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Glial abnormalities in substance use disorders and depression: Does shared glutamatergic dysfunction contribute to comorbidity?

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Abstract

Objectives—Preclinical and clinical research in neuropsychiatric disorders, particularly mood and substance use disorders, have historically focused on neurons; however, glial cells – astrocytes, microglia, and oligodendrocytes – also play key roles in these disorders.

Methods—Peer-reviewed PubMed/Medline articles published through December 2012 were identified using the following keyword combinations: glia, astrocytes, oligodendrocytes/glia, microglia, substance use, substance abuse, substance dependence, alcohol, opiate, opioid, cocaine, psychostimulants, stimulants, and glutamate.

Results—Depressive and substance use disorders are highly comorbid, suggesting a common or overlapping aetiology and pathophysiology. Reduced astrocyte cell number occurs in both disorders. Altered glutamate neurotransmission and metabolism – specifically changes in the levels/activity of transporters, receptors, and synaptic proteins potentially related to synaptic physiology – appear to be salient features of both disorders. Glial cell pathology may also underlie the pathophysiology of both disorders via impaired astrocytic production of neurotrophic factors. Microglial/neuroinflammatory pathology is also evident in both depressive and substance use disorders. Finally, oligodendrocyte impairment decreases myelination and impairs expression of myelin-related genes in both substance use and depressive disorders.

Conclusions—Glial-mediated glutamatergic dysfunction is a common neuropathological pathway in both substance use and depression. Therefore, glutamatergic neuromodulation is a rational drug target in this comorbidity.

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Statement of Interest

Dr Niciu and Ms Henter have no potential conflicts of interest to disclose, financial or otherwise.

Keywords

Glia; depression; glutamate; alcohol use disorders; drug use disorders

Introduction

Substance use disorders (SUDs) frequently co-occur with other psychiatric illnesses. Conversely, primary psychiatric disorders can be mistaken for, or masked by, substance misuse. Several epidemiological surveys have demonstrated that co-occurring psychiatric disorders and SUDs are associated with a greater burden of illness and poorer longitudinal course (Mueser et al. 1998; Ziedonis 2004; Niciu et al. 2009); furthermore, clinical features alone are insufficient to diagnose depressive episode subtype in substance-abusing populations (Niciu et al. 2009). With the exception of genetic studies of depression and alcohol dependence (Kertes et al. 2011; Su et al. 2011; Edwards et al. 2012), few preclinical or clinical neuroscience investigations of dual disorders have been conducted. A number of hypotheses, however, have been proposed to explain their shared aetiology and pathophysiology, as there is considerable overlap in neural circuitry and neurotransmitter systems. In particular, the glutamatergic system is critically important in both depressive disorders and SUDs, especially impaired glial (astrocytes, microglia, and oligodendrocytes) home ostasis (Kalivas 2009; Valentine et al. 2009). This review discusses glial cell dysfunction in depressive disorders and SUDs, and attempts to synthesize neuronal-glial glutamatergic dysfunction in their comorbidity.

Methods

Peer-reviewed PubMed/Medline articles published through December 2012 were identified using the following keyword combinations: glia, astrocytes, oligodendrocytes/glia, microglia, substance use, substance abuse, substance dependence, alcohol, opiate, opioid, cocaine, psychostimulants, stimulants, and glutamate. Both preclinical and clinical investigations were reviewed. All articles were written in English. Reviewing the titles and abstracts uncovered 187 relevant reports, which were examined in full and cited herein when relevant.

Astrocytes

Alcohol—Historically, astrocyte activation has been defined by glial fibrillary acidic protein (GFAP) upregulation, although this is an oversimplification (Oberheim et al. 2012). GFAP levels increase in response to acute stressors like ischaemia and neurotoxins. Acute and chronic ethanol exposure in rats dose-dependently increases GFAP expression in several brain regions (Vongvatcharanon et al. 2010; Udomuksorn et al. 2011). However, with chronic ethanol exposure, GFAP *downregulation* and astrocyte cell death have been observed (Khokhrina et al. 1991). Miguel-Hildago and colleagues confirmed decreased astrocyte density in the dorsolateral and orbitofrontal cortices of alcoholics without Wernicke-Korsakoff syndrome (Miguel-Hidalgo et al. 2002, 2006). In contrast, astrocyte density *increases* with age and in long-standing alcoholism, which may represent gliosis due to chronic neurotoxicity (Miguel-Hidalgo et al. 2006).

Preclinical studies have demonstrated that pre-frontal cortex (PFC) GFAP-immunoreactive cell density is lower in alcohol-naive and alcohol-preferring rats relative to non-alcohol-preferring rats (Miguel-Hidalgo 2005) (see Table I). Glial cell dysfunction also *predates* alcohol exposure in this susceptible rodent strain. In the adult rat medial PFC, binge-like alcohol administration during adolescence decreases glial density without affecting neuronal density in male but not female rodents and without affecting cell density in the basolateral amygdala (Koss et al. 2012). However, earlier bingelike alcohol exposure increases bromodeoxyuridine-labelled (dividing) cells; 60% of these cells express glial markers into adulthood (Helfer et al. 2009). Moreover, gliotoxin or gap junction blocker infusion into the prelimbic cortex transiently increases alcohol self-administration (Miguel-Hidalgo et al. 2009; Miguel-Hidalgo 2007). In contrast to these preclinical findings, a postmortem study of alcohol-dependent depressed suicide completers revealed *increased* glial packing density in the anterior cingulate cortex (ACC) relative to non-alcoholic individuals with depression who committed suicide as well as sudden (non-suicide) deaths (Hercher et al. 2009). Taken together, the results suggest that altered astrocyte density may be a cause instead of a consequence of alcoholism.

Next, alcohol induces glutamatergic neurotransmission abnormalities in astrocytes. Under physiological conditions, synaptic glutamate is removed by specific astrocyte transporters. The astrocytic excitatory amino acid transporter (EAAT)2 [glial glutamate transporter (GLT-1) in rodents] reuptakes glutamate from the extracellular space where it is intracellularly converted to glutamine for synaptic recycling (Niciu et al. 2012). Excessive extrasynaptic glutamate receptor stimulation initiates apoptosis, and the physiological activity of EAAT2/GLT-1 reduces excitotoxicity from synaptic spillover (Hardingham et al. 2010). In a rodent model of alcoholism, alcohol upregulates EAAT2/GLT-1 (Wu et al. 2011). EAAT2/GLT-1 is also upregulated in the amygdala and cingulate cortex of alcohol-dependent rats, and exposure-induced (but not spontaneously-induced) alcohol use can be antagonized with acamprosate, a glutamatergic neuromodulator (Rimondini et al. 2002; Hoffman et al. 2003). Although its expression is increased, alcohol *disrupts* EAAT2/ GLT-1-mediated functions, e.g., the modulation of potassium channel (Kv2.1)-dependent hyperpolarization of rat hippocampal neurons (Mulholland et al. 2009). In addition, the pharmacological inhibition or genetic deletion of equilibrative nucleoside transporter, a transmembrane glycoprotein responsible for nucleotide reuptake (Griffiths et al. 1997), increases alcohol consumption by decreasing the expression of EAAT2/GLT-1 and aquaporin, a channel involved in regulating brain water homeostasis, blood flow, glucose transport and metabolism, blood-brain barrier integrity, glutamate turnover, and syn-aptic plasticity (Lee et al. 2013). The cephalosporin antibiotic ceftriaxone not only restores expression of these transporters but also curtails drinking, which suggests crosstalk between adenosine and glutamate (Lee et al. 2013). As a potential genetic underpinning, a silent G→A mutation in exon 5 of EAAT2/ GLT-1 increases vulnerability to alcohol dependence and impulsivity (Foley et al. 2004; Sander et al. 2000). In addition to EAAT2/GLT-1, the other major astrocyte-expressed EAAT (EAAT1/GLAST) also affects alcohol consumption. In mice, a circadian period gene ($Per2^{Brdm1}$) deletion decreases EAAT1/GLAST expression and increases alcohol consumption; similarly, acamprosate reduces glutamate levels and decreases alcohol intake (Spanagel et al. 2005). Human *Per2* single nucleotide

polymorphisms are also associated with increased alcohol consumption and may also be associated with sleep problems in alcoholism (Comasco et al. 2010).

Taken together, the evidence from preclinical alcoholism models as well as clinical studies suggests that alcohol alters glial cell density and has profound effects on glutamatergic neurotransmission that may be responsible for neurotoxicity and the modulation of treatment response. Excessive alcohol intake also affects glutamate transporter expression, and vice versa, possibly in an attempt to maintain homeostasis. Furthermore, altered transporter expression/function leads to increased vulnerability for alcohol preference/consumption. Finally, genotypic variations also alter glutamate transporter expression/function and alcohol intake in both rodents and humans.

Illicit drugs—Drugs of abuse also adversely affect astrocytes, providing potential pathophysiological mechanisms for initiation, maintenance, and relapse (see Table I). As in alcohol use disorders, astrocytic glutamate transporters play a pivotal role in the development and maintenance of cocaine misuse. In rodents, cocaine self-administration decreases glutamate in the nucleus accumbens (NAcc) core, which temporally coincides with decreased expression of EAAT2/ GLT-1 and xCT, the catalytic subunit of the glutamate antiporter system xC^- which exchanges extracellular cysteine for intracellular glutamate (Knackstedt et al. 2010). Ceftriaxone prevents cocaine-induced reductions in the expression of both transporters and normalizes extracellular glutamate levels, which provides a viable mechanism to reverse cocaine-induced synaptic potentiation, e.g., decreased spontaneous excitatory postsynaptic currents, in the NAcc core and reduce cue- and cocaine-mediated reinstatement (Knackstedt et al. 2010; Trantham-Davidson et al. 2012). *N*-Acetylcysteine, a cystine prodrug that also stimulates xCT and GLT-1 expression (Knackstedt et al. 2010), decreases rodent cocaine seeking and other cocaine-related behaviours and reduces cravings in non-treatment-seeking cocaine-dependent subjects (Baker et al. 2003; Madayag et al. 2007; Amen et al. 2011). Diffuse astrogliosis has also been linked to methamphetamines (Pubill et al. 2003).

On a behavioural level, the infusion of astrocyte-conditioned media into the rodent NAcc incites locomotor sensitization and reward processing with methamphetamines (Narita et al. 2005, 2006b). The evidence, therefore, suggests that glial-mediated dysfunction, especially in glutamatergic neurotransmission, leads to adverse behavioural sequelae associated with initiation, maintenance, and relapse to cocaine and other psychostimulants. In short, cocaine alters the ability to maintain extracellular levels of glutamate and decreases synaptic plasticity in the NAcc. This renders both mice and humans more susceptible to cue-induced reinstatement. Drugs that increase xCT and/or EAAT2/GLT-1 expression restore extracellular glutamate levels, thus preventing reinstatement.

Similar to the effects of methamphetamines, chronic morphine treatment increases GFAP expression in brain regions involved in addictive disorders: ventral tegmental area (VTA), NAcc, and PFC (Beitner-Johnson et al. 1993; Song et al. 2001; Marie-Claire et al. 2004). Furthermore, the gliotoxin fluorocitrate reduces morphine-induced GFAP immunoreactivity and mitigates tolerance (Song et al. 2001). Finally, morphine tolerance and blunted analgesia correlate with glutamate transporter down-regulation in the spinal cord (Mao et al. 2002).

The glutamate transporter stimulator MS-153 significantly reduces conditioned place preference (CPP) in mice treated with opioids (and psychostimulants) without altering locomotion (Nakagawa et al. 2005). MS-153 also attenuates morphine tolerance and reduces the signs/symptoms of opioid dependence (Nakagawa et al. 2001). Furthermore, adenovirally mediated intra-NAcc shell EAAT2/GLT-1 transduction *reduces* morphine-induced CPP (Fujio et al. 2005). Therefore, astrocyte-based glutamatergic dysfunction is important in the initiation and maintenance of opioid misuse, and targeting these deficits reduces some of the core features of dependence, e.g., CPP.

In addition to their critical role in neurotransmitter dynamics, activated astrocytes also secrete neurotrophic factors, e.g., glial-derived neurotrophic factor (GDNF) (Appel et al. 1997; Lee et al. 2006). GDNF is neuroprotective for medial striatal and VTA dopaminergic neurons on exposure to psycho-stimulants (Cass 1996; Boger et al. 2007). Intra-VTA GDNF infusion blocks numerous biochemical and behavioural sequelae of chronic cocaine and morphine misuse; conversely, intra-VTA anti-GDNF antibodies augment cocaine-induced stereotypy (Messer et al. 2000). Finally, infusion of the dipeptide leucine-isoleucine – an identified GDNF and tumour necrosis factor alpha (TNF-α) inducer of expression – inhibits psychostimulant-induced CPP and sensitization (Niwa et al. 2007).

Depression—Astrocytes have also been implicated in the aetiopathogenesis of preclinical models of despair and clinical depression (see Table I). Postmortem studies of major depressive disorder (MDD) demonstrate decreased glial cell density in several brain regions, including orbitofrontal cortex, dorsolateral PFC (dlPFC) (Rajkowska et al. 1999), ACC (Cotter et al. 2001), and amygdala (Bowley et al. 2002). An age-dependent reduction in GFAP-immunoreactive astrocyte density has also been observed in the PFC of younger individuals with MDD (Miguel-Hidalgo et al. 2000), but not in the supragenual ACC in late-life depression relative to age-matched controls (Khundakar et al. 2011). There is also a significant reduction in aquaporin-immunoreactive astrocytic end feet contacting gray matter vessels in the PFC of individuals with MDD, which suggests that blood-brain barrier permeability may be altered in depression (Rajkowska et al. 2013).

Data are mixed regarding diagnostic specificity, e.g., decreased GFAP expression in the amygdala of individuals with MDD, but not those with bipolar disorder (BD) (Altshuler et al. 2010), and in the cerebellum of individuals with MDD but not those with schizophrenia (Fatemi et al. 2004). Another report identified dlPFC *layer-specific* GFAP reductions in individuals with schizophrenia compared to healthy controls (Rajkowska et al. 2002). In addition, there is *increased* GFAP expression in subcortical brain structures in schizophrenia and MDD relative to non-psychiatric controls (Barley et al. 2009). Finally, serum levels of glial-derived S100β are increased in MDD, and these levels are not affected by antidepressant treatment (Schroeter et al. 2008). The preponderance of the above evidence, at the very least, suggests astrocytic dysfunction in the MDD brain.

In reverse translational studies, rats subjected to 15 days of chronic unpredictable stress (CUS) – a validated rodent model of depression – had a 35% decrease in cellular proliferation in the cingulate, motor, and prelimbic cortices; the selective serotonin reuptake inhibitor (SSRI) fluoxetine reversed this deficit and increased sucrose preference, a

surrogate marker of anhedonia (Banasr et al. 2007). Interestingly, this study reported reduced endothelial and oligodendrocyte progenitor proliferation but no change in astrocytes and microglia (Banasr et al. 2007). Chronic social defeat by an aggressive conspecific decreased medial PFC gliogenesis and hippocampal dentate gyrus neurogenesis, but had minimal trophic effects in non-limbic brain structures; again, SSRIs reversed these impairments (Czeh et al. 2007), further suggesting the importance of serotonergic circuitry in astrocyte-mediated dysfunction.

In addition to morphological deficits, stress-induction paradigms also affect neurotrophin secretion by astrocytes. Social defeat stress reduces GFAP expression (Araya-Callis et al. 2012); this effect is not reversed by citalopram, but is partially rescued by brain-derived neurotrophic factor (Ye et al. 2011). Central inhibition of astrocyte glutamate reuptake by the EAAT2/GLT-1 inhibitor dihydrokainic acid impairs reward processing and hippocampal-dependent spatial working memory, which correlates with anhedonia-like and cognitive-like symptoms, respectively (Bechtholt-Gompf et al. 2010). The anhedonia-like phenotype could be replicated by dihydrokainic acid injection into the PFC alone (John et al. 2012). In addition, PFC astrocyte ablation by the toxin L-alpha-amino-adipic acid results in despair-like behaviours (Banasr et al. 2008). In contrast, the excito-neurotoxin ibotenate has no effect in depressogenic behavioural paradigms, suggesting that gliotoxicity may be more important than neuronal cell death in rodent despair (Banasr et al. 2008).

Astrocytes secrete many neurotrophins in response to antidepressants; amitriptyline increases basic fibroblast growth factor (FGF-2/bFGF) mRNA expression in astrocyte but not neuronal primary cultures. In the learned helplessness model, imipramine's effects were attenuated by fluorocitrate (a reversible astrocyte inhibitor) into the hippocampal CA3/dentate gyrus (Iwata et al. 2011). Intracere-broventricular and intra-PFC infusion of FGF-2/bFGF reverses anhedonia-like behaviours, and this effect can be blocked by infusion of a specific FGF receptor antagonist (Elsayed et al. 2012). As a result, glial-derived neurotrophins are both necessary and sufficient for antidepressant efficacy in rodent models of depression.

Astrocyte perturbations have also been studied in suicide. Astrocytic *hypertrophy* with longer-ramified processes was reported in ACC white matter (Torres-Platas et al. 2011) with downregulation of the dlPFC astroglial cytoskeletal proteins connexins 30 and 43 (Ernst et al. 2011). In addition, decreased expression of truncated TrkB (TrkB. T1), an astrocyte-specific neurotrophin receptor associated with epigenetic promoter methylation (Ernst et al. 2009), was observed in the frontal cortex of a subpopulation of suicide completers. The secreted calcium-binding astroglial extracellular matrix protein SPARC-like 1/hevin expression stimulates astrocyte-mediated excitatory synaptogenesis (Kucukdereli et al. 2011) and neurodevelopment (Eroglu 2009). Like TrkB.T1, SPARC-like 1/hevin expression is decreased in suicide completers (Zhurov et al. 2012).

Preclinical/mechanistic investigations have been conducted into the aetiopathophysiology of impaired gliogenesis, gliotoxicity, and/or altered synaptic function in depressive disorders. As with SUDs, decreased synaptic glutamate reuptake, synaptic spillover, and extrasynaptic glutamate receptor stimulation were the hypothesized substrates of glutamatergic

dysfunction. In rat models, expression of EAAT1/GLAST, EAAT2/GLT-1, EAAT4, and vGluT1 (a vesicle-bound glutamate transporter) is suppressed (Zink et al. 2010; Gourley et al. 2012). Decreased expression of these transporters coincides with increased levels of D-serine (a differential partial agonist at the glycine$_B$ coagonist site on the *N*-methyl-D-aspartate (NMDA) receptor (Sheinin et al. 2001)), which attenuates excitotoxic extrasynaptic stimulation (Papouin et al. 2012; Gomez-Galan et al. 2013). Amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid (AMPA) receptor membrane localization and activation may also be critical in treatment response to mood stabilizers (Du et al. 2007) and the NMDA receptor antagonist ketamine (Maeng et al. 2008). Finally, the glutamate-modulating drug riluzole stimulates astrocytic glutamate reuptake via EAAT2/GLT-1 upregulation and reverses both glial cell metabolic impairments and GFAP mRNA expression in CUS-exposed rats (Banasr et al. 2010; Gourley et al. 2012).

Adding support for a central role for glutamate, glutamate transporter downregulation has been observed in postmortem neocortical MDD micro-arrays (e.g., *SLC1A2* , *SLC1A3*, and *L-glutamate-ammonia ligase*) (Choudary et al. 2005). In the locus ceruleus, glial-expressed high-affinity glutamate transporters (*SLC1A2*, *SLC1A3*, and *GLUL*) are downregulated, while neuronal presynaptic vesicular glutamate transporters (*SLC17A6/VGLUT2*) and postsynaptic glutamate receptors (*GRIA1*, *GRIK1*, *GRM1*, and *GRM5*) are upregulated in MDD vs. BD and non-depressed controls (Bernard et al. 2011), suggesting both regional and diagnostic specificity.

Microglia

Alcohol—There is a burgeoning literature on microglia in alcohol use disorders (see Table II). In adolescent Sprague–Dawley rats, binge-like alcohol intake stimulates hippocampal microglial activation for up to 30 days after last consumption, suggesting that circumscribed exposure over a relatively brief neurodevelopmental window has long-lasting consequences (McClain et al. 2011). Ten days of intragastric ethanol administration to C57BL6/J mice also activates microglia, as detected by increasing nicotinamide adenine dinucleotide phosphate oxidase expression and increased reactive oxygen species production (Qin et al. 2012). In addition to stimulating neuroinflammatory cascades, in hypothalamic mixed cultures, ethanol's apoptotic effects are mediated by microglia (Boyadjieva et al. 2010). Microglial activation is also critical in treatment response: minocycline, a tetracycline antibiotic and microglial inhibitor, decreases drinking in C57BL/6J mice (Agrawal et al. 2011). In a rodent model of drinking cessation, microgliosis preceded neurogenesis and volumetric recovery (Nixon et al. 2008).

In response to alcohol, several microglial proteins are differentially regulated across multiple brain regions. Genetic deletion of monocyte chemoattractant protein (MCP-1/CCL2), a microglial-derived chemokine, decreases drinking and alcohol preference in mice (Blednov et al. 2005). In another preclinical study, overexpression of MCP-1/CCL2 preserved long-term potentiation and fear conditioning with alcohol exposure (Bray et al. 2013). MCP-1/ CCL2 expression is also globally increased in postmortem brain homogenates from alcohol-dependent subjects (He et al. 2008). In the cingulate cortex, ionized calcium binding adaptor protein-1 (Iba-1) and glucose transporter-5 are increased in

alcoholics relative to healthy controls (He et al. 2008). In the VTA and thalamus, however, glucose transporter-5 expression is elevated, but Iba-1 expression is unaffected. Finally, in the amygdala, no microglial marker differences were observed in alcoholics relative to healthy volunteers (He et al. 2008). In addition to these activation markers, alcohol affects the expression of microglial cell surface receptors. Acute alcohol administration induces Toll-like receptor (TLR)4/type I interleukin (IL)-1 receptor signaling mediators: nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen activated protein kinase signal transduction cascades (Blanco et al. 2005). In contrast, alcohol impairs microglial activation in TLR4 null mice (Fernandez-Lizarbe et al. 2009). Although the literature on TNF-α expression is varied (Nelson et al. 1990; Nair et al. 1994; Avogaro et al. 2003), the most recent study indicates that alcohol *increases* brain TNF-α expression (Qin et al. 2008), which may be neuroprotective; indeed, low concentrations of TNF-α (20 ng/ml) in slice cultures synergize neurotoxicity by impairing EAAT2/GLT-1-mediated glutamate reuptake (Zou et al. 2005). Butylated hydroxytoluene, an antioxidant, reverses this inhibition and blocks the nuclear translocation of the NF-κB subunit p65 (Zou et al. 2005). Finally, in abstinent alcoholics, etanercept (a soluble TNF-α receptor antibody with demonstrated efficacy in the treatment of autoimmune disorders) reduces rapid eye movement sleep, a prognostic indicator for future alcohol relapse (Irwin et al. 2009).

Taken together, the evidence suggests that alcohol has complex temporal and brain area-specific effects on neuroinflammatory cascades that culminate in the differential expression of pro- and anti-inflammatory chemo/cytokines and downstream effectors. As a result, neuroinflammatory modulation (including microglial-mediated glutamate receptor downregulation) may be a rational future target for therapeutic intervention in alcoholism.

Illicit drugs—Unlike alcohol, scant evidence links microglia to drug use disorders (DUDs) (see Table II). Microglia express opioid receptors that inhibit chemotaxis (Chao et al. 1997) and induce apoptosis when stimulated (Hu et al. 2002). On a behavioural level, increased rodent maternal handling inhibits reinstatement of morphine-induced CPP in adulthood by increasing microglial expression of the anti-inflammatory IL-10 in the rat NAcc (Schwarz et al. 2011). Furthermore, microglial p38 (a mitogen activated protein kinase/extracellular signal-related kinase pathway intermediate) in the NAcc also mediates the acquisition and maintenance of morphine-induced CPP (Zhang et al. 2012). Microglial TLRs, e.g., TLR2 (Zhang et al. 2011), TLR4 (Watkins et al. 2009), and TLR9 (He et al. 2011), also modulate the neurochemical and behavioural effects of opioids in rodents.

Other substances of abuse have only been tangentially linked to microglial dysfunction. Striatal microglia are activated by psychostimulants, and a temporal correlation exists between microglial activation and methamphetamine-induced neurotoxicity/tolerance (Thomas et al. 2004a,b). Microglia also mediate some of methamphetamine's behavioral effects; for instance, minocycline attenuates striatal methamphetamine-induced neurotoxicity and reduces hyperlocomotion (Zhang et al. 2006).

Depression—In rodents, repeated restraint stress activates medical PFC microglia, an effect reversible by minocycline (Hinwood et al. 2012) (see Table II). TNF receptor ($TNFR1^{-/-}$ and $TNFR2^{-/-}$) knockout mice are more resilient when stressed (Simen et al

2006). TNFR1$^{-/-}$ mice also have reduced fear conditioning, and TNFR2 null mice increase their sucrose ingestion after water deprivation stress. However, no difference has been observed between wild-type and knockout littermates on anxiety-related tests such as the open field and elevated plus maze tests (Simen et al. 2006).

As in SUDs, proinflammatory cytokines are implicated in the pathophysiology of depression. Like bacterial lipopolysaccharide, exogenous TNF-α and IL-1 administration to rodents (both centrally and peripherally) produce“sickness behaviour“, a con stellation of physical and neuropsychiatric symptoms resembling depression (Dantzer 2001a; 2001b). In non-human primates, a ligand that recognizes activated microglia found lipopolysaccharide-induced microglial activation within hours, an effect most likely mediated through cytokine secretion (Hannestad et al. 2012). Likewise, proinflammatory cytokine levels are elevated in isolated and co-occurring depressive disorders (Penninx et al. 2003; Kahl et al. 2006; O’Brien et al. 2007) and abate with antidepressant therapy (Lanquillon et al. 2000; Narita et al. 2006a; O’Brien et al. 2007).

In addition, SSRIs and the serotonin norepinephrine reuptake inhibitor venlafaxine are anti-inflammatory as demonstrated by their ability to decrease proinflammatory cytokine expression in vitro (Liu et al. 2011; Tynan et al. 2012). The SSRIs paroxetine and sertraline inhibit nitric oxide and TNF-α expression in interferon-gamma-activated microglia in a calcium-dependent manner. In contrast to other antidepressants, the monoamine oxidase inhibitor phenelzine *increases* the proinflammatory cytokines TNF-α and IL-6 in an NF-κB-dependent manner, indicating differential effects based on anti-depressant class (Chung et al. 2012). Interestingly, kinin B1 receptor antagonists, important modulators of microglial TNF-α, reduce depressive-like behaviours in mice (Viana et al. 2010).

Experimental TNF-α findings are being translated into humans. In a novel immunomodulatory treatment study, 618 subjects with moderate-to-severe psoriasis were randomized to the anti-TNF-α antibody etanercept or placebo. Etanercept decreased standard clinical depression scores by ~50% – independent of dermatological and/or musculoskeletal improvement (Tyring et al. 2006). Although a recent placebo-controlled trial of infliximab (another TNF-α neutralizing antibody) revealed a lack of global efficacy in treatment-resistant MDD, an antidepressant response was observed in individuals with a baseline C-reactive protein >5 mg/L (Raison et al. 2012).

Taken together, the evidence suggests that microglia have important and overlapping aetiopathological roles in SUDs and depression.

Oligodendrocytes

Alcohol—Numerous studies have demonstrated white matter dysfunction in alcoholics (Shear et al. 1994; Pfefferbaum et al. 2000; Harper et al. 2003), as well as in rodent models of alcohol use disorders (Pons-Vazquez et al. 2011) (see Table III). At the molecular level, microarray studies revealed altered oligodendrocyte/myelin gene expression in heavy drinkers (Lewohl et al. 2000; Mayfield et al. 2002; Liu et al. 2004). Specifically, alcohol decreases the expression of peroxisome proliferator activated receptor-beta, a transcription factor important for lipid metabolism, in oligodendrocyte-like B12 cells (Leisewitz et al.

2003). Molecular dysfunction is also seen in animal models; in rodents, chronic exposure to alcohol decreases oligodendrocyte myelin glycoprotein mRNA in the hippocampus (Okamoto et al. 2006).

The specific mechanisms of oligodendrocyte dysfunction have been explored with mixed results. In cortical cultures, both Th1 (pro-inflammatory) and Th2 (anti-inflammatory) cytokines decrease alcohol-induced oligodendrocyte cell death (Benjamins et al. 2011). Furthermore, alcohol downregulates oligodendroglial c-Fos (an immediate early gene) and upregulates myelin basic protein (MBP) in a protein kinase C-dependent manner (Bichenkov et al. 2009). However, myelin gene expression (including MBP) is *less* disrupted (with decreased concomitant neurodegeneration) in TLR4 knockout mice after chronic ethanol exposure (Alfonso-Loeches et al. 2012).

Illicit drugs—Extensive white matter tract and oligodendrocyte abnormalities are seen in cocaine misuse (Chang et al. 1997, 1999; Bartzokis et al. 1999) (see Table III). For example, MBP, proteolipid protein-1 (PLP-1), and myelin-associated oligodendrocyte basic protein (MOBP) are downregulated in chronic cocaine abuse (Albertson et al. 2004). In another microarray study, increased dlPFC PLP-1 levels were observed in four cocaine abusers, and decreased levels were observed in three other cocaine abusers (including two alcohol co-abusers); interestingly, increased dlPFC PLP-1 correlated with recent crack cocaine use (Lehrmann et al. 2003).

Oligodendrocyte dysfunction has also been observed in opioid dependence. In rodents, low-level perinatal buprenorphine exposure increases fetal MBP expression and oligodendrocyte maturation; however, excessive perinatal exposure delays oligodendroglial development and decreases MBP expression (Sanchez et al. 2008). These biphasic effects are mediated by μ-opioid and nociception/orphanin FQ receptors, which are also implicated in the pathogenesis of chronic pain disorders (Eschenroeder et al. 2012).

Depression—Oligodendrocytes have been studied in depressive disorders (Edgar et al. 2012) (see Table III). There is white matter attenuation in MDD, especially in geriatric samples (Taylor et al. 2003, 2004), and this has been confirmed in several postmortem MDD studies (Regenold et al. 2007; Hayashi et al. 2011). Oligodendrocyte density is also decreased in the postmortem MDD brain (−19%) in PFC layer VI and surrounding white matter (Brodmann's area 9) compared to non-psychiatric controls (Uranova et al. 2004). Decreased oligodendrocyte density has also been observed in sublayers IIIa, IIIb, and IIIc of Brodmann's area 9 (Vostrikov et al. 2007) and in the amygdala of individuals with MDD but not BD (Hamidi et al. 2004). Other white matter corticolimbic circuitry abnormalities have been observed in BD (Mahon et al. 2010).

As with SUDs, numerous myelin-related genes are downregulated in the depressed brain (Aston et al. 2005; Honer et al. 1999). Quaking homolog, KH domain RNA-binding, an oligodendrocyte-specific RNA-binding protein critical for oligodendrocyte progenitor differentiation, is also reduced in the neocortex, hippocampus, and amygdala of depressed suicide victims (Klempan et al. 2009). Oligodendrocytes are transiently activated by electroconvulsive therapy (Ongur et al. 2004) and rodent electroconvulsive seizures (Jansson

et al. 2009). As further molecular evidence of electroconvulsive seizure response, neuronglial antigen 2-expressing oligodendrocyte progenitor cells proliferated and selectively differentiated into mature oligodendrocytes in the rat amygdala (Wennstrom et al. 2004). Thus, overlapping white matter dysfunction and oligodendrocyte cytopathology occurs in both SUDs and depression.

Glial cell-mediated glutamatergic dysfunction in co-occurring SUDs and depression

Most of the studies discussed have focused on *isolated* SUDs or depressive disorders. To date, only one study has directly compared glial cell pathology in subjects with comorbid depressive symptoms of escalating severity, alcohol dependence alone, and an MDD cohort from an earlier study by the same group (Miguel-Hidalgo et al. 2002). In this study, subjects with a history of alcohol dependence and depressive symptoms (n = 8) had decreased dlPFC glial cell density compared to subjects with alcohol dependence and no depressive symptoms (n = 9) and the historical MDD group (n = 12) (Miguel-Hidalgo et al. 2002).This suggests that subjects with comorbid depression and alcohol dependence may have even *more severe* glial cell dysfunction than in either illness alone.

Although depression and SUD comorbidity has not been extensively studied (Miguel-Hidalgo et al. 2003), glial cell dysfunction may be particularly important. The following hypotheses may be postulated:

1. Multiple episodes of substance intoxication/ withdrawal kindle substance-induced depressive episodes, which have cumulative deleterious effects on glia;
2. Depressed subjects attempt to“self-medicate” their neuropsychiatric symptoms with alcohol and illicit substances, which have cumulative deleterious effects on glia; and
3. A complex interplay exists between depressive and substance use pathologies that has cumulative and potentially synergistic deleterious consequences on glia.

The first and second hypotheses may pertain to some dually diagnosed subjects (Crum et al. 2013), but these disorders rarely develop in isolation and almost never arise linearly. Therefore, the third cumulative/synergistic hypothesis appears most consistent with the clinical phenomenology of comorbidity.

Ketamine as a glutamatergic probe in comorbidity—In addition to shared glial cell dysfunction, several studies conducted with the NMDA receptor antagonist ketamine support shared glutamatergic dysregulation in comorbid depression and SUDs (Miguel-Hidalgo et al. 2010). Ketamine recreates ethanol-like effects in recently detoxified alcoholics in a dose-dependent manner, which more closely resembles alcohol’s sedative rather than euphoric effects (Krystal et al. 1998). Recently detoxified alcoholics also display fewer dissociative-like symptoms, acute dysphoria, or cognitive/executive dysfunction during ketamine administration relative to non-dependent controls, suggesting that chronic alcohol-induced NMDA receptor antagonism attenuates ketamine’s adverse effects (Krystal et al. 2003). Alcohol-dependent patients may also not experience the negative cognitive and psychological signals to stop drinking beyond the point of mild-to-moderate intoxication

(Krystal et al. 2003). Even non-dependent individuals with a family history of alcohol dependence display a more blunted response to ketamine than subjects without this genetic loading (Petrakis et al. 2004).

Although acute and transient ketamine-induced dysphoria is an identified adverse effect, subanesthetic ketamine also has rapid and robust antidepressant effects in patients with treatment-resistant MDD (Berman et al. 2000; Zarate et al. 2006) and bipolar depression (Diazgranados et al. 2010a; Zarate et al. 2012).This enhanced glutamatergic responsivity has also been observed in MDD (Phelps et al. 2009) and bipolar depressed (Luckenbaugh et al. 2012) patients with a first degree relative with alcoholism as these individuals have an augmented anti-depressant response to ketamine.

Future directions/conclusions

Although astrocytes are now known to be critical in synaptic glutamate reuptake, microglia and oligodendrocytes also function in glutamatergic homeostasis [see recent reviews by Wong et al. (2011) and Bakiri et al. (2009) on microglia and oligodendrocytes, respectively]. Microglial upregulation of the NMDA receptor complex has been observed in MDD but not BD (Steiner et al. 2011). Nevertheless, additional research is critically needed on non-astrocyte-based amino acid neurotransmitter dysfunction in both SUDs and depression to better comprehend convergent pathways and offer novel treatment approaches.

There are several exciting avenues for future comorbidity research. First, preclinical models of co-occurring disorders, e.g., rodents exposed to both CUS and alcohol/illicit drugs, may expand our neuropathological understanding of this comorbidity. Ketamine's improved antidepressant response in those with a family history of alcoholism suggests that subjects with comorbid depression and alcohol dependence may have *enhanced* antidepressant effects relative to non-alcohol dependent depressed patients. If efficacious, alternative non-parenteral NMDA receptor antagonists with lower addictive liability are better long-term strategies in this population (Ibrahim et al. 2012; Zarate et al. 2013). Despite the great wealth of preclinical data on glial-mediated glutamatergic dysregulation in DUDs (Kalivas et al. 2005, 2011), there are presently no pathophysiological or treatment studies in co-occurring MDD/bipolar depression and DUDs.

Depressed subjects with co-morbid SUDs are at increased risk for suicide (Niciu et al. 2009). Interestingly, ketamine decreases suicidality in high-risk populations (Price et al. 2009; DiazGranados et al. 2010b), including in the emergency setting (Larkin et al. 2011), but it remains to be seen if ketamine or other glutamatergic modulators have anti-suicidal properties in this high risk population.

In summary, the evidence reviewed in this paper highlights the critical role of glia in the aetiopathogenesis of isolated depressive disorders and SUDs. We synthesize the evidence and hypothesize that glial cell-mediated glutamatergic dysfunction may be critical in comorbidity.

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Table I

Astrocyte dysfunction in SUDs and depression.*

SUDs	Depression
Decreased astrocyte density in PFC and other brain regions (AUDs)	*Decreased astrocyte density in PFC and other brain regions*
Altered glutamate transporter expression e.g., decreased astrocytic EAAT2/ GLT- 1 in DUDs (cocaine, opioids)	*Impaired glutamate transport, e.g., decreased expression of EAAT1/GLAST, EAAT2/GLT-1, EAAT4, and vGluT1*
Changes in neurotrophic factors, e.g GDNF, BDNF, and FGF-2/bFGF	*Decreased neurotrophic factor production/secretion, e.g., BDNF*
Reactive gliosis (DUDs)	Altered glutamate and glutamine levels in several brain regions
Astrocyte-mediated tolerance in DUDs (opioids)	Gliotrophic effects of traditional antidepressants, *e.g* SSRIs, TCAs
	Gliotrophic effects of experimental antidepressants, *e.g* riluzole

SUD, substance use disorder; PFC, prefrontal cortex; AUD, alcohol use disorder; EAAT2, excitatory amino acid transporter-2; GLT-1, glial glutamate transporter-1; GDNF, glial derived neurotrophic factor; BDNF, brain derived neurotrophic factor; FGF-2/bFGF, basic fibroblast growth factor-2; DUD, drug use disorder; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

* Italicised text denotes potential convergent mechanisms in SUDs and depressive disorders.

Table II

Microglial dysfunction in SUDs and depression.*

SUDs	Depression
Increased microglial activation	*Increased microglial activation*
Increased cytokine production/secretion, e.g MCP1/CCL2, TNF-α	*Neurobehavioral response to cytokines, e.g.,"sickness behaviour", and increased cytokine production/secretion*
TNF-α receptor antagonists and minocyclin's therapeutic benefits in AUDs	*TNF-α receptor antagonists' therapeutic benefits , e.g depression in psoriasis*
TLR activation→ MAPK/NF-κB signal transduction	Normalized cytokine levels with standard antidepressants, *e.g.*, SSRIs, MAOIs
Microglial apoptosis in DUD (opioid)	

MCP1, microglia chemoattractant protein-1; CCL2, chemokine (C-C motif) ligand 2; TNF-α, tumor necrosis factor-α ; AUD, alcohol use disorder; TLR, toll-like receptor; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; DUD, drug use disorder; SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor.

* Italicised text denotes potential convergent mechanisms in SUDs and depressive disorders.

Table III

Oligodendrocyte dysfunction in SUDs and depression.*

SUDs	Depression
Enhanced programmed cell death/apoptosis (AUDs)	*Decreased cell density*
Decreased expression of myelin-related genes, e.g., MBP, PLP-1	*Decreased expression of myelin-related genes, e.g., MBP, MOG, PLP-1*
Decreased immediate-early gene expression, *e.g* c-Fos	Decreased RNA binding protein expression
	Increased activation after ECT/ECS

SUDs, substance use disorders; MBP, myelin basic protein, PLP-1, phospholipid protein-1; MOG, myelin-oligodendrocyte glycoprotein; RNA, ribonucleic acid; ECT, electroconvulsive therapy; ECS, electroconvulsive seizure.

* Italicised text denotes potential convergent mechanisms in SUDs and depressive disorders.