cortex 49 (2013) 2711–2727

Available online at www.sciencedirect.com

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Journal homepage: www.elsevier.com/locate/cortex

Research report

Is the right frontal cortex really crucial in the mentalizing network? A longitudinal study in patients with a slow-growing lesion

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ARTICLE INFO

Article history:
Received 11 May 2013
Reviewed 7 July 2013
Revised 21 July 2013
Accepted 5 August 2013
Action editor Jordan Grafman
Published online 14 August 2013

Keywords:
Mentalizing network
Right frontal cortex
Brain surgery
Brain plasticity
Longitudinal design

ABSTRACT

Assessing the subjective experience of others in terms of mental states, a brain function referred to as mentalizing, is achieved in the brain through a set of low-level perceptual and high-level inference-based processes. Because of its recurrent implication in fMRI studies, the right frontal cortex, especially in its inferolateral and dorsomesial parts, is posited to be a "core system" in the sustenance of these neurocognitive mechanisms. In this context, we reasoned that if the right frontal cortex is really crucial for mentalizing, its surgical resection, following diffuse low-grade glioma invasion, should induce irreversible impairments. To test this hypothesis, we designed a longitudinal experimental setup in which ten patients harboring a low-grade glioma in right frontal areas were assessed just before, immediately after and three months after a brain surgery. Two well-validated behavioral tasks, thought to evaluate both aspects of mentalizing, were administered. The results obtained provide evidence that widespread surgical excisions of the right prefrontal cortex do not induce a long-term worsening of both aspects of mentalizing, although some transitory effects are observed immediately after the surgery. They suggest also for the first time in the same sample of patients a possible double functional dissociation between low-level perceptual (posterior inferolateral prefrontal) and high-level inference-based (dorsomesial prefrontal) mentalizing processes. This overall finding challenges the traditional view according to which the right frontal cortex is an "essential cortical node" in the mentalizing network since it might be expected that massive surgical excisions of this brain area would have induced more definitive impairments.

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0010-9452/$ – see front matter
http://dx.doi.org/10.1016/j.cortex.2013.08.003

1. Introduction

Current thinking about the anatomo-functional organization of the brain is progressively shifting from a long-standing "modular" view, in which cognitive functions are thought to be processed by discrete and hyper-specialized cortical areas, to a more interactive and dynamic "network paradigm" (Bressler & Menon, 2010). In this latter approach, it is believed that cognitive processes are the result of sophisticated interactions between functionally and structurally interconnected cortical areas operating within complex and large-scale neural networks at the whole brain level (Bressler, 1995; Fuster, 2006; Hickok & Poepple, 2007; Just & Varma, 2007). Although this is not a new idea in cognitive neuroscience, brain connectivity studies are currently providing compelling evidence for such holistic organization, by revealing at the physiological level the functional interaction dynamics occurring in these neurocognitive networks and their underlying structural architecture (Bullmore & Sporns, 2012; Catani, 2007; Honey et al., 2010; Mesulam, 2009). Neuropsychological studies have also offered substantial contribution. For example, it was demonstrated that disrupting the functional interconnectivity between cortical nodes shaping a cognitive network, by direct electrostimulation of white matter pathways, led to severe cognitive disturbances (Duffau, 2005; Duffau et al., 2008; Thiebault de Schotten et al., 2005). In the same vein, stroke injury of these association pathways has been shown to induce irreversible cognitive deficits (Catani & Ffytche, 2005; Shinoura et al., 2009), probably related to an alteration of the functional connectivity (He et al., 2007). These recent results have strengthened the validity of the network view in explaining how high-level processes are generated in the brain.

If brain connectivity is a central principle of the anatomo-functional organization, plasticity is the fundamental property characterizing its functioning (Pascual-Leone et al., 2011). This means that the brain is constantly and dynamically reshaping its functional networks as one goes along the experience (Power, Fair, Schlaggar, & Petersen, 2010; Sagi et al., 2012). The most striking evidence of this potentiality comes however from the brain pathology, especially from slow-growing lesions like diffuse low-grade glioma (DLGG).

DLGG is a rare lesion of the central nervous system known to induce, because of its continuous and slow-growing progression (Mandonnet et al., 2003), dramatic functional plasticity phenomena (Desmurget et al., 2007; Duffau, 2005). As a consequence, contrary to acute lesions, functional disturbances are generally limited despite impressive lesions and resections (Anderson et al., 1990; Klein, Duffau, & De Witt Hamer, 2012), making this pathological condition particularly challenging for the classic modular view of neural organization (Duffau, 2009). For example, it has been possible to surgically remove the so-called Broca's area without inducing long-term expressive language impairment (Plaza, Gatignol, Leroy, & Duffau, 2009) or the prefrontal cortex without inducing any dysexecutive syndrome (Duffau, 2012), providing convincing evidence that the brain reshapes its functional networks in reaction to the lesion and its resection and cognitive functions cannot be the byproduct of the neural activity of an isolated cortical area. However, such functional plasticity has been recently demonstrated to be limited and some cortical epicenters might be reluctant to functional compensation, probably because of their central role within the neural network and their characteristics of connectivity (De Benedictis & Duffau, 2011, 2011).

In this respect, Ius, Angelini, Thiebaut de Schotten, Mandonnet, and Duffau (2011) have shown that the functional resectability of certain cortical and subcortical areas infiltrated by the tumor, as determined by direct electrical stimulations during awake surgery, was very low. It is for example the case of the right angular gyrus for visuospatial cognition or the posterior part of the left temporal gyrus for language processes. At the subcortical level, the stimulation of the left inferior fronto-occipital fascicule induces almost systematically a disturbance in semantic processing (i.e., semantic paraphasia). That led to the proposal of a minimal common brain that is a core of connectivity indispensable in sustaining cognitive functions. However, if direct anatomo-functional correlations can help to puzzle out the essential nodes and hedges of a given function, it only applies to a limited number of basic cognitive processes, those evaluated during "awake" surgery. In this context, longitudinal neuropsychological-based studies offer a unique opportunity to study functional plasticity, its limits, and neural implementation of cognitive processes. Yet, they are actually non-existent.

In this article, our attention was focused on mentalizing, a brain function thought to be the pedestal on which social cognition is supported (Amodio & Frith, 2006). It allows agents to tune into how else might be thinking or subjectively experiencing. In other words, mentalizing allows agents to ascribe a variety of mental/psychological states like intentions or emotions to understand and subsequently predict behaviors. Several neurocognitive processes have been described to explain how this function is achieved in the brain, ranging from low-level perceptive-based to high-level inference-based processes. Whereas the low-level subcomponent of mentalizing makes it possible the rapid and automatic detection (identification) of mental states on the basis of perceptual cues, the high-level subcomponent reflects the reflexive process associated with the inference. Both aspects of mentalizing would be processed by two distinct but interactive neural subnetworks, namely the mirror neural network for low-level/perceptive mentalizing and the mentalizing network *per se* for high-level/inferential mentalizing (Bolh & van den Bos, 2012; Coricelli, 2005; Frith & Frith, 2006; Keyzers & Gazzola, 2007; de Lange et al., 2008; Liebermann, 2007; Lombardo et al., 2010; Sabbagh, 2004; Spunt & Liebermann, 2012, 2013; Spunt, Satpute, & Lieberman, 2011; Uddin, Iacoboni, Lange, & Keenan, 2007).

Current literature suggests that the frontal cortex, especially in its medial (inference-based mentalizing) and posterior inferolateral parts (perceptive-based mentalizing), is an important cortical node within the neural system mediating these sociocognitives processes (Abu-Akel & Shamay-Tsoory,