Published in final edited form as:
Harv Rev Psychiatry. 2014 ; 22(6): 334–337. doi:10.1097/HRP.0000000000000060.

GLIAL ABNORMALITIES IN MOOD DISORDERS

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Abstract

Multiple lines of evidence indicate that mood disorders are associated with abnormalities in the brain's cellular composition, especially in glial cells. Considered inert support cells in the past, glial cells are now known to be important for brain function. Treatments for mood disorders enhance glial cell proliferation, and experimental stimulation of cell growth has antidepressant effects in animal models of mood disorders. These findings suggest that the proliferation and survival of glial cells may be important in the pathogenesis of mood disorders and may be possible targets for the development of new treatments.

In this chapter, we will review the evidence for glial abnormalities in mood disorders. We will discuss glial cell biology and evidence from postmortem studies of mood disorders. This is not carry out a comprehensive review; rather we selectively discuss existing evidence in building an argument for the role of glial cells in mood disorders.

Keywords

oligodendrocyte; astrocyte; microglia; postmortem; prefrontal

INTRODUCTION

Neuroimaging and *postmortem* studies have now demonstrated that mood disorders, including both major depressive disorder (MDD) and bipolar disorder (BD), are associated with significant abnormalities in the cellular composition of brain areas involved in processing emotional stimuli and setting mood[1, 2]. Among these abnormalities are altered densities of neurons and a class of support cells collectively referred to as glia[3, 4]. The term glia is derived from the Greek word for glue, which reflects the now-classic conceptualization of the primary role of these cells in the brain[5]. Recent conceptualizations propose more active roles for glia in normal brain function, as well as the pathophysiology and relief of psychiatric illness. For example, currently known treatments for mood disorders enhance cell proliferation, including the proliferation of glia, and experimental stimulation of cell growth has antidepressant effects in animal models of mood disorders [6]. These findings imply that signaling cascades or processes regulating cell proliferation and survival may be targets for existing and new treatments of mood disorders [7].

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Despite the recent excitement in the field there are many unanswered questions regarding the relationship between specific anomalies of cellular configuration and function and the pathophysiology of mood disorders. In this article, we will review the evidence for cellular abnormalities in mood disorders, with a focus on glial rather than neuronal cells. We will discuss glial cell biology and *postmortem* studies relevant to glial cell number and function. Given space limitations, we will not carry out a comprehensive review of the topic; rather we will speculate in this context on the consequences of glial cell dysfunction for brain activity in general and mood regulation in particular. As a consequence of this approach, the selection of papers cited in this paper was not all-inclusive and focused only on those required for the discussion at hand. For a more complete assessment, the reader is referred to other comprehensive reviews of the topic by other authors[3].

GLIAL CELL BIOLOGY

In the brain, glia are usually divided into three main sub-types: astrocytes, oligodendrocytes and microglia (**Figure 1**). Particularly enriched in the grey matter, near synapses, astrocytes are metabolically and morphologically activated by a variety of signals [8]. These cells are essential for numerous processes in the brain including, but not limited to: gliotic response to brain injury [9]; the coupling of neuronal activity with cerebral metabolism [10, 11]; and the synthesis of ion channels and neurotransmitter transporters [12]. Astrocytes are frequently found ensheathing synapses, and they modulate neurotransmission by taking up glutamate and GABA from the synaptic cleft [13]. This close apposition has led to the coining of the term “tripartite synapse”, acknowledging the astrocyte as an essential part of the synapse along with the presynaptic and postsynaptic neurons (**Figure 2**) [14]. In addition to being modulators of neurotransmission, astrocytes also modulate synapse numbers in cell culture, indicating that they play a role in inducing and stabilizing synapses [15]. Notably, astrocytes synthesize a number of molecules with neuromodulatory effects, including d-serine, a partial agonist at the NMDA glutamate receptor site [16], adenosine, a tonic suppressor of synaptic transmission [17], and glutathione, the main antioxidant in the brain [18].

Oligodendrocytes are smaller than astrocytes, enriched in the white matter, and primarily responsible for myelin synthesis in the brain. The interaction between oligodendrocytes and the axons they ensheath is complex; these glia can help generate sprouting of axons, while axonal signals are needed in turn for oligodendrocyte survival [19]. Abnormalities of oligodendrocytes have been reported in studies of schizophrenias, but there are few reports in the literature of studies in mood disorders[20, 21]. Oligodendrocyte precursor cells (OPCs) positive for the proteoglycan NG2 are less-differentiated cells found in the grey matter, and are capable of proliferating into new oligodendrocytes [22]. NG2-positive OPC processes receive synaptic contacts from pyramidal neurons in the hippocampus, and generate excitatory post-synaptic currents [23]. This is the only known example of a non-neuronal postsynaptic cell in the brain, indicating that OPCs monitor and modulate ongoing neuronal activity. Several but not all studies have identified NG2-positive OPCs as a major proliferating cell type in response to antidepressant treatments (see below).

Microglia are derived from peripheral blood macrophages, and mediate the inflammatory response in the brain [24]. Although they have been implicated in a variety of neuropsychiatric

conditions including Alzheimer's Disease[25], autism spectrum disorders[26], and AIDS-related dementia, they have not yet been the focus of study in mood disorders.

In summary, glial cells serve multiple important purposes in the brain, and glial cell dysfunction can impact synaptic transmission, cerebral metabolism, neuroplasticity, and myelination. In fact, neuronal-glial interactions are ubiquitous in health and disease states [27] and there may be no brain functions that would not be affected by glial cell anomalies. As discussed below, there are clues from postmortem and animal studies that glia are involved in the pathogenesis of mood disorders. However, it appears that multiple glial cell types are involved (see below), and much work needs to be done to deepen our insight into glial cell function in mood disorders.

HISTOPATHOLOGY IN MOOD DISORDERS

Studies of brain tissue from patients with MDD and BD were not widely reported until the last decade. In very promising findings, much recent work has provided consistent evidence that there are substantial reductions in the density and number of glial cells in areas of the prefrontal cortex (PFC) and in the amygdala in mood disorders [1, 20, 28-31]. In one study, researchers attempted to subtype glial cells in mood disorders and concluded that it was oligodendrocytes that were selectively reduced in the amygdala [32]. Similar reductions in glial number were not seen in somatosensory area 3b, an area not implicated in emotional processing [29]. Gene expression studies in *postmortem* brain have led to findings that suggest glial abnormalities, including reduced expression of astrocyte related genes in the cerebral cortex of individuals with MDD [33] and oligodendrocyte related transcripts in BD [34]. *Postmortem* studies have also led to reports of reductions in glial number in the hippocampus [35] and dorsolateral PFC in alcoholism, with and without comorbid mood disorder [36]. No abnormalities were reported in one study documenting cell numbers in the hippocampus in MDD [37] and a second suggested loss of neuropil without cell loss [38].

These results suggest that patients with affective disorders have a perturbation in glial cells in some parts of the brain implicated in emotional processing and, further, that these perturbations are not seen throughout the brain. The selectivity of these cellular changes raises the possibility that they are causally relevant to the pathophysiology of mood disorders. Note that this is not a comprehensive review of the relevant literature. For that purpose, refer to work by Rajkowska [39], Cotter [40], and others [1].

FUTURE DIRECTIONS

Although multiple lines of evidence indicate that glial cells are abnormal in the brains of patients with mood disorders and that treatments for these conditions enhance glial cell proliferation, multiple questions need to be answered before these insights can be translated into diagnostic and therapeutic advances.

One basic question has to do with the meaning of reduced glial cell numbers in vivo. Reduced cell number could be either a cause or an effect of illness. For example, reductions may be due to a lack of adequate cell growth during development or to the death of existing cells, reduced proliferation of new cells, or reduced survival rates of proliferating cells. In

addition, it is not known whether fewer glial cells actually means reduced glial cell function. As discussed above, we only have indirect evidence of glial cell functional abnormalities in mood disorders, from *postmortem* work. ^{13}C magnetic resonance spectroscopy (MRS) is a non-radioactive, noninvasive MRI methodology which tracks the movement of ^{13}C labeled molecules through metabolic pathways in brain cells. Studies of glial cell metabolism using this approach, which can indirectly quantitate astrocyte number and activity, will be invaluable to study this issue, as will a more detailed characterization of glial subtype related transcript expression in the human brain. In addition, glial cell numbers may be just one facet of glial cell abnormalities present in mood disorders. Other possible factors include cell size, length of cell processes, cell activity, or the relationship between glial cells and synaptic function and plasticity. Genomic studies are underway to determine if genes involved in determining glial number and function may also be associated with determining risk of illness.

Another important issue is identifying the specific glial subtypes that are abnormal in mood disorders. Detailed immunohistochemistry studies on *postmortem* brains, as well as more detailed phenotyping of newly generated cells in the PFC and amygdala following treatments for mood disorders can provide a more complete description of glial cell dynamics. Genomics can again help by identifying a role for genes specific to subtypes of glia. If one glial subtype is selectively implicated, this could change the direction of glial cell research in mood disorders and generate new vistas for treatment development focused on the properties of that specific cell type.

It appears that the identification of factors leading to glial dysfunction in mood disorders is essential if we are to gain a complete understanding of these illnesses. Glial proliferation in the brain is controlled by a variety of molecular factors depending on glial subtype, inciting stimulus, and developmental stage [41-45]. Specific developmental/genetic factors must be relevant to glial cell health and function. Toxic factors, too, may dysregulate glial proliferation and function. For example, it is known that corticosteroids released from the adrenal gland under stressful conditions are chronically over-secreted in many patients with mood disorders and they inhibit proliferation of multiple glial cell types [46, 47]. It is likely that glial cell numbers reflect the state of balance between multiple trophic and toxic factors acting on the brain during development of the nervous system and throughout adult life. Defining these factors and their relationship to health and illness should lead to new treatments for those already suffering and to measures to prevent mood disorders in those at risk.

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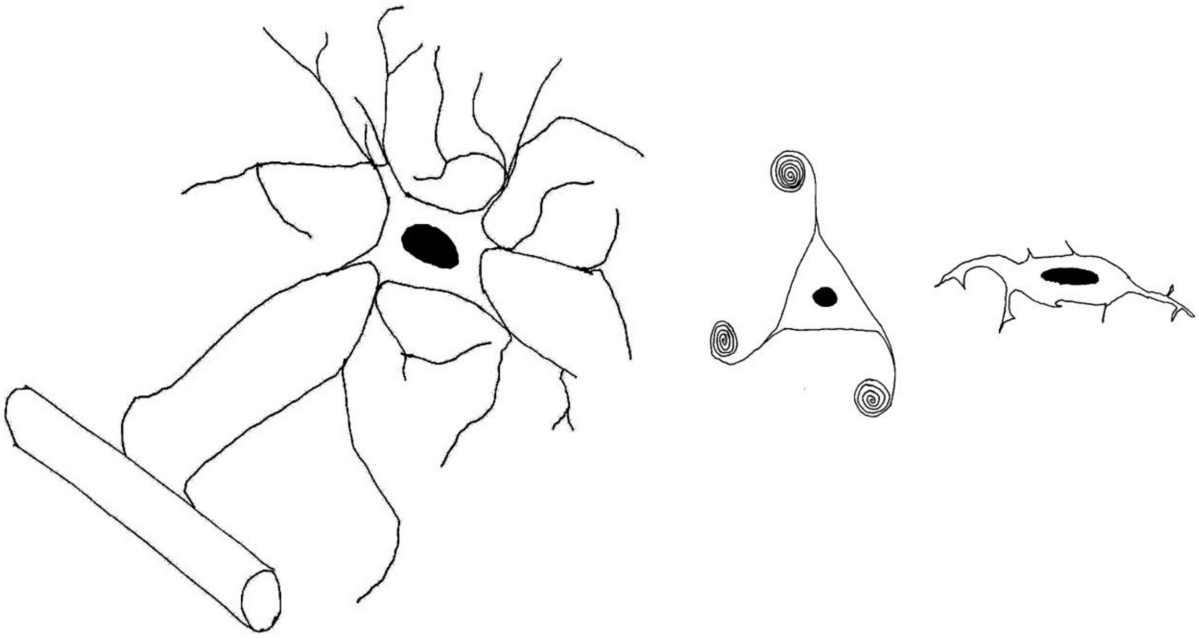

Figure 1. The major glial cell subtypes

Line drawings of the three glial subtypes, drawn approximately to scale and depicting key features of each cell type. On the left is an astrocyte, depicted in close apposition to a blood vessel. Astrocytes have multiple processes extending in multiple directions, giving these cells a “star-like” appearance. The middle panel depicts an oligodendrocyte with a few processes wrapping around and myelinating nearby axons. Oligodendrocytes have smaller cell bodies and are more numerous than astrocytes in the brain. The panel on the right shows a microglial cell, which is oblong in appearance, with short processes extending from the cell body.

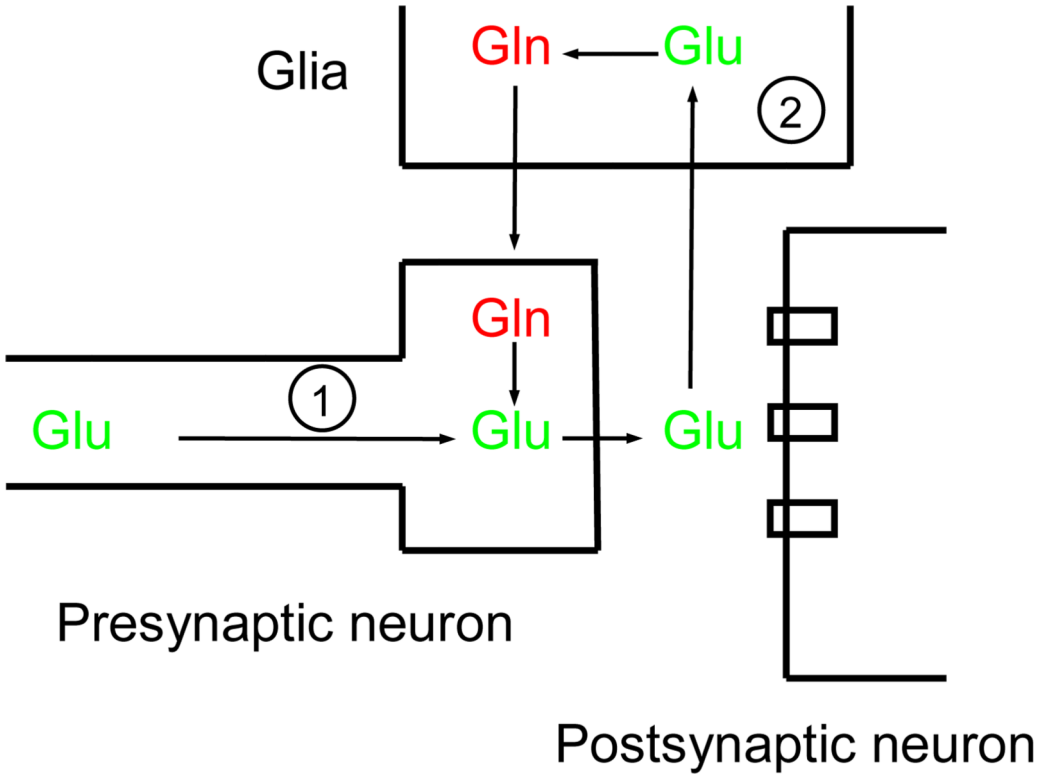

Figure 2. The role of glia at the glutamatergic synapse

Glutamate (Glu) is synthesized in the presynaptic neuron (1) from metabolic sources, and it is released into the synaptic cleft when the action potential arrives in the presynaptic bouton. The action of glutamate on postsynaptic glutamate receptors is terminated by uptake into the glial cell (2), which converts it to glutamine (Glu). Glutamine is then shuttled back to neurons where it is converted back to glutamate. The levels of glutamate in the synapse are thus determined by the balance of interactions between neurons (1) and glial cells (2).