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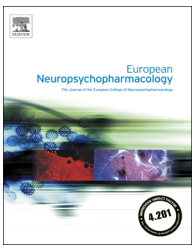

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REVIEW

A systematic review and meta-analysis of proton magnetic resonance spectroscopy and mismatch negativity in bipolar disorder

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Abstract
Aberrant glutamate neurotransmission has been implicated in the pathophysiology of bipolar disorder with accumulating evidence from imaging, post-mortem and pathology studies. Studies investigating in vivo changes to the glutamatergic system have not been as consistent and warrant clarification. Studies utilizing proton-magnetic resonance spectroscopy (^{1}H-MRS) have reported increased levels of combined glutamate and glutamine ("Glx"), which have been linked to impairments in *N*-methyl-*d*-aspartate (NMDA) receptor function. Similarly, neurophysiological studies utilising mismatch negativity (MMN) as an index of NMDA receptor function, have reported impairments in bipolar disorder. Here, we provide a systematic review of the literature in regards to the concentration of Glx and the magnitude of MMN in bipolar disorder. Separate meta-analyses revealed that bipolar disorder was associated with increased Glx concentration and decreased MMN—both measured frontally. The current findings corroborate previous evidence indicating that bipolar disorder is characterized by a perturbed frontal glutamate system. These observed changes in bipolar disorder might manifest as impairments in neuronal-glial interactions that lead to disrupted neuronal output and ultimately result in the characteristic neurocognitive sequelae associated with this disorder.

Contents

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1. Introduction

Glutamate is the brain's most abundant excitatory neurotransmitter, mediating transmission of approximately 60% of pyramidal and thalamic relay neurons in the brain (Nieuwenhuys, 1994). Glutamate homeostasis is crucial to normal brain function, and accurate information processing is dependent on fast and efficient modulation of glutamate at the synaptic cleft (Verkhratsky and Kirchhoff, 2007). In recent years, a confluence of evidence has emerged indicating that changes in the glutamate system may assume a significant role in the evolution of mood disorders (Kugaya and Sanacora, 2005). More specifically, abnormal levels of glutamate have been reported in cerebrospinal fluid, serum and plasma of patients with bipolar disorder (Sanacora et al., 2008). Post-mortem studies have reported elevated brain glutamate and decreased levels of the glutamatergic *N*-methyl-*d*-aspartate (NMDA) receptor subunits in the frontal cortex of individuals with bipolar disorder (Hashimoto et al., 2007; Rao et al., 2010). Additionally, separate neuroimaging investigations involving structural, functional and spectroscopic analyses have consistently reported frontal abnormalities, particularly for the anterior cingulate cortex (ACC) (Haldane and Frangou, 2004). These neuroimaging findings corroborate an existing neuropsychological literature that has consistently reported frontal lobe-mediated impairments in bipolar disorder (Olley et al., 2005). Indeed, evidence suggests that cognitive impairments are not confined to acute periods of illness as indicated by findings that euthymic patients continue to show deficits in response inhibition, visual memory and verbal fluency (Bora et al., 2009). There is considerable conjecture as to how these observed impairments vary across the phases of the disease (mainly due to the paucity of longitudinal studies), but more recently attention has shifted towards an understanding of the neurochemical aberrations that may underlie these observed changes (Malhi et al., 2007).

Proton magnetic resonance spectroscopy (^{1}H-MRS) is an in vivo tissue-based imaging modality that provides a measure of neurochemistry, and presents a unique opportunity to investigate glutamatergic transmission. Traditionally, ^{1}H-MRS studies have typically reported "Glx", an overlapping resonance of glutamate, glutamine and gamma-aminobutyric acid (GABA). However, given the negligible concentration of GABA in this composite, Glx is most often evaluated as a measure of glutamate and its precursor, glutamine. The glutamate/glutamine cycle describes the synthesis and exchange of these two metabolites between the neurons and astrocyte. Specifically, glutamate is synthesized from glutamine within the glutamatergic neurons via glutaminase, which is then stored in synaptic vesicles ready for release. Approximately 80% of the total brain glutamate concentration is stored in these vesicles. The remaining 20% is involved in glutamine synthesis taking place within the adjacent astrocyte (Heath and Shaw, 2002) where glutamate is recycled from the synaptic cleft through excitatory amino acid transporters (EAATs). Once in the astrocyte, glutamate is converted to glutamine by glutamine synthetase. Glutamine is then transported from the astrocyte to the neuron where it is converted back to glutamate and stored in vesicles ready for release (Bak et al., 2006). The similar structural forms of glutamate and glutamine as well as their shared neurochemistry render the two as tightly coupled and not able to be differentiated without using specialized imaging techniques.

Two narrative reviews (Yildiz-Yesiloglu and Ankerst, 2006; Yuksel and Ongur, 2010) and a meta-analysis (Gigante et al., 2012) have previously investigated the nature of Glx disturbances in bipolar disorder. Each review reported increased levels of Glx across all mood states of bipolar disorder. These results build upon accumulating evidence implicating an abnormal glutamatergic system in the pathophysiology of bipolar disorder. Nonetheless, interpretation of ^{1}H-MRS results is limited in that it captures the total concentration of a given metabolite in the acquisition voxel without differentiating between intracellular or synaptic levels. Thus, making inferences about dynamic changes that may occur within the cycle (e.g. glutamate release or synthesis) difficult. Some have argued that Glx concentration can be used to capture more information than glutamate concentration alone (Ongur et al., 2008). For example, Yuksel and Ongur (2010) noted a pattern of differing glutamate/glutamine ratio between different mood states in bipolar disorder, with depressive episodes associated with lower glutamine levels relative to glutamate.