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The “frontal syndrome” revisited: Lessons from electrostimulation mapping studies

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ABSTRACT

For a long time, in a localizationist view of brain functioning, a combination of symptoms called “frontal syndrome” has been interpreted as the direct result of damages involving the frontal lobe(s). The goal of this review is to challenge this view, that is, to move to a hodotopical approach to lesion mapping, on the basis of new insights provided by intraoperative electrostimulation mapping investigations in patients who underwent awake surgery for cerebral tumors. These original data reported in the last decade break with the traditional dogma of a modular and fixed organization of the central nervous system, by switching to the concepts of cerebral connectivity and plasticity – i.e., a brain organization based on dynamic interrelationships between parallel distributed networks. According to this revisited model, “frontal symptoms” can be generated by tumor or electrostimulation not only of the frontal lobes, but also of cortical and subcortical (white matter pathways/deep gray nuclei) structures outside the frontal lobes: especially, stimulation of the superior longitudinal fascicle may elicit speech production disorders, syntactic disturbances, involuntary language switching or phonemic paraphasia (arcuate fascicle), stimulation of the inferior fronto-occipital fascicle can generate semantic paraphasia or deficit of cross-modal judgment, stimulation of the subcallosal fasciculus may elicit transcortical motor aphasia, while stimulation of the striatum induces preservations. On the other hand, it is also possible to perform extensive right or left frontal lobectomy in patients who continue to have a normal familial, social and professional life, without “frontal syndrome”. Therefore, this provocative approach may open the door to a renewal in the modeling of brain processing as well as in its clinical applications, especially in the fields of cerebral surgery and functional rehabilitation. These findings illustrate well the need to reinforce links between cognitive neuroscience and clinical neurology/neurosurgery.

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1. Introduction

Since more than one century ago, numerous lesion studies have related specific neurological symptoms to damages of the frontal lobes, leading to the proposal of the so-called “frontal syndrome”. Traditionally, this syndrome can combine language disorders when the lesion involves the left dominant hemisphere (especially nonfluent aphasia or transcortical motor aphasia due to injury of Broca’s area or supplementary motor area, respectively), deficit of executive functions (in particular working memory, attention, control, planning and problem-solving), and behavioral changes (notably concerning emotional, social and metacognitive processes) (Stuss and Benson, 1986; Alexander et al., 1989). It is nonetheless worth noting that the role of the frontal lobes has been matter of controversies in the literature over the decades, with authors who contested that the frontal lobes played no special role. For example, although agrammatism is implied to be traditionally characterized as being caused by frontal damage, data indicating that agrammatism is a far more complex entity have been provided by cross-language studies (Sasanuma, 1989). More recently, it was suggested that there were discrete categories of functions within the frontal lobe, explaining why various deficits may occur in cases of distinct frontal lesions according to their locations – e.g., the “dysexecutive syndrome” when the “executive system” is damaged (Stuss and Alexander, 2007). However, in a classical localizationist view, the frontal lobe continues to be considered as a specific focal entity, while its subcortical connectivity has received less attention.

The goal of the present review is to propose an alternative hodotopical and dynamic approach to revisit the concept of “frontal syndromes”, based on the recent findings provided by intraoperative electrical stimulation mapping in patients who underwent awake surgery for cerebral tumors. Indeed, the use of direct brain stimulation, which can be assimilated to a transient virtual lesion, enables to perform on-line anatomo-functional correlations both at cortical and subcortical levels. In addition, combination of intrasurgical mapping data with results of pre- and post-operative neurocognitive assessments, especially following extensive frontal lobectomy, open the door to a “plastic” view of brain processes which call into question the role of the frontal lobe as thought according to traditional models.

2. Frontal tumors and stimulation may give “frontal symptoms”

Although for a long time neuropsychological assessment was only exceptionally performed in patients with brain tumors, recent studies have begun to test neurocognition in a more systematic way before treatment. Not surprisingly, deficits of higher functions have regularly been observed, even in patients who presented a normal “standard” neurological examination, in particular in cases of slow-growing tumor such low-grade gliomas usually revealed by seizures (Taphoorn and Klein, 2004). For tumors involving the frontal lobe(s), symptoms belonging to the classical “frontal syndrome” have regularly

been identified, that is language, cognitive, emotional and behavioral deficits (Reijneveld et al., 2001; Mainio et al., 2006; Bosma et al., 2007; Teixidor et al., 2007; Correa et al., 2008; D’Angelo et al., 2008; Tucha et al., 2000; Ruge et al., 2011).

Interestingly, in the past decade, a growing number of patients bearing a brain tumor underwent surgery under local anesthesia (in both hemispheres), with intraoperative functional mapping using direct cortical and subcortical electrical stimulation, in order to preserve the eloquent structures and thus the quality of life (Duffau, 2010; Duffau et al., 2008a, 2008b). Interestingly, many studies reported the transient induction of “frontal symptoms” during electrostimulation of the frontal lobe, with most of the time elicitation of only one specific deficit according to the location of the stimulation, therefore supporting the theory of discrete categories of functions within the frontal lobe. First, in the left dominant hemisphere (Fig. 1), stimulation of the ventral premotor cortex (that is, the lateral part of the precentral gyrus) generated speech arrest, while stimulation of the dorsal premotor cortex elicited anomia – i.e., typical symptoms of a “nonfluent” aphasia (Duffau et al., 2003a). Moreover, stimulation of the left inferior frontal gyrus induced paraphasias (usually phonemic paraphasia more posteriorly and semantic paraphasia more anteriorly) (Duffau et al., 2002a, 2005a), with also possible syntactic errors (grammatical disturbances in particular concerning the gender, generally by stimulating over the pars triangularis) (Vidoretta et al., 2011) – thus in accordance with the classical agrammatism often observed in the so-called “Broca’s aphasia” (Bastiaanse et al., 2003). In addition, stimulation of the left supplementary motor area may induce a mutism, especially in its anterior part (Fontaine et al., 2002), in agreement with a “transcortical motor aphasia”. Of note, stimulation of the right frontal lobe can also generate the same mirror symptoms in left-handers and ambidextrous (Duffau et al., 2008a), as well as in a subgroup of right-handed patients, thus inducing a transitory crossed aphasia (Vassal et al., 2010). Writing was also disrupted by stimulation over the Exner’s area, namely, the inferior and posterior part of the left middle frontal gyrus (Roux et al., 2009). Beyond pure oral or written language disturbances, other cognitive disorders have been induced by cortical mapping: deficit of cross-modal judgment by stimulating the left dorsolateral prefrontal cortex (Plaza et al., 2008) (Fig. 2); disturbances of monitoring and control, by eliciting in bilingual patients an involuntarily switch from one language to another during the stimulation of the left inferior frontal gyrus (Kho et al., 2007); disorders of initiation by stimulating the supplementary area or negative motor phenomena during stimulation of the “negative motor area” (Lüders et al., 1995); inhibition of ocular saccades involved in attention when stimulating the frontal eye fields (Milea et al., 2002); disturbances of recent verbal memory by stimulation during retrieval (Ojemann, 2003) or even interference with mental rotation by stimulation over the primary motor cortex (Tomasino et al., 2005).

In addition to these cognitive and language disturbances observed during cortical mapping, it is worth noting that axonal stimulation performed throughout the surgical resection can also reproduce the same kind of deficits (Fig. 3), such as anarthria by stimulating the fibers coming from the ventral

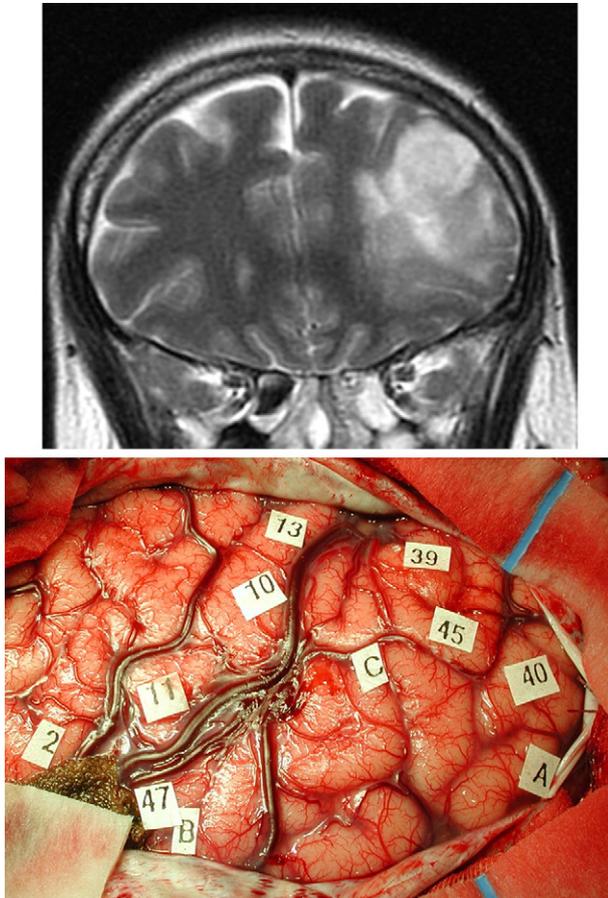


Fig. 1 – Upper: coronal Fluid attenuation inversion recovery (FLAIR)-weighted MRI showing a left frontal World Health Organization (WHO grade II glioma, essentially involving the middle frontal gyrus, and revealed by seizures in a young patient with a normal neurological examination. Lower: intraoperative photograph (the anterior part is right, the back is left). Awake mapping allowed the detection of the ventral premotor cortex (lateral part of the precentral gyrus) eliciting speech arrest during stimulation (10 and 13), the primary motor cortex of the face (11) and of the hand (2) behind the dorsal premotor cortex (47) – which generated anomia when stimulated. Interestingly, stimulation of the left inferior frontal gyrus “Broca’s area” did not induce speech arrest, but phonemic paraphasias over the pars opercularis (39), syntactic disorders over the pars triangularis (45) and semantic paraphasias over the pars orbitaris (40). Letter tags marked the boundaries of the tumor.

premotor cortex (Duffau et al., 2003a) or the anterior part of the lateral portion of the superior longitudinal fascicle (Duffau et al., 2003b); phonemic paraphasia during stimulation of the anterior part of the deep part of the superior longitudinal fascicle (i.e., the arcuate fascicle) (Duffau et al., 2002a); semantic paraphasia during stimulation of the anterior part of the inferior fronto-occipital fascicle (Duffau et al., 2005a); transcortical motor aphasia by stimulating the subcallosal fasciculus (connecting the supplementary motor area to the

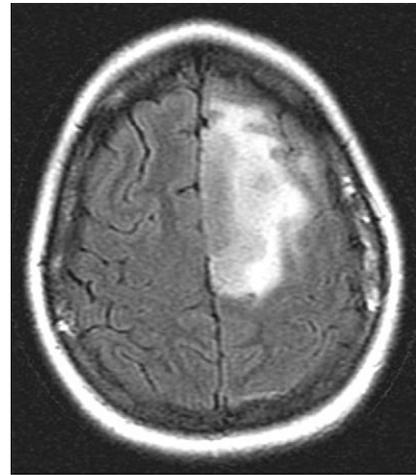


Fig. 2 – Upper: axial FLAIR-weighted MRI showing a left frontal WHO grade II glioma, essentially involving the superior frontal gyrus, and revealed by seizures in a young patient with a normal neurological examination. Lower: intraoperative photograph (the anterior part is right, the back is left). Awake mapping allowed the detection of the primary motor area of the hand (1 and 2), primary motor area of the face (10 and 11), ventral premotor area inducing speech disturbances when stimulated (20 and 21), dorsal premotor area inducing naming disorders during stimulation (12 and 13). Interestingly, stimulation over the dorsolateral premotor cortex (22, green circle) in front of the dorsal premotor area produced reproducible specific cross-modal visual–verbal errors but no naming disturbances (modified from Plaza et al., 2008). Letter tags marked the boundaries of the tumor.

cingulum and head of the caudate) (Duffau et al., 2002a); disturbances of monitoring with unintentional language switching during stimulation of the anterior and deep part of the superior longitudinal fascicle in bilingual patients, or even deficit of cross-modal judgment during stimulation of the anterior and superior part of the inferior fronto-occipital fascicle under the dorsolateral prefrontal cortex (Plaza et al., 2008). Furthermore, transitory electrical inactivation of the left striatum may also elicit anarthria (stimulation of the lentiform nucleus) or disturbances of control (such as

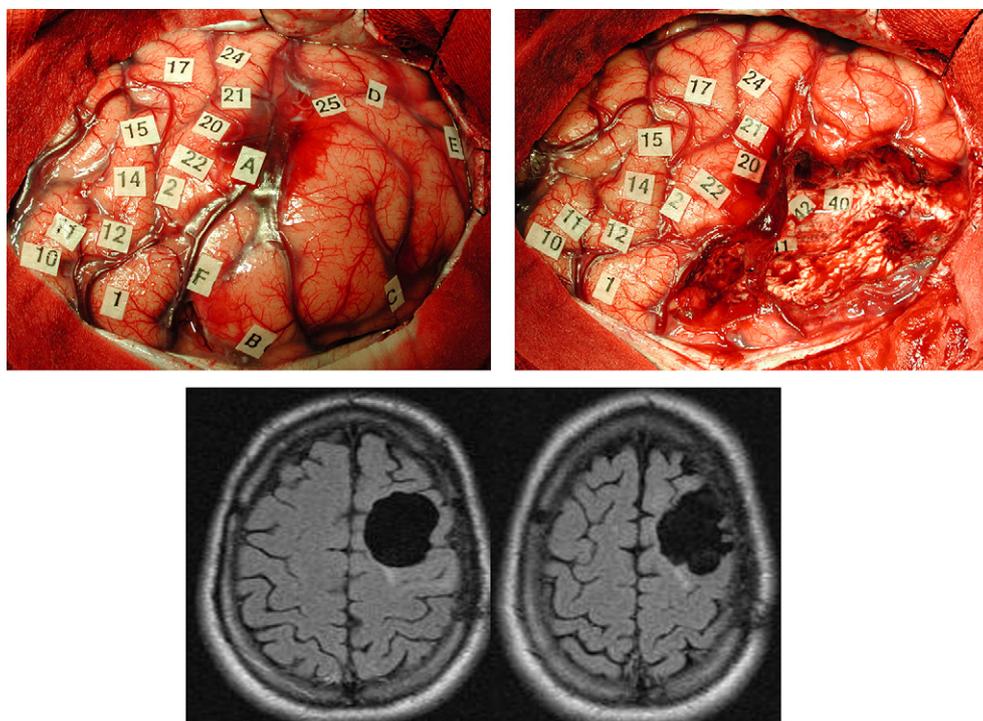


Fig. 3 – Upper: intraoperative photograph (the anterior part is right, the back is left), in a patient bearing a left frontal WHO grade II glioma. Left: photograph before resection. Awake mapping allowed the detection of the primary sensory-motor areas (central region) and language areas (number tags) behind and lateral to the tumor (marked by letter tags). Right: photograph after the resection, performed according to functional boundaries, both at cortical and subcortical level. Interestingly, language pathways have been identified in the white matter (40, 41 and 42), that is, anterior part of the superior longitudinal fascicle inducing phonemic paraphasia when stimulated, frontal part of the inferior fronto-occipital fascicle eliciting semantic paraphasia when stimulated, and fibers coming from the ventral premotor cortex, eliciting speech production disorders during stimulation. This subcortical connectivity has been preserved. Lower: axial FLAIR-weighted MRI showing an extensive glioma resection, in a patient who experienced a transient language deficit, and then returned to a normal social and professional life with no neurological deficit after several weeks of functional rehabilitation.

perseveration by stimulating the head of the left caudate nucleus) (Gil Robles et al., 2005). As at the cortical level, stimulation of the right frontal subcortical structures can also generate the same mirror symptoms in left-handers and ambidextrous (Duffau et al., 2008a), as well as in a subpopulation of right-handed patients (Vassal et al., 2010).

In summary, these findings mean that “frontal symptoms” may be induced by transient virtual lesion of discrete frontal cortical areas, but also by inactivation of the frontal connectivity – both horizontal cortico-cortical (frontal cortex to non-frontal cortex, see below) as well as vertical cortico-subcortical (cortex to deep gray nuclei) connectivity. Following surgery within the frontal lobe, extensive neuropsychological examinations again detected several “frontal symptoms”. Beyond the frequent transient language worsening in the immediate postsurgical period, deficits of (verbal) working memory, attention as well as high level of cognitive control have regularly been reported (du Boisgueheneuc et al., 2006; Teixidor et al., 2007; Volle et al., 2008; Klein and De Witt Hamer, *in press*). For example, patients demonstrated mild worsening in attention following resection of frontal or pre-central tumors (Goldstein et al., 2003; Braun et al., 2006) with a selective attentional impairment in Stroop test performance

more frequent after resection of the right rather than the left prefrontal cortex (Vendrell et al., 1995). After resection of the supplementary motor area, patients experienced worsening of procedural learning and agraphia (Ackermann et al., 1996; Scarone et al., 2009). Impaired sequence ordering of novel material was noted, especially in right-sided frontal lesions (Swain et al., 1998), as well as planning and executive impairment (Owen et al., 1990). In addition, severe executive deficits in a reward learning task were observed in patients after bilateral fronto-orbital resections (Hornak et al., 2004) as well as impaired virtual planning of real life activities following surgical removal of the left and right prefrontal cortex (Goldstein et al., 1993; Miotto and Morris, 1998).

Surgical removal of the posterior part of the anterior cingulate cortex, known as the cingulate eye field, resulted in antisaccade errors (Milea et al., 2003). Furthermore, unilateral resection of prefrontal cortex, including the fronto-orbital or anterior cingulate cortex, generated emotional dysregulation with impaired voice and face expression identification (Hornak et al., 2003). Moreover, negative mood changes were described after tumor resection involving heteromodal prefrontal cortex, while positive mood changes were noted following lateral frontal resections (Irle et al., 1994). Finally,

the theory of mind ability was significantly worsened in patients with either right or left frontal lobe resections (Rowe et al., 2001).

3. “Frontal symptoms” can be induced by non-frontal tumors and stimulation: toward hodotopy

Although the previous paragraph described non-surprising data, namely, that “frontal symptoms” may be induced by frontal lesion, the goal is now to detail more original findings, showing that “frontal symptoms” may be elicited by non-frontal lesions (Budisavljevic and Ramnani, 2012, this issue).

First, before any treatment, it was demonstrated that (verbal) working memory and attention deficit could be detected in patients bearing a tumor within the parietal lobe (Teixidor et al., 2007). Interference in dual-fluency tasks have also been observed in posterior lesions, as already reported in frontal injury (Vilkkki et al., 2002). Other disorders such as deficits in problem-solving, rule deduction, cognitive flexibility and strategy may also be impaired in patients with non-frontal damages (Godefroy, 2003).

Using the same method of intraoperative functional mapping in awake patients than detailed above, it is interesting to note that several “frontal symptoms” previously described can also be elicited by stimulating non-frontal structures. For example, speech production disorders may be generated during the stimulation of both the left supra-marginal cortex and/or the posterior part of the lateral portion of the superior longitudinal fascicle (Duffau et al., 2003b) (Fig. 4). Thus, these results support the existence of a fronto-parietal loop involved in articulation (also supposed to be implied in working memory) (Duffau et al., 2003b), rather than a single “area of speech” located within the frontal lobe. Similarly, articulatory disturbances may be generated by stimulating the left anterior insula (Duffau et al., 2009), again pleading in favor of a wide network underlying speech articulation, with implication of the ventral premotor cortex, supramarginal gyrus, anterior insula, lateral part of the superior longitudinal fascicle and lentiform nucleus (Duffau, 2008a). In the same state of mind, phonemic paraphasias can be elicited by stimulating the left parietal and temporal cortices, as well as the deep part of the superior longitudinal fascicle (arcuate fascicle) (Duffau et al., 2002a, 2008b). Moreover, semantic paraphasias may be induced by stimulating the left temporal cortex and the temporo-occipital junction, as well as the inferior fronto-occipital fascicle (Duffau et al., 2002a, 2008b). These two other examples support a brain organization in wide cortico-subcortico-cortical networks rather than in isolated frontal cortical areas. Interestingly, the same anatomo-functional circuits can be identified within the right hemisphere in left-handers and ambidextrous (Duffau et al., 2008a) and even in a subgroup of right-handers (Vassal et al., 2010). Another illustration is the elicitation of syntactic disturbances (grammatical errors) by stimulating both the left posterior temporal cortex (mainly the posterior part of the middle temporal gyrus) as well as the white matter pathways lateral to the caudate (Vidoretta et al., 2011) – as elicited by stimulation over the pars triangularis of the left

inferior frontal gyrus. Also, stimulation of the posterior part of the left superior temporal cortex as well as the deep part of the superior longitudinal fascicle generates the same disorders of monitoring and control, i.e., involuntarily language switching in bilingual patients, than previously reported by stimulating the left inferior frontal gyrus (Moritz-Gasser and Duffau, 2009). These results also support the existence of a large fronto-temporal network underlain by a long-distance association pathway. The same observations have been made for other cognitive or emotional functions, such as deficit of recent verbal memory during stimulation of the temporal lobe (Ojemann, 2003), or interference for facial emotion recognition during stimulation of the temporal or parietal cortex (Giussani et al., 2010).

Following resection within non-frontal areas, it was also possible to identify similar symptoms than those reported during frontal lesions. For instance, verbal and visual working memory (as well as attention) deficits were regularly observed, after surgery involving the parietal lobe (Teixidor et al., 2007) or the temporal lobe (Owen et al., 1990), respectively. Removal of the inferior parietal lobe may also generate nonfluent aphasia (Duffau et al., 2003b). Agraphia was described after tumor removal within the parietal and the insular lobes (Roux et al., 2003; Scarone et al., 2009). Also, athymhormic syndromes, with slowness of ideation and disorders of the affect, have been generated by resection of insular gliomas involving the right striatum (Duffau et al., 2002b; Krause et al., 2012, this issue).

In addition, cognitive flexibility and mental programming were impaired following posterior cerebral excisions, as described after frontal resections (Vilkkki, 1992). Finally, negative mood changes were observed after brain tumor resection involving heteromodal temporoparietal cortices, as reported in tumor removal within the prefrontal cortex (Irle et al., 1994).

In summary, these new insights provided by brain tumor surgery, and especially by intraoperative electrical mapping, argue in favor of a hodotopical view rather than in favor of a classical localizationist view of cerebral processing – that is, a brain organization based on dynamic interrelationships between parallel distributed networks. According to this concept of brain function underlain by intersecting large-scale neural networks that contain interconnected cortical and subcortical components (Mesulam, 1990), even if individual anatomic sites within a network display a relative (but not absolute) specialization for different behavioral aspects of the relevant function, a single domain such as language or emotion can be disturbed by lesion to any one of several areas, as long as these areas belong to the same networks. This explains why phonemic paraphasia may be elicited whatever the cortical or subcortical site stimulated within the “dorsal pathway”, if these sites are connected by the superior longitudinal fascicle, and why semantic paraphasia may be elicited whatever the cortical or subcortical site stimulated within the “ventral pathway”, if these sites are connected by the inferior fronto-occipital fascicle (Duffau, 2008a). In addition to these long-distance cortico-cortical circuits, this also explains why articulatory or cognitive control disorders may be induced by stimulating both (frontal) cortical areas as well as deep grey nuclei – that is, by stimulating the vertical cortico-subcortical connectivity. In other words, both neuroscientists and

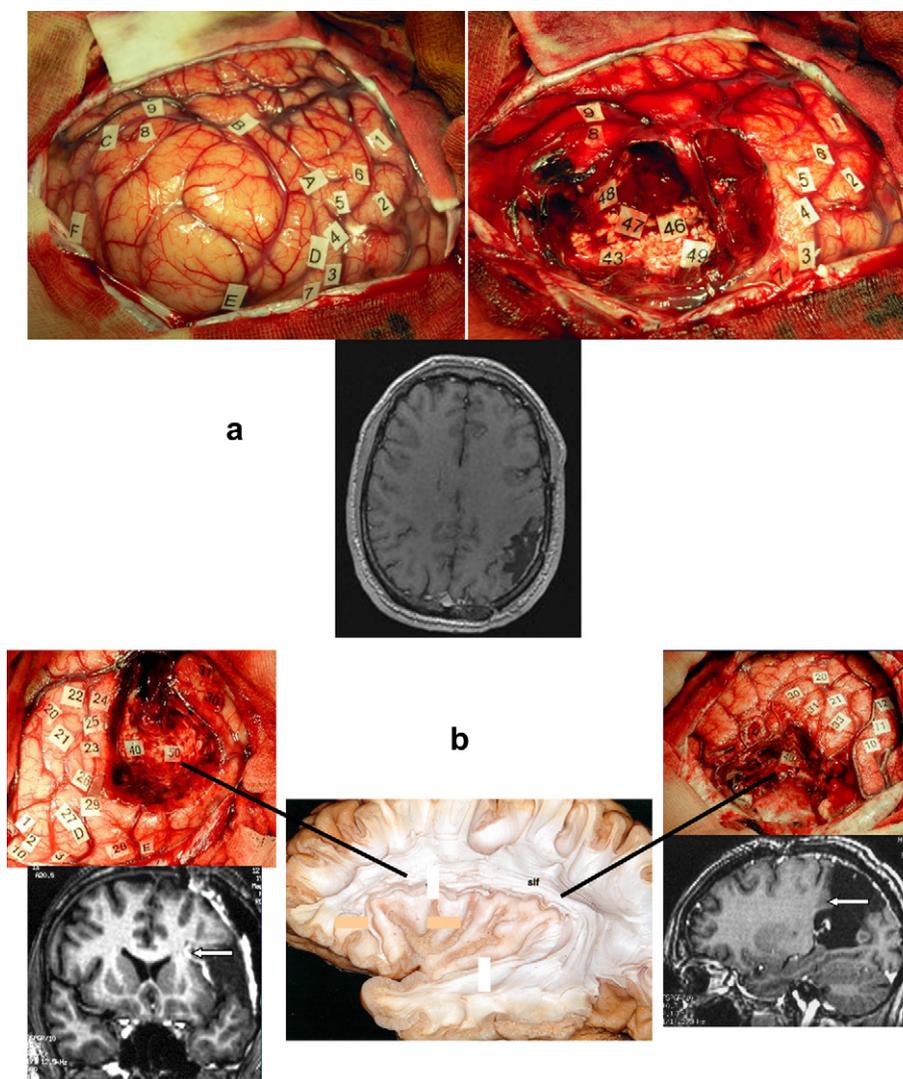


Fig. 4 – (a) Upper: intraoperative photograph (the anterior part is right, the back is left), in a patient with a left parietal WHO grade II glioma. Left: photograph before resection. Awake mapping allowed the detection of the primary motor area of the face (2), primary somatosensory areas of the face (5 and 6) and upper limb (3, 4 and 7), as well as the ventral premotor cortex eliciting speech arrest during stimulation (1). Interestingly, stimulation of the junction between the supramarginalis gyrus (8) and the posterior part of the superior temporal gyrus (9) elicited a complete arrest of language production, mimicking a stimulation of “frontal areas”. The tumor was marked by letter tags. Right: photograph after the resection, performed according to functional boundaries, both at cortical and subcortical level. Interestingly, language pathways have been identified in the white matter, that is, the lateral part of the superior longitudinal fascicle inducing articulatory disturbances when stimulated (46, 47 and 48), thus underlying the articulatory loop which connects the ventral premotor cortex to the supramarginalis gyrus; and the arcuate fascicle more deeply (43 and 49) (deep part of the superior longitudinal fascicle) inducing phonemic paraphasia when stimulated. This subcortical connectivity has been preserved. Lower: axial T1-weighted MRI showing an extensive glioma resection, in a patient who experienced a transient language worsening, and then returned to a normal social and professional life with a complete neurological recovery after several weeks of functional rehabilitation. **(b)** Combination between anatomic dissection of the superior longitudinal fascicle, intraoperative functional mapping and post-operative MRI (the fascicle is marked by an arrow). Evidence of such fronto-parietal loop based on anatomic-functional correlations explained why it is possible to obtain similar symptoms by inducing a (transient or definitive) lesion within the frontal or the parietal lobe (modified from Duffau et al., 2008b).

neurologists/neurosurgeons should have a perfect knowledge of the anatomic-functional connectivity of the brain in order to accurately interpret the functional consequences related to a focal lesion in a hodological framework, making possible the occurrence of a “frontal symptom” in non-frontal areas – in

agreement with the principles of “disconnection syndrome” (Catani, 2007; Catani and Ffytche, 2005; Catani and Mesulam, 2008). To this end, both the renewal of the technique of white matter fibers dissection in cadavers, which offers the opportunity to study not only the relationships between

anatomical pathways but also their cortical terminations (Martino et al., 2010), as well as advances in diffusion tensor imaging tractography, which allows in vivo dissection of the tracts (Catani et al., 2002; Catani et al., in press; Thiebaut de Schotten et al., 2012, this issue) – even if more validation is still needed, especially for language pathways (Leclercq et al., 2010) – would likely enable to better understand relationships between brain structure and function, especially if they are combined with the data provided by direct brain stimulation (Duffau, 2008a).

4. “Frontal symptoms” may be mild or absent in frontal lesion: toward plasticity

Another concept in a hodological view of cerebral functioning is based on the fact that, if a lesion confined to a single area can give rise to multiple deficits, involving the functions of all subnetworks that intersect in this region, a lesion to a subnetwork component may nonetheless give rise to minimal or transient deficits if other parts of the network undergo compensatory reorganization. This is one of the main principles of brain plasticity, that is, a continuous process allowing short-term, middle-term and long-term remodeling of neuronosynaptic maps, to optimize the functioning of brain networks (Duffau, 2006). The mechanisms advocated include unmasking of latent connections and networks, but also modifications of synaptic weight, changes in the synchrony, glial modulation, regulation by the extracellular matrix, phenotypic changes and neurogenesis (Duffau, 2006). Interestingly, the dynamical plasticity, which is the ability of brain networks to redistribute after a focal injury their global dynamical behavior over the intact areas, on a time scale ranging from seconds to hours, may likely more be based on unmasking of redundancies. It is different from the biological plasticity, where biological changes in the properties of neurons and axons and their branching will allow brain function changes on a time scale from days to months – involving the other mechanisms. Furthermore, it is worth noting that the considerable inter-individual anatomo-functional variability should be taken into account (Ojemann, 2003): for example, a bilateral language network could a priori be more advantageous than an extremely lateralized pattern (Catani et al., 2007). These parameters may explain why it is possible to perform extensive frontal lobectomy without “frontal syndrome”, especially in slow-growing tumor such as low-grade gliomas (Duffau, 2005). Indeed, it has been demonstrated that thanks to their long natural history (many years), these tumors known to frequently involve the frontal lobe may give enough time to the brain to reorganize itself (Desmurget et al., 2007). As a consequence, despite possible cognitive, behavioral and emotional disorders observed when extensive neuropsychological assessments are performed (see above), many patients with a huge tumor infiltrating the frontal lobe are nevertheless able to enjoy a normal life until the first inaugural seizure (Duffau, 2005).

Interestingly, intraoperative electrical investigation in awake patient allows a better understanding of mechanisms of functional reshaping, which took place before resection of frontal tumors (Duffau, 2006). First, by performing cortical

mapping before any resection, perilesional functional redistribution has frequently been observed, especially around the so-called “Broca’s area” (i.e., pars opercularis and pars triangularis of the left dominant inferior frontal gyrus). Therefore, in many patients with a glioma involving this region, compensatory recruitment was underlain by the ventral premotor cortex, the insula, the dorsolateral prefrontal cortex – and sometimes by the orbitofrontal cortex (Duffau, 2005). As a consequence, it was possible to remove Broca’s area in a large amount of patients, with on-line functional assessment performed by a speech therapist/neuropsychologist/neurologist throughout the resection, enabling the preservation not only of the crucial cortical areas but also of the subcortical language pathways already described (Benzagmout et al., 2007). In addition to this mechanism of functional reorganization around the tumor, also observed for other regions within the frontal lobe (e.g., the supplementary motor area), repeated cortical mappings during the resection also revealed acute functional reshaping, probably due to unmasking of latent redundant subnetworks (Duffau, 2001). Such remapping enabled to open the door to the resection of tumors classically considered as not operable, for instance for tumors involving the precentral gyrus.

On the basis of these original observations made intraoperatively, traditional “eloquent” frontal areas were removed in many patients, with no permanent postsurgical deficit, especially with no “frontal syndrome” (Fig. 5). Indeed, in spite of a frequent transient worsening in the immediate postoperative period, patients recovered thanks to a specific functional rehabilitation performed during several weeks (Duffau et al., 2008b). Thus, objective neuropsychological examinations made 3 months after surgery were into normal ranges in the vast majority of patients, despite the resection of “Broca’s area”, of the supplementary motor area (usually after a transitory supplementary area syndrome combining mutism – in the dominant hemisphere – akinesia and slowness of ideation) (Fontaine et al., 2002; Krainik et al., 2004), of the whole frontal lobe (even within the left dominant hemisphere, with no cognitive disorders – see for an example of extensive neuropsychological examination by Plaza et al., 2009), of the right striatum (with no movement disorders) (Duffau et al., 2002b) and even of the anterior/mid-part of the corpus callosum combined with frontal lobectomy (see the example of a patient who was able to play a recital of Rachmaninov’s work for piano 3-month after surgery in Duffau et al., 2004). In some patients with huge fronto-temporo-insular “paralimbic” low-grade gliomas, it was also possible to remove the insula and the anterior-mid temporal structures in addition to the frontal resection, with both cognitive and emotional assessment before and after surgery. These results showed an improvement of the presurgical deficit of working memory and attention 3 months after the resection, while no emotional disorders was noted (especially no deficit of the recognition of face expression) (unpublished data).

In summary, despite surgery within the frontal lobe (possibly with an extensive frontal lobectomy, even in the left dominant hemisphere), thanks to the use of cortico-subcortical mapping in a hodotopical framework, almost all patients (except in rare cases of post-operative vascular injury) were able to return to a normal familial, social and

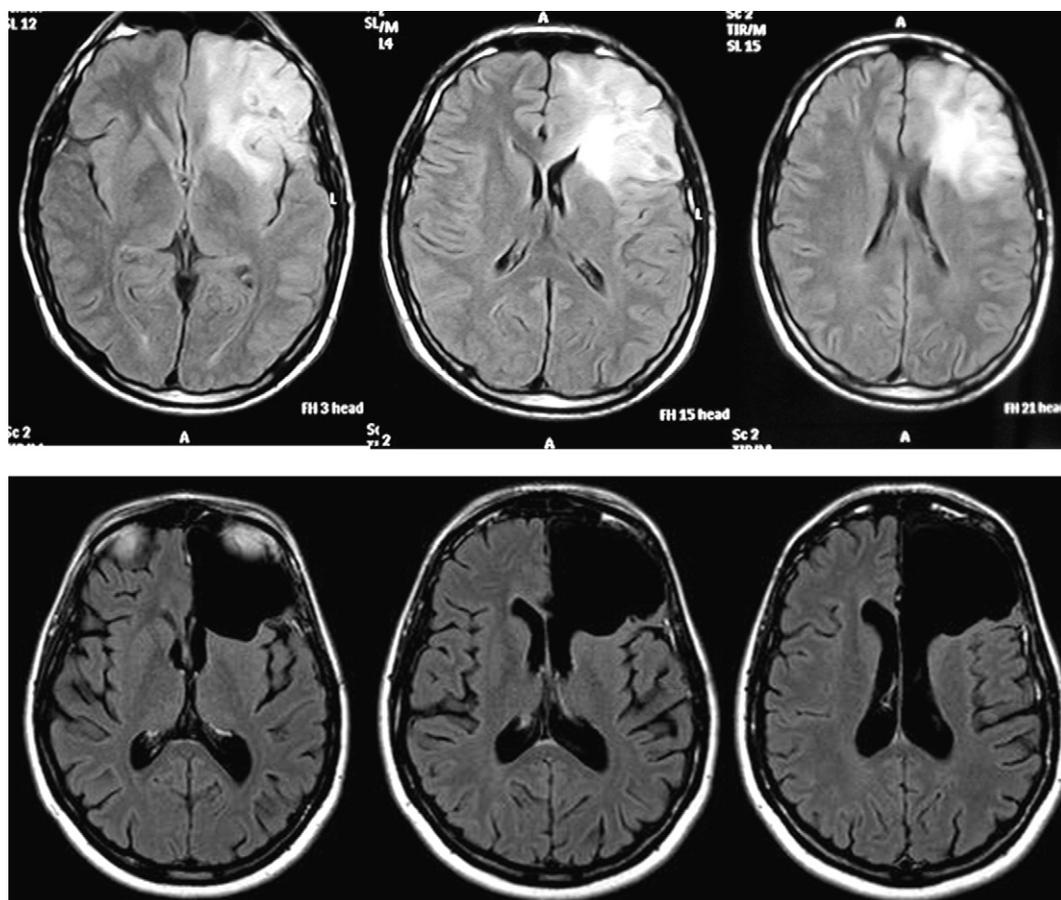


Fig. 5 – Upper: axial FLAIR-weighted MRI showing a huge WHO grade II glioma involving the whole left lobe in a patient with seizures. Lower: axial FLAIR-weighted MRI showing an extensive left frontal lobectomy. The patient had a normal neurological, neuropsychological and language examination 3 months after surgery. He returned to a normal familial, social and professional life, with no seizures, no deficit – especially with no frontal syndrome.

professional life, with “no frontal syndrome”. These results are not in agreement with the classical neurosurgical literature, because there are many studies that show quite the opposite. However, it is worth noting that frontal removals were traditionally performed under general anesthesia, without any considerations regarding the inter-individual anatomic-functional variability. A tailored resection according to functional boundaries at the individual level and taking into account the concepts of white matter connectivity as well as cerebral plasticity in awake patients may dramatically change the surgical outcomes.

These provocative data, in opposition with the classical concept of “frontal syndrome” almost systematically induced in cases of (extensive) frontal damage, lead to several considerations.

Firstly, with regard to the mechanisms of brain plasticity at the ultrastructural level, while several hypotheses have been suggested (see above), the exact patho-physiology remains poorly known. However, three points seem crucial. The first is the absolute necessity to preserve the subcortical connectivity to allow efficient reorganization. In other words, it is important to highlight the concept that subcortical connectivity is more important than cortical specialization. Indeed, even if it

was demonstrated that certain subpathways could be compensated by alternative circuit (for instance, the subnetwork comprising the anterior part of the left inferior longitudinal fascicle in front of the visual word form area, with a relay in the temporal pole, and then continuing by the uncinate fascicle to the orbitofrontal cortex can be compensated for language by the direct inferior fronto-occipital fascicle) (Mandonnet et al., 2007a), lesion of the white matter tracts have a higher risk to induce a more severe and a more prolonged (even permanent) deficit than cortical lesions (Duffau, 2009). For example, disconnection of the uncinate fasciculus in a group of patients who underwent tumor surgery may result in a famous faces naming impairment, while no such impairment exists in another group of patients who had a frontal resection without damage to the uncinate fasciculus (Papagno et al., 2011). Therefore, a perfect knowledge of the subcortical connectivity is crucial. In this state of mind, lessons from stimulation taught us which tracts were essential to avoid a frontal syndrome and which frontal symptoms could be generated in cases of damage: injury of the superior longitudinal fascicle may elicit speech production disorders, syntactic disturbances, involuntary language switching or phonemic paraphasia (arcuate fascicle), damage of the

inferior fronto-occipital fascicle can generate semantic paraphasia or deficit of cross-modal judgment, lesion of the subcallosal fasciculus may elicit transcortical motor aphasia, while injury of the striatum induces preservations with control disorders. The second parameter is the timing of the lesion, with compensatory mechanisms more efficient in cases of slow-growing tumor such as low-grade glioma than in acute lesion such as stroke (Desmurget et al., 2007). The third point is that plasticity mainly regards more complex functions such as language, cognitive or behavioural/emotional functions. Indeed, it seems that sensory-motor functions are less prone to plasticity, may be due to a different and older time of maturation of these systems. Another explanation could also be that sensory-motor acts as input or output areas: input sites convey or are the first relay of information entering the brain, whereas output sites are the last relay or the fiber tracts sending information outside the brain. These areas are mainly unimodal and probably organized serially. The absence of parallel alternative pathway explains the difficulty or even the impossibility to restore their function after any damage. On the contrary, high-order cognitive processes are mediated by short- and long-range parallel networks (Catani et al., in press; Thiebaut de Schotten et al., 2012, this issue; Yeterian et al., 2012, this issue), with a higher potential of functional reshaping thanks to a more dynamic hodotopical organization (Ius et al., 2011; Berthier et al., in press).

Thus, in the results presented here, a bias due to the selection of slow lesions must be acknowledged. On the other hand, these original data give strong argumentation in favor of the fact that the plastic potential has been underestimated until now, and could be guided to allow a better recovery (Gehring et al., 2008). To this end, functional rehabilitation should be more extensively used, especially in brain tumors, since a recent prospective randomized trial has demonstrated the positive impact of such rehabilitation on functional outcome (Gehring et al., 2009). Of note, after surgery of frontal lesion, followed by a specific cognitive rehabilitation and then a functional recovery, it has recently been shown that additional remapping might occur – in addition to the reorganization already induced by the tumor before surgery. Such demonstration was made by performing pre- and post-operative functional magnetic resonance imaging (fMRI), which showed functional reshaping – for instance, recruitment of the contralateral supplementary motor area and premotor cortex following a resection of the fronto-mesial structures with a transient postsurgical supplementary motor area syndrome (Krainik et al., 2004). On the basis of these preliminary neuroimaging data, reoperations have been performed in “eloquent” areas when the first resection was not complete, for functional reasons (that is, with interruption of the tumor removal according to functional boundaries). Thanks to functional reshaping confirmed using intraoperative cortical mapping in awake patients before the second resection, it was possible to extent the tumor removal beyond the limits identified during the first surgery, while preserving the function. For instance, such kind of dynamic “multiple surgical approach” allowed the resection of the left premotor area in several patients with no permanent deficit, and with no “frontal symptoms” (Gil Robles et al., 2008).

Secondly, one may argue that the mapping results obtained in patients with cerebral tumors (thus which induced phenomena of plasticity), cannot give reliable information concerning the functional anatomy of the brain – especially concerning the frontal lobe. However, we have to keep in mind that, so far, lesion-map in neurosciences has essentially been based on stroke, i.e., usually corresponding to a wide lesion which involves both cortical and subcortical structures. As a consequence, anatomo-functional correlations made from these unique results, the most often in a localizationist rather than in a hodotopical framework (that is, with few considerations about connectivity and plasticity) led to build dogmas not always in agreement with the clinical reality. The example of surgery for low-grade glioma illustrates perfectly well this discrepancy between the “classical models” of cognition and the real brain potential: for instance, the fact that “Broca’s area” is not the area crucial for motor speech in all cases, since its resection can be made with a real preservation of language allowing to enjoy a normal life (e.g., a lawyer able to plead without “Broca’s area”), or again, the possibility to remove completely the (left dominant) frontal lobe without “frontal syndrome” (see also Bizzi et al., in press). In addition, brain tumor surgery opens the door to intraoperative electrostimulation mapping, which is of course by definition not indicated in stroke. It is important to insist on the fact that brain stimulation does not mean stimulation of a unique area, but actually means stimulation of a whole (sub) network, namely, stimulation of an entry door to a large-scale circuit (Mandonnet et al., 2010). So far, it is the sole technique able to induce a specific symptom within a distributed (sub)network, allowing the realization of very accurate and very reliable on-line anatomo-functional correlation at the individual scale (in this patient, at this moment, at this location) never provided by other mapping methods or by probabilistic maps – the limitation being that stimulation is in essence invasive. Furthermore, the use of intraoperative mapping in awake patient now enables to perform brain resection according to individual functional boundaries (now, but with the possibility to see remapping several months or years after), both at cortical and subcortical levels, thus leading to create “clean lesion” in opposition to large infarct. Therefore, it represents a unique opportunity to provide new data not only on the actual anatomo-functional connectivity, but also on plastic potential and its limitations. Indeed, despite the slow growth of low-grade gliomas, if a structure of the brain is still detected as functional by the mapping (i.e., eliciting the same reproducible and transient deficit during each stimulation performed at its level), it means that this structure is not only involved in a large-scale network, but is an “epicenter” crucial for function of the whole network – and thus cannot be compensated. Interestingly, it was possible to build a probabilistic map of all the residues of infiltrative gliomas which were not removed due to the persistence of function within these structures (Mandonnet et al., 2007b). This original lesion-map (since based on a previous functional selection based on the results of intrasurgical mapping) showed some cortical areas (primary motor cortex of the hand, left ventral premotor cortex) but essentially the

main subcortical pathways detailed above. Thus, it means that despite its plastic potential, it seems to exist a “minimal common brain” very reproducible from patient to patient, crucial for cerebral functioning, mainly involving the white matter connectivity (Duffau, 2009; Ius et al., 2011). It is worth noting that the frontal areas did not appear in this map. Finally, in the same state of mind, it must be acknowledged that only unilateral lesions have been reviewed here. It is nevertheless important to underline that permanent deficits have regularly been reported in the literature following bilateral frontal damages, as also observed in other locations such as the temporal lobe (Scoville and Milner, 1957). These findings support a bilaterally-distributed theory, i.e., the existence of a bilateral system in which “frontal functions” are represented in at least a semi-redundant fashion across the two hemispheres.

Finally, from a methodological point of view, it could also be possible to learn from extraoperative stimulation studies, especially by using cortico-cortical evoked potential from implanted macroelectrodes, able to analyze the functional link between frontal lobe and other brain regions (Matsumoto et al., 2004). However, this technique cannot map the subcortical white matter pathways. Furthermore, incorporation of preoperative diffusion tractography within intrasurgical navigation system could bring additional information (Bello et al., 2010; Ellmore et al., 2009). It is nonetheless crucial to keep in mind that, beyond the problem of intraoperative shift, diffusion tractography provides only anatomic and not functional data with regard to the fibers, and that its reliability is not yet optimal – as recently demonstrated for language pathways by comparing tractography to subcortical stimulation (Leclercq et al., 2010).

5. Conclusions

This review proposes an alternative view to the classical concept of “frontal syndrome”, a syndrome which seems to be possible only in a localizationist framework. In a hodotopical (interconnected) and plastic (dynamic) view of brain organization, even if it is still possible to link “frontal symptoms” to a frontal lesion, it is also possible to link similar “frontal symptoms” to a non-frontal lesion. In addition, extensive frontal lesion (even a total left dominant lobectomy) can occur with neither “frontal syndrome” nor consequences on the daily familial, social and professional life. Such data show that an improvement of the knowledge of dynamic anatomic-functional connectivity is crucial for both neuroscientists and neurologists/neurosurgeons, based on a more distributed view, preventing to rigidly relate a syndrome to the injury of a specific cerebral area – but rather to analyze each symptom without a priori concerning the location of the damage. A reinforced link between models of cognitive neurosciences, functional neuroimaging, anatomic dissection and intraoperative electrostimulation mapping are thus mandatory to better understand relationships between structure and function of the brain, and to revisit some dogmas – as illustrated by the present data, finally raising the following question: does the frontal syndrome exist?

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