Alcohol use in bipolar disorder: A neurobiological model to help predict susceptibility, select treatments and attenuate cortical insult

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Abstract

In a series of neurophysiological and neuroimaging studies we investigated the neurobiology related to alcohol use in young people with bipolar disorder. Impairments were identified across frontal and temporal representations of event-related potential and proton magnetic resonance spectroscopy markers; mismatch negativity and *in vivo* glutathione, respectively. We propose these findings reflect impairments in the N-methyl-D-aspartate receptor and antioxidant capacity. This review seeks to place these findings within the broader literature in the context of two propositions:

1. ***Pathophysiological impairments in N-methyl-D-aspartate receptor functioning in bipolar disorder contribute to susceptibility toward developing alcohol problems***

2. Alcohol aggravates bipolar disorder neuroprogression via oxidative stress

. A neurobiological model that incorporates these propositions is presented, with a focus on the potential for N-methyl-D-aspartate receptor antagonism and glutathione augmentation as potential adjunctive pharmacotherapies to treat the comorbidity. While this review highlights the importance of alcohol monitoring and reduction strategies in the treatment of bipolar disorder, the clinical impact of the proposed model remains limited by the lack of controlled trials of novel pharmacological interventions.

Keywords: bipolar disorder; mismatch negativity; magnetic resonance spectroscopy; NMDA receptor, glutathione

1.0 Introduction

Alcohol use, abuse and dependence are highly prevalent in bipolar disorder (BD) representing the most common mental disorder and alcohol comorbidity (Grant et al, 2004; Hermens et al, 2013; Regier et al, 1990). The negative implications of alcohol use on the trajectory of bipolar illness are severe (Feinman and Dunner, 1996; Oquendo et al, 2010; Rakofsky and Dunlop, 2013; Salloum and Thase, 2000), a fate that has been well-documented since the 1970's with the first report of heightened suicide risk associated with this comorbidity (Morrison, 1974). Decades later with a wealth of information regarding the impact of this destructive comorbidity, it is still highly prevalent (Di Florio et al, 2014), which indicates there is room for improvement in prevention, early intervention and treatment strategies.

This may be largely because many of the identified risk factors for development of alcohol problems in people with BD cannot be controlled, for example, risk factors such as gender (Tsai et al, 2012), personality traits such as sensation-seeking (Bizzarri *et al*, 2007) or impulsivity (Nery *et al*, 2013), and comorbid diagnoses such as attention-deficit hyperactivity disorder (Tamam et al, 2008) or anxiety disorders (Kauer-Sant'Anna et al, 2007). Or risk factors that have occurred before the patient presents to mental health services, for example, childhood maltreatment (Sala et al, 2014) or abuse (Du Rocher Schudlich et al, 2014). There is therefore a crucial need for a shift in research focus toward understanding the preventable and treatable causes, as well as the correlates, of this comorbidity. One of the most promising avenues is to probe the underlying neurobiology of this comorbidity, with a view to developing targeted psychopharmacological strategies.

The potential to identify neurobiological biomarkers associated with a shared vulnerability is largely supported by evidence that people with BD may have an

inherited susceptibility to developing problems with alcohol, a theory which has been long hypothesized (Carmiol *et al*, 2014; Johnson and Leeman, 1977; Pitts and Winokur, 1966). This susceptibility is illustrated by familial and behavioural evidence. People with BD have a high prevalence of positive family history of alcohol dependence (FHP) (Biederman *et al*, 2000; Johnson et al, 1977; Mantere *et al*, 2012; Todd *et al*, 1996), and people with BD who have FHP are more likely to develop an alcohol use disorder compared to those with a negative family history (FHN) (Wilens *et al*, 2014). Causal genes that are associated with this comorbidity have not yet been identified. Though there is evidence of genetic variants that increase the risk for both illnesses (Carmiol et al, 2014; Levey et al, 2014), with a recent correlational study estimating that 47 – 57% of the genetic variance predisposing BD also influences the risk for alcohol use disorders (Carmiol *et al*, 2014). However, not all studies have concluded that the two illnesses share familial risk factors (Sbrana *et al*, 2007).

Behavioural evidence also provides support for a shared vulnerability. Diagnosis of BD aside, the predominant theories behind the increased risk of developing alcohol use problems in those with FHP is (an inherited) reduced sensitivity to the behavioural consequences of alcohol use (Schuckit, 1994; Schuckit and Smith, 1996; Schuckit *et al*, 2004). This "tolerance" to the subjective effects of alcohol is also a symptom of alcohol dependence. Inherited tolerance has been put forth as one of the prominent phenotypic risk factors for heavy drinking and the subsequent development of alcohol dependence (Schuckit et al, 1996). This notion has since been supported by a meta-analytic finding that FHP individuals have reduced subjective responses to alcohol compared to those with FHN (Quinn and Fromme, 2011). Importantly, it has been hypothesized that reduced sensitivity to the effects of alcohol is also present in

people with BD who go on to develop problems with alcohol (Le Strat and Gorwood, 2008). Early investigations into this theory have found that young at-risk BD males show "blunted" subjective effects to acute alcohol administration compared to controls. Notably, this finding is not attributed to FHP in these participants (Yip *et al*, 2012).

The second key aspect in understanding neurobiological biomarkers of the BD-alcohol misuse comorbidity is to tease out the 'neural consequences' of the interaction itself, in other words, what is happening to the brain when people with BD drink alcohol? Answering this question allows us to determine how alcohol use contributes to worse illness outcomes, thereby providing another avenue for identification of treatment targets and better guidance for treatment selection. For example, identifying the neural sequela associated with the comorbidity may enable an understanding of the mechanisms responsible for the severe consequences of the comorbidity, such as suicide, and hence develop targets to diminish these disturbed pathways (in conjunction with alcohol reduction strategies).

Whilst there is a dearth of BD-alcohol comorbidity studies with a neurobiological approach there is a wealth of evidence addressing BD and alcohol separately, and from this we have investigated two neurobiological commonalities heavily associated with the two. The first of these was the NMDA receptor. The NMDA receptor has been implicated in the pathophysiology of BD (for review see: (Ghasemi et al, 2014)), is a well-known recipient of the neural effects of alcohol, including tolerance (for review see: Krystal *et al*, 2003c) and it is an established treatment target for mood (Sanacora et al, 2008) and alcohol use (Krystal et al, 2003c) disorders with genetic links to both BD and alcohol dependence (Schuckit *et al*, 2003). The second BD-alcohol neurobiological 'intersection' we selected for enquiry was neural oxidative

stress. Oxidative stress is believed to contribute to the neuroprogression of BD (Berk *et al*, 2011) which may be a consequence of the effects of xenobiotic substances in the brain, such as alcohol (Tsai *et al*, 1998; Zhong *et al*, 2012).

While these are certainly not the only commonly affected neurobiological systems between BD and alcohol, both are targets of treatments available for other indications; hence investigation within these domains may result in pre-existing treatment options for the BD-alcohol comorbidity. Furthermore they are both systems that can be probed clinically via electroencephalography (EEG) and magnetic resonance imaging (MRI). Through a number of studies we have investigated the neurobiology associated with alcohol use in BD using these measures (Chitty et al, 2014a; Chitty *et al*, 2013a; 2014b; Chitty *et al*., 2015a; 2015b).

In this current review, we summarise our findings in the context of the broader literature. Collectively, our findings have led us to consider two key propositions: 1. Pathophysiological impairments in NMDA receptor functioning in BD contribute to susceptibility toward developing problems with alcohol use. As such, agents that target the NMDA receptor may show treatment efficacy, and 2. Alcohol aggravates BD neuroprogression predominantly through oxidative stress pathways (either directly or indirectly), as a result of its allostatic load on other neural systems. Pharmacological implications for both propositions are discussed highlighting the potential firstly, for memantine as an adjunctive pharmacotherapy for both treatment of BD and reduction of alcohol use and secondly, N-acetly-cysteine (NAC) as an add-on therapy for reducing the neural sequela of alcohol use in BD. Finally, we tie the propositions together in order to formulate the beginnings of a neurobiological model for the BD-alcohol comorbidity.

2.0 Proposition 1: Pathophysiological impairments in NMDA receptor functioning in BD contribute to susceptibility toward developing problems with alcohol use. As such, agents that target the NMDA receptor may show treatment efficacy

2.1. Introduction to the NMDA receptor

The NMDA receptor (see Figure 1) is one of three ionotropic glutamate receptors in the central nervous system (CNS), along with AMPA (α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate receptors. The NMDA receptor is a target of much neuroscience and psychiatric research owing to its central role many CNS functions, including brain plasticity.

The molecular composition of NMDA receptors is diverse, a consequence of a number of possible subunit compositions that vary across brain regions and developmental stages and exhibit distinct permeation and gating properties (Paoletti *et al*, 2013). Each receptor is composed of a tetrameric combination of a possible 7 subunits: GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A and GluN3B. Each receptor contains an obligatory glycine-binding GluN1 subunit, of which binding of glycine or D-serine is required for NMDA receptor activation by glutamate. Under baseline conditions, the NMDA receptor channel is blocked by magnesium and when the membrane depolarizes as a result of glutamate binding the magnesium is displaced allowing Ca^{2+} to enter the neuron. Hyper-excitability of the NMDA receptor is neurotoxic, hence tight regulation of channel opening is mediated by multiple regulatory sites are embedded within the ionophore. Binding at these sites allows either positive or negative allosteric modulation, which is again specific to the subunit composition of the receptor (Paoletti et al, 2013).

Synaptic plasticity of NMDA receptors occurs via NMDA receptor mediated long-term potentiation (LTP) and long-term depression (LTD), which are induced after an increase in synaptic activity (as a result of a post-synaptic rise in Ca^{2+}) following a brief and intense stimulus. These sustained changes in NMDA receptor components are responsible for altered regulation of the neuron. This profound mediation of brain plasticity underlies the role of the NMDA receptor in higher order cognitive functions, particularly learning and memory (Paoletti et al, 2013; Woodward, 2000).

Next, we describe the NMDA receptor system in BD and alcohol use, separately; followed by the potential intersection of the NMDA with the comorbidity.

2.1.1 Bipolar disorder and NMDA receptors

The role of NMDA receptors in the pathophysiology of BD is receiving increased attention and has been described in depth previously (Ghasemi et al, 2014; Sanacora et al, 2008). There have been several investigations that have revealed abnormalities in NMDA receptor expression, binding and functioning in BD. Many of these abnormalities have been detected in the temporal region, with hippocampal decreases in GluN1 mRNA (Law and Deakin, 2001), decreased transcript expression of GluN1 and GluN2A in the hippocampus (McCullumsmith et al, 2007), GluN1 and GluN2B in the perirhinal cortex (Beneyto et al, 2007), and hippocampal reductions in open NMDA receptor ion channels (Beneyto et al, 2007; Scarr et al, 2003). Cumulatively these results suggest a reduction in the total number of NMDA receptors in this region and accordingly, decreases in GluN1 binding in the superior temporal cortex has been found (Nudmamud-Thanoi and Reynolds, 2004). Though conversely, increased binding at the glycine site of the NMDA receptor was shown in the hippocampus of BD indicating an increase in the number of NMDA-receptor containing glycine-binding sites in this region (Beneyto et al, 2007).

In the prefrontal cortex decreased density of interneurons that express the NMDA GluN2A subunit has been found in BD (Woo *et al*, 2004), as well as a decrease in mRNA expression of GluN1 (Beneyto and Meador-Woodruff, 2008; Rao et al, 2010) and GluN3 (Rao et al, 2010), with no changes in GluN2B or GluN2D (Beneyto et al, 2008). Despite this decrease, changes in NMDA receptor binding were not evident leading authors to suggest that while there is no change in total receptor number, the stoichiometry of these receptors is abnormal (Beneyto et al, 2008). It is noteworthy that these post-mortem findings seem to be specific to NMDA receptors, with no corresponding abnormalities found in AMPA or kainate receptors (Beneyto et al, 2007; Scarr et al, 2003). Given this evidence, especially with regards to the GluN1 receptor, it is not surprising that linkage disequilibrium between the gene coding for GluN1 (GRIN1) has been found in BD, suggesting that this may confer susceptibility to the disorder (Mundo *et al*, 2003). Additionally, abnormalities in the neurometabolites involved in the regulation and modulation of the NMDA receptor have been reported. Perhaps the most convincing evidence implicating NMDA receptors in BD pathophysiology is the treatment success of NMDA receptor antagonists. For example, memantine and ketamine (which are reviewed in more detail in section 2.3), amantadine, D-cycloserine, magnesium and zinc have all shown therapeutic action in BD, and in many cases have shown efficacy in treatment resistant patients (for review see Ghasemi et al, 2014).

2.1.2 Alcohol and NMDA receptors

The NMDA receptor is a high affinity target for both the acute and chronic actions of alcohol in the brain and has therefore been proposed as a critical mediator of vulnerability toward alcohol use disorders (Krystal et al, 2003c). Evidence of this relationship originated from a patch-clamping experiment showing that ethanol

decreased NMDA receptor current flow in the hippocampus, and this decrease was proportional to the dose and the potency of the ethanol used (Lovinger et al, 1989). Collective research since then suggests that ethanol acts to inhibit the NMDA receptor by decreasing the frequency and duration of the opening time for the channel, rather than competitive action at agonist binding sites (Ren *et al*, 2012; Woodward, 2000). There does not appear to be a specific site on the receptor where ethanol exerts this action but rather a number of various residues arising from a combination of transmembrane domains (Smothers and Woodward, 2006) predominantly located within GluN1 (Ronald *et al*, 2001; Smothers et al, 2006) and GluN2 (Honse *et al*, 2004; Ren et al, 2012) subunits (see Figure 1). As such differing subunit compositions of NMDA receptors mediate differences in ethanol sensitivity from receptor to receptor (Woodward, 2000).

Chronic blockade of the NMDA receptor by ethanol as a result of continuous heavy drinking leads to compensatory up-regulation of NMDA receptor activity (Krystal et al, 2003c). The result of which is reduced sensitivity to ethanol that is believed to contribute to alcohol tolerance (Krystal et al, 2003c). This is evidenced by post-mortem studies of people with alcohol dependence that found an increased binding capacity of NMDA receptors in cortical tissue (Freund and Anderson, 1996), suggesting that a greater amount of alcohol is required to elicit the same effect. Notably, the same study found no differences in binding capacity at AMPA and kainite receptors between groups, highlighting the specificity of these effects (Freund et al, 1996).

The NMDA receptor system is also implicated in state and trait behavioural effects of alcohol. Acutely, ethanol's blockade of the NMDA receptor, and the corresponding inhibition of LTP, is believed to contribute to the cognitive effects associated with

intoxication, such as alcohol-induced blackout and amnesia (Ryabinin, 1998; Woodward, 2000). Furthermore, there is compelling evidence implicating the NMDA receptor in dampened subjective effects of alcohol which are associated with increased vulnerability to developing drinking problems (Krystal *et al*, 2003a; Krystal et al, 2003c). This has been demonstrated in studies of FHP individuals showing increased tolerance (or reduced sensitivity) to NMDA receptor antagonism compared with FHN individuals. For example, one study that found that the otherwise strong dysphoric effects of intravenous ketamine (non-competitive NMDA receptor antagonist) in individuals with FHP were significantly "blunted" compared to FHN (Petrakis *et al*, 2004). Likewise, FHP individuals also show reduced sensitivity to the inhibitory effects of memantine (uncompetitive NMDA receptor antagonist) on fMRI activity (Jamadar *et al*, 2012) and in an EEG study differential effects in event-related oscillations between FHP and FHN were found after a dose of memantine (Narayanan *et al*, 2013). Specifically, less marked decreases in theta activity and increased alpha activity in FHP during P300 trials were found with authors concluding this provides further evidence that NMDA receptor regulation is distinct between groups.

2.2 Investigations leading to proposition 1

We believe the evidence described above supports the hypothesis that people with BD (or those who go on to develop BD) are susceptible to alcohol misuse due to pathophysiological impairments in the NMDA receptor. This proposition is reinforced by preliminary evidence from our lab, whereby an electrophysiological marker for NMDA receptor functioning (described below) has been utilized to investigate this intersection.

2.2.1 Mismatch negativity

Mismatch negativity (MMN) is an event-related potential (ERP) elicited

automatically around 200ms after a deviant stimulus is presented within a set of standard stimuli. There are two identified intracranial processes that contribute to the generation of MMN, a temporal component and a frontal component (Naatanen et al, 2007). MMN has been extensively used as a model in psychopharmacology (Kenemans and Kahkonen, 2011), in part due to its reliable and replicable modulation by the NMDA receptor system (Garrido *et al*, 2009). Studies with NMDA receptor antagonists have shown that signaling through the NMDA receptor is necessary for MMN elicitation (Javitt *et al*, 1995; Javitt *et al*, 1996), and therefore this ERP is considered a robust marker for detecting NMDA receptor disturbances (Javitt *et al*, 2011). Cognitively, MMN is thought to index the formation of memory and cortical plasticity (Baldeweg and Hirsch, 2014), both of which are neural processes reliant on intact NMDA receptor functioning (Bennett, 2000; Woodward, 2000). MMN "impairments" are predominantly viewed as decreased electrophysiological amplitudes compared with a healthy control group, though increased MMN amplitudes and/or lengthened MMN latencies, have also been found in various populations and are thought to reflect a hyper-excitatory state.

2.2.1.1 Mismatch negativity, bipolar disorder and alcohol

Within the psychiatric literature, MMN impairments were largely believed to be specific to schizophrenia (Umbricht et al, 2003; Umbricht and Krljes, 2005), especially given that initial experiments in BD samples found no significant differences in MMN when compared to controls (Catts *et al*, 1995; Hall *et al*, 2007; Umbricht et al, 2003). However, recent evidence suggests that MMN impairments also exist in BD (Andersson *et al*, 2008; Jahshan *et al*, 2012; Kaur *et al*, 2012; Shimano *et al*, 2014), which was corroborated by our meta-analysis of the seven available studies suggesting that overall, frontal MMN amplitude is moderately

impaired in BD (Chitty *et al*, 2013b). It is noteworthy however, that the calculated effect size was considerably smaller than that reported in a schizophrenia MMN meta-analysis (Umbricht et al, 2005), which may suggest that the impairments in BD are not as pronounced, or may reflect the substantially lower number of available studies in BD.

MMN has been used as a tool to study the effects of alcohol, in both rodents and humans (Ahveninen *et al*, 2000a; Strelnikov, 2007), with findings that have accurately reflected the known action of alcohol on the NMDA receptor. Acutely, alcohol has been shown to decrease MMN amplitude (He *et al*, 2013; Jaaskelainen *et al*, 1995a; Jaaskelainen *et al*, 1995b; Jaaskelainen *et al*, 1996; Kenemans *et al*, 2010), supporting the notion that alcohol elicits a blockade of the NMDA receptor (Lovinger et al, 1989). Additionally, increased MMN amplitudes have been found in alcohol dependent patients (Ahveninen *et al*, 2000b) supporting the upregulation of NMDA receptor functioning as a result of continued alcohol use (Krystal *et al*, 2003b). Further, increased MMN amplitudes have been reported in those at-risk for developing alcohol dependence (Zhang *et al*, 2001) or risky alcohol use (Chitty et al, 2015b). These latter findings appear to support the role of the NMDA receptor in vulnerability toward heavy drinking, with a higher MMN representing a higher NMDA receptor output, suggesting a higher dose of alcohol would be necessary to achieve NMDA blockade and subsequent intoxication. However, not all MMN findings align with the NMDA-alcohol model, with some studies finding no differences in MMN between individuals with alcohol dependence and controls (Fein *et al*, 2004a; Fein *et al*, 2004b; Marco-Pallares *et al*, 2007).

There has been a paucity of research specifically linking the MMN impairments observed in the context of alcohol misuse and in psychiatric populations (in particular, those with a known propensity toward alcohol use disorders). This is an important line of enquiry for preventative research, and one that we sought to investigate in youth with BD.

2.2.1.2 Using mismatch negativity to investigate NMDA receptor disturbances in the comorbidity

In our cross-sectional study we found that both risky drinking status and diagnosis of BD were both significant predictors of impaired temporal MMN (Chitty et al, 2014a). Such findings suggest that risky drinking (as opposed to alcohol dependence) is associated with reduced at the NMDA receptor output (as reflected by a reduced MMN) and this is compounded in those with a diagnosis of BD. Given this was a cross-sectional study it is unclear whether these MMN effects were a result of alcohol use, for example the direct effects of alcohol on the NMDA receptor further perturb existing disturbances at this receptor in BD, or that instead of being a result of the high risk drinking impaired MMN may be a biomarker for increased propensity to risky alcohol use. If the former were the case, a valid hypothesis would be that if risky drinking patterns were continued in this BD sample, the continued antagonistic actions on the NMDA receptor system would be compensated for. More specifically, the NMDA receptor activity is increased to compensate for substantial and frequent blockade (as demonstrated in alcohol dependence) (Krystal et al, 2003a). Accordingly this was observed when we followed up the same BD participants approximately 18 months later, with an increase in drinking over time associated with an *increase* in frontal MMN (Chitty et al, 2015b). However, the opposite effect was found in

temporal MMN, namely that an increase in drinking over time corresponded with a *decrease* in temporal MMN.

There are different theories as to why these MMN components could be exhibiting differential effects. Spatially, of course, frontal and temporal MMN are distinct, which may suggest that impaired regulation of NMDA receptors in BD is specific to temporal regions. Given the poor spatial resolution associated with MMN, the exact brain regions corresponding to frontal and temporal generators are unclear. However, there is evidence to suggest that frontal MMN is derived from dorsolateral prefrontal cortex (Alho *et al*, 1994), while the hippocampus has been proposed as a potential source of the temporal MMN component (Ruusuvirta *et al*, 2013). Furthermore, in our studies we have found that temporal MMN amplitudes in controls are negatively associated with *in vivo* levels of GSH (Chitty *et al*, 2014c) and positively associated with *in vivo* glutamate (Chitty et al., 2015c) in the hippocampus.

Another theory as to why we see contradictory effects in frontal and temporal MMN may be reflective of different effects of alcohol in different parts of the brain and the differential NMDA receptor densities and subunit compositions between regions (Woodward, 2000). For example, a recent study has shown a hippocampal specific increase in expression of GluN1, GluN2A, GluN2C and GluN2D receptor subunit mRNA in post mortem brains of people with alcohol dependence compared to healthy controls (Jin *et al*, 2014). Importantly these altered expressions were not observed in the orbitofrontal or prefrontal cortex, suggesting that the distinct domains may be differentially affected by chronic alcohol use. This theory may be especially relevant with regards to BD in light of the substantial hippocampal-specific NMDA subunit abnormalities that were noted earlier in this review (see section 2.1.1).

There is only one study to our knowledge that has investigated the relationship between different NMDA receptor subunits and MMN generation, with a reported association between frontal MMN and a gene that codes for the GluN3B subunit (GRIN3B) (Lin *et al*, 2014). The authors suggested that GluN1/GluN2 and GluN1/GluN3 NMDA receptors might interact in the generation of frontal MMN. The sensitivity of GluN3 subunits to alcohol are not extensively researched and early reports have contradicting findings for (Jin *et al*, 2008) and against (Smothers and Woodward, 2003). At this point there is not enough information available to disentangle the specific NMDA receptor subunits responsible for different MMN effects, but this information highlights the potential for different receptor stoichiometry's to influence MMN.

The differential effects of alcohol on MMN subcomponents can also be explained via cognitive differences between the subcomponents, as described previously by Jaaskelainen and colleagues (1996). Temporal MMN is hypothesized to reflect the detection of the deviant from the sensory-memory trace (Naatanen *et al*, 1978), the formation of which presumably reliant on memory processes such as LTP- which as mentioned early in this review (see section 2.1), is a neural phenomenon heavily reliant on NMDA functioning (Woodward, 2000). Hence alcohol-induced impairments in temporal MMN may be related to its inhibition of LTP and subsequent impact on memory (Ryabinin, 1998). Frontal MMN on the other hand is thought to reflect the involuntary attention-switch that occurs after detection of the deviant (Giard *et al*, 1990; Jaaskelainen et al, 1996; Naatanen et al, 2007). Accordingly, it has been suggested that the effect of alcohol on frontal MMN is primarily associated with attention difficulties (Jaaskelainen et al., 1996).

2.3 Pharmacological implications from proposition 1

Given the evidence presented above, it is not surprising that agents which target the NMDA receptor have shown promise in treating both BD and alcohol use disorders. To our knowledge however, there have not been any randomized controlled trials evaluating these agents in the treatment of comorbid BD and alcohol use. However, there is preliminary evidence showing agents targeting the glutamatergic system such as acamprosate (Tolliver *et al*, 2012) and valproate (Salloum *et al*, 2005) are efficacious in treating the comorbidity. Here we will focus on NMDA receptor antagonists, memantine and ketamine, that have shown some promise in treating both BD and alcohol.

2.3.1 Memantine

Memantine is a well-tolerated, uncompetitive, moderate-affinity, NMDA receptor antagonist approved for the treatment of Alzheimer's Disease (Rammes *et al*, 2008). Though limited to naturalistic, case and open label studies there is preliminary evidence for memantine as an effective add-on mood-stabilising treatment for treatment-resistant BD patients ((Koukopoulos *et al*, 2012; Lee *et al*, 2014; Serra *et al*, 2015), and pilot data has revealed it may be an effective monotherapy comparable to gold-standard BD treatments, lithium and valproate (Keck *et al*., 2009) Randomised clinical trialing of memantine for BD treatment are underway (Serra *et al*., 2014) and results are eagerly awaited. Memantine has also shown promise in treating symptoms of alcohol withdrawal (Krupitsky *et al*, 2007b) and in reducing alcohol craving despite inducing mild subjective effects (Bisaga and Evans, 2004; Krupitsky *et al*, 2007a).

Given our MMN findings of potential alcohol-induced effects at the NMDA receptor system being heightened in BD, memantine may be efficacious as an add-on therapy for BD patients with alcohol problems, or those identified as at risk of developing alcohol problems. Thus, memantine may help to reduce problematic drinking whilst also treating the symptoms of BD. This appears to be an important avenue for future investigation, considering it is a safer and more viable treatment option than non-competitive, high-affinity NMDA receptor antagonist, ketamine. While ketamine has displayed rapid antidepressant effects in BD (Diazgranados *et al*, 2010; Zarate *et al*, 2012) and has demonstrated effective adjunctive therapy, along with benzodiazepine, in treating alcohol withdrawal (Wong *et al*, 2014), a recent meta-analysis has revealed controversial results (McGirr *et al*, 2015). When used as an augmentation agent for electroconvulsive therapy, effect sizes revealed that not only did ketamine show no clinical efficacy but was associated with enhanced adverse effects. Indeed it is the psychomimetic and cognitive effects of this agent which precludes it from being used as a chronic treatment (Sanacora *et al*, 2008). Though, an important finding in line with the NMDA receptor as a potential treatment target for the BD-alcohol comorbidity was that FHP patients with BD showed greater improvement in depressive symptoms after ketamine administration than FHN (Luckenbaugh *et al*, 2012). Hence, it may be that pathophysiology related to impaired NMDA receptors represents a subtype of BD and these patients are more prone to alcohol use disturbances, and accordingly, those who respond better to NMDA receptor agents. Furthermore, it may be that, like the findings in ketamine (Luckenbaugh et al, 2012; Niciu *et al*, 2014), memantine is especially efficacious in people with BD with comorbid alcohol use and/or FHP.

3.0 Proposition 2: Alcohol aggravates BD neuroprogression predominantly through oxidative stress pathways either directly, or indirectly as a result of its allostatic load on other neural systems.

Many of the deleterious outcomes associated with the BD-alcohol comorbidity are due to chronic aspects of the disorder that tend to arise as the illness progresses. Thus, BD has been proposed as a 'neuroprogressive illness' (Post, 2007), reflecting the sustained worsening of the course of the disorder in the absence of adequate treatment. This illness progression refers to symptom worsening, episode reoccurrence, cycle acceleration (i.e. shorter times between episodes) and the transition to spontaneous episodes (which may also have been precipitated by stressors in the early presentation) – all of which are also exacerbated by comorbid alcohol use (Carvalho *et al*, 2014; Cassidy *et al*, 2001; Finseth *et al*, 2014; Jaffee *et al*, 2009; Rakofsky et al, 2013; Uher *et al*, 2013). This collective evidence suggests that the misuse of alcohol may be "speeding up" the natural progress of the disorder, and as such, alcohol has been suggested as one of environmental factors that plays a key role in the aggravation of BD neuroprogression (Berk et al, 2011; Kapczinski *et al*, 2008).

Kapczinski et al., (2008) proposed that environmental factors may aggravate neuroprogression by inducing 'allostatic load', which in neurobiology, is the chronic reliance of physiological systems to compensate for environmental challenges and thereby causing cumulative damage (Kapczinski et al, 2008). In the context of alcohol, this may be related to the 'wear and tear' of neural compensatory upregulation of the NMDA receptor that occurs as a result of chronic alcohol use (see section 2.1.2). Alternatively, the direct effects of alcohol and its substrates on the

brain could also be identified as a source of aggravation, as a xenobiotic substance known to promote oxidative stress (Tsai et al, 1998; Zhong et al, 2012).

Recently, the BD model of neuroprogression has evolved to focus on the underlying neurobiology, more specifically, the notion that stage of BD illness is commonly associated with significant changes in neurobiological markers (Berk et al, 2011). Hence it has been suggested that investigating the potential neurobiological determinants of neuroprogression may provide opportunities to design treatments that modify or interrupt the course of the illness (Berk et al, 2011). Certainly this concept would extend to identifying the neurobiology of the BD-alcohol comorbidity, with the potential to dampen, cease or even reverse the effects of alcohol on the brain. An ideal neurobiological target for investigation is neural oxidative stress, as a system that is implicated in the effects of alcohol on the brain (Nordmann *et al*, 1990; Tsai et al, 1998; Zhong et al, 2012) and is a key target for research into BD neuroprogression (Berk et al, 2011).

3.1 Oxidative stress

Oxidative stress is a damaging endogenous consequence resulting from the balance of antioxidants and oxidants in the favour of the latter, that is, the buildup of reactive oxygen species (ROS) that cannot be adequately cleared. ROS are continuously generated via normal physiological processes as well as exogenic insults. To avoid oxidative damage caused by their production antioxidative processes exist to prevent ROS generation or at least reduce them to inactive substrates (Dringen, 2000). Without the antioxidant capacity to detoxify ROS, the ensuing oxidative stress causes cellular dysfunction and cell death (Berk et al, 2008b). Neural tissue is especially vulnerable to such stress due to its: (i) high consumption of oxygen and resultant production of ROS; (ii) easily oxidized substrates such as lipids with unsaturated fatty

acids; and (iii) relatively low activity of antioxidant defense molecules (Dringen, 2000; Halliwell, 1992; 2006).

Production of ROS and the resultant oxidative stress is believed to play a role in the pathophysiology of BD (Andreazza *et al*, 2008; Steckert *et al*, 2010). The most recent meta-analysis in the field identified a number of oxidative stress markers that were impaired in BD, suggesting an underlying abnormality in in oxidative energy generation (Brown *et al*, 2014). Evidence suggests that levels of oxidative stress are linked to mood episodes (Andreazza *et al*, 2007) and stage of illness (McGorry *et al*, 2014), supporting the potential role of oxidative stress in BD neuroprogression (Berk et al, 2011).

Ethanol has a demonstrated propensity to stimulate the formation of ROS and resultant oxidative stress in the brains of rats (Agar *et al*, 2003; Montoliu *et al*, 1994; Nordmann et al, 1990) and humans (Tsai et al, 1998). The mechanisms by which alcohol promotes oxidative stress in the brain are largely unknown, although it has been posited that they may be attributable to the production of ROS and lipid peroxidation associated with its metabolism (Tsai et al, 1998; Zhong et al, 2012). Oxidative stress and associated by-products are believed to play a key role in brain damage associated with alcohol dependence (Crews and Vetreno, 2014; Matsuda-Matsumoto et al, 2007).

3.1.1. Measuring oxidative stress via in vivo levels of glutathione

Glutathione (GSH) is the brain's primary antioxidant. It is a tripeptide (ϒ-L-glutamyl-L-cysteinylglycine) present in the brain in concentrations between 1 – 3mM, predominantly located within astrocytes (Dringen, 2000). GSH is synthesized intracellularly and is formed via the dipeptide combination of glutamate and cysteine,

which is then combined with glycine, with availability of cysteine being the rate-limiting step (Dringen, 2000). During acute states of oxidative stress, GSH reduces ROS and in the processes GSH is consumed and converted to its oxidized form: glutathione disulfide (GSSG) (Janaky *et al*, 1993). GSH also plays many other roles within the brain in order to maintain antioxidant defense, therefore a higher intracellular concentration of this metabolite is associated with increased cell protection against ROS-induced damage (Dringen, 2000).

Recent advances in proton magnetic resonance spectroscopy (^{1}H-MRS) have enabled the quantification of absolute GSH concentration in the brain (Chitty et al, 2013a; 2014b; Duffy *et al*, 2014; Godlewska *et al*, 2014; Lagopoulos *et al*, 2013). This provides a new avenue of research that allows *in vivo* probing of the oxidative stress system in regions throughout the brain, though there is conjecture about whether GSH levels are revealing state or trait characteristics of oxidative stress. If *in vivo* GSH is trait-related this would suggest GSH levels reflect anti-oxidant capacity, whereas if it is state-related this would suggest GSH levels reveal acute oxidative stress, or it could reflect both state and trait aspects. Either way, there is general consensus that reduced GSH is indicative of heightened oxidative stress either directly (as GSH has been utilized to reduce ROS and hence has been converted to its oxidized form, GSSG) or indirectly (as a pre-existing reduction in antioxidant capacity and subsequent buildup of ROS would result in increased vulnerability to oxidative injury (Janaky et al, 1993)).

As a general limitation of all ^{1}H-MRS research, it is impossible to determine the location within the synapse of the measured GSH. Though notably GSH is 1000 times more concentrated within the intra- compared to extra- cellular compartment (Dringen, 2000), so we can assume the spectroscopy signal reflects intracellular GSH

levels. That said, the amount of GSH released into the extracellular space (by astrocytes in response to oxidative stress) is suggested to be proportional to intracellular levels (Sagara *et al*, 1996). This is of relevance as extracellular GSH plays significant neuromodulatory roles (Oja *et al*, 2000).

3.2 Investigations leading to proposition 2

3.2.1 Glutathione, bipolar disorder and alcohol

We have attempted to investigate oxidative stress associated with alcohol use in BD by measuring *in vivo* GSH via ^{1}H-MRS in the anterior cingulate cortex (ACC) and hippocampus. We found that higher levels of drinking were associated with reduced GSH in both regions and this was specific to BD and not controls (Chitty et al, 2013a; 2014b). We concluded that this highlights that people with BD are be more susceptible to the oxidative effects of alcohol. Our longitudinal data demonstrates that patients who decreased their drinking after 18 months had an associated increase in GSH, which was supported by the regression model, showing that decrease in alcohol consumption was a significant predictor of increased GSH at follow-up (Chitty et al, 2015a). Importantly these findings suggest that the oxidative effects of alcohol in youth with BD are potentially reversible with a reduction in drinking.

It is noteworthy to mention that both cross-sectionally and longitudinally, our findings appeared to be compounded by tobacco use, which were not controlled for. Tobacco use has previously been found to exacerbate deficits noted in other neurometabolites investigated in alcohol ^{1}H-MRS studies (Meyerhoff *et al*, 2013). Due to the high comorbidity between drinking and smoking, the individual effects of alcohol and tobacco are unlikely to be reconciled using available technologies, but given they are both associated with worse illness outcomes in BD (Berk *et al*, 2008c; Goldstein *et al*,

2008) and production of ROS (Li and Wang, 2004; Zhang *et al*, 2007), a reasonable interpretation is that comorbid alcohol and tobacco use exhibit a greater, combined oxidative effect. It is unclear whether the compounded neurobiological effect of the alcohol-tobacco comorbidity is associated with a greater impact on neuroprogression of BD nonetheless it would be logical to speculate that it does.

We interpreted the GSH findings in this set of ^{1}H-MRS studies as reflecting the direct effects of both alcohol and tobacco on neural oxidative stress in BD, and more specifically, that these substances (via production of ROS) contribute to a heightened consumption of GSH (indexed by significantly lower levels in risky drinkers). Longitudinally we found that changes in GSH were associated with changing alcohol patterns and we proposed that a reduction in the use of these substances results in improved antioxidant capacity (indexed by increased GSH, which is then available to combat oxidative stress).

Together these findings support Proposition 2 - that alcohol (and tobacco) contributes to oxidative stress implicated in BD neuroprogression.

3.2.2 Indirect effects of oxidative stress – the allostatic load of alcohol

While alcohol can, and likely does, directly impact *in vivo* GSH levels and NMDA receptor functioning, there is substantial evidence that these two systems are involved in the regulation of the other (despite the effects of substances such as alcohol). Hence it is possible that a breakdown in one system would have a flow on effect due to its role in the compensatory regulation of the other system. Here we will discuss the evidence of links between these two systems, and then a new proposal related to the effect of alcohol. Of course there are a host of other systems that would also be

impacted as a result of impairments in either the NMDA receptor or GSH system, a discussion of which is beyond the scope of this review.

NMDA receptors are highly redox sensitive (Steullet *et al*, 2006), and fluctuate between a fully oxidized and a fully reduced state. Reducing agents (i.e. GSH) prevent the oxidization of these sites, thereby enhancing the frequency of channel opening (Woodward, 2000) whereas oxidization of these sites diminishes receptor function (Sucher and Lipton, 1991). Of note, both GSH and GSSG have been found to interact with the extracellular redox-sensitive sites of the NMDA receptor to mediate this oxidative balance (Woodward, 2000). GSH can also facilitate NMDA receptor functioning by preventing oxidation of thiol groups and breaking disulphide bonds, which exist within the ionophore, allowing an increased influx of calcium (Janaky et al, 1993).

In addition, GSH can affect NMDA receptor function via non-redox mechanisms (Oja et al, 2000; Steullet et al, 2006). The neuromodulatory role of GSH in NMDA receptor activity is proposed to have a biphasic effect, depending on its concentration (Oja et al, 2000; Varga *et al*, 1997). For example, GSH can enhance the NMDA receptor response to glutamate binding (Kohr *et al*, 1994) but it has also been found to act as an antagonist of glutamate-induced calcium influx by displacing glutamate from its binding site (Janaky et al, 1993).

Conversely, action at the NMDA receptors can also have an effect on oxidative stress. Excess glutamate activation of the NMDA receptor leads to sustained influx of calcium, which results in excitotoxicity. Oxidative products are formed during this process, including ROS and nitric oxide, which if inadequately compensated for result in oxidative stress and cell death (Gunasekar *et al*, 1995). GSH also protects neurons

against glutamate-induced hyper-excitability and neurotoxicity (Levy *et al*, 1991). Oja and colleagues (2000) argue that the overall cumulative evidence for the GSH and NMDA receptor interaction is supported by evidence that GSH primarily acts as an NMDA receptor antagonist, corresponding to its neuroprotective role in NMDA-mediated neurotoxicity (Levy et al, 1991; Oja et al, 2000).

It has been hypothesised that deficits in brain GSH could be a causal factor for the impaired NMDA receptor observed in schizophrenia (Steullet et al, 2006). Investigation into field excitatory postsynaptic potentials in rat hippocampal slices found that a 40% induced GSH deficit was associated with a reduction in NMDA receptor activity, the authors concluded this was likely due to excessive oxidization of the extracellular redox sensitive sites on the receptor (Steullet et al, 2006). It is difficult to compare findings in humans, without pharmacologically inducing pronounced GSH deficits and using an indirect measure of NMDA receptor functioning such as MMN. However, when attempting to look at the relationship between ^{1}H-MRS GSH levels and MMN we found a negative association in controls (Chitty et al, 2014c), which can be interpreted in line with the hypothesis that GSH has a neuromodulatory role in NMDA receptor functioning (Oja et al, 2000). While we did not find the same relationship in patients with BD, there were no differences in GSH concentrations between patients and controls. This suggests that in our clinical sample (at early stages of illness) oxidative stress is not immediately apparent but that regulation of an oxidative stress marker may be impaired, which may lead to future oxidative stress.

Similarly, correlations between MMN and plasma levels of GSH have been found in controls, but not in schizophrenia (Ballesteros *et al*, 2013). In an editorial based on the results of the latter study, Harms et al (2013) proposed these findings suggest that the

MMN impairments seen in schizophrenia are removed from those associated with oxidative stress (Harms and Michie, 2013). We propose an alternative explanation in line with our proposition, which is that in clinical samples the deregulated relationship between GSH and NMDA suggests that impairments in either system are not being adequately compensated for by the other, hence no correlation between the two. The reader should be warned however, that there are many limitations to this type of analysis (correlating an electrophysiological measure with an unknown source location to a precise voxel GSH concentration or serum levels). For example, it is possible no relationship was found in our study due to the effects of psychotropic medications in the sample of patients with BD (Chitty et al, 2014c).

While we did not investigate these relationships with respect to alcohol, it provides a potential pathway by which alcohol induces more chronic effects on either system in BD compared to controls. For example, the lack of association between MMN and in vivo GSH (even if deregulated due to the influence of psychotropic medications), suggests the effects of alcohol on either system may not be adequately compensated for leading to a compounded effect on each system compared to controls - as reflected in all our studies (Chitty et al, 2014a; Chitty et al, 2013a; 2014b).

The noted relationships between the NMDA receptor and GSH support the notion that alcohol may be contributing to neuroprogression not only through its direct oxidative effects but also via the allostatic load placed on the NMDA receptor system, which then may contribute further to oxidative stress. This idea aligns with a proposal by Post (2007), that more severe illness in BD may be due to gradual dissipation of endogenous compensatory mechanisms that would normally reduce the impact of CNS insult (Berk et al, 2011; Post, 2007). Indeed the stage-dependent changes in

oxidative stress markers in BD are hypothesized to form part of the progressive failure of compensatory mechanisms over time (McGorry et al, 2014).

3.3 Pharmacological implications from proposition 2: Neuroprotection

Given the evidence supporting a role of oxidative stress in psychiatric disorders it is not surprising that GSH augmentation has been suggested as a novel treatment target (Berk et al, 2008b). It is important to re-state here, that in our follow-up study an increase of GSH was found with a decrease in drinking and smoking in BD (Chitty et al, 2015a), suggesting that in the context of the BD-alcohol comorbidity the first line treatment in reducing oxidative stress should be to reduce alcohol consumption and tobacco use.

Pharmacologically, GSH augmentation can be achieved through administration of N-acetyl cysteine (NAC) (Arakawa and Ito, 2007). NAC is a membrane-permeable cysteine precursor, which is rapidly absorbed via oral administration and is then hydrolyzed to release cysteine, the limiting precursor in GSH synthesis (Arakawa et al, 2007). GSH augmentation provides a defense against ROS and has also been found to affect the NMDA receptor, through a release of the oxidative state of the NMDA receptor (as described in section 3.2.2) (Berk *et al*, 2013). Accordingly, NAC administration has been associated with an improved MMN in schizophrenia (Lavoie *et al*, 2008).

NAC as an add-on therapy has shown therapeutic effects on depression in BD, as evidenced by a randomized controlled trial (Berk *et al*, 2008a), with preliminary evidence that it can also improve manic symptoms and functional outcomes (Magalhaes *et al*, 2011a; b) and suicidal ideation (Waterdrinker *et al*, 2015). There have also been studies investigating NAC as a novel treatment for several addictive

disorders (Berk et al, 2013). To our knowledge however, only one study has investigated its affects in alcohol, showing that NAC reduces ethanol-induced oxidative damage in the rat brain (Varma *et al*, 2004). While NAC may not be able to decrease the use of alcohol, it has promise in reducing the oxidative stress associated with alcohol – which may interrupt neuroprogression. Theoretically however, there is potential for GSH augmentation to reduce alcohol use by acting as an antagonist at the NMDA receptor (Oja et al, 2000), which may then reduce alcohol tolerance (Krystal et al, 2003c).

There have been other agents, already approved for the treatment of BD, that have also been shown to be neuroprotective against oxidative stress (Berk et al, 2008b; Cui *et al*, 2007). Lithium, valproate, lamotrigine and carbamazepine have been shown to increase GSH levels in cultured rat cerebral cells, leading authors to suggest that augmentation of GSH may contribute to the therapeutics of mood stabilizing drugs (Cui et al, 2007). Again these agents have not been shown to reduce the amount of alcohol consumed. Nevertheless these may be good treatment options for risky drinking patients with BD, to reduce the effects of alcohol (along with alcohol-reducing interventions) whilst also providing mood stabilising properties to treat the symptoms of BD.

4.0 A neurobiological model of alcohol use in BD

We propose an empirically supported working model of the neurobiology of susceptibility and impact of alcohol use in BD (Figure 2). The model ties in propositions 1 and 2, and the wider literature discussed in this review. Briefly the model shows potential pathways that the NMDA receptor system confers susceptibility to developing alcohol use disorders and that alcohol mediates its effects

on BD neuroprogression predominantly through triggering oxidative stress pathways. Additionally there is the potential that these two pathways can compound the effects in the other (see Section 3.2.2).

Within this model there may be opportunity to select treatments that will modify or interrupt the high risk drinking, but also to reduce the neurobiological impact of drinking. Given the evidence provided we have proposed memantine as a potential compound for the former and NAC for the latter. Both may be extremely useful add-on therapies to consider in treating people with BD at risk of, or already exhibiting, alcohol use problems. These are both safe and efficacious treatments yet to be investigated in this context and if successful could dramatically reduce drinking and its neurobiological consequences in BD.

5.0 Limitations

There are a number of limitations to our model, and to the studies presented throughout this review. We have chosen to present these two pathways in the most simplistic form in order to represent how they could be attributed to the BD-alcohol comorbidity and its neural consequences. This is a working model and we do not wish to make claims of specificity. Clearly a number of other pathways would be affected and are also likely to contribute to the susceptibility and neural sequela of the comorbidity.

Our studies have several limitations, which we refer the reader to the individual papers (Chitty et al, 2014a; Chitty et al, 2013a; 2014b; c; 2015a; b). Briefly, as with most clinical psychiatry, our studies assess indirect measures of our neurobiological

lines of enquiry. Firstly, we utilize an ERP and then make assumptions about its ability to index the functioning of the NMDA receptor. While there is a wealth of evidence that implicates the NMDA receptor as the primary pharmacological correlate of MMN, there is also other compounds that have also been implicated in its generation (Garrido et al, 2009) of particular relevance to alcohol is the influence of gamma-amino butyric acid (GABA). Secondly, in terms of our oxidative stress measure, there is conjecture about what levels of GSH are actually revealing. For discussion of this we refer the reader to section 3.1.1.

There are also limitations to the model presented herein. Our studies are conducted in young people with BD aged between 16 and 30, and hence represent risky drinkers rather than people with alcohol dependence. While there are numerous strengths to looking at this age group, including the potential to recognize early risk factors and early intervention strategies, our results may not be generalizable in terms of the wider literature. This is because the large majority of previous research has been conducted in people with established diagnosis and/or established problems with drinking. It will be necessary to test the hypotheses surrounding oxidative stress and NMDA receptors in older age groups with more pronounced problems with alcohol. For the time being the model should be viewed as neurobiology associated with risky drinking patterns (such as abuse but not dependence).

6.0 Conclusion

Overall there is limited available evidence regarding the neurobiology underlying the susceptibility and consequences of alcohol use in BD. The current review along with our investigations (Chitty et al, 2013a; 2014a; b; 2015a; b) have aimed to address this gap, focusing on two well-documented neurobiological systems separately implicated

in the pathophysiology of BD and the neural effects of alcohol on the brain. Interpretation of our findings in light of review of the wider literature has introduced some important areas for consideration and future research.

Firstly, an extremely important link may be that increased oxidative stress is a consequence of the BD-alcohol comorbidity and implicated in the progressive worsening of the disorder (Berk et al, 2011). This may indicate that the negative effects associated with drinking in BD including the most devastating consequences such as suicide are associated with heightened neural oxidative stress – as has been previously proposed (Vargas *et al*, 2013). Hence this review supports the recent suggestions that antioxidative therapies are agents for serious consideration in psychiatry (Berk, 2012; Berk *et al*, 2010; Berk et al, 2008a; Berk et al, 2008b; Scapagnini *et al*, 2012).

Without supporting evidence from randomized controlled trials, the pharmacological recommendations presented here have limited relevance for current clinical practice, however, we hope that this review highlights to clinicians the importance of monitoring and reducing alcohol use in BD. The studies presented revealed an impaired neurobiology specifically associated with the comorbidity and the potential for this to be reversed with a reduction in drinking. Hence, educating young patients of the risks and implementing psychological strategies for tackling this potentially devastating comorbidity should be considered as a primary treatment focus.

Other take-home messages from this review include the considerations that MMN may be used as a tool to help predict those who are more susceptible to developing an alcohol use problems, and hence who may benefit more from NMDA receptor antagonists, such as memantine. If this avenue does prove fruitful, this will allow us

to better predict who will go on the develop problems with alcohol use, and therefore enable us to intervene early. Furthermore it will guide better treatment selection, as to which individual will respond better to certain treatments.

In conclusion, treatment, early intervention and prevention of alcohol use problems in BD are all areas that need to be improved. We propose a neurobiological model for the BD-alcohol comorbidity, though in its infancy, provides a basis for further investigation and testing pharmacological intervention.

Acknowledgements

The authors express their gratitude to all the people who participated in the studies that helped us to draw the conclusions for this paper. This study was funded by an NHMRC Australia Fellowship awarded to IBH (No. 464914). KC was supported by an Australian Postgraduate Award and DFH by a grant from the NSW Health, Mental Health and Drug & Alcohol Office. IBH is a Senior Principal Research Fellow of the Australian National Health & Medical Research Council (AppID 1046899). These funding agencies had no role in the analysis or interpretation of these data; or in the writing of this report; or the decision to submit the paper for publication.

Contributors

KC put conception of the article forth and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

IBH is the executive director of the Brain and Mind Research Institute (BMRI), at the University of Sydney, which operates two early-intervention youth services under contract to headspace. He is a commissioner of the Australian National Mental Health commission and was previously the CEO of beyondblue: the national depression initiative and a director of headspace: the national youth mental health foundation until January 2012. Previously, he has led a range of community-based and pharmaceutical industry-supported depression awareness and education and training programs. He has led depression and other mental health research service

evaluation or investigator-initiated research projects that have been supported by a variety of pharmaceutical partners. Current investigator-initiated studies are supported by Servier (manufacturers of agomelatine) and Pfizer. He has received honoraria for his contributions to professional educational seminars related to depression, youth mental health and circadian-rhythms research. He has received travel support from Servier to attend scientific meetings related specifically to circadian-rhythm disorders.

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Figure captions:

Fig 1: A schematic of the NMDA receptor within phospholipid postsynaptic membrane.

NMDA receptors are ligand-gated ion channels composed of a tetrameric combination of a possible 7 subunits: GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A and GluN3B, all receptor combinations contain an obligatory glycine-binding GluN1 subunit. Glycine or D-serine binding at GluN1 is required for NMDA receptor activation by glutamate, whose binding site is on GluN2 subunits. Under baseline conditions, the NMDA receptor channel is blocked by magnesium and when the membrane depolarizes as a result of glutamate binding the magnesium is displaced allowing calcium to influx the neuron. There does not appear to be a specific site on the receptor where ethanol exerts this action but rather a number of various residues arising from a combination of transmembrane domains predominantly located within GluN1 and GluN2 subunits. There does not appear to be a specific site on the receptor where ethanol exerts this action but rather a number of various residues arising from a combination of transmembrane domains predominantly located within GluN1 and GluN2 subunits.

Black ovals, *GluN1***; grey ovals**, *GluN2A***; A,** *Potential ethanol binding site.*

Ca^{2+}, calcium; COOH, carboxyl group; NH_2, amine group.

Figure 2: A neurobiological model for the bipolar disorder and alcohol comorbidity, focusing on the NMDA receptor and oxidative stress systems

A: The NMDA receptor is implicated in the pathophysiology of BD (Ghasemi et al., 2014). **B:** Oxidative stress is implicated in the pathophysiology of BD (Andreazza et al., 2008) **C:** BD is a neuroprogressive illness and oxidative stress is believed to contribute to the gradual worsening of the disorder over time (Post, 2007; Berk et al., 2011). **D:** The symptoms associated with BD neuroprogression and alcohol use in BD overlap, supporting the theory that alcohol acts an aggravator of neuroprogression (Kapczinski et al., 2008). **E:** Alcohol promotes production of ROS through a number of mechanisms (Tsai, 1998). **F:** The NMDA receptor is a high affinity target for both the acute and chronic actions of alcohol in the brain (Krystal et al., 2003c). Risky drinkers with BD have more impaired MMN than non-drinking peers and controls suggesting a compounded impairment at the NMDA receptor (Chitty et al., 2014). **G:** GSH is the major antioxidant in the brain. GSH reduces ROS and in the process is consumed (converted to its oxidized form) (Janaky et al., 1993). **H:** Oxidative stress arises when the balance of oxidants and antioxidants are in favour of the oxidants (e.g. when presence of ROS cannot be compensated for). Augmenting GSH may help to combat ROS formed from alcohol use and BD, and reduce associated oxidative stress. **I:** GSH can modulate the function of the NMDA receptor through both redox and non-redox mechanisms (Oja et al., 2000). **J:** Excessive activation of the NMDA receptor by glutamate results in an sustained influx of calcium causing excitotoxicity. ROS are one of the oxidative species formed during this process, and largely contribute to excitotoxicity-mediated cell death (Gunasekar et al., 1995). **K:** Impaired NMDA receptor functioning is believed to contribute the increased tolerance to alcohol, and hence increase susceptibility to drink heavily and develop problems with alcohol

(Krystal et al., 2003c). Agents which target the NMDA receptor system have shown to reduce alcohol use (Krupitsky et al., 2007). **L:** Proposition 1: It is the pathophysiological impairments in NMDA receptor functioning in BD are driving their increased susceptibility to risky drinking. **M:** Proposition 2: Alcohol aggravates BD neuroprogression predominantly through oxidative stress pathways. Note this could either be due to the promotion of ROS production due to alcohol use and resultant oxidative stress (E – G – H) or via allostatic load on the NMDA receptor which promotes production of ROS (F – J – G – H) or directly effects GSH levels (F – I – G – H). BD, bipolar disorder; GSH, glutathione; NMDA, N-methyl-D-aspartate; ROS, reactive oxygen species

Solid black lines, *established neurobiological pathways;* **solid grey lines,** *pathophysiological associations;* **grey dotted lines,** *associated symptoms/traits;* **black dotted lines**, *theoretical pathways (propositions 1 and 2);* **lightening bolts**, *potential pathways that can be pharmacologically modulated;* **grey boxes outlined in black dotted lines**, *neurobiological pathways associated with the BD-alcohol comorbidity*.

Figure 1

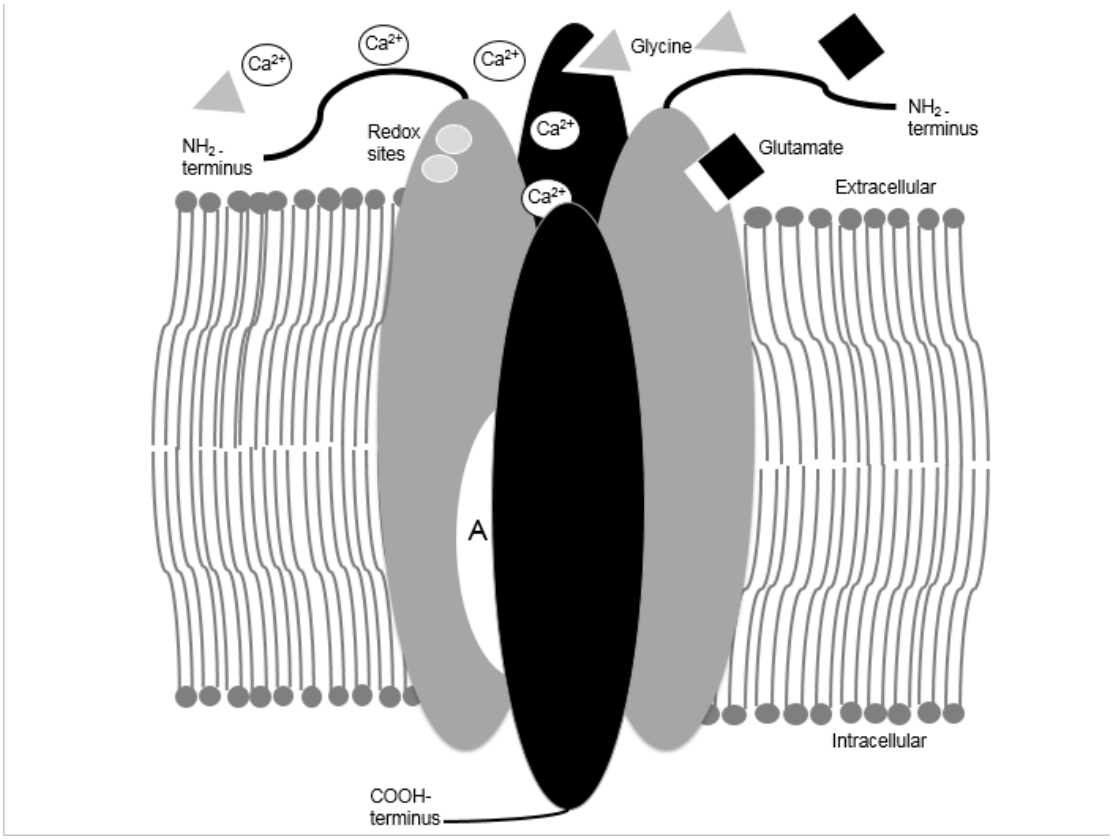
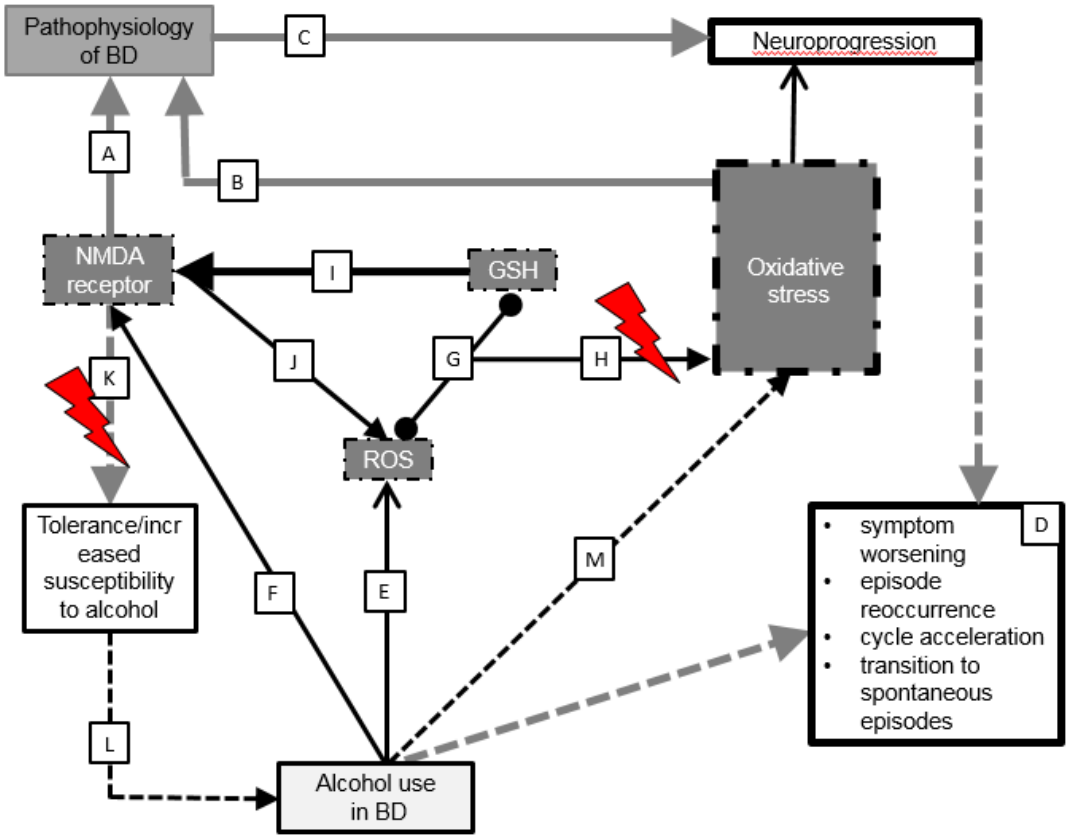

Ca2+
Ca2+
Ca2+
Glycine
NH2 - terminus
Redox sites
Ca2+
Glutamate
NH2 - terminus
Ca2+
Extracellular
A
Intracellular
COOH- terminus

Figure 2


Pathophysiology of BD
C
Neuroprogression
A
B
NMDA receptor
I
GSH
Oxidative stress
J
G
H
K
ROS
Tolerance/increased susceptibility to alcohol
F
E
M
D
• symptom worsening
• episode reoccurrence
• cycle acceleration
• transition to spontaneous episodes
L
Alcohol use in BD