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Neurochemistry of Drug Action: Insights from Proton Magnetic Resonance Spectroscopic Imaging And Their Relevance to Addiction

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Abstract

Proton magnetic resonance spectroscopy (^{1}H MRS) is a non-invasive imaging technique that permits measurement of particular compounds or metabolites within the tissue of interest. In the brain, ^{1}H MRS provides a snapshot of the neurochemical environment within a defined volume of interest. A search of the literature demonstrates the widespread utility of this technique for characterizing tumors, tracking the progress of neurodegenerative disease, and for understanding the neurobiological basis of psychiatric disorders. As of relatively recently, ^{1}H MRS has found its way into substance abuse research, and it is beginning to become recognized as a valuable complement in the brain imaging toolbox that also contains positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI). Drug abuse studies employing ^{1}H MRS have identified a number biochemical changes in the brain. The most consistent alterations across drug class were reductions in *N*-acetylaspartate and elevations in *myo*-inositol, while changes in choline, creatine, and amino acid transmitters also were abundant. Together, the studies discussed herein provide evidence that drugs of abuse may have a profound impact on neuronal health, energy metabolism and maintenance, inflammatory processes, cell membrane turnover, and neurotransmission, and these biochemical changes may underlie the neuropathology within brain tissue that subsequently gives rise to the cognitive and behavioral impairments associated with drug addiction.

Keywords

proton magnetic resonance spectroscopy; human; brain imaging; drug abuse

Introduction

Proton magnetic resonance spectroscopy (^{1}H MRS) is a non-invasive neuroimaging technique that has become a useful tool for a number of applications in drug abuse research. As reviewed herein, ^{1}H MRS is gaining popularity in studies aimed at elucidating the cerebral mechanisms underlying drug-induced neuronal injury and the subsequent behavioral and cognitive changes that can contribute to addiction. Beyond simply determining the cerebral consequences of drug abuse, however, ^{1}H MRS has the potential

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for tracking disease and/or treatment progression. For instance, studies examining the effect of short-term abstinence on the brain of alcoholics demonstrated metabolic changes that were indicative of neuronal and glial regeneration[1–5], while Streeter et al.[6] attempted to correlate changes in neurotransmission to efficacy of candidate treatments for cocaine dependence. Recently, Meyerhoff and Durazzo[7] proposed the idea of correlating levels and patterns of metabolites not only with cognition and behavior, but with genetic information in order to understand better alcohol use disorder. Taken together, ^{1}H MRS is emerging as an informative technique that will become an invaluable instrument for understanding the etiology of drug abuse, as well as for monitoring the long-term recovery from this disease.

I. MEASURABLE COMPOUNDS

In ^{1}H MRS, the visible spectrum depends on the energy absorbed by specific organic molecules, which is determined by the number of hydrogen atoms in the compound as well as in its environment (for a brief overview of the basic principles of MRS, please see[8]). In the brain, current detection limits permit the quantification of a number of chemical peaks in the spectrum once the overwhelming water and lipid signals are suppressed (Figure 1). Most commonly reported include peaks for the metabolites *N*-acetylaspartate (NAA), creatine (Cr), choline (Cho), and *myo*-inositol (mI). Also visible are the metabolically available cellular pools of the amino acids γ-aminobutyric acid (GABA), glutamate (Glu), and glutamine (Gln). To some extent, the visible proton spectrum has begun to transform the way in which drug abuse researchers think about the mechanistic landscape underlying addiction. Neurotransmitters that have dominated the literature such as acetylcholine, norepinephrine, dopamine, and serotonin, are of insufficient concentrations to be visible with the current technology. Similarly, a number of second messengers and ribonucleic acids also are outside of range. However, a good deal of information has been provided by measuring those MR-visible metabolites.

N-acetylaspartate

The most prominent signal in the water-suppressed proton spectrum arises from NAA (for a comprehensive review on NAA, see [9]). Although approximately 15–25% of this signal is due to the contribution of N-acetylaspartylglutamate (NAAG),[10] the spectral peak (at 2.02 ppm) primarily is attributable to the acetyl groups of NAA. Brain concentrations of NAA are rather high[11] and relatively homogeneous,[12] although there is significantly more NAA in grey matter than in white matter.[13] Moreover, Nadler and Cooper[14] demonstrated that NAA is localized almost exclusively to neuronal tissue in comparison to glia, thus rendering NAA a neuronal marker. Reductions in NAA often have been interpreted as being representative of neuronal damage and/or loss (e.g.,[15–18]), or markers for reduction in synaptic density, as well as dysregulated neuronal function and/or neurotransmission (see discussion[19]). Alternatively, as discussed thoroughly in Stork and Renshaw,[20] NAA may serve as a measure of mitochondrial function due to its role in mitochondrial energy production. Taken together, these studies suggest that NAA sub serves several putative functions within the brain.

Creatine

Similar to NAA, Cr is distributed evenly throughout the brain, with higher concentrations in grey matter.[12] The Cr peaks (at 3.03 and 3.94 ppm) are more accurately referred to as total Cr (tCr), since Cr and phosphocreatine (PCr) are indistinguishable from one another. Together the Cr/PCr system has been believed to provide a stable source of energy that typically has been used as an internal reference to normalize ^{1}H MRS data (e.g., [21]) However, concentrations of Cr and PCr have been shown to be unstable not only across disease states,[22–23] but it can vary across regions of healthy brain and with age.[24]

Choline

While Cho is the precursor of acetylcholine within cholinergic neurons, it is the Cho-containing compounds glycerophosphocholine and phosphocholine that contribute to the Cho peak (at 3.2 ppm). Since both are involved in the synthesis and degradation of cellular membranes,[25] they are found in higher concentrations within myelin, and therefore within white matter.[12] The distribution of Cho throughout the brain also is regionally-dependent;[12] as a result, the Cho resonance has the potential to vary quite a bit across disease states, particularly when membrane turnover has been implicated in the etiology.[25–26]

myo-inositol

The exact significance of the mI peak (at 3.56 ppm) is unclear, as there is still much speculation about the precise function of mI within the brain. It has been suggested that mI is an osmoregulator[27] or that it contributes to glucose storage.[28] Other studies have shown that mI is an integral component of the calcium-mobilizing phosphatidylinositol (PI) second messenger system,[29] and abnormalities in this system may contribute to the pathophysiology of several psychiatric illnesses.[30] Most commonly though, mI is used as a marker for glial content.[31]

Glutamate, Glutamine, and GABA

Glu, Gln, and GABA not only maintain an optimal balance between excitation and inhibition within the brain, but they work together to regulate neuronal energy metabolism (see[32]). Although the Glu, Gln, and GABA signals are derived from the large metabolically active cellular pools, they are notoriously difficult to measure with ^{1}H MRS. A number of methods have been developed to circumvent the complicated spectral patterns that arise from their overlapping resonances,[33] but typically the peak (at 2.4 ppm) which is attributed primarily to resonances arising from both Glu and Gln, is considered “Glx”. Similarly, the GABA peak (at 3.03 ppm) comprises Cr and macromolecules[34] as well as homocarnosine.[35] Despite a preponderance of evidence supporting critical roles for altered Glu and/or GABA neurotransmission underlying drug addiction (see reviews[36–37]), the majority of spectroscopic studies have restricted their investigations to metabolites that are comparatively less technically demanding to measure.

II. USING ^{1}H MRS TO UNDERSTAND ILLICIT DRUG USE

PSYCHOSTIMULANTS

Amphetamine congeners—Amphetamine (AMPH), methamphetamine (METH), and its derivative 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy), are highly abused CNS stimulants that have been shown to produce long-lasting neurotoxic effects. A wealth of data exists demonstrating that administration of AMPH is toxic to dopaminergic neurons, MDMA is toxic primarily to serotonergic neurons, and METH damages both dopaminergic and serotonergic nerve terminals while also altering the glutamatergic system (e.g., see reviews[38–39; 40]). This stimulant-induced toxicity is believed to be mediated by oxidative stress and activation of apoptotic pathways, and subsequently, may contribute to the observed cognitive, neurological, and psychiatric disturbances that persist following prolonged use.[41–42]

Amphetamine: To date, the ^{1}H MRS studies examining the neurochemical effects of AMPH have not been from a drug abuse perspective, but rather, AMPH has been administered as a lithium-sensitive model of mania.[43–44] Specifically, dextroamphetamine was administered to healthy volunteers in order to address the hypothesis that lithium-induced depletion of inositol underlies the anti-manic effects of treatment.[45–46] While the

results from a preliminary study indicated that dextroamphetamine increased levels of mI (as a ratio of PCr-Cr) in the temporal lobe,[44] a follow-up study using a sequence optimized for mI[47] failed to demonstrate any change in mI within the dorsal medial prefrontal cortex.[43] The authors concluded that when all things were considered dextroamphetamine had no effect on mI, and thus, changes in mI cannot be relied upon solely to understand the etiology of mania. However, in the context of drug abuse, these data suggest that although AMPH is toxic to dopaminergic neurons,[39] AMPH-induced reductions in dopamine synthesis, dopamine metabolites, and dopamine uptake[48–51] may not be manifested as glial disturbances or inflammatory processes. Of course it should be noted that the clinical MRS studies mentioned here examined an acute dose of dextroamphetamine, while the other studies cited employed a chronic regimen of AMPH administration.

Methamphetamine: METH has been shown to have long-lasting neurotoxic effects in both preclinical and clinical studies. Human neuroimaging studies of METH abusers in particular have demonstrated profound drug-induced changes not only in the dopaminergic[52–53] and serotonergic[54] neurotransmitter systems, but also in cerebral glucose metabolism,[55–57] and the structural integrity of the brain.[58–61] Ernst et al.[62] was the first group to report alterations in metabolite concentrations in METH users relative to healthy controls. In the basal ganglia, they found that NAA and Cr both were reduced,[62] while concentrations of Cho and mI were elevated in frontal gray matter.[62] Subsequent studies corroborated their findings by reporting both reductions in NAA/Cr[63–65] and elevations in Cho/NAA[64–65] within frontal gray matter, frontal white matter elevations in mI,[66] and reduced Cr + PCr/Cho in the basal ganglia.[67] Although together these studies imply that METH exposure leads to subsequent neuronal injury, presently the literature contains only a few studies that provide evidence supporting this hypothesis.

Ernst et al.[62] also demonstrated an inverse relationship between the concentration of NAA in frontal white matter and cumulative lifetime METH exposure, while more recently Sung et al.[66] showed that NAA was reduced in METH users who had consumed a ‘large’ cumulative dose relative to those who had consumed a ‘small’ dose.[66] The reduction in NAA also was shown to be correlated with reduced levels of attentional control as measured by interference on the Stroop test.[65] Finally, decreased levels of Cr + PCr/Cho were correlated not only with longer duration of METH use, but also with severity of residual psychiatric symptoms resulting from METH use.[67] Together, these findings suggest a tangible functional relationship between METH-induced neurochemical alterations and cognitive impairment and/or psychiatric disturbances.

In addition to the effect duration of use may have on metabolite levels and subsequent neuronal injury, varying durations of abstinence from METH use may impact reported values of metabolites. For example, although reductions in NAA have not been consistent across studies, differences in the reported periods of abstinence among participants may explain the apparent discrepancies. When abstinence ranged from 0 to approximately four months NAA levels were reduced compared to controls,[62–63,65] while NAA was not significantly decreased compared to controls when the duration of abstinence was approximately two years.[66] Moreover, NAA was shown to be positively correlated with duration of abstinence, suggesting not only that metabolite levels may recover, but that the neurotoxicity produced by METH may be reversed over time.[66] While Nordahl et al.[64] contradicted this hypothesis by showing no differences in NAA/Cr between those individuals who had been abstinent for 1–5 years (long) vs. those who had been abstinent for six months or less (short), they reported higher ratios of Cho/NAA in the brains of ‘short’ relative to the ‘long’ abstinence participants. These results imply that Cho normalizes as abstinence increases, and they underscore further the hypothesis that the brain may recover from METH-induced insult over time. However, functional studies demonstrating a reversal

in altered metabolite levels concomitant with improvements in cognitive processes and/or psychiatric symptoms have yet to be undertaken.

Recently, Ernst and Chang[40] extended their findings beyond NAA, Cr, Cho, and mI, to include spectroscopic measures of METH-induced adaptations in glutamatergic neurotransmission. Preclinical studies have shown that in addition to serotonin and dopamine, glutamate levels are altered by METH,[68] which may contribute to the mechanisms underlying METH's neurotoxicity.[69] Glx was shown to be low in frontal gray matter, but not in frontal white matter or basal ganglia. Levels of Glx were lowest at the beginning of abstinence (≤ 1 month), and while correlational analysis suggested a normalization of Glx over time with progressive abstinence, a down-regulation of glutamate and/or glutamine during early METH abstinence may have potentially significant implications with respect to METH craving. Participants in the Ernst and Chang[40] study who reported experiencing symptoms of craving had lower Glx in the frontal cortex relative to those who did not; this finding was in agreement not only with a preclinical study that demonstrated reduced levels of basal glutamate during cocaine-seeking,[70] but also with clinical studies that have demonstrated a decrease in drug-taking and cue-reactivity when cocaine-dependent participants were administered medication to increase concentrations of basal glutamate in the brain.[71–72] Although these findings have not been replicated in METH users, Ernst and Chang's report[40] not only provided novel evidence of glutamatergic dysfunction associated with METH use in humans, but it has provided an impetus for improving the methods to permit the measurement of glutamate and glutamine separately for use in drug abuse research.

3,4-methylenedioxymethamphetamine: Despite discrepancies between the animal and human literature, the preponderance of evidence supporting the toxic potential of MDMA suggests that there are residual alterations in serotonergic neurotransmission among human MDMA users.[73] The ramifications of this putative neurotoxicity include the emergence of neurological, psychiatric, and somatic disturbances that have been associated with serotonergic imbalance. Accordingly, case reports suggest that MDMA use may lead to the appearance of a host of problems such as psychosis as well as anxiety, panic, and depressive disorders (for example, see[74–77]). Similarly, more in-depth reports describe MDMA-induced sleep disturbances and cognitive deficits (for references, see[78]).

In ^{1}H MRS studies it has been hypothesized that similar to METH, regular users of MDMA exhibit neuronal loss or dysfunction and/or glial activation. Indeed, levels of NAA (expressed as ratios of both Cr and Cho) have been demonstrated to be reduced in frontal gray matter[79–80] and approaching a significant reduction in the left hippocampus,[81] while mI was elevated in parietal white matter.[82] Moreover, study participants who had lifetime histories of heavy use (i.e., taking upwards of 700+ tablets of ecstasy) exhibited deficits in delayed verbal recall that were strongly associated with the prefrontal reductions in NAA.[79]

The majority of studies, however, have not supported these hypothesized alterations in NAA and/or mI. In fact, there is little consistency among reports of ^{1}H MRS data (reviewed[83]). NAA was found to decrease within brain regions that mediate verbal memory in association with lifetime cannabis use in MDMA polydrug abusers,[84] while it was unchanged in single voxels placed within frontal gray or parietal white matter[82,85–87], neocortex,[81] hippocampus,[89] or occipital regions.[82,85–88] Similarly, mI was unaffected in many of the same regions.[80,84,86–88] Although these studies suggest that MDMA does not induce lasting neuronal injury, it should be noted that they evaluated participants who reported polydrug abuse. In fact, it is difficult to find pure MDMA abusers within the population, as most also co-abuse cannabis, alcohol, or other stimulants.[90] Additionally, participants reported variable estimates of lifetime MDMA exposure. However, data obtained in non-human

primates demonstrated reductions in hypothalamic NAA after exposure to a recreational dose of MDMA.[91] Furthermore, MDMA use in general has been associated with impaired delayed memory function even in the absence of changes in levels of NAA and mI (e.g.,[92]), together suggesting that the sensitivity of current methods may not permit the measurement of long-term neuroadaptations that occur as a result of repeated exposure to MDMA.

Cocaine—Cocaine, like the other psychostimulants, has cognitive, neurological, and psychiatric consequences associated with prolonged use. These effects may be due in part to cocaine's vasoconstrictive effects which are believed to underlie cocaine-related strokes, intracranial hemorrhage, and persistent perfusion deficits (for more details, please see[93]), but they also may be attributed to its ability to increase intracellular calcium,[94] thereby facilitating seizure activity[95] and/or cell death.[96] A number of studies have shown that biochemical mechanisms within the brain (i.e., alterations in brain metabolites) also are associated with cocaine use and may contribute to the etiology of cocaine-induced neuronal dysfunction.

Among the changes in brain metabolites believed to result from prolonged cocaine use, alterations in NAA have been the most commonly reported. Retrospective studies that examined the effects of cocaine have demonstrated decreased thalamic NAA in current cocaine users[19] as well as decreased levels of NAA in mid-frontal gray matter regions among abstinent cocaine-dependent individuals[97] relative to healthy normal controls. However, neither Chang et al.[98] nor Ke et al.[99] observed any alterations in NAA when they examined mid-occipital gray or temporoparietal white matter of abstinent individuals or the left prefrontal lobe of current users, respectively. The predominating dogma regarding the significance of NAA suggests that while levels of NAA may be dynamic and reflective of ongoing processes within neurons (reductions in NAA observed in neurological disease states or brain injury have been shown to be reversible[100–101]), the decrease in NAA associated with chronic cocaine use may result from loss or damage to neurons, a reduction of synaptic density, or even a cocaine-induced depletion of brain monoamines (see discussion[19]). Indeed, a number of imaging studies have shown reductions in brain volume or tissue density consistent with cocaine-induced injury [102–104].

In contrast, opposite findings have been reported after a single acute administration of cocaine. A preliminary report described a significant increase in thalamic NAA (as well as a non-significant increase in Cho) following administration of cocaine to cocaine-dependent participants.[105] Similarly, in men who were only occasional users, an intravenous infusion of cocaine resulted in a dose-dependent increase in NAA (as well as in Cho) within the left basal ganglia.[106] While these results are consistent with an increase in cocaine-induced phospholipid turnover, Christensen et al.[106] hypothesized that cocaine's ability to inhibit Na^+/K^+-ATPase[107] may have led to augmented intracellular water content and cellular swelling,[108–109] and this subsequent osmotic stress may have affected the transverse relaxation times (T_2*) of the NAA and Cho peaks. Although the significance of these collective results still is unclear, NAA may be regulated differentially by acute cocaine vs. prolonged exposure to cocaine over time.

Several other brain metabolites also are believed to be modified following chronic cocaine abuse such as Cr, mI, and GABA. Levels of Cr and mI were shown to be elevated in the temporoparietal white matter of abstinent users, and were correlated with the frequency and duration of use, respectively.[98] A follow-up study examining frontal white matter regions in a younger, less cocaine-experienced cohort found similar results, albeit to a lesser extent.[97] Elevations in mI typically are hypothesized to represent increased glial hypertrophy and/or proliferation, and may suggest a reactive process in response to the chronic insult incurred in the brain by cocaine. Glial hypertrophy subsequently may have led to the increase in Cr

since glial cells contain more Cr than neuronal cells,[31] and Cr levels typically are assumed to remain stable (but see[110]). In order to complicate things further, Chang et al.[97] also reported on sex-related differences in metabolite levels among cocaine users. While males in that study exhibited a reduction in NAA (gray matter) in addition to elevated Cr (white matter) and mI (both white and gray matter), the only abnormality observed in females was elevated mI in frontal white matter. If these differences in metabolite levels truly indicate differences in cocaine-induced brain injury, then not only are they in agreement with previous work showing that women experience fewer cerebral perfusion deficits,[111] but they also provide further support for examining the role of gonadal hormones as potential therapeutics.

Two recent studies have shown that cocaine-dependent individuals have lower prefrontal[99] and occipital[112] GABA levels than healthy controls. In the prefrontal cortex, there was a 30% difference in GABA between groups,[99] while there was a 23% difference in GABA in the occipital cortex.[112] The finding within the prefrontal cortex in particular is significant because the profound impairments in inhibitory control, executive functioning, and decision-making displayed by cocaine-dependent individuals have been localized repeatedly to prefrontal cortical regions.[113] Interestingly, the GABA system has been a promising target for therapeutics aimed at treating cocaine dependence (see review[114]). However it is unclear at this time if increasing levels of GABA, particularly in the prefrontal cortex, is sufficient to have clinical significance with respect to treatment for addiction (e.g.,[6]).

OPIATES

Opiates such as morphine and heroin are powerful analgesics with high abuse liability. Synthetic opioid compounds such as methadone also possess high abuse potential, although methadone's utility extends beyond pain relief to include playing an integral role in the process of opiate detoxification. In addition to the risk of respiratory depression, viral infection, and/or liver damage associated with intravenous administration, current and former opiate abusers tend to display persistent neurocognitive deficits that may result from opiate-induced brain injury (see review[115]). Like many other drugs of abuse, the rewarding effects of opiates are mediated primarily by the mesocorticolimbic dopamine system.[116] It is prefrontal regions, however, that have been implicated in a number of neuropsychological studies demonstrating profound impairments in executive functioning,[115] as well as in brain imaging studies demonstrating reduced activity[117–119] and cerebral blood flow[120–123] in opiate-dependent individuals. Moreover, both T_2-weighted MRI[124] and voxel-based morphometry[125] in opiate-dependent participants have revealed prefrontal white matter hyperintensities and reduced gray matter density, respectively, indicative of neuropathology.

To date, comparatively fewer studies have employed proton MRS to study opiate-induced alterations in neurochemistry. The most commonly reported alteration in metabolite concentration is a non-specific reduction in NAA. For example, NAA was reduced to a similar extent in both the dorsal anterior cingulate[119] and frontal gray matter[126] of opiate-dependent participants maintained on opioid replacement therapy. Case reports also demonstrated cerebellar white matter reductions in NAA among individuals who suffered from heroin-induced leukoencephalopathy, a toxic spongiform encephalopathy resulting from inhaling heroin vapors.[127–128] That the opiate-induced alteration in NAA is similar to that observed among cocaine[97] and methamphetamine [62] abusers suggests that changes in NAA may be non-specific. Indeed, it has been hypothesized that reductions in NAA are indicative of the cerebral hypoxic-ischemic events associated with drug abuse in a more general sense.[126]

Other notable changes in brain chemistry include an increase in lactate in those patients who suffered from leukoencephalopathy.[127–128] Since elevated lactate levels typically are

observed as a result of mitochondrial dysfunction (e.g.,[129]), this finding was interpreted to be indicative of abnormal cellular energy metabolism resulting from the neuropathology associated with this particular condition; this change was not seen in opiate-dependent individuals maintained on stable methadone or buprenorphine.[119] In addition to elevations in lactate, opiate dependence also has been shown to be associated with a decrease in Glx within the dorsal anterior cingulate.[119] Although it is unknown what the subsequent reduction in neuronal excitability contributes to the processes that accompany and/or underlie opiate addiction, the reduction in Glx may represent abnormalities in reward-based learning and decision making, or in the modulation of dopaminergic neurotransmission.[119] Interestingly, despite little clinical spectroscopic evidence supporting the involvement of lactate and Glx in opiate dependence, a recent study in the preclinical literature described similar changes in both the thalamus and somatosensory cortex of rats treated chronically with morphine.[130] Together, these data invite further investigation regarding the role of energy metabolism and neuronal excitability in opiate dependence.

CANNABIS

Of all the illicit drugs of abuse, cannabis causes the most controversy. While reports indicate that cannabis-based drugs provide relief to those who suffer from chronic pain or disease-induced spasticity, there is a vast literature demonstrating impairment in cognitive function, increased incidence of psychotic behavior, and not surprisingly, risk of abuse and/or dependence (see review[131]). Moreover, although cannabis is believed by many to be harmless, both preclinical[132–133] and clinical[134] findings indicate that chronic cannabis use is neurotoxic and has harmful effects on the integrity of brain tissue.

In as much as chronic cannabis consumption surely has an effect on neurochemistry, there only are a couple of studies describing such investigations. Chang et al.[135] demonstrated that in the basal ganglia of individuals who had smoked marijuana almost daily for at least one year, levels of NAA, Cho, and Glu were reduced. Glu also was reduced in the thalamus, while Cr was elevated in this region.[135] In occasional or recreational users, NAA was reduced in the dorsolateral prefrontal cortex, but no metabolite changes were found in the anterior cingulate, striatum, thalamus, or hippocampus.[136] The implication of both studies was that the reduction in NAA could be interpreted as a marker for neuronal dysfunction, although the specific functional significance of such impairment is unclear. Neuropsychological testing returned equivocal results as Chang et al.[135] did not find any deficits in their participants. In contrast, the younger cohort examined by Hermann et al.[136] exhibited cannabis-related deficits on tests assessing attention as well as short-term memory. While there was no correlation between those neuropsychological results and the dorsolateral prefrontal NAA decrease,[136] it is intriguing not only that similar findings have been reported in studies investigating the neurochemical basis of schizophrenia,[137–138] but cannabis use is believed to be a risk factor for schizophrenia in genetically predisposed individuals.[139] Finally, while these results all together highlight the difficulty in drawing inferences about brain function from observed changes in brain metabolites, they provide support for the argument that cannabis indeed may have neurotoxic effects within the brain.

III.USING ^{1}H MRS TO UNDERSTAND LICIT DRUG USE

ALCOHOL

The neurotoxicity of chronic alcohol consumption has been revealed by imaging and histopatholgical studies showing significant atrophy in the brains of alcoholics (see reviews[140–141]). Regions of the brain that appear to be the most sensitive to the effects of chronic alcohol include the neocortex, limbic system, and cerebellum. Subsequently, alcoholics exhibit a host of cognitive and behavioral abnormalities including deficits in

executive functioning, learning and memory, as well as problems with emotion and personality[142].

In order to understand better the neurobiological substrates of the profound brain damage common in alcoholism, a number of ^{1}H MRS studies have been performed (reviewed recently[7]). Reduced levels of NAA[2–5 143–146,148] and Cho[2–3,5, 143–144,148–150] were observed as putative evidence of general neuronal dysfunction in the gray and white matter brain regions of treatment-seeking alcohol-dependent volunteers. Also, levels of mI were elevated, particularly during short-term abstinence from alcohol.[147] This finding suggests a temporary increase in glial activation or an attempt to regulate cell volume in a state of alcohol-induced osmotic stress.[147] Although metabolite reductions did not correlate necessarily with specific brain atrophy, recovery of NAA was correlated with a gain in global brain volume.[1] The recovery of NAA and/or Cho observed in abstinence[1–5,151] is consistent with a study that found no differences in metabolites between healthy individuals and those who had been alcohol-abstinent for two years.[152] Moreover, the reversal of those metabolite abnormalities sometimes was correlated with cognitive improvements.[1–2,5] Together, these findings suggest that similar to the alcohol-induced structural and functional deficits that are at least partially reversible with abstinence (see references[147]), the metabolite abnormalities associated with those impairments also may recover in time.

Metabolite alterations also were observed in studies examining cohorts of active drinkers relative to light drinkers or treatment-seeking abstinent alcoholics. Compared to light drinkers, active heavy drinkers exhibited lower levels of frontal white mater NAA, as well as higher levels of Cho, Cr, and mI in parietal gray matter.[153] While active heavy drinkers also exhibited elevated levels of Cho, Cr, and mI across a number of gray and white matter regions compared to abstinent alcoholics,[154] NAA was higher in the current drinkers.[154] These slightly different patterns of alcohol-induced effects on metabolites in the actively drinking cohort could reflect any number of factors that may modulate neurochemistry differentially (e.g., age, gender, co-morbid psychiatric illness, lifetime exposure to alcohol, withdrawal symptoms, etc.).

Aside from these metabolic alterations, changes in glutamatergic and/or GABAergic neurotransmission have been implicated in the etiology of alcohol abuse (see reviews[36,155]). Consistent with chronic alcohol-induced $GABA_A$ receptor abnormalities and the subsequent glutamatergic hyperactivity observed during withdrawal,[156–157] Glx and Glu/Cr were increased in the basal ganglia[150] and the anterior cingulate[149] of detoxified alcoholics, respectively, while GABA was reduced by approximately 30% in the absence of any other metabolic changes within the occipital cortex.[158] Interestingly, Mason et al.[159] found no differences in occipital GABA levels when comparing alcohol-dependent and healthy volunteers. However, their data revealed that during early abstinence the alcohol-dependent patients who were smokers had significantly lower levels of GABA relative to the non-smokers.[159] While a thorough examination of these data in the context of the literature regarding GABAergic mechanisms mediating alcohol dependence and withdrawal is beyond the scope of this review, a brief discussion of the effect smoking has on the neurochemical findings in alcohol-dependent individuals is warranted and can be found in the next section.

NICOTINE

Nicotine is the component of tobacco that gives rise to the addictive properties of cigarette smoking. Nicotine is an agonist at nicotinic acetylcholine receptors, and like most other drugs of abuse, exerts its reinforcing effects ultimately by increasing dopaminergic neurotransmission within the mesolimbic reward circuitry.[160] A great deal of the nicotine literature has focused on understanding how nicotine and/or smoking may enhance neurotransmission within cortico-basal ganglia-thalamic circuits[161] to have subsequent

effects on learning, memory, and attention (see reviews[162, 163]), as well as reward processing and dependence.[164–165] Brain imaging studies in particular have demonstrated that acute and chronic exposure to nicotine and/or cigarette smoking results in decreased global brain activity but focal activations within prefrontal regions, thalamus, and the visual system.[166] Moreover, nicotine also has been associated with morphological abnormalities in frontal subregions and cerebellum.[164–165]

Preclinical studies have implicated GABA and glutamate in the neurobiological effects of nicotine,[167] and the clinical literature employing ^{1}H MRS supports this claim. Nicotine-dependent women exhibited lower baseline GABA compared to nicotine-dependent men within the occipital cortex,[168] and comparisons of nicotine-dependent women to nonsmoking women revealed reductions during the follicular phase of the menstrual cycle that could not be attributed to differences in smoking habits. Although subsequent investigations have not followed up on those preliminary smoking-related sex differences in GABA, Gallinat and Schubert[169] demonstrated that hippocampal Glu was unchanged between smokers, former smokers, and individuals who had never smoked. In contrast, examination of other metabolites revealed that hippocampal (but not ACC) NAA levels were reduced when smokers were compared to nonsmokers.[170] This finding is consistent with a body of preclinical work suggesting that nicotine has neurotoxic effects on hippocampal neurons (e.g.,[171–173]). To the extent that NAA is a marker for synaptic density and/or neuronal viability,[19] the null result in the ACC does not support previous work demonstrating reduced grey matter volume and grey matter density within that brain region of smokers compared to nonsmokers.[164–165] However, involvement of NAA has been corroborated by a report showing that chronic cigarette smoking was correlated with lower midbrain NAA.[143] Moreover, that study also demonstrated reductions in Cho within the midbrain and cerebellar vermis,[143] together confirming that nicotine and/or smoking has an adverse effect on neuronal function.

As previously discussed, alcohol has a deleterious effect on the brain similar to that of smoking. Interestingly, upwards of 80% of alcohol-dependent individuals also smoke regularly.[174–175] It has been argued that consumption of alcohol facilitates the consumption of nicotine, and subsequently, the co-dependent population may represent a sub-population having unique needs with respect to smoking and/or drinking cessation.[176] However, while chronic cigarette smoking was shown to be detrimental to gray matter tissue volume and perfusion in alcohol-dependent individuals,[163,177] most of the studies demonstrating the effect of alcohol on brain metabolites failed to control for the effects of concurrent nicotine dependence.[1–2,4–5,144–151] Therefore, the extent to which those reported alcoholism-induced metabolite alterations reflected the effects of the combination is unknown.

Studies in which smokers were separated from nonsmokers to determine how smoking affected brain metabolites and neurocognitive functioning in alcohol dependence found that during the first week of abstinence smokers had lower frontal, midbrain, and medial temporal lobe NAA,[143,178] as well as lower Cho within midbrain[143] and medial temporal lobe.[178] After a month of sobriety, smokers exhibited less metabolite recovery while their nonsmoking counterparts exhibited increases in NAA and Cho, as well as more improved cognitive performance.[3,178] Together, these findings indicate that smoking not only compounds the brain damage resulting from alcohol dependence, but it also influences the brain's recovery from the chronic alcoholic insult. Although it is not known how the long-term trajectory of recovery beyond one month is affected by smoking, these preliminary data support the campaign to encourage treatment for both dependencies simultaneously.

TOLUENE

Toluene (methyl benzene) is an organic solvent that is the main component of many commercial and household products such as paint, thinner, glue, and lighter fluid. Because it is legal and readily accessible, it is one of the most commonly abused substances among adolescents.[179] The adolescent brain is particularly vulnerable to toluene-induced toxicity not only because toluene's highly lipophilic nature leads to its accumulation in the lipid-rich white matter regions of the brain,[180–181] but also because the proportion of white matter is increased during this time of neuronal development consequent to an increase in myelination.[182] Accordingly, much of the damage observed in the brains of individuals who were exposed to toluene chronically was localized to white matter regions (in addition to periventricular and subcortical regions)[183] and correlated significantly with neurological,[184] psychological,[185] and cognitive deficits.[186]

Although the brain abnormalities as well as subsequent encephalopathy and neuropsychological deficits associated with toluene abuse in humans have been acknowledged in a number of publications,[187–190] there is no consensus regarding the mechanism underlying this damage. However, a number of animal studies have demonstrated changes in neurochemistry by measuring levels of acetylcholine,[191] dopamine,[192–193] GABA,[194] and glutamate,[195] following administration of toluene. Similarly, the few studies employing MRS in humans have used this technology as a way to probe the neurochemical processes underlying toluene exposure in an effort to provide mechanistic substantiation of toluene-induced brain damage. For example, NAA was reduced within white matter in two individuals (ages 19 and 20) who had abused organic solvents for 6–7 years and who also experienced symptoms of encephalopathy such as unsteady gait, tremor, diplopia, dysarthria, and impaired IQ relative to healthy controls.[196] Likewise, young adults (ages 15–23) who had abused paint thinner for 2–3 years had lower levels of NAA as well as higher levels of mI in cerebral and cerebellar white matter, but not in the thalamus, relative to their age-matched controls.[197] Moreover, these neurochemical changes were correlated with the self-reported duration of use.[197]

A reduction in NAA typically has been interpreted to represent a reduction in neuronal number or loss of neuro-axonal integrity in general,[9] but these results were interpreted to be indicative primarily of axonopathy. Because NAA levels were spared within the thalamus, an area with higher neuronal density compared to the white matter and cerebellum, the authors concluded that the etiology of toluene encephalopathy did not involve the targeting of neurons per se.[197] This conclusion is supported by other studies that failed to identify neuronal loss or morphological abnormalities,[183,198] but demonstrated degeneration of axons,[199] in post-mortem tissue. Additionally, the elevated levels of mI observed by Aydin et al.[197] may reflect toluene-induced gliosis and astrocytic activation rather than neuronal death following chronic exposure to toluene. Indeed, glial cell marker proteins have been shown to be increased, particularly in cerebellum, of rats exposed to toluene in a chronic dosing paradigm.[200–202] Taken together, these data suggest that axonopathy and gliosis seem to underlie the encephalopathy observed following chronic toluene exposure.

It has been suggested that in addition to gliosis, the demyelination observed in post-mortem tissue[183,199] also may underlie the toluene-induced white matter lesions observed with MRI.[184] This hypothesis has been supported by findings in the basal ganglia showing that levels of Cho/NAA and Cho/Cr + PCr (but not NAA/Cr + PCr or mI/Cr + PCr) were elevated among abstinent toluene abusers relative to controls.[203] An increase in the Cho peak as measured with MRS is indicative of an increase in membrane phospholipids which may be released during membrane decomposition, thereby representing active demyelinating processes.[25] However, five of the 12 participants in this study also were taking neuroleptic medication to manage their psychiatric symptoms, and Cho has been shown previously to be

sensitive to this type of medication.[204–206] Moreover, alterations in white matter Cho did not reach statistical significance in the results reported by Aydin et al.[197], together suggesting that demyelination may occur in toluene abuse, but most likely it is not the primary mechanism of neurotoxicity.

IV.SYNTHESIS OF METABOLIC CHANGES IN DRUG ABUSE AND FUTURE DIRECTIONS

Of all the changes in metabolites (Table 1) and amino acids (Table 2) that have been measured to date, there is considerable overlap across drug classes (Table 3). Reductions in NAA and elevations in mI were observed almost universally, thus indicating that drugs of abuse in general have a profound impact on neuronal health, energy metabolism, and inflammatory processes. The next most common metabolite changes involved alterations in Cho and Cr, suggesting that methamphetamine, cocaine, cannabis, and alcohol influence cell membrane turnover as well as energy maintenance. Methamphetamine, opiates, cannabis, and alcohol were found to alter Glx to some extent, while GABA was reduced by cocaine, alcohol, and nicotine, together suggesting that drugs of abuse impact neurotransmission. While not all drugs of abuse were associated with changes in all the metabolites represented, it should be noted that not every study measured every visible metabolite. In fact, quantifying metabolites with strongly coupled spins such as mI, Glx, and GABA require specific advanced techniques as well as stronger magnetic field strength.[47,207] However, as ^{1}H MRS becomes more widely recognized as a means to evaluate the substrates of drug action, the technology has the potential to evolve into a more automated and user-friendly procedure.

These ^{1}H MRS data add a new dimension to the existing wealth of knowledge regarding the detrimental effects of drugs of abuse on the brain. Specifically though, what have we learned about addiction from measuring brain metabolites? Studies investigating the etiology of other brain diseases have begun using ^{1}H MRS to probe functional relationships between metabolite alterations and other measures of pathology. For example, levels of NAA have been shown to correlate with hippocampal volume, memory, and intelligence in patients with medial temporal lobe epilepsy (e.g.,[208]). Similarly, drug abuse research has begun to benefit from examining the relationships between metabolites and drug-induced impairments in neurocognitive function. Correlation analyses have revealed associations between reduced NAA in frontal regions and attentional control as well as impaired verbal memory among participants who had histories of abusing methamphetamine[65] and MDMA, [79] respectively. These results are in agreement with other research that has shown a correlation between levels of frontal NAA and measures of selective attention[209] and memory.[210] Moreover, they agree with findings obtained in alcoholics showing that various measures of learning and memory improved as levels of NAA (and Cho) recovered during abstinence.[3] In general, a great deal of research has shown that deficits in attention[211] and memory[212] may contribute to processes that underlie drug-seeking behavior, thereby necessitating an understanding of the neurochemical mechanisms mediating those processes and subsequent behavioral output.

Although other metabolite-behavior relationships have been demonstrated (e.g., Ernst and Chang[40] showed that reduced frontal Glx correlated with ratings of craving while Sekine et al.[67] correlated reduced Cr in the basal ganglia with the severity of residual psychiatric symptoms after use), all together, the information gleaned from ^{1}H MRS studies at this point mostly seem to corroborate decades of previous research. Moreover, several studies have demonstrated that metabolite reductions recover during abstinence from alcohol[1–5,151] or methamphetamine,[64,66] suggesting that perhaps the long-term neuroadaptations that maintain drug-seeking and drug-taking behaviors cannot be explained by the particular

changes in neurochemistry that are measurable with ^{1}H MRS. Meyerhoff and Durazzo[7] suggested recently that in addition to relating metabolite levels to cognition, genetic polymorphism data might provide an additional piece of information that could help elucidate not only the neurobiological mechanisms underlying substance abuse disorder, but also to identify risk factors and disease severity.

Indeed, the strength of this technology in drug abuse research may lie in its utility as a diagnostic tool to predict treatment matching, to monitor the progress of treatment, or to prevent relapse. Although currently ^{1}H MRS is used routinely to monitor the course of treatment and determine therapeutic strategies in a number of other brain illnesses such as tumors, multiple sclerosis, and Alzheimer's disease,[213] the potential of these applications has not been explored thoroughly in the context of drug abuse. A recent study by Streeter et al.[6] demonstrated the use of ^{1}H MRS as a tool for assessing treatment efficacy. The study aimed to correlate changes in the level of prefrontal GABA with reduced cocaine consumption in cocaine-dependent volunteers after eight weeks of treatment with modest doses of the candidate therapeutics pramipexole or venlafaxine. Previous studies had shown that GABA was reduced in the left prefrontal lobe of cocaine-dependent volunteers,[99] and that GABA-enhancing drugs reduced cocaine self-administration in laboratory animals[214–215] and humans.[216–219] Although both pharmacologic treatments increased levels of GABA significantly relative to placebo, cocaine use was not reduced in either treatment group.[6] However, the maximum increase in GABA was still approximately 19% lower than control levels,[99] suggesting that dose of drug may have been partly to blame. Regardless, this study is a prime example demonstrating the usefulness of ^{1}H MRS within a treatment paradigm.

Although this review focused on metabolite changes that occur following exposure to drugs of abuse in the adult brain, drug abuse may begin in childhood and/or adolescence, and exposure may occur even in utero. ^{1}H MRS has the potential to be an invaluable method for studying these vulnerable populations. The lack of ionizing radiation makes ^{1}H MRS suited for undertaking longitudinal studies, particularly during the more active periods of brain development. In fact, ^{1}H MRS already has been used to begin understanding the biochemical maturation of the brain not only in terms of specific metabolites, but also in terms of water content, relaxation properties, and myelination.[220–221] In drug abuse, ^{1}H MRS was used in a small study that employed children to examine the neurotoxic effects of prenatal exposure to methamphetamine on the developing brain.[222] Findings showed that despite the absence of structural abnormalities, exposed children (ages 3–16) had relatively normal levels of NAA but elevated levels of Cr in the striatum relative to age-matched controls.[222] These results were in contrast to the reduction of Cr (and NAA) observed in this region of adults who have abused methamphetamine.[62,67] They suggest that although methamphetamine-induced biochemical alterations occur in both children and adults, prenatal exposure to methamphetamine can disrupt energy metabolism differentially in children, which may have clinical implications with respect to cognitive function in these individuals as their development progresses.[222] Moreover, these results underscore the importance of utilizing ^{1}H MRS technology to study the effects of drugs of abuse in the developing brain.

Finally, ^{1}H MRS may prove to be a useful modality for studying the etiology of addiction in general. A great deal of research has suggested that chronic drug abuse shares neurobiological underpinnings with other addictive disorders such as bulimia nervosa, pathological gambling, and sexual addiction.[223] Although to date the findings have been restricted to the effects of those reinforcers on the monoamine and opioid receptor system and their downstream signaling cascades, it is likely that other addictive disorders would yield to study with ^{1}H MRS just as well. In fact, it would be interesting to determine if pathological gambling, eating, or sexual appetite reduced NAA to a similar extent as drugs

of abuse. While it is unlikely that these non-chemical reinforcers would reduce neuronal health and/or viability on their own (independent of a history of head trauma or some type of brain injury), a reduction in NAA would give pause with respect to its hypothesized function as an outcome measure indicating neuronal viability. Such results may hint at metabolite differences as predisposing factors, although the recovery of NAA during abstinence from drugs of abuse argues against that idea. However, ^{1}H MRS studies investigating the effects of natural reinforcers on brain chemistry would help elucidate some of the neurobiological mechanisms contributing to reward and reinforcement in general.

Other spectroscopy methods

Without going into much detail, it should be noted that in addition to ^{1}H, ^{31}P and ^{13}C MRS also hold a great deal of promise for in vivo drug abuse research. Phosphorous spectra contain information regarding phospholipid metabolism, tissue bioenergetics, and pH. Specifically, the major peaks in the spectra correspond to phosphomonoesters (PME) and phosphodiesters (PDE), both of which contribute to phospholipid metabolism.[224–225] Major peaks also correspond to high-energy phosphates phosphocreatine (PCr), inorganic phosphate (Pi), and α-, β-, and γ-nucleoside triphosphate (NTP). Using ^{31}P MRS, several studies have reported abnormalities in phospholipid and bioenergetic metabolism in the brains of cocaine-dependent polydrug abusers[226–227] and heroin-dependent individuals early in their methadone maintenance therapy.[228–229] These results are consistent with those obtained using ^{1}H MRS, altogether suggesting drug-induced changes in cerebral bioenergetic states that may shift with increased abstinence and/or treatment, as well as putative membrane changes that may be associated with neuronal viability.[19,82,119,126]

^{13}C MRS has been developed relatively recently as a non-invasive measure of specific metabolic fluxes within the human brain. This technique exploits the rapid synthesis of glutamate, glutamine, and GABA by monitoring the incorporation of ^{13}C atoms of labeled precursors (e.g., [^{1}–^{13}C]-glucose) into the intermediate metabolites of the tricarboxylic acid (TCA) and glutamate-glutamine cycles.[230] Subsequently, ^{13}C MRS provides information regarding the basic mechanisms governing glial-neuronal interactions, particularly with respect to glutamatergic function.[231] Previous ^{13}C MRS studies have demonstrated an inextricable link between glutamate neurotransmission and glucose consumption (which undoubtedly has been advantageous for interpreting the brain activation observed using functional imaging modalities),[232–233] but the potential for this technique to be used drug abuse research is untouched. In fact, the use of ^{13}C MRS in human psychiatric research in general is still in its infancy, most likely owing in part to the trade-off between long infusion times of substrate or reduced sensitivity when it is administered orally.[234] However, the need to understand better how abnormalities in glia and/or amino acid neurotransmission contribute to the etiology of substance abuse (as well as a multitude of other psychiatric illnesses), will drive the technology to evolve.

Limitations

When considering the ^{1}H MRS findings as a whole, there are several methodological and technical and limitations to take into account. First, many of the drug abuse studies summarized here relied on self-report of retrospective drug use. Although self-report is a critical aspect of many drug abuse studies, underreporting drug use is common, it varies across participant populations and with specific drug of abuse,[235] and it can become challenging when the purity of the drug consumed is in question (e.g., only 63% of ecstasy pills contain actual MDMA).[236] Moreover, MDMA abusers in particular are notorious for being polydrug abusers,[90] further complicating interpretation of any metabolite alterations in this group of individuals. The retrospective study design is problematic in that one cannot draw inferences about a causative link between drug intake and putative neurobiological

consequences. However, given the ethical issues surrounding administering potentially toxic drugs of abuse to human volunteers (e.g., cocaine's effects extend beyond brain injury and include cardiovascular damage),[237] most studies to date have used this design which, while somewhat dissatisfying, is at least consistent across studies.

Although ^{1}H MRS has proven to be an amazing research tool, there are limitations to this technology with respect to the acquisition, quantification, and interpretation of the spectra. A number of these practical issues have been described at length elsewhere (please see[238–239]), but a few shortcomings stand out. For example, ^{1}H MRS does not have the spatial or temporal resolution of some other imaging techniques. The user must consider employing a single-voxel design versus chemical-shift imaging of a slab across the brain (potentially upwards of 40–50 voxels). A single-voxel design permits control of localization, improved shimming and water suppression, and requires shorter measurement times,[240–241] but these advantages are predicated on having chosen the correct voxel for the measurement of interest. Chemical-shift imaging, on the other hand, can cover a larger region of interest, but as a result it precludes precise localization, requires a longer acquisition time, and increases field inhomogeneity.[240–241] Importantly, neither design is capable of providing information about a specific compartment where metabolite changes are taking place. For instance, while the overall concentration of glutamate in the brain is approximately 12 mM, concentrations vary between gray matter and white matter due to different rates of synthesis and oxidation across tissue.[28] Moreover, ^{1}H MRS does not permit differentiation between the cytosolic vs. vesicular pools within those gross compartments.[242] Therefore, it is difficult to pinpoint the origin of any metabolite changes, which ultimately does limit interpretation of spectral changes.

Similarly, regardless of the fact that the chemical-shift approach allows the investigator to obtain multiple spectra simultaneously while the single-voxel approach results in one spectrum, the spectra themselves are only "snapshots" of the neurochemical environment during the acquisition. Although temporal resolution is determined in part by the strength of the magnetic field, even at high-fields (≥ 3 T) data is acquired on the order of minutes.[207] This timeframe is acceptable for studies that employ retrospective or longitudinal designs, but using ^{1}H MRS for human behavioral pharmacology during acute drug administration (e.g., [243]) may benefit from faster acquisition. Taken together, although ^{1}H MRS provides a non-invasive window into neurochemical changes associated with substance abuse, it still can be considered a crude measurement.

Conclusions

Neuroimaging techniques such as ^{1}H MRS are invaluable tools for understanding the brain. The studies presented here suggest that reduced NAA and elevated mI may be neurochemical hallmarks of drug abuse-induced injury within the brain. Whether these changes are a result of the effects of the chemicals on the brain specifically or whether they reflect the neurobiology driving the addictive process in general (i.e., impairments in motivation-reward, affect regulation, and behavioral inhibition as reviewed[223]), is unknown. In addition to gaining insight regarding the neurochemical outcomes of drug abuse, ^{1}H MRS also may provide an opportunity to match individuals with the most suitable treatment, monitor treatment efficacy, and predict and/or prevent relapse. Consequently, ^{1}H MRS potentially could have a profound impact on future drug abuse research.

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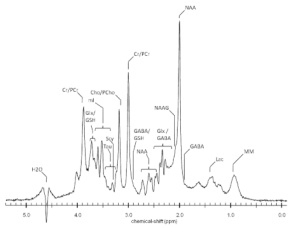

Figure 1.

Proton spectrum acquired at 4 tesla from a 16cc voxel within the parieto-occipital cortex of a 26-year old healthy male volunteer. Cho/PCho: choline/phosphocholine, Cr/PCr: creatine/phosphocreatine, GABA: γ-aminobutyric acid, Glx: glutamate/glutamine, GSH: glutathione, H2O: water, Lac: lactate, mI: *myo*-inositol, MM: macromolecules, NAA: *N*-acetylaspartate, NAAG: *N*-acetylaspartylglutamate, Scy: *scyllo*-inositol, Tau: taurine. [Courtesy of J. Eric Jensen, Ph.D., Brain Imaging Center, McLean Hospital/Harvard Medical School].

Table 1

Summary of reported metabolite changes with drugs of abuse

	NAA	Cho	Cr	mI
Amphetamine[a]	----------	----------	----------	Increase (TL) None (PFC)
Methamphetamine[b]	Decrease (BG, FGM)	Increase (FGM)	Decrease (BG)	Increase (FGM, FWM)
MDMA[c]	Decrease (FGM, HP) None (FGM, PWM, NC, HP, OCC)	----------	----------	Increase (PWM) None (FGM, PWM, OCC)
Cocaine[d]	Decrease (FGM, TH) Increase (BG, TH) None (OCC, PWM)	Increase (BG)	Increase (PWM)	Increase (FGM, PWM)
Opiates[e]	Decrease (ACC, FGM, CBL)	----------	----------	----------
Cannabis[f]	Decrease (BG, PFC)	Decrease (BG)	Increase (TH)	
Alcohol[g]	Decrease (CBL, FGM, FWM, TH, TL)	Decrease (PGM, TH, CBL) Increase (PGM, TL)	Increase (PGM)	Increase (ACC, PGM, TH)
Nicotine[h]	Decrease (HP) None (ACC)	----------	----------	----------
Toluene[i]	Decrease (CBL, CWM) None (BG, TH)	Increase (BG)	----------	Increase (CBL, CWM) None (BG, TH)

ACC= anterior cingulate, BG= basal ganglia, CBL= cerebellar white matter, CWM= cerebral white matter, FGM= frontal gray matter, FWM= frontal white matter, HP= hippocampus, NC= neocortex, OCC=occipital cortex, PFC= prefrontal cortex, PGM= parietal gray matter, PWM= parietal white matter, TH= thalamus, TL= temporal lobe

[a]McGrath et al. 2008; Silverstone et al. 2002

[b]Ernst et al. 2000; Nordahl et al. 2002, 2005; Salo et al. 2007; Sung et al. 2007; Sekine et al. 2002

[c]Chang et al. 1999; Cowan et al. 2007; Daumann et al. 2004; de Win et al. 2007, 2008; Obergriesser et al. 2001; Reneman et al. 2001, 2002

[d]Chang et al. 1997, 1999; Christensen et al. 2000; Li et al. 1998, 1999

[e]Haselhorst et al. 2002; Kriegstein et al. 1999; Offiah et al. 2008; Yücel et al. 2007

[f]Chang et al. 2006; Hermann et al. 2007

[g]Bartsch et al. 2007; Bendszus et al. 2001; Durazzo et al. 2004, 2006; Ende et al. 2005; Gazdzinski et al. 2008a; Jagannathan et al. 1996; Lee et al. 2007; Martin et al. 1995; Meyerhoff et al. 2004; Miese et al. 2006; Parks et al. 2002; Schweinsburg et al. 2000, 2001, 2003; Seitz et al. 1999

[h]Durazzo et al. 2004; Gallinat et al. 2007

[i]Noda et al. 1996; Aydin et al. 2003; Takebayahsi et al. 2004

Table 2

Summary of reported amino acid changes with drugs of abuse

	Glx	GABA
Methamphetamine	FGM: Decrease (Ernst and Chang, 2008)	----------
Cocaine	----------	PFC: Decrease (Ke et al. 2004) OCC: Decrease (Hetherington et al. 2000)
Opiates	ACC: Decrease (Yücel et al. 2007)	----------
Cannabis	BG, TH: Decrease (Chang et al. 2006)	----------
Alcohol	ACC: Increase (Lee et al. 2007) BG: Increase (Miese et al. 2006)	OCC: Decrease (Behar et al. 1999); No change (Mason et al. 2006)
Nicotine	HP: No change (Gallinat and Schubert, 2007)	OCC: Decrease (Epperson et al. 2005)

ACC= anterior cingulate, BG= basal ganglia, FGM= frontal gray matter, HP= hippocampus, OCC=occipital cortex, PFC= prefrontal cortex, TH= thalamus

Table 3

Simplified summary of overlapping metabolite findings across drug classes

Metabolite	Decrease	Increase
NAA	Methamphetamine, MDMA, Cocaine, Opiates, Cannabis, Alcohol, Nicotine, Toluene	Cocaine (acute administration)
Cho	Cannabis, Alcohol	Methamphetamine, Cocaine, Alcohol
Cr	Methamphetamine	Cocaine, Cannabis, Alcohol
mI	------	Amphetamine, Methamphetamine, MDMA, Cocaine, Alcohol, Toluene
Glx	Methamphetamine, Opiates, Cannabis	Alcohol
GABA	Cocaine, Alcohol, Nicotine	------