Two dissociable semantic mechanisms predict naming errors and their responsive brain sites in awake surgery. DO80 revisited.

Marika Gobbo[1], Serena De Pellegrin[1], Camilla Bonaudo[2], Carlo Semenza[3,4], Alessandro della Puppa[2], Elena Salillas[3].

[1]UOC Neurologic Clinic, University Hospital of Padova, Padova, Italy

[2]Neurosurgery, Department of NEUROFARBA, University Hospital of Careggi, University of Florence, Florence, Italy.

[3]Department of Neurosciences, University of Padova, Padova, Italy

[4]IRCCS San Camillo Hospital, Venice, Italy

ABSTRACT

How do we choose words, and what affects the selection of a specific term? Naming tests such as the DO80 are frequently used to assess language function during brain mapping in awake surgery. The present study aimed to explore whether specific semantic errors become more probable under the stimulation of specific brain areas. Moreover, it meant to determine whether specific semantic characteristics of the items may evoke specific types of error. A corpus-based qualitative semantic analysis of the DO80 items, and the emitted naming errors to those items during direct cortical electrostimulation (DCE) revealed that the number of hyperonyms (i.e. 'vehicle' for car') of an item predicted the emission of a synonym ('automobile' for 'car'). This association occurred mainly in frontal tumor patients, which was corroborated by behavior to lesion analyses. In contrast, the emission of co-hyponyms was associated with tumors located in temporal areas. These two behavior-lesion associations thus dissociated, and were also dependent on item semantic characteristics. Co-hyponym errors might generate from the disruption in a temporal semantic-to-lexical process, and the production of synonyms could be the result of an impairment in a frontal lexical-selection mechanism. A hypothesis on the lexical selection mechanisms exerted by the inferior frontal gyrus is proposed. Crucially, the present data suggest the need for more restrictive naming tasks, with items conditioned by tumor location.

KEYWORDS: Direct Current Electrostimulation; Awake Brain Surgery; Lexical Retrieval; Naming; Inferior Frontal Gyrus (IFG); Middle Temporal Gyrus (MTG).

1. INTRODUCTION

How do we choose our words, and what affects the selection of a specific term? Lexical retrieval is the core process of word production, the mechanism by which a semantic representation associates with lexical access. Several theoretical models of lexical retrieval have also been used in neuropsychology (Dell et al., 1999; Garrett, 1992; Levelt, 1989). While varying widely in several respects, these models agree in distinguishing a concept level, in which a set of more or less distinct semantically related candidates would be coactivated, and a level which operates the selection of the intended word (Riès et al., 2016; Snyder et al., 2011). According to such models, in picture naming, the target concept (HORSE) is activated with other semantically related concepts (i.e., ANIMAL or GOAT). Therefore, conceptually related items, including concepts within the same semantic category or the upper semantically related concepts (i.e., ANIMAL or MAMMAL), are activated and in competition. All of them activate a corresponding lexical item (i.e., animal, goat), stored in the mental lexicon of the speaker. Finally, after lexical selection, the target word form (horse) is selected among items competing as possible responses (Dell et al., 1999; Indefrey and Levelt, 2004; Levelt, 2001; Levelt et al., 1999). The process of lexical selection implies differences of activation between candidates, where the appropriate and selected word is the more active and overcomes the competing noise (Dell et al., 1999), or surpasses a given threshold (Levelt et al., 1999).

Segregated brain representations have been proposed for the main stages of lexical retrieval: lexical activation would be associated with temporal regions, while lexical selection would be linked to lateral-frontal regions (Riès et al., 2016). Specifically, the mid-to-posterior portion of the middle temporal gyrus (MTG) seems to play a role in the lexical-semantic mechanism (Baldo et al., 2013). The inferior frontal gyrus (IFG) would not be related to semantic retrieval per se, but rather to the selection of an item among a set of competing alternatives (Thompson-Schill et al., 1999, 1997). Indeed, stroke lesions in IFG were found to compromise semantic processing only in a condition of high selection demands (Thompson-Schill et al., 1998).

Naming tasks have been traditionally used in both healthy and neurological populations to study psycholinguistic models of word production and to understand their anatomo-functional basis. Because of their sensitivity, their use in clinical assessment is widespread. In particular, and relevant to the present study, naming is a very sensitive task to test language functions in time-limited conditions like during surgical procedures (Duffau et al., 2014). Not surprisingly, picture-naming is indeed the most commonly used method to test linguistic functions during brain mapping with direct cortical electrostimulation (DCE) in awake surgery (De Witte and Mariën, 2013; Rofes et al., 2017; Talacchi et al., 2013b). This surgical technique is used for the treatment of tumors in eloquent areas of the brain. It prevents postoperative impairments of naming while maximizing tumor resection. However, the importance of DCE goes beyond clinical applications. DCE may indeed be considered the "gold standard" to directly investigate cortical functions and their localization in the brain (Tate et al., 2014).

Naming errors elicited during intraoperative language mapping have been studied to explore the stages of lexical retrieval. Through the observation of differences in the types of those errors, the components of lexical retrieval have been mapped both cortically and sub-cortically (Corina et al., 2010; Duffau et al., 2014, 2005; Hamberger et al., 2016; Herbet et al., 2016b; Miozzo et al., 2017; Miozzo and Hamberger, 2015; Moritz-Gasser et al., 2013; Rofes et al., 2019; Sierpowska et al., 2019; Tate et al., 2014). Some of these studies supplied a precise classification of semantic errors generated by DCE: from the broader classification of Miozzo et al. (2017) to the more detailed one of Corina et al. (2010), and Duffau et al. (2005). All of them converged, albeit using different nomenclature, in the subdivision of semantic paraphasias into coordinate (i.e., lion>tiger), associate (foot>shoe), and superordinate (pear>fruit) errors. Relations of subordination (flower>rose), part-to-whole (hand>finger), holonym (foot>leg), visual (nail>knife), functional access (apple>can be eaten), or opposite (low/high) were also described (Corina et al., 2010; Duffau et al., 2005; Mandonnet et al., 2009). These distinctions reflect those made in the study of semantic associations produced by normal subjects (Garrett, 1992) and in the aphasia literature (Coltheart et al., 1980, pp. 146–159; Kohn and Goodglass, 1985; Semenza et al., 1980; Semenza et al., 1992). Within DCE studies, only Miozzo et al. (2017) proposed a neuroanatomical localization of semantic errors considering their sub-categories. They found a higher prevalence for coordinate errors, after associated and superordinate, and showed their occurrence upon stimulation of the middle temporal gyrus (MTG). Other than DCE studies, different neuropsychological studies have also addressed similar semantic structures on errors to investigate neurofunctional correlates of semantic cognition models (Jackson et al., 2015; Jefferies and Lambon-Ralph, 2006; Lambon-Ralph et al., 2017; Schwartz et al., 2011). The relevance of this approach entails that the committed errors point to where in the naming process, the alteration is located (Caramazza and Hillis, 1990; Garrett, 1992).

The aim of this investigation is to develop DO80 into a more sensitive test. Thus, the present study is a first attempt for relating specific semantic characteristics of the named items with the kind of error made upon DCE stimulation. Importantly, a link must also be established with brain-related areas. The overarching goal is to be able to select items for the naming task so that the stimulation process is more sensitive, avoids false negatives, and ideally reduces the testing time. In turn, this should shorten the number of items required to evoke an error. Hence, we will maintain that the named items are not equivalent, and the item-error link might depend on the specific characteristics of the items, together with tumor location. Therefore, the present study tries to start an exploration of item-error-brain area links, departing from the DO80. Indeed, at the same time, the anatomo-functional bases of lexical retrieval can be further characterized.

In order to make the aforementioned findings on semantic errors in DCE suitable for the practical purposes of neurosurgery, the linguistic classifications of semantic errors need consistency and usability. Semantic classifications need to be based on independent corpora-based operators, rather than ratings made by judges. Corpora-based classifications should allow the extrapolation of conclusions to other naming sets, hence obtaining increasing reproducibility. Moreover, a neuro-anatomical correlate should explicitly rely on those precise classifications. This procedure as a whole would ultimately favor a selection of items or, at least, a reordering of items, attending to a higher sensibility of a stimulation site depending on the item's characteristics, which acquires relevance considering the time limitations of the awake surgery procedure.

In this study, a linguistic semantic database has been queried to revisit semantic errors in awake surgery while also informing the research on lexical retrieval. Further, the present study asks whether the semantic structure of the items influences patients' intraoperative response. In doing so, we aim to replicate and extend the earliest findings in semantic errors but also increase the sensibility of language mapping, improving error detection. Specifically, we focus on the inner semantic structure of a standardized naming test used intraoperatively (DO80 (Metz-Lutz et al., 1991)). Similarly, we classified the semantic errors committed by the patients using the same database, to then relate the structure of DO80 items with the semantic structure of patients' naming errors.

Based on this corpora-based method, we focus on semantic errors: (1) Synonyms: words with the same referent that differ lexically, (i.e. "bicycle" and "bike)"; (2) Hyperonyms or hypernyms: words that are superordinate to a more specific word, (i.e. "vehicle" for "bicycle"); (3) Hyponyms: words that are subordinate to a more general word, (i.e. "tandem" for "bicycle"); and (4) Co-hyponyms: words that share the same Hyperonym, (i.e. "train" and "bicycle" that are both "vehicles"). These different errors imply different aspects of semantic processing, located in different brain areas. Specifically, hyperonyms and hyponyms regard the hierarchical semantic structure of a specific word, while co-hyponyms imply the 'horizontal,' same-level semantic nodes triggered from the semantic to lexical process. Finally, synonyms imply accuracy for the selection of a word in a set of lexical possibilities.

Importantly, we will observe the tumor location associated with specific item-error characteristics. Tumor location determines the specific part of the cortex that will be stimulated using DCE. Hence, relating the tumor location to the elicited semantic error can inform about the neural bases for specific aspects of semantics. The present study samples the frontal and the temporal lobes.

Hence, possible dissociations between these two brain areas are explored. In word production, frontal and temporal regions belong to a distributed network that accounts for lexical-semantic activation and selection (Riès et al., 2016). Which role is associated with these two brain regions is still a matter of investigation.

2. MATERIALS AND METHODS

2.1. Participants

A retrospective exploration was conducted on 61 patients who underwent awake surgery within nine years (2011-2020) in the Neurosurgical center of the University Hospital of Padua. All patients were informed of the surgical procedure and gave their consent to it, in accordance with the Declaration of Helsinki. The present study did not involve further testing than the one routinely applied for clinical purposes.

Inclusion criteria were brain tumors in eloquent language areas of the left hemisphere and intraoperative evaluation of language function with DCE. A DO80 naming task was one of the language tests in the surgical approved protocol to map language within eloquent areas. A total of 34 patients matched the inclusion criteria (19 females and 15 males). Patients ranged in age from 26 to 70 years (mean=48.3) and presented an educational level between 5 to 22 years (mean=11.6). Across patients, brain locations of tumors were temporal (n=10), frontal (n=9), parietal (n=3), insular (n=2). There were ten patients with more than one lobe involved.

2.2. Language mapping procedure

DO80 is a standardized naming test used for language mapping during surgical DCE stimulation. The test consists of 80 black and white images selected according to frequency, familiarity, age of acquisition and level of education (Metz-Lutz et al., 1991; Talacchi et al., 2013b). Images are displayed centrally on a computer screen and presented continuously every 4 seconds. An introduction sentence (“This is a...”) must be emitted before the noun, to disregard dysarthria. The patients take the test pre-surgically, and the pictures in which errors occur are eliminated for the surgical testing. During awake surgery, the patient is asked to name the picture precisely. The usual procedure implies that if the patient produces an error in a 2/3 proportion after stimulation of a specific brain locus, the area is taken as a functional limit and tagged (Talacchi et al., 2013a). The patients are blind to neurosurgeon stimulation.

Following the intraoperative procedure described in precedent studies (Duffau et al., 2005; Talacchi et al., 2013b; Tate et al., 2014), stimulation was applied with a bipolar electrode delivering a biphasic current (pulse frequency of 60 Hz, single pulse duration of 1 ms). The amplitude of stimulation is adapted for each patient, through a progressive increase from 1mA to a maximum of 3.5mA, while the patient performs an automatic task (repetitive counting from 1 to 10). With this optimal amplitude, the naming DO80 task starts.

Language impairment during brain stimulation was intraoperatively detected by a trained speech therapist and concurrently transcribed by a colleague. Errors were analyzed and codified in anomia (no naming response within the 4 seconds of picture presentation), speech arrest (impossibility to articulate sounds), semantic paraphasia (a response that is semantically related to the target, i.e., "chair" for "table"), phonological paraphasia (a response with a deviation from the target at the phonological level, i.e., "pable" for "table"), perseveration (in a new picture the repetition of a response already given), visual paraphasia (a response that shares visual features with the target, i.e., "pencil" for "screw" (Mandonnet et al., 2009)), or verbal paraphasia (a word response not-related to the target, i.e., "table" for "tomato") (Corina et al., 2010; Duffau et al., 2005).

A postoperative neuropsychological assessment was conducted four to ten days after surgery as well as an additional follow-up assessment one month after surgery. Of the 34 patients considered in the present study, seven patients showed anomia in the initial evaluation. Two patients showed Wernicke's aphasia, and two patients displayed Broca's aphasia. In the one-month follow-up, all except four patients recovered completely. These four patients implied two with persistent anomia, one with mild deficit receptive aphasia, and one with persistent Broca's aphasia.

2.3. DO80 and semantic errors analyses through ItalWordNet

ItalWordNet (IWN) is a semantic database that provides information about meanings, concepts, and connections between word senses (synsets) for Italian (Roventini et al., 2000). It is part of a broader multilingual Wordnet. The semantic structure of DO80 items was analyzed according to IWN relations. Items were described in terms of (1) their number of Synonyms (SYNs): words with the same referent that differ lexically, (i.e. "bicycle" and "bike)"; (2) Hyperonyms or hypernyms (HYPERs): words that are superordinate to a more specific word, (i.e. "vehicle" for "bicycle"); (3) Hyponyms (HYPOs): words that are subordinate to a more general word, (i.e. "tandem" for "bicycle"); and (4) Co-hyponyms (CO-HYPOs): words that share the same Hyperonym, (i.e. "train" and "bicycle" that are both "vehicles").

Similarly, IWN was used to analyze the errors emitted during electrostimulation. Since IWN concerns the semantic connections of synsets, only semantic paraphasias were considered. Hence, when a semantic paraphasia occurred, it was classified in terms of the semantic relation with the original item, as described by IWN: synonym, hypernym, hyponym, co-hyponym, meronym (part-to-whole relation, i.e., "nail" for "finger") or holonym (whole-to-part relation, i.e., "hand" for “finger”) error. In turn, IWN ensured an objective qualitative analysis of naming errors and DO80 items.

After items and error classification, item structure was related to the kind of error and fitted through linear and nonlinear regression analyses. The variables considered for each item were: number of SYNs, HYPERs, HYPOs, CO-HYPOs. The type of errors considered were synonyms and co-hyponyms because they were the most frequently committed errors.

Only errors after cortical stimulation were considered for further analyses because cortical stimulation was performed on all patients, while subcortical stimulation was not required in all of them. Hence subcortical effects were underrepresented. Only four semantic errors were emitted during subcortical stimulation: two synonyms and two cohyponyms.

2.4. Voxel-wise tumor-behavior mapping.

Once the most frequent types of errors were established (i.e., co-hyponym and synonym), they were related to tumor distribution. The brain-behavior mapping also considered possible relationships between the errors and the structure of the items eliciting them (i.e., number of HYPERs of the item for the cases of synonym emission).

For the voxel-wise lesion analysis, the probability of committing a co-hyponym, or a synonym, under the total of semantic errors was considered as the continuous variable (i.e., co-hyponym errors/total of semantic errors for each patient).

Structural T1-weighted MRIs were acquired before surgery as needed by the internal medical care protocol. In order to draw the tumor outlines on a standard space, structural MRIs were registered to an MNI brain template (MNI152_T1_1mm) using FSL. The extent of brain tumors, identified through the registered T1-MRI images, was then drawn manually with MRIcron software (Rorden et al., 2007). Hence for each patient, a volume of interest (VOI) of the tumor was drawn and then smoothed (5mm).

Statistical maps were obtained through NiiStat software, setting 2000 permutation for multiple comparisons and considering lesions affecting at least one patient of the group. The one modality-multiple behavioral lesion analysis was restricted to two regions of interest (ROIs). These ROIs were determined by the overlap map (sum) in the sample, one covering the temporal lobe and another covering the frontal lobe. After items and error classification, item structure was related to the kind of error through correlational analyses. The variables considered for each item were: number of SYNs, HYPERs, HYPOs, CO-HYPOs. The type of errors considered were synonyms and co-hyponyms because they were the most frequently committed errors.

3. RESULTS

3.1. DO80 and semantic errors analyses

A total of 226 naming errors committed during language mapping was analyzed retrospectively. Semantic errors were 33.6 % of the total, occurring in 29 of the initial 34 patients. The most frequent non-semantic errors were anomia (27.4%) and phonological alterations (14.1%). Regarding semantic errors, co-hyponym (64.5%) and synonym (17.1%) were the most frequent. They were followed by hyponym (10.5%), holonym (4%), hyperonym (2.6%), and meronym (1.3%) errors. All subsequent correlational analyses were performed only on co-hyponym and synonym errors.

Related to those DO80 items implying at least one synonym, a significant linear association between synonym emissions and the number of HYPERs was shown (number of HYPERs - averaged number of synonym errors emitted for each HYPERs number: Pearson r= 0.801, p = 0.02; r (p-percentage bend) = 0.88, p= 0.004. However, the association fitted better with an exponential function (Figure 1; R2= 0.64 for the linear association; R2= 0.97 for the exponential function). Therefore, the higher the number of HYPERs the item had, the higher the probability of emitting a synonym (a word with the same referent that differs lexically). More specifically, this relation depended on the number of HYPERs following an exponential increase.

On the other hand, seven out of the nine patients who emitted synonyms presented tumors in the frontal lobe (78 per-cent of all frontal tumor patients); the other two patients were temporal tumor patients (20 per-cent of all temporal tumor patients). Only for frontal stimulation, the HYPERs – synonym linear association held (r = 0.82, p = 0.012; r(p)= 0.87, p= 0.004; for frontal stimulation and r= 0.57, p= 0.134, n.s.; r(p) non-applicable for temporal stimulation). Again, the linear fit had lower goodness of fit for the frontal tumor patients than the exponential function (Figure 1; linear R2= 0.68; exponential R2= 0.91). For the cases implying subcortical stimulation, the pattern of errors convergently showed that synonyms were emitted on the stimulation of white matter within the frontal lobe. The cohyponyms were emitted after stimulation of white matter in the temporal lobe in one case, and in a frontotemporal tumor patient in another case. No structural image was available for this patient.

As examples of synonym emissions, for “aereo” (“airplane”; HYPERs = 9), “aeroplano” was emitted. For “carrozzina” (“wheelchair”; HYPERs = 7) “carrozzella” was emitted. For “automobile” (“car” HYPERs = 8) “macchina” was emitted. In turn, all these emissions differed from the most used noun by the patient, as set pre-surgically. Hence, when a patient always chose a given lexical item as a response, the usual word as established pre-surgically was changed by a synonym upon stimulation.

Finally, a tendency was detected for a link between the number of SYNs and the average number of synonyms emitted: for items with one SYN, the average of emitted synonyms was 0.29; for items with two SYNs, it was 0.56, and for items with three SYNs it was 1.33. Again, this trend only held for frontal tumor stimulation (0.29 - 0.33 - 1.33 in frontal vs. 0 – 0.22 – 0 in temporal). More variability in the number of synonyms implied in the DO80 is needed to confirm this trend. Finally, the number of SYNs did not correlate with the number of HYPERs (r= -0.058; p=0.78; n.s.). In turn, independently from SYNs number, the synonyms were always emitted when the number of HYPERs were high: For SYNs equal to 1, the items with synonym error always had 9 HYPERs; for SYNs equal to 2, the items with a synonym error had 9 or 7 HYPERs; for SYNs equal to 3, the items a with a synonym always had 8 HYPERs. Hence, a link between HYPERs and synonym errors was shown. And a tendency in a link between SYNs and synonym errors was detected. However, the mechanisms behind these associations might be independent.

3.2. Lesion analysis

Of the total 34 patients, 29 patients emitted semantic errors during electrostimulation. From these 29 patients, the structural image was available in 22 patients (see Table 1), because some had been scanned in other institutions. The summed location of the tumors in these patients had temporal, insular, and inferior frontal distribution (see Figure 2), which agrees with previous studies (Herbet et al., 2016a, 2016b; Tate et al., 2014). The anatomo-behavioral exploration was therefore restricted to these areas, set as two ROIs for analyses. Hence, inferior frontal and temporal areas were well described by the group, with a maximum overlap in the superior temporal lobe. This distribution agrees with the ROIs reported in the literature on semantic processing (Friederici, 2011; Hickok and Poeppel, 2007; Riès et al., 2016; Sarubbo et al., 2020), and allowed to observe possible dissociations occurring (at least) between the frontal and temporal lobes for semantic processing.

Voxel-based lesion analyses revealed precisely that co-hyponyms and synonyms dissociated in their most probable brain tumor location, to which stimulation was delivered. Co-hyponym errors were related to tumors located in the temporal lobe, specifically in the middle temporal gyrus (MTG). In contrast, synonym productions were associated with tumors in the inferior frontal gyrus (IFG) (see Figure 3).

Furthermore, this last effect was related to the link found between the number of HYPERs and the probability of emitting a synonym. A final voxel-wise analysis was conducted considering the average of HYPERs as the behavioral variable for the items leading to synonym errors emitted by each patient. The use of this variable led to the same effect in IFG, meaning that both semantic item structure and the location of stimulation in IFG conditioned the emission of a synonym.

Interestingly, an opposite, negative relation emerged with co-hyponym errors and the IFG, strengthening the observed dissociation between co-hyponyms errors with stimulation in the temporal lobe vs. the emission of synonyms upon stimulation directed to the IFG. Similarly, an opposite negative relation was found for the emission of synonyms and the MTG. Finally, a stronger negative relation was shown for the number of HYPERs of synonym errors and the MTG. Hence, these types of errors appear to be dissociated. Table 2 shows significant clusters for each variable and brain mask ($p<0.05$ permutation corrected Z values).

4. DISCUSSION

The ability to name an object is as complicated as automatic in healthy conditions. Errors generated from the temporary disruption of this process, as in language mapping with DCE stimulation, provide information about the inner mechanisms of word production. Our data support the neurofunctional dissociation between stages of lexical retrieval. Notably, the role of IFG in the lexical selection mechanism contrasted to the involvement of MTG in semantic-to-lexical activation is shown in synonym and co-hyponym errors, respectively.

A qualitative analysis of naming errors, with a link to the most probable associated tumor location, may allow a pre-identification of critical areas and their associated errors. The application of such analysis, in turn, as it will be argued later in this discussion, can help to reduce false negatives during DCE stimulation. For achieving this, accuracy and objectivity in errors and item classification are fundamental.

We addressed this issue with a linguistically-based method for the classification, based on a sizable semantic database of word meanings (IWN software). Its semantic categories mirrored those previously used in Miozzo et al. (2017), Corina et al. (2010), Duffau et al. (2005), but were objectively obtained querying a database. Moreover, for the first time, the semantic structure of the items was contrasted with the patient's behavioral response and subsequently contrasted with brain areas of stimulation. Results replicated previous works (Corina et al., 2010; Miozzo et al., 2017) in finding co-hyponym errors as the most frequent type of semantic errors associated with a brain tumor located in the MTG.

Crucially, thanks to IWN classification, we could also explore synonyms in items and error distribution. Note that clinically, so far, this category was not considered an error; in fact, synonyms are alternative names used to label the same object. According to IWN, these words share the same semantic representation but differ lexically: it is a repeated divergence in the selection of a synonym instead of the usual retrieved word that determines the error during stimulation. Furthermore, our results described the neurofunctional bases of synonym deviations, with tumors in the IFG. Interestingly, this association with the IFG was also strong when considering the number of HYPERs upon synonym errors.

Finally, this neural dissociation between co-hyponyms, associated with the MTG, and synonyms associated with the IFG was again shown in a negative relation between the co-hyponym errors and the IFG, and between synonyms or the HYPERs upon synonym errors, and the MTG. Traditional psycholinguistic models of word production require one to pass across different stages, where coordination and interaction are still debated. Commonly accepted is the distinction between a prelexical conceptual level that provides input to the lexicalization process and the following lexical levels (Dell et al., 1999; Jescheniak and Schriefers, 1998; Levelt, 1989).

In picture naming, according to some models (Dell et al., 1999), an object's concept may map the target-word representation jointly with those of its semantic neighbors, words that are somehow linked to the main concept. During a semantic competition, the correct concept must overcome the noise implied by the other active competitors. DCE probably generates an alteration in this process, whose result is a semantic neighbor instead of the item: co-hyponym error. Therefore, co-hyponym localization in MTG could be seen as the interruption of semantic-to-lexical mapping, a view that agrees with previous studies (Python et al., 2018) and the ventral pathway of the dual-route models of speech (Duffau et al., 2014; Friederici, 2011; Hickok and Poeppel, 2007). Moreover, it confirms the role of MTG in lexical activation (Python et al., 2018; Riès et al., 2016; Snyder et al., 2011).

On the other hand, we ascribe the production of a synonym to a post-semantic difficulty fixed on the lexical-selection level. Synonym errors would be the result of an alteration in the selection mechanism between highly competitive alternatives. In normal conditions (Figure 4A), the dominant term, which is also the most frequently used, is coactivated with the alternative synonym (Dylman and Barry, 2018), overcoming the selection threshold to be produced. It is something similar to what happens in bilinguals between the dominant and non-dominant languages (Dylman and Barry, 2018), with different lexical entries for the same concept in each of the languages. In this regard, there are DCE studies provoking language switch errors when stimulating inferior frontal regions (Kho et al., 2007). According to precedent studies on aphasic speakers (Python et al., 2018), IFG deals with this lexical selection. Inspired by those studies, we propose that DCE stimulation (lesion) on the IFG could generate difficulty in adjusting the lexical selection threshold, likely lowering the level compared to normal conditions. Consequently, and crucially, the probability of emitting an alternative-synonym would be increased. Hence with DCE stimulation, the result is the higher likelihood of production of a synonym during language mapping in IFG (Figure 4B). The case outlined in Figure 4B is also supported by the overall higher probability of synonyms in frontal lobe patients. Finally, the hypothesis predicts an association between the number of SYNs of an item and the production of a synonym, only for frontal tumor patients. This tendency observed in our data needs further testing with alternative items. Overall, results support the hypothesis of an IFG recruitment not in lexical retrieval per se, but the following lexical selection process (Thompson-Schill et al., 1999, 1997).

Furthermore, the effect we found of HYPERs on synonym errors, as well as its locus in the IFG, could be described as a facilitatory effect from items' number of HYPERs on lexical candidates. Accordingly, patients with lesions in IFG have shown to be sensitive to semantic facilitation, like priming (Python et al., 2018). In the naming task, the HYPERs structure of a given item would decrease the retrieval effort for the preferred lexical item, and the synonym (Snyder et al., 2011).

Hence, we suggest a 'vertical' semantic influence that might positively interact with the lowered threshold by DCE on IFG, increasing the alternative-synonyms probability of winning the lexical selection. Following this hypothesis, the creation of a new list of items balanced for the presence of synonyms and the number of HYPERs should augment the production of synonym errors during stimulation in IFG. In this scenario, it has to be noticed that the dominant word's status is still of preference, but its power on the alternatives is less overcoming due to the HYPERs facilitatory effect (Figure 4C). Further tests to this hypothesis might come from stroke patients with a lesion in the IFG.

Overall, the current study replicated previous data on the brain locus for co-hyponym erroneous production, appearing during MTG temporary disruption through DCE. Importantly, we extend the investigation and specify other phenomena upon IFG temporary disruption, associated with the deviation to a synonym. This dissociation provides new information on the different stages of lexical retrieval based on DCE causal data. Based on our hypothesis, the association between synonyms and the IFG responds to a failure in a specific lexical selection mechanism carried by this area. In turn, the present results broadly illustrate two components of semantic cognition, namely semantic control and semantic storage. The IFG would be behind the executive component of semantic cognition (e.g., Bookheimer, 2002; S. Thompson-Schill et al., 1997; Wagner et al., 2001; Whitney et al., 2011). The temporal cortex has been long-term proposed crucial as semantic storage (e.g. Hickok and Poeppel, 2004; Indefrey and Levelt, 2004; Patterson et al., 2007). However, the role of the temporal cortex in semantics appears to be more heterogenous: it might also be crucial within the semantic control network in its middle most posterior part (Whitney et al., 2011b) but would certainly sustain the processing of semantic competition and storage as its exact loci become rostral (Snijders et al., 2009; Whitney et al., 2011b).

Hence in our study, the disruption of this interconnected system (Lambon-Ralph et al., 2017; Whitney et al., 2011a) resulted in two behavioral realizations: co-hyponyms and synonyms errors. Cortical stimulation in MTG and IFG may alter these intertwined components within the network, evoking functionally different difficulties, respectively, in retrieval (co-hyponyms) and selection (synonyms) processes. The present data also clarifies the neural bases for relational knowledge and feature-based approaches to semantics, whose study within the control semantic cognition framework was largely unexplored (Lambon-Ralph et al., 2017).

These data have thus implications for our understanding of lexical processing. However, they are also essential for neurosurgery. They, in fact, also imply an in-depth analysis of the DO80, which could apply to other naming tests in surgical contexts. DCE elicited errors were approached through a systematic exploration of the item – error associations, and with a further link to the areas of stimulation evoking those errors. Hence, they are a first attempt to use naming tests in a more programmed way, reducing the testing time and decreasing the probability of error. These first data imply that temporal tumors are likely to produce co-hyponym errors. Therefore, using items with larger associated co-hyponyms while testing temporal tumors should decrease the probability of error, reducing false negatives. It must be noted that our regression analyses were limited by the specific DO80 items under study, with a small set of data points. More variability should be used in follow-up studies, through the consideration of other naming tests. The item analyses, however, converged with the lesion analyses.

Additionally, our data stress the role of the IFG in lexical selection processes, such as in the mechanisms elicited by items with a higher number of hyperonyms, and for which synonyms are available. In other words, all the items included in the DO80 do not have the same semantic characteristics, as described here. Hence, they should have no equivalent probability of provoking an error, depending on the stimulated area. We are currently collecting finer-grained confirmatory data. This information further includes the collection of reaction times for semantically different items. Other tests, such as verb generation, should be retrospectively explored using similar approaches with the ultimate goal of decreasing testing time and increasing item sensitivity.

Acknowledgments - This work was supported by Horizon 2020 Marie Skłodowska-Curie actions 2017 (project number 793071) to E.S. **Corresponding author** – Elena Salillas or Marika Gobbo; email: salillas.elena@gmail.com / elena.salillas@unipd.it / gobbomarika@gmail.com Address: Department of Neurosciences, University of Padova. Via Giustiniani 5 – 35128 - Padova, Italy.

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Table 1. Patients included in the voxel-lesion analyses.

Pat: patient, Loc: tumor localization, H/L: high/low grade of malignancy (IV/III-II), NE: neurological examination (only language data are reported), F= frontal, T=temporal, P=parietal, I=insular, O=occipital; r = tumor recurrence.

Pat	Loc	Diagnosis	Grading	Preoperative NE	Postoperative NE (4-10 days after)	Follow-up NE (1 month after)
1	F	glioma	L	no language disorder	transitory anomic aphasia	no disorder
2	TO	glioma	L	no language disorder	transitory anomic aphasia	no disorder
3	T	glioma	\	no language disorder	Wernicke's aphasia	mild disorder
4	P	cavernoma	\	no language disorder	no language disorder	
5	FT	glioma (r)	H	no language disorder	no language disorder	
6	I	glioma (r)	L	no language disorder	no language disorder	
7	F	glioma	H	no language disorder	Broca's aphasia	disorder
8	FI	glioma	L	mild language alteration (anomia)	dysarthria	no
9	FT	glioma	H	slow speech rate	transitory anomic aphasia	no disorder
10	F	glioma	\	no language disorder	transitory anomic aphasia	no disorder
11	T	glioma	H	no language disorder	no language disorder	
12	F	glioma	L	no language disorder	no language disorder	
13	T-I	glioma	L	no language disorder	no language disorder	
14	P-T	cavernoma	\	no language disorder	no language disorder	
15	F	glioma	L	no language disorder	no language disorder	
16	F	glioma	L	mild language alteration	anomic aphasia	disorder
17	T	glioma	H	no language disorder	Wernicke's aphasia	no disorder
18	T	glioma (r)	H	mild language alteration (anomia and semantic paraphasia)	anomic aphasia	disorder
19	T	glioma	H	\	\	
20	T	glioma (r)	L	\	\	
21	FT	glioma (r)	H	\	\	
22	P	glioma	L	no language disorder	no language disorder	

*Transitory aphasia: aphasia only in the acute phase.

Table 2 - Significant clusters from the lesion analyses. With the frontal mask, significant clusters were shown for the synonym and IFG association. This association was also evident when considering the HYPERs. A negative association was shown between the co-hyponym errors and the IFG. Conversely with the temporal mask, significant clusters for the co-hyponym and MTG association appeared. A negative association appeared at similar cluster when considering the HYPERs for synonym errors.

Frontal	Direction	Variable	Z corrected interval	Z	Location	Peak MNI	Cluster BAs
	positive	**Synonym**	-1.14 > Z > 2.23	3.14	IFG: triangularis; orbitalis, opercularis MFG	[-34,18,-14]	44,45,46,47
	positive	**HYPERs**	-1.39 > Z > 1.87	2.93	IFG: triangularis; opercularis MFG	[-46,24,22]	44,45,46
	negative	Co-hyponym	-1.78 > Z > 1.31	-2.84	IFG: triangularis, orbitalis, opercularis MFG	[-36, 20,30]	45,46,47
Temporal	**Direction**	**Variable**	**Z corrected interval**	**Z**	**Location**	**MNI**	**Cluster BAs**
	negative	Synonym	-1.31 > Z > 1.96	-1.34	MTG	[-56 -22 -8]	21
	negative	HYPERs	-1.53 > Z > 1.84	-1.67	MTG	[-56 -22 -8]	21
	positive	**Co-hyponym**	-1.81 > Z > 1.49	1.86	MTG MTG MTG, STG	[-58, -22, -8] [-58 -16 -18] [-56, -8, -4]	21 21 22,21

FIGURE CAPTIONS

Figure 1. Effect of hyperonyms (HYPERs) on synonym errors. The left figure shows an exponential growth (b = 0.82) for the number of synonyms as a function of the number of HYPERs of the item, in all patients. Only those DO80 items implying synonyms in their WordNet structure were considered. The average number of emitted synonyms by each HYPERs value is plotted on the Y-axis. However, this effect appeared mostly in patients with tumors involving the frontal lobe.

Figure 2. Lesions overlap of 22 patients on a standard MNI152 template. On the left, Temporal and Frontal lesion volume masks costumed as ROIs in the lesion-analyses: only voxels within them were considered. MNI Z coordinates are displayed above each slice.

Figure 3. Brain dissociation between co-hyponym and synonyms errors. Statistical maps calculated with NiiStat software and implemented on a standard template (MNI152). Positive Z-scores are displayed starting from the minimal threshold set for the statistical significance (corrected $p<0.05$); MNI coordinates and regions localization (AAT-atlas) was based on xjview software. Top: the probability of committing a *co-hyponym* error during language mapping increased when patients presented a tumor in the MTL. Maxima (Z=1.86) in middle MTG (MNI -58,-22,-8), Brodmann area 21. Bottom: the probability of producing a synonym during language mapping was associated with tumors in the IFG. Maxima (Z=3.14) in pars orbitalis of IFG (MNI -34,18,-14), Brodmann area 47, extending to other sections of the IFG. MNI Z coordinates are displayed above each slice.

Figure 4. Hypothesis of lexical selection mechanism upon synonyms production. The probability to select a synonym instead of the dominant name (item) progressively increases from normal (A) to brain stimulation conditions (B-C). The adjustment of the lexical selection threshold (dotted line) is lower than the normal under DCE stimulation over the IFG. In C the facilitatory effect (plus sign) of the item's HYPERs is taken in account, increasing the relative activation status of the non-preferred synonym. The relative probability of emitting a dominant noun vs. the non-preferred synonyms progressively increases from A to C.