Journal of Psychiatric Research 47 (2013) 1101–1109

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

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

Developmental differences in diffusion tensor imaging parameters in borderline personality disorder

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ARTICLE INFO

Article history:
Received 27 August 2012
Received in revised form
27 February 2013
Accepted 28 March 2013

Keywords:
Borderline personality disorder
Diffusion tensor imaging
Inferior longitudinal fasciculus
Development
Neuroimaging

ABSTRACT

Background: Borderline personality disorder (BPD) often presents during adolescence. Early detection and intervention decreases its subsequent severity. However, little is known about early predictors and biological underpinnings of BPD. The observed abnormal functional connectivity among brain regions in BPD led to studies of white matter, as the neural substrate of connectivity. However, diffusion tensor imaging (DTI) studies in adult BPD have been inconclusive, and, as yet, there are no published DTI studies in borderline adolescents.
Methods: We conducted DTI tractography in 38 BPD patients (14-adolescents, 24-adults) and 32 healthy controls (13-adolescents, 19-adults).
Results: We found bilateral tract-specific decreased fractional anisotropy (FA) in inferior longitudinal fasciculus (ILF) in BPD adolescents compared to adolescent controls. ILF FA was significantly higher in adolescent controls compared to BPD adolescents, BPD adults and adult controls (Wilks $F(3,57) = 3.55$, $p < 0.02$). Follow-up voxelwise TBSS analysis demonstrated lower FA in BPD adolescents compared to adolescent controls also in uncinate and occipitofrontal fasciculi.
Discussion: FA generally develops along an inverted U-shape curve, increasing through adolescence, and slowly decreasing in adulthood. Our findings suggest that, in adolescent BPD, this normal developmental "peak" in FA, which is seen in healthy controls, is not achieved. This suggests a possible neural substrate for the previously reported OFC-amygdala disconnect in adults with BPD. It raises the possibility that a white matter tract abnormality in BPD present in adolescence may not be appreciable in adulthood, but a functional abnormality in the coordination among brain regions persists. Our finding represents a possible biological marker to identify those at risk for developing BPD.

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1. Introduction

Borderline personality disorder (BPD) is a complex and serious mental disorder characterized by emotional dysregulation, poor impulse control and impaired interpersonal relationships (New et al., 2008b) with a substantial risk for completing suicide (Leichsenring et al., 2011). The full manifestations of BPD become evident during adolescence (Goodman et al., 2011), and it is in adolescence when individuals with BPD usually seek treatment (Chanen et al., 2008a). BPD can be diagnosed in adolescents using similar diagnostic instruments to those used in adults (Chanen et al., 2008b). Early detection and intervention in BPD has been shown to decrease symptom severity and improve functioning (Chanen et al., 2008a). However, little is known about early predictors and biological underpinnings of BPD. In the present study, we aimed to fill this gap in knowledge by searching for a biomarker that could help with earlier identification of BPD in young people.

1.1. Neuroimaging findings in adult BPD

The neuroimaging literature in BPD patients is rapidly growing (Mauchnik and Schmahl, 2010; New et al., 2008a), and studies support the hypothesis of a dysfunctional frontolimbic network in BPD, which appears to involve anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC),

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0022-3956/$ – see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.jpsychires.2013.03.021

hippocampus, and amygdala. It is believed that alterations in this network are related to the diminished top-down control of affective and aggressive responses (Leichsenring et al., 2011; New et al., 2008b). The most consistent structural imaging finding in adult BPD is a decrease in gray matter volume in ACC (Hazlett et al., 2005; Minzenberg et al., 2008; Tebartz van Elst et al., 2003) and hippocampus (Brambilla et al., 2004; Irle et al., 2005; Nunes et al., 2009; Zetzsche et al., 2007). Other findings include volume reduction in the left OFC (Tebartz van Elst et al., 2003) and amygdala (Nunes et al., 2009).

One theory as to what might underlie the striking symptoms of emotional lability and hyper-reactivity which characterizes BPD is that the coordinated function among brain areas is abnormal, and in fact, we previously showed a marked functional disconnect between OFC and amygdala in adult BPD (New et al., 2007). This observation led to an examination of white matter in BPD as the neural substrate of connectivity. To date, only three diffusion tensor imaging (DTI) studies have been published in adults with BPD (Grant et al., 2007; Rusch et al., 2010; Rusch et al., 2007). One found decreased fractional anisotropy (FA) in the OFC in women with BPD compared to controls (Grant et al., 2007), although another showed no significant difference in DTI between adults with both BPD and attention-deficit hyperactivity disorder (ADHD) and controls, but did find a correlation between FA and lifetime depressive symptoms (Rusch et al., 2007). The same group recently found impaired inter-hemispheric structural connectivity in BPD subjects with ADHD (Rusch et al., 2010).

1.2. Neuroimaging findings in adolescent BPD patients

Structural neuroimaging data in adolescent BPD is limited. One study found volume reduction in left ACC (Whittle et al., 2009), while another found reductions in dorsolateral PFC and OFC, but not ACC (Brunner et al., 2010). Other studies reported right-sided OFC gray matter reduction in adolescent BPD, but not in amygdala or hippocampus (Chanen et al., 2008c). In a sample overlapping with the present sample, we found that adolescents with BPD and MDD had decreased ACC gray matter volume compared to healthy controls (Goodman et al., 2011). There have been no published DTI studies in borderline adolescents to date.

1.3. Developmental changes in DTI

While structural imaging provides quantitative information about brain tissue volume, DTI provides information about the white matter tracts connecting brain regions. There are profound developmental changes in white matter, reflected in the outcome measure of DTI most commonly used, Fractional Anisotropy (FA), thought to reflect both myelination and organized directionality of white matter tracts (Madler et al., 2008). The developmental trajectory exhibited in most white matter tracts includes a sharp increase in FA up to the age of 2–3 years, followed by a gradual increase through adolescence and into the mid-third decade (Asato et al., 2010; Bava et al., 2010; Trivedi et al., 2009; Westlye et al., 2010). While FA increases progressively through adolescence, there is a leveling off and slow decrement of FA in adulthood (Hasan et al., 2010).

Little is known to date about the developmental trajectory of either structural brain imaging or DTI in BPD. Some structural alterations in BPD are observed both in adolescents and adults, while others have only been reported either early or late in the development of the disorder. It has been suggested that volume changes in prefrontal cortex may appear early in BPD, while volume changes in limbic structures might appear later as a function of the course and/or severity of BPD (Brunner et al., 2010; Chanen et al., 2008c). Since there are no published DTI studies in borderline adolescents, the developmental trajectory of white matter tracts in BPD remains unanswered. The present study aims to address this question by comparing DTI findings in two samples of BPD patients (adolescents and adults) and two age- and sex-matched healthy control (HC) samples.

2. Methods

2.1. Adolescent samples

Twenty-seven adolescents (14 BPD, 13 HC matched by age and sex) underwent diagnostic and structural brain imaging with DTI. BPD patients met DSM-IV (SCID-II) (First, 1997) and Diagnostic Interview for BPD-revised (DIB-R) criteria for BPD (Zanarini et al., 2002), while controls had no current axis I or II diagnosis as assessed by the SCID-I/P (First, 2002) and SCID-II. The DIB-R was included to ensure that adolescent BPD subjects met a high threshold level for BPD diagnosis. Adolescent BPD patients were recruited from the adolescent psychiatric inpatient service at The Mount Sinai Hospital in New York City, and HC were recruited from the surrounding community by advertisements. All except one adolescent BPD subject also met criteria for current MDD. Adolescents were excluded for 1) history of serious head injury or neurological disorder; 2) schizophrenia, any other psychotic disorder, bipolar disorder type I or pervasive developmental disorder.

2.2. Adult samples

Twenty-four adult BPD patients and 19 adult HC (1 excluded due to MRI artifact) matched by sex and age completed the study. Individuals from 18 to 55 years of age were recruited through local newspaper advertisements and clinical referral. Subjects were excluded for: 1) history of serious head injury or neurological disorder; 2) current alcohol and/or drug abuse or dependence; 3) schizophrenia, any other psychotic disorder or bipolar disorder type I; or 4) current psychiatric medication. Axis I disorders were assessed with the SCID-I/P and Axis II with the SIDP-IV (Pfohl et al., 1996). Healthy controls had no personal history of Axis I or II diagnoses.

This study was approved by Mount Sinai's Institutional Review Board. All adult participants provided written informed consent prior to participation. Assent was obtained for adolescents and written informed consent was obtained from each adolescent subject's parent or guardian.

2.3. Self report measures

Depressive symptoms were assessed with the Beck Depression Inventory (Beck et al., 1961); trait aggression was measured with the Buss Perry Aggression Questionnaire (BPAQ), a 29-item questionnaire (Buss and Perry, 1992), and the State-Trait Anger Expression Inventory (STAXI) (Spielberger et al., 1983). Affect lability was measured with the Affect Lability Scale (ALS), a 54-item self-report measure in which subjects rate their agreement with statements regarding the tendency of their mood to shift (Harvey et al., 1989). Impulsivity was measured with the Barratt impulsivity scales-11 (BIS) (Barratt, 1965), a 34-item questionnaire that assess motoric (acting without thinking), cognitive (hasty decisions) and nonplanning (failure to plan ahead) impulsiveness. Each item is rated on a 4-point scale ranging from "Rarely/Never" to "Almost always/Always" (Patton et al., 1995).

2.4. DTI methods

DTI was acquired on a 3T Allegra MRI scanner (Siemens, Ehrlangen, Germany) with the following parameters: a pulsed-gradient spin-echo sequence with EPI-acquisition (TR = 4100 ms,