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Review article

Age-related parieto-occipital and other gray matter changes in borderline personality disorder: A meta-analysis of cortical and subcortical structures

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ABSTRACT

Previous research suggests that core borderline personality disorder (BPD) symptoms vary in severity with advancing age. While structural neuroimaging studies show smaller limbic and prefrontal gray matter volumes (GMV) in primarily adult and adolescent BPD patients, respectively, findings are inconsistent. Using the effect-size signed differential mapping (ES-SDM) meta-analytic method, we investigated the relationship between advancing age and GMV abnormalities in BPD patients. A total of nine voxel-based morphometry (VBM) studies comparing regional GMV of 256 BPD patients and 272 healthy control subjects were included. Meta-analysis identified lower GMV in the right superior/middle temporal gyri and higher GMV in the right supplementary motor area of BPD patients. Meta-regression showed that increasing age was significantly associated with increased GMV in the left superior parieto-occipital gyri, with younger-aged patients starting at lower GMV compared to controls. In contrast, increasing age was associated with decreased GMV in the right amygdala. These findings suggest that while GMV deficits in limbic structures may become pronounced with advancing age in the course of BPD, parieto-occipital rather than frontal GMV deficits could be especially prominent in younger-aged BPD patients.

Contents

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1. Introduction

Borderline personality disorder (BPD) is defined as a lifelong condition in which environmental factors act upon pre-existing neurobiological substrates to produce a dynamic symptom constellation presenting as significantly impaired affect regulation and psychosocial functioning from early adolescence onward (Chanen and Kaess, 2012; Hughes et al., 2012; Glenn and Klonsky, 2013; Morgan et al., 2013). Crowell and colleauges' extended biosocial model of BPD (2009) states that biologically-driven temperamental vulnerabilities such as emotional sensitivity and impulsivity interact with an invalidating caregiving environment to produce emotional lability with heightened negative affectivity. In line with this model, cross-sectional and longitudinal studies of BPD patients suggest that impulsivity/disinhibition tends to peak in adolescence and then sharply decrease in adulthood whereas negative affect either remains stable or steadily increases well into middle adulthood (Stevenson et al., 2003; Paris, 2004; Stepp and Pilkonis, 2008; Arens et al., 2013). This observed age-related symptom presentation is thought to in part result from specific structural deficits, including decreased gray matter integrity within fronto-limbic structures (Hughes et al., 2012). Specifically, researchers have posited the theory that prefrontal gray matter deficits are present early in the disorder (e.g., adolescence) whereas limbic gray matter deficits develop later in the course of the disorder (e.g., adulthood; Hughes et al., 2012; Goodman et al., 2013).

The theory that gray matter volume (GMV) deficits in BPD are related to age is supported by structural neuroimaging data comparing regional GMV of BPD patients to those of healthy control subjects. When primary structural neuroimaging studies of BPD patients are examined, the majority of the research implicates mainly dorsolateral prefrontal (DLPFC), orbitofrontal (OFC), and anterior cingulate (ACC) abnormalities in adolescents (Chanen et al., 2008; Whittle et al., 2009; Brunner et al., 2010; Goodman et al., 2011) compared to hippocampal and amygdala abnormalities in adults (Soloff et al., 2012; Kuhlmann et al., 2013; Niedtfeld et al., 2013; O'Neill et al., 2013; Rossi et al., 2013; Araujo et al., 2014; Boen et al., 2014). Most published meta-analyses of primary neuroimaging data for BPD patients are restricted to adults; these region-of-interest (ROI) meta-analyses unanimously show hippocampal and amygdala GMV deficits (Nunes et al., 2009; Hall et al., 2010; Rodrigues et al., 2011; de-Almeida et al., 2012; Ruocco et al., 2012). Age-related decreases in GMV in BPD subjects were found in the hippocampus but not the amygdala in a single meta-analysis, supporting the argument that there is age-related neuronal atrophy in the hippocampus (Hall et al., 2010). However, given the lack of neuroimaging meta-analyses focusing on adolescents with BPD pathology, it is difficult to determine whether or not the paucity of primary findings in the hippocampus and amygdala is robust.

The mechanism of the observed fronto-limbic neurodevelopmental pattern in BPD is not yet well understood. Some researchers have hypothesized that initial gray matter deficits in prefrontal regions contribute to the development of limbic system dysfunction over time, as weak prefrontal inhibitory control can lead to hyper-arousal and eventual cellular damage to limbic structures (Chanen et al., 2008). However, since emotional dysregulation is considered the core symptom of BPD (Linehan, 1993), the focus of most neuroimaging meta-analyses has been the amygdala and hippocampus, which precludes the ability to examine the role of prefrontal structures in the etiology of the disorder. Obtaining a comprehensive understanding of GMV as a neurodevelopmental marker in BPD requires meta-analysis of whole-brain voxel-based morphometry (VBM) studies examining adolescent and adult subjects at various developmental stages.

The current whole-brain VBM meta-analysis focuses on age-related cortical and subcortical GMV changes in BPD. Using Effect-Size Signed Differential Mapping (ES-SDM, also known as Seed-based *d* Mapping), a coordinate-based meta-analytical method, our study aims were to (1) identify the most consistent areas of lower or higher GMV in BPD patients relative to healthy control subjects and (2) explore whether there are specific regional GMV abnormalities in BPD patients that are age-related.

Drawing from previous research, we hypothesized that lower GMV in limbic regions, particularly the hippocampus and amygdala, would be a robust finding among BPD patients. We additionally hypothesized that a number of cortical regions implicated as central to BPD symptomology would be significantly associated with age. Specifically, we predicted that volumetric deficits in prefrontal regions (i.e., DLPFC, OFC) would be uniquely associated with younger sample mean age, suggesting that these regions are impaired early in the course of BPD but approach normal volumes as patients age. We further predicted that prominent volumetric deficits in limbic regions (i.e., hippocampus, amygdala) would be associated with older sample mean age, suggesting that these deficits might not be present early in the disorder and develop later on as the disorder progresses.

2. Methods

2.1. Data sources

A systematic and comprehensive literature search was performed to identify whole-brain VBM studies comparing patients with BPD to healthy control subjects. To ensure comprehensiveness, two researchers performed the searches independently using such keywords as "borderline personality," "neuroimag*," "mri," "magnetic resonance," "brain imaging," "morphometry," "voxel," and "vbm." One of the researchers performing the searches had received training in database searching at PsycINFO and worked as a database search analyst for six years; this researcher was thus able to use advanced features of databases involved such as Medical Subject Heading terms and controlled vocabulary searching. In addition, reference lists of articles thus obtained were manually checked to identify any additional relevant studies not identified by the computerized search. Potentially included articles were limited to those published online or in print before May 2014.

2.2. Study criteria and data extraction

To be considered for inclusion, studies had to meet the following criteria: (1) published as an original paper in a peer-reviewed journal, (2) reported a GMV (including "gray matter density" or "gray matter concentration") comparison between patients with BPD and healthy control subjects, (3) used a whole-brain VBM imaging approach, and (4) reported stereotactic coordinates (Talairach or MNI) for whole-brain comparisons of GMV. A study