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A disconnection account of subjective empathy impairments in diffuse low-grade glioma patients

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ABSTRACT

Human empathic experience is a multifaceted psychological construct which arises from functional integration of multiple neural networks. Despite accumulating knowledge about the cortical circuitry of empathy, almost nothing is known about the connectivity that may be concerned in conveying empathy-related neural information. To bridge this gap in knowledge, we studied dispositional empathy in a large-sized cohort of 107 patients who had undergone surgery for a diffuse low-grade glioma. The self-report questionnaire used enabled us to obtain a global measure of subjective empathy but also, importantly, to assess the two main components of empathy (cognitive and emotional). Data were processed by combining voxelwise and tractwise lesion-symptom analyses. Several major findings emerged from our analyses. First of all, topological voxelwise analyses were inconclusive. Conversely, tractwise multiple regression analyses, including all major associative white matter pathways as potential predictors, yielded to significant models explaining substantial part of the behavioural variance. Among the main results, we found that disconnection of the left cingulum bundle was a strong predictor of a low cognitive empathy ($p < 0.0005$ Bonferroni-corrected). Similarly, we found that disconnection of the right uncinate fasciculus and the right inferior fronto-occipital fasciculus predicted, respectively, a low ($p < 0.05$ Bonferroni-corrected) and a high ($p < 0.05$ Bonferroni-corrected) subjective empathy. Finally, although we failed to relate emotional empathy to disruption of a specific tract, correlation analyses indicated a positive association between this component of empathy and the volumes of residual lesion infiltration in the right hemisphere ($p < 0.01$). Taken as a whole, these findings provide key fundamental insights into the anatomical connectivity of empathy. They may help to better understand the pathophysiology of empathy impairments in pathological conditions characterized by abnormalities of long-range anatomical connectivity, such as autism spectrum disorders, schizophrenia and fronto-temporal dementia.

1. Introduction

Humans have a natural propensity to engage in sophisticated interpersonal relationships and to exhibit prosocial attitudes (Eisenberg and Miller, 1987; Roberts and Strayer, 1996; De Vignemont and Singer, 2006). Pivotal in the success of such complex other-directed behaviours is empathy, basically defined as the ability to share and understand emotional experiences of others (e.g. Decety and Jackson, 2004; Decety and Moriguchi, 2007). Not surprisingly, Empathy dysfunction is common in individuals displaying aggressive behaviours toward other peoples, as in psychopathy (Hare et al., 1991, 1993; De Vignemont and Singer, 2006), or showing profound disinterest in social interactions, as in certain forms of psychopathology (e.g. autism spectrum disorders) (Blair, 2005; Iacoboni and Dapretto, 2006; Farrow and Woodruff, 2007;

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Iacoboni, 2009; Schulte-Ruther et al., 2011) or after neurological insult, leading sometimes to what has been coined under the term of acquired sociopathy (Damasio, 1994; James and Blair, 2002). Better understanding the precise anatomo-functional architecture of empathy and the pathophysiological basis of its disruption in brain pathology is a necessary prerequisite for the development of effective therapeutic strategies.

Most researchers agree that human empathy is not a unitary but rather a complex and multifaceted psychological construct. In current theoretical models, *at least* two forms of empathy are described: (i) the emotional and (ii) the cognitive component of empathy (Davis, 1983; De Waal, 2008; Rameson and Lieberman, 2007; Decety and Moriguchi, 2007; Shamay-Tsoory et al., 2009; Shamay-Tsoory, 2011). Emotional empathy is thought to be an automatic process triggered in response to the perception of emotional, visceral or motor states of a social agent. Cognitive empathy – a synonymous term for *mentalizing* or *theory of mind* – is a higher-level reflexive process that requires one to reason about the emotional state of an agent. Research undertaken this last decade in functional neuroimaging has supported this long-standing distinction made beforehand in the field of psychology (Davis and Association, 1980), by repeatedly pinpointing two physically non-overlapping distributed neural systems – the so-called mirror and mentalizing networks (Zaki and Ochsner, 2012; Kennedy and Adolphs, 2012; Stanley and Adolphs, 2013). The mirror network, in its extended version, is formed by a collection of cortical areas including the pars opercularis of the inferior frontal gyrus and the neighbouring ventral premotor cortex, the rostral inferior parietal lobule, the anterior insula and the posterior part of the anterior cingulate gyrus (Wicker et al., 2003; Carr et al., 2003; Keysers et al., 2004; Singer et al., 2004; Rizzolatti and Craighero, 2004; Shamay-Tsoory et al., 2009; Bzdok et al., 2012; Bernhardt and Singer, 2012). The mentalizing network is a large fronto-temporo-parietal system, mainly comprising the medial prefrontal cortex, the ventral precuneus/posterior cingulate cortex and the temporo-parietal junctions (Gallagher and Frith, 2003; Van Overwalle and Baetens, 2009; Carrington and Bailey, 2009; Mar, 2011; Schurz et al., 2014). Although a few recent neuropsychological studies have provided evidence for this dual-process model of empathy in brain-damaged patients (Shamay-Tsoory et al., 2004, 2009; Herbet et al., 2013) or in psychopathological conditions such as schizophrenia and autism spectrum disorders (Blair, 2005; Montag et al., 2007), results from neuroimaging studies have yield to a more integrative view, by showing for instance that both systems predicted empathic accuracy (Zaki et al., 2009) or that functional integration between both systems, as indexed by effective connectivity measures, is observed during emotional state attribution (Spunt and Lieberman, 2012). Consequently, although there does seem to exist a dual-route for empathy from an anatomical standpoint, integration of empathy subprocesses may be a necessary condition for an optimal subjective experience of others (Shamay-Tsoory et al., 2011).

In this study, we aimed at focusing on the anatomical connectivity that may be concerned in conveying empathy-related neural processes. Despite accumulating data on the cortical organization of this sociocognitive and socio-affective function, the scope of our knowledge about the white matter connectivity subserving empathy is dramatically restricted. Only a very few studies have successfully addressed this issue. For instance, a recent work revealed positive associations between interindividual variability in emotional empathy and fractional anisotropy (FA) values in discrete portions of several associative pathways, including the superior longitudinal, the inferior longitudinal, the inferior fronto-occipital and the uncinate fasciculus (Parkinson and Wheatley, 2014). In a population of schizophrenic patients, certain dimensions of empathy as indexed by the interpersonal reactivity index (IRI; Davis, 1983) were shown to differentially correlate with FA measurements in white matter fibres belonging to the left inferior fronto-occipital fasciculus and the splenium of the corpus callosum (Fujino et al., 2014). Remarkably, a causal link was found between damage to the right uncinate fasciculus and emotional empathy in a sample of 30 patients with stroke injury in a very recent study (Oishi et al., 2015). Aside from these studies, the relationships between disturbance in empathic functioning and damage to white matter connectivity has not been yet explored in a large-scale neuropsychological population. Beyond the fundamental interest in better understanding the overall anatomical architecture of the empathy network, such neuropsychological data will be important in translational neuroscience considering that a range of neuropsychiatric or neurodevelopmental conditions (such as autism spectrum disorders and schizophrenia) show both empathy impairments and profound abnormalities of white matter tract integrity.

We collected self-reports of empathy from a large sample of 107 homogenous patients who had previously undergone surgery for a diffuse low-grade glioma (DLGG). This rare slow-growing tumour constitutes an ideal pathophysiological model for inferring function from white matter associative fasciculi, at least for three reasons: (i) this tumour preferentially migrates along white matter pathways; (ii) Although DLGG is known to induce functional plasticity phenomena (Duffau, 2005; Bonnetblanc et al., 2006; Desmurget et al., 2007), this is only true for cortical structures, not for subcortical pathways that show a low potential of functional compensation (Ius et al., 2011); (iii) for the latter reason, major part of the white matter connectivity are spared during “awake” neurosurgery in our medical center despite lesion invasion, thanks to a functional mapping via direct electrostimulation of axonal connectivity (Duffau, 2005; Moritz-Gasser et al., 2013; Khan et al., 2013; Herbet et al., 2014a). As a consequence, contrary to any other brain diseases, it is possible to gauge the respective roles of cortical and white matter damage in the occurrence of functional disturbances, independently (see Herbet et al. (2014b)).

We used the *empathy quotient* (EQ) developed by Baron-Cohen and Wheelwright (2004) as the main measure of interest. The rationale of using the EQ was motivated by the fact that we sought to probe the different components of empathy and not a specific aspect as in most studies (e.g. empathy for pain). In addition, this self-report measure shows very good psychometric properties and has been proposed in multiple clinical populations. Of great interest, the EQ has been used as a complementary measure of empathy in functional neuroimaging studies. For example, it has been shown that the degree of neuronal reactivity across different cortical structures classically belonging to both the mirror and the mentalizing networks during empathy-eliciting stimuli (such as, among others, the premotor cortex, the precuneus and the medial and ventrolateral portion of the prefrontal cortex) was positively correlated with EQ scores (Chakrabarti and Baron-Cohen, 2006; Lamm et al., 2007; Rameson et al., 2012; Schulte-Ruther et al., 2011; Horan et al., 2014).

For the purposes of our study, each patient's resection cavity and residual lesion infiltration (mainly located on the trajectory of associative tracts) were mapped based on structural imaging data acquired in the chronic phase (i.e. at least three months after surgery), at the time of the behavioural data collection. Based on a recent fine-grained DTI-based white matter atlas (Thiebaut de Schotten et al., 2011), we estimated each associative pathway's degree of disconnection. Adopting a fully exploratory approach, justified by the lack of prior knowledge on the connectional anatomy of empathy and made possible by the relatively large number of patients included, data were analyzed with two concurrent methods: (i) a topological (i.e. conventional voxelwise lesion-symptom mapping, VLSM), (ii) a hodological one (i.e.

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