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Mapping the connectivity underlying multimodal (verbal and non-verbal) semantic processing: A brain electrostimulation study

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ABSTRACT

Accessing the meaning of words, objects, people and facts is a human ability, made possible thanks to semantic processing. Although studies concerning its cortical organization are proficient, the subcortical connectivity underlying this semantic network received less attention.

We used intraoperative direct electrostimulation, which mimics a transient virtual lesion during brain surgery for glioma in eight awaken patients, to map the anatomical white matter substrate subserving the semantic system. Patients performed a picture naming task and a non-verbal semantic association test during the electrical mapping.

Direct electrostimulation of the inferior fronto-occipital fascicle, a poorly known ventral association pathway which runs throughout the brain, induced in all cases semantic disturbances. These transient disorders were highly reproducible, and concerned verbal *as well as non-verbal output*.

Our results highlight for the first time the essential role of the left inferior fronto-occipital fascicle in multimodal (and not only in verbal) semantic processing. On the basis of these original findings, and in the lights of phylogenetic considerations regarding this fascicle, we suggest its possible implication in the monitoring of the human level of consciousness related to semantic memory, namely noetic consciousness.

1. Introduction

Accessing the meaning of words, objects, people and facts is a human ability, made possible thanks to semantic processing. This ability is essential not only to understand and produce language, but also to understand the whole world. Semantic information is stored in networks constituting semantic memory (Anderson, 1983; Collins & Loftus, 1975; Collins & Quillian, 1969). How and where semantic knowledge is organized and is processed in the brain remains matter of debate.

Studies concerning the cortical organization of semantic processing are numerous (for a review, see Binder, Desai, Graves, & Conant, 2009), and suggest the involvement of a large-scale network throughout the brain, including frontal, temporal and parietal areas (Price, 2010; Vigneau et al., 2006). Within semantic processing, it is important to distinguish semantic representation itself and the mechanisms of control involved in its processing. Some authors propose that semantic knowledge is distributed along distinct and interconnected cerebral areas, such as lateral and medial portion of the fusiform gyrus, posterior part of the superior temporal sulcus (pSTS), posterior part of the mid temporal gyrus (pMTG), inferior parietal sulcus (IPS), and ventral premotor cortex (VPMC) in the left hemisphere (Martin, 2007; Mion et al. 2010; Turken & Dronkers, 2011). In contrast, other authors propose a unified semantic representation highlighting the anterior temporal lobes as an amodal representational hub – with nevertheless important differences between the ventrolateral part which might be multimodal and the superior part which might be more crucial for auditory stimuli (Visser & Lambon Ralph, 2011) – receiving integrated information from modality-specific areas throughout the brain (Lambon Ralph, Sage, Jones, & Mayberry, 2010; Patterson, Nestor, & Rogers 2007; Rogers et al., 2004; Visser, Embleton, Jefferies, Parker, & Lambon Ralph, 2010). In order to access and activate this semantic knowledge, i.e. to achieve a successful semantic processing in a given context, two basic interacting components have to be efficient: the semantic store itself on one hand and the mechanisms of control underlain by executive functioning on the other hand (Jefferies & Lambon Ralph, 2006; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies,

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2011). The neural bases of this executive functioning are described in many studies and encompass the left Inferior Frontal Gyrus (left IFG) and the left Pre Frontal Cortex (left PFC) (Bookheimer, 2002; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001; Ye & Zhou, 2009).

However, the subcortical connectivity underlying this semantic network received less attention, and the scarce data available are controversial. Although current studies agree on the existence of a ventral pathway sub-serving semantic processing, parallel to a dorsal pathway sub-serving phonological processing (Hickok & Poeppel, 2004), the anatomical substrate of the ventral route is not clearly established. Distinct associative white matter pathways have been suggested by different authors: the Inferior Longitudinal Fascicle (ILF) and Uncinate Fascicle (UF) (Agosta et al., 2010), the extreme capsule (Saur et al., 2008; Saur et al., 2010), and the Inferior Fronto-Occipital Fascicle (IFOF) (De Zubicaray, Rose, & Mc Mahon, 2011; Duffau et al., 2005; Turken & Dronkers, 2011).

In a previous study, we have demonstrated using intraoperative subcortical mapping in awaken surgeries, that electrical stimulation of the left IFOF elicited semantic paraphasia with a high level of reproducibility during picture naming. As a consequence, we suggested that this pathway was critical for the connectivity underlying language semantics (Duffau et al., 2005). Nonetheless, the involvement of the IFOF in non-verbal semantic processing remains matter of debate.

Here, we used intraoperative direct electrical stimulations (DES), which mimics a transient virtual lesion during glioma brain surgery in awaken patients, to study both verbal and non-verbal semantic processing skills. Indeed, when removing a brain tumour, it is common clinical practice to awake the patient, and temporarily inactivate small brain regions with DES, while the patient performs cognitive tasks. If the patient produces incorrect responses, the surgeon leaves the region intact, to preserve the patient's cognitive abilities. Electrically inactivated regions can be precisely identified, using postoperative magnetic resonance imaging. Therefore, DES allowed us mapping the white matter tracts underlying the semantic ventral pathway. On the basis of our original data, we suggest the crucial role of the left IFOF in multimodal (i.e. not only in verbal but also in non-verbal) semantic processing and possibly in noetic consciousness.

2. Patients and methods

Experimental procedures described below constitute the standard management of glioma patients undergoing a surgery in awaken conditions in our institution, for which they gave their informed consent.

2.1. Patient population

Eight patients (6 men, mean age 41.6 years; SD 11.2; range 21–52) who underwent a surgical resection in awaken condition for a World Health Organization grade 2 glioma (G2G) located in the left temporal or temporo-occipital regions took part to the study. Seven patients were right-handed and one was ambidextrous according to the Edinburgh inventory. All patients had a Karnofsky Performance Status of 90 or 100%, with no functional deficit on a standard neurological examination. Seizures were the presenting symptoms in all patients. The preoperative magnetic resonance imaging localized the tumor within the left temporal lobe in six patients, the left fronto-temporo-insular region in one patient and the left temporo-occipital junction in another patient (Table 1).

2.2. Assessment of semantic processing

All patients performed an assessment of semantic processing the day before surgery, using three standardized tests: a visual naming test (DO 80) (Metz-Lutz, Kremin, & Deloche, 1991), a semantic fluency task (Cardebat, Doyon, Puel, Goulet, & Joanette, 1990), and a non-verbal semantic matching test (Pyramid and Palm Trees Test, PPTT) (Howard & Patterson, 1992).

During surgery, the same tests except semantic fluency task were administered (with only the items passed the day before) in loop, during the resection and while the neurosurgeon applied DES, at the level of cortical and subcortical areas. Patients' skills were checked continuously by a speech-therapist.

Five days and six months after surgery, the same assessment as preoperatively was administered to the patients.

Table 1
Demographic and behavioral data.

Pat	Sex/age	Hand	Loc	PPTT/52			DO/80		
				Pre	Post5d	Post6m	Pre	Post5d	Post6m
1	M/48	R	left T	50	49	49	79	70	76
2	M/34	A	left T	51	50	49	76	53	66
3	M/21	R	left T	47	41	48	80	12	76
4	M/48	R	left T	43	42	44	62	31	46
5	F/32	R	left T	46	44	43	80	74	79
6	F/49	R	left T	45	46	47	79	77	79
7	M/49	R	left FTI	50	44	47	80	76	80
8	M/52	R	left TO	49	41	51	80	70	79
Mean				47.63	44.63	47.25	77.00	57.88	72.63
SD				2.83	3.46	2.66	6.21	24.20	11.66

Note: PPTT cut-off score=49/52; DO cut-off score=77/80.
Abbreviations: pat=patient; hand=handedness; loc=tumor location; PPTT=pyramid and palm trees test (non-verbal visual semantic association task); DO=French naming task; pre=pre-operatively; post5d=5 days post-operatively; post6m=6 months post-operatively; *T*=temporal; FTI=fronto-temporo-insular; TO=temporo-occipital.

2.3. Description of the tests used

The DO 80 (Metz-Lutz et al., 1991) is a French standardized naming test, constituted of 80 black and white drawn pictures presented on a computer screen. The patient is asked to name each picture the most accurately as possible. If all the pictures are correctly named, the patient obtains 80/80. Different kinds of errors may occur: anomia (no response), semantic paraphasia (production of a word semantically related to the target word, e.g. cow for horse), verbal paraphasia (production of a word non-related to the target word, e.g. table for horse), phonological paraphasia (production of the target word with phonological deviations, e.g. pheletant for elephant), speech arrest or dysarthria (disorder in the articulation motor programming), perseveration (repetition of a prior word in front of a new picture), delay of a correct response (Duffau et al., 2005). Each error removes 1 point on the final score.

The semantic fluency task (Cardebat et al., 1990) is a French standardized test consisting in a semantic lexical evocation test, for which the patient is asked to produce during 2 min the largest number of animals names.

Each correct word is noted 1 point. Each incorrect or repeated word is not counted.

A phonological fluency task (letter/p/) was also administered to all patients according to the same modalities.

The PPTT (Howard & Patterson, 1992) is a standardized visual non-verbal semantic association test, constituted of 52 black and white drawn pictures presented on a computer screen. For each target picture, two new pictures are proposed and the patient is asked to match one of both with the target one according to a semantic link, by pointing it out. If all the decisions are correct, the patient obtains 52/52. Each error removes 1 point on the final score.

2.4. Surgical procedure and intraoperative mapping

G2G are slow-growing pre-cancerous tumors invading the central nervous system of young adults for which surgical resection is the most appropriate management (Soffietti et al., 2010). Given that G2G are preferentially located in functional areas for language or sensory-motor functions, this surgical resection has to be led in awaken conditions with the goal to maximize the resection of the tumor while preserving the integrity of functional networks by performing both cortical and subcortical electrical mapping (Duffau, 2005, 2009). To achieve this challenge, as previously reported (Duffau et al., 2005; Maldonado, Moritz-Gasser, & Duffau, 2011), language and sensory-motor skills are checked continuously during awake period while the neurosurgeon applies direct electrical stimulation (DES) at the cortical level and then at the subcortical level throughout the resection (bipolar electrode, biphasic current, 60 Hz, intensity from 1.5 to 4 mA, Nimbus, Hemodia, Newmedic). DES has the transient effect (about 4 seconds) of a virtual lesion. Therefore, if the region stimulated is critical within a functional network, the function sub-served by this cortical area or this white matter tract will be disturbed during a few seconds.

In practice, a wide craniotomy was performed under sedation. The tumor margins were verified in relation to the sulcal and gyral brain surface anatomy with