Drug and Alcohol Dependence 150 (2015) 120–128

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Brain perfusion in polysubstance users: Relationship to substance and tobacco use, cognition, and self-regulation

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ARTICLE INFO

Article history:
Received 25 October 2014
Received in revised form 17 February 2015
Accepted 17 February 2015
Available online 26 February 2015

Keywords:
MRI
Perfusion
Blood flow
Polysubstance
Alcohol
Smoking

ABSTRACT

Background: Brain perfusion is altered in both alcohol dependence and stimulant dependence. Although most substance users also abuse/depend on alcohol concurrently (polysubstance users; PSU), rigorous perfusion research in PSU is limited. Also, the relationships of perfusion abnormalities with cognition, impulsivity, or decision making are not well known.
Methods: Arterial spin labeling MRI and neuropsychological measures assessed perfusion levels and neurocognition in 20 alcohol-dependent individuals with comorbid-stimulant dependence (PSU), 26 individuals dependent on alcohol only (ALC), and 31 light/non-drinking controls (LD). The patient groups included smokers and non-smokers.
Results: ALC had lower perfusion than LD in subcortical and cortical brain regions including the brain reward/executive oversight system (BREOS). Contrary to our hypothesis, regional perfusion was generally not lower in PSU than ALC. However, smoking PSU had lower perfusion than smoking ALC in several regions, including BREOS. Lower BREOS perfusion related to greater drinking severity in smoking substance users and to greater smoking severity in smoking ALC. Lower regional perfusion in ALC and PSU correlated with worse performance in different cognitive domains; smoking status affected perfusion–cognition relationships in ALC only. Lower BREOS perfusion in both substance using groups related to higher impulsivity.
Conclusion: Although regional perfusion was not decreased in PSU as a group, the combination of cigarette smoking and polysubstance use is strongly related to hypoperfusion in important cortical and subcortical regions. As lower perfusion relates to greater smoking severity, worse cognition and higher impulsivity, smoking cessation is warranted for treatment-seeking PSU and ALC.

1. Introduction

Arterial spin labeling magnetic resonance imaging, a non-invasive measurement of regional cerebral blood flow, provides functional information which is tightly coupled with glucose metabolism (Chen et al., 2011; Jueptner and Weiller, 1995). Regional cerebral blood flow (aka, perfusion) and glucose metabolism are intimately linked to brain function (Raichle et al., 1976).

Perfusion is altered in individuals with stimulant dependence and also in those with alcohol dependence. For instance, in cocaine dependence, frontal and temporal brain regions show relatively low perfusion (see review by Nnadi et al., 2005). In alcohol-dependent individuals (ALC) at 1–8 weeks of abstinence from alcohol, reduced perfusion is observed in frontal and parietal regions and does not recover with abstinence (Durazzo et al., 2010a; Gazdzinski et al., 2006; Mon et al., 2009; Sullivan et al., 2013; see review by Moselhy et al., 2001). Similarly, glucose metabolism is decreased in frontal regions of ALC and cocaine-dependent individuals (Adams et al., 1993; Dao-Castellana et al., 1998; Volkow et al., 1992a,b, 1994; Wang et al., 1993). In alcoholism, both chronic alcohol and tobacco use are associated with altered perfusion: higher alcohol consumption is associated with lower frontal and parietal perfusion (Kuruoglu et al., 1996; Melgaard et al., 1990; Nicolas et al., 1993), and greater cigarette smoking severity is

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http://dx.doi.org/10.1016/j.drugalcdep.2015.02.022
0376-8716/

associated with lower frontal and/or parietal perfusion in smoking ALC (sALC) (Gazdzinski et al., 2006; Mon et al., 2009, but also see Sullivan et al., 2013). These reductions in regional blood flow and glucose metabolism are of functional importance as they are associated with relapse to drinking within the first year after treatment (Durazzo et al., 2010a) and poorer neurocognition in cocaine dependence (Browndyke et al., 2004; Goldstein et al., 2001, 2004; see review by Hanlon et al., 2013) and in alcohol dependence (Adams et al., 1993; Dao-Castellana et al., 1998; Goldstein et al., 2004; Melgaard et al., 1990; Nicolas et al., 1993; Nixon et al., 1998; Wang et al., 1993), although with some contradictions (Demir et al., 2002; Gazdzinski et al., 2006; Mon et al., 2009). Furthermore, research has been conducted on measures of self-regulation/inhibitory control (e.g., impulsivity, risk taking, decision making) in alcohol dependence (Bjork et al., 2004; Fein et al., 2004; Gonzalez et al., 2007; Noel et al., 2007; Tomassini et al., 2012), cocaine dependence (LoBue et al., 2014; Moeller et al., 2001), and in polysubstance-dependent alcoholics (De Wilde et al., 2013a,b). However, the relationships of these measures, highly relevant to sustained abstinence and relapse, with regional cerebral perfusion have generally not been studied in substance users.

Furthermore, most substance users today are polysubstance users (PSU), with diagnoses of concurrent dependence on or abuse of more than one substance including alcohol. PSU are currently the largest group needing treatment in the United States (SAMHSA, 2011). However, brain perfusion research in PSU is sparse. Only two reports compared a PSU group (cocaine + alcohol) and a group dependent on cocaine only to controls. Both showed lower frontal and parietal perfusion in PSU abstinent from substances for a few days compared to the cocaine only group, with frontal perfusion deficits recovering after 21 days of abstinence (Gottschalk and Kosten, 2002; Kosten et al., 1998). However, these studies did not report on measures of neurocognition or self-regulation known to be impacted in PSU (De Wilde et al., 2013a,b).

Currently, it is unclear whether ALC and PSU differ on magnitude and pattern of regional perfusion—concurrent multiple substance use may impact cerebral blood flow stronger than monosubstance use—and whether the relationships of regional perfusion with cognition and self-regulation vary between these groups. Discerning such group differences could inform better treatments targeted at the requirements of different substance-dependent populations. Here, we compared primary alcohol-dependent individuals (i.e., ALC) to those with alcohol + stimulant dependence (i.e., PSU) and also compared these treatment-seeking groups to light drinking healthy controls (LD). We measured cortical and subcortical perfusion, with a focus on regions which are associated with the development and maintenance of addictive disorders, largely localized to specific regions in frontal and mesial temporal lobes, limbic system, and striatum (e.g., Haber and Knutson, 2010; Makris et al., 2008). In this report, these regions are collectively referred to as the brain reward/executive oversight system (BREOS; Durazzo et al., 2012a, 2014b), also termed the extended brain reward system (Durazzo et al., 2010b, 2011). Substance-use disorders are associated with long-lasting plastic changes in neuronal and glial tissue of BREOS regions subserving 'top-down' inhibitory control/executive functions (Volkow et al., 2011). Compromised integrity of top-down regulatory BREOS regions is related to dysregulation of striatum and limbic regions involved in reward and motivation (George and Koob, 2010) and also to dysfunction in traditional neurocognitive abilities involving executive functions, working memory, processing speed, and visuospatial skills (Gazzaley and D'Esposito, 2007). We hypothesized that: (1) ALC and PSU at 1 month of abstinence have greater perfusion deficits in the BREOS than LD and that alcohol-dependent PSU have greater regional perfusion deficits than ALC after controlling for potentially different alcohol consumption, (2) in both ALC and PSU, greater drinking and smoking severities are associated with lower perfusion, and (3) regional hypoperfusion is associated with poorer neuropsychological performance. In additional analyses, we examined the effects of smoking status on regional perfusion and its dependence on age.

2. Materials and methods

2.1. Participants

All participants provided written informed consent for procedures approved by University of California, San Francisco and San Francisco VA Medical Center. Twenty-six ALC and 20 PSU treatment-seekers were recruited from VA and Kaiser Permanente substance abuse treatment centers. ALC and PSU met DSM-IV criteria for alcohol dependence, and PSU met additional criteria for dependence on at least one psychostimulant (cocaine 100%, methamphetamine 40%) and marijuana use disorder (60%). ALC and PSU were 1 month abstinent from all substances except nicotine, with no group difference in duration of abstinence. Inclusion and exclusion criteria for all groups are described elsewhere (Abe et al., 2012; Durazzo et al., 2007). Briefly, exclusions were neurological and psychiatric disorders which affect neurobiology or neurocognition, but not hepatitis C, type-2 diabetes, hypertension, and unipolar mood disorder, highly prevalent in addiction (Hasin et al., 2007; Stinson et al., 2005). Thirty-one LD (25 nonsmokers, 6 smokers) recruited from the community served as controls. Smokers were allowed to smoke ad libitum before each assessment and during breaks.

2.2. Substance use and neurocognitive assessment

The clinical and neurocognitive assessments are detailed elsewhere (Durazzo et al., 2007). Briefly, ALC and PSU completed the Structured Clinical Interview for DSM-IV Axis I disorders Patient Edition, v2.0 (SCID-I/P; First et al., 1998); LD were administered the screening module. All participants completed the Beck Depression Inventory (BDI; Beck, 1978). Alcohol consumption was estimated with the lifetime drinking history interview (Skinner and Sheu, 1982; Sobell et al., 1988). Nicotine dependence was assessed with the Fagerstrom Tolerance Test for Nicotine Dependence (Fagerstrom et al., 1991). For PSU, lifetime substance use history (other than alcohol) was assessed with an in-house interview (Abe et al., 2012; Mon et al., 2014). In PSU, the average monthly use of cocaine ($n = 20$) and methamphetamine ($n = 8$) noted in parenthesis was 80 ± 123 (24 ± 34) g in the previous year, 68 ± 108 (16 ± 16) g over lifetime, with an average duration of 25 ± 8 (19 ± 5) years. A standard neurocognitive battery was administered and cognitive domains were calculated (see Durazzo et al., 2006, 2012b). The Barratt Impulsivity Scale (BIS-11; Patton et al., 1995) assessed self-reported impulsivity and task-based tests assessed risk taking (Balloon Analogue Risk Task, BART; Lejuez et al., 2002) and decision making (Iowa Gambling Task, IGT; Bechara et al., 1994).

2.3. MR data acquisition and processing

MR imaging was performed on a 4 T Bruker MedSpec system with a Siemens Trio console (Siemens, Erlangen, Germany) and an 8-channel transmit-receive head coil. The 3D sagittal T1-weighted sequence ($1 \times 1 \times 1\ mm^3$) used a magnetization prepared rapid gradient echo acquisition and the 2D axial T2-weighted sequence ($0.9 \times 0.9 \times 3\ mm^3$) a turbo-spin echo. Perfusion-weighted MRIs used a continuous arterial spin labeling (ASL) single-shot echo-planar imaging sequence (Detre et al., 1992), producing 16 oblique-axial 5-mm-thick slices oriented along the orbital-meatal line (in-plane resolution = $5 \times 3.8\ mm^2$, 1.45 mm slice gap, TR/TE = 5200/9 ms repetition/echo time, 1590 ms post-labeling delay, 90° flip angle).

All participants were instructed to remain awake with eyes closed during the 7 min whole-brain ASL perfusion sequence. Structural MRI data were aligned with perfusion data using a fluid-flow warping based distortion correction algorithm, and corrections for partial volume effects controlled for brain atrophy; method details are described elsewhere (Tosun et al., 2010). Regional cerebral blood flow images were corrected for partial volume effects and co-aligned with FreeSurfer v5.1 parcelated labels (Fischl et al., 2002, 2004) to yield subject-specific perfusion averages in pre-defined regions. The inferior 2–3 slices from all ASL datasets were removed due to distortions in inferior slices. FreeSurfer regions with at least 50% gray matter tissue were included in statistical analyses. The perfusion regions were voxel-weighted and combined into distinct regions of interest (ROIs: BREOS, Cortical, Subcortical) and subregions.[1] The BREOS ROI in this report was comprised of the anterior cingulate cortex (ACC), dorsal prefrontal cortex (dorsal PFC), inferior frontal gyrus (IFG), insula, and orbitofrontal cortex (OFC), while the Cortical ROI was the sum of all cortical regions including BREOS.

[1] Supplementary material can be found by accessing the online version of this paper. For more details see Appendix A.