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Research paper

Impact of early and recent stress on white matter microstructure in major depressive disorder

Poletti Sara[a,b,*], Aggio Veronica[a,b], Brioschi Silvia[a], Bollettini Irene[b,d], Falini Andrea[b,c], Colombo Cristina[a], Benedetti Francesco[a,b]

[a] Scientific Institute and University Vita-Salute San Raffaele, Department of Clinical Neurosciences, Milan, Italy
[b] C.E.R.M.A.C. (Centro di Eccellenza Risonanza Magnetica ad Alto Campo), University Vita-Salute San Raffaele, Milan, Italy
[c] Scientific Institute and University Vita-Salute San Raffaele, Department of Neuroradiology, Milan, Italy
[d] PhD Program in Philosophy and Sciences of Mind, University Vita-Salute San Raffaele, Milan, Italy

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ABSTRACT

Background: Major Depressive Disorder (MDD) is a worldwide-spread pathology, characterized by lifetime-recurrent episodes. Adverse childhood experiences (ACE) increase the lifetime risk of developing depression and affect the structure of the brain. Recent stressful events (RSE) can trigger the onset of depressive episodes, and affect grey matter volume. The aim of our study is to analyse the effect of both early and recent stress events on white matter microstructure in MDD patients and healthy volunteers.

Methods: Sixty-five MDD inpatients and fifty-nine healthy controls underwent MRI acquisition of diffusion tensor images with a 3.0 T scanner. Severity of ACE and RSE was rated, respectively, on the Risky Families Questionnaire and on the Social Readjustment Rating Scale.

Results: A significant effect of diagnosis was observed, with MDD subjects showing reduced fractional anisotropy (FA) and axial diffusivity (AD) compared to healthy controls in all the major association, projection and commissural tracts. In patients with MDD, but not in healthy controls, both ACE and RSE correlated with measures of WM microstructure: ACE correlated negatively with AD and MD, whereas RSE correlated negatively with FA.

Limitations: The two diagnostic groups differed for age and education, previous and current medications, and treatment periods. Conclusions. Exposure to both early and recent stress exerts a widespread effect on WM microstructure of MDD patients, with a different impact possibly depending from the developmental period in which the stress has occurred.

1. Introduction

Major Depressive Disorder (MDD) is a worldwide-spread pathology, representing one of the leading causes of disability in western countries (Vos et al., 2012). Its characteristic evolution, characterized by lifetime-recurrent episodes, underlines the severity and global impairment consequent to the illness. Family and twin studies report that genetic factors contribute up to 40% of the risk for depression (Arloth et al., 2015), and exposure to environmental factors contribute then to the aetiology of depression (Kendler, 1998).

Psychosocial stress has been repeatedly associated to psychiatric disorders (Kendler et al., 2000; Lu et al., 2013; Nelson et al., 2002; Nemeroff, 2016). Stressful life events, both early and recent, can increase the vulnerability to psychopathology (Boyce and Ellis, 2005), and promote the insurgence of new depressive episodes in diagnosed patients (Mullins et al., 2016) both immediately after the events and years later (Assari and Lankarani, 2016).

Adverse childhood experiences (ACE), including physical and psychological abuse, neglect, parental substance/alcohol abuse, domestic violence, sexual abuse, parental separation and other forms of parental loss, increase the lifetime risk of developing depression (Wiersma, 2015), accelerate MDD onset, increase suicide rate and symptoms severity, and decrease treatment response (Hayashi et al., 2015; Nemeroff, 2016). These effects could be underpinned by brain structural and functional correlates of ACE exposure (Teicher and Samson, 2013).

ACE influence neural plasticity in cerebral structures that are still maturating (Calabrese et al., 2009). Widespread grey matter (GM) volume reductions have been reported in healthy humans exposed to ACE (Cohen et al., 2006; Lim et al., 2014), but the detrimental effect of ACE on the brain extends to white matter (WM) integrity. Maltreated rhesus monkeys show reduced fractional anisotropy (FA) and increased radial

* Corresponding author at: Istituto Scientifico Ospedale San Raffaele, Department of Clinical Neurosciences, San Raffaele Turro, Via Stamira d'Ancona 20, Milano, Italy.
E-mail address: poletti.sara@hsr.it (P. Sara).

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diffusivity (RD) in several WM clusters, suggesting a detrimental effect of ACE on WM maturation from childhood to adolescence (Howell et al., 2013). Tract-based spatial statistics (TBSS) and tractographic studies show a general reduction of FA in the inferior longitudinal fasciculus, arcuate fasciculus, cingulum bundle, and fornix (Choi et al., 2012, 2009). Few studies have been performed on the effect of recent stressful events (RSE), showing a volumetric decrease of the amygdala and dentate gyrus in depressed patients (Sublette et al., 2016; Treadway et al., 2015).

Neuroimaging studies in patients with mood disorder consistently reported an effect of ACE on both WM and GM microstructure (Benedetti et al., 2014b; Poletti et al., 2016b; Tatham et al., 2016; Teicher and Samson, 2016). MDD diagnosis influence both GM and WM microstructure independent of exposure to stressful events, and brain structural alterations have been suggested as possible biomarkers of the disorder. In vivo Diffusion Tensor Imaging (DTI) studies reported abnormalities in the superior longitudinal fasciculus, corpus callosum, hippocampus, internal and external capsule, uncinate fasciculus, and fornix (Guo et al., 2012; Murphy and Frodl, 2011; Zuo et al., 2012), which have been linked to illness severity and duration (Zou et al., 2008). These effects could be influenced by the individual history of exposure to stress. In the present study we explored the effects of both ACE and recent stress on WM microstructure in a sample of MDD patients and healthy volunteers.

2. Methods

2.1. Participants

Sixty-five inpatients with MDD, consecutively admitted for a major depressive episode (DSM-IV criteria, SCID interview) and 59 healthy controls (HC) were studied. Exclusion criteria were: other diagnosis on axis I, mental retardation, pregnancy, previous history of epilepsy or major medical disorders, and history of alcohol or drug dependency in the last 6 months. All MDD patients were under antidepressant treatment (SSRI: n = 35, SNRI: n = 17, TCA: n = 4, antipsychotic: n = 9) and 19 patients had more than one antidepressant prescription. After complete description of the study, written informed consent was obtained. All research activities were approved by the local ethical committee. Depression severity was rated on the Hamilton Depression Rating Scale (Hamilton, 1960). ACE were assessed through the Risky Families Questionnaire (RFQ) (Taylor et al., 2006), an instrument that rates the degree of conflict, deficient nurturing and harsh parenting in the family environment during childhood. The scores can range from 13 (no ACE) to 65 (very high ACE). The Social Readjustment Rating Scale (SRRS) (Holmes and Rahe, 1967) was used to measure the occurrence of recent (number of events in the last three years) stressful events (RSE). The scale focuses on events that led to changes in usual activities that frequently precede illness onsets, and yields two different measures of stress: one score obtained as the sum of the number of stressful events that had occurred in the last three years; one score obtained as the weighted probability that these stressful events are followed by detrimental effects, such as illness. For the analyses the weighted score was used. Both RFQ and SRRS have been successfully used by our group to study the biological correlates of stress in patients with mood disorders (Benedetti et al., 2014a; Poletti et al., 2016a, 2016b).

2.2. Image acquisition and processing

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 × 2.71 × 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. Using the same magnet 22 Turbo Spin Echo (TSE) on the same occasion, 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.

Image analyses and tensor calculations were done using the "Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library" (FSL 5.0; 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 $b = 0$ vol 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 (Basser et al., 1994; Le Bihan, 2003; Taylor et al., 2004). Axial diffusivity (AD, λ_1), the tendency to diffuse along the principal direction of the fibre reflects the integrity of axons and myelin sheaths, and the bundle coherence of WM tracts (Boretius et al., 2012). An increase in RD (the average of λ_2 and λ_3), perpendicular to axonal walls, suggests disrupted myelination (Song et al., 2002). Mean diffusivity (MD) (average of λ_1, λ_2 and λ_3) is a measure of the average molecular motion, independent of tissue directionality. 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 non-brain tissue (Smith, 2002), least-square fits were performed to estimate the FA, eigenvector, and eigenvalue maps.

Next, all volumes were skeletonized and transformed into a common space as used in Tract-Based Spatial Statistics (Smith et al., 2006, 2007). TBSS focuses on the centres of all fibre bundles that are common to the participants (the most compact WM skeleton), thus improving the probability that the given spatial voxels contain data from the same part of the same WM tract of each participant. 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 at FA > 0.20 to reduce the likelihood of partial voluming in the borders between tissue classes. Individual FA values were warped onto this mean skeleton mask by searching perpendicular from the skeleton for maximum FA values. The resulting tract invariant skeletons for each participant were fed into voxelwise permutation-based cross-subject statistics. Similar warping and analyses were used on MD, AD, and RD data sampled from voxels with FA > 0.20. Threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009) was used to avoid defining arbitrary cluster-forming thresholds and smoothing levels. Voxelwise levels of significance, corrected for multiple comparisons, were then calculated with a standard permutation testing (10,000 permutations for each contrast) by building up the null distribution of the maximum TFCE scores. Corrected $p < 0.05$ in a minimum cluster size of k = 100 was considered significant.

Voxelwise DTI analyses were performed using nonparametric permutation-based testing (Nichols and Holmes, 2002) as implemented in randomize in FSL with general linear model (GLM). An ANOVA was performed with diagnosis and stress as factors, and DTI measures of WM integrity (FA, MD, AD, and RD) as dependent variables. We tested the effect of ACE and RSE separately in the two groups of HC and patients with MDD. All analyses were corrected for the effects of nuisance covariates which could influence WM structure: age (Kochunov et al.,