Schizophrenia Research 108 (2009) 41–48

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Reduced fractional anisotropy of corpus callosum in first-contact, antipsychotic drug-naive patients with schizophrenia

Roberto Gasparotti [a,b], Paolo Valsecchi [c,d], Francesco Carletti [a], Alessandro Galluzzo [c,d], Roberto Liserre [a], Bruno Cesana [e], Emilio Sacchetti [b,c,d,f,*]

[a] Department of Diagnostic Imaging, Neuroradiology Unit, Brescia University School of Medicine and Brescia Spedali Civili, Brescia, Italy
[b] Centre of Behavioural and Neurodegenerative Disorders, Brescia University and EULO, Brescia, Italy
[c] University Psychiatric Unit, Brescia University School of Medicine and Brescia Spedali Civili, Brescia, Italy
[d] Department of Mental Health, Brescia Spedali Civili, Brescia, Italy
[e] Department of Biomedical Sciences and Biotechnologies, Section of Medical Statistics and Biometry, Brescia University School of Medicine, Brescia, Italy
[f] Department of Psychiatry, Brescia University School of Medicine, Brescia, Italy

ARTICLE INFO

Article history:
Received 16 June 2008
Received in revised form 20 October 2008
Accepted 8 November 2008
Available online 21 December 2008

Keywords:
Splenium fractional anisotropy
Genu fractional anisotropy
First-contact schizophrenia patients
Drug-naïve schizophrenia patients

ABSTRACT

Background: Corpus callosum is the most important commissure of the brain and therefore represents a first-choice candidate to challenge hypotheses of disrupted inter-hemispheric connectivity and white matter pathology in patients with schizophrenia. Recent studies on diffusion tensor imaging (DTI) of corpus callosum yielded promising but equivocal evidence of reduced fractional anisotropy (FA) in schizophrenia patients who were, for the most part, chronic cases on medication for a lengthy period of time. To exclude potentially confounding effects of the course of the disorder and its treatment, we compared callosal FA of first-contact, antipsychotic drug-naive schizophrenia patients (n=21) and healthy controls (n=21).

Methods: Splenium and genu FA were obtained by two independent observers utilizing large, rectangular, tractography-guided regions of interest outlined on directional color-coded maps. Inter-observer agreement on FA was evaluated by means of the Bland and Altman and the Passing and Bablok procedures together with an estimate of the intra-class correlation coefficient.

Results: Strong inter-observer agreement of FA values emerged from each of the three statistical approaches utilized. ANCOVA showed a significant effect on FA for the interaction between patient–control membership and callosal region (F=5.354; p=0.026); post hoc multiple comparisons demonstrated that, when compared to the controls, the patients had lower mean FA values (p=0.005) in the splenium but not in the genu and that this difference tended to be more evident in males (p=0.090).

Conclusions: Lowered mean FA values in the splenium of first-contact, antipsychotic drug-naïve patients with respect to healthy controls strongly support the hypothesis that processes operant at least since the earliest phases of the disorder and independent from exposition to antipsychotic drugs contribute to reduced anisotropy in schizophrenia.

1. Introduction

The hypothesis that schizophrenia may be a disease of connectivity among different brain regions, although far from new (Kraepelin, 1919; Wernicke, 1906), has gained increasing focus in recent years (Andreasen et al., 1999; Burns, 2004;

* Corresponding author. University Psychiatric Unit, Brescia Spedali Civili, piazza Spedali Civili 1, 25123 Brescia, Italy. Tel.: +39 030 3995233/381749; fax: +39 030 3384089.
E-mail address: sacchett@med.unibs.it (E. Sacchetti).

0920-9964/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2008.11.015

Crow et al., 2007; Friston, 2005; Friston and Frith, 1995; Hoffman and McGlashan, 2001; Stephan et al., 2006). As a consequence, corpus callosum has also become a topic of a major interest in schizophrenia research; corpus callosum is indeed the most important inter-hemispheric commissure of the brain and is crucially involved in the establishment of cortico-cortical connections and lateralization (Bloom and Hynd, 2005; Gazzaniga, 2000).

A number of post-mortem investigations and structural brain imaging studies in vivo have supported the presence of gross callosal abnormalities in patients with schizophrenia (Highley et al., 1999; Shenton et al., 2001;Woodruff et al., 1995). In addition, research based on diffusion tensor imaging (DTI), a recently developed technique that offers opportunities for study of the microscopic integrity and organization of the white matter in vivo (Basser and Pierpaoli, 1996), has so far yielded promising but equivocal results. A preponderance of reports demonstrate reduced callosal anisotropy in schizophrenia patients (Agartz et al., 2001; Ardekani et al., 2003; Brambilla et al., 2005; Buchsbaum et al., 2006; Cheung et al., 2008; Douaud et al., 2007; Federspiel et al., 2006; Foong et al., 2000; Hubl et al., 2004; Kanaan et al., 2006; Kyriakopoulos et al., 2008; Price et al., 2007; Rotarska-Jagiela et al., 2008; Shergill et al., 2007), but findings of increased (Hubl et al., 2004) and normal (Buchsbaum et al., 1998; Foong et al., 2002; Kumra et al., 2004; Miyata et al., 2007; Price et al., 2005; Seok et al., 2007; Sun et al., 2003) anisotropy have also been reported. Patient–control differences in callosal anisotropy also varied discretely between the studies as to their topography, with the preponderance of the literature involving the compartments of the splenium (Agartz et al., 2001; Ardekani et al., 2003; Brambilla et al., 2005; Cheung et al., 2008; Douaud et al., 2007; Federspiel et al., 2006; Foong et al., 2000; Kyriakopoulos et al., 2008; Price et al., 2007; Rotarska-Jagiela et al., 2008), and of the genu (Ardekani et al., 2003; Brambilla et al., 2005; Buchsbaum et al., 2006; Douaud et al., 2007; Hubl et al., 2004; Kanaan et al., 2006; Price et al., 2007; Rotarska-Jagiela et al., 2008; Shergill et al., 2007). The preferential localization in the anterior and posterior segments of the corpus callosum indicates that fibres of small diameter, which are predominantly assigned to the temporo-parietal and prefrontal cortical areas, respectively, are a major contributor to low anisotropy (deLacoste et al., 1985; Hofer and Frahm, 2006); therefore, data on callosal anisotropy may be reconciled to some degree with the hypothesis (Crow, 1997; Pearlson et al., 1996; Pearlson and Marsh, 1989) of an involvement of heteromodal association cortex in schizophrenia.

Several factors pertaining to the patients, DTI methods, or both, may have reasonably contributed to inconsistencies between the studies. For example, mixed samples of patients with different diagnoses from the schizophrenia spectrum, variable illness duration, and a heterogeneous history of exposition to antipsychotic drugs have been almost systematically enrolled in the absence of demonstrations that DTI data are not or are only marginally affected by these variables. In turn, the frequent recruitment of a limited number of participants generally prevented an adequate statistical control of these and other putative confounders, although their negative impact is magnified especially when, as in schizophrenia, one is dealing with a clinically and possibly etiopathogenetically heterogeneous disorder. Furthermore, DTI studies of corpus callosum have adopted whole-brain voxel-based analyses (VBA) (Agartz et al., 2001; Ardekani et al., 2003; Cheung et al., 2008; Douaud et al., 2007; Federspiel et al., 2006; Foong et al., 2002; Hubl et al., 2004; Kyriakopoulos et al., 2008; Seok et al., 2007; Shergill et al., 2007) or different ROI techniques (Agartz et al., 2001; Foong et al., 2000; Kumra et al., 2004; Price et al., 2005, 2007; Sun et al., 2003). Direct comparisons indicate non-equivalence between methods. Indeed, the application of VBA (Foong et al., 2002) in a subgroup of subjects previously included in a positive ROI study (Foong et al., 2000) failed to confirm patient–control differences of callosal fractional anisotropy (FA); similarly, the genu FA of schizophrenia patients was found to be inferior to that of healthy controls at a non-significant and a significant level when (Kanaan et al., 2006) conventional and tractography-guided ROI measurements were used, respectively.

Studies involving numerically representative samples generally exceed the short-term possibilities of single research centres when restrictive recruitment criteria are adopted. Experimental designs tailored to exclude a discrete number of plausible confounders and the use of optimized FA measurements seem instead more feasible. In particular, research restricted to recent-onset, drug-naive patients merit priority because they offer unique possibilities to challenge the association between callosal FA and schizophrenia net of the eventual moderating effects of the chronicity of the disorder and treatments. Unfortunately, first-episode patients have been the focus of only four studies to date (Cheung et al., 2008; Federspiel et al., 2006; Price et al., 2005, 2007). Of these, the sole report (Cheung et al., 2008) on drug-naïve patients showed significantly lower mean FA values in the splenium but not in the genu of the affected participants with respect to the controls.

We report here a new comparative study on splenium and genu FA between first-contact, antipsychotic drug-naive patients with an unequivocal DSM-IV-TR diagnosis of schizophrenia and healthy individuals. An ROI rather than a VBA approach was chosen because the former seems preferable in non-exploratory, hypothesis-driven studies; the latter is probably less able to reveal subtle abnormalities and is more subject to miss-registrations and partial volume artefacts (Federspiel et al., 2006; Kanaan et al., 2006; Kubicki et al., 2007). In turn, the use of large, rectangular, tractography-guided ROIs allowed extended contingents of fibres to be included and subjectivity related to conventional ROI placements on FA maps to be reduced (Kanaan et al., 2006).

2. Subjects

The study involved an equal number of Caucasian patients and healthy controls living within a 25 km radius from Brescia. To be eligible, both patients and controls had to: (1) be aged between 18 and 45 years and right-handed; (2) have no relatives among the other prospective participants; (3) have a negative history of seizures and/or head trauma with loss of consciousness; (4) have no evidence of concomitant medical or neurological disorders of clinical relevance; (5) have given written informed consent; and (6) fulfil predefined group-specific inclusion and exclusion criteria.