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REVIEW

# A putative functional role for oligodendrocytes in mood regulation

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**Altered glial structure and function is implicated in several major mental illnesses and increasing evidence specifically links changes in oligodendrocytes with disrupted mood regulation. Low density and reduced expression of oligodendrocyte-specific gene transcripts in postmortem human subjects points toward decreased oligodendrocyte function in most of the major mental illnesses. Similar features are observed in rodent models of stress-induced depressive-like phenotypes, such as the unpredictable chronic mild stress and chronic corticosterone exposure, suggesting an effect downstream from stress. However, whether oligodendrocyte changes are a causal component of psychiatric phenotypes is not known. Traditional views that identify oligodendrocytes solely as nonfunctional support cells are being challenged, and recent studies suggest a more dynamic role for oligodendrocytes in neuronal functioning than previously considered, with the region adjacent to the node of Ranvier (i.e., paranode) considered a critical region of glial–neuronal interaction. Here, we briefly review the current knowledge regarding oligodendrocyte disruptions in psychiatric disorders and related animal models, with a focus on major depression. We then highlight several rodent studies, which suggest that alterations in oligodendrocyte structure and function can produce behavioral changes that are informative of mood regulatory mechanisms. Together, these studies suggest a model, whereby impaired oligodendrocyte and possibly paranode structure and function can impact neural circuitry, leading to downstream effects related to emotionality in rodents, and potentially to mood regulation in human psychiatric disorders.**
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## Oligodendrocytes

In the adult central nervous system (CNS), glial cells refer to a set of non-neuronal cells that provide support to neurons, and that include astrocytes, oligodendrocytes, ependymal cells and microglia. Glial abnormalities are postulated to be involved in the pathophysiology of a variety of neuropsychiatric illnesses.[1–4] Oligodendrocytes, the main myelin forming cells of the central nervous system, have recently begun to garner more attention owing to reports of widespread disruption of oligodendrocytes across psychiatric disorders.[4] In addition, recent findings suggest that myelin constitution can influence neuronal properties in ways not previously considered, and may be a source of essential trophic and metabolic support for maintaining axonal integrity,[5] thereby opening new research avenues into the functional role of oligodendrocytes in disease.

**Overview of oligodendrocyte structure and function.** Oligodendrocytes have a small round cell body and about four to six branching processes, which can myelinate up to 60 axons depending upon the diameter.[6] Total oligodendrocyte numbers vary across brain regions[7] and the local density depends on axonal density.[8] Myelin consists of lipids (70%) and a variety of proteins (30%), including myelin basic protein (MBP), proteolipid protein (PLP) and 2′,3′-cyclic nucleotide-3′-phosphodiesterase (CNP), which together represent the major protein components of myelin.[9,10] When ensheathing axons, the opposing lipid bilayers are fused and then form compacted concentric layers (lamellae) around the bare axon (typically 10–100 lamellae). Functionally, mature oligodendrocytes provide critical insulation to facilitate axonal conduction by increasing the resistance and lowering the capacitance of the axonal membrane, which allows faster conduction speed in myelinated axons compared to unmyelinated axons of the same diameter. Oligodendrocytes also have a role in regulating the development and periodicity of nodes of Ranvier, spaces of bare axon, which contain ion channels critical for action potential propagation along the axon. At the ends of the internodal regions, the myelin lamellae form a tight association (septate-like junction) with the axon, termed the paranode region, with the axonal proteins Contactin and Caspr (contactin-associated protein) interacting with the glial protein NF155 to form the junction (Figure 1; reviewed in Poliak and Peles[11] and Pedraza *et al.*[12]). The paranode appears to have three primary roles in maintaining a stable saltatory conduction: (1) spatial separation of $Na^+$ and $K^+$ channels, (2) sealing the myelin sheath in a way that allows only selected nutrients to diffuse into the internodal periaxonal space (space between the myelin and axon) and (3) stabilization of the entire structure in the face of mechanical stressors.[13] Recent reports have

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focused on the paranode region as the critical interface of communication between the myelin and the axon (see below).

**Techniques to identify oligodendrocyte-specific alterations.** Human postmortem studies frequently use stains for Nissl bodies and nuclei to distinguish between neuronal and glial cell populations, and close morphological examination has been used to distinguish between glial subtypes.[14] However, this technique limits the distinction between different types of glial cells to morphological markers (e.g. oligodendrocytes are characterized by compact and uniformly darker nuclei). Fewer studies have examined differences in glial cell subpopulations using immunocytochemistry. Mature oligodendrocytes are derived from oligodendrocyte precursor cells (OPC), which develop in specific ventricular zones, migrate to their final site in the brain, and then differentiate. During this time, a variety of proteins are expressed marking the developmental stages of the cell, which could be utilized for immunohistochemical identification of both oligodendrocyte precursor cells and mature oligodendrocytes in postmortem subjects.

A relatively newly identified cell type expressing the proteoglycan protein nerve/glial antigen-2 (NG2) shares a common lineage with oligodendrocytes[15] and resembles oligodendrocytes morphologically,[16] making it difficult to distinguish NG2+ cells from oligodendrocytes. NG2+ cells express several markers common in oligodendrocyte precursor cells, including platelet-derived growth factor receptor, alpha subunit and Olig1 and Olig2, however they do not express markers for mature oligodendrocytes such as MBP, PLP, CNP and O1.[17] In addition, NG2+ cells are able to fire action potentials,[18] express-voltage-gated ion channels,[19] and form unique contacts with neurons, oligodendrocytes and astrocytes (reviewed in Verkhratsky and Butt[9]), suggesting a unique functional role that is only beginning to be explored. Although not the focus of this review, imaging techniques provide an alternative means of investigating biological disturbances that relate to oligodendrocytes in live human subjects, as myelin sheaths form the majority of brain white matter. Magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) can detect certain parameters that relate to white matter integrity. Recently, significant improvements in resolution and analysis of imaging data have been made,[20] which will allow more thorough investigations of large-scale oligodendrocyte-related alterations in live subjects.

## Oligodendrocyte alterations in neuropsychiatric disorders

There is evidence for oligodendrocyte alterations across most psychiatric conditions, including but not limited to attention deficit and hyperactivity disorder, autism, bipolar disorder, major depressive disorder (MDD), Alzheimer's disease and schizophrenia (reviewed in Fields[4]). In schizophrenia, evidence for oligodendrocyte disruption has been reported using genetic, imaging and postmortem studies. Decreased oligodendrocyte-related gene expression,[21–25] decreased oligodendrocyte numbers and density,[26–28] and aberrant myelin morphology[29] have been reported in various brain regions in postmortem tissue from subjects with schizophrenia compared to normal controls, including dorsolateral prefrontal cortex, anterior cingulate cortex, superior temporal gyrus, and hippocampus. Imaging studies using diffusion tensor imaging indicate decreased white matter integrity in similar regions that may exist prior to disease onset (reviewed in Takahashi *et al.*[30]). Functional investigations of oligodendrocyte genes altered in schizophrenia point toward disruptions in cell cycle activity and axoglial interactions, particularly at the node, thereby hinting at pathophysiological mechanisms.[31,32] Although evidence in bipolar disorder is more limited, reports indicate similar decreases in oligodendrocyte density,[26] oligodendrocyte-related genes primarily in the frontal cortex,[25,33,34] and white matter abnormalities[35] (reviewed in McIntosh *et al.*[36] and Mahon *et al.*[37]). Together, the current evidence in bipolar disorder and schizophrenia has led to the support of a model of disconnectivity via white matter tracts between the frontal cortex and emotion regulation regions.[37,38] Thus, although some regional specificity in white matter disruptions may differentiate these disorders, it cannot be overlooked that disruption of mood regulation is a common feature in these disorders. In accord, patients with neurological disorders affecting white matter (e.g. multiple sclerosis) often display a high degree of comorbidity with psychiatric symptoms, including depression,[39,40] and display similar patterns of dysregulation in transcriptome profiles,[41] supporting the hypothesis of a connection between disrupted oligodendrocyte function and mood dysregulation.

**Primary evidence for oligodendrocyte alterations in MDD.** Primary evidence for glial alterations has been reported for most of the major glial subtypes in MDD (reviewed in Rajkowska and Miguel-Hidalgo,[2] Hercher *et al.*[42] and Tham *et al.*[43]). However, these changes are often described under a broad nonspecific 'glial umbrella', which we briefly summarize here, before focusing on oligodendrocyte-related changes in MDD. Postmortem studies of brain regions implicated in MDD report volumetric changes,[44] which may potentially reflect glial alterations. For instance, studies in corticolimbic regions of MDD subjects have described reductions in glial density or glia/neuron ratio in the subgenual prefrontal cortex,[45] dorsolateral prefrontal cortex,[46,47] orbitofrontal cortex,[46] anterior cingulate cortex[48] and amygdala.[49,50] In addition to reduced cell density, increases in glial cell size were reported in the dorsolateral prefrontal[46] and anterior cingulate cortices[51] of MDD subjects. In contrast, a recent meta-analysis reported an increase in S100B, a glial marker that is expressed primarily in astrocytes, in MDD subjects compared with controls,[52] suggesting that MDD may be associated with increases in glial cells. In addition, several recent studies using morphometric analyses have reported no changes in overall glial cells in the orbitofrontal cortex and dorsolateral prefrontal cortex of late-life MDD subjects,[53,54] all together leaving a muddled consensus on total glial alterations in MDD.

Investigations with glial specific markers have now begun to provide insight into glial subtype-specific disruptions in MDD subjects. Decreases in several astrocytic markers (GFAP, EAAT1, EAAT2) have been described in postmortem human MDD subjects[55–57] and a recent report described the

presence of hypertrophic astrocytes in white matter of anterior cingulate cortex of depressed subjects as evidence for a state of chronic inflammation in white matter.[58] Rodent studies have confirmed and augmented these findings,[59–61] together suggesting a model of astrocyte-mediated dysfunction/depletion of prefrontal cortex glutamatergic cycling and homeostasis in MDD (reviewed in Valentine and Sanacora[62]). Increases in microglial density (using HLA-DR, a known microglial marker for neurodegeneration and neuroinflammation) have been reported in a variety of brain regions in psychiatric subjects who committed suicide, but normal microglial densities have been reported in nonsuicide MDD subjects.[63] In contrast, decreased proliferation of microglial cells were reported in an animal model of MDD[64] leaving an undefined picture of microglial alterations not only in MDD, but also in other neuropsychiatric disorders.[65]

Recently, research has begun to focus on oligodendrocyte and white matter abnormalities in human MDD subjects, including postmortem tissue and live subjects, using imaging approaches (reviewed in Tham *et al.*[43]). Tissue level analysis using the Kluver–Barrera staining method revealed that staining intensity of deep white matter in the dorsolateral prefrontal cortex was significantly less intense in MDD subjects compared with controls.[35] On a cellular level, staining of Nissl bodies using morphological cell-type determination revealed that previously reported decreases in glial cell number in amygdala and prefrontal cortex of MDD subjects could be attributed to reduced oligodendrocyte numbers.[26,50] A more recent study found a decreased density of oligodendrocytes in the frontopolar cortex of human MDD subjects using a novel approach of flow cytometry on fluorescently labeled suspended nuclei.[66] However, to our knowledge, no studies have examined oligodendrocyte changes in MDD subjects using immunohistochemical techniques for oligodendrocyte-specific markers.

Patterns of downregulation of oligodendrocyte-related gene transcripts have been reported in human postmortem subjects with MDD compared with control subjects in regions including the amygdala,[67] the nearby temporal cortex,[22] the dorsolateral prefrontal cortex[68] and prefrontal cortex (BA 9) of MDD subjects.[69] No significant changes in a set of oligodendrocyte genes selected *a priori* were observed in several subcortical brain regions of MDD subjects, including putamen, internal capsule and two thalamic nuclei,[70] suggesting selective corticolimbic-specific and potentially other region-specific oligodendrocyte disruptions in MDD. Other *a priori* studies of myelin-associated genes revealed reductions in neurite outgrowth inhibitor isoform B mRNA in the frontal cortex of MDD subjects,[71] reductions in Quaking protein (an oligodendrocyte-associated RNA-binding protein) in the cortex, hippocampus and amygdala of MDD subjects[72] and downregulation of MBP in the anterior frontal cortex of MDD subjects.[73]

Areas of local demyelination appear on magnetic resonance imaging scans as white matter hyperintensities (WMH). WMHs are associated with normal aging, but are thought to be particularly prevalent in MDD subjects (reviewed in O'Brien *et al.*[74]). Studies using *in vitro* magnetic resonance imaging on postmortem elderly human MDD subjects revealed that these WMH may be due to vascular problems leading to cerebral ischemia and eventual white matter lesions, in support of a 'vascular depression' hypothesis.[75] There is also an extensive literature of magnetic resonance imaging studies in live MDD subjects, which have revealed abnormalities in white matter (reviewed in Tham *et al.*[43]). Briefly, patients with late onset depression (after age 45) have more frequent and intense WMHs compared with early onset subjects, suggesting that neuropathological changes in white matter may underlie late onset depression, but not early onset depression.[76] WMHs are also associated with cognitive impairments in late-life depression,[77] and elderly MDD subjects with more pronounced WMH have more severe longitudinal courses of depression,[78] suggesting that WMHs could serve as markers for clinical MDD diagnoses. Diffusion tensor imaging studies have also revealed white matter abnormalities, particularly in elderly subjects with late-life MDD (reviewed in Tham *et al.*[43] and Sexton *et al.*[79]). White matter fractional anisotropy, a measure of tract alignment and integrity, is consistently reduced in frontal and temporal regions in MDD subjects,[80,81] is higher in antidepressant-resistant subjects,[82] and is increased following electroconvulsive therapy (ECT).[83] More recent diffusion tensor imaging studies in young MDD subjects have also revealed altered white matter integrity.[84]

**Oligodendrocyte changes in animal models of MDD.** Evidence implicating decreased oligodendrocyte components in MDD is paralleled by several studies in rodent models. Rodents exposed to chronic stress show a reduction in the proliferation of oligodendrocytes and NG2+ cells in the frontal cortex, a pattern that is reversible with antidepressant treatment.[85,86] Similarly, chronic corticosterone stress hormone exposure in rodents resulted in decreased cortical and amygdala oligodendrocyte[86] and NG2+ cell proliferation,[64,87] together suggesting that oligodendrocytes may be particularly susceptible to stress-related and corticosterone-induced toxicity. Following electroconvulsive seizures, a rat model for ECT in humans, nonstressed rats showed increased proliferation of NG2+ cells in amygdala and hippocampus[64,88,89] and increased proliferation of mature oligodendrocyte cells in the frontal cortex.[90] In addition, similar to human studies, oligodendrocyte transcripts were selectively downregulated in the amygdala of mice exposed to unpredictable chronic mild stress and these changes were reversed by two types of antidepressant treatments.[91] Interestingly, nonstressed rats or mice treated chronically with the antidepressant fluoxetine displayed no changes in oligodendrocyte proliferation in prelimbic cortex[92] or in oligodendrocyte-related gene expression in cingulate cortex and amygdala,[91] suggesting that oligodendrocyte changes are specific to chronic stress-induced pathology and may not be involved in the mechanism of pharmacological antidepressant treatment.

## Oligodendrocytes and neurons: a disease-prone bidirectional balance?

New reports suggest that proper neuronal function depends on a bidirectional balance between myelin and axons. This may be a critical element that is disrupted in neuropsychiatric disorders.

**Potential mechanisms leading to oligodendrocyte alterations in neuropsychiatric disorders.** Although it is clear that oligodendrocyte deficits are frequently observed in neuropsychiatric disorders, the actual mechanisms that induce oligodendrocyte alterations in the human brain remain unknown; however, several models have been proposed: (1) disturbances in chromatin regulation are implicated in MDD[93] and are suggested to lead to disruption of oligodendrocyte differentiation and/or excitotoxicity;[94] (2) oligodendrocytes express AMPA and kainate type glutamate receptors, and are thought to be sensitive to excitotoxic damage from excessive glutamate-mediated activation;[95] (3) the hypothalamic–pituitary–adrenal axis is disrupted in MDD[96] and glucocorticoids target oligodendrocytes[97] leading to decreased proliferation,[86,87] suggesting that glucocorticoid-mechanisms are involved in oligodendrocyte-related pathology; and (4) finally, disruptions in dopaminergic transmission in MDD[98] could also interfere with oligodendrocyte maturation via the expression of D2 and D3 receptors on oligodendrocytes.[99] Notably, most current models converge on oligodendrocytes being vulnerable to stress-related insults, suggesting that these changes may be more frequent in MDD, owing to the prevalent role of stress in precipitating MDD. This notion provides support for the hypothesis that oligodendrocyte-related changes are not specific to a particular psychiatric disorder, and in fact may correspond to a cellular endophenotype that is frequently observed across stress-related and mental disorders. Hence, characterizing the etiological causes and functional consequences of oligodendrocyte dysregulations may have implications for major mental illnesses at large.

**Oligodendrocyte alterations elicit functional consequences in neurons.** The functional and mechanistic consequences of disrupted oligodendrocyte structure are poorly characterized, and it is not known whether they could elicit downstream consequences related to mood disorders. Although all glial cell types are important mediators of neuronal function, increasing evidence is pointing toward oligodendrocytes as a crucial component in the maintenance of axonal integrity.[5,100] One of the primary functions of oligodendrocytes is to promote axonal conduction and to actively regulate neuronal properties.[11] However, oligodendrocytes also monitor neural activity through a variety of receptors including glutamatergic (AMPA, NMDA, and kainate) and GABAergic ($GABA_A$) receptors, which both depolarize the cell, the latter is caused due to high intracellular levels of $Cl^-$ at rest (reviewed in Verkhratsky and Butt[9]). For instance, activation of glutamate receptors on oligodendrocytes leads to depolarization of the cell, an action that rapidly modulates axonal conduction velocity.[101,102] In turn, action potentials in the ensheathed axons can stimulate depolarization of oligodendrocytes.[101]

Direct manipulation of myelin structure also leads to alterations in neuronal properties. Cuprizone, a copper chelator, which causes global demyelination in rodents when administered orally, alters the distribution of ion channels at the critical nodal region,[103] and produces changes in axonal conduction velocity.[104] Mice deficient in PLP, an oligodendrocyte-specific structural protein involved in lamellae fusion, show disruption of fast axonal transport,[105] while PLP-overexpressing mice have altered neuronal conduction velocity and refractory periods.[106] Furthermore, mice lacking structural myelin components, including PLP, CNP, and myelin-associated glycoprotein, all have relatively normal myelin assembly, but develop progressive neurodegeneration (reviewed in Nave and Trapp[107]), pointing toward myelin as a regulator of axon trophic support. Nave and colleagues have proposed that trophic support from oligodendrocytes (for example, metabolites or neurotrophic factors) is required for mitochondrial energy metabolism in axons, as the myelin sheath itself restricts axonal access to extracellular metabolic substrates.[5,108] Thus, oligodendrocyte disruptions may cause reduced metabolic coupling between the myelin and the axon, leading to structural and functional impairments.

## Alterations in oligodendrocytes elicit mood-related symptoms in rodents

Whether the previously described decreased oligodendrocyte components in neuropsychiatric illnesses and rodent models of the disorder are causal to the behavioral phenotype is unknown. To address this question, several studies have used chemically induced lesions or genetic manipulations to investigate the behavioral consequences of oligodendrocyte disruption.

**Chemical lesions.** The cuprizone model of demyelination in mice has mainly been utilized in schizophrenia-related behavioral studies.[109] Mice treated with cuprizone show reduced anxiety-like behavior in the open field and elevated plus maze tests, decreased social interaction, decreased pre-pulse inhibition, less spontaneous alternation in the Y-maze and decreased motor coordination.[110–112] Cuprizone treatment also causes deficits in frontal cortex-mediated cognitive tasks in rats along with decreased oligodendrocyte transcripts specifically in prefrontal regions (not hippocampus or striatum).[113] However, the cuprizone model induces widespread demyelination in the brain and causes severe locomotor, social and cognitive consequences that could confound behavioral tasks, together making it difficult to discern emotionality changes specific to myelin disruption. Another demyelinating agent, lysolecithin, induced anxiety-like behaviors in the elevated plus maze and open field tests along with hyperactivity when injected directly into the hippocampus.[114] Furthermore, early weaning induces anxiety-like behaviors in adulthood that are associated with alterations in whole-brain MBP expression[115] and early myelin formation, specifically in the amygdala of male, but not female mice.[116] Together, this evidence indicates that demyelination can influence anxiety- and depression-related behaviors (i.e. emotionality) in rodents.

**Genetic approaches.** Similar to rodents with chemically induced lesions, mice mutant for certain oligodendrocyte-specific genes (e.g. *MBP*, *MOBP*, *CASPR*, *CNP1*) also display altered locomotor activity and motor coordination deficits.[5,107] However, emotionality behaviors have rarely been examined in these mutants. Our laboratory recently tested the potential mechanistic link between altered oligodendrocyte function and emotionality in mice by

thoroughly examining behavioral characteristics in mice lacking CNP1 ($CNP1^{KO}$), an oligodendrocyte-specific gene that is localized to the paranode and that has previously been implicated in MDD[67] and schizophrenia.[117–119] $CNP1^{KO}$ mice display motor coordination deficits beginning at 7–9 months of age.[120,121] Therefore, we examined emotionality-related behaviors before the onset of these deficits in order to avoid those potential confounding effects. We found that $CNP1^{KO}$ mice display a progressive age-related (3, 6 and 9 months) decrease in emotionality (anxiety- and depressive-like behaviors) under nonstressed conditions.[120] Interestingly, young (3- and 6-months old) $CNP1^{KO}$ mice were resistant to developing high emotionality states following exposure to either unpredictable chronic mild stress or chronic corticosterone, two well-established paradigms to induce high emotionality, with construct, face and predictive validities as rodent models of depression.[120] In addition, $CNP1^{KO}$ mice show low fear expression during the extinction phase of a fear conditioning paradigm,[120] a behavior that is indicative of a disruption in emotion-related circuits. In humans, stress resilience is associated with the ability to adapt to chronic stress[122] and the ability to perceive stressful events in a less threatening way.[123] In addition, resilient individuals are thought to have optimal functioning of fear extinction mechanisms[122] and 'an ability to quickly attenuate learned fear through a powerful extinction process'.[124] Hence, the pattern of behavioral and amygdala-mediated dysfunctions observed in $CNP1^{KO}$ mice suggests a phenotype characteristic of stress resilience. It is currently not known whether this apparent contradiction—low CNP in human MDD and resiliency in $CNP1^{KO}$ mice — results from maladaptive compensatory changes, or from the selective disruption in mice of a single component extracted from a broader dysregulated gene pattern in human MDD (see Edgar *et al.*[120] for discussion). Similar to $CNP1^{KO}$ mice, mice overexpressing PLP display reduced anxiety-like behaviors in the elevated plus maze, along with significantly reduced axonal conduction velocity.[125]

In combination with reports using chemical lesions of myelin, these data suggest that oligodendrocytes have a role in regulating stress responsiveness and that changes in oligodendrocyte structure and function can impact circuits mediating emotionality in mice; although the precise mechanisms underlying these effects are unclear. However, mouse behaviors are often difficult to interpret and categorize, and an alternative interpretation of the $CNP1^{KO}$ phenotype could be a manic-like phenotype (i.e. hyperactivity and low anxiety-like behaviors), more akin to aspects of bipolar disorder. Thus, studies using genetic manipulation or demyelinating agents in region- and time-specific manners, combined with functional (i.e., electrophysiology) and broader phenotypic characterizations are needed to further refine the role and contribution of oligodendrocytes in the function of neural circuits underlying mood and associated disorders.

## The paranode as a proposed site of dysregulation in neuropsychiatric disorders

The paranode region of oligodendrocytes is a critical site of interaction between myelin and axons (reviewed in Rosenbluth[13]), and recent studies investigating the putative role of oligodendrocyte alterations in psychiatric disorders, including MDD and schizophrenia, suggest that the nodal and paranodal regions of oligodendrocytes may represent important sites of dysregulation (Figure 1).[4,100,126]

Ablation of paranodal proteins, such as CNP1 and CASPR, cause structural disorganization at the paranode,[127,128] which could lead to electrophysiological changes in the axon. Indeed, in mice lacking CASPR, the paranode region fails to form, and these mice exhibit decreased nerve conduction velocity,[129] supporting a role for the paranode region in maintaining proper axonal signal transmission. In addition, mice overexpressing PLP exhibit abnormal paranodal structure, including everted paranodal loops, lack of proper cell junctions and abnormal CASPR clustering in forebrain regions, in parallel with behavioral and electrophysiological abnormalities.[125] Yamazaki *et al.*[130] speculate that structural changes such as swelling, particularly at the paranode, could drastically alter neuronal insulation properties resulting in changes to leak currents that could impact the speed of depolarization. Conversely, repetitive action potential propagation in neurons leads to paranodal swelling,[131] perhaps due to osmotic water flux,[102] again highlighting the balance between axons and their myelin sheath. Structural changes to the paranode (e.g. CASPR ablation) also result in accumulation of mitochondria at the node and paranode (in peripheral samples),[132] supporting Nave's hypothesis of altered metabolic coupling between the myelin and axon.[5]

As described above, the lack of CNP1, a paranodal-associated gene product, can impact the function of the amygdala, a critical region within a broader corticolimbic circuitry of affect-regulation and associated behaviors in mice. This evidence supports an active contribution of altered oligodendrocyte structure and function to mood-related behavioral phenotypes and symptom dimensions observed in human MDD, and possibly schizophrenia. However, the $CNP1^{KO}$ rodent studies are somewhat surprising, in that they point to a potential decrease in emotionality, which may also relate to behavioral aspects of bipolar disease. Together, the data suggest a complex balance between neuron and oligodendrocyte functions in modulating the function of neural networks underlying affect regulation. The accumulated evidence points toward the paranode, as a significant structural and functional interface between axons and the myelin sheath, which may be selectively vulnerable to glucocorticoids, stress-related insults or more simply, to increased and sustained recruitment, as occurring in emotion-processing areas such as the amygdala. These events would in turn lead to altered homeostasis (e.g. osmotic and metabolic stress) at this critical region of axoglial communication. In a simplified model (Figure 1), impaired paranode integrity may lead to local cellular dysfunction and improper axonal conduction, resulting in loss of integrity of information transfer; which, in the context of amygdala dysfunction in MDD, we speculate may underlie the deregulated affect-related phenotype.

In summary, oligodendrocytes provide critical support to neuronal function and display patterns of dysregulation in MDD, schizophrenia and bipolar disorder, which are distinct

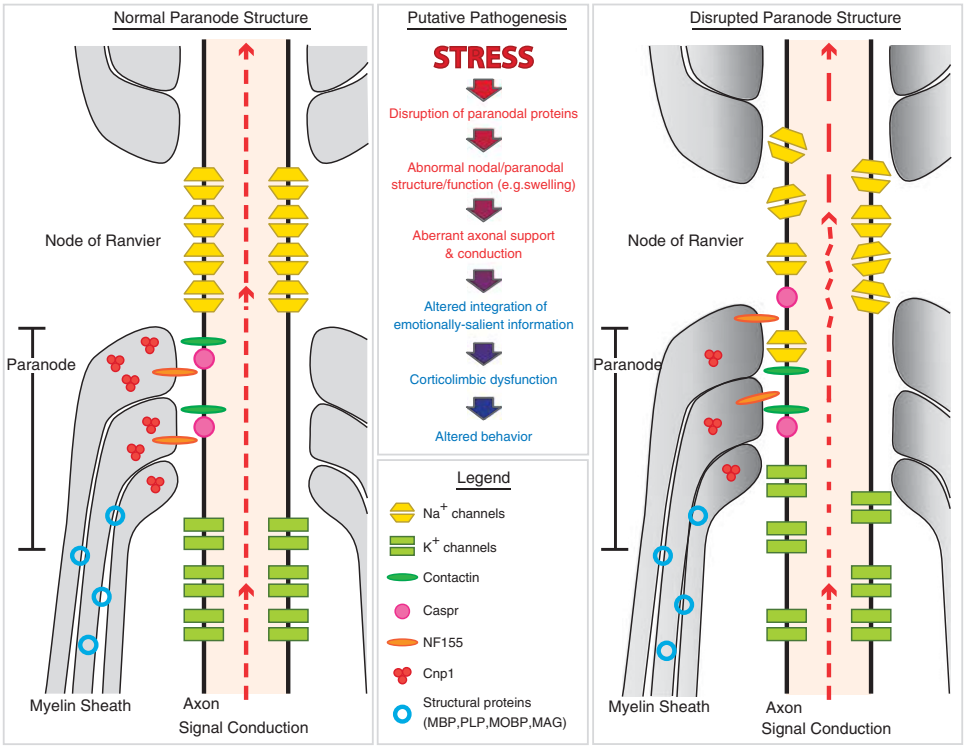


**Figure 1** Schematic model of a putative stress-induced pathogenic process at the paranode and node of Ranvier. Evidence suggests that disruption of paranode molecule composition (e.g., stress or CNP1/CASPR ablation) can affect its structural integrity (Right panel: swelling (gray shading), lower junction delineation). This could lead to altered support of axonal function within the node of Ranvier, and suboptimal conduction of action potentials along the axon (dotted red line), leading to decreased integrity of information transfer, to or within, critical brain regions, such as the amygdala. In turn, the integration of this altered information (e.g., emotional stimuli) may propagate throughout the corticolimbic circuitry involved in mood regulation, ultimately resulting in abnormal integration of emotional salience, and affecting subsequent related behaviors.

from those of other glial cell subtypes. The primary evidence in the human postmortem brain demonstrates shared features across major mental illnesses, and current models of oligodendrocyte pathophysiological vulnerability converge on stress-related insults. Together, this suggests that oligodendrocyte-related changes are not specific to any psychiatric disorder, and may instead represent a cellular endophenotype that is downstream from etiological and pathophysiological events that are frequently recruited in major mental illnesses. The critical role of stress in precipitating depressive episodes may explain the more prevalent corticolimbic patterns of oligodendrocyte changes in MDD. On the other hand, emerging data from rodent studies suggest that oligodendrocyte dysfunction, including both structural and functional changes of the axoglial paranode interface, may exert modulatory roles on neural circuitry underlying mood regulation. It is conceivable that these disruptions may manifest as different phenotypes (or illnesses) depending upon the developmental timing, affected region and extent of pathophysiology. Hence, investigating the etiological factors that lead to oligodendrocyte dysfunction, and their bidirectional links with neuronal dysfunction, while characterizing the functional consequences of such disruptions, may have implications for mechanisms and treatments of symptom dimensions across major mental illnesses.

## Conflict of interest

The authors declare no conflict of interest.

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