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Polysubstance and alcohol dependence: Unique abnormalities of magnetic resonance-derived brain metabolite levels

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ABSTRACT

Background: Although comorbid substance misuse is common in alcohol dependence, and polysubstance abusers (PSU) represent the largest group of individuals seeking treatment for drug abuse today, we know little about potential brain abnormalities in this population. Brain magnetic resonance spectroscopy studies of mono-substance use disorders (e.g., alcohol or cocaine) reveal abnormal levels of cortical metabolites (reflecting neuronal integrity, cell membrane turnover/synthesis, cellular bioenergetics, gliosis) and altered concentrations of glutamate and γ-aminobutyric acid (GABA). The concurrent misuse of several substances may have unique and different effects on brain biology and function compared to any mono-substance misuse.
Methods: High field brain magnetic resonance spectroscopy at 4 T and neurocognitive testing were performed at one month of abstinence in 40 alcohol dependent individuals (ALC), 28 alcohol dependent PSU and 16 drug-free controls. Absolute metabolite concentrations were calculated in anterior cingulate (ACC), parieto-occipital (POC) and dorso-lateral prefrontal cortices (DLPFC).
Results: Compared to ALC, PSU demonstrated significant metabolic abnormalities in the DLPFC and strong trends to lower GABA in the ACC. Metabolite levels in ALC and light drinking controls were statistically equivalent. Within PSU, lower DLPFC GABA levels are related to greater cocaine consumption. Several cortical metabolite concentrations were associated with cognitive performance.
Conclusions: While metabolite concentrations in ALC at one month of abstinence were largely normal, PSU showed persistent and functionally significant metabolic abnormalities, primarily in the DLPFC. Our results point to specific metabolic deficits as biomarkers in polysubstance misuse and as targets for pharmacological and behavioral PSU-specific treatment.

1. Introduction

Magnetic resonance imaging (MRI) and proton MR spectroscopy (1H MRS) are invaluable tools in addiction research, as they permit non-invasive interrogation of the integrity of multiple aspects of neurobiology. MRS studies that investigate the neurobiological effects of cocaine, amphetamines, or marijuana (i.e., mono-substance dependence) have revealed abnormal levels of markers of neuronal integrity (N-acetylaspartate, NAA), cell membrane turnover/synthesis (choline-containing metabolites, Cho), cellular bioenergetics (Creatine, Cr), astrogliosis (myo-Inositol, mI) and alterations of glutamate (Glu) and γ-aminobutyric acid (GABA), which are the primary excitatory and inhibitory neurotransmitter/neuromodulators in the human brain (for review see Licata and Renshaw, 2010). Alterations in brain metabolite concentrations have also been observed in alcohol dependent individuals (ALC), primarily in the frontal lobes (Buhler and Mann, 2011; Durazzo and Meyerhoff, 2007; Mon et al., 2012; Sullivan et al., 2000). We showed recently that concentrations of Glu, NAA and Cr in the anterior cingulate cortex (ACC) of nine-days-abstinent ALC were significantly lower than in healthy controls; mI and γ-aminobutyric acid (GABA) in ACC as well as the other metabolite levels in the dorsolateral prefrontal cortex (DLPFC) and parieto-occipital cortex (POC) were normal (Mon et al., 2012). Over 30 days of abstinence from alcohol, the ACC metabolite concentrations largely normalized (Mon et al., 2012). Furthermore, mono-substance abuse/dependence is associated with neurocognitive dysfunction (Abi-Saab et al., 2005; Di Sclafani et al., 2002; Hester and Garavan, 2004; Lundqvist, 2005; Moeller et al., 2005;

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Oscar-Berman, 2000; Salo et al., 2002; Simon et al., 2000; Verdejo-Garcia et al., 2011; Volkow et al., 2001), and improvements in functions such as learning, processing speed and working memory have been shown to relate to metabolic changes during abstinence (Meyerhoff et al., 2011).

Alcohol use disorders (AUD) are often accompanied by comorbid misuse of illicit drugs, such as cocaine and methamphetamine (Stinson et al., 2005), and their misuse, individual or combined, is associated with significant neurobiological, neurocognitive and psychiatric abnormalities (Licata and Renshaw, 2010). Individuals with concurrent abuse/dependence on more than one substance including alcohol (i.e., polysubstance abusers or PSU) represent the largest group of individuals seeking treatment for substance use disorders in the United States today (Kedia et al., 2007; Medina et al., 2004). Furthermore, more than 50% of patients treated for drug abuse relapse within one year of treatment (McLellan et al., 2000). Identification of the unique and common neurobiological abnormalities and related neurocognitive characteristics in PSU and ALC will facilitate the development of more efficacious pharmacological and behavioral interventions for these groups. Thus, measuring potentially unique neurobiological abnormalities and related neurocognitive characteristics in treatment seeking PSU and ALC is thought to be of high clinical importance.

Each class of substances alters neuronal integrity and neurotransmission via different mechanisms (Buttner, 2011; Licata and Renshaw, 2010). Their combined abuse may have unique, even different adverse effects on the brain than any mono-substance abuse. While there are numerous neuroimaging studies on effects of individual substances on brain biology, few studies have investigated drug effects in PSU. These can be summarized as follows: two-week-abstinent PSU had prefrontal gray matter (GM) atrophy (Liu et al., 1998). Cocaine use disordered ALC tended to have greater age-related white matter (WM) volume decreases (Bjork et al., 2003) and persistently lower NAA concentrations in the DLPFC than ALC (Meyerhoff et al., 1999). During early withdrawal, PSU demonstrated cerebral phosphorus metabolite alterations (Christensen et al., 1996). Actively using PSU had higher glucose metabolism rates in frontotemporal cortex than drug-free controls (Stapleton et al., 1995); those rates, however, were lower in the right orbitofrontal cortex of one-week-abstinent individuals abusing both methamphetamine and marijuana compared to "pure" methamphetamine abusers (Voytek et al., 2005). Non-abstinent cocaine dependent ALC showed lower frontal GABA levels than controls (Ke et al., 2004). Abstinent ALC with concurrent cocaine dependence had less WM in prefrontal brain regions than those dependent on only one substance (O'Neill et al., 2001). Consistent with these neurobiological abnormalities, studies in PSU have also indicated impaired cognition compared to controls (Di Sclafani et al., 2002; Ersche et al., 2011; Horner, 1997; Selby and Azrin, 1998; Verdejo-Garcia et al., 2004, 2007). These few reports illustrate that neurobiological correlates of polysubstance use disorders, as well as their associations with neurocognition, are complex and still unclear.

To better understand metabolic alterations in a well-characterized cohort of abstinent PSU, the specific goals of this study were to measure metabolite concentration differences between abstinent PSU and ALC using high-field MRS in brain regions with relevance to the development and maintenance of substance use disorders, and to measure potentially associated neurocognitive (dys)function. Based on the cited literature, we hypothesized unique and functionally significant regional metabolite concentration differences between one-month-abstinent PSU and ALC as well as light drinking controls (LD), and specifically lower cortical NAA (in the DLPFC) and GABA levels in PSU compared to both ALC and LD.

2. Materials and methods

2.1. Participants

All participants provided written informed consent prior to study according to the Declaration of Helsinki and underwent procedures approved by the University of California, San Francisco and the San Francisco VA Medical Center. Twenty eight treatment seeking PSU and 40 ALC were recruited from substance abuse treatment programs of the VA and Kaiser Permanente. All ALC and PSU participants met DSM-IV criteria for alcohol dependence. In addition, PSU participants met DSM-IV criteria for dependence on at least one psychostimulant, with and without marijuana use disorder: cocaine ($n = 18$), methamphetamine ($n = 4$), cocaine and methamphetamine ($n = 4$); 2 PSU were dependent on other substances (opiates, marijuana, and/or ecstasy). Group demographics and relevant substance use characteristics are given in Table 1.

At study date, ALC and PSU were abstinent from alcohol and other substances, except nicotine, for approximately one month. Further inclusion and exclusion criteria are fully detailed elsewhere (Durazzo et al., 2004). Participants were excluded for neurological or psychiatric disorders known to affect neurobiology or neurocognition. Hepatitis C, type-2 diabetes, hypertension, and unipolar mood disorders were permitted given their high prevalence in substance use disorders (Hasin et al., 2007; Mertens et al., 2003, 2005; Parekh and Klag, 2001; Stinson et al., 2005). Sixteen light drinking controls (LD) without history of biomedical and/or psychiatric conditions known to influence the measures obtained in this study were recruited from the local community. Data from 85% of ALC and 94% of LD participants contributed to previous analyses (Mon et al., 2012).

2.2. Clinical assessment

ALC and PSU participants completed the Structured Clinical Interview for DSM-IV Axis I Disorder Patient Edition, Version 2.0 (First et al., 1998), and LD participants were administered the accompanying screening module. Within one day of the MR study, all participants filled out questionnaires that assessed depression (Beck Depression Inventory; Beck, 1978) and anxiety symptomatologies (State-Trait Anxiety Inventory, Y-2; Spielberger et al., 1977). Alcohol consumption was assessed with the lifetime drinking history semi-structured interview (Skinner and Sheu, 1982; Sobell and Sobell, 1990; Sobell et al., 1988), which yielded estimates of the average number of alcoholic drinks consumed per month over 1 year and 3 years, before enrollment and over lifetime. For PSU, lifetime substance use history (other than alcohol) was assessed with an in-house interview questionnaire based on the Addiction Severity Index (McLellan et al., 1992), NIDA Addictive Drug Survey (Smith, 1991), drinking history, and Axis I disorders Patient Edition, Version 2.0 (SCID-I/P; First et al., 1998). This instrument gathers information relevant to phases of drug use for each substance a participant has a current or past disorder diagnosis on; including age of first and last use, number of total lifetime phases, duration of individual and total lifetime phases (including phases of abstinence), frequency and quantity of use during each phase, and route of administration. It includes conversion of money spent per day to one metric, using catchment area-specific conversion norms. Thus, monthly averages for grams of cocaine and/or methamphetamine over 1 year prior to enrolment and over lifetime were estimated. Level of nicotine dependence was assessed via the Fagerstrom Tolerance Test for Nicotine Dependence (Fagerstrom et al., 1991), and total numbers of years of smoking and average daily cigarettes currently smoked were recorded. To evaluate basic nutritional and erythrocyte status and hepatocellular injury, we obtained laboratory tests for serum