Neuroscience and Biobehavioral Reviews 42 (2014) 132–147

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Neuropathological and neuromorphometric abnormalities in bipolar disorder: View from the medial prefrontal cortical network

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ARTICLE INFO

Article history:
Received 7 October 2013
Received in revised form 20 January 2014
Accepted 19 February 2014

Keywords:
Depression
Bipolar disorder
Neuropathology
Magnetic resonance imaging
Neuron
Oligodendrocyte
Postmortem
Gene expression
Medial prefrontal cortex
Developmental

ABSTRACT

The question of whether BD is primarily a developmental disorder or a progressive, neurodegenerative disorder remains unresolved. Here, we review the morphometric *postmortem* and neuroimaging literature relevant to the neuropathology of bipolar disorder (BD). We focus on the medial prefrontal cortex (mPFC) network, a key system in the regulation of emotional, behavioral, endocrine, and innate immunological responses to stress. We draw four main conclusions: the mPFC is characterized by (1) a decrease in volume, (2) reductions in neuronal size, and/or changes in neuronal density, (3) reductions in glial cell density, and (4) changes in gene expression. These data suggest the presence of dendritic atrophy of neurons and the loss of oligodendroglial cells in BD, although some data additionally suggest a reduction in the cell counts of specific subpopulations of GABAergic interneurons. Based on the weight of the *postmortem* and neuroimaging literature discussed herein, we favor a complex hypothesis that BD primarily constitutes a developmental disorder, but that additional, progressive, histopathological processes also are associated with recurrent or chronic illness. Conceivably BD may be best conceptualized as a progressive neurodevelopmental disorder.

Contents

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http://dx.doi.org/10.1016/j.neubiorev.2014.02.008
0149-7634/

1. Introduction

The monoamine-deficiency hypothesis of mod disorders continues to receive empirical support (Hasler et al., 2008; Roiser et al., 2009; Savitz et al., 2013b). Nevertheless, bipolar disorder (BD) and other forms of affective illness increasingly are viewed as neuropathological conditions as more sensitive methods of detecting histological abnormalities are employed at *postmortem*. This conceptual shift has been driven by evidence of abnormalities of neuronal and glial cells at *postmortem*, as well as evidence of dendritic and neuronal atrophy in preclinical chronic stress models that serve as putative analogs of depression, MRI-defined reductions in gray matter (GM) volume, and cognitive deficits that do not fully resolve with improvement in mood (Savitz and Drevets, 2009a; Savitz et al., 2005a). Congenital abnormalities are one possible explanation for the neurophysiological changes observed in BD, but the neurotrophic effects of mood stabilizing medications like lithium (Moore et al., 2000; Savitz et al., 2010), coupled with longitudinal studies demonstrating volumetric changes over time, also raise the possibility that BD is underpinned by a (presumably) excitotoxicity-mediated histopathological process (Savitz and Drevets, 2009a).

Here we review the evidence for, and the nature of the neuropathological changes in the medial prefrontal cortex (mPFC) network in primary BD and interpret these data within the context of the structural MRI, diffusion tensor imaging, and magnetic resonance spectroscopy literature. Based on these data we then discuss the phenomenological but clinically important issue of whether the BD-associated changes observed *postmortem* should be considered to be a form of neuropathology, and if so whether BD can be considered to be a progressive, neurodegenerative illness. Here we use the term "neuropathology" in the same sense as (Harrison, 2002), i.e. morphometric abnormalities of circuits, neurons, glia and synapses rather than abnormalities solely of receptors and/or neurochemistry. We do not claim that the mPFC is the only region of the brain that shows neuropathological or neurophysiological abnormalities in BD. In contrast, based on our reading of the literature as well as the conclusions of other reviews (Gigante et al., 2011; Harrison, 2002), the abnormalities observed in BD *postmortem* do not differ *qualitatively* between subcortical and cortical regions. Further, because of widespread evidence implicating the mPFC in BD and the importance of the mPFC in regulating bodily homeostasis and adaptation to stress along with neurophysiological and neuroendocrine responses to stress, we hypothesize that the mPFC serves as a reasonable vehicle for discussing the broader implications of the nature of the neuropathological changes in BD.

2. Methods

Relevant studies published in English were identified through a MEDLINE search, National Library of Medicine, NIH (http://www.pubmed.gov) and cross-referenced papers in the field. The following key words were used: "bipolar disorder", "*postmortem*", "prefrontal cortex", "anterior cingulate", "orbitofrontal cortex". Morphometric *postmortem* studies are emphasized in this review. That is, we included studies that measured GM volume, and the number and/or density of neurons or glial cells in BD patients and controls. Neuroimaging studies and *postmortem* studies of gene expression were not systematically reviewed but were included where relevant to the interpretation or evaluation of morphometric *postmortem* data. Similarly, the schizophrenia and major depressive disorder (MDD) *postmortem* literature was beyond the focus of this review and these studies were only discussed in order to contextualize the findings in BD or in cases that samples of both unipolar and bipolar depressives were dominated by the latter subgroup.

3. Results

The anterior cingulate cortex (ACC) carries out a diverse array of integrative functions. It is often heuristically divided into dorsal "cognitive", and ventral "affective" streams. The dorsal ACC (dACC) lies along the superior portion of the cingulate sulcus running dorsal to the corpus callosum (CC), while the regions ventral and/or anterior to the genu of the CC comprise the ventral ACC. A general heuristic is that the dACC forms part of an "executive" attention system that supports response selection, error detection and performance monitoring while the ventral ACC regulates emotional and visceromotor responses (Bush et al., 2000).

3.1. The subgenual ACC (sgACC)

Drevets et al. (1997) first demonstrated a reduction of GM volume, cerebral blood flow (CBF), and glucose metabolism in the mPFC ventral to the corpus callosum genu ("subgenual" ACC) in patients with BD and major depressive disorder MDD relative to healthy controls (Fig. 1). The reduction in GM has since been replicated by a number of independent groups and appears to apply to both males and females, individuals scanned early in the course of illness, as well as patients with affective psychosis and bipolar spectrum illness (Drevets et al., 2008); although the abnormality may be specific to, or at least more salient in familial cases (Drevets et al., 1997; Hirayasu et al., 1999; Koo et al., 2008; McDonald et al., 2004). Further, chronic lithium treatment, which exerts robust neurotrophic effects in animal models (Moore et al., 2000), largely normalizes subgenual ACC (sgACC) volume in treatment responders (Moore et al., 2009). These data are supported by magnetic resonance spectroscopy (MRS) studies which find that higher levels of N-acetylaspartate (NAA) in the sgACC, a marker of neuronal integrity, are associated with lithium treatment (Moore and Galloway, 2002; Forester et al., 2008), potentially consistent with the neurotrophic effects associated with chronic lithium administration in preclinical studies.

Consistent with the weight of the volumetric imaging data, a 3-D stereological study reported a reduction in the number of nissl-stained glia identified morphometrically together with an increase in neuronal density in the sgACC of two independent samples of patients with familial BD as well as familial MDD (Ongur et al., 1998). The groups were similar in age, sex, postmortem interval, and brain pH (an indicator of premortem acidosis that can confound *postmortem* measurements) although the storage time in fixative was significantly shorter for control brains than for BD brains. Medication effects cannot be ruled out since the majority of subjects in the MDD group were receiving fluoxetine and/or tricyclic antidepressants whereas the BD subjects typically were receiving lithium and/or anticonvulsants. However, both the MDD and the BD groups showed reductions in glial number, suggesting that the reduction in glial cells is not secondary to treatment with specific