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Neuroimaging markers of glutamatergic and GABAergic systems in drug addiction: relationships to resting-state functional connectivity

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Abstract

Drug addiction is characterized by widespread abnormalities in brain function and neurochemistry, including drug-associated effects on concentrations of the excitatory and inhibitory neurotransmitters glutamate and gamma-aminobutyric acid (GABA), respectively. In healthy individuals, these neurotransmitters drive the resting state, a default condition of brain function also disrupted in addiction. Here, our primary goal was to review *in vivo* magnetic resonance spectroscopy and positron emission tomography studies that examined markers of glutamate and GABA abnormalities in human drug addiction. Addicted individuals tended to show decreases in these markers compared with healthy controls, but findings also varied by individual characteristics (e.g., abstinence length). Interestingly, select corticolimbic brain regions showing glutamatergic and/or GABAergic abnormalities have been similarly implicated in resting-state functional connectivity deficits in drug addiction. Thus, our secondary goals were to provide a brief review of this resting-state literature, and an initial rationale for the hypothesis that abnormalities in glutamatergic and/or GABAergic neurotransmission may underlie resting-state functional deficits in drug addiction. In doing so, we suggest future research directions and possible treatment implications.

Keywords

Drug addiction; glutamate; GABA; neurochemistry; magnetic resonance spectroscopy; positron emission tomography; resting-state; fMRI

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Disclosure/Conflict of Interest

None declared.

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1. Introduction

Drug addiction is characterized by dysfunction in corticolimbic networks subserving attentional, emotional, and inhibitory processes (Goldstein and Volkow, 2011). Insights into these systems-level deficits have been primarily advanced through *in vivo*, non-invasive brain imaging methodologies, such as functional magnetic resonance imaging (fMRI). Increasingly, these methods are being used to examine resting-state functional connectivity (RSFC), a measure of intrinsic activity that provides information on network-level function and its disruption in neuropsychiatric disorders (Rosazza and Minati, 2011), including substance use disorders (Fedota and Stein, 2015; Lu and Stein, 2014; Sutherland et al., 2012) (for an overview of the resting state, see Box 1).

Although the neurochemical bases of RSFC differences between addicted individuals and healthy controls are presently unclear, evidence from studies of healthy research participants suggests important contributions of the excitatory and inhibitory neurotransmitters glutamate and gamma-aminobutyric acid (GABA), respectively, to the resting state. In particular, glutamate and GABA appear to drive the metabolic and neuronal mechanisms underlying the resting state to sustain the excitation-inhibition balance (Duncan et al., 2014). Indeed, resting-state metabolic activity of the brain is linearly coupled to its neuronal activity (Hyder et al., 2013), largely reflecting the actions of glutamatergic and GABAergic neurons (Hyder et al., 2006; Rothman et al., 2011). Several combined fMRI-magnetic resonance spectroscopy (MRS) studies have provided evidence supporting such relationships. For example, the higher the glutamate concentrations and the lower the GABA concentrations in the posterior cingulate cortex (PCC), the higher was the RSFC between PCC and pregenual anterior cingulate cortex (pACC) (Duncan et al., 2014; Hu et al., 2013; Kapogiannis et al., 2013). GABA concentrations, measured with MRS in the resting-state, were also negatively correlated with task-evoked fMRI activity in the pACC, visual cortex, and somatomotor cortex (Duncan et al., 2014). The relationship between resting-state glutamate level and task-related activity is less clear (Duncan et al., 2014), though it appears that glutamate mainly exerts transregional effects by acting on the long-range axons of pyramidal cells to enable cortico-cortical connections (whereas GABA and GABAergic interneurons mainly exert local effects by acting on pyramidal-cell dendrites to affect the regional processing of inputs). In support of this view are observations that glutamate mediates the transition from resting-state activity in one region (e.g., pACC or PCC) to stimulus-induced and resting-state activity in the same or different regions (Duncan et al., 2011; Duncan et al., 2013; Hu et al., 2013).

The goals of the current article were: primarily to review evidence that human drug addiction is marked by abnormalities in brain glutamate and GABA; and secondarily to use findings of this literature in combination with select RSFC findings to build toward an initial plausible neurochemical framework underlying RSFC deficits in drug addiction, emphasizing important roles for glutamate and GABA. In the primary section, we reviewed *in vivo* neurochemical imaging studies that tested for glutamatergic and GABAergic abnormalities in drug-addicted individuals as compared with healthy controls. The addictions considered were alcohol, nicotine/tobacco, opiates, cocaine, methamphetamine, and cannabis, each reviewed in turn. Imaging methods included magnetic resonance

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spectroscopy (MRS), which provides information on neurotransmitter or metabolite concentrations; and positron emission tomography (PET) and single proton emission computed tomography (SPECT). PET and SPECT are nuclear medicine procedures that use tracer kinetic modeling to provide indices of neurotransmitter receptor binding, including: binding potential (BP_{ND}), the product of receptor density and affinity; volume of distribution (V_T), the ratio at equilibrium of the sum of the concentrations of specifically bound, nonspecifically bound, and free radiotracer to that of parent radioligand in plasma, separated from radiometabolites; and distribution volume ratio (DVR), the volume of distribution normalized to nonspecific binding. Because abnormal activity of metabotropic glutamate receptors predisposes an individual to multiple disorders including addiction, the glutamate system has been assessed by PET with [^{11}C]ABP688, a radioligand for the metabotropic glutamate receptor subtype 5 (mGluR5) (Terbeck et al., 2015). In examining GABA neurotransmission, PET/SPECT studies have concentrated on the $GABA_A$ receptor, a Cl^- ion channel that produces fast electrical signals and directly controls the efficacy of GABAergic synaptic transmission (Luscher et al., 2011; Xu et al., 2014). These studies have primarily utilized three radiotracers: [^{11}C]flumazenil and [^{123}I]iomazenil, which bind to the benzodiazepine site on the $GABA_A$ receptor; and [^{11}C]Ro15 4513, which binds to the $GABA_A$ receptor alpha-5 subunit (Ravan et al., 2014). Signaling through $GABA_A$ receptors, particularly those containing an alpha-5 subunit, contributes to the reinforcing effects of alcohol in non-human animal studies (Cook et al., 2005; McKay et al., 2004; Stephens et al., 2005).

We stress from the outset that many interpretative difficulties emerge in reviewing this MRS and PET/SPECT literature, including multiple sources of variation between studies that can produce inconsistent findings. One notable difficulty is variation in participant characteristics. Participants often report the use of multiple drugs of abuse in varying amounts and at different times relative to testing, and their self-reports may contain inaccuracies; this difficulty is often accentuated in individuals addicted to illicit drugs, who regularly have more expansive drug use histories. For example, many drug abusers are also cigarette smokers, and smoking independently affects glutamate and other metabolites (below). Although most studies employ safeguards against effects of recent use (e.g., exclusionary urine toxicology), fine-grained information about participants' secondary drug use histories are not routinely provided; understandably, most studies concentrate on the primary substance of abuse. Other sources of participant variation could include psychiatric comorbidities and their treatments. Methodologically, sources of variation include the use of small sample sizes in some imaging studies, and differing and/or evolving sets of approaches and dependent variables. For example, MRS studies have measured glutamate signals in multiple ways [e.g., glutamate, glutamine, glutamate/glutamine, glutamine/glutamate, and/or glutamate+glutamine (Glx)]. In keeping with the glutamate-glutamine cycle [i.e., the conversion of glutamate to glutamine in astrocytes is catalyzed by glutamine synthetase, and, in turn, glutamine is reconverted into glutamate in neurons by glutaminase (e.g., Walls et al., 2015)], ratios reflecting increased glutamate and/or decreased glutamine both putatively indicate increased brain glutamate levels. Glutamate-related concentrations are sometimes further expressed as a ratio to creatine, often used as an internal reference metabolite (Licata and Renshaw, 2010). Given this heterogeneity of reporting, we attempted

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throughout to focus on effects from the perspective of glutamate or Glx. Such difficulties can also occur for GABA, although less so. Finally, it is possible that changes in the MRS glutamate/GABA resonance more immediately reflect changes in energy metabolism, and that changes in functional networks measurable by RSFC may stem more directly from such metabolic changes rather than from specific neurotransmission *per se*. This potential issue provides an important reason for including PET/SPECT studies that measured markers of glutamate and GABA neurotransmission. Taken together, even if these issues preclude full clarity regarding the directionality of effects at this time, our review of this literature serves to provide a macroscopic overview of the field and brings to light some inconsistencies that can be specifically addressed in future work.

In the second section of this article, we reviewed select RSFC studies of addiction that followed from, and were informed by, the primary section (and by neurochemical/RSFC studies in health, above). We did not intend for this section to exhaustive, nor did we describe each constituent study in complete depth and report every available analysis. Rather, we described representative RSFC findings in drug addiction, obtained using seed-based and data-driven methodologies, which examined connectivity differences between addicted individuals and healthy controls in select corticolimbic brain regions [e.g., ACC, medial prefrontal cortex (PFC), striatum, and insula]. We marshaled this RSFC evidence, as well as evidence from the primary MRS/PET section, to support a new neurochemical framework in which we hypothesize that glutamatergic and/or GABAergic deficits may underlie RSFC abnormalities in drug addiction. RSFC, then, may serve as an intermediate phenotype bridging neurochemical abnormalities and addiction-relevant behaviors (e.g., craving, drug-seeking, or engagement with treatment). We anticipate that this perspective can spearhead future hypothesis-driven research on this topic. In addition, an understanding of the neurochemical bases of the resting-state in drug addiction can also help advance the development of new therapeutics that target the relevant neurotransmitters and/or RSFC deficits.

2. Glutamatergic Alterations in Drug Addiction (Table 1)

2.1. Alcohol

2.1.1. MRS—Compared with controls, alcohol-addicted individuals had lower glutamate levels in the occipital cortex (Bagga et al., 2014) and ACC (Pennington et al., 2014) [at least among individuals who had achieved remission (Thoma et al., 2011)]. These lower occipital or ACC (into adjacent white matter) glutamate levels were correlated with greater drinking severity [e.g., more alcohol-related consequences (Thoma et al., 2011), loss of control over drinking (Ende et al., 2013)] or poorer neuropsychological functioning [e.g., more impaired visual-motor or attentional functioning (Bagga et al., 2014; Pennington et al., 2014)]. In contrast, other studies reported no differences between alcohol-addicted individuals and controls in glutamate or Glx in the cerebellar vermis (Seitz et al., 1999), dorsolateral PFC (DLPFC) (Nery et al., 2010), or dACC (Yeo et al., 2013). For the latter, somewhat surprisingly, higher Glx was correlated with more years of drinking (Yeo et al., 2013). Finally, earlier studies reported higher Glx in alcohol-addicted individuals compared with controls (e.g., in basal ganglia) (Jalan et al., 2000; Miese et al., 2006). However, it is

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important to note that in these latter studies, the samples of alcohol-addicted individuals were older than in most studies and were not medically healthy (presence of cirrhosis). Moreover, these latter studies examined Glx, which includes both glutamate and glutamine, and this difference also might have contributed to inconsistencies between studies.

Other MRS studies have examined the effects of short-term alcohol abstinence on glutamate concentrations. Multiple studies reported that, compared with healthy controls, short-term abstinent alcohol-addicted individuals exhibited *higher* glutamate levels in the ACC (Hermann et al., 2012b; Lee et al., 2007) and ventral striatum (Bauer et al., 2013). In these studies, higher ACC and/or striatal glutamate levels were also correlated with more alcohol craving (Bauer et al., 2013) and more recent (e.g., 1 month, 3 month) alcohol consumption (Hermann et al., 2012b; Lee et al., 2007), and with better memory retention (Lee et al., 2007). However, this view is complicated by other studies reporting that pACC concentrations of glutamate, which were initially lower in alcohol-addicted individuals (who were abstinent for approximately 1-day or 1-week) than healthy controls, returned to control levels over 2–5 weeks of abstinence (Hermann et al., 2012b; Mon et al., 2012). Higher glutamate levels were also correlated with more days of current abstinence (Mon et al., 2012).

2.1.2. PET/SPECT—No studies were found.

2.2 Smoking

2.2.1. MRS—An interesting recent study indicated that smokers had lower glutamate levels in the pACC and DLPFC than nonsmokers, and that such differences were accentuated with increasing age (Durazzo et al., 2015). Moreover, in the DLPFC, higher glutamate levels were correlated with better neuropsychological functioning, measured by a battery of tasks (Durazzo et al., 2015). Other studies did not report differences in glutamate levels between smokers and ex-smokers in either the hippocampus or ACC (Gallinat and Schubert, 2007), or in the thalamus (O'Neill et al., 2014). In the latter study, however, glutamate levels measured in smokers were negatively correlated with the frequency and duration of smoking (O'Neill et al., 2014), further supporting the idea that lower glutamate levels are associated with poorer outcomes (i.e., decreased functioning, increased use).

In examining effects of withdrawal, Glx levels were higher in the left dACC in smokers than in nonsmokers, but this effect did not emerge when the smokers were in withdrawal (Mennecke et al., 2014). Unlike Glx, which was lowered during withdrawal, glutamine in the insula was higher during withdrawal (Gutzeit et al., 2013).

2.2.2. PET/SPECT—In studies that used [^{11}C]ABP688 as a radioligand for mGluR5, both DVR and BP_{ND} in multiple limbic and PFC brain regions were lowest in current smokers, followed respectively by short-term ex-smokers, long-term ex-smokers, and controls (highest) (Akkus et al., 2013; Akkus et al., 2015).

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2.3. Opiates

2.3.1. MRS—Compared with controls, opiate-addicted individuals receiving methadone or buprenorphine maintenance therapy had lower dACC glutamate concentrations than controls (Verdejo-Garcia et al., 2013; Yücel et al., 2007) [but see (Greenwald et al., 2015)]. It is unclear to what extent this finding reflected a pre-existing condition or effects of the ongoing treatment. Concentrations of dACC glutamate were also positively correlated with the number of previous withdrawals (Hermann et al., 2012a).

2.3.2. PET/SPECT—No studies were found.

2.4. Cocaine

2.4.1. MRS—Compared with controls, chronic cocaine users had lower pACC glutamate levels (Yang et al., 2009). Other studies did not report MRS-measured group differences in glutamate in occipital cortex, pACC, DLPFC, or striatum (Chang et al., 1997; Hulka et al., 2014a; Martinez et al., 2014), although lower pACC glutamate measures were correlated with higher frequency of cocaine use (Hulka et al., 2014a) but also (again somewhat surprisingly) fewer years of cocaine use (Chang et al., 1997; Yang et al., 2009).

2.4.2. PET/SPECT—Compared with controls, cocaine-addicted individuals showed lower striatal BP_{ND} for [^{11}C]ABP688, consistent with lower mGluR5 glutamate receptor availability (Martinez et al., 2014; Milella et al., 2014). Other regions showing lower BP_{ND} for [^{11}C]ABP688 in cocaine-addicted individuals compared with controls included the amygdala and insula, and lower BP_{ND} in these regions was correlated with more days of abstinence (though still within a withdrawal period) (Milella et al., 2014).

2.5. Methamphetamine

2.5.1. MRS—Methamphetamine-addicted individuals had lower glutamate concentrations in the pACC/dorsomedial PFC compared with healthy controls and even with non-stimulant-using, psychotic patients (Crocker et al., 2014). Similar results were observed for Glx levels in the PCC, precuneus, and right inferior frontal cortex (O'Neill et al., 2015), but not glutamate levels in the occipital cortex (Sailasuta et al., 2010). Moreover, lower PCC Glx levels were correlated with more years of methamphetamine abuse (O'Neill et al., 2015). Glx concentrations in the frontal cortex were also reduced in addicted individuals with ≤ 1 month of abstinence (but not after longer abstinence), and reduced Glx levels were correlated with fewer days of abstinence and higher craving (Ernst and Chang, 2008). In another study, however, neither glutamate nor Glx levels in the dACC or DLPFC differed between methamphetamine-using participants and controls (Howells et al., 2014).

2.5.2. PET/SPECT—No studies were found.

2.6. Cannabis

2.6.1. MRS—Compared with controls, chronic marijuana users had lower glutamate levels in the ACC (Prescot et al., 2011) and in basal ganglia regions (Chang et al., 2006; Muetzel et al., 2013), although one study reported that the basal ganglia effect was specific to women (Muetzel et al., 2013).

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2.6.2. PET/ SPECT—No studies were found

2.7. Multiple Substances

2.7.1. MRS—Although Glx levels in the occipital cortex did not differ between alcohol-addicted individuals and healthy controls, Glx levels were higher in alcohol-addicted smokers than in alcohol-addicted nonsmokers (Mason et al., 2006).

2.7.2. PET/SPECT—A study compared cocaine-addicted individuals and healthy controls using PET with [^{11}C]ABP688. Results revealed no effects of cocaine use disorder, but robust effects of smoking status were observed. In particular, compared with nonsmokers, smokers (especially those who had smoked recently) had lower V_{norm} (defined as BP_{ND} + 1) in multiple cortical (e.g., ACC, medial PFC, DLPFC) and subcortical brain regions (e.g., striatum, amygdala, hippocampus) (Hulka et al., 2014b).

2.8. Summary (see also Figure 1)

Individuals who abused addictive substances spanning alcohol, nicotine/tobacco, opiates, methamphetamine, and cannabis showed lower brain glutamate concentrations and/or mGluR5 receptor availability than corresponding measurements in controls. Differences most consistently emerged in multiple subregions of the ACC and in basal ganglia regions (e.g., striatum). A few exceptions to the general pattern of lower glutamate in addiction deserve mention: (A) studies of cocaine users yielded some equivocal findings, although the findings were generally more consistent with the hypothesis of lower glutamate levels than higher glutamate levels; (B) more research is needed on cannabis, especially while incorporating PET, before firm conclusions can be drawn; and (C) when examining the use of multiple substances, MRS and PET studies yielded results that differed in direction, although each modality only had one relevant study and included different substances (alcohol versus cocaine, though both were examined in conjunction with cigarette smoking).

Although with multiple exceptions, markers of reduced glutamatergic neurotransmission were often correlated with greater drug-related impairment (e.g., higher craving and substance-related consequences, reduced neuropsychological function). A notable exception to this pattern was seen in some studies that showed positive correlation of glutamate levels with years of use. These findings suggest that the extent of dysregulation may vary with length of abuse (O'Neill et al., 2015). Interestingly, acute withdrawal (and possibly the number of withdrawals) instead tended to correlate with higher brain glutamate associated with the use of some substances (especially alcohol and opiates, which perhaps not coincidentally produce the most severe withdrawal syndromes). More work is needed to corroborate this withdrawal effect, however, as it was not consistently observed across all studies of early abstinent individuals even within the same substance (e.g., alcohol). Nevertheless, this pattern of effects squares with findings showing that glutamate neurotransmission may be accentuated during acute withdrawal (Burnett et al., 2015).

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3. GABAergic Changes in Drug Addiction (Table 2)

3.1. Alcohol

3.1.1. MRS—Compared with controls, GABA levels in the occipital cortex were lower in alcohol-addicted individuals (Behar et al., 1999). In examining the dACC, groups comprising alcohol-addicted individuals with PTSD, PTSD only, and controls did not significantly differ on GABA levels (Pennington et al., 2014). However, within this comorbid group, higher GABA levels were correlated with better verbal learning/memory (Pennington et al., 2014).

3.1.2. PET/SPECT—In studies using [^{11}C]flumazenil and [^{123}I]iomazenil, alcohol-addicted individuals generally exhibited lower ratiotracer uptake V_T than controls in the cerebellum and medial PFC including the pACC and/or dACC, consistent with reduced $GABA_A$ receptor availability (Abi-Dargham et al., 1998; Gilman et al., 1996; Lingford-Hughes et al., 1998), and such decreases have been correlated with greater severity of alcohol dependence in some studies (Lingford-Hughes et al., 1998) but not in others (Abi-Dargham et al., 1998). More recently, alcohol-addicted participants exhibited lower (than controls) [^{11}C]Ro15 4513 V_T in the nucleus accumbens, parahippocampal gyri, right hippocampus, and amygdala, suggesting reduced $GABA_A$ receptor availability (Lingford-Hughes et al., 2012). Within these alcohol-addicted individuals, higher V_T in hippocampus and parahippocampal gyri was correlated with better performance on a delayed verbal memory task (Lingford-Hughes et al., 2012).

Other studies disagreed on whether there were differences in $GABA_A$ receptor measures between cases and controls. When a saturation method or V_T was used with [^{11}C]flumazenil or [^{123}I]iomazenil, group differences were either absent (Lingford-Hughes et al., 2000; Lingford-Hughes et al., 2005; Litton et al., 1993) or reversed (Jalan et al., 2000). However, recall that this latter study included alcohol-addicted individuals of older age and with liver disease, which may have affected findings.

3.2. Smoking

3.2.1. MRS—Smokers had lower GABA in the occipital cortex than non-smokers, though this effect was only observed in women (Epperson et al., 2005).

3.2.2. PET/SPECT—$GABA_A$ receptor availability, indexed by [^{11}C]Ro15 4513 V_T, in the pACC and parahippocampal gyrus was higher in current/past smokers than non-smokers (Stokes et al., 2013).

3.3. Opiates

No studies were found.

3.4. Cocaine

3.4.1. MRS—In cocaine addiction, GABA levels were reduced in the pACC/dorsomedial PFC compared with controls (Ke et al., 2004).

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3.4.2. PET/SPECT—No studies were found.

3.5. Methamphetamine

No studies were found.

3.6. Cannabis

No studies were found.

3.7. Multiple Substances

3.7.1. MRS—Compared with controls and alcohol-only addicted individuals, polysubstance-addicted individuals had lower pACC GABA levels (a difference that met nominal but not Bonferroni-corrected significance), and such lowered pACC GABA was correlated with worse verbal memory within the polysubstance users (Abe et al., 2013). In the occipital cortex, however, GABA levels were increased in non-smoking (but not smoking) alcohol-addicted individuals; these increased GABA levels declined after 1 month of alcohol abstinence (Mason et al., 2006).

3.7.2. PET/SPECT—Several studies reported increased radiotracer uptake (V_T of [^{123}I]iomazenil) in individuals with alcohol use disorder, but that these effects were blunted by active smoking. In particular, alcohol-addicted individuals in withdrawal (approximately 5-day abstinence) had higher $GABA_A$ receptor availability, indexed by [^{123}I]iomazenil V_T, in the medial PFC, ACC, hippocampus-amygdala, and cerebellum, but these effects were less pronounced either if they were active smokers or after they achieved 4 weeks of alcohol abstinence (Staley et al., 2005). In the alcohol-addicted smokers, higher $GABA_A$ receptor availability was correlated with longer initial abstinence from alcohol (1–7 days) (Staley et al., 2005). In a subsequent corroborative study, alcohol-addicted participants, further stratified by smoking status, were evaluated at 3, 10, and 30 days into withdrawal. Both alcohol-addicted smokers and non-smokers had higher $GABA_A$ receptor availability, indexed by [^{123}I]iomazenil V_T, compared with smoking-matched controls (Cosgrove et al., 2014). However, smoking status modulated the neuroadaptations seen during withdrawal. Alcohol-addicted non-smokers showed the highest and most widespread differences from controls at the 10-day assessment versus the 3-day and 4-week assessments, whereas the alcohol-addicted smokers had a more consistent pattern of differences from controls across all assessment time points. In the alcohol-addicted smokers, higher $GABA_A$ receptor availability was correlated with more craving for alcohol (at 10-day withdrawal) and cigarettes (at 3-day withdrawal) (Cosgrove et al., 2014).

3.8. Summary (see also Figure 1)

Overall, GABA was less studied than glutamate. MRS studies suggested lower GABA concentrations in abusers of alcohol, nicotine, and cocaine, which was also the typical direction of MRS effects for glutamate. Perhaps due to availability of more radiotracers, and/or because of their availability for a longer period of time, there were more PET/SPECT studies related to GABA than for glutamate, particularly for alcohol (which is unsurprising given alcohol's known effects on the $GABA_A$ receptor). These studies generally showed

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decreased $GABA_A$ receptor availability/distribution volume in the addicted individuals compared with controls. Nicotine, however, showed an opposite pattern of effects. History of smoking was not only associated with higher $GABA_A$ receptor availability on its own, but smoking also modulated the early abstinence course of individuals with alcohol dependence. Interestingly, the effects of smoking on alcohol dependence showed an opposite pattern of effects to that of glutamate. Examining the joint effects of smoking and alcohol abuse, while incorporating markers of both glutamate and GABA neurotransmission, will be an interesting and important direction for future research.

It is also important to note that, similarly to glutamate, GABA effects appeared to be sensitive to study participant characteristics, such as the length of abstinence and/or drug-related medical diseases (less evidence for the latter). We did not locate any PET/SPECT studies labeling the $GABA_B$ receptor, which unlike the fast ligand-gated action of the $GABA_A$ receptor, is instead associated with long-term modulation through G protein-regulated gene transcription and protein synthesis (Xu et al., 2014). More research, both MRS and PET, is also needed in opiates, methamphetamine, and cannabis.

4. Evidence of Resting-State Functional Connectivity Deficits in Drug Addiction

A large literature has examined RSFC deficits in drug addiction (Fedota and Stein, 2015; Lu and Stein, 2014; Sutherland et al., 2012), and we did not reprise all of this important work here. Rather, our current goal was to provide evidence that some of the same regions implicated in glutamate and GABA MRS and PET studies in addiction are also functionally disrupted as revealed by RSFC. We focused on studies that examined RSFC differences between addicted individuals and healthy controls [using approaches that were seed-based and/or whole-brain (e.g., independent components analysis (ICA) or the graph theory-based metric degree (i.e., number of connections exceeding a specified correlation threshold)] in the (A) ACC extending into the dorsomedial and/or ventromedial PFC, (B) insula, and (C) striatum (for more discussion of the advantages and disadvantages of using RSFC in psychopathology, see Box 2).

The rationales for focusing on these regions are as follows. The ACC (especially, pACC) and adjacent medial PFC (encompassing dorsomedial and ventromedial subsections) form part of the default mode network (DMN), which is activated during the resting state (Gusnard et al., 2001; Molnar-Szakacs and Uddin, 2013). Moreover, the resting state is a condition replete with mind-wandering and self-generated thinking (Smallwood and Schooler, 2015), and these self-referential functions have been linked with activation of cortical midline regions, including the pACC and medial PFC, in healthy individuals (Abraham, 2013; D'Argembeau, 2013; de Greck et al., 2008; van der Meer et al., 2010) and addicted individuals (de Greck et al., 2009; Moeller and Goldstein, 2014). Thus, although larger regions, such as the ACC and medial PFC, have sometimes been selected as regions of interest in MRS studies for practical reasons (i.e., large area to position the sequence), effects in these regions are nonetheless highly anticipated for both MRS studies and RSFC studies; recent combined fMRI-MRS studies in healthy participants further speak to this point (see Introduction). The insula has a critical role in mediating interoception (Craig,

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2009) and the detection of behaviorally relevant stimuli (Uddin, 2015). In drug addiction, these functions subserved by the insula appear vital for the experience of drug craving (Naqvi et al., 2007; Verdejo-Garcia et al., 2012). The striatum forms a key part of the mesocorticolimbic dopamine projections that mediate the reinforcing effects of addictive drugs; chronic perturbation of this system ultimately leads to enduring changes in striatal-PFC glutamatergic projections (Kalivas, 2007, 2009). Although MRS measurement of glutamate and GABA is more difficult in the striatum than in the insula (Wiebking et al., 2014), some studies included in this review indeed have reported striatal effects. Importantly, prior resting-state studies of healthy individuals have revealed functional connections between these three regions (Margulies et al., 2007; Uddin et al., 2009).

4.1. Alcohol

Alcohol-addicted individuals had weaker connectivity between subregions of the ACC with the insula (Sullivan et al., 2013) and subthalamic nucleus (Morris et al., 2015). Using ICA, it was shown that alcohol-addicted individuals had stronger connectivity than controls within and between various networks, including an orbitofrontal cortex (OFC) network, an amygdala-striatum network, and a DMN network (Zhu et al., 2015).

4.2. Smoking

Smokers in withdrawal showed stronger RSFC between the ACC and dorsal striatum compared with controls; these same smokers showed stronger RSFC between the ACC and bilateral insula in a withdrawal study condition compared with a satiated study condition (Huang et al., 2014). Similarly, 12-hour abstinent smokers showed stronger global connections to the insula compared with controls, and this difference was not observed when the smokers were satiated (Wang et al., 2014). Interestingly, strengthened connections with the insula (e.g., to regions of the DMN, such as the ventromedial and dorsomedial PFC) were abolished by a nicotine challenge (Sutherland et al., 2013). A different pattern of effects was observed with ICA, however. Relative to non-smokers, satiated smokers exhibited stronger connectivity between the medial PFC and a left fronto-parietal network (including ACC, DLPFC, and insula extending into putamen) (Janes et al., 2012).

4.3. Opiates

The most RSFC studies have been conducted with individuals addicted to opiates. Opiate-addicted individuals had weaker RSFC between the pACC with the dACC, DLPFC, medial PFC, and PCC/precuneus (Ma et al., 2010; Ma et al., 2015; Wang et al., 2013; Yuan et al., 2010); and between the caudate and DLPFC (middle frontal gyrus) (Wang et al., 2013). In ICA or other whole-brain approaches, compared with controls, opiate-addicted individuals had weaker resting-state functional connectivity of the ACC and basal ganglia regions (including the striatum) (Liu et al., 2011a; Ma et al., 2011; Schmidt et al., 2015).

Other studies, however, have shown stronger connectivity in opiate-addicted individuals: higher RSFC between the pACC, dACC, or precuneus with the striatum (Ma et al., 2010; Zhang et al., 2015) and insula (Zhang et al., 2015) [but see (Upadhyay et al., 2010)]. Stronger connectivity between the IFG with the dACC and ventromedial PFC also has been reported (Ma et al., 2010; Wang et al., 2013). Connectivity between the insula and the

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amygdala was also stronger in opiate-addicted individuals compared with controls (Xie et al., 2011). In whole-brain RSFC approaches, heroin-addicted individuals had stronger overall connectivity of the ACC, midcingulate, insula, OFC, and putamen (Liu et al., 2009; Liu et al., 2011a).

4.4. Cocaine

Compared with controls, cocaine-addicted individuals generally had weaker RSFC of the pACC and dACC with subcortical regions, including the striatum, amygdala, thalamus, hippocampus, and parahippocampal gyrus (Gu et al., 2010; Hu et al., 2015; Verdejo-Garcia et al., 2014) [but see (Wilcox et al., 2011)]. In one study, pACC-amygdala connectivity was also associated with clinical outcome (30-day relapse after treatment) (McHugh et al., 2014).

Other studies have reported stronger connectivity between the ACC subregions and other cortical regions (e.g., middle frontal gyrus, inferior parietal lobe, or supramarginal gyrus) in cocaine-addicted individuals than controls (Camchong et al., 2011; Konova et al., 2013), with the dACC and ventromedial PFC in particular receiving an abnormally high number of short- and long-range functional connections (Konova et al., 2015).

The directionality of limbic-limbic connectivity was less clear. Cocaine-addicted individuals had weaker connectivity between the bilateral putamen and the left posterior insula compared with controls, and this effect was driven by data from individuals who relapsed 30 days after treatment discharge (McHugh et al., 2013). However, cocaine-addicted individuals had stronger connectivity between the ventral striatum and dorsal striatum than controls (Konova et al., 2013).

4.5. Methamphetamine

Compared with healthy controls, methamphetamine-addicted individuals exhibited greater RSFC between a midbrain seed and a number of subcortical (e.g., putamen and insula) and cortical regions (e.g., OFC) (Kohno et al., 2014).

4.6. Cannabis

Chronic marijuana users showed weaker RSFC between an insular seed and the ACC (Pujol et al., 2014).

4.7. Summary

As also articulated elsewhere (Lu and Stein, 2014), RSFC in addiction remains an emerging field, and conflicting findings have been quite common. One potentially interesting pattern of results for opiates and cocaine, perhaps the most widely studied addictions in this field, appears to be that cortical-cortical connections generally appear to be weakened, whereas corticolimbic connections generally appear to be strengthened; more research is clearly required, however, before firm conclusions can be drawn, especially for certain substances (e.g., methamphetamine, marijuana). Despite these inconsistencies of directionality, these studies have revealed reliable RSFC differences between cases and controls in regions that have also been investigated using MRS or PET/SPECT (e.g., ACC, medial PFC, insula, and striatum), and these group differences have been relatively large in magnitude (see Box 2).

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5.0. Working Hypothesis: Abnormal Glutamatergic and/or GABAergic Neurotransmission Underlies Corticolimbic RSFC Deficits in Addiction

Taken together, the literature indicates that drug-addicted individuals exhibit abnormal neurotransmission involving glutamate and GABA in corticolimbic brain regions of core relevance to their disease (e.g., ACC, medial PFC insula, and striatum), and that these same regions also show disruptions in RSFC. Because glutamatergic and GABAergic neurotransmission in such regions also drive the resting state in health, we raise the hypothesis that corticolimbic RSFC can provide an intermediate phenotype to explain associations between addiction-relevant glutamatergic and/or GABA dysregulation and addiction symptomatology (e.g., craving, drug-seeking, engagement with treatment) (Figure 2). Future work can center on the following areas.

5.1. Finer Specification of the Model

It is crucial to incorporate the modulating influences of clinical characteristics, especially withdrawal/abstinence and smoking (Figure 2). Withdrawal carries a high vulnerability to relapse, which may partially stem from associated perturbations in brain glutamate or GABA (Mashhoon et al., 2011). Smoking history, as shown above, exerts important independent effects on brain glutamate and GABA metabolites. Current smoking also modulates the effects of other substances, such as alcohol (especially during withdrawal), and the resulting effects on brain glutamate and GABA may differ depending on which neurotransmitter is examined. Future studies might also investigate whether neurochemical deficits in one corticolimbic brain region have reverberations across the brain. This may be especially true for deficits in glutamate, which has more global (transregional) effects (Duncan et al., 2013). RSFC methods, especially using whole-brain graph theory approaches, are ideally suited to test such hypotheses. Finally, future studies can incorporate direct measures of brain metabolism, such as PET with [^{18}F]fluorodeoxyglucose. Indeed, energy metabolism may represent an intermediary process between fast neurotransmission and the slow RSFC blood-oxygen-level dependent (BOLD) response, and this kind of precision would increase mechanistic understanding.

5.2. Integration and Translation between Human Data and Animal Models

Another important future direction for enhancing mechanistic understanding is to conduct studies with tighter experimental control, as can be achieved in animal models. Animal models offer the advantages of more controlled drug histories and more invasive assessments, which could clarify how addiction may causally change glutamate/GABA neurotransmission and metabolite levels in select brain regions, as well as their consequent associations with RSFC.

In such animal studies, lower Glx levels in the dorsal striatum of rhesus monkeys due to chronic methamphetamine exposure showed a linear pattern of recovery with abstinence over one year (i.e., returning to control levels) (Yang et al., 2015) [but see (Liu et al., 2011b), where cocaine administration over the course of 9 months increased levels of glutamate and glutamine in squirrel monkeys]. In another study, rats received subcutaneous twice-daily injections of 2.5mg/kg methamphetamine for one week. This drug exposure

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resulted in decreased MRS-measured glutamate, glutamine, and GABA in hippocampus, nucleus accumbens, and PFC (Bu et al., 2013). Interestingly, a different study revealed decreased RSFC in cocaine-exposed rats between the nucleus accumbens and the dorsomedial PFC as a function of the degree of cocaine self-administration escalation (Lu et al., 2014). These combined studies generally support our hypothesized model.

Alternatively, drug-administration schedules *not* intended to produce addiction have largely produced opposite results. For example, following short-term administrations of cocaine (Li et al., 2012) or alcohol (Zahr et al., 2015), rats showed transient striatal (Li et al., 2012) or whole-brain (Zahr et al., 2015) increases in glutamate and/or GABA [but see (Lee et al., 2014)]. Such results are consistent with the idea that addiction-related decreases in glutamate or GABA could reflect neuroadaptations to chronic drug exposure. Such conclusions are difficult, if not impossible, to achieve in studies of already-addicted humans.

5.3. More Comprehensive Methods

Because human studies cannot achieve the level of precision attained in animal studies, mechanistic clarity needs to rely on more comprehensive and innovative experimental methods. A drug challenge model, if employed in combination with fMRI and with MRS or PET, can address causality by modulating underlying glutamate/GABA neurotransmission that can then be correlated with resting-state fMRI and then other clinical variables.

We are aware of no previous studies in this field that have attempted this kind of ambitious design, though some have incorporated various components. For example, one study showed that acute alcohol administration reduced occipital GABA levels (Gomez et al., 2012). However, because this experiment was conducted in social drinkers (not in alcohol-addicted individuals), the potential relevance to addiction is unclear. Another study found that a heroin challenge (versus placebo) in opiate-addicted individuals strengthened connectivity within an ICA-defined basal ganglia network (including striatum) (Schmidt et al., 2015). Similarly, opiate-addicted individuals receiving high methadone doses showed higher ACC glutamate levels (Greenwald et al., 2015; Verdejo-Garcia et al., 2013). However, these studies did not incorporate both neurochemical measurements and RSFC. Finally, perhaps the most methodologically rich study to date evaluated the effects of 12-week varenicline administration on dACC Glx levels and fMRI BOLD response (during a color-word Stroop task) (Wheelock et al., 2014). The varenicline regimen decreased dACC Glx levels, modulated DMN regions (including pACC and PCC) during task performance, and changed dACC-DMN connectivity as revealed by psychophysiological interaction (PPI) analysis (Wheelock et al., 2014). Future iterations of this study type would need to include a control group and could benefit from using a pharmacological probe that modulates the neurotransmitter system of interest more directly (i.e., because varenicline is a nicotinic receptor partial agonist, the Glx results could represent secondary effects). A future study that integrates these various components within a single design promises to be highly informative.

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5.4. Testing for Substance-Specific Effects

It would be interesting to test whether addiction-related effects on brain glutamate and GABA are specific to addiction related to substances rather than behaviors. One could compare and contrast effects in individuals with substance use disorders with those in individuals who have behavioral addictions, such as gambling (Clark and Limbrick-Oldfield, 2013). We are aware of no MRS or PET studies that contrasted substance addiction and gambling addiction, but several studies on this front have been conducted using RSFC. For example, whereas increased intrinsic local connectivity of the PCC was observed for both behavioral (gambling) and substance (alcohol) addictions, decreased connectivity of the ACC was specific to alcohol addiction (Kim et al., 2015). Moreover, cocaine addiction was uniquely associated with enhanced connectivity between the subgenual ACC with OFC or striatum (in further correlation with measures of impulsivity) (Contreras-Rodriguez et al., 2015a; Contreras-Rodriguez et al., 2015b). In contrast, connectivity in cocaine addiction overlapped with that in gambling addiction in the OFC and dorsomedial PFC, and in the amygdala and insula (Contreras-Rodriguez et al., 2015b) [note that this latter connection was also reported in opiate dependence (Xie et al., 2011)].

5.5. Potential Applications to Treatment

A relatively small but growing literature suggests that glutamatergic and/or GABAergic medications modulate neural activity in brain regions spotlighted in this review. In smokers, the $GABA_B$ receptor agonist baclofen, given both acutely and after 3 weeks of treatment, decreased cerebral blood flow during perfusion fMRI in several regions including the dACC (Franklin et al., 2012; Franklin et al., 2011). In an animal model (rhesus monkeys), baclofen reversed neuropsychological deficits owing to acute cocaine injections in association with normalized metabolic activation in the PFC (Porrino et al., 2013). Acamprosate, despite continuing debates regarding its clinical mechanism of action, appears to exert effects on brain glutamate (Bolo et al., 1998). Consistent with this idea, 4-week treatment of acamprosate reduced MRS-measured pACC glutamate levels in recently abstinent alcohol-addicted individuals; such reductions appeared to be clinically warranted, as glutamate levels in cerebrospinal fluid were positively correlated with alcohol dependence severity (Umhau et al., 2010). Moreover, in an animal model (rats), acamprosate reduced Glx levels in the ventral striatum during alcohol withdrawal (Hinton et al., 2012). In healthy controls, the GABA reuptake inhibitor (i.e., transporter blocker) tiagabine, which notably has been shown to decrease cocaine-positive urines in pilot clinical trials (Gonzalez et al., 2003), increased (either significantly or at trend level) the V_T and/or BP_{ND} of [^{11}C]flumazenil and [^{11}C]Ro15 4513 in multiple PFC regions, including the ACC (Frankle et al., 2012; Frankle et al., 2009; Stokes et al., 2014).

We hypothesize that these medications – as well as potentially novel medications yet to be developed that act on these respective systems – could also modulate corticolimbic RSFC, providing a potential therapeutic target for intervention in drug addiction. In this regard, modulation of brain glutamate and GABA signaling may be particularly important during acute withdrawal, a time period when neurotransmission seems especially perturbed.

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6. Conclusion

Glutamatergic and GABAergic neurotransmission drives the resting state in healthy individuals. As drug-addicted individuals exhibit abnormalities in concentrations of these neurotransmitters and in the resting state, we posited that abnormal glutamate and/or GABA concentrations – especially in corticolimbic brain areas – might underlie the abnormal RSFC in addiction. This hypothesis remains to be empirically verified. If supported, our perspective can provide mechanistic insight into the disordered resting state in drug addiction, potentially also elucidating the mechanisms of existing therapeutics and ultimately even informing the development of novel therapeutics that target this disordered resting state. Future research can also expand concepts in our review to other psychopathologies marked by deficits in the resting state; the resting state, because it does not rely on disease-specific tasks, is one of the most robust, consistent, and far-reaching deficits in psychiatry and neurology. Accordingly, our framework could have important transdiagnostic mechanistic and therapeutic implications.

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Box 1

Overview of the Resting State

Resting-state activity is a heterogeneous concept (Cabral et al., 2014; Mantini et al., 2013; Morcom and Fletcher, 2007; Northoff, 2014). The term resting state itself is an operational term that describes the absence of any particular external stimulus, such as a specific tactile or visual (or otherwise) stimulus or cognitive task. Instead, resting state focuses on internally generated mental activity with internal mental contents (e.g., thoughts or imagery) as distinguished from externally generated mental contents (e.g., perceptions). Psychologically, resting-state activity of the brain can manifest in what is described as mind-wandering (Smallwood and Schooler, 2015), random thoughts (Doucet et al., 2012), or self-generated thoughts (Smallwood and Schooler, 2015).

Different terms are used to describe the resting state, largely reflecting different investigative perspectives. In addition to “resting-state activity,” other terms include “spontaneous activity,” “baseline,” or “intrinsic activity” (Deco et al., 2014; Fox et al., 2015; Mantini et al., 2013; Northoff, 2014). The term “spontaneous activity” highlights the idea that resting-state activity is not induced by any particular external stimulus or task but instead is generated naturally (Cabral et al., 2014; Deco et al., 2014; Mantini et al., 2013). Imaging specialists often prefer the term “baseline,” indicating that the resting state (which occurs pre-stimulus, pre-task, or between stimuli/tasks) can serve as a reference condition that is subtracted from a task condition (Morcom and Fletcher, 2007). The term “intrinsic activity” highlights the idea that the resting-state has its origin within the brain itself [i.e., as distinguished from extrinsic activity that originates from stimulus-induced or task-evoked activity (Northoff, 2014)].

Both spatial and temporal measures can assess resting-state activity. Spatially precise modalities such as fMRI use RSFC approaches to target different neural networks that co-activate spontaneously within and between different networks (Cabral et al., 2014; Raichle et al., 2001). This method captures the synchronicity of low-frequency, spontaneous fluctuations in blood-oxygen-level-dependent (BOLD) signals that reflect fluctuations in neuronal activity (Shmuel and Leopold, 2008) between brain regions in the absence of external stimulation (Fox and Raichle, 2007), but that are linked to task-related functioning of brain regions comprising the same circuits (Hampson et al., 2006) and to corresponding behavior (Hampson et al., 2006; Kelly et al., 2008). These synchronous fluctuations are confined to gray matter and can be observed for monosynaptic or polysynaptic anatomical connections (Damoiseaux and Greicius, 2009; Shmuel and Leopold, 2008). Temporally precise modalities, such as EEG or MEG, can measure resting-state activity in electrophysiological or magnetic activity (Cabral et al., 2014; Mantini et al., 2013), which targets neural activity changes in different frequency ranges and their cross-frequency coupling (Engel et al., 2013). Research participants, while undergoing these assessments, are often instructed to close their eyes and not think about anything in particular (Logothetis et al., 2009); this eyes-closed condition is taken as the operational or methodological gold standard to measure resting-state activity.

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Box 2

Methodological Advantages and Disadvantages of Resting-State Functional Connectivity (RSFC)

Assessment of RSFC is a sensitive and highly generalizable fMRI methodology. Using RSFC, group differences between cases and controls have emerged across numerous psychiatric and neurological conditions even in the absence of gross morphological abnormalities (Barkhof et al., 2014). Furthermore, because this approach does not depend on a particular experimental context (task), it becomes possible to identify commonalities and differences between individuals in clinical groups, who otherwise probably would not undergo similar experimental paradigms [e.g., addicted individuals are routinely exposed to drug cues (Jasinska et al., 2014), whereas depressed individuals are routinely exposed to emotional faces (Stuhrmann et al., 2011)]. It even becomes possible to scan individuals unable to perform task-based fMRI at all, including individuals with altered or diminished states of consciousness, or severe cognitive decline (e.g., coma, psychosis, Alzheimer's disease, etc.) (Brier et al., 2014; Demertzi et al., 2014; Satterthwaite and Baker, 2015). Because many discrete psychopathologies share deficits in network-level functional connectivity, it is possible that this transdiagnostic tool can suggest previously unrecognized overlap among disorders that may be targeted for previously unrecognized therapeutic interventions [e.g., consistent with the Research Domain Criteria (RDoC) approach]. RSFC, then, may indeed be regarded an intermediate phenotype that may be compared across different diagnostic groups.

Nevertheless, it is also important to note some of the interpretative issues of RSFC, which have been well-articulated elsewhere (Weinberger and Radulescu, 2015). In brief, such issues include systematic differences in the use of (potentially multiple) substances; inability to discern what participants are thinking and feeling during the resting-state scan, with possible group differences in these psychological states; and the possibility of prominent artifacts resulting from head movement and other motion, which may also differ at the group level. However, even with these potential sources of variability, effect sizes of RSFC studies generally have been large in magnitude. In particular, the select studies/findings included in the current review were estimated to have following $M \pm SD$ effect sizes [Cohen's d, calculated based on sample sizes and means ± standard deviations (or t-values), where available]: alcohol (d=0.84 ± 0.0), nicotine (d=1.32 ± 0.22), opiates (d=2.39 ± 1.66), cocaine (d=1.01 ± 0.22), methamphetamine (d=1.04 ± 0.0), and cannabis (d=0.98 ± 0.0). (Note that because this manuscript is not a meta-analysis and includes only a portion of possible resting-state studies and a portion of possible effects within those studies, extensive discussion about these effect size estimates or their interpretations is outside the scope of this review; rather, the goal here was to provide macroscopic view of the magnitude of effects in these kinds of studies.)

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Highlights

- We review glutamate and GABA alterations in addiction, observed via MRS and PET/SPECT.
- These neurotransmitters drive the resting state in healthy individuals.
- Brain regions showing glutamate and GABA abnormalities are also functionally disrupted in addiction.
- We link these literatures to suggest a neurochemical basis of resting-state abnormalities in addiction.
- We identify possible research and treatment directions that can follow from this framework.

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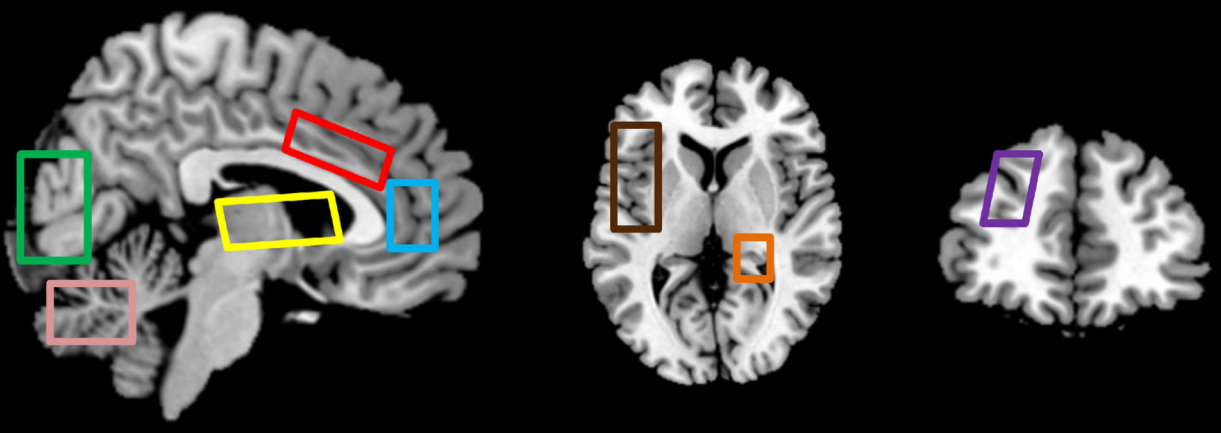

Drug	Glu: MRS	Glu: PET	GABA: MRS	GABA: PET
Alcohol	↓	--	↓	↓
Nicotine/Smoking	↓	↓	↓	↑
Opiates	↓	--	--	--
Cocaine	↔	↓	↓	--
Methamphetamine	↓	--	--	--
Cannabis	↓	--	--	--
Multiple	↑	↓	↓	↑

Figure 1.

Overview of the MRS and PET/SPECT studies. Figure displays regions of interest common to many studies (blue: rostral/pregenual anterior cingulate cortex, sometimes extending into medial prefrontal cortex; red: dorsal anterior cingulate cortex; yellow: basal ganglia/ thalamus; green: occipital cortex; pink: cerebellum; brown: insula; orange: hippocampus; purple: dorsolateral prefrontal cortex) and a table showing the general direction of effects. Arrows in the table reflect the preponderance of evidence while also prioritizing studies with larger and/or more homogeneous samples and not considering acute clinical features such as short-term withdrawal (which can be associated with opposite effects). ↓ = lower in addiction; ↑ higher in addiction; ↔ = nonsignificant differences between groups; -- no studies found.

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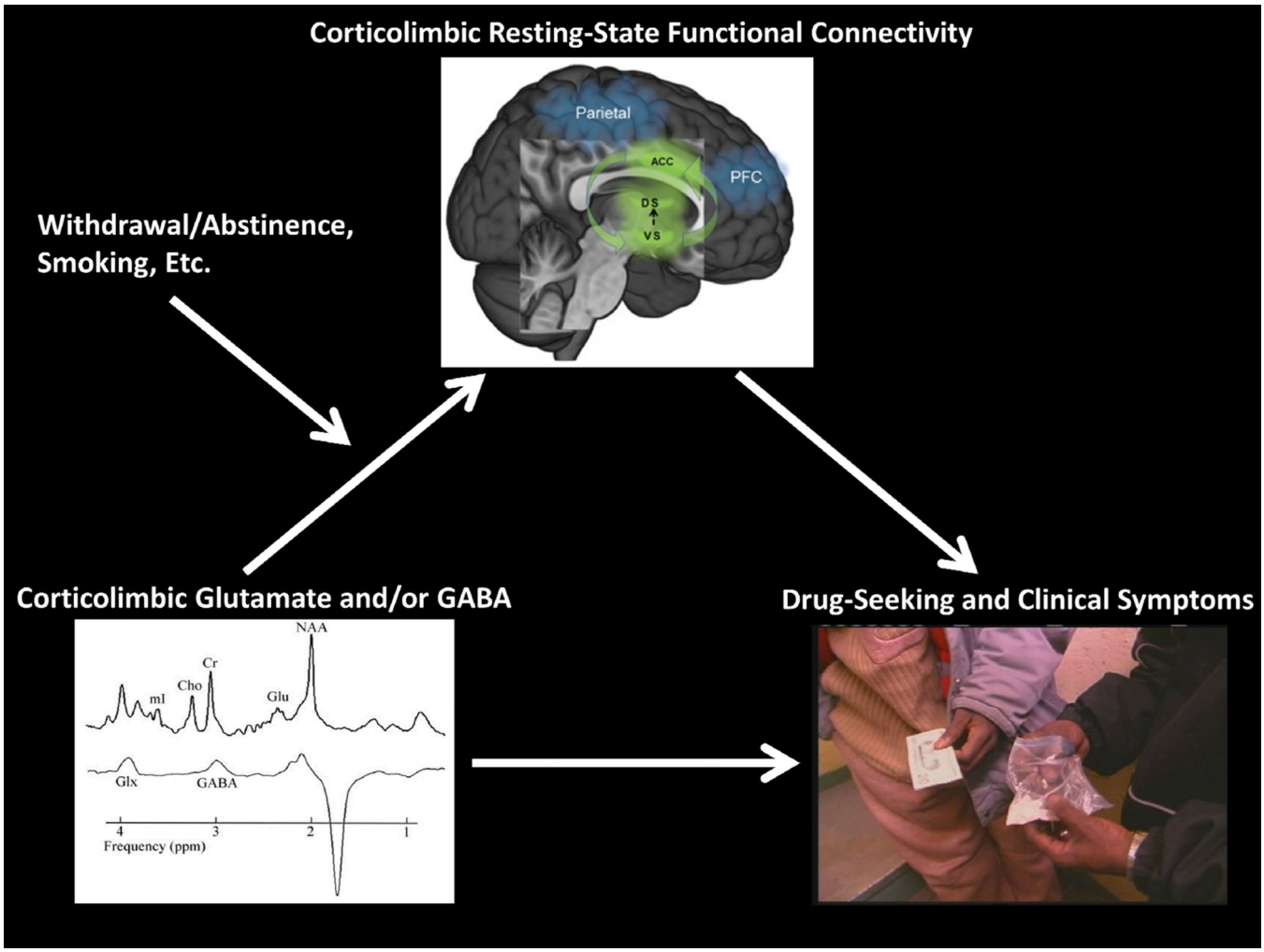

Figure 2.

Schematic of the hypothesized model. Deficits in glutamate and/or GABA, which are further modulated by clinical characteristics including withdrawal/abstinence, are associated with deficits in brain resting-state functional connectivity (e.g., anterior cingulate cortex with the dorsal and ventral striatum), which in turn are associated with drug-related symptoms. [The metabolite image (left) is adapted from (Abe et al., 2013), with permission from Elsevier; the brain image (top) is adapted from (Garland et al., 2014), under the Creative Commons Attribution License; and the drug image (right) is adapted from (Moeller et al., 2009), with permission from Elsevier].

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Table 1

MRS and PET glutamate studies in drug addiction.

Reference	Sample	Mean Age (SD)	Sex	Mean Abst Duration (SD)	Medication and/or Tx	Other Drug Use	Psychiatric or Medical	Regions of Interest	Imaging Method	Primary Glutamate Imaging Outcome (vs Controls)	Clinical or Neuropsych Correlates
Alcohol											
(Bagga et al., 2014)	35 AUD 35 HC	36.5 (5) 35.2 (3.7)	35M/0F 35M/0F	17.5 (4.3) d	NR	NR	NR	R Occip	MRS	↓ Glu-Gln/Cr	AUD: ↓ Glu-Gln/Cr corr ↓ visual-motor functioning
(Bauer et al., 2013)	29 AUD 31 HC	29M/0F 31M/0F	40.2 (7.5) 36.6 (10.1)	≤ 10 d	Inpatient Detox; Benzos	Nic	NR	pACC, VS	MRS	↑ VS Glu	AUD: ↑ VS & ACC Glx corr ↑ craving
(Ende et al., 2013)	21 AUD 9 HC	13M/8F 8M/1F	48.5 (10.7) 40.9 (4.5)	Unspec	NR	Nic	NR	dACC into adjacent WM)	MRS	NS Glu (modulation by loss of control)	AUD: ↑ Glu corr ↓Alc severity
(Hermann et al., 2012b)	47 AUD 57 HC	46.3 (1.5) 45.1 (1.5)	38M/9F 44M/13F	1 d, 14 d (within)	Inpatient Detox; clonidine, Benzos	Nic	NR	ACC	MRS	1 d: ↑Glu	AUD, 1 d: ↑ Glu corr ↑ breath Alc & 3-mo severity
(Jalan et al., 2000)	6 AUD 11 HC	61 55	4M/2F 8M/3F	≥ 6 mo	NR	NR	Cirrhosis	Cereb, Cerebel, BG	MRS	↑ Glx/Cr	NA
Lee et al., 2007)	13 AUD 18 HC	33.8 (5.8) 32.9 (0.9)	13M/0F 18M/0F	15.5 d (min 14 d)	Thiamine	Nic	NR	ACC, Ins	MRS	↑ ACC Glu/Cr	↑ ACC Glu/Cr corr ↑ memory & recent Alc use
(Miese et al., 2006)	26 AUD 18 HC	61.1 (12.4) 54.3 (12.7)	18M/8M 14M/5M	During study (Unspec)	NR	NR	Cirrhosis	BG, Occip	MRS	↑ Glx/Cr	NA
(Mon et al., 2012)	44 AUD 16 HC	53.9 (8.8) 49.0 (10.1)	39M/5F 14M/2F	TP1: 9 (4) TP2: 34 (7)	VA Medical Center, Other Tx; Benzos	Nic	Hep C, type 2 diabetes, ↑ BP, depress	pACC, DLPFC, Occip	MRS	↓ ACC Glu	↑ ACC Glu corr ↑ Abst
(Nery et al., 2010)	22 AUD 54 HC	39.1 (11.4) 38.7 (12.4)	6M/16F 14M/40F	6.8 (6.5) y	Lithium, AntiDepress, antiPsy, Benzos	Mari, Coc, Stim, opioids	Bipolar, anxiety	DLPFC	MRS	NS Glu, Glx	NS
(Pennington et al., 2014)	10 AUD 28 PTSD 20 HC	51.9 (13.9) 35.4 (10.5) 36.3 (12.4)	10M/0F 28M/0F 20M/0F	NS	VA Medical Center	NR	AUD also had PTSD	ACC Occip Temp	MRS	↓Glu	AUD: ↑ Glu corr ↑ divided attention
(Seitz et al., 1999)	11 AUD 10 HC	44 (10) 38 (12)	8M/3F 9M/3F	3–6 d	Inpatient Detox	NR	Frontal & cerebellar atrophy	Vermis	MRS	NS Glx/Cr	NA

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Reference	Sample	Mean Age (SD)	Sex	Mean Abst Duration (SD)	Medication and/or Tx	Other Drug Use	Psychiatric or Medical	Regions of Interest	Imaging Method	Primary Glutamate Imaging Outcome (vs Controls)	Clinical or Neuropsych Correlates
(Thoma et al., 2011)	7 AUD 6 AUD Abst 17 HC	35.5 (8.2) 35.4 (5.7) 32.3 (7.9)	5M/2F 5M/1F 9M/8F	≥48 h	University Tx	Nic, sedatives, Marij, opioids, Coc, Halluc	Abnormal liver function, bipolar, Depress, Psy, anxiety, OCD, PTSD, phobias	dACC	MRS	↓Glu (AD Abst only), ↑ Gln (AD only)	AUD: ↓Glu corr ↑drinking consequences
(Yeo et al., 2013)	213 AUD 66 HC	31.0 (9.0) 29.5 (8.3)	153M/60F 37M/29F	≥24 h	Unspec Tx (n=97/213)	Nic, Marij	Depres	dACC	MRS	NS Glu-Gln	↑ Glu-Gln corr ↑ years drinking & ↑ smoking severity
Nicotine/Smoking											
(Akkus et al., 2013)	14 SM 14 SM Abst 14 HC	36.1 (10.2) 37.7 (10.1) 36.8 (9.6)	6M/8F 8M/6F 6M/8F	None 25.0 (19.4)	NR	NR	Depress, anorexia	6 Cereb, 3 Limbic, STR, Thal, 1 brainstem	PET [^{11}C]ABP688	↓ DVR Amyg, Striat (caudate), PFC, Temp, PCC	Sh Abst: ↓ BP_{ND} brainstem corr ↑ cigs per day
(Akkus et al., 2015)	14 SM 14 Sh Abst 14 Lg Abst 14 HC	36.1 (10.2) 37.7 (10.1) 37.8 (10.1) 36.8 (9.6)	6M/8F 8M/6F 8M/6F 6M/8F	None 25.0 (19.4) 473.6 (336.1)	NR	NR	Depress, anorexia	6 Cereb, 3 Limbic, STR, Thal	PET [^{11}C]ABP688	↓ BP_{ND} ACC, Temp, MedOFC (SM, Sh Abst only)	NS
(Durazzo et al., 2015)	35 SM 30 HC	48.6 (10.1) 49.1 (12.0)	26M/4F 31M/4F	Unspec	NR	Alc	NR	pACC, DLPFC	MRS	↓ Glu (acceleration with ↑ age)	All: ↑ DLPFC Glu corr ↑ NP function
(Gallinat and Schubert, 2007)	13 SM 9 SM Abst 16 HC	35.4 (10.0) 41.5 (9.7) 32.8 (9.6)	5M/8F 5M/4F 8M/8F	None 16.5 (2.9) y	NR	Alc	NR	ACC, Hipp	MRS	NS Glu	NS
(Gutzeit et al., 2013)	14 SM 10 HC	50.4 (12.6) 36.6 (9.2)	14M/0F 10M/0F	None, 24 h (within)	NR	NR	NR	Ins	MRS	↑ Gln (withdrawal)	NA
(Mennecke et al., 2014)	12 SM 12 HC	25.7 (3.1) 26.2 (2.7)	6M/6W 6M/6W	None, 3 d (within)	NR	NR	NR	dACC, Hipp	MRS	↑ left dACC Glx/Cr	NA
(O'Neill et al., 2014)	18 SM 16 HC	35.4 (2.1) 33.2 (2.6)	11M/7F 8M/8F	Unspec	NR	Marij, Alc, anorexia	NR	Thal	MRS	NS Glu	SM: ↓ Glu & Glx corr ↑ Cigarettes/day and pack-years
Opiates											
(Greenwald et al., 2015)	7 HD 5 HC	42.4 (7.5) 45.2 (7.2)	6M/1F 3M/2F	Unspec	Methadone (high vs. low, within)	Nic	NR	pACC, Thal	MRS	NS Glu (versus either methadone dose)	NS

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Reference	Sample	Mean Age (SD)	Sex	Mean Abst Duration (SD)	Medication and/or Tx	Other Drug Use	Psychiatric or Medical	Regions of Interest	Imaging Method	Primary Glutamate Imaging Outcome (vs Controls)	Clinical or Neuropsych Correlates
(Hermann et al., 2012a)	17 HD 20 HC	36.9 (9.7) 36.4 (10.3)	11M/6F 13M/9F	Unspec	Opiate maintenance	Marij, Alc, Benzos, Amph, MDMA	NR	dACC	MRS	NS Glu or Glx (moderation by age)	HD: ↑ Glu & Glx corr ↑ #withdrawals
(Verdejo-Garcia et al., 2013)	24 HD 24 HC	29.8 (6.9) 29.6 (6.5)	13M/11F 13M/11F	≥24 h	Methadone (n=10), Bup (n=14)	Marij, benzos, heroin	NR	dACC	MRS	↓ Glx (hemisphere x medication effects)	HD: ↑ Glx corr ↑ methadone dose
(Yücel et al., 2007)	24 HD 24 HC	29.8 (6.9) 29.6 (6.5)	13M/11F 13M/11F	≥24 h	Methadone (n=10), Bup (n=14)	Marij, Benzos, heroin	NR	dACC	MRS	↓ Glx (across medication)	NS
Cocaine											
(Chang et al., 1997)	11 CD 16 HC	32.0 (7.9) 32.6 (9.1)	26M/0F 26M/0F	66.4 (26.2) mo	NR	Alc, Marij, Amph, PCP	NR	Mid Occip	MRS	NS Glx/Cr	CD: ↓ Glx corr ↓ Coc use yrs
(Hulka et al., 2014a)	18 CD 18 HC	36.2 (7.6) 35.8 (8.3)	18M/0F 18M/0F	7.6 (6.8) d	NR	Nic, Alc, Marij, MDMA	Depress	pACC, R DLPFC	MRS	NS Glu/Cr or Gln/Cr	CD: ↓ pACC Gln/Cr corr ↑ Coc frequency
(Martinez et al., 2014)	15 CD 14 HC	43 (3) 41 (4)	14M/1F 13M/1F	10–14 d	University Inpatient	Nic	NR	STR	MRS; PET [11C]ABP688	↓ BP_{ND} VS, putamen; NS Glx/H_2O	NS
(Milella et al., 2014)	9 CD 9 HC	37.7 (8.7) 37.2 (8.8)	7M/2F 6M/3F	5.7 (4.1) d	NR	Nic, Alc, Marij	NR	3 STR, 4 PFC, 4 Limbic	PET [^{11}C]ABP688	↓ BP_{ND} striatum, Amyg, Ins	↓ BP_{ND} striatum, Amyg, Ins
(Yang et al., 2009)	14 CD 14 HC	37 (4.9) 34 (9.0)	10M/4F 7M/7F	44 (21) h	NR	Nic	NR	pACC	MRS	↓Glu/Cr	↓ Glu/Cr corr ↓ Coc use yrs
Methamphetamine											
(Crocker et al., 2014)	29 MA 29 Psy 45 HC	25.6 (2.6) 21.9 (3.4) 22.4 (3.3)	18M/11F 23M/6F 36M/9F	370 d (median)	Unspec Tx; Psy: Antipsychotic	NR	NR	ACC / MedPFC	MRS	↓ Glu	NS
(Ernst and Chang, 2008)	25 MA 28 HC	31.8 (7.4) 32.6 (8.8)	11M/14W 14M/14W	2.1 (3.0) mo	Unspec Tx	Nic	NR	PFC, BG	MRS	↓ PFC Glx (≤ 1 mo Abst)	MA: ↓ PFC Glx corr ↓ Abst & ↑ craving
(Howells et al., 2014)	16 MA 10 MA-Psy 19 HC	24.0 (3.7) 24.0 (1.3) 25.0 (5.7)	13M/3F 10M/1F 16M/3F	56 (60) d 60 (53) d	Unspec Rehab, Hospital; MA-Psy: Haloperidol	Nic, Alc, Marij, Quaalude	NR	Bilat ACC, DLPFC	MRS	NS: Glu or Glx	NA

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Reference	Sample	Mean Age (SD)	Sex	Mean Abst Duration (SD)	Medication and/or Tx	Other Drug Use	Psychiatric or Medical	Regions of Interest	Imaging Method	Primary Glutamate Imaging Outcome (vs Controls)	Clinical or Neuropsych Correlates
(O'Neill et al., 2015)	44 MA 24 HC	33.0 (9.4) 33.0 (7.4)	25M/19F 13M/11F	7–10 d	University Inpatient	Nic, Marij, Alc	NR	PCC, Precun, Bilat PFC	MRS	↓ Glx PCC, Precun, R PFC	MA: ↓ Glx PCC corr ↑ use yrs
(Sailasuta et al., 2010)	18 MA 22 HC	35.0 (9.3) 31.9 (9/7)	11M/7F 12M/10F	3–8 wk (7), >20 wk (11)	Rehab or "halfway house"	Coc, Marij, Alc	NR	Med Occip	MRS	NS Glu	NA
Cannabis											
(Muetzel et al., 2013)	27 MJ 26 HC	19.5 (0.6) 19.3 (3.1)	16M/11F 10M/16F	≥12 h	NR	Alc	NR	Dorsal STR	MRS	↓ Glx (F only)	NA
(Chang et al., 2006)	24 MJ 30 HC	36.3 (2.3) 42.2 (2.2)	20M/4F 24M/6F	51.8 (16.7) mo	NR	Nic, Alc, Coc	NR	BG, Thal	MRS	↓ Glu BG	NS
(Prescot et al., 2011)	17 MJ 17 HC	17.8 (1.1) 16.2 (2.1)	15M/2F 8M/9F	Unspec	AntiD	Alc	Depress	ACC	MRS	↓ Glu	NS
Multiple Substances											
(Hulka et al., 2014b)	18 CD 18 HC	36.2 (7.6) 36.2 (8.4)	18M/0W 18M/0W	Unspec	Unspec Tx centers & hospitals	Nic, Alc, Marij, Amph, MDMA	Depress	5 PFC, 2 STR, 5 limbic	PET [^{11}C]ABP688	↓Vnorm (all regions) in smokers (no CD effect)	↓ Vnorm corr more recent smoking
(Mason et al., 2006)	12 AD 8 HC	39 (8.2) 39 (9.0)	12M/0F 8M/0F	5.0 (4.0) d	Inpatient Tx	Marij, Nic, Coc	NR	Occip	MRS	NS Glx; AD: ↑ Glx SM versus non-SM	NA

Abbreviations: (p or d)ACC = (pregenual or dorsal) anterior cingulate cortex, Abst = abstinence, Alc = alcohol, AntiD = antidepressant medication, Approx = approximated values, AUD = alcohol use disorder, Amyg = amygdala, Amph = amphetamine, BG = basal ganglia, Benzos = benzodiazepines, BP = blood pressure, Bup = buprenorphine, Cereb = cerebral cortex, Coc = cocaine, corr = was correlated with, Cr = creatine, Depress = depression, Detox = detoxification program, F= females, GM = gray matter, Glu = glutamate, Hall = hallucinogen use disorder, Hipp = hippocampus, Ins = insula, Lg = long, M = males, MA = methamphetamine use disorder, MJ = marijuana, MDMA = ecstasy, Med = medial, Mid = middle, MJ = marijuana use disorder, mo = month, MRS = magnetic resonance spectroscopy, NA = not applicable, Nic = nicotine, NR = none reported, NS = not significant, Occip = occipital lobe, OCD = obsessive compulsive disorder, OFC = orbitofrontal cortex, ParHipp = parahippocampal gyrus, Pariet = parietal cortex, PET = positron emission tomography, PFC = prefrontal cortex, Pos = posterior, PS = polysubstance users, Psy = psychosis, PTSD, posttraumatic stress disorder, R =right, Sh = short, SM = smoker, Stim = stimulants, STR = striatum, Subco = subcortical regions, Temp = temporal cortex, Thal = thalamus, TP = time point, Tx = treatment, Unspec = unspecified, VS = ventral striatum, wk = week

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Table 2

MRS and PET GABA studies in drug addiction.

Reference	Sample	Mean Age (SD)	Sex	Mean Abst Duration (SD)	Medication and/or Tx	Other Drug Use	Psychiatric or Medical	Regions of Interest	Imaging Method	Primary Glutamate Imaging Outcome (vs. Controls)	Clinical or Neuropsych Correlates
Alcohol											
(Abi-Dargham et al., 1998)	11 AUD 11 HC	44 (8) 43 (10)	11M/0F 11M/0F	98 (46) d	VA Medical Center (Unspec Tx)	NR	NR	5 Cereb, 4 Subco, Cerebel	SPECT [^{123}I]iomazenil	↓V_T PFC ACC, Cerebel	NS
(Behar et al., 1999)	5 AUD 10 HC	46 (11) 35 (7)	Unspec	34 (20) d	VA Medical Center	Nic	NR	Occip	MRS	↓ GABA (+homocarnosine)	↓ GABA corr ↑ delayed memory
(Gilman et al., 1996)	17 AUD 14 HC	52 (Approx) 46 (13)	17M/0F 14M/0F	≥17 d	VA Medical Center (Unspec Tx)	NR	Cerebel degeneration (n=8)	pACC, Cerebel, Pariet, Cereb	PET [^{11}C]flumazenil	↓ V_T pACC	NA
(Jalan et al., 2000)	6 AUD 11 HC	61 55	4M/2F 8M/3F	≥ 6 mo	NR	NR	Cirrhosis	Cereb, Cerebel, BG	PET [^{11}C]flumazenil	↑ V_T	NA
(Lingford-Hughes et al., 1998)	12 AUD 14 HC	43.2 (10.9) 39.9 (8.5)	12M/0F 14M/0F	22.5 (50.2)	Unspec SSRI	MJ, MDMA	Depress	Whole brain	PET [^{123}I]iomazenil	↑ V_T MPFC Pariet	↓ V_T corr ↑ Alc severity
(Lingford-Hughes et al., 2000)	9 AUD 13 HC	42.9 (7.6) 38.1 (9.0)	0M/9F 0M/13F	30.4 (53.2) mo	fluoxetine, venlafaxine, amitriptyline	Coc, Amph	Depress, anxiety, bulimia	Whole brain	PET [^{123}I]iomazenil	NS V_T	NA
(Lingford-Hughes et al., 2005)	11 AUD 10 HC	44.5 (1.8) 46.2 (2.6)	11M/0F 10M/0F	7.3 (5) mo	midazolam challenge; paroxetine or clomipramine	MJ	Depress	ACC, OFC, Occip, Thai, Cerebel	PET [^{11}C]flumazenil	NS V_T	NA
(Lingford-Hughes et al., 2012)	8 AUD 11 HC	44 (7) 43 (7)	8M/0F 11M/0F	33.4 (44.7) mo	Fluoxetine	Nic, MJ	Depress	STR, ACC, Hipp, Ins, OFC	PET [^{11}C]Ro15 4513	↓ V_T Striat, Hipp	AD: ↑ V_T Hipp & ACC, ↑ delayed recall
(Litton et al., 1993)	5 AUD 5 HC	37 25	5M/0F 5M/0F	17 d	Detox, oxazepam	Nic	NR	DLPFC/ MedPFC, Temp, Occip, Cerebel	PET [^{11}C]flumazenil	NS B_{max}	NA
(Pennington et al., 2014)	10 AUD 28 PTSD 20 HC	51.9 (13.9) 35.4 (10.5) 36.3 (12.4)	10M/0F 28M/0F 20M/0F	NS	VA Medical Center (Unspec Tx)	NR	AUD also had PTSD	ACC Occip Temp	MRS	NS GABA	AD: ↑ GABA corr ↑ verbal memory

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Reference	Sample	Mean Age (SD)	Sex	Mean Abst Duration (SD)	Medication and/or Tx	Other Drug Use	Psychiatric or Medical	Regions of Interest	Imaging Method	Primary Glutamate Imaging Outcome (vs. Controls)	Clinical or Neuropsych Correlates
Nicotine/Smoking											
(Stokes et al., 2013)	8 SM 12 HC	48.4 (6.8) 46.4 (7.9)	8M/0F 12M/0F	NS	NR	MJ, Alc, Stim, MDMA	NR	STR, Ins, ACC, pACC, Amyg, Hipp, ParHipp	PET [^{11}C]Ro15 4513	↑ V_T pACC, ParHipp	NS
(Epperson et al., 2005)	16 SM 20 HC	36.0 (16.0) 32.3 (5.9) (Approx)	10M/6W 7M/13W	0h, 48 h (within)	NR	NR	NR	Occip	MRS	↓GABA (women only)	NS
Opiates											
None											
Cocaine											
(Ke et al., 2004)	35 CD 20 HC	43.2 (7.4) 39.2 (8.0)	26M/9F 7M/13F	NS	NR	Alc	NR	pACC/ MedPFC	MRS	↓UGABA	GABA corr years Coc use (Unspec direction)
Methamphetamince											
None											
Cannabis											
None											
Multiple Substances											
(Abe et al., 2013)	28 AUD/PS 40 AD 16 HC	45.3 (9.6) 52.1 (9.1) 49.0 (10.1)	26M/2F 37M/3F 15M/1F	~1 mo	Local VA Tx	Opiates, MJ, MDMA	Hep C, type-2 diabetes, ↑BP, depress	pACC, DLPFC, Occip	MRS	AD/PS: ↓ pACC GABA (uncorrected)	AD/PS: ↓ pACC GABA, ↑ verbal memory
(Cosgrove et al., 2014)	17 AUD/SM 10 AUD 15 HC/SM 10 HC	42 (11) 49 (9) 40 (9) 48 (10)	15M/2F 7M/3F 13M/2F 8M/2F	Alc: Abst Sm: Unspec	Inpatient Tx	NR	Abnormal liver function (3x higher allowed)	Whole brain	PET [^{123}I]iomazenil	↑ $GABA_A$ V_T (buffered by smoking)	AD/SM: ↑ $GABA_AV_T$ corr ↑ crave alc and cig
(Mason et al., 2006)	12 AUD 8 HC	39 (8.2) 39 (9.0)	12M/0F 8M/0F	5.0 (4.0) d	Inpatient Tx	MJ, Nic, Coc	NR	Occip	MRS	↑ GABA (non-SM)	NA

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(Staley et al., 2005)	15 AUD/SM 8 AUD 5 HC/SM 10 HC	40.9 (8.1) 39.9 (8.6) 41.2 (9.2) 35.9 (7.5)	15M/0F 8M/0F 5M/0F 10M/0F	5.0 (2.9) d 4.6 (1.8) d -- --	1 mo Tx	Nic, Benzos	Abnormal liver function (3x higher allowed)	MedPFC, ACC, Amyg, Hipp, Cerebel	PET [^{123}I]iomazenil (baseline &1 mo later)	AD (short Abst): ↑ $GABA_A$ V_T	AD: ↑ MPF $GABA_A$ V_T corr Alc Abst d

Abbreviations, (p or d)ACC = (pregenual or dorsal) anterior cingulate cortex, Abst = abstinence, Alc = alcohol, AntiD = antidepressant medication, Approx = approximated values, AUD = alcohol use disorder, Amyg = amygdala, Amph = amphetamine, BG = basal ganglia, Benzos = benzodiazepines, BP = blood pressure, Bup = buprenorphine, Cereb = cerebral cortex, Coc = cocaine, corr = was correlated with, Cr = creatine, Depress = depression, Detox = detoxification program, F = females GM = gray matter, Glu = glutamate, Hipp = hippocampus, Ins = insula, MA = methamphetamine use disorder, M = males, Marij = marijuana, MDMA = ecstasy, Med = medial, Mid = middle, MJ = marijuana, mo = month, MRS = magnetic resonance spectroscopy, NA = not applicable, Nic = nicotine, NP = neuropsychological, NR = none reported, NS = not significant, Occip = occipital lobe, ParHipp = parahippocampal gyrus, Pariet = parietal cortex, PET = positron emission tomography, PFC = prefrontal cortex, Pos = posterior, PS = polysubstance users, R =right, SM = smoker, Stim = stimulants, STR = striatum, Subco = subcortical regions, Temp = temporal cortex, Thal = thalamus, Tx = treatment, Unspec = unspecified, wk = week