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Adverse childhood experiences influence white matter microstructure in patients with schizophrenia

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ABSTRACT

Integrity of brain white matter (WM) tracts in adulthood could be detrimentally affected by exposure to adverse childhood experiences (ACE). Changes of diffusion tensor imaging (DTI) measures suggesting WM disruption have been reported in patients with schizophrenia together with a history of childhood maltreatment. We therefore hypothesized that ACE could be associated with altered DTI measures of WM integrity in patients with schizophrenia. We tested this hypothesis in 83 schizophrenia patients using whole brain tract-based spatial statistics in the WM skeleton with threshold-free cluster enhancement of DTI measures of WM microstructure: axial, radial, and mean diffusivity (MD), and fractional anisotropy (FA). We observed an inverse correlation between severity of ACE and DTI measures of FA, and a positive correlation with MD in several WM tracts including corona radiata, thalamic radiations, corpus callosum, cingulum bundle, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus. Lower FA and higher MD are indexes of a reduction in fibre coherence and integrity. The association of ACE to reduced FA and increased MD in key WM tracts contributing to the functional integrity of the brain suggests that ACE might contribute to the pathophysiology of schizophrenia through a detrimental action on structural connectivity in critical cortico-limbic networks.

1. Introduction

Consistent findings in healthy subjects suggest that the integrity of brain white matter (WM) tracts in adulthood could be detrimentally affected by exposure to adverse stressful experiences in early life.

WM microstructure can be investigated in vivo via diffusion tensor imaging (DTI), a method which measures the diffusion of water molecules within WM tracts. The tendency to diffuse along the principal direction of the fibre (axial diffusivity-AD) reflects the integrity of axons and myelin sheaths, and the bundle coherence of WM tracts (Boretius et al., 2012). An increase in radial diffusivity (RD), perpendicular to axonal walls, suggests disrupted myelination (Song et al., 2002). Mean diffusivity (MD) is a measure of the average molecular motion, independent of tissue directionality. Finally, fractional anisotropy (FA) reflects the dominance of the largest axial component and may reflect fibres' organization, fibres' directional coherence, and/or fibres' integrity (Beaulieu, 2002).

Early severe socioemotional deprivation has been associated with reduced FA in the left uncinate fasciculus (Eluvathingal et al., 2006), paralleling glucose hypometabolism in limbic and paralimbic structures (Chugani et al., 2001). In healthy adults, Choi et al. (2009), reported an association between parental verbal abuse during childhood and a significantly reduced FA in arcuate fasciculus, left superior temporal gyrus, cingulum bundle, and left body of the fornix (Choi et al., 2009). The same group then documented an increased MD and RD with decreased FA in the corpus callosum and corona radiata of adults exposed to peer verbal abuse during childhood (Teicher et al., 2010), and a reduction of FA values in the inferior longitudinal fasciculus of left lateral occipital lobe in adults who had witnessed domestic violence during childhood (Choi et al., 2012). Adolescents exposed to childhood maltreatment had lower FA in the superior longitudinal fasciculus, right cingulum bundle projecting to the hippocampus, left inferior fronto-occipital fasciculus, and splenium of the corpus callosum, with lower values being associated with emerging depression in the follow up (Huang et al., 2012).

Our group extended this research perspective to patients affected by psychiatric conditions, showing that adverse childhood experiences (ACE) inversely correlate with AD in the corona

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radiata, thalamic radiations, corpus callosum, cingulum bundle, superior longitudinal fasciculus, inferior fronto-occipital fasciculus and uncinate fasciculus in adult patients affected by Bipolar Disorder (Benedetti et al., 2014). These findings suggest that ACE might contribute to psychiatric pathophysiology by hampering structural connectivity in critical cortico-limbic networks.

Changes of DTI measures suggesting WM disruption have been consistently reported in patients with schizophrenia (Ardekani et al., 2003; Burns et al., 2003; Hubl et al., 2004), in individuals at high genetic risk (Hoptman et al., 2008), in never medicated chronic patients (Liu et al., 2013), in adolescent-onset schizophrenia (Douaud et al., 2007) and in first-episode, drug naïve patients (Begre et al., 2003; Cheung et al., 2008; Gasparotti et al., 2009; Guo et al., 2012; Mandl et al., 2013). A decreased FA in schizophrenia patients has been reported in the prefrontal cortex, temporo-parietal and parieto-occipital regions, splenium, cingulum, uncinate fasciculus, bilateral arcuate fasciculus, posterior capsule and adjacent occipital WM (Agartz et al., 2001; Buchsbaum and Hazlett, 1998; Foong et al., 2000; Lim et al., 1999). These findings highlight that WM diffusivity changes might be of clinical relevance in schizophrenia, and that DTI could provide new biomarkers to estimate the susceptibility to the disorder (Chua et al., 2007; Moriya et al., 2010).

A history of childhood maltreatment is highly prevalent in patients with schizophrenia, increasing the risk of developing the illness (Jones et al., 1994) and worsening outcome (Rosenberg et al., 2007). A number of studies have demonstrated that ACE associate with more severe positive symptoms (increased hallucinations, delusions), dissociative phenomena, levels of general psychopathology, social impairments, and worse cognitive functioning (Gil et al., 2009; Holowka et al., 2003; Lysaker et al., 2001; Rosenberg et al., 2007; Ross et al., 1994; Schafer et al., 2012; Schenkel et al., 2005). ACE also influence brain activity in response to emotional stimuli in amygdala, hippocampus, prefrontal, and cingulate cortex, thus affecting grey matter structure and function in healthy subjects and in patients with schizophrenia (Benedetti et al., 2011a).

The documented association between ACE and WM microstructure in healthy subjects and bipolar patients, between schizophrenia and WM microstructure, and between ACE and schizophrenia, led us to hypothesize that ACE could be associated with altered DTI measures of WM integrity in patients with schizophrenia. Using tract-based spatial statistics (TBSS) we tested this hypothesis in a homogeneous sample of patients affected by schizophrenia.

2. Methods

2.1. Sample and clinical assessment

The sample included 83 patients with a diagnosis of chronic schizophrenia. Patients were biologically unrelated, clinically stabilized outpatients meeting The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV TR) criteria for chronic schizophrenia, and were responders to typical and/or atypical antipsychotics in monotherapy. Doses had been stable in the 3 months before enrolment. Schizophrenia diagnosis was made by trained psychiatrists using the SCID-I questionnaire and mental retardation was assessed by a trained psychologist through WAIS-R. Exclusion criteria were: additional diagnoses on axis I, mental retardation on axis II, pregnancy, major medical and neurological disorders, history of drug or alcohol abuse or dependency within the previous year. Physical examination, laboratory tests and electrocardiograms were performed at admission. After complete description of the study to the subjects, a written informed consent was obtained. The local ethical committee approved the study protocol.

Severity of ACE was rated on the Risky Families Questionnaire (RFQ) (Taylor et al., 2006). The RFQ has been adapted from an instrument originally developed to assess the relationship of family stress to mental and physical health outcomes in adulthood (Felitti et al., 1998). The instrument is aimed at rating the degree of harsh parenting with overt family conflict and deficient nurturing experienced by the children in their familial environment, and has been validated in assessing the relationship between early stress and adult brain structure in healthy controls and in patients with psychiatric conditions (Benedetti et al., 2011a, 2011b, 2012, 2014; Poletti et al., 2014). Severity of symptoms was rated on the Positive and Negative Syndrome Scale (Kay et al., 1987)

2.2. Image acquisition

Diffusion tensor imaging was performed on a 3.0 T scanner (Gyroscan Intera, Philips, Netherlands) using SE Eco-planar imaging (EPI) and the following parameters: TR/TE=8753.89/58 ms, FoV (mm) 231.43 (ap), 126.50 (fh), 240.00 (rl); acquisition matrix $2.14 \times 2.71 \times 2.31$; 55 contiguous, 2.3-mm thick axial slices reconstructed with in-plane pixel size 1.88×1.87 mm^2; SENSE acceleration factor= 2; 1 b0 and 35 non-collinear directions of the diffusion gradients; b value=900 s/mm^2. Fat saturation was performed to avoid chemical shift artefacts. On the same occasion and using the same magnet 22 Turbo Spin Echo (TSE), T2 axial slices (TR=3000 ms; TE=85 ms; flip angle=90°; turbo factor 15; 5-mm-thick, axial slices with a 512×512 matrix and a 230×230 mm^2 field of view) were acquired to rule out brain lesions.

2.3. Data processing and analyses

Image analyses and tensor calculations were done using the "Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Statistical Library" (FSL 5.1; www.fmrib.ox.ac.uk/fsl/index.html) (Smith et al., 2004; Woolrich et al., 2009). First, each of the 35 DTI volumes was affine registered to the T2-weighted $b=0$ volume using FLIRT (FMRIB's Linear Image Registration Tool) (Jenkinson and Smith, 2001). This corrected for motion between scans and residual eddy-current distortions present in the diffusion-weighted images. Anisotropy can be estimated through the application of diffusion-sensitizing gradients and the calculation of elements of the diffusion tensor matrix, i.e. the three eigenvalues λ_1, λ_2 and λ_3 (Le Bihan, 2003; Taylor et al., 2004). Fractional anisotropy (FA) is the square root of the sum of squares (SRSS) of the diffusivity differences, divided by the SRSS of the three diffusivities. After removal of nonbrain tissue (Smith, 2002), least-square fits were performed to estimate the FA, eigenvector, and eigenvalue maps. Mean diffusivity (MD) was defined as the mean of all three eigenvalues $[(\lambda_1+\lambda_2+\lambda_3)/3]$, axial diffusivity (AD) as the principal diffusion eigenvalue (λ_1), and radial diffusivity (RD) as the mean of the second and third eigenvalues $[(\lambda_2+\lambda_3)/2]$.

Next, all individuals' volumes were skeletonized and transformed into a common space as used in Tract-Based Spatial Statistics (Smith et al., 2006, 2007). Briefly, all volumes were nonlinearly warped to the FMRIB58_FA template supplied with FSL (http://www.fmrib.ox.ac.uk/fsl/tbss/FMRIB58_FA.html) and normalized to the Montreal Neurological Institute (MNI) space, by use of local deformation procedures performed by FMRIB's Non-Linear Image Registration Tool (FNIRT) (www.fmrib.ox.ac.uk/fsl/fnirt/index.html), a nonlinear registration toolkit using a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, a mean FA volume of all subjects was generated and thinned to create a mean FA skeleton representing the centres of all common tracts. We thresholded and binarized the mean skeleton