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Neuropsychological evidence for the crucial role of the right arcuate fasciculus in the face-based mentalizing network: A disconnection analysis

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ABSTRACT

Recent evidence from axonal stimulation mapping studies suggests that at least two white matter connectivities in the right hemisphere may be involved in face-based mentalizing, i.e. the ability to infer complex cognitive and affective states from human faces: the inferior fronto-occipital (IFOF) and the superior longitudinal/arcuate (SLF/AF) fasciculi. However, to date, only a handful of neuropsychological studies have focused on the white matter tracts subserving mentalizing in general, and face-based mentalizing in particular. Therefore, the main goal of this study was to confirm the abovementioned results by applying voxelwise and tractwise lesion-symptom analyses to a set of behavioral data obtained from a large and homogeneous group of neurological participants. More precisely, 122 patients operated on for diffuse low-grade glioma were assessed post-operatively with the well-validated "Reading the Mind in the Eyes" (RME) test. For each patient, the resection cavity and the residual tumor infiltration were mapped separately on the respective postoperative structural MRI. Behavioral data, previously controlled for sociodemographic factors, were then submitted to a standard voxel-based and to a less conservative, region-of-interest (ROI)-based, lesion-deficit analyses. Results were invariably the same: no anatomo-functional relationships were pinpointed by these investigations, making thus impossible the cortical topological localization of mentalizing deficits. In a second time, two kinds of tractwise lesion-symptom analyses based on the damaged volume and the disconnection probabilities of the white matter tracts, were performed. All results were corrected with the Bonferroni correction. Converging and strong evidence was found that resection-related disconnection of the right AF is especially deleterious for face-based mentalizing. More anecdotally, we identified the involvement of certain ventral tracts, especially the IFOF and the uncinate fasciculus (UF). Taken as a whole, the reported findings confirm the critical role of the right AF in mentalizing abilities. From a more clinical standpoint, they highlight the necessity to perform an intraoperative map of this connectivity during awake surgery in order to avoid long-lasting social cognition disorders.

1. Introduction

Human beings are especially talented in understanding and predicting others' behavior. This complex ability, commonly referred to as 'mentalizing' or 'Theory of Mind' (Premack and Woodruff, 1978), is one of the main foundation on which social cognition is built (Frith and Frith, 2012; Gallagher and Frith, 2003; Lieberman, 2007), and is unsurprisingly disrupted in a wide range of neuropsychiatric conditions, especially those in which social communication is highly problematic, such as autism spectrum disorders and schizophrenia (Baron-Cohen et al., 2001; Biedermann et al., 2012). Currently, mentalizing is no longer theorized as a unitary process but is rather thought to engage a variety of social, affective and cognitive subprocesses such as emotion recognition, face identification, biological movement recognition, inferential reasoning and self-other distinction, some of which are non-specific for mentalizing or for social cognition in general (Frith and Frith, 2003; Schaafsma et al., 2015). The level of participation of each of these subprocesses in optimally tracking others' mental dispositions would depend upon the social context.

Over the last twenty years, a plethora of neuroimaging and

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neuropsychological studies has specifically focused on the neural bases of mentalizing. Considerable evidence has accumulated that this function is underpinned by a complex neural system, which includes areas distributed on both the lateral and the medial cortical surfaces (Amodio and Frith, 2006; Carrington and Bailey, 2009; van Overwalle, 2009; Bzdok et al., 2012; Schurz et al., 2014). Some of them are invariably activated, regardless of the psychological states under consideration (e.g. intention, belief), and the task modalities. They constitute the 'core' mentalizing network and comprise the precuneus and the adjacent to it posterior cingulate gyrus, the medial prefrontal cortex (including the anterior cingulate gyrus), and the temporo-parietal junction, along with the posterior superior temporal sulcus (Amodio and Frith, 2006; Frith and Frith, 2003; Mar, 2011; Molenberghs et al., 2016; Schurz et al., 2014; Van Overwalle, 2009). The functional commitment of other cortical regions, such as the inferior frontal gyrus and the temporal pole, appears to be more dependent on the parameters of the task (Carrington and Bailey, 2009; Molenberghs et al., 2016).

Recent works have begun to give important clues about the involvement of certain white matter connections in mentalizing. This knowledge is absolutely vital to better understand the general architecture of large-scale neurocognitive networks, and to construct appropriate anatomo-functional models of social cognition, in particular mentalizing. It allows also to gain a better comprehension of the pathophysiological mechanisms of brain conditions with quintessential mentalizing deficits and compromised integrity of white matter connectivity. Actually, several white matter tracts have been implicated in the mentalizing network. Two successive studies have shown that disconnection of the cingulum – a white matter tract that connects two 'core' areas of the mentalizing network (the medial frontal and parietal cortices) – predicted a significant decline in inferential mentalizing (Herbet et al., 2014b) and cognitive empathy (Herbet et al., 2015). These studies have also pinpointed the role of other white matter fibers, especially those belonging to the perisylvian connectivity. Namely, disconnection of the right lateral SLF/AF was associated with a disturbance of mental state identification, i.e. the lower, pre-reflective aspect of mentalizing (Herbet et al., 2014a). Taken as a whole, these recent findings have led to the proposal that mentalizing may be governed by at least two streams, working in concert for an optimal mapping of mental states: a medial stream, involved in the reflective aspect of mentalizing (mental state inference/reasoning) and subserved by the cingulum, and a more lateral stream, involved in the pre-reflective aspect of mentalizing (mental state identification), and subserved by the perisylvian connectivity. This division of labor is in accordance with the implicit versus explicit view of social cognition in general (i.e. dual-processing account), and of mentalizing in particular (Frith and Frith, 2008; Keysers and Gazzola, 2007; Lieberman, 2007).

In a very recent neuromodulation study performed by our group (Yordanova et al., 2017), we used the Reading the Mind in the Eyes (RME) Task (Baron-Cohen et al., 2001) to intraoperatively assess face-based mentalizing in a relatively large group of patients undergoing awake surgery for right-sided diffuse low-grade glioma. This well-validated and well-tried behavioral task consists of the attribution of complex affective and cognitive states to others on the basis of the eye region of human faces. The RME task rather probes the pre-reflective, lower-level and identification aspect of mentalizing to the extent that its successful completion is partly constrained by the efficient processing of perceptive cues such as gaze, gaze direction and motor configuration of the eye region (even if inferential processes are also required since an explicit attribution is required). Consistent with this view, classical mentalizing-related areas, such as the temporoparietal junction and the medial prefrontal cortex, are regularly engaged by the RME task, but other structures, such as the posterior inferior frontal gyrus and the posterior dorsolateral prefrontal cortex, could also be activated as shown in a recent meta-analysis of neuroimaging data partly focusing on this behavioral task (Schurz et al., 2014), but also in previous neuropsychological studies (Campanella et al., 2014; Herbet et al., 2013). Moreover, contrary to other classical mentalizing tasks (e.g. false belief task), it appears that brain structures associated with the RME task do not have high correspondence with the default mode network, as the precuneus is not activated during the RME task. In accordance with these observations, in our neuromodulation study (Yordanova et al., 2017), critical cortical sites were identified in pars opercularis and pars triangularis of the inferior frontal gyrus, the posterior dorsolateral prefrontal cortex, and the posterior superior temporal gyrus. More importantly, numerous subcortical sites were also found to be involved in face-based mentalizing. They were distributed in the perisylvian white matter following the spatial course of two associative connectivities – the IFOF and the SLF/AF. The disconnectome analyses performed in this study confirmed the very high probability of the right IFOF to be disconnected during mentalizing-related temporal stimulations, while this probability was lower, but still significant, for the right SLF/AF during mentalizing-related frontal stimulations.

In the current study, the main goal was to replicate these new findings by applying a comprehensive lesion mapping approach to the behavioral data of a large group of neuropsychological patients. Specifically, a standard voxelwise mapping analysis and a ROI-based lesion-symptom analysis, as well as two kinds of tractwise lesion-symptom analysis, were performed to disentangle the contribution of anatomical connections in mentalizing. The second goal of our work was to study more thoroughly the possible implication of different left-sided white matter tracts in face-based mentalizing.

2. Materials and methods

2.1. Participants

The patient group was composed of 122 native French speakers (57 females and 65 males) having undergone resection of histologically proven diffuse low-grade glioma between 2012 and 2016 (note that a part of these patients was already recruited in a previous work (Herbet et al., 2014a)). Among them, 110 were right-handed, nine left-handed, and three ambidextrous. The mean ± SD age was 38.3 ± 10.5 (range: 22–65), and the mean education level (years of full-time education) 14.5 ± 3.2 (range: 9–22). All patients were recruited from Montpellier University Hospital's Department of Neurosurgery (see Table 1 for a detailed overview of sociodemographic and clinical data) and operated on by the same neurosurgeon (H.D.). The exclusion criteria were previous radiotherapy (because potentially affecting cognition), neurological deficits that could prevent an objective behavioral testing (i.e. hemianopsia, spatial neglect, reading difficulties), and previous history of neurologic or psychiatric disorders.

Because of the kind of the analyses performed in this study (see above), patients were divided into two subgroups based on the laterality of the tumor: right lesion group (n = 92), and left lesion group (n = 30). These two subgroups were not different in terms of age ($t(120) = 0.17$, $p = .87$), educational level ($t(120) = 0.13$, $p = 90$), resection

Table 1
Patients' sociodemographic and clinical characteristics.

	All patients (n = 122)	Right lesion (n = 92)	Left lesion (n = 30)
Age	38.3 ± 10.5	38.7 ± 10.6	38.0 ± 10.2
Gender (M/F)	65/57	44/48	21/9
Education (years)	14.5 ± 3.2	14.5 ± 3.0	14.4 ± 3.8
Handedness (R/L/A)	110/9/3	83/7/2	27/2/1
Volume of RC (voxels [1 * 1 * 1 mm])	56,696 ± 45,080	59,110 ± 42,282	49,292 ± 52,049
Volume of LI (voxels [0.898 * 0.898 * 6 mm])	13,533 ± 17,464	14,156 ± 18,814	11,623 ± 1224

RC, resection cavity; LI, lesion infiltration; M, male; F, female; R, right; L, left; A, ambidextrous.