)	SemL	PhL (Output)	OrL (Output)	SynL
Non-semantic processes							
Automated speech				*	✓		
Phonemic identification	✓				✓		
Word/non-word repetition	✓			*	✓		
Lexico-semantic processes							
Action-naming		✓		✓	✓		
(Visual) Object naming		✓		✓	✓		
(Auditory) Object naming	✓			✓	✓		
Naming famous faces		✓		✓	✓		
PPTT (with drawings)		✓		✓			
PPTT (with written words)			✓	✓			
PPTT (with words and drawings)	✓	✓	✓				
Reading words/non-words aloud	*		✓	✓	✓		
Verb generation		✓		✓	✓		
Writing words			✓	✓		✓	
Grammatical processes							
Naming actions with finite verbs		✓		✓	✓		✓
Reading sentences aloud			✓	*	✓		*
Sentence completion			✓	✓	✓		✓
Sentence repetition	✓			*	✓		✓
Translating paragraphs			✓	✓	✓		✓
Writing sentences			✓	✓		✓	✓
Writing sentences (to dictation)	✓		✓	✓		✓	✓

Notes. Check marks (✓) indicate that the process is assessed in the task, asterisks (*) that it may be assessed, and blank spaces that it is not assessed. PPTT = Pyramids and Palm Trees test, PhL = Phonological lexicon, StrD = Structural description, OrL = Orthographical lexicon; SemL = Semantic level; SynL = Syntactic level (morphosyntactic features).

5.1.3.1. Non-semantic processes

Automatic speech tasks require motor planning and articulatory processing. Patients can be asked to count from one to ten, to recall the months of the year, the days of the week, etc. These language stimuli do not pose high demands on linguistic knowledge as they typically contain overlearned sequences of words (Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 2000). Such tasks are administered to set the intensity of the electrical stimulator and to check for effects on the peripheral nervous system (Duffau et al., 1999). Some teams have asked patients to count from one to fifty (e.g., Sanai, Mirzadeh, & Berger, 2008; Chacko et al., 2013). Oral diadochokinesis or fast naming of sequences of phonemes (e.g., pa-ta-ka, pa-ta-ka, pa-ta-ka) could also be used, as they do not pose high demands on lexico-semantic processes (e.g., Hukrmans, Jonkers, Boonstra, Stewart, & Reinders-Messelink, 2012). Ojemann and Mateer (1979) asked patients to make orofacial movements, such as mimicking postures of lip protrusion when seeing the action performed on a picture. Special attention may be paid to the rate at which the patient is asked to produce automatic speech, as a fast speech rate may induce undesired spontaneous errors, leading intraoperatively to false positives.

Phonemic identification was used by Ojemann and Mateer (1979). Patients were presented with plosive consonants embedded in a nonsense syllable (e.g., a[p]ma vs a[b]ma), and were asked to decide which plosive consonant they heard. The task may detect the inability to recognize and isolate phonemes within a word, which may in turn prevent access to phonological word forms (e.g., [b]all vs [t]all), and hence, their comprehension. We are not aware of other studies administering this task during awake surgery. Caplan, Gow and Makris (1995) reported the scores of people with acoustic-phonetic processing deficits after stroke. They reported that patients with lesions in the left posterior supramarginal gyrus as well as in the parietal operculum are more likely to present poor phonemic identification. The question remains as to whether it may be useful to modify the original task proposed by Ojemann and Mateer (1979), and ask patients to identify target phonemes in different word positions (e.g., onset vs coda position), or to assess specific contrasts (e.g., voicing, manner and place of articulation, etc.).

Word/non-word repetition may be useful to tap on language routes that do not require semantic access or to identify the language level(s) affected by electrical stimulation. Tomasino et al. (2015) asked Italian-speaking patients to repeat non-words such as “bolata”. Moritz-Gasser and Duffau (2013) asked patients to repeat the target word whenever they produced it incorrectly in an object naming context during stimulation mapping. Successfully repeating the target word after a previous naming error during stimulation may indicate a temporary failure to access the phonological output lexicon. Similarly, an inability to name the target word may signal disruption in processing its structural description (if images are used), or in accessing the phonological/orthographic input lexicon or the semantic level (if spoken/written words are used as stimuli). This may be particularly useful in perioperative assessments.

5.1.3.2. Lexico-semantic processes

Action-naming assesses the ability to produce a verb as the label for the action depicted in a drawing/picture. The task has been used, although not extensively (see Rofes & Miceli, 2014 for a review). Patients are given a black-and-white drawing or a video of an action, and they are asked to answer with a verb in the infinitive (e.g., “to jump”) or in the progressive form (“jumping”). Bogka et al. (2003) ran three studies on healthy people and showed that naming actions may be slower than naming objects – but, still within the 4-second window allowed in awake surgery (e.g., mean=1051 milliseconds, sd= 171 milliseconds). The processes engaged by action-naming are similar to those of object naming. The main limitation of action-naming resides in the fact that it does not require the production of inflectional features which, in many languages, encode time and person information, and are involved in lexical and grammatical processes in discourse (Tyler, Bright, Fletcher & Stamatakis, 2004). This relevant linguistic information may be left unassessed when an action-naming task is used instead of a task that requires production of a finite verb (see later in this section).

Visual object naming assesses the ability to produce a noun (e.g., “book”) as the label for the object depicted in a drawing/picture. This task has been used by the pioneers of awake surgery (Ojemann & Mateer, 1979), is mentioned in current surgical guidelines (Kayama, 2012), and has been reported as a good predictor of the patient’s likelihood to go back to work, and of overall quality of life (Moritz-Gasser, Herbet, Maldonado, & Duffau, 2012). In versions of this test for Dutch, English, French, Italian, and Japanese an introductory sentence has been added above the image to induce the production of the determiner with the noun (e.g. “This is... *an* apple” instead of “apple”). As a result, patients are asked to produce a sentence with a light verb “to be” (This is… *an apple*) or a determiner phrase (*Ecco la mela*, Here the apple). This latter task requires the overt production of grammatical information, as the selection of the appropriate determiner requires the patient to encode number (i.e., *an* apple vs *some* apples), reference to the noun in previous discourse (i.e., *the* apple vs *an* apple), and in some languages the noun’s grammatical gender (i.e., “*la*.$_{f.sg.}$ *mela*” instead of “the.$_{m.sg.}$ apple”). As stressed by Ojemann and Mateer (1979), the introductory sentence “this is” allows to distinguish anomic errors (patients read the introductory sentence but are unable to produce the determiner and the noun) from speech arrest, in which patients are unable to speak. Similar arguments are found in recent reports (e.g., Zemmoura, Herbet, Moritz-Gasser, & Duffau, 2015). This interpretation is open to discussion, as the inability to produce the introductory sentence is not necessarily due to problems in motor production or planning. It can also result from other problems, such as the inability to read the introductory sentence, due to difficulty accessing the orthographic input lexicon.

Auditory object naming (or naming objects to visual description) is similar to visual object naming, insofar as the response required of the patient is the name of an object. However, instead of being presented with a drawing/picture, patients hear a spoken description of an object, of which they have to provide the name (e.g., "a hand-held instrument used for cutting paper" for scissors). This task requires accurate auditory word and sentence comprehension (not necessary in visual object naming), and the ability to retrieve the target name that matches the stimulus sentence. It may be particularly sensitive in patients with left temporal lobe epilepsy, compared to visual object naming (Hamberger & Tamny, 1999; Hamberger et al., 2005). Bird, Howard and Franklin (2000) successfully used this task in people with post-stroke aphasia. By not using visual stimuli, the task can be relevant to assess the semantic level in patients who cannot read, or when the patient position may difficult the presentation of visual stimuli such as in midline (sub)occipital craniotomies. Also, it is suitable to assess word types that cannot be easily depicted (e.g. ego, welfare, attractive, deny, promote, scent, noticeably, etc.)

Naming famous faces requires similar processes to object naming, as well as facial feature encoding and accessing semantic/biographic information of the person that is portrayed. The final output required from the patient is a proper name such as "Chaplin" or "Madonna". Giusanni et al. (2009) used a task with 30 famous faces during surgery. The authors argue that famous faces are more complex than objects, as the visual and lexico-semantic characteristics required to process a famous face correspond to a unique entity, while those required for the correct processing of an object correspond to a category. As any other task, a standardization process is required to decide which famous figures are better known to patients – age and cultural background may influence these results. Giusanni et al. (2009) were able to find specific areas for this task compared to object naming in the left frontal and anterior temporal gyri, and propose that naming tasks should be adapted to the brain region studied. In perioperative studies of people with brain tumors, temporal lobe epilepsy, and other neurological disorders, damage to the left anterior temporal lobe can disrupt access to the names of famous people, particularly when damage extends to the uncinate fasciculus (e.g., for a review, see Papagno, 2011)

The *Pyramids and palm trees test* assesses “the person’s ability to access detailed semantic representations from words and from pictures” (Howard & Patterson, 1992). The test consists of triads of pictures or written/spoken words. A stimulus item is presented, centered at the top of the page (e.g., a pyramid) and two alternatives are presented below it: a target (e.g., palm tree) and a distracter (e.g., pine tree). The patient’s task is to choose which of the two items is associated with the item presented on top. To do so, patients need to access information from the three items in each triad (i.e., recognize the items, retrieve information, perform the association). Moritz-Gasser et al. (2013) and Motomura, Fujii, Maesawa, Kuramitsu, Natsume, and Wakabayashi (2014) used the version containing three images during stimulation of the IFOF and as a complement to object naming. The authors argue that this task allows the identification of brain regions related to non-verbal semantic memory. They report that during DES patients were unable to make a semantic choice, looked startled and perplexed, and sometimes answered with sentences like “I don’t know at all”, “I do not understand anything” “what do I have to do?”. Howard and Patterson (1992) indicated that six other versions of the test are possible (three written words, three spoken words, and combinations of those with pictures as stimuli or as alternative choices). These authors emphasize that patients may not be assessed with all versions routinely. Rather, a specific version may be selected depending on which language level must be further assessed. For example, the version with three auditorily presented words may be recommended to evaluate access to semantics via the phonological input lexicon.

This version of the task should be used in patients with good phonological short-term memory, as it requires the subject to hold information from the three words in memory in order to provide the correct answer.

Reading words/non-words aloud requires access to the orthographic input lexicon. Sanai et al. (2008) used this task during surgery. Similarly to auditorily presented tasks, reading tasks can be useful to assess words that are difficult to depict. The task allows the assessment of very specific types of words, if needed, while allowing to control for psycholinguistic variables such as frequency, age of acquisition, imageability (see Brendt, Mitchum, Haendiges, & Sandson, 1997; for an example in people with post-stroke aphasia). Zemmoura et al. (2015) asked patients to read 20 single words shown on a computer screen for 4 seconds, after a beep presented 500ms before item presentation. The task includes regular words (i.e., words with a transparent phoneme-grapheme relationship: *bilatéral*, bilateral), irregular words (i.e., words with opaque orthography-to-phonology relationship: for example, the word *oignon*, onion, is read out /ɔ.ɲɔ̃/) and non-words/pseudowords (i.e., letter sequences that are not represented in the vocabulary: *bafiko*). The three types of stimuli were presented randomly. The patients' performance allowed the assessment of both non-lexical reading mechanisms (non-words) and reading mechanisms that required lexical-semantic processing (irregular words). Since the task uses individual stimuli, pre-stimulus triggers may be administered during electrical stimulation.

Verb generation tasks require comprehending a noun in order to produce a conceptually-related verb in the infinitive. Patients are shown the picture or told the name of an object (e.g., "book") to which they have to associate the first verb that comes to mind (e.g., "to read"). Verb generation involves language processes that impact on the semantic level and can be perturbed by stimulation in multiple brain areas (Ojemann, Ojemann, & Lettich, 2002; Roux, Boetto, Sacko, Chollet & Trémoulet, 2003). However, this task does not assess syntactic processes. In addition, if electrical stimulation disrupts performance, it is difficult to establish if it interfered with noun comprehension, verb retrieval, or both. This distinction has relevant implications for mapping language processes, as nouns and verbs may have a partially segregated representation in the brain, also as suggested by studies using DES (Corina, Gibson, Martin, Poliakov, Brinkley, & Ojemann, 2005; Havas et al., 2015; Lubrano, Filleron, Démonet, & Roux, 2014). Verb generation tasks should not be confounded with *word generation or fluency tasks*, in which patients are given one minute to produce as many words as possible starting with one specific letter or referring to a specific semantic category (Goldstein, Obrzut, John, Hunter, & Armstong, 2004). These latter tasks may be appropriate for perioperative testing, as a way to assess cognitive control and executive functions in general (Moritz-Gasser & Duffau, 2013). However, the use of fluency tasks to map language during surgery is questionable, as it is hard to establish an appropriate stimulation time to trigger specific language errors. Furthermore, in normal settings subjects do not produce a continuous flow of words, probably due to word search processes.

Writing words to dictation may be useful to tap lexical-semantic knowledge of words that are difficult to depict. Since this is a one-stimulus task, instead of a sentence-production task, electrical stimulation may be applied right after word dictation, before the patient provides an answer. The task may be easier to perform and to administer than writing sentences. Magrassi, Bongetta, Bianchini, Berardesca, Arienta (2010) reported on a patient who wrote words correctly under dictation or spontaneously, but was unable to write simple sentences. In some languages, this task can be used to assess different writing systems. Motomura et al. (2014) took advantage of the Japanese writing system and asked a participant to write kanji (morphograms) when cued with kana (syllabograms). For example, the patient read the word grass in kana (クサ - /kusa/) and was asked to write it down in kanji (草). Similar work could be performed in languages like Serbian, which is normally written in both Latin and Cyrillic alphabets.

5.1.3.3. Grammatical processes

Naming actions with finite verbs requires the patient to retrieve an inflected verb – i.e., the verb root that corresponds to the action and the specific morphosyntactic features that relate the subject of the sentence and the verb. Patients are presented with a picture or video of an action. An introductory sentence may be added above the image, consisting either of a determiner phrase referring to the object (i.e., “the woman”) or of a pronoun (“she”). Patients are required to read the introductory sentence and to produce a verb in its correct inflected form. This task targets verb production, involves semantics, lexical retrieval and the syntax required to establish the agreement relation between subject and verb, time reference, etc. Importantly, these processes can be performed within the 4-second window allowed by current electrical stimulation procedures (Kayama, 2012). Rofes, Capasso and Miceli (2015) showed that this task is a good predictor of language abilities in daily living, based on data of individuals with post-stroke aphasia. The authors recommend to associate this task to object naming when assessing language functions, as the production of nouns and verbs may dissociate, even when items are matched for relevant psycholinguistic variables.

Reading sentences aloud has typically been implemented by asking patients to read sentences of 8 to 10 words slowly (e.g., Ojemann, Ojemann, Lettich, & Berger, 1989; Roux, Lubrano, Lawers-Cances, Trémoulet, Mascott, & Démonet, 2004). Lubrano et al. (2004) asked patients to read two unrelated sentences that were not semantically related and that had not been previously trained (e.g., *La chaise est jolie. Le vent du nord souffle fort;* The chair is pretty. The north wind blows hard). A caveat of this task is that the stimulation point is hard to establish. Roux et al. (2004) reported that "stimulation was applied randomly on the cortex while [patients] were reading". Other than that, due to the non-semantic grapheme-to-phoneme conversion route, patients may perform well on this task without accessing semantics. And obviously, this task is not appropriate for patients who cannot read.

Sentence completion involves similar processes to Naming actions with finite verbs. Patients are given a string of 7 to 8 words forming a sentence, in which one component is missinOjemann and Mateer (1979) presented sentences of this kind: "If it's sunny next Saturday she … to the beach", where the target is "will go". When the missing word is the lexical verb (e.g., "to go"), this task directly taps lexical-semantic and syntactic mechanisms, as it requires the ability to retrieve the appropriate verb for the context provided by the sentence. This task also allows the assessment of verb inflection, as well as of different time frames (e.g., past, present, future) and agreements between subject and verb (i.e., first person, second person, etc.). Patients could also be asked to produce a noun (e.g., "If it's sunny next Saturday she will go to ...; where the target could be "the beach"). The task is not suitable for people who cannot read. Stimulation may be applied before the production of the target word, as at this point in time the processes necessary to complete the sentence may be engaged. The fact that patients need to complete the task with one word poses greater demands on lexico-semantic processing than reading sentences aloud.

Sentence repetition adds the grammatical processes that are required in sentence processing to those engaged by word repetition. Tomasino et al. (2015) asked patients to repeat active and passive sentences from an Italian language battery (BADA, Miceli, Capasso, Laudanna, & Burani, 1994). Patients produced phonemic paraphasias that extended to more than one word in the sentence (**il* <u>*cavàno incine*</u> *il cane* instead of *il cavallo insegue il cane;* the horse chases the dog). Errors like these raise the possibility that electrical stimulation affects speech output not only at the single-word level but also at the sentence level, similar to other tasks that use sentences. Also in this case it is difficult to establish when in time (and where in the brain) electrical stimulation should be applied.

Translating paragraphs is only applicable to proficient bilinguals. Borius et al. (2012) asked patients to translate paragraphs from newspapers from L2 to L1 and reported no specific sites for translation (as compared to naming or sentence reading). Stimulation during this task may lead to relevant but difficult-to-interpret results, as translation requires many language processes to be concomitantly activated (i.e., reading and understanding in L2; finding the appropriate words, building the correct syntactic frame, and reading it out in L1). Further work is needed to establish the relevance of this task in mapping protocols with proficient polyglots. Until then, it may still be profitable to assess patients with similar tasks, or parallel versions of the same task, in the two languages (e.g., object naming in French and Occitan).

Writing sentences can be used to trigger errors at various stages of written output (semantic level, syntactic level, orthographic word forms, orthographic short-term memory, graphomotor routines, etc.). Since the task requires reading of the text that is being written, in addition to engaging the orthographic input lexicon. Errors arising at this latter level may be difficult to detect, as written word form recognition processes are covert. Stimuli similar to those used in sentence reading tasks can be administered. Patients are asked to write sentences of seven or eight words. They may be active sentences (e.g., *La chaise est jolie;* The chair is pretty; Lubrano et al., 2004; Roux et al. 2003; 2014), or more syntactically-complex constructions (i.e., *Quando il gatto non c'è i topi ballano*; When the cat is away the mice will play; *Luca mangia un panino e abbraccia Carlino*; Luca eats a sandwich and hugs Carlino; Magrassi et al., 2010). Sentences are typically dictated by the examiner, thus engaging the phonological input lexicon and allowing in principle the task to be performed without accessing semantic-lexical information (via conversion routes). Roux et al. (2014) reported that in rare cases patients may present difficulty understanding the task. In such instances, the authors complemented it with other tasks tapping the phonological output lexicon and conversion routes (e.g., word repetition), and with tasks that require access to the semantic system such as choosing one picture (e.g., a flower, a dog, a hammer, a boat) and is asked to indicate "where is the boat?" Similar to sentence reading, writing sentences to dictation poses the problem to decide when to apply electrical stimulation. The types of errors that may be encountered during electrical stimulation are: irregular handwriting, drift from the initial line of the sentence, disorganization of the text in space, letter/phoneme displacements or substitutions, repetitions, using upper-case letters instead of lower-case letters within words, inability to write (i.e., writing arrest). Roux et al. (2014) divide errors in two categories: semantic or verbal paragraphias and phonological paragraphias. Further work is needed to improve task administration, as in order to write while being operated upon, patients may need to take an uncomfortable position. Lubrano, Roux, & Démonet (2004) report that "patients used a pencil to write horizontally on A4 sheets of paper, which lay on a stiff pad that a nurse had presented to them vertically".

All the tasks that require producing sentences, orally or in writing, can be influenced by disorders of working memory. These might be diagnosed in perioperative stages by administering cognitive tasks such as the Digit Span, the Corsi's block-tapping test (e.g. Orsini, Grossi, Laiacona, Papagno, & Vallar, 1987), the Immediate Visual Memory test (Gainotti, Caltragione, & Miceli, 1978), etc.

5.1.4. Adminsitration of tasks during surgery

Little research exists onto the order in which the tasks are administered. Automatic speech tasks may be used first to assess non-linguistic motor processes, and to regulate the amperage of the electrical stimulator (e.g., Duffau et al., 1999). Subsequently, the patient may be presented with language tasks (typically object naming) during cortical stimulation, in order to delineate a cortical language map. During tumor resection, some groups engage the patient in naming tasks in the absence of any electrical stimulation. These tasks may be paired with a motor task, such as moving the right arm to obtain further on-line feedback (e.g., Gil-Robles & Duffau, 2010). Another possibility is to engage the patient in a spontaneous conversation. Patient may be asked questions about their lives that may have been learned by the examiner in the preoperative assessment (e.g. "You told me that you have two children. Which is the one who is married?"). Questions related to whether the patient feels pain, is comfortable, thirsty, etc. may also be asked. Language-driven approaches may also be used in which patients are engaged in semi-structured interviews instead of spontaneous conversations, as these allow further control on speech production and can be contrasted with the same patient's preoperative assessments, and with those of a non-brain-damaged control group (Prins & Bastiaanse, 2004; Saffran, Berndt & Schwartz, 1989). Finally, the same tasks used for cortical stimulation may be used for subcortical stimulation. Some groups used the Pyramids and Palm trees test for subcortical mapping (e.g., Moritz-Gasser et al., 2013; Motomura et al., 2014). Other groups (De Witte et al., 2015) propose a fast-sequencing of different language and non-language tasks (i.e., word and sentence repetition, naming, calculating, and line bisection).

The ordering of tasks may become relevant when a patient does not respond to one task but responds to the other. For example, Magrassi et al. (2010) asked the patient to write words, as she was unable to write sentences. It could be argued that the task the patient is more respondent to may be used first for language mapping. This raises the question of whether any other task may be more sensitive or specific (either because of the localization of the lesion, or because of the nature of the tasks). If a patient performs poorly in a specific modality (e.g., oral production), another modality may be used (e.g., written production). Whenever the patient unexpectedly fails to respond to all the tasks that engage semantic and lexical processes (e.g., object naming, action-naming by finite verbs), it may be relevant to consider the results of tasks that do not require semantic processing, such as automated speech tasks, non-word repetition, non-word reading, etc. These procedures may diminish the number of spontaneous errors, while increasing the sensitivity and specificity of DES mapping.

Another example where task order may become relevant is when tasks with verbs and sentences are used together with object naming tasks (see below). Task order may differ depending on lesion location and on the hypotheses the surgical team has. Surgical teams can choose to use verb tasks first in the case of prefrontal lesions, as aphasiological and lesion studies indicate a greater involvement of the prefrontal cortex in the processing of verbs, as opposed to the processing of nouns (e.g., Mätzig, Druks, Masterson, & Vigliocco, 2009). The opposite considerations apply in the case of temporal tumors, where object naming may be used first. Irrespective of any considerations on task order, the results of the various tests should be interpreted together.

5.2. A three-task approach for prefrontal tumors

Our current approach to intraoperative language mapping includes an automated speech task (counting from one to ten) and two overt language production tasks: naming objects (determiner + noun) and naming actions by producing finite verbs (pronoun + finite verb). The two naming tasks have been standardized for Italian and validated on an aphasic population (Rofes et al., 2015). The approach builds on modern surgical procedures (Duffau et al., 1999; Hamberger & Tamny 1999; Kayama, 2012; Ojemann & Mateer 1979; Ojemann et al. 2002; Sanai et al. 2008), and stresses the need to administer standardized tasks. The choice of the two naming tasks was driven by current knowledge in the cognitive neuroscience of language, and may be particularly efficient in patients with prefrontal lesions (Kemmerer, Rudrauf, Manzel, & Tranel, 2012; Mätzig et al., 2009; Rofes & Miceli, 2014). The approach we advocate is conservative, insofar as it does not implement too many tasks. At this stage, it is also suitable, as there are no standardized Italian versions available for all the tasks that could be used for language mapping. A good understanding of which tasks are preferable during surgery may require rigorous analyses and contrastive results pointing to the sensitivity, specificity, and predictive values of newer tests. In the final section of the study we describe our experience with this three-task approach.

5.2.1. Participants

Three Italian-speaking subjects (all male) with supratentorial glial lesions in left-dominant prefrontal areas were included. Age ranged from 37 to 63 years, education from 8 to 17 years. TT was operated for an anaplastic astrocytoma (WHO III) occupying the superior frontal gyrus (SFG) and middle frontal gyrus (MFG). PR was operated for a fronto-polar astrocytoma (WHO

III) extending to the MFG. MG was re-operated for an oligodendroglioma (WHO III) in the precentral gyrus and posterior part of the SFT, MFG, and inferior frontal gyrus (IFG).

5.2.2. Materials and procedure

Object naming and naming actions with finite verbs were administered intraoperatively. These were also administered preoperatively, to decide which items could be administered during surgery. The tasks were part of a broader perioperative language and cognition screening protocol. Detailed information on the tasks is reported elsewhere (Rofes et al., 2015). Items were presented for 4 seconds, as proposed in current surgical protocols (Kayama, 2012). Trains of electrical stimulation (60Hz, 0.2msec) lasting 4 seconds were delivered with a bipolar electrode. The amperage of the stimulator was regulated with an automated task (i.e., counting from one to ten). It varied for each participant and ranged from 2.5-4.5mA. All surgeries were video-recorded. We report areas where brain stimulation induced at least two errors out of three stimulations during language mapping with object naming, naming actions with finite verbs, and with both tasks. These areas were considered as critical for language processes and were not removed during surgery. Post-hoc two-tailed Fisher’s exact tests (FE) were calculated to assess whether the number of correct and incorrect responses differed between the stimulation and non-stimulation condition in each stimulated area.

5.2.3. Results

Results for each patient are summarized in Figure 5.2.

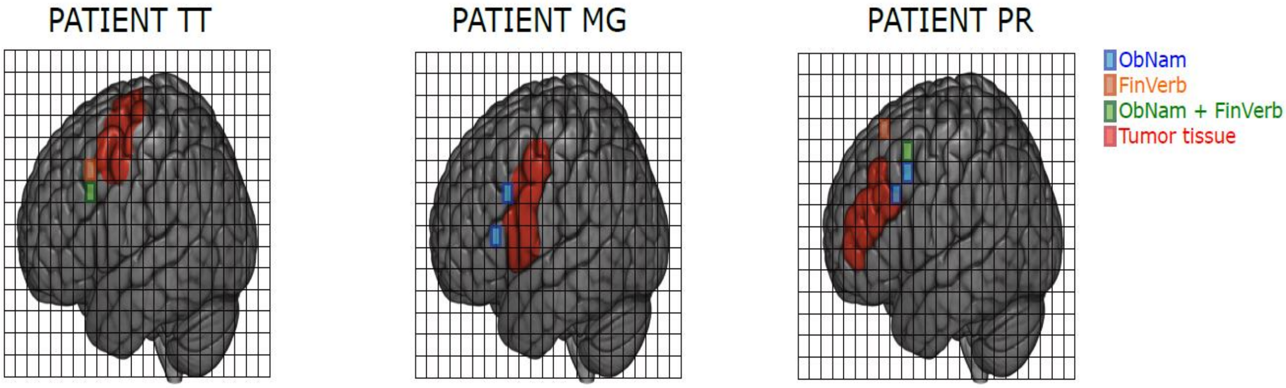

Figure 5.2. Summary of language maps. Areas where cortical stimulation induced a significant representative amount of errors and that were therefore considered as responsive during surgery are indicated. *Blue squares* indicate areas where errors were triggered during DES and object naming; *Orange squares* areas where errors were triggered during finite verb naming; and *Green squares* areas where errors were triggered with both object naming and finite verb naming. The area occupying the tumor is marked in red.

In patient TT errors appeared with both object naming and naming actions with finite verbs during stimulation of the posterior part of the MFG. In a more superior area of the MFG, errors where only detected during DES with finite verbs. At the cortical level, 2 errors in 21 stimulations appeared during object naming (p=0.1364) and 4 errors in 20 stimulations during naming actions with finite verbs (p=0.2213). At the subcortical level, 6 errors in 13 stimulations were elicited during object naming (p=0.08) and 6 errors in 16 stimulations during naming actions with finite verbs (p=1.000). Response latencies longer than 4 seconds were the most common error type, followed by anomia.

In patient PR, DES to the posterior part of the MFG triggered 2 errors with object naming. These were semantic paraphasias that where self-corrected within the 4-second time window (i.e., *ecco la sedia, il tavolo* – here the chair, the table; *ecco la chitarra, il violino* – here the guitar, the violin). A more superior area within the MFG was detected during DES with both object naming and naming actions with finite verbs. Incorrect responses resulted in latencies that resolved after removing the electrical dipole. Errors in the posterior part of the SFG were only triggered when naming actions with finite verbs. PR produced the introductory sentence, but failed to produce the verb in the correct inflected form (i.e., *lui… lui…*; he… he…). Subcortical stimulation was delivered to areas corresponding to the fronto-polar cortex. During DES with object naming the patient produced a semantic paraphasia (*ecco la prugna* for *ecco il peperone* – "Here the plum" for "Here the pepper") and two anomias (*non mi ricordo* – "I don't remember"). During the task with finite verbs the patient perseverated, while producing the pronoun in the incorrect gender in the introductory sentence (*lui lei pettina, lei pettina, lei lui pettina, lei lui pettina, lui pettina* – he she combs, she combs, she he combs, she he combs, he combs – the target is "she combs"). Statistical analyses are not provided, as this surgery could not be fully videotaped.

In patient MG no errors were triggered during naming actions with finite verbs. During object naming, errors occurred in 3/12 stimulations of the middle part of the IFG (p=0.001) and 3/10 stimulations of the MFG (p=0.005). Errors were phonological in nature. The patient produced a phonemic paraphasia or a fragment of the target, always followed by the correct response (e.g., *ecco la cigliere, ciliegia* – here the cherry; *ecco la gira, giraffa* – here the giraffe; *ecco il pf, peperone* – here the pepper). Stimulation to the subcortical area corresponding to the inferior part of the prefrontal cortex during naming actions with finite verbs induced a phonological error and anomias, that persisted when no stimulation was applied.

To sum up, mapping with object naming and naming-finite verbs seemed relevant in this population. *Post-hoc* analyses do not indicate a superiority for any of the tasks. The two tests can complement each other: in TT and PR areas in the posterior MFG and STG were only detectable when naming actions with finite verbs and/or object naming, while in MG errors were triggered only during object naming.

5.3. Discussion: future steps of language tests in awake surgery

We reviewed 17 different task types that have been used in awake surgery. These tasks cover non-semantic, lexico-semantic, and grammatical processes, mostly for overt production. The fact that such a wide range of tasks already exists indicates both the interest and the need to provide surgical teams with sensitive and specific tasks for intraoperative language mapping. In the next years, we expect to see a large number of tests, carefully controlled and standardized for each specific language. In fact, some surgery groups are already using standardized tests instead of home-made tasks (e.g., De Witte et al., 2015; Moritz-Gasser et al., 2012; Połczyńska 2009; Rofes et al., 2015). We also expect to see an increase in the variety of tasks.

Sufficient discussion of the different tasks will need to rise, so that surgical teams have an adequate understanding of the benefits and risks that each task entails. We believe that progress in this area requires that awake surgery teams add one or two new tasks to their current protocols, so that it is possible to learn whether new methodologies provide more specific and reliable results than the current gold standard. Roux et al. (2014), for example, administered three tasks in their patients provided that “brain mapping in awake surgery can be rather time consuming and some patients can obviously be tired (with some loss of attention) after several tasks”. Our team is also administering two-language tasks and an automated speech task. This is similar to the regular surgical procedure adopted by other teams (e.g., Lubrano et al., 2014;

Motomura et al., 2014; Moritz-Gasser et al., 2014; Tomasino et al., 2015). Further discussion on the tasks and paradigms used is essential.

The question arises of whether new tasks may give a direct oncological benefit by enhancing the patient's quality of life and survival time. Certain new tasks may be given priority, since they are more sensitive and specific, and of greater predictive value than the old ones. Histopathological, demographic, neurofunctional and many other factors may play a role in answering this question. Research into relations between functional and impairment-based scores could reveal the extent in which damage to specific components of the language system may affect language abilities in everyday life and, therefore, quality of life (e.g., Moritz-Gasser et al., 2012; Rofes et al, 2015). Further work may also be devoted to understanding the extent in which mild postoperative language damage may be tolerable or acceptable by an individual patient (e.g., Sanai et al., 2008).

At this stage, overt production tasks are more widely used than comprehension tasks. This could be because they are easier to score and provide better on-line feedback (Gil-Robles & Duffau, 2010). Other production tasks (e.g., writing words, producing sentences, naming actions with finite verbs) may be put to regular use in the near future. Reading individual words as well as sentence completion tasks may provide a bridge from the current, noun-centered processing approaches to tasks that require reading and writing, while controlling the timing of electrical stimulation. At the same time, given the paucity of comprehension tasks (note that the Pyramids and Palm Trees task is the only one used currently), we expect researchers and clinicians to be also interested in them. Of course, we do not expect nor wish that automatic speech or object naming tasks be left aside. The former are necessary to establish the amperage of the stimulator, and the latter will probably maintain their prominent role in tackling semantic and lexical processing.

Irrespective of the specific task(s), advances in this area are contingent on reporting for each task detailed information on its theoretical background and internal structure. We refer to the types of stimuli used, whether or not stimuli were standardized, which language processes were tapped by the task, etc. Efforts may also be devoted to describing test administration and scoring procedures, such as how long the stimulus was available on-screen, when stimulation was applied, the statistical methods used to identify specific brain areas (e.g., comparison of stimulation sites between two tests, comparison of correct and incorrect responses, etc.), and which error types emerged during stimulation.

5.4. Conclusion

We reviewed tasks currently used in awake surgery. Advantages and disadvantages of these tasks were assessed within a theoretical framework based on language components that are largely agreed upon in cognitive neuropsychology models of language processing. We reviewed our current approach, based on three tasks for prefrontal gliomas and showed that a task that uses object naming and naming actions with finite verbs is relevant. Progress in this area will be forthcoming if surgical teams work on the standardization of tasks in their respective languages and report their experiences when administering new tasks, compared to current gold standards. This work should involve the collaboration of different professional figures in the surgical team and researchers working in the neurobiology of language.

Chapter 6
Surgical mapping of language production in sentence context: a single-case series[6]

Abstract

Introduction: Object naming has been traditionally used to map language production in patients undergoing awake surgery procedures. Tests that use verbs in sentence context can be an appropriate addition to reach the same goal, as they use actions instead of objects and assess lexical verb retrieval mechanisms and sentence formation processes that cannot be tapped by object naming alone.

Aim: To investigate the contribution of finite verb production in sentence context for language mapping in awake surgery. Emphasis is placed on individual results, on subcortical mapping and on the types of errors elicited during DES, for which consistent information is currently scarce.

Methods: Six Italian-speaking participants with gliomas in the left, language-dominant hemisphere. Two overt production tests were administered: an object naming task (noun task) and a task requiring the production of finite verbs in sentence context (verb task). Factors affecting correct and incorrect responses were evaluated by non-parametric statistics. We contrasted the performance in all sites during DES v no-DES collapsing across nouns and verbs, or considering performance on nouns and verbs separately. Also, we contrasted noun and verb production during DES independently of site, and for each stimulation site separately.

Results: More errors were detected during DES v no-DES. The cortico-subcortical representation of nouns and verbs and the error types observed during DES are partially consistent with the current literature. In four participants we detected language-relevant areas only with object naming, in one participant only with the verbs task, and in one participant with both tasks.

Conclusions: The production of finite verbs in sentence context may provide complementary information to object naming, as it may permit to map language production when object naming is unaffected by DES.

Keywords: brain mapping, language production, verbs, nouns

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6.1. Introduction

Direct electrical stimulation (henceforth, DES) is the current gold standard for language mapping in individuals undergoing surgery for glial tumors in left perisylvian areas (e.g., Desmurget, Song, Mottolese, & Sirigu, 2013). Patients are kept awake under local anesthesia and are asked to perform cognitive tasks, while short trains of electricity are delivered in cortical or subcortical structures structures (e.g., Ojemann & Mateer, 1979; patient 22 in Penfield & Boldrey, 1937). Brain tissue in which DES triggers reproducible errors is not excised, as it is deemed that its removal may affect relevant cognitive functions (cf. Borchers et al., 2011). Keeping the patient awake during surgery offers advantages over fully asleep procedures, as it allows obtaining direct feedback on the patient's cognitive abilities, thus shedding light on the integrity of the underlying representations and processes (e.g., Surbeck, Hildebrandt, & Duffau, 2015).

Various cognitive processes can be assessed during surgery. In the language domain, object naming has been traditionally used to prevent functional damage (e.g., Hamberger & Tamny, 1999; Lubrano, Filleron, Démonet, & Roux, 2014; Ojemann & Mateer, 1979). This task has a long tradition in lesion studies. It is sensitive to lexical-semantic damage, which affects word production and comprehension, and is known to heavily impact on quality of life (Gainotti, Silveri, Villa, & Miceli, 1986; Goodglass & Wingfield, 1997; Moritz-Gasser, Herbet, Maldonado, & Duffau, 2012). Therefore, in all likelihood it will keep a central role in awake surgery. However, a mapping procedure based exclusively on object naming does not provide a sufficiently detailed intraoperative evaluation of language skills. From the strictly cognitive/linguistic viewpoint, object naming does not tap onto other relevant language functions, such as the processing of action words and morphosyntax, which are necessary for sentence formation and correlate with language abilities in daily living more strongly than object naming itself (e.g., Rofes, Capasso, & Miceli, 2015). From the clinical perspective, it has been repeatedly shown that nouns and verbs can be selectively affected/spared by brain damage (for reviews, see Pillon & d'Honincthun, 2011; Vigliocco et al., 2011), and that difficulties with verbs may selectively affect verb retrieval or verb morphology (e.g., Shapiro & Caramazza, 2003; Miceli, Mazzucchi, Menn & Goodglass, 1983; Miceli, Silveri, Romani, & Caramazza, 1989), in the context of spared object naming.

A finer-grained mapping of language may be obtained by adding simple intraoperative tasks that require the ability to produce verbs in a phrasal context, such as completing or reading sentences, or producing verbs in sentential context. A test that requires the production of a finite verb in a sentence, in response to a pictured event, for example, requires interpreting the stimulus picture, retrieving the meaning of the verb, building its corresponding argument structure, assigning thematic roles (agent, theme, beneficiary, etc.) to the different components of the sentence, and producing the verb in its correct inflected form (e.g., in agreement with the preceding subject, and in the correct time frame). Adding a finite verb production task to an object naming task would allow us to evaluate intraoperatively, and in a short time, not only semantics, lexicon and phonology, but also lexical-grammatical properties and morphosyntax (for a discussion of intraoperative language tests, see Rofes, Spena, Miozzo, Fontanella, Miceli, 2015).

Studies of neurological populations and of healthy volunteers with non-invasive neuroimaging techniques serve as a stepping stone for the introduction and development of mapping tools in awake surgery. Regardless of the origin of the differences between nouns and verbs, lesion studies indicated that verb processing is more frequently and severely impaired than noun processing (for reviews see Mätzig, Druks, Masterson, & Vigliocco, 2009; Pillon &

d'Honichthun, 2011). Analyses of the anatomoclinical correlates in these studies led to propose that deficits in producing nouns most likely arise from temporal damage, and deficits in producing verbs from frontal and (to a lesser extent) parietal and temporal damage (e.g., Damasio & Tranel, 1993; Goodglass, Klein, Carey, & Jones, 1966; Kemmerer, Rudrauf, Manzel, & Tranel, 2012; Miceli, Silveri, Noncentini, & Caramazza, 1988; Silveri & Di Betta, 1997).

Functional Magnetic Resonance Imaging (fMRI) studies of noun and verb production in healthy volunteers show activations in large perisylvian areas, that are more extensive and widely distributed than previously hypothesized (for reviews see, Cappa & Perani, 2003; Crepaldi, Berlingeri, Paulesu, Luzzatti, 2011; Vigliocco, Vinson, Druks, Barber, & Cappa, 2011). Several accounts can be proposed for these findings. One possibility is that, since fMRI paradigms show task-correlated activation that may not be essential for naming, some hyperactive foci may not be specific to verbs. For example, Thompson-Schill, D'Esposito, Aguirre, and Farah (1997) found significant activation in the left inferior frontal gyrus (IFG) during several semantic tasks (i.e., verb generation, noun classification, noun comparison). They interpreted their results as evidence that the left IFG is critical for "selection of information among competing alternatives from semantic memory", rather than for the retrieval of semantic information, or for verb processing. It is also possible that verbs activate widely distributed neural networks because, unlike nouns, they also entail complex lexical-grammatical properties (e.g., argument structure, subcategorization restrictions, etc.), and are typically inflected for tense, aspect and person, thus playing a crucial role for morphosyntactic processes (e.g., the Italian form *mangia*, refers to a third person singular agent that performs the action of eating in the present moment). Each of these verb properties may involve at least partially distinct neural networks, and therefore be responsible for widespread activations in fMRI studies. Another possibility is that these diverse observations result from the different focus of various investigations of the noun/verb distinction, and hence on how stimuli were selected in the original studies. For example, Saccuman et al. (2006) found no differences between nouns and verbs, but reported fronto-parietal activations in the contrast between manipulable or hand action words (e.g., the scissors/to comb) v non-manipulable words (e.g., the pyramid/to walk). By contrast, Bedny and Caramazza (2011) found a posterior region of the middle temporal gyrus (MTG) to be more activated by verbs than by nouns, and by syntactic properties of verbs, irrespective of motion properties.

Like fMRI studies, Transcranial Magnetic Stimulation (TMS) investigations failed to document the involvement of specific cortical regions in naming pictures of objects v actions, but demonstrated that object naming tasks are more sensitive than verb naming tasks when mapping language in the perisylvian cortex, and that both tasks induce errors as compared to a no-TMS condition (Hernandez-Pavon, Mäkelä, Lehtinen, Lioumis, & Mäkelä, 2014). Some TMS studies also highlight the role of psycholinguistic dimensions. For example, Oliveri, Finocchiaro, Shapiro, Gangitano, Caramazza and Pascual-Leone (2004) found no differences in the production of singular/plural nouns and third-person singular/plural verbs during TMS of the motor cortex, but reported differences in the production of action-related words, regardless of grammatical category (e.g., the axe/to bite v the cloud/to adore).

Even though agreement on the underpinnings of the noun/verb distinction is only partial, mapping the processes underlying noun and verb production during surgery, and understanding the neural mechanisms underlying such distinction would be relevant to surgical teams. In fact, DES of brain sites that are more (or, selectively) involved in processing one or the other word type may increase the probability to detect functionally relevant tissue in the periphery of the tumor (Fernández Coello, Moritz-Gasser, Martino, Martinoni, Matsuda, & Duffau, 2013; Roux & Trémoulet, 2002; Rofes & Miceli, 2014). To support the relevance of this issue, in one of the few studies that used verbs intraoperatively, Lubrano et al. (2014) indicated that nouns and verbs may be represented in partially segregated networks. They compared the production of verbs in sentence context with that of object names, and found specific object naming sites in the temporal cortex and inferior frontal gyrus (IFG), and specific action naming sites in the IFG and posterior middle frontal gyrus (MFG). Similar data emerged from intraoperative studies that used non-finite verbs (e.g., to play, playing) (i.e., Bello et al., 2007; Corina, Gibson, Martin, Poliakov, Brinkley, & Ojemann 2005, Havas et al., 2015).

Knowledge gathered from studies on the cognitive neuroscience of nouns and verbs can be applied to construct or to refine assessment and treatment tools for patients with neurological damage, and to draw hypotheses on the sensitivity and specificity of brain regions involved in noun and verb processing (e.g., de Aguiar, Paolazzi, & Miceli, 2015; Vigliocco, Vinson, Druks, Barber, & Cappa, 2011). Neurosurgical studies are particularly useful to address these issues. In fact, the intraoperative sensitivity and specificity of DES in detecting functionally-relevant tissue are difficult to achieve preoperatively with non-invasive neuroimaging techniques, such as fMRI or TMS, due to aspects of the so-called brain shift such as drainage of cerebrospinal fluid, tissue swelling/damage, patient position, etc. (e.g., Nabavi, Stark, Dörner, & Mehdorn, 2012; Picht et al., 2013).

The neurosurgical approach to the intraoperative study of finite verb production (and of language mapping in general) may benefit from rigorous methodological approaches, in order to overcome some current limitations. A first step in this direction could be the systematic use of standardized tasks, developed specifically to meet the constraints of intraoperative mapping. So far, many potentially relevant results were obtained with home-made tasks, that are exposed to the influence of nuisance factors and therefore pose obvious problems of duplicability of results. Another resource could be provided by careful quantitative and qualitative analyses of the responses produced by patients during DES.

In the operating room, patients’ responses are typically scored dichotomously, and only general qualitative information is provided (but, see e.g. Hamberger & Tamny, 1999; Lubrano et al., 2014, for exceptions). A response produced correctly within 4 seconds (i.e., the maximum duration allowed for DES to prevent seizures Duffau, 2004; Kayama, 2012) is taken to indicate that the stimulated structure has no role in the function tapped by the task. By contrast, any response that differs from the target or is produced later than the allowed response time counts as an error, and is taken to show that the stimulated site plays a relevant role in the cognitive function under exam. More detailed error analyses could lead to a better understanding of brain-behavior relations and therefore to preventing functional damage during surgery.

Different types of incorrect responses can occur during intraoperative language mapping with both object and action naming, pointing to different underlying neurofunctional processes. For example, the fact that DES in the temporal lobe and/or along ventral associative pathways (e.g., the inferior fronto-occipital fasciculus, IFOF) may trigger whole-word errors (e.g., semantic paraphasias and failures to respond), has been taken to suggest that these brain structures are involved in lexical-semantic processes (e.g., Caplan, Vanier, & Baker, 1986; Caramazza, Papagno, & Ruml, 2000; Sarubbo et al., 2015). At segment-level errors (e.g., phonemic paraphasias) during DES of the prefrontal cortex and/or dorsal associative pathways (e.g., arcuate fasciculus, AF) may indicate that these latter structures play a role in retrieving and producing segmental information (e.g., Binder, Desai, Graves, & Conant, 2009; Hickok & Poeppel, 2007; Lubrano et al., 2014).

6.1.1. Aims and predictions

The present study evaluates the relevance of tasks that assess language in sentence context. We sought to identify cortical regions involved in the production of nouns and in the production of verbs in sentence context, using similar methods to recent studies (Corina et al., 2005; Herbet, Lafargue, Moritz-Gasser, Bonnetblanc, & Duffau, 2014; Lubrano et al., 2014). To provide sensitive and specific surgical mapping results, we administered tasks designed and standardized for awake surgery (Rofes, de Aguiar, & Miceli, 2015), performed a rigorous preoperative examination, looked for significant DES sites on individual subjects, and contrasted the results of each individual in a single-case series fashion. To complement the current literature, we also provided data on subcortical DES and a careful examination of error types.

Based on the current literature, we expected the DES condition to yield more errors as compared to the no-DES condition. DES may interfere more with finite verb production than with noun production, when delivered to the prefrontal cortex, as suggested by some DES, TMS and lesion studies (e.g., Cappelletti, Fregni, Shapiro, Pascual-Leone, & Caramazza, 2008; Lubrano et al., 2014, cf. Crepaldi et al., 2011; Hernandez-Pavon et al., 2014 for more distributed representations in neuroimaging studies). As regards error types, DES of cortical and subcortical regions corresponding to dorsal pathways (e.g., frontal and parietal cortices; AF) should elicit mainly phonological paraphasias, and DES of cortical and subcortical regions corresponding to ventral pathways (e.g., infero-mesial and infero-lateral temporo-occipital cortices; inferior-frontal occipital fasciculus, IFOF) should elicit mainly semantic paraphasias (Sarubbo et al., 2015, cf. Caplan et al., 1986; Caramazza et al., 2000, Lubrano et al., 2014). No specific predictions were formulated as regards anomias, since failure to name has been associated with damage to a largely distributed network including MFG, STG, IPL and corresponding subcortical sites (e.g., Lubrano et al., 2014; Rofes & Miceli, 2014; Sarubbo et al., 2015).

6.2. Methods

6.2.2. Participants

Six Italian-speaking, right-handed subjects with supratentorial tumors in the left hemisphere participated in this study. Subject characteristics and tumor variables are summarized in Table 6.1.

Table 6.1

Subject characteristics and tumor variables

	Age	Gender	Edu.	Job	Hand.	Grade	Type	Site
CRA	39	F	8	Homemaker	Right	II	Oligodendroglioma	Parietal (IPL)
CRO	70	F	13	Retired	Right	IV	Glioblastoma	Prefrontal (MFG)
MG*	63	M	17	Stock trader	Right	III	Oligodendroglioma	Prefrontal (SFG,MFG,IFG)
PR	41	M	13	Builder	Right	III	Astrocytoma	Prefrontal (FP, MFG)
SO*	45	M	8	Carpenter	Right	II	Oligoastrocytoma	Prefrontal (IFG, MFG)
TT	37	M	8	Builder	Right	III	An.astrocytoma	Prefrontal (SFG, MFG)

Notes. An. = anaplastic.; Hand.=handedness; Edu. = Education in years; FP = Fronto polar; IFG = Inferior frontal gyrus; IPL = Inferior parietal lobe; MFG = Middle frontal gyrus; STG = Superior temporal gyrus; *Subject had been previously operated at another institution.

6.2. Materials

A three-task intraoperative protocol was administered. It included an automated speech task (counting from 1 to 10) and two oral naming tests: an object naming task and a task that requires the production of finite verbs in a simple sentence context. Both tests are standardized and have been specifically designed for awake surgery procedures. In the object naming task, patients are asked to produce a noun and a determiner phrase (*Ecco la mela*; “Here [is] the apple”[7]). In the production of finite verbs, patients produce a pronoun and an action verb in the correct inflected form (*Lei abbraccia*; “She hugs”). In the finite verb production task, 74% of the agents are masculine (e.g. "He irons") and 26% are feminine (e.g., "She sings"). For a detailed description, see Rofes et al., 2015a. To minimize errors not triggered by DES, intraoperative tests were constructed with items and item-categories to which patients responded flawlessly before surgery. The following psycholinguistic contrasts were implemented in the experimental lists administered pre-operatively: frequent v non-frequent words; long v short words (in phonemes); biological v non-biological nouns (“apple” v “table”); instrumental v non instrumental verbs (“to sew” v “to jump”); manipulable v non-manipulable verbs (“to type” v “to jump”); verbs name-related to a noun v verbs not-name-related to a noun (“to brush” v “to sew”); regular v irregular verbs (“to play” v “to sing”); and transitive v intransitive verbs (“to cook” v “to walk”). These dimensions were considered in constructing the finite verb production task based on the evidence reported in the literature (for review, see Rofes & Miceli, 2014; Rofes et al., 2015a; Rofes et al., 2015b). All stimuli were selected based on the controls’ ability to respond correctly in 4 seconds. This is standard practice in awake surgery, as it indicates a safe DES time that triggers language errors reliably and with minimal risk of intraoperative seizures (e.g., Duffau, 2004; Kayama, 2012). A bipolar electrode delivering 4-second trains of DES (50~60Hz, 0.2msec) was used. The amperage of the stimulator ranged from 2.5-10mA.

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[7] This utterance is grammatical in Italian.

6.2.4. Procedure

An awake craniotomy was performed to expose cortical structures. Sterilized tags were placed in the periphery of the tumor. The counting task was administered to detect areas relevant to oral movements and to set the amperage of the stimulator. Patients were asked to respond to the two picture-naming tasks to reveal areas relevant for language production. The naming tasks were administered intraoperatively at least twice: for cortical and for subcortical DES. Each stimulus was presented for 4 seconds on a computer laptop. Areas where at least 2 out of 3 instances of DES triggered errors were considered relevant for language production and were not removed.

All surgical procedures (with the exception of subject PR's, see below) were video recorded to perform post-hoc quantitative and qualitative error analyses. Responses were counted as correct if the target item was produced within 4 seconds. Barnard’s tests were used to compare the number of correct/incorrect responses in the different conditions: DES v no-DES, object naming v finite verb production, by test and by area. This test is particularly powerful for data analysis in 2x2 contingency tables. We used one-tailed statistics because we expected that DES would interfere with performance, and therefore that the number of correct responses in the DES condition would be lower. The types of errors observed during DES were also noted (e.g., anomia, phonological paraphasia, fragment, semantic paraphasia, latency, morpho-syntactic error). Stimulated areas were discussed with the neurosurgeon on the basis of sulcal and gyral anatomy (e.g., SFG, MFG, IFG, etc.). A similar methodology has been reported in the literature (e.g., Lubrano et al., 2014; Herbet et al., 2014).

6.3. Results

6.3.1. Quantitative analyses

In pre-operative assessments, none of the potentially relevant psycholinguistic dimensions (e.g., frequency, word length, semantic category, instrumentality, transitivity, etc.) significantly constrained performance in any participant (Table 6.2). Therefore, all categories were used for intraoperative testing, and for each category only the items to which patients had responded incorrectly in the preoperative assessment were eliminated from intraoperative mappining.

Table 6.2

Preoperative differences in psycholinguistic dimensions (subsets)

		CRA	CRO	MG	PR	SO	TT
Nouns	Bio_Sub	FE=0,476	FE=0,737	FE=1,000	FE=1,000	FE=0,604	FE=1,000
	Frequency	FE=1,000	FE=0,741	FE=0,342	FE=1,000	FE=0,342	FE=0,605
	Length	FE=0,738	FE=0,065	FE=0,346	FE=1,000	FE=1,000	FE=1,000
Verbs	Tr_Sub	FE=0,459	FE=1,000	FE=0,233	FE=0,489	FE=1,000	FE=1,000
	Reg_Sub	FE=1,000	FE=1,000	FE=1,000	FE=1,000	FE=0,484	FE=0,226
	NRN_Sub	FE=0,576	FE=0,153	FE=1,000	FE=0,471	FE=1,000	FE=1,000
	MN_Sub	FE=1,000	FE=0,088	FE=0,490	FE=1,000	FE=1,000	FE=0,189
	Length	FE=0,349	FE=0,258	FE=1,000	FE=1,000	FE=1,000	FE=1,000
	Frequency	FE=1,000	FE=1,000	FE=0,485	FE=1,000	FE=0,485	FE=1,000
	Inst_Sub	FE=0,666	FE=1,000	FE=0,234	FE=1,000	FE=0,489	FE=1,000

Notes. FE = Fisher's Exact Test for count data, p-value. Biol = biological v non-biological entities ("apple" v "table"); Frequency = frequent v non-frequent words; Length = long v short words (in phonemes); Inst = Instrumental v non instrumental verbs ("to sew" v "to jump"); MN= Manipulable v non-manipulable verbs ("to type" v "to jump"); NRN = Name related to a noun v non-name related to a noun ("to brush" v "to sew"); Reg. = Regular v non-regular verb ("to sing" v "to play"); Tran. = Transitive v intransitive verb ("to cook" v "to walk"). Each of the subsets is explained in Rofes et al. 2015b.

Intraoperative results for the different conditions are reported in Table 6.3. Figure 6.1 shows the brain areas where a statistical difference was found between the number of correct and incorrect responses during DES with object naming, production of finite verbs, or both. DES-positive cortical sites are reported in Figure 6.1A, subcortical DES sites in Figure 6.1B.

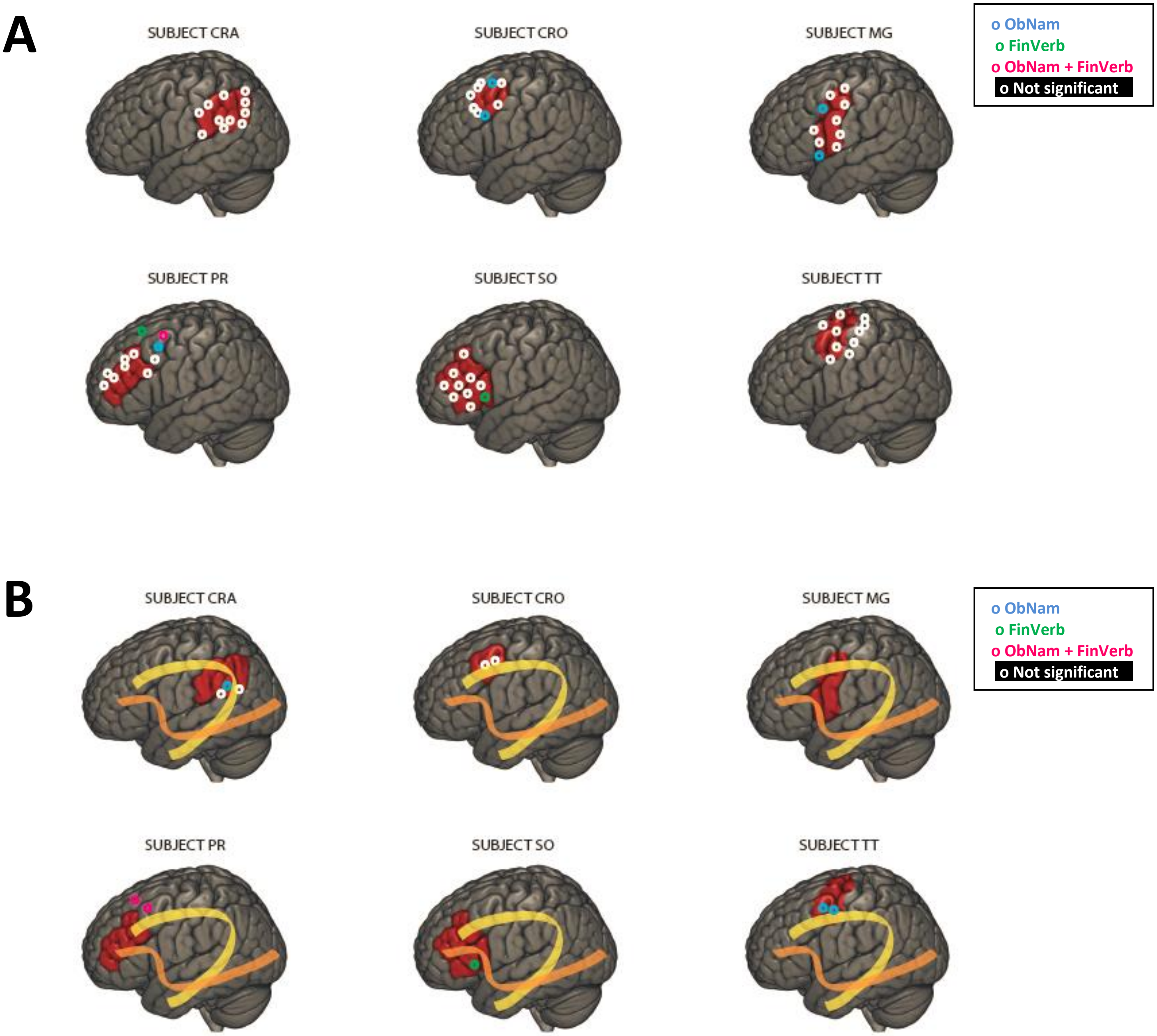

Figure 6.1. Significant DES sites per subject. A = cortical, B = subcortical. The number of stimulations is higher during cortical than subcortical DES in subjects CRA (68 v 17), SO (56 v 25), and TT (44 v 25). Cortical and subcortical stimulations were equal for CRO (14). Subcortical DES was not performed to MG. The number of stimulations could not be counted in PR.

Subject CRA produced no errors in 32 stimulations during object naming (henceforth, 0/32 errors, where the numerator indicates the total number of errors and the denominator the total number of stimulations per test) and 9/36 errors in the production of finite verbs. The difference between the DES condition for objects and finite verbs was significant (Wald=2.752; Nuisance=0.414; p=0.003*). CRA produced a significantly greater number of errors during the DES v no-DES condition at the subcortical level (7/10 v 3/31, Wald=2.646; Nuisance=0.112; p=0.006*). Object naming triggered a significant number of errors during subcortical DES, possibly in the posterior part of the arcuate fasciculus (3/7 errors, Wald=1.922; Nuisance=0.223; p=0.037*). Mapping with the finite verb task fell just short of significance, at the subcortical level (4/10 errors; Wald=1.922; Nuisance=0.111; p=0.051).

In subject CRO, mapping with the finite verb task was not possible due to the large number of spontaneous errors (5/12) produced in the absence of DES. In object naming, this subject produced more object naming errors during DES as compared to no-DES (6/8 v 1/20 errors, Wald=2.556, Nuisance=0.223; p=0.006*). This was particularly obvious following DES in the middle part of the MFG (3/4 errors; Wald=3.122; Nuisance=0.131; p=0.001*) and in the posterior part of the MFG (3/3 errors; Wald=3.521, Nuisance=0.182; p=0.001*), which also corresponded to a face motor area, as indicated by intraoperative motor mapping. No significant differences were observed during subcortical mapping.

Subject MG produced 0/11 errors during DES with finite verbs, and 7/33 errors during object naming. Error rate was greater in the DES than in the no-DES condition (Wald=4.062; Nuisance=0.061; p=0.001*), specifically for object naming (Wald=3.485; Nuisance=0.091; p=0.001*), and in the middle part of the IFG (3/11 errors; Wald=3.766; Nuisance=0.021; p=0.001*), the middle and posterior parts of the MFG (2/8 errors; Wald=3.503; Nuisance=0.041; p=0.003*; and 2/5 errors; Wald=4.311; Nuisance=0.031; p=0.002*, respectively). DES was applied three times to 2 subcortical areas corresponding to the middle and posterior MFG. The patient produced errors in 2 of 3 stimulations for a total number of 10 verb picture stimuli.

However, MG failed to respond to 3 stimuli in the no-DES condition. Therefore, the mapping procedure was interrupted.

Subject PR produced errors to both objects and finite verbs when DES was delivered to the dorsal premotor cortex, anterior to an area in the superior motor cortex where motor hand movements were affected. Object naming errors were only detected when DES was delivered to an area of prefrontal cortex anterior to the mouth area in the middle part of the premotor cortex. Errors with finite verbs were only detected when DES was delivered to a posterior part of the SFG. During subcortical DES, errors were elicited with both tasks, possibly when stimulating subcortical areas corresponding to the posterior part of the MFG and SFG. These areas were deemed significant for language processing, as errors were elicited 2/3 times during DES. It was not possible to run statistical analyses on the mapping data of this participant, as a full video of the surgical procedure could not be acquired.

Subject SO produced a significant number of errors when DES was applied to the IFG (pars opercularis), during the production of finite verbs in sentence context (2/9 errors; Wald=3.263, Nuisance=0.122; p=0.004*). In the same area, results of DES during object naming did not reach significance (2/4 errors; Wald=1.511, Nuisance=0.131; p=0.091). A significant number of errors was obtained during DES, particularly with finite verbs, in a subcortical area corresponding to the most anterior-medial part of the insula, possibly corresponding to the IFOF (2/3 errors; Wald=2.653, Nuisance=0.152; p=0.014*).

Subject TT produced a significant number of errors during object naming when subcortical DES was applied (4/13; Wald=2.267; Nuisance=0.0454; p=0.013*), particularly in two subcortical areas corresponding to the MFG, close to the premotor cortex: one posterior (3/3;

Wald=4.141; Nuisance=0.161; p=0.001*) and one inferior-posterior (1/3 errors; Wald=2.216; Nuisance=0.1212; p=0.033*). No significant differences were observed at the cortical level.

Table 6.3

Individual comparisons per condition.

		CRA	CRO	MG	SO	TT
Cortical	S v NS	W=0.449 Np=0.021 p=0.374	W=1.288 Np=0.04 p=0.167	W=4.062 Np=0.061 p=0.001*	W=1.569 Np=0.969 p=0.078	W=0.101 Np=9.969 p=0.494
	S Obj v NS Obj	W=0.386 Np=0.949 p=0.397	W=2.556 Np=0.223 p=0.006*	W=3.485 Np=0.091 p=0.001*	W=0.846 Np=0.939 p=0.218	W=0.208 Np=0.929 p=0.454
	S Fv v NS Fv	W=0.657 Np=0.031* p=0.321	NA	W=1.191 Np=0.031 p=0.178	W=0.902 Np=0.02 p=0.272	W=0.267 Np=9.929 p=0.449
	S Obj v S Fv	W=2.75 Np=0.414 p=0.004*	NA	W=1.103 Np=0.888 p=0.167	W=0.687 Np=0.08 p=0.317	W=0.716 Np=0.04 p=0.307
Subcortical	S v NS	W=2.646 Np=0.112 p=0.006*	W=0.522 Np=0.07 p=0.392	NA	W=3.821 Np=0.141 p=0.001*	W=1.094 Np=0.021 p=0.218
	S Obj v NS Obj	W=1.922 Np=0.223 p=0.037*	W=0.522 Np=0.07 p=0.392	NA	W=1.654 Np=0.394 p=0.091	W=2.267 Np=0.454 p=0.013*
	S Fv v NS Fv	W=1.771 Np=0.112 p=0.051	NA	NA	W=3.442 Np=0.192 p=0.002*	W=0.716 Np=0.939 p=0.277
	S Obj v S Fv	W=0.127 Np=0.787 p=0.492	NA	NA	W=0.422 Np=0.323 p=0.418	W=0.716 Np=0.939 p=0.277

Notes. Statistics per individual area are reported in the results. S = DES, NS = no-DES; Obj = object naming; FV = production of finite verbs in sentence context. Wald = Wald statistic, Np= Nuisance parameter, p= p-value (two-tailed).SFG = Superior frontal gyrus, MFG = Middle frontal gyrus; IFG = Inferior frontal gyrus; STG =Superior temporal gyrus; MTG = Middle temporal gyrus; ITG = Inferior temporal gyrus; IPL = Inferior parietal lobe. NA = Not applicable because DES in one of the conditions was not possible. Statistical analyses were not possible for patient PR. Significant results per area are indicated in text.

6.3.2. Error analyses

The cortical (6.2A) and subcortical (6.2B) location of the various types of error produced by each subject are indicated in Figure 6.2.

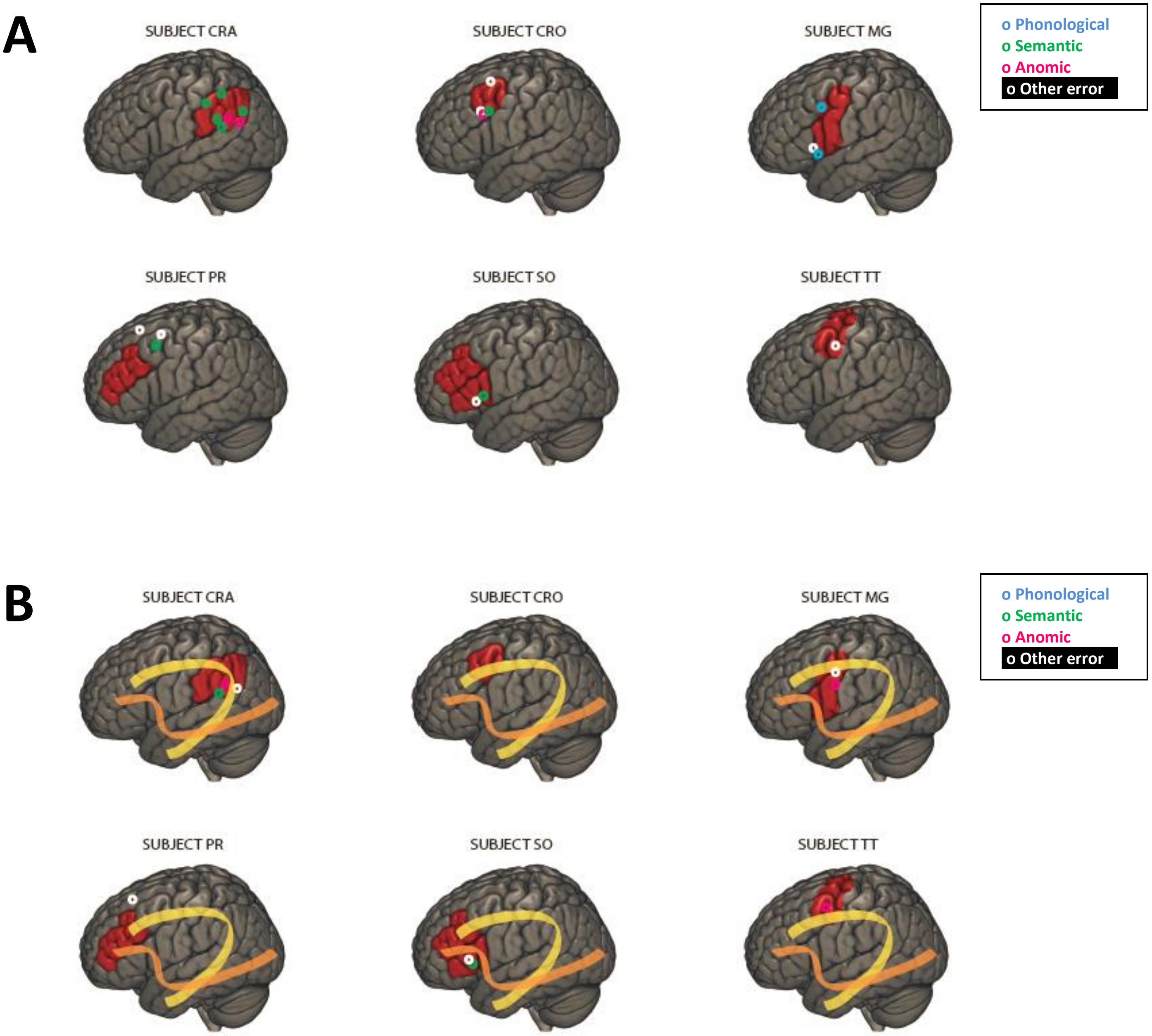

Figure 6.2. Error types during DES per subject. A = cortical, B = subcortical. The number of stimulations is higher during cortical than subcortical DES in subjects CRA (68 v 17), SO (56 v 25), and TT (44 v 25). Cortical and subcortical stimulations were equal for CRO (14). Subcortical DES was not performed to MG. The number of stimulations could not be counted in PR.

Subject CRA asked for a break when responding to the test with finite verbs, while this did not happen while responding to object naming. She produced 5 semantic paraphasias in 32 stimulations (henceforth, 5/32 semantic paraphasias, where the numerator indicates the number of specific errors and the denominator indicates the total number of stimulations per test) and 3/32 anomias when the finite verb production task was administered during cortical DES. Subcortical DES elicited 2/7 semantic paraphasias and 1/7 unrelated word for object naming, and 2/10 semantic paraphasias and 4/10 anomias during the production of finite verbs.

Subject CRO produced 4/7 latencies (i.e., responses produced beyond the allowed, 4-second limit), 1/7 fragment, 1/7 anomia, and 1/7 semantic error ("*hammer*" for "*cherry*"), when stimulated in the MFG during object naming. No stimulation was applied during the finite verb production task, due to the high number of spontaneous errors (i.e., 7/12 errors), most of which were lexical-semantic: 3 anomias, 2 semantic paraphasias, 1 change of category ("*He lion*" for "*He roars*"), and 1 noun-centered circumlocution in response to a lexical verb (i.e., "*She does gymnastics*" for "*She jumps*").

Subject MG produced phonological errors during cortical DES with object naming: 4/33 fragments (e.g., "*Ecco il pf peperone" "Ecco il po peperone"* for "*Here [is] the bell pepper"*), 2/33 phonological paraphasias (e.g., "*Ecco il cia caccivite* [target: *cacciavite*] for "*Here [is] the screwdriver*"), and 1/33 part/whole error ("*Here* [is] *the foot*, for "*Here* [is] *the leg*"). DES in the subcortical areas corresponding to the middle premotor cortex induced 1/3 anomia and 1/3 fragment (*"Lui stra…"* for *"Lui strappa"*, he tears).

As for subject PR, we cannot provide error counts, as only a partial video of the surgery was available. This subject produced latencies and semantic paraphasias (e.g., "*onion*" for "*tomato*") when DES was delivered to the middle premotor cortex, during object naming.

Semantic errors and anomias were observed in object naming during subcortical DES. During cortical DES of the SFG, production of finite verbs yielded responses in which the correctly produced introductory pronoun was followed by an anomia (i.e., "*He*…" instead of "*He jumps*"). During subcortical DES of the same region, perseverative errors on the verb emerged, along with difficulty on pronoun gender (e.g., "*He…, he she combs, he combs, he she combs, he combs*" for "*She combs*).

Subject SO produced 1/6 latencies to finite verbs, and 2/6 latencies and 1/6 semantic paraphasias (i.e., guitar for violin) to object names, when DES was delivered to the IFG. During subcortical DES to an area corresponding to the IFG (possibly involving the IFOF, before it turns medially to the caudate nucleus), he produced 1/1 fragment (i.e., *ca…* for *carciofo*, artichoke) during object naming. During finite verb production, errors resulted in 1/3 change of category ("*He hair.$_{noun}$*" for "*He listens.$_{verb}$*"), and 1/3 error resulting in incorrect pronoun gender followed by a semantic paraphasia (i.e., "*She writes*" for "*He licks*").

Subject TT complained of problems with his eyes, arm/hand, and face during DES in the posterior part of the IFG and MFG, close to the premotor cortex (i.e., "I cannot see", "I cannot keep my eyes still"; "I cannot move the arm/hand", "I did not feel it"; "I cannot feel my face"). He produced 2 errors during cortical DES (1/25 anomia during object naming and 1/19 latency during the production of finite verbs), and 5 anomic errors during subcortical DES in an area corresponding to the posterior part of the MFG, close to the premotor cortex (3/3 during object naming and 2/7 during the production of finite verbs).

6.4. Discussion

We carried out quantitative and qualitative analyses of the performance on spoken production tasks in patients undergoing awake surgery for the removal of supratentorial tumors in the left, language-dominant hemisphere. We administered an automated speech task (i.e., counting from one to ten) and two overt picture-naming tasks (i.e., object naming and production of finite verbs in sentence context). Test items for intraoperative use were selected for each individual so as to minimize spontaneous errors during surgery. We assessed whether significant differences emerged when DES was applied as compared to when it was not applied, when DES was used during object naming as opposed to finite verb production (regardless of DES site), and when DES was directed to specific perisylvian areas. In all subjects, brain sites relevant for the production of object names, of finite verbs, or of both were detected. This is in agreement with studies in which DES allowed the mapping of language processes (e.g., Ojemann & Mateer, 1979), and also with more recent investigations, specifically focused on noun and verb production (e.g., Bello et al., 2007; Corina et al., 2005, Havas et al., 2015; Lubrano et al., 2014). Critical DES sites and errors partially agreed with the current literature.

6.4.1. DES v no-DES (collapsing across nouns and verbs)

Three of five subjects showed significant differences between the DES and the no-DES condition. Subject MG showed differences when DES was delivered to cortical sites, and subjects CRA and SO during subcortical DES. The figures entered in this contrast correspond to the sum total of correct and incorrect responses, collapsed across word types, tasks and brain sites. Therefore, the fact that 2/5 subjects (CRO and TT) did not show significant differences between the two conditions does not indicate that DES failed to map language areas in these patients. Rather, it stresses that significant differences between correct and incorrect responses are found only when DES is delivered to a specific brain site, and during a specific cognitive task – hence, that language mapping in the brain requires that an appropriate task be selected to map the brain site under investigation (e.g., Fernández-Coello et al. 2013, Rofes & Miceli, 2014). In our sample, this is indicated by subjects CRA and CRO (Table 6.3.). In these two subjects, no differences were observed between the cortical DES and no-DES conditions when data were collapsed across tasks, but a significant difference appeared during finite verb production (CRA) and during object naming (CRO), respectively.

From a methodological standpoint, the mere figures of the incidence of correct and incorrect responses across cumulated tasks in the DES v no-DES condition may be misleading. Results may be biased, as performance may be affected by several factors, such as task difficulty (i.e., one task may be intrinsically more difficult than the other and trigger errors that are not related to DES), order of task administration (i.e., the second task may trigger more errors than the first, because by the time it is administered the patient is more tired), brain site stimulated (i.e., one of the two tasks may trigger more errors than the other in a specific brain area), etc. Therefore, regardless of the results of this comparison, looking at differences between tasks and across brain sites provides more relevant information than collapsing across nouns and verbs.

6.4.2. Object naming and finite verbs (independently of stimulation site)

Data confirm that DES resulted in more incorrect responses than the no-DES condition, at the cortical and/or at the subcortical level. Subjects CRO and MG produced more errors in object naming during cortical DES. Subjects CRA and TT showed the same effects during subcortical DES. Subject CRA produced significantly more errors to finite verbs than to nouns when DES was applied at the cortical level, even though no differences between specific brain sites were observed. Subject SO showed the same tendency during subcortical DES, but the number of stimulations was too small to allow strong conclusions.

These results show that neither the object naming task nor the finite verb production task is by itself more or less appropriate for language mapping, as in different subjects one or the other can be disproportionately impaired, regardless of DES site. However, the same observation shows that a finite verb production task does allow the detection of language areas that are not responsive during object naming. Therefore, the combination of the two tasks during awake surgery provides a more adequate language map during DES than object naming alone. In our study, as in others (e.g., Havas et al., 2015; Lubrano et al., 2014), using two intraoperative tasks did not noticeably increase fatigue in the patient, nor the time needed to complete surgical procedures, as compared to object naming alone.

Differences between naming objects and producing finite verbs may be difficult to document in patients who are operated awake, as these subjects typically suffer from mild deficits and the items administered during surgery are those they named correctly in the preoperative assessment. This latter point raises the question of whether patients who score below the norm before surgery already should be considered for awake surgery. This issue is relevant, because functional language areas cannot be detected during fully asleep surgeries, and because subjects who currently are not operated awake may still benefit from an awake procedure, if intraoperative items are selected carefully. In the present study, the problem arose with CRO, who performed below the norm on both finite verbs (53% correct) and objects (70% correct) before surgery. Since her tumor affected the posterior part of the MFG, the awake surgery protocol was applied in order to spare as much critical tissue as possible. The intraoperative use of finite verbs to map language in the brain was ruled out, because during surgery CRO produced 7/12 errors on verbs in the no-DES condition. However, language was successfully mapped by administering the object naming task. Two areas relevant for object naming were mapped in MFG, which would not have been detected if the patient had undergone a fully asleep surgery. One week after surgery, CRO's scores in object naming were similar to those obtained in preoperative assessments object naming (70% v 76% correct, Barnard's test z=0.527, p=0.263 one tailed), whereas a significant decline was observed on finite verbs (53% v 29% correct, Barnard's test z=2.924, p=0.001 one-tailed), which had not been presented during surgery. In our view, observations like this invite to increase efforts aimed at finessing the interpretation and exploitation of preoperative results, so as to set up the best possible intraoperative mapping (i.e., one that allows to map language in a minimal time even in the presence of abnormal baseline performance on language tasks).

6.4.3. Object naming and finite verbs (by stimulation site)

The cortical sites where object naming or finite verb production triggered a significant number of errors were highly variable, and in partial agreement with available lesion data (e.g., Kemmerer et al., 2012; Lubrano et al., 2014; Mätzig et al., 2009; Pillon & d'Honichtun, 2011; Rofes & Miceli, 2014; Rofes et al., 2015b). For example, patients in Lubrano et al. (2014) produced more errors when DES was applied in posterior areas of the MFG and SFG during finite verb production than during noun production. In subjects CRO and MG, significant areas were found only during object naming. They were distributed across different sites in the posterior part of the inferior, middle, and superior frontal gyri. In subject SO, a significant language site was found only in the pars opercularis of the IFG during DES with finite verbs. In subjects CRA and TT, no significant DES sites were found during cortical DES with either language task. In subject PR, an area in the SFG could only be mapped during finite verb production, and a posterior area of the MFG elicited errors to both object names and finite verbs. Even though no specific area could be systematically tied to object naming or to finite verb production, our results confirm that nouns and verbs may be represented in partly separable neural substrates. In two subjects, only one task was affected during DES – object naming in CRA, finite verb production in MG. In subject PR, cortical DES to the dorsal premotor cortex yielded comparable results in the two tasks, but DES anterior to the middle motor cortex only interfered with object naming, whereas DES to the posterior part of SFG yielded errors in verb naming only.

Observations collected during subcortical DES are variable and do not show a specificity for object naming or finite verb tasks. Two subjects could not be mapped at all; CRA and TT could be mapped only during object naming; SO only during finite verb production, and PR during both tasks. One of the reasons for these less-than-satisfactory results is that subcortical DES is typically less exhaustive than cortical DES. When it is started, surgery has been underway for a long time already – the patient has undergone cortical DES with language monitoring during tumor resection, and is likely to be tired. Consequently, fewer brain sites can be stimulated and fewer data points can be obtained. In our sample, more sites were stimulated during cortical than subcortical DES in subjects CRA (68 cortical v 17 subcortical), SO (56 v 25), and TT (44 v 25) and the same number was stimulated in CRO (14). Only 3 subcortical stimulations were applied to MG, due to a sudden cluster of anomias in the no-DES condition, possibly due to tiredness; and stimulated sites could not be counted in PR.

At a more theoretical level, it is worth asking to what extent the fact that we used picture naming paradigms to elicit nouns and finite verbs may have influenced results. In an object naming task, the stimulus picture typically represents the corresponding object (e.g., an apple). In verb naming tasks, however, representing the to-be-named action often imposes constraints that may influence results. For example, representing the stimulus “to roar” involves a picture that includes an agent (e.g., a lion) who is performing that action. Responding “roars” requires not only selecting the target action word but also inhibiting the production of the name “lion”. In other words, executive control mechanisms must inhibit noun selection and focus on verb retrieval, to allow producing the target verb. When these mechanisms are interfered with by DES, patients may produce errors such as those of subject CRO who said “*He lion*” for “*He roars*”, or of subject SO who produced “*He hair*” for “*He listens*”. To circumvent these problems, one may choose to only use pictures of actions that do not include objects. This could be accomplished by selecting only stimuli that represent non-manipulable nouns and verbs (e.g., Saccuman et al., 2006), or by deleting objects from the action drawings that may require them (e.g. deleting or blurring the ball in the image corresponding to the verb "to kick"). Another possibility is to use paradigms based on naming to oral description (e.g., Hamberger & Tamny, 1999). In this latter case, pictorial constraints are bypassed and the sentence describing the action may still include an agent/object (e.g., the stimulus sentence for the verb “to kick” could be “To strike with one’s foot”).

6.4.4. Error analyses

Anomias, fragments, and latencies were detected across subjects, during DES of the IFG and MFG. DES of the IFG also elicited pronoun gender errors (e.g., "*She combs*" for "*He combs*"), while DES of the MFG triggered phonological and semantic paraphasias. DES of the SFG triggered perseverations and change of pronoun gender, and DES of the IPL yielded anomic and semantic errors. Subcortical DES elicited anomias in all cases. These resulted in failures to respond altogether, or in responses that included only the determiner in object naming (i.e., "The…") or only the pronoun in finite verb production (i.e., "She…"). In subcortical areas corresponding to the IFG and MFG, phonological errors and fragments were elicited. Semantic paraphasias occurred during DES of subcortical areas corresponding to the IPL. DES of segments of the arcuate fasciculus elicited anomic errors in CRA and MG, and TT.

The current literature hypothesizes that dorsal networks are putatively more critical for phonological processing and ventral networks for semantic processing (e.g., Binder et al., 2009, Hickok & Poeppel, 2007; Sarubbo et al., 2015). In agreement with these claims, we found phonological errors when DES was applied to dorsal structures (e.g., to the posterior part of the MFG in subject MG), and semantic errors when DES was delivered to ventral structures (e.g., to the anterior part of the IFOF in subject SO,). Based on our overall data set and on the current literature, however, such a distinction is either too sharp or very difficult to replicate in neurosurgical studies. For example, stimulation to the prefrontal cortex elicited semantic errors in subjects CRO, PR, and SO. Similar results were found in a recent meta-analysis Sarubbo et al., 2015). Furthermore, although posterior temporal areas were not stimulated in our study, DES in the posterior part of the MTG elicited more phonemic than semantic paraphasias (Lubrano et al., 2014), and diffuse temporal lobe damage has already been reported to trigger phonological errors in the absence of semantic errors (subject DM, Caramazza et al., 2000).

The occurrence of semantic paraphasias in CRA during DES of the IPL is also at variance with some current observations. For example, DES of dorsal pathways elicited mainly phonological paraphasias (e.g., Sarubbo et al., 2015), and lesions extending to the posterior part of the arcuate fasciculus can yield phonological errors in the absence of semantic errors (e.g.

Caplan et al., 1986, Caramazza et al., 2000). In addition, Lubrano et al. (2014) reported 3/3 phonological paraphasias but no semantic paraphasias, during DES of the supramarginal gyrus in the course of object naming and action naming. Having said that, semantic errors during IPL stimulation were described in other surgical mapping studies (for review, Rofes & Miceli, 2014). These errors may be due to the involvement of the IPL in semantic processing, as suggested by neuroimaging studies (Binder et al., 2009).

Anomic errors were ubiquitous. They occurred following cortical and subcortical DES regardless of task and of brain site, in accordance to other studies (e.g., Rofes & Miceli, 2014; Sarubbo et al., 2015). This was probably because failure to name a stimulus may result from an impairment of lexical and/or semantic knowledge, and therefore result from damage to a widespread neural substrate (Gainotti et al., 1986). Finally, pronoun gender errors are difficult to interpret. They could be artifactual, and result from a list bias, since 52/70 targets in our verb task are masculine. This could be the case in subject PR, who produced a masculine pronoun instead of the feminine target (i.e., "*He combs*" for "*She combs*"). However, this account is unlikely in subject SO, who produced the reverse error type (a feminine pronoun instead of a masculine pronoun), perhaps due to a genuine difficulty with pronoun selection. Clearly, more observations are needed to reliably interpret this observation.

6.5. Conclusion

An approach based on an object naming task and a finite verb production task allows the assessment of language production, within a safe time frame. Furthermore, it allows a more thorough mapping of the brain in patients with perisylvian gliomas than an object naming task alone. In subject SO, finite verb production was successfully used to map language function at the cortical and subcortical levels, when object naming provided null results. In subject PR, it allowed the identification of language function in the SFG and MFG, and during subcortical DES. Errors varied across patients and were in partial agreement with the current literature. Further work should be directed at carrying out exhaustive neurocognitive diagnoses in subjects who are being considered for awake procedures, and at achieving a fine-grained understanding of preoperative results – patients who present with preoperative language deficits may still benefit from awake surgery. Current standards in language mapping during awake surgery can be steadily improved by interactions between neurosurgery and the neuroscience of language, and by the development of new, standardized tools.

Chapter 7
General discussion

This dissertation aimed to contribute to the effort to include current knowledge from aphasiology, neurolinguistics, and cognitive neuroscience in the practice of awake surgery. Awake surgery is a surgical procedure applied to people with brain tumors or pharmacologically intractable epilepsy (Berger, 1996; Duffau et al., 1999; Hunke, Van de Wiele, Itzhak, & Rubbinstein, 1998; Ojemann & Mateer, 1979). As the term implies, patients are kept awake during surgery, so that they can perform language tasks during electrical stimulation of cortical and subcortical brain structures (Bello et al., 2007; Benzagmout, Gatignol, & Duffau, 2007; Duffau et al. 2003; Ojemann, Ojemann, Lettich, & Berger, 1989; Skirboll, Ojemann, Berger, Lettich, & Winn, 1996). If the patient can respond correctly to a language stimulus when an electrical pulse is applied to the brain, it is concluded that the stimulated area is not relevant for that language function, and therefore, can be safely removed without inducing postoperative language deficits (cf. Borchers, Hummelbach Logothetis, & Karnath, 2011; Desmurguet, Bonnetblanc, & Duffau, 2013). By contrast, when the application of electrical pulses to the brain repeatedly triggers errors, this is taken as an indication that the area is critically involved in the language skills probed by the task, and therefore should not be removed, as this would result in postoperative language deficits (e.g., Penfield & Boldrey, 1937; Ojemann & Mateer, 1979, Duffau, 2004).

One impetus for this dissertation was the lack of tasks and standardized materials available for and used in the assessment of people with brain tumors (e.g., Finch & Copland, 2014; Połczyńska 2009; Rofes & Miceli, 2014). Object naming is in many cases the only task used for intraoperative language mapping, and one of the few tasks regularly used to assess language deficits before or after surgery (for a review see De Witte & Mariën, 2013). However, object naming tasks are not sufficient for thorough intraoperative testing. This is for several reasons: despite object naming being intact other language abilities can be impaired (Santini et al., 2012; Satoer et al., 2014; e.g., verb production can be impaired, Caramazza & Hillis, 1991); object naming tasks do not assess some everyday language processes such as sentence formation, reference to action, or to moments in time (e.g., Vigliocco et al., 201); and nouns and other word categories, such as verbs may be partially segregated in the brain (e.g., Mätzig et al., 2009, Kemmerer et al., 2012).

In addition, language skills are often evaluated using informal assessments. However, failure to control for critical psycholinguistic variables that may constrain performance may yield results that are difficult to interpret. Consequently, we developed a new set of standardized tasks for awake surgery. Such tasks may contribute to improving the sensitivity of intraoperative language mapping, as well as that of preoperative and postoperative assessments in this population. The novelty of the tasks we proposed is that they are standardized; controlled for linguistic variables that affect the performance of people with aphasia; validated in people with aphasia; and have been compared to current tests used in awake surgery.

We argued that tasks thus constructed allow the examiner to obtain better control over the patient's performance, and ultimately help the neurosurgeon to reach their goals – more extensive tumor removal whilst ensuring preservation of language skills (e.g., De Witt Hammer et al., 2012; Sanai & Berger, 2009). Furthermore, information obtained with these tasks, and for example with the administration of object naming and a new task before, can contribute to more accurate language assessments before and after surgery. Moreover, it may lead to a better understanding of the neural underpinnings of language: through the use of controlled language tasks in people with brain tumors, it may be possible to replicate results obtained in other lesion studies, as well as in work from aphasiology and neurolinguistics (e.g., Anderson, Damasio, & Tranel, 1990; Havas et al., 2015; Lubrano, Filleron, Démonet, & Roux, 2012; Moritz-Gasser & Duffau, 2013).

In this thesis we focused on the role of production tasks using finite verbs and the evaluation of their ability to assess language processing in comparison with the current gold standard (i.e., object naming). As a preliminary step in the development of novel, controlled object and verb production tasks, we critically reviewed the literature twice. First, we discussed published studies that proposed intraoperative tasks requiring the production of verbs in isolation and in sentences, and we graphically represented the stimulation sites and error types that were reported in each study (Chapter 2). Subsequently, we reviewed the tasks reported as used intraoperatively, and discussed the advantages and disadvantages of each from a cognitive and neurolinguistic perspective (Chapter 5). With this information in mind, we constructed and validated two naming tasks for native speakers of Italian undergoing awake surgery – an object naming task and a finite verb production task (Chapter 3). We administered the finite verb production task and other picture naming tasks to subjects with post-stroke aphasia, to establish which tasks showed the strongest correlation with communicative abilities in daily life (Chapter 4). Also, we introduced and compared our standardized finite verb task in the operating theatre and compared it with an object naming task (Chapter 6).

In this final section we discuss the results obtained in this dissertation with a focus on theoretical and clinical issues of importance in awake surgery.

8.1. Applying language knowledge to functional neurosurgery

Chapters 2 and 5 included a review of the seminal work by Penfield in the 1930-40s, Ojemann, and Mateer in the 1970-80s, and more contemporary work of figures such as Berger, Bello, Duffau and Démonet. With few exceptions (e.g., Fernández Coello, Moritz-Gasser, Martino, Martinoni, Matsuda, & Duffau, 2013; Sanai, Mirzadeh, & Berger, 2008; Zemmoura, Herbet, Moritz-Gasser, & Duffau, 2015), contemporary practice in awake surgery focuses on production tasks, rather than comprehension or verification tasks. This approach is understandable from a neurosurgical perspective. In the most widely used production task (i.e., object naming), the patient is asked to produce the name of an object, thus providing the neurosurgeon and the neuropsychologist/clinical linguist with direct feedback on language abilities while surgery is carried out. Long response latencies, failures to respond, semantic or phonemic paraphasias, etc., all provide clear indication that linguistic skills are being interfered with.

Comprehension and verification tasks are less demanding than overt production tasks, as the patient is not required to speak. For example, in the Pyramids and Palm Trees Test (Howard & Patterson, 1992), patients see a stimulus picture/word and are asked to point to one of two pictures/words (a semantically related and a semantically unrelated alternative). In addition, in such comprehension tasks a correct response can be produced even if knowledge of the item under scrutiny is not entirely spared. For example, for an image of two hands, given the choice between a pair of gloves and a pair of shoes, the subject may respond correctly either because he knows what gloves are, or because he does not know what gloves are, but knows that shoes are not worn on hands. Furthermore, due to the intraoperative setup, only the person assessing language can see the response of the patient, whereas the neurosurgeon cannot. This may render intraoperative comprehension tasks more cumbersome to administer and interpret, while also being less sensitive to language impairments.

As discussed in Chapters 2 and 5, and noted above, of the tasks proposed for intraoperative use, object naming is the most frequently implemented in regular practice, and the one regarded as best practice (i.e., the gold standard). The central role assigned to object naming accrues from the fact that producing the word that corresponds to a visually-presented object engages a number of cognitive and linguistic processes (e.g., Coltheart 2001; Whitworth, Webster, & Howard, 2005). It requires the ability to obtain an abstract structural representation of the stimulus, to retrieve its meaning representation and the corresponding phonological lexical information, and to program and produce the corresponding string of sounds. Since damage to any of these stages is very likely to have a disruptive effect on language production and/or comprehension (e.g., Goodglass & Wingfield, 1997), identifying the brain structures involved in these processes is necessary in order to prevent permanent post-operative damage. However, in this context an important contribution of chapters 2 and 3 to the current literature is the argument that object naming may not provide a sufficiently comprehensive evaluation of language skills, and therefore may not be sufficient to avoid language impairment during surgery.

Applying current knowledge from neurolinguistics, aphasiology, and cognitive neuroscience to tasks used during awake surgery entails spelling out the language processes engaged by each task and their neural correlates. This preliminary step should allow a principled, pre-operative evaluation of the benefits accruing from the use of a specific task in opposition (or in addition) to others. In this context, asking a patient to produce a noun when seeing a picture of an object, or a verb when seeing a picture of an action may seem to require very similar processes. This is because, *prima facie*, and regardless of the specific functional architecture of the language system (for contrasting views see, for example, Caramazza, 1997 and Levelt, 1989), both tasks involve understanding the pictorial stimuli, accessing their meaning, finding the corresponding lexical form, and articulating it correctly. However, when the two tasks are considered more carefully from a neurolinguistic perspective, clear distinctions emerge.

Verbs, and particularly verbs in sentence context, have certain characteristics that nouns lack. For example, they entail a predicate-argument and a thematic structure (Carlson & Tanenhaus, 1989), require agreement relations with their subject (Hale & Keyser, 1998), and allow reference to time and events within a specific time frame (Bastiaanse, Bamyaci, Hsu, Lee, Yarbay Duman, & Thompson, 2011). Nouns and verbs also differ from the neural perspective. Verb processing may mostly involve the frontal and inferior-parietal lobe, while noun processing may mainly recruit neural structures in the temporal lobe (Damasio & Tranel, 1993; Lubrano, Filleron, Démonet, & Roux, 2014; Miceli, Silveri, Nocentini, & Caramazza, 1988). Therefore, unsurprisingly, verbs and nouns may be differentially affected in people with aphasia (Whitworth, Webster, & Howard, 2005; Vigliocco, Vinson, Druks, Barber, & Cappa, 2011). In light of these contrasts, we developed two standardized tasks, specific to intraoperative language mapping (Chapter 3), in order to establish whether the neurofunctional distinctions between the two word categories resulted in dissociated performance during direct cortical stimulation procedures (Chapter 6).

8.2. Developing new and standardized tasks in awake surgery

At the end of Chapter 2, we argued that neurosurgery teams should carefully consider the tasks they implement. Tasks should be specifically designed for awake surgery, should be standardized for a specific language, and should be developed so as to allow an in-depth assessment of language – one that goes beyond the dichotomy of correct/incorrect performance on a specific task or item. Some of these issues were considered and put to work in Chapter 3 where we provided new materials for language mapping in Italian: an object naming test similar to the current gold standard (e.g., DO-80; Metz-Lutz, Cremin, Deloche, Hannequin, Ferrand, Perrier, & Blavier, 1991), and a task for the production of finite verbs in sentence context.

One of the purposes of Chapter 3 was to show that standardized protocols can be set up with relatively modest resources. Hopefully, this will encourage neurosurgical teams to apply the same or similar approaches. Amongst other things, the duration of picture presentation must be considered in test preparation. This is because naming must occur during electrical stimulation, which cannot be applied for more than 4 seconds in order to prevent epileptic discharges (Duffau, 2004; Kayama, 2012). Therefore, only stimuli that healthy volunteers name in less than 4 seconds should be selected, even though from a neurolinguistic point of view a more prolonged presentation might be preferable (in fact, some studies indicate that in people with aphasia performance accuracy may peak when items are shown for 5 seconds or more; e.g., Brookshire, 1971).

In item selection, several psycholinguistic variables were considered. This was to make sure that items were easy to produce (i.e., that there was a high agreement between the expected name of the picture and the response provided by healthy volunteers), and to permit identification of critical dimensions that could be affected in each patient (e.g., low and high frequency words, transitive and intransitive verbs, objects and actions, etc.). A first objective of this procedure is to decrease the number of false positives by ensuring that not only the *items* that patients are unable to produce before surgery, but also *item categories* that patients have difficulty with preoperatively are not used intraoperatively. A second objective is to establish, before and after surgery, whether deficits in the tasks used during surgery (in this case, object naming and finite verb production) are due to semantic, lexical, or grammatical deficits, while at the same time ruling out that differences between noun and verb production are due to a mismatch between the psycholinguistic characteristics of the two sets of stimuli. For example, in Chapter 4, we constructed four stimulus sets that were psycholinguistically matched in all respects, except that they were used for distinct tasks (i.e., producing a noun, an infinitive, a finite verb, or a noun-related infinitive). Keeping frequency, imageability, age of acquisition and other critical variables under control in the four experimental sets licensed the conclusion that finite verbs are more accurate predictors of language abilities in daily living than nouns.

In Chapter 6, the patients included in our sample did not show preoperative deficits for specific psycholinguistic variables. Therefore, a personal intraoperative test could be prepared by removing the items that a particular patient was unable to respond to, without needing to control for specific psycholinguistic variables (frequency, imageability, etc.). This lack of psycholinguistic effects - which contrasts with the effects often reported in other brain-damaged populations (e.g., Jonkers & Bastiaanse, 2007; Kemmerer & Tranel, 2000; Kittredge, Dell, Verkuilen & Schwartz, 2008; Lambon Ralph & Howard, 2000; Luzzatti, Raggi, Piastrini, Contardi, & Pinna 2002) - could be due to the fact that preoperative deficits in our subjects were very mild. This is generally true of patients undergoing awake surgery, as the lack of severe deficits is one of the inclusion criteria for this procedure (e.g., Bello et al., 2007). Replication of the results presented in Chapter 6 and further work in people with brain tumors will help to decide whether or not controlling the items for different variables is essential in the preoperative assessments of people with brain tumors. Nevertheless, the control of the variables described in Chapter 3 and used in Chapters 4 and 6 may allow development of stimuli for intraoperative assessment also in patients with more marked naming deficits, particularly if these can be ascribed to specific items or item variables. For these patients, it should still be possible to select a sufficient number of correct items for intraoperative use (i.e., at least 3 items per stimulation site).

While we did not consider this aspect, finer-grained results could be obtained from the same intraoperative materials by considering spoken response times (e.g., (Arévalo, 2002; Székely et al., 2005; cf. Tsigka, Papadelis, Braun, & Miceli, 2014). Reaction time measures may be a more sensitive index than mere error rates, and allow detection of mild language deficits in patients with brain tumors. If this is the case, items to which patients respond after longer delays before surgery can be removed from the intraoperative assessment, as a measure to minimize false positives. However, reaction times may also be more difficult to interpret, as they will be susceptible both to practice effects (leading to faster responses) and to potential interference from effects of anaesthesia (general slowing) or the surgical environment more generally. Consequently, our choice to use accuracy rather than reaction times is likely to lead to results that are both more straightforward to interpret and more reliable.

8.3. The production of finite verbs (in awake surgery)

In Chapter 4, we contrasted the impairments displayed on four different naming tasks (i.e., object naming, producing finite verbs, action naming with infinites and verb generation) with those of a role-playing test (CADL2, Italian version; Carlomagno et al., 2013). All picture-naming tasks were found to be sensitive probes of language abilities in everyday life, as they all correlated significantly with the CADL2. Importantly, however, the finite verb production task correlated more strongly with the CADL2 than object naming. This result might reflect the intrinsic differences between verbs and nouns discussed above and in chapters 2, 3, and 5. However, it does not necessarily entail that finite verbs tasks are more sensitive *per se* than object naming tasks. In fact, the analysis of individual results showed that some patients scored worse on object naming than in verb tasks. Therefore, it is advisable to use object naming and the production of finite verbs to assess patients with aphasia (regardless of etiology), rather than to risk missing relevant data by restricting the evaluation to object naming or finite verb production only.

Based on theoretical and empirical knowledge of the mechanisms underlying the production of verbs and nouns, in Chapter 6 we studied the neurofunctional correlates of object naming and finite verb production during surgery - in Chapter 5 we piloted some of the analyses. The novelty of this work is that we tackled three issues that typically are not addressed in the literature: the subcortical mapping of finite verbs, an intraoperative analysis of error types, and a discussion of the effects of electrical stimulation. Similar to other studies, the investigation attests to the feasibility and usefulness of an approach to language mapping that uses both nouns and finite verbs (see also Lubrano et al., 2014; Havas et al. 2015): patients produced more errors during electrical stimulation than when naming in the absence of stimulation. Furthermore, some patients produced errors only in object naming, while for others the verb tests were more sensitive.

From a neurofunctional perspective, the distinction between more fronto-parietal involvement in grammatical processes (and hence, in the production of finite verbs) and more temporal involvement in lexical processes (and hence, in the production of nouns) has been inconsistently documented (e.g., Damasio & Tranel, 1993; Mätzig et al., 2009; Vigliocco et al., 2011, also Chapters 2 and 3). We worked with six people with brain tumors during surgery. Four of these participants produced more errors during stimulation mapping for object naming. In two cases this happened when stimulation was delivered to cortical frontal areas, and in two other cases when stimulation was delivered to subcortical areas in the inferior parietal lobe, and in the posterior part of the middle frontal gyrus. In a fifth participant with a frontal tumor, stimulation yielded errors during both object naming and finite verb production at the cortical and subcortical levels. And in a sixth participant with a lesion in the inferior and middle frontal gyri, cortico-subcortical stimulation only yielded errors during finite verb production.

Error types were inconsistent with the hypothesis that ventral networks are more involved in semantic processing and dorsal networks are more involved in phonological processing (e.g., Binder et al., 2009; Caplan, Vanier, & Baker, 1986; Caramazza, Papagno, & Ruml, 2000; Hickok & Poeppel, 2007; Sarubbo et al., 2015). Semantic paraphasias and phonological paraphasias were observed when stimulating dorsal networks (e.g., a subcortical area corresponding to the inferior parietal lobe, possibly a posterior segment of the arcuate fasciculus), and when stimulating cortical areas connected by ventral pathways, for example, as indicated by stimulation of a surgical marker of the inferior fronto-occipital fasciculus in the insula.

Similarly to Chapter 4, the results of Chapter 6 lead us to conclude that an approach to intraoperative language mapping based on at least two tasks (finite verb production and object naming) is preferable to an intraoperative assessment that only includes object naming. Neither task alone provides a satisfactory evaluation of language skills. Since both tasks probe partially distinct types of knowledge and recruit partially distinct neural substrates, their joint use during surgery guarantees a more reliable assessment of language and a greater likelihood of language sparing. Hence, in order to improve the quality and the sensitivity of language assessment during awake surgery, we believe that at least these two standardized tasks are required. Surgical teams should be aware of the theoretical implications and intraoperative advantages of each task (e.g., brain areas/networks where tasks may be more sensitive and specific, types of language errors that may emerge and what do they mean, what level of language is being tackled with the task and which other levels can be tested, etc.), based on current knowledge in aphasiology, neurolinguistics, and cognitive neuroscience.

8.4. Conclusion

New and more refined techniques are being applied to meet surgical needs such as removing more tumor tissue, improving survival rates, and preserving the patients' language processes and quality of life. This dissertation contributed to further the implementation of the production of finite verbs, which is a task that until now had not been routinely considered. Other than that, we strengthened the need of administering standardized tasks and comparing new tasks with gold standards.

We are currently considering pairing naming tasks with other imaging methods during surgery an in the different follow-ups (e.g., electrocorticography, encephalography). We are also considering the introduction of tasks to assess writing, comprehension, and working memory processes. Simultaneously, we are working on a fast protocol of narrative speech that could be in part analyzed semi-automatically, and used in follow-up assessments and even during surgery. This is because formal testing cannot be administered too often, as it may result in test-retest effects and time constraints in clinical practice, and also because narrative speech integrates different language levels and comes closest to language use in daily life. Above all, efforts may be directed at understanding the attributes and neural underpinnings of each task, and the benefit that it may bring to each patient, possibly directing us towards clearer answers to questions posed in aphasiology, neurolinguistics, and cognitive neuroscience.

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APPENDICES

APPENDIX A: Cortico-subcortical areas where language processing was detected and error types during electrical stimulation mapping (Chapter 2)

Table A2.1

Cortical areas in language dominant hemisphere where language processing was detected with each task and error types per area and per test

	ACTN	**VSC**	**NOOD**	**RSEN**	**SCOMPL**	**SCOMPR**	**TRANSLP**	**VGEN**	***Error type***
SFG	Bello et al. 2006, 2007 a, c	Lubrano et al. 2014					Borius et al. 2012 g	Ojemann et al. 2002	Anomia and paraphasias
MFG	**Bello et al. 2006, 2007**	Lubrano et al. 2014 b, e		Roux et al. 2004 e	Ojemann & Mateer, 1979			**Ojemann et al. 2002 ; Roux et al. 2003**	Anomia and paraphasias
IFG	**Bello et al. 2006, 2007**	Lubrano et al. 2014 b, h		Roux et al. 2004 e	Ojemann & Mateer, 1979		Borius et al. 2012 h	**Ojemann et al. 2002 ; Roux et al. 2003**	Anomia and semantic paraphasias
PrG				Roux et al. 2004 f	Ojemann & Mateer, 1979			**Ojemann et al. 2002 ; Roux et al. 2003**	+
PoG				Roux et al. 2004 f	Ojemann & Mateer, 1979			Ojemann et al. 2002	+
SMG		Lubrano et al. 2014 a		Roux et al. 2004	Ojemann & Mateer, 1979	Bello et al. 2007	Borius et al. 2012	Ojemann et al. 2002	Sentence comprehension error ; Phonemic and semantic paraphasias

AnG				Roux et al. 2004	Ojemann & Mateer, 1979	Bello et al. 2007		Ojemann et al. 2002	Sentence comprehension error ; Phonemic and semantic paraphasias
STG	Bello et al. 2007	Lubrano et al. 2014 a	**Hamberger et al. 2003, 2007**		Ojemann & Mateer, 1979	Bello et al. 2007		Ojemann et al. 2002	Anomia; sentence comprehension error; semantic and phomemic paraphasias
MTG	Bello et al. 2007	Lubrano et al. 2014 a	**Hamberger et al. 2003, 2007**	Roux et al. 2004 e	Ojemann & Mateer, 1979			Ojemann et al. 2002	Anomia and phonemic and semantic paraphasias
ITG			Hamberger et al. 2003, 2007 i						Anomia
Error type	Anomia and semantic paraphasias	Anomia; Phonemic and semantic paraphasias, neologism, hesitation	Anomia Phonemic and semantic paraphasia	Anomia. Hesitation, phonemic and semantic paraphasias	Anomia, paraphasias, grammatical errors	Sentence comprehension error	Anomia	Anomia, hesitation, paraphasias	

Notes. ACTN = Action naming; VSC = Producing a finite verb in sentence context; NOOD = Naming objects to oral description; RSEN = Reading sentence aloud; SCOMPL = Sentence completion; SCOMPR = Sentence Comprehension; TRANSLP = Translating Paragraphs (No areas where detected where translation was the only language procedure affected); VGEN = Verb Generation. Cortical areas: SFG = Superior Frontal Gyrus, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, PrG = Precentral Gyrus, PoG = Postcentragyrus, SMG =Supramarginal gyrus, AnG = Angular Gyrus, STG = Superior temporal gyrus, MTG = Middle temporal gyrus, ITG = Inferior temporal gyrus. References in boldface indicate that language processing was frequently detected with the test or that the language process was specific to that area (e.g., Naming to Oral description was specific for STG and MTG). The sign (+) indicates that the error types were not clearly specified per brain area. a = area common to object naming, b = area specific to verbs, c = area specific to the periphery of the tumor, e = area specific to the posterior part of the gyrus, f = area specific to the inferior part of the gyrus, g = area specific to the superior part of the gyrus, h = area specific to Broca's area, i = area not frequent

Table A2.2

Subcortical areas in the language-dominant hemisphere where language processing was detected by action naming and error types produced by patients during stimulation of that area

	ACTN	*Error type*
AF	Bello et al. (2006,2007)	Anomia; Phonemic paraphasias
IFOF	Bello et al. (2007, 2008)	Semantic paraphasias
ILF	Bello et al. (2007)	Anomia; Reduction of spontaneous speech Semantic paraphasias.
PV	Bello et al. (2006)	
SLF	Bello et al. (2008)	Phonemic paraphasias
SuF	Bello et al. (2006, 2007)	Anomia; Reduction of spontaneous speech; Phonemic paraphasias
UNC	Bello et al. (2007, 2008)	Semantic paraphasia

Notes. ACTN = Action Naming; Subcortical areas: AF = Arcuate fasciculus, IFOF = Inferior fronto-occipital-fasciculus, ILF = Inferior longitudinal fasciculus, PV = Periventricular white matter, SLF = Superior longitudinal fasciculus, SuF = Subcallossal fasciculus and UNC = Uncinate fasciculus.

APPENDIX B: Description of psycholinguistic variables of the tests, instructions for on-line questionnaires, and MATLAB code to calculate the H-STATISTIC (Chapter 3)

1. VISC subsets: description, number of items per condition, matching

FAL_Sub

Action-related verbs describe actions performed with face/mouth, arm/hand and leg/foot. Hauk, Johnsrude and Pulvermüller (2004) argue that this type of actions (e.g., ‘to lick’, ‘to pick’ and ‘to kick’) activate the motor strip in a somatotopic manner (Leyton & Sherrington, 1917; Penfield & Boldrey, 1937). These verbs are similar to manipulation verbs, but “manipulation” refers to hand actions that require an object (e.g., ‘to type’ needs a keyboard) whereas “arm/hand action” does not entail object use (e.g., ‘to point’ is not a manipulation action as it does not require an object, even though it is an action, typically performed with the hand). *FAL_Sub* includes 8 items per condition: face action (1), arm action (2), leg action (3). Items were matched for Picture Name Agreement (PNA<75), H-statistic (H-STAT), Visual complexity (Vcomplex), Age of Acquisition (AOA), Imageability (Imag), Frequency (Freq, Log10+1Freq, HighLowFq), Length in phonemes (LPh, LongShortPh), Instrumentality (Inst), Name-relatedness to a noun (NRN), Manipulation (MN) and Regularity (Reg_Sub). Items could not be matched for Transitivity (TR) and Number of Internal arguments (NIA) as no transitive verbs could be added in face actions (1).

HighLowFqV_Sub

Effects of frequency were described in the VISC subsets. HighLowFqV_Sub includes 17 items per condition: high frequency (1) and low frequency (0) based on the median of the sample (median=6.28). Conditions were matched for Picture Name Agreement (PNA<75), H-statistic (H-STAT), Visual complexity (Vcomplex), Age of Acquisition (AOA), Imageability (Imag), Instrumentality (Inst)m Action relatedness (FAL), Manipulation (MN).

No matching was possible for Transitivity (Tr), Name-relatedness to a noun (NRN) and Regularity (Reg_Sub).

Inst_Sub/NRN_Sub

The term *instrumental verbs* refers to actions requiring the use of an instrument that is not a body part. Instrumental verbs are divided in two categories: *name-related* (i.e., verbs that are phonologically identical to the name of the instrument, for example ‘to brush’) and verbs that are *not name-related* to the instrument (e.g., ‘to sew’). Instrumental verbs are easier than non-instrumental verbs for patients with aphasia (Jonkers & Bastiaanse, 2007), possibly because they activate two lemmas: one corresponding to the verb, one to the instrument. This coactivation may facilitate retrieval of the word form (the lexeme) but not necessarily of the lemma (Bastiaanse & Van Zonneveld, 2004). *Inst_Sub* contains 24 items per condition: instrumental verb (1), non-instrumental verb (0). Items were matched for picture name agreement (PNA<75), H-statistic (H-STAT), Visual complexity (Vcomplex), Age of Acquisition (AOA), Imageability (Imag), Frequency (Freq, Log10+1, HighLowFq), Length in phonemes (LPh, LongShortPh), Manipulation (MN) and Regularity (Reg_Sub). Items are not matched for Transitivity (Tr), Name-relatedness (NRN), Action-related verbs (FAL). *NRN_Sub* contains 9 items per condition: verb that is related to a noun (1), verb that is not related to a noun (0). Items were matched for picture name agreement (PNA<75), H-statistic (H-STAT), Visual complexity (Vcomplex), Age of Acquisition (AOA), Imageability (Imag), Frequency (Freq, HighLowFq), Transitivity (Tr), Length in phonemes (LPh, LongShortPh), Action relatedness (FAL), Manipulation (MN) and Regularity (Reg_Sub). Matching for Picture Name Agreement was low (p=0.070). No matching was possible for Instrumentality (p=0.31), as all noun-related items were also instrumental.

LongShortPhV_Sub

Effects of word length in naming were described in the ECCO subsets. *LongShortPhV_Sub* includes 25 items per category: short verbs (0) and long verbs (1) based on the median of the infinitive in the sample (median=6). Items are matched for Picture Name Agreement (PNA<75), H-statistic (H-STAT), Visual complexity (Vcomplex), Age of Acquisition (AOA), Imageability (Imag), Frequency (Freq, Log10+1Freq, HighLowFq), Instrumentality (Inst), Name-relatedness to a noun (NRN), Action relatedness (FAL), Manipulation (MN) and Regularity (Reg_Sub).

MN_Sub

The term *manipulation* refers to objects that are used with the hand (e.g., cellphone) and to actions that are performed by manipulating an object (e.g., to type). It is used to explain relations between body and mind. Some authors argue that words related to manipulation are represented (at least partially) in the motor strip, as suggested by studies using neuroimaging and motor evoked potentials (Willems & Hagoort, 2007, for review) as well as by lesion data (Saygin, Wilson, Dronkers, & Bates, 2004; Tranel et al., 2003). *MN_Sub* includes 25 items per condition: non-manipulable verb (0), and manipulable verb (1). Items are matched for Picture Name Agreement (PNA<75), H-statistic (H-STAT), Visual complexity (Vcomplex), Age of Acquisition (AOA), Imageability (Imag), Frequency (Freq, Log10+1Freq, HighLowFq), Length in phonemes (LPh, LongShortPh), Name-relatedness to a noun (NRN), and Regularity (Reg_Sub). Items were not matched for Transitivity (Tr), Instrumentality (Inst), and Action relatedness (FAL) as these variables correlate with Manipulation (MN). For example non-manipulable verbs (0) typically are non-instrumental, and vice-versa.

Reg_Sub

Regular verbs follow a typical conjugation paradigm and do not change their stem. *Irregular* verbs, by contrast, either do not follow the typical conjugation paradigm or change their stem form. English examples of irregular verbs are ‘sing’ and ‘take’, that change their root form into ‘sang’ and ‘took’ in the past, and ‘sung’ and ‘taken’ in the past participle. The debate on regular and irregular verbs focuses on whether or not they are processed by the same cognitive mechanisms and represented in the same neural network. Connectionist models assume no differences in the processing and representation of regular and irregular verbs (Sach, Seitz, & Indefrey, 2003), whereas dual-process models argue for different cognitive mechanisms and localization (Pinker & Prince 1988; Ullman et al., 1997). On the latter view, irregular verbs are stored as whole lexical forms and hence engage more heavily lexical mechanisms located in the temporal lobe and right cerebellum. Forms of regular verbs, on the other hand, are not stored as lexical entries, and their inflectional processes are triggered by morphosyntactic operations located in the left frontal lobe and basal ganglia (Howard et al., 1992; Ullman, 2004). According to dual-process models, a selective difficulty producing regular verbs is consistent with a disruption of grammatical processes, whereas deficits in retrieving irregular verb forms occur in the context of lexical damage. *Reg_Sub* contains 16 items per condition. These refer to verbs that are regular in their whole conjugation (0) and verbs that have an irregular form in their conjugation (1). This form does not need to correspond to the third person singular. Items are matched for picture name agreement (PNA<75), H-statistic (H-STAT), Visual complexity (Vcomplex), Age of Acquisition (AOA), Imageability (Imag), Frequency (Freq, Log10+1Freq, HighLowFq), Transitivity (Tr), Length in phonemes (LPh, LongShortPh), Instrumentality (Inst), Action relatedness (FAL), Manipulation (MN) and Regularity (Reg_Sub). All items are not name-related to a noun (NRN)

Tr_Sub

Transitive verbs are accompanied by a direct object (e.g., to cook, to kiss); *intransitive* verbs (e.g., to walk, to swim) cannot be accompanied by a direct object. *Intransitive* verbs are further divided in two categories: unergative verbs have one external argument that functions as an agent (e.g., to pray in ‘the nun prays’) and unaccusatives have one internal argument that functions as a theme and raises to subject position (e.g., to fall in ‘the kid$_i$ falls t$_i$’). Therefore, a specific deficit for unaccusative verbs may denote difficulty with syntactic movement operations. People with aphasia typically fare worse with unaccusative and transitive than unergative verbs (e.g., Luzzatti et al., 2002); however, the reverse pattern is also on record (De Bleser & Kauschke, 2003). *Tr_Sub* contains 23 items per condition: transitive verbs (1), intransitive verbs (0). Items are matched for picture name agreement (PNA<75), H-statistic (H-STAT), Visual complexity (Vcomplex), Age of Acquisition (AOA), Imageability (Imag), Frequency (Freq, Log10+1Freq, HighLowFq), Length in phonemes (LPh, LongShortPh), Instrumentality (Inst), Name-relatedness to a noun (NRN), Action relatedness (FAL), Manipulation (MN) and Regularity (Reg_Sub).

Ac_Balanced

Differences between nouns/objects and verbs/actions were described in the ECCO subsets. Ac_Balanced includes 20 items matched with a subset of 20 items extracted from the ECCO (Ob_Balanced). The items are matched for picture name agreement (PNA<75, PNA+75), H-statistic (H-STAT), Age of Acquisition (AOA), Imageability (Imag), Frequency (Freq, Log10+1Freq, HighLowFq), biological/artifactual entities (Bio), Length in phonemes (LPh, LongShortPh), and semantic category (SemCat). Items could not be balanced for objective Visual Complexity (Forsythe et al. 2008) as indicated in the Ob_Balanced section.

2. ECCO subsets: description, number of items per condition, matching

Bio_Sub

The term *biological* entities refers to conspecifics, animals, fruits, and vegetables: whereas *non-biological* entities correspond to inanimate objects (musical instruments, tools, means of transportation, furniture, etc.). Within biological entities, a further distinction is drawn between those provided (animals) and those not provided (plants) with self-generated movement. Selective impairment and sparing of these categories have been reported, and typically signify semantic damage (see Capitani, Laiacona, Mahon, & Caramazza, 2003, for a review). *Bio_Sub* includes 17 items per condition: biological (1) entities such as conspecifics, animals, fruits, vegetables and non-biological (0) or artifactual entities such as instruments, means of transportation, and furniture. Conditions are matched for Picture Name Agreement (PNA<75), H-statistic (H-STAT), Visual complexity (VcomplexGIF), Age of Acquisition (AOA), Imageability (Imag), Frequency (Freq, Log10+1Freq, HighLowFq), Length in Phonemes (LPh, LongshortPh), and Semantic category (SemCat).

HighLowFqN_Sub

Written frequency estimates can be obtained by counting the number of times that a word appears in a corpus (e.g., the CELEX database). Effects of frequency on response times and accuracy are reported in healthy populations (Oldfield & Wingfield, 1965) and in aphasia (Kemmerer & Tranel, 2000; Kittredge, Dell, Verkuilen, & Schwartz, 2008). Difficulty naming low-frequency items is generally attributed to deficits in lexical processing (Lesser & Milroy, 1993), but may be due also to semantic impairment or to a difficulty mapping semantic representations into lexical entries (Whitworth, Webster, & Howard, 2005). *HighLowFqN_Sub* includes 18 items per condition: high (1) and low (0) frequencies calculated based on the median of the sample (median=6.28). Conditions are matched for picture name agreement (PNA<75), H-statistic (H-STAT), Visual complexity (VcomplexGIF), Age of Acquisition (AOA), Imageability (Imag), Length in Phonemes (LPh, LongshortPh), Biological/artifactual entities (Bio), and Semantic category (SemCat).

LongShortPhN_Sub/LPhN_Sub

Effects of *word length* in naming speed were found in healthy young individuals (Barry, Morrison, & Ellis, 1997), in elderly people (Hodgson & Ellis, 1998) and in aphasic speakers. Nickels and Howard (2004) disentangled ‘number of phonemes’ from ‘number of syllables’ and ‘syllabic complexity’, finding that number of phonemes (but not number of syllables) predicted word repetition accuracy in nine aphasic speakers showing effects of length. The typical length effects result in longer words being more difficult to process, usually as a consequence of post-lexical damage. The opposite pattern has been also occasionally reported (Lambon Ralph & Howard, 2000), and has been attributed to a difficulty accessing output phonology (Whitworth, Webster, & Howard, 2005) - longer words have fewer phonological neighbors and thus fewer competitors for activation. *LongShortPhN_Sub* includes 21 items per condition: long words (1) and short words (0) based on the median of the sample (median = 6). *LPhN_Sub* includes 10 items per condition: 0 = 4 phonemes; 1 = 5 phonemes; 2 = 6 phonemes; 3 = 7 phonemes. The conditions in both subsets are matched for Picture Name Agreement (PNA<75), H-statistic (H-STAT), Visual complexity (VcomplexGIF), Age of Acquisition (AOA), Imageability (Imag), Frequency (Freq, Log10+1Freq, HighLowFq), Biological/artifactual entities (Bio) and Semantic category (SemCat).

Ob_Balanced

Differences between nouns and verbs exist along semantic and morphosyntactic dimensions. Verbs typically refer to actions while nouns to objects. Verbs entail thematic role assignment, subject-verb agreement, complex argument structure, time reference, while nouns function as arguments of the predicate (e.g., Rofes & Miceli, 2014). Accuracy, reaction times and electrophysiological measures may be different between verbs and nouns, particularly when verbs are used in sentence context (Mätzig et al., 2009; Vigliocco et al, 2011, for reviews). *Ob_Balanced* includes 20 items. These items are matched with a subset of 20 items extracted from the VISC (Ac_Balanced). Items are matched for Picture Name Agreement (PNA<75, PNA+75), H-statistic (H-STAT), Age of Acquisition (AOA), Imageability (Imag), Frequency (Freq, Log10+1Freq, HighLowFq), Biological/artifactual entities (Bio), Length in phonemes (LPh, LongShortPh), and Semantic category (SemCat). Items could not be balanced for objective Visual Complexity (Forsythe et al. 2008), as the lossless GIF compression measures we proposed for both tests were not comparable, as the drawings had been made by different authors, probably using different softwares and different compression measures.

3. VISC: materials and procedure, imageability and age-of-acquisition ratings

Materials and procedure

Stimuli consist of 85 black-and-white drawings, similar to those of other tests (Bastiaanse, Edwards, Maas, & Rispens, 2003; Hammelrath, 2000; Metz-Lutz et al., 1991; Snodgrass & Vanderwart, 1980). Stimuli were presented by using Psychtoolbox for MATLAB. A beep was presented 500ms prior to stimulus presentation, and each stimulus was shown for 4000ms. The Psychsound commands of Psychtoolbox were used to record the responses produced by each subject to each item. Responses that corresponded to the expected target or were rated as plausible given the ratings of healthy participants in the first study, and that were produced within the 4000ms time frame, were rated as correct.

Imageability and age-of-acquisition ratings

Imageability and age-of-acquisition ratings were collected through an on-line questionnaire to obtain ratings for all test items. We assessed the AoA of the target objects and that of the synonyms produced by healthy participants in the first step of the picture-name agreement study. Participants were asked to estimate on a 5-point Likert scale at which age they thought they had learned the word in either its spoken or written form (0-3 years, 4-6 years, 7-10 years, 10-12 years, older than 12 years). The procedure is similar to Carroll and White (1973). To assess Imageability, we asked participants to indicate on a 5-point Likert scale how difficult it was to imagine the object (very difficult, difficult, average, easy, very easy). A series of low-imageability action verbs was included in the list of to-be-rated words (e.g., categorize, deviate, define, tolerate). To the best of our knowledge, there is no exhaustive list of imageability of Italian verbs. Therefore, 65 low-imageability verbs from the list in Bird, Franklin and Howard (2001) were translated into Italian. Below we provided the instructions for each questionnaire, in English and Italian.

3. ECCO: materials and procedure, imageability and age-of-acquisition ratings

Materials and procedure

Sixty-two object drawings from the Snodgrass and Vanderwart set (1980) were used. Stimuli were presented individually on a computer screen, and the starter word *Ecco…* (This is…) was shown above each stimulus. Participants were asked to produce the name of the object preceded by its determiner (e.g., *Ecco la pera*, ‘Here [is] the pear’).

Imageability and age-of-acquisition ratings

The same procedure as for the VISC was followed. In addition to the 57 target items, all corresponding to concrete objects, the imageability questionnaire included 65 low-imageability nouns (e.g., philosophy, consciousness, reputation, merit), that had been rated between 2 and 3 on a 7-point scale in a study by Della Rosa, Catricalà, Vigliocco, and Cappa (2010). In order to prevent list biases, the names of low-imageability items were pseudo-randomly interspersed with those of the high-imageability, target objects. This ensured that stimuli in this task covered a wide imageability range, and prevented participants from inappropriately rating test items (all concrete objects) as being of low imageability. We followed the procedure of Paivio, Yuille and Madigan (1968).

5. Instructions for imageability and age of acquisition in English and in Italian

Age-of-acquisition

For an experiment regarding some properties of the memory of words, we need your opinion on the age-of-acquisition of some words. We are interested to know when you learned for the first time the meaning of a series of words, in the spoken or in the written form. In the following questionnaire, you will be asked to read some words. You are asked to answer on a scale from 1 to 5 if you estimate to have learned the word, in its spoken form or written form, when you were ‘0 to 5 years’, ‘4 to 6 years’, ‘7 to 9 years’, ’10 to 12 years’ or when you were ‘older than 12’.

For example you will read the word ‘pasta’ (specific to ECCO)/ ‘to snow’ (specific to VISC), and will estimate when you learned that word. If you think you learned it when you were around 0 to 3 years, please tick the first box of the scale.

ITALIAN. *Per un esperimento che riguarda alcune proprietà della memoria di parole, abbiamo bisogno del tuo giudizio sull’età di acquisizione di alcune parole. Ci interessa sapere quando, nel corso della tua vita, hai imparato per la prima volta il significato di una serie di parole, in forma parlata o scritta. Nel seguente questionario ti viene chiesto di leggere alcune parole. Dovrai rispondere su una scala da 1 a 5 se ritieni di aver appreso la parola, verbalmente o in forma scritta, quando avevi dagli '0 ai 3 anni', dai '4 ai 6 anni', dai '7 ai 9 anni', tra i '10 e i 12 anni' o 'dopo i 12 anni'.*

Per esempio vedrai la parola ‘pasta’ (specific to ECCO)/ ‘nevicare’ (specific to VISC). Dovrai stimare quando l’hai imparata per la prima volta. Se pensi di averla imparata nella fascia d’età compresa tra 0 e 3 anni, dovrai segnare la prima casella della scala.

Imageability

Words differ in their capacity to be imageable. Some words can be imagined very easily, others need more effort. The goal of this experiment is to estimate the difficulty to construct a visual image for each noun (specific to ECCO)/ verb (specific to VISC) on a list. You will answer on a scale from 1 to 5, indicating if constructing a mental image for each word is ‘very easy’, ‘easy’, ‘average’, ‘difficult’ or ‘very difficult’.

(Specific to ECCO). For example, think about the nouns ‘house’ and ‘love’ (in Italian, the latter is indicated by an unambiguous noun). Probably it is easy to construct a mental image of ‘house’: you could think of the image of a building divided in different floors and rooms. Instead, constructing the mental image for ‘love’ is probably more difficult. Think of the feeling and of the instinct that unites two people.

(Specific to VISC). For example, think about the verbs ‘to eat’ and ‘to know’. Probably, ‘to eat’ is easy to imagine: you could think of a man eating a piece of cake. Instead, constructing the mental image for ‘to know’ is probably more difficult. Think about what do you do when you ask yourself ‘Do I know that?’. You could touch your head and look surprised. Therefore, you could think of the image of a woman who touches her head in surprise.

ITALIAN. *Le parole differiscono per la loro immaginabilità. Alcune parole possono essere immaginate facilmente, altre richiedono un maggior impegno. Lo scopo di questo esperimento è di stimare la difficoltà di costruire un'immagine mentale per ogni nome* (specific to ECCO) / *verbo* (specific to VISC) *in una lista. Dovrai rispondere su una scala con valori da 1 a 5; dovrai stabilire se per ogni parola è ‘molto facile’, ‘facile’, ‘medio’, ‘difficile’, ‘molto difficile’ costruire un'immagine mentale.*

(Specific to ECCO) Per esempio, pensa ai nomi ‘casa’ e ‘amore’. Probabilmente è facile costruire un'immagine mentale per ‘casa’: basta pensare all’immagine di un edificio suddiviso in piani e vani, adibito ad abitazione. Invece per ‘amore’ è probabilmente più difficile. Pensa al sentimento ed all’istinto che lega due persone. (Specific to VISC) Per esempio, pensa ai verbi ‘mangiare’ e ‘conoscere’. ‘Mangiare’ probabilmente è facile da immaginare: basta pensare all’immagine di un uomo che sta mangiando un pezzo di torta. Invece ‘conoscere’ probabilmente è più difficile da immaginare. Pensa a cosa fai quando ti chiedi ‘questo lo conosco?’. Potresti toccarti la testa e sembrare sorpreso. Quindi potresti pensare all’immagine di una donna sorpresa che si tocca la testa.

6. MATLAB script to calculate the H-STATISTIC

```
function H = StatisticH(p)

% STATISTICH
%   It computes the statistic H for a given set of proportions.
%   It is based on the formula provided by Snodgrass & Vanderwart (1980)
%
% SCORING INSTRUCTIONS
% a) Eliminate: do not know responses
% b) Include with correctly name word: mispronunciations, diminutives
% c) Include with unabbreviated forms: uncommon abbreviations (b carriage
for
%    baby carriage)
% d) Count as separate words: not target word (vehicle for airplane, potato
%    for carrot); commonly accepted abbreviations (TV for television),
%    elaborations (bell pepper for pepper)
% e) Count the first response only: when two correct names are used
% f) Count the correct response: when two names are used within the given
%    time
%
% EXAMPLES OF USAGE
% I) For the picture "plane", 30 people said "plane" 30 times. The result
is
%    0 which indicates perfect agreement.
%    StatisticH ([30/30])
%
% II)For the picture "plane", 15 people said "plane", and 15 people said
%    "airplane".
%    The result is 1.
%    StatisticH ([15/30, 15/30])
%
% III)For the picture "plane", 10 people said "plane", 10 people
"airplane",
%    and 10 people said "I do not know"
%    The result is 1
%    StatisticH ([10/20, 10/20])
%
% IV)For the picture "plane", 10 people said "plane", 10 people "airplane",
5
%    people "I do not know", and 5 people "vehicle".
%    The result is 1.5219
%    StatisticH ([10/25, 10/25, 5/25])
%
% ------ Error handling ------
if(sum(p < 0) > 0) % We don't want negative p's
    error('Input error: at least one p coefficient is negative');
end
if(sum(p > 1) > 0) % We don't want p's greater than 1
    error('Input error: at least one p coefficient is greater than one');
end
pSum = sum(p);
if(pSum ~= 1) % The sum is expected to be 1
    disp('Warning: the p coefficients are not summing up to 1');
end
% ------ Calculation ------
elementsToBeSummed = p.*log2(1./p);
%
% When some p is zero, the function will throw a NaN ...
positionsOfZeros = find(p == 0); % ... so we find them ...
```

```
elementsToBeSummed(positionsOfZeros) = 0; % ... and use the limit when p
tends to zero instead of direct evaluation
%
H = sum(elementsToBeSummed);
%
End
```

APPENDIX C: Matcihng for linguistic variables, post-hoc tests, and individual results (Chapter 4)

Table C4.1

Matching of the tests for relevant linguistic variables including imageability

	FinVerb	ActNam	Vgen	ObNam	NVgen	Significance
Frequency	32.32(8.5)	44.01(19.2)	42.9(12)	34.73(13.26)	45(14.4)	$\chi^2(4,100)=1.203$, p=1.616
Imageability	1.19(0.02)	1.2(0.02)	1.18(0.02)	1.14(0.01)		$\chi^2(3,80)=5.358$, p= 0.147
Age of Acquisition	1.91(0.11)	1.84(0.09)	1.78(0.12)	1.98(0.12)		$\chi^2(3,80)=1.883$, p= 0.597
Length in Phonemes	5.65(0.25)	6.3(0.3)	5.75(0.3)	6.2(0.4)	6.3(0.48)	$\chi^2(4,100)=$ 1.616, p=0.806
Manipulable	14	12	11	9	10	
Non-Manipulable	6	8	9	11	10	
Transitive	12	14	13			
Instransitive	8	6	7			
Internal Arguments	12	14	13			
Instrumental	11	11	8			
Non-Instrumental	9	9	12			
Irregular	7	3	4			
Regular	13	17	16			
Name Related	4	3	4			
Non-Name Related	16	17	16			
Face	3	1	0			
Arm	12	13	12			
Leg	3	3	3			
Face/Arm	1	2	3			
Arm/Leg	1	0	0			
Non-Face/Arm/Leg	0	1	2			
Biological				8	4	
Non-Biological				12	16	

Notes. ActNam: Action Naming; ObNam: Object Naming; FinVerb: Producing a finite verb in sentence context; Vgen: Verb generation; NVgen: Name of the picture for which the verb is produced in the Verb Generation task (e.g., ball > to play). Standard deviation is reported in parentheses. N=20 items per task.

Table C4.2

Individual behavioral data (percentage correct).

	CADL-2	CETI	CAL	ObNam	Vgen	FinVerb	ActNam
AL	100	93.8	96.7	95	80	80	100
BL	83	73.8	81.1	90	75	80	75
BS	59	75	83.3	0	25	0	5
CB	93	78.8	73.3	90	55	60	0
CC	82	92.5	91.1	85	90	60	55
CK	56	42.5	53.3	35	5	5	25
ES	90	68.8	80	55	55	65	40
FT	95	68.8	41.1	35	45	70	60
GC	93	83.8	78.9	5	25	40	40
GM	53	65	52	0	0	0	0
LF	89	57.6	65.6	10	0	35	10
OS	84	81.3	92.2	85	80	80	65
OT	88	82.5	83.3	50	30	75	10
PG	70	51.3	41.1	0	0	0	5
PI	90	73.8	67.8	85	80	90	75
PS	49	70	72	65	15	20	10
RA	97	82.5	83.3	90	90	90	70
RG	80	53.8	52.2	0.0	15.0	25.0	30.0
RL	89	78.8	77.8	30	45	50	25
TG	67	57.5	55.6	65	30	30	5
UA	87	83.8	62.2	80	15	60	40
m(sd)	81 (15)	72 (14)	71 (16)	50 (36)	41 (32)	48 (31)	37 (30)

Notes. ActNam: Action Naming; ObNam: Object Naming; FinVerb: Producing a finite verb in sentence context; Vgen: Verb generation. m(sd): mean and standard deviation.

Table C4.3

Post-hoc tests of picture-naming tasks (Z and FDR corrected p-values).

	VGen-ObNam	FinVerb-ObNam	ActNam-ObNam	FinVerb-VGen	ActNam-VGen	ActNam-FinVerb
	Z= -1.542 p=0.1845	Z=-0.308 p=0.7577	Z=-2.015 p=0.0878	Z=-2.017 p=0.0878	Z=1.073 p=0.3399	Z=-2.546 p=0.0653

Notes. ActNam: Action Naming; ObNam: Object Naming; FinVerb: Producing a finite verb in sentence context; Vgen: Verb generation.

Table C4.4

Spearman correlations of picture-naming tasks and functional-measures (rho and p-value).

	CADL-2	CETI	CAL	ObNam	VGen	FinVerb	ActNam
CADL-2	1	0.511*	0.324	0.441*	0.561*	0.727*	0.538*
	p=0	p=0.0215	p=0.1516	p=0.0492	p=0.0129	p=0	p=0.0147
CETI	0.511*	1	0.763*	0.541*	0.611*	0.564*	0.452*
	p=0.021	p=0	p=0	p=0.0147	p=0.006	p=0.0129	p=0.0454
CAL	0.324	0.763*	1	0.554*	0.701*	0.542*	0.437*
	p=0.1516	p=0.	p=0	p=0.0136	p=0	p=0.0148	p=0.0494
ObNam	0.441*	0.541*	0.544*	1	0.779*	0.776*	0.577*
	p=0.0494	p=0.0148	p=0.0136	p=0	p=0	p=0	p=0.0113
VGen	0.561*	0.611*	0.701*	0.780*	1	0.830*	0.683*
	p=0.0129	p=0.0064	p=0.0009	p=0	p=0	p=0	p=0.0014
FinVerb	0.727*	0.554*	0.542*	0.776*	0.830*	1	0.793*
	p=0	0.0129	0.0148	p=0	p=0	p=0	p=0
ActNam	0.538*	0.462*	0.437*	0.578*	0.683*	0.792*	1
	p=0.0148	p=0.0454	p=0.0495	p=0.0113	p=0.0013	p=0	p=0

Notes. ActNam: Action Naming; ObNam: Object Naming; FinVerb: Producing a finite verb in sentence context; Vgen: Verb generation. We calculated false discovery rate (FDR) adjusted p-values to correct for multiple comparisons. *Significant at p≤0.05

Table C4.5

Comparisons of overlapping correlations (Steiger's Z)

	ObNam-Vgen	ObNam-FinVerb	ObNam-ActNam
CADL-2	Z=-0.92509	Z=-2.34918	Z=-0.53177
	p=0.2662	p=0.0282*	p=0.2975
CETI	Z=-1.02434	Z=-0.17940	Z=0.49075
	p=0.4290	p=0.4290	p=0.4290
CAL	Z=-1.25967	Z=0.09320	Z=0.64510
	p=0.3120	p=0.4629	p=0.3891

Notes. ActNam: Action Naming; ObNam: Object Naming; FinVerb: Producing a finite verb in sentence context; Vgen: Verb generation. We calculated false discovery rate (FDR)-adjusted p-values to correct for multiple comparisons. *Significant at p≤0.05

Table C4.6

Paired tests on picture-naming tasks (Fisher Exact – two tailed)

	ObNam vs Vgen	ObNam vs FinVerb	ObNam vs ActNam	Vgen vs FinVerb	Vgen vs ActNam	FinVerb vs ActNam
BL	p=0.168	p=1	p=1	p=0.168	p=0.364	p=1
CB	p=0.004*	p=0.078	p=<0.001*	p=1.000	p=<0.001*	p=<0.001*
CC	p=1	p=0.232	p=0.164	p=0.164	p=0.164	p=1
CK	p=0.003*	p=0.003*	p=0.8772	p=1	p=0.273	p=0.273
GC	p=0.04*	p=0.04*	p=0.04*	p=0.601	p=0.601	p=1
LF	p=0.731	p=0.254	p=1	p=0.04*	p=1	p=0.254
OT	p=0.333	p=0.282	p=0.028*	p=0.028*	p=0.282	p=<0.001*
PS	p=0.009*	p=0.02*	p=<0.001*	p=1	p=1	p=0.992
TG	p=0.084	p=0.084	p=<0.001*	p=1.000	p=0.109	p=0.084
UA	p=<0.001*	p=0.045*	p=0.044*	p=0.002*	p=0.186	p=0.343

Notes. ActNam: Action Naming; ObNam: Object Naming; FinVerb: Producing a finite verb in sentence context; Vgen: Verb generation. = Fisher exact (two tailed). We calculated false discovery rate (FDR) adjusted p-values to correct for multiple comparisons. *Significant at p≤0.05

Table C4.7

Major error types per task and participant

	AL	BL	BS	CB	CC	CK	ES	FT	GC	GM	LF	OS	OT	PG	PI	PS	RA	RG	RL	TG	UA	TOTAL
ActNam																						
AN	0	1	16	8	2	7	6	5	4	13	9	0	1	2	2	9	0	6	8	10	9	118
PHON	0	0	0	0	0	1	0	0	0	4	0	2	0	1	2	0	3	1	1	0	1	16
SEM	0	3	3	2	2	1	0	0	0	1	1	1	2	2	1	0	2	1	1	1	0	24
LATE	0	0	0	0	2	2	1	0	1	0	2	3	0	0	1	0	0	0	4	0	0	16
CAT/S	0	0	0	1	0	2	0	0	4	2	1	0	1	5	0	6	0	0	2	3	0	27
MSYNT	0	0	0	9	0	0	0	0	0	0	4	0	17	4	1	3	0	0	0	3	0	41
ObNam																						
AN	0	0	17	1	1	1	4	7	3	6	14	1	2	1	1	1	1	6	3	4	3	77
PHON	1	0	0	0	0	0	0	2	1	3	1	0	1	6	0	1	1	0	0	1	0	18
SEM	1	1	3	1	1	3	4	0	2	1	1	0	3	0	1	5	0	0	1	1	1	30
LATE	0	1	0	0	0	1	0	0	5	2	0	2	0	0	1	0	0	0	9	0	0	21
FinVerb																						
AN	1	0	18	4	1	10	1	5	4	6	7	2	0	1	1	5	1	6	4	5	8	90
PHON	0	0	0	0	2	1	0	1	1	1	2	1	0	6	0	0	0	0	0	2	0	17
SEM	1	2	1	2	2	5	2	0	0	3	1	0	4	0	0	1	0	0	1	1	0	26
LATE	0	1	0	0	2	0	0	0	2	0	3	1	0	0	0	0	0	0	2	0	0	11
CAT/S	0	0	0	0	0	1	0	0	0	1	0	0	0	2	0	6	1	0	0	3	0	14
MSYNT	0	0	0	2	0	0	0	0	0	1	0	0	0	0	0	2	0	0	0	0	0	5
Vgen																						
AN	0	0	13	6	2	9	4	3	7	12	11	1	2	1	1	11	0	2	7	3	11	106
PHON	0	0	0	0	0	1	0	0	1	6	0	0	0	0	0	0	1	1	0	1	0	11
SEM	2	3	2	0	0	0	2	1	1	0	0	0	1	0	2	1	1	3	0	2	0	21
LATE	0	1	0	0	1	0	1	0	3	0	0	2	0	0	1	0	0	0	1	1	0	11
CAT/S	0	0	0	2	0	8	1	0	0	7	8	0	8	4	0	5	0	1	0	8	5	57

Notes. AN: Anomia; PHON: Phonemic paraphasia; SEM: Semantic paraphasia; LATE: Answer later than 4 seconds; Cat/S: Category substitution (e.g., “chair” instead of “sitting”); MSYNT = Morpho-syntactic errors (i.e., errors of name agreement between the pronoun and the noun, e.g. “She paint” instead of “She paints”; also omission of the infinitival suffix “-re”); ActNam: Action Naming; ObNam: Object Naming; FinVerb: Finite verbs; Vgen: Verb generation.

EPILOGUE

ABOUT THE AUTHOR

I am a PhD candidate of the IDEALAB program (International Doctorate for Experimental Approaches to Language and Brain) at the University of Trento, the University of Groningen, and Macquarie University. I work on the neural correlates of noun and verb production in aphasia and their application to assessment of language in people with brain tumors and post-stroke aphasia. I also study non-fluent aphasia in Ibero-Romance.

During the PhD, I published 6 peer-reviewed articles and 7 abstracts, gave 17 invited talks and presented 4 posters, co-advised a master's student, and helped out in the organization of 4 events/conferences. I also took advantage of the many courses offered at my home and host universities, mastered my knowledge of Italian and Portuguese (which add up to Catalan, Spanish, and English), and I took courses at other centers (e.g., a tractography course in Padova, a neuroatomy course in Sydney, and a virtual and classical brain dissection course in Paris). As a master's student, I graduated from Joint European Erasmus Mundus Master’s Program in Clinical Linguistics (MSc) held at the University of Groningen and Potsdam University. I visited Neurosurgery Department in Montpellier to be trained in functional brain mapping, oncological neurosurgery and brain dissection. Before graduating in Catalan and English philology (double BA) at the Autonomous University of Barcelona, I was given a grant from the Center for Theoretical Linguistics to work on Comparative Linguistics. I also spent one year at the University of California in Santa Cruz, where I took courses in Syntax, Pragmatics, and Scientific Writing.

Currently, I am a member of the European Low Grade Glioma Network, and the Collaboration of Aphasia trialists. I was also very happy to be offered the opportunity to review for Aphasiology. My research interests embrace clinical linguistics (acquired disorders, assessment, awake surgery, post-stroke aphasia, rehabilitation, test standardization), brain mapping (direct electrical stimulation, functional magnetic resonance imaging, and tractography) and language processing (lexico-semantics, morpho-syntax, nouns and verbs, spontaneous speech, and time reference).

After the PhD thesis, I would be glad to continue on the academic path, become an independent researcher and a university professor, and contribute notably to the advance of functional approaches to language and cognition in awake surgery, post-stroke aphasia, language learning and treatment, and related subfields. I recently moved to Dublin (Ireland) together with my wife, and so far, I like it a lot here.

PUBLICATIONS, PUBLISHED ABSTRACTS, AND AWARDS

Publications

Rofes, A., Spena, G., Miozzo, A., Fontanella, M., & Miceli, G. (in press). Advantages and disadvantages of intraoperative language tasks in awake surgery: A three-task approach for prefrontal tumors. *Journal of Neurosurgical Sciences.*

Rofes, A., Capasso, R., & Miceli, G. (2015). Verb production tasks in the measurement of communicative abilities in aphasia. *Journal of Clinical and Experimental Neuropsychology, 37*(5), 483-502. doi:10.1080/13803395.2015.1025709

Rofes, A., de Aguiar, V., & Miceli, G. (2015). A minimal standardization setting for language mapping tests: An Italian example. *Neurological Sciences, 36*(7), 1113-9. doi:10.1007/s10072-015-2192-3

Martínez-Ferreiro, S., de Aguiar, V., & Rofes, A. (2015). Non-fluent aphasia in Ibero-Romance: a review of morphosyntactic deficits, *Aphasiology, 29*(1), 101-126. doi:10.1080/02687038.2014.958915

Rofes, A., & Miceli, G. (2014). Language mapping with verbs and sentences in awake surgery: A Review, *Neuropsychology Review, 24*(2), 185-99. doi:10.1007/s11065-014-9258-5

Rofes, A., Bastiaanse, R., & Martínez-Ferreiro, S. (2014). Conditional and future tense impairment in non-fluent aphasia, *Aphasiology, 28*(1), 99-115. doi:10.1080/02687038.2013.850650

Published abstracts

Rofes, A., Santini, B, Ricciardi, G.K., Talacchi, A., Pinna, G., Nickels, L., & Miceli, G. (2015). Nouns and verbs: Perioperative comparisons in brain tumors. *Stem- Spraak- en Taalpathologie, 20*(S01), 14-16. doi:32.8310/supplement/1914

Rofes, A., Talacchi, A., Santini,B., Cappelletti, G.,& Miceli, G. (2015). Intraoperative language mapping: A two-task approach. *Stem- Spraak- en Taalpathologie, 20*(S01), 191-194. doi:32.8310/supplement/1914

Rofes, A. & Miceli, G. (2014). Naming finite verbs predicts language abilities in daily living. *Stem- Spraak- en Taalpathologie, 19*(S04), 134-136. doi:32.8310/supplement/1914

Rofes, A., Santini, B., Mirtuono, P., Foroni, R., Pinna, G., Nickels, L., & Miceli, G. (2014). Lexico-semantic dissociations in patients with brain tumors in the posterior temporal lobe. *The Society for the Neurobiology of Language*, 194.

Rofes, A., De Witte, E., Mariën, P., & Bastiaanse, R. (2013). Object naming may overestimate patients' language performance after neuro-oncological surgery: A case study. *Stem- Spraak- en*

Taalpathologie, 18(S01), 59-63. doi:32.8310/S01/1813-59

Scientific communication/disclosure

Rofes, A. (2015). La neurocirugía con el paciente despierto [Spanish: Awake neurosurgery] Cuaderno de Cultura Científica (KZK), Cátedra de Cultura Científica, University of the Basque Country, Aug. 3 [Invited article, press here]

Posters, talks and invited presentations

Rofes, A., Santini, B, Ricciardi, G.K., Talacchi, A., Pinna, G., Nickels, L., & Miceli, G. (2015). Nouns and verbs: Perioperative comparisons in brain tumors. XV Science of Aphasia Conference, Sep. 17-22, Aveiro, Portugal [Talk]

Rofes, A., Talacchi, A., Santini,B., Cappelletti, G.,& Miceli, G. (2015). Intraoperative language mapping: A two-task approach. XV Science of Aphasia Conference, Sep. 17-22, Aveiro, Portugal [Talk]

Rofes, A., & Miceli, G. (2015). When object naming may not be enough: Two single cases. European Low Grade Glioma Network Meeting. Jun. 25-27, Paris, France [Invited presentation]

Dallabona, M., & Rofes, A. (2015). Neuropsychological assessment: pre-, intra-, and postoperative. Connect Brain. Apr. 23-26, Trento, Italy [Invited presentation]

Rofes, A. (2015). Awake surgery: O papel do Terapeuta da Fala [Portuguese: Awake surgery: the role of the Speech and Language Therapist] University of Algarve, Mar. 26, Faro, Portugal [Guest Lecture at Bachelor's in Speech and Language Therapy, Prof. Susana Rodrigues and Prof. Ana Catarina Baptista]

Rofes, A. (2015). Nouns and verbs in awake surgery: needs and answers. University College London, Mar. 5, London, UK [Invited presentation at Prof. Vigliocco's lab]

Rofes, A. (2015). Awake surgery: theory and praxis. University of Groningen, Jan. 12, Groningen, The Netherlands [Guest lecture at European Master's in Clinical Linguistics]

Rofes, A. & Miceli, G. (2014). La valutazione comprensiva del linguaggio nella chirurgia da sveglio [Italian: Comprehensive language assessment in awake surgery] Habilita: La rieducazione neurocognitiva nelle malattie degenerative del sistema nervoso centrale. Nov. 22, Bergamo, Italy [Invited presentation]

Di Giacopo, R., Calanni, M., Rofes, A., Fortis, P., Malaguti, M., Ottaviani, D., & Miceli, G. (2014). La riabilitazione delle funzioni esecutive e viso-spaziali nella malattia di Parkinson: la nostra esperienza [Italian: Executive and visuo-spatial functions rehabilitation in Parkinson's Disease: our experience] III Congresso nazionale congiunto LIMPE/DISMOV-SIN, Nov.14, Salerno, Italy [Poster]

Rofes, A., Santini, B., Mirtuono, P., Foroni, R., Pinna, G., Nickels, L., & Miceli, G. (2014). Lexico-semantic dissociations in patients with brain tumors in the posterior temporal lobe. CIMeC Doctoral School Day, Sep. 26, Rovereto, Italy [Talk]

Rofes, A., Capasso, R., & Miceli, G. (2014). Naming finite verbs predicts language abilities in daily living. XV Science of Aphasia Conference, Sep. 19-24, Venice, Italy [Talk]

Rofes, A., Santini, B., Mirtuono, P., Foroni, R., Pinna, G., Nickels, L., & Miceli, G. (2014). Lexico-semantic dissociations in patients with brain tumors in the posterior temporal lobe. The Society for the Neurobiology of Language Conference, Aug. 27-29, Amsterdam, The Netherlands [Poster]

Rofes, A., Talacchi, A., Santini, B., Zoccatelli, G., Alessandrini, F., Nickels, L., & Miceli, G. (2014). The language-role of the inferior fronto-occipital fasciculus. Center for Neurocognitive Rehabilitation, University of Trento. May 21, Rovereto, Italy [Invited presentation]

Rofes, A., Talacchi, A., Santini, B., Zoccatelli, G., Alessandrini, F., Nickels, L., & Miceli, G. (2014). The language-role of the inferior fronto-occipital fasciculus: Evidence from awake surgery. Rovereto Workshop on Concepts, Actions, and Objects: Functional and neural perspectives. May 8-11, Rovereto, Italy [Poster]

Martínez-Ferreiro, S. Reyes Gómez, A.F., & Rofes, A. (2014). Métodos neurocientíficos [Spanish: Neuroscientific methods]. Workshop: Cerebro y Lenguaje, El Bosque University. Apr. 9, Bogotá, Colombia [Invited presentation]

Rofes, A. (2014). Language research in brain tumor surgery.Neuroanatomy course HLTH214, Macquarie University. Jan. 10, Sydney, Australia [Invited presentation]

Rofes, A. (2013). Language in brain tumor patients and language testing in awake surgery. ARC Centre of Excellence in Cognition and its Disorders (CCD). Aphasia group, Macquarie University. Oct. 10, Sydney, Australia [Invited presentation]

Rofes, A., & Miceli, G. (2013). Language mapping in awake surgery: A critical review of tests with verbs and sentences. CCD Annual Workshop, Nov. 27-28, Sydney, Australia [Poster]

Rofes, A., De Witte, E., Mariën, P., & Bastiaanse, R. (2013). Object naming may overestimate patients' language performance after neuro-oncological surgery: A case study. XIV Science of Aphasia Conference,Sep. 20-25, Brussels, Belgium [Talk]

Rofes, A. (2013). Functional surgical neuro-oncology: relevant language tests, better outcomes. Faculty of Medicine and Surgery, University of Verona. Apr. 17, Verona, Italy [Invited presentation]

Arsenijević, B., Martínez-Ferreiro, S., & Rofes, A. (2011). Determiners in Catalan agrammatism: A case study. XII Science of Aphasia Conference, Sep. 01-05, Barcelona, Spain [Poster]

Grants and awards

2012-2015 Erasmus Mundus Joint Doctorates (EMJDs) grant, IDEALAB PhD program (International Doctorate in Experimental Approaches to Language And Brain) - em-idealab.com (127.200€)

2013-2014 Cognitive Science Postgraduate Research Grant (CSPRG) R4. Macquarie University ($600)

2010-2012 Erasmus Mundus Master Course (EMMCs) grant, EMCL program (European Master in Clinical Linguistics) - emcl-mundus.com (12.000€)

2011 Premi Extraordinari de Titulació – Special Award BA in Catalan philology and BA in English philology. Autonomous University of Barcelona (fee exemption)
2010 Collaboration grant (COLAB). Department of Catalan philology and Center for Theoretical Linguistics at the Autonomous University of Barcelona.

2009 Grant and Grant with Honors. Becas de Movilidad Internacional Fernando Alonso 2008-

2009. Banco Santander (3.000€ + 600€)

2009 Bancaja Grants to best academic records of the Autonomous University of Barcelona International Mobility's program (1.500€)

2009 International Mobility program grants of the Autonomous University of Barcelona International Mobility's program (1.500€)

2009 General grant to undergraduates (GRAL). Agaur/Ministerio (fee exemption)

2007-2008 Four grants. Summer courses at University of Girona, symposium in Mallorca (DRAC, 250€), and general grants (GRAL) for undergraduates (fee exemption)