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Structural Neuroimaging in Polysubstance Users

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Abstract

The simultaneous and/or concurrent use of licit and illicit substances (polysubstance use, PSU) is most common today. Structural magnetic resonance imaging (MRI) has been applied extensively to study individuals ostensibly using a single substance. These studies have produced a picture of regional gray matter and white matter alterations with each substance or class of substances. Very few studies measured regional brain morphometry in today's polysubstance users. This limited data suggest morphometric alterations with PSU that are not simply additive but often different from those of monosubstance users. Specifically, subcortical volume enlargements are observed that may be tied to mechanisms that also oppose volume reductions in cortical brain regions, thereby underestimating actual cortical atrophy. The complex actions of polysubstance use on brain structure and function need greater scrutiny with strong methodological approaches to inform more efficient treatment of polysubstance users.

Introduction

Polysubstance use (PSU), the simultaneous or concurrent use of two or more psychoactive substances has become the most common form of chronic substance use today in the developed world. Most alcohol dependent individuals are also chronic consumers of tobacco products, many cocaine and/or amphetamine dependent individuals also smoke cigarettes and consume alcohol regularly, and many of these substance users also smoke marijuana (cannabis) [1–3]. Monosubstance use appears to be a thing of the past, except perhaps for nicotine dependence and when substance use is first initiated. This is reflected in the changing profile of the clientele at substance abuse treatment centers in the developed world, where the majority of individuals with alcohol use disorders, for example, also chronically misuse illicit drugs.

Research aimed at understanding the effects and correlates of substance use on the brain has traditionally focused on studying the substance of interest by excluding or minimizing the concurrent use of other substances. While this valid scientific approach has provided

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invaluable insights into the neural correlates of individual substances misused, it also raises questions about generalizability: How relevant are these findings to today's substance users? Can these insights inform properly on brain changes related to PSU so that they can intelligently inform the design and development of effective treatment for PSU?

The current knowledge of brain structural alterations in polysubstance users is very limited, and we dare say that this contributes not only to a lack of understanding of the functional ramifications of such alterations, but more importantly also to the lack of effective treatment and the lack of guidance for clinical management of the majority of individuals seen in treatment today. Here, we first give a brief summary of brain structural alterations described for different classes of abused substances and then review the limited literature on brain structural alterations associated with PSU. Throughout the narrative, we highlight brain morphometric differences between mono- and polysubstance users, which we believe are reason for targeted treatment approaches based on the class of substances abused.

Monosubstance Use Studies by Name

Brain tissue loss with concomitant cerebral spinal fluid enlargements is well established in *alcohol use disorders (AUD)* (for recent reviews see e.g., [4, 5]). Quantitative structural magnetic resonance imaging (MRI) in chronic alcohol users showed that the gray matter regions primarily reduced are the bilateral prefrontal cortices, the posterior cingulate cortex, the insula, and subcortical brain regions, including the bilateral dorsal striatum (caudate, putamen, and nucleus accumbens), the hippocampi, and the amygdala; additional periventricular white matter loss is a common finding in severe alcohol users [6]. By enlarge, these are brain regions commonly described as abnormal in the general drug addiction literature, and most belong to a neural network referred to as the brain reward/executive oversight system (BREOS), which enables cognition, adaptive and appropriate goal-related behavior including reward and affect. Because the prefrontal brain is involved in drug-craving, impulsive/compulsive behavior and decision-making, its structural (and underlying metabolic) injury - be it as a consequence of chronic drinking and/or as a premorbid risk factor - may explain some of the difficulties encountered by substance users to achieve and maintain longterm abstinence.

Structural brain alterations are also detected in *chronic stimulant users*. A recent review [7] found fairly consistently across most imaging studies that chronic stimulant users had cortical gray matter reductions in the ventromedial prefrontal cortices (including the anterior cingulate (ACC)) and the insula. Individuals with primary cocaine dependence, but not those with methamphetamine dependence, also showed volume loss in the temporal cortices. Less consistently, gray matter volume reductions were reported in cerebellum, amygdala, and parahippocampal gyrus; in contrast to AUD, hippocampal volume was generally not reduced in stimulant dependence. Also in contrast to AUD, volume increases have been reported in the striatum of chronic psychostimulant users compared to drug-free controls [8–13].

The structural brain imaging findings in *chronic amphetamine users* are quite similar to those in chronic cocaine users, with most studies showing smaller volume in the medial frontal cortex and insula; temporal lobe volume reductions however have not been reported.

Frontal atrophy appears persistent in longterm abstinent methamphetamine users, similar to findings in cocaine dependence. The globus pallidus and putamen were enlarged in longterm abstinent methamphetamine users [12], but not in a dose-dependent manner. Substance users usually do not restrict their use to one type of stimulant; in as much as MDMA ("ecstasy") and amphetamines ("speed") are commonly used concurrently (amphetamine-type stimulants), often together with significant marijuana and alcohol consumption, this form of PSU in experienced users was associated with cortical thinning and/or volume loss primarily in lateral and medial prefrontal cortices [14, 15]. Similarly, when amphetamine disorder is comorbid with heavy alcohol consumption, cortical thinning in prefrontal brain regions is increased [16]. Significant medial frontal cortex and insula atrophy was not observed in occasional young stimulant users; they instead showed smaller right cerebellum and inferior parietal cortex volumes, but, similar to chronic users, they also showed larger putamen volume; furthermore, stimulant use measures in these occasional young users correlated with larger volumes of right ventromedial frontal cortex and left insula [17]. Taken together, it is unclear if the striatal volume increases seen in stimulant users constitute a premorbid risk factor for stimulant use or are a result of chronic use, potentially related to compensatory neural processes, to extracellular dopamine increases with drug use or to neuroinflammatory processes [18, 19]. It is also not known if factors that contribute to volume increases in subcortical brain regions also affect cortical morphometry, thereby potentially underestimating measured cortical injury in chronic stimulant users.

We are aware of only one truly longitudinal structural MRI study in psychostimulant users; it involved methamphetamine abusers over 5 months of abstinence [20]. In numerous serial studies of abstinent alcoholics, we and others showed substantial neurobiological, including structural and cognitive recovery with abstinence [4, 5, 21].

Recent evidence has emerged for atrophy related to both *chronic tobacco and marijuana (cannabis) use*, which are both highly comorbid with other substance use. A recent review of imaging studies in chronic smokers (who did not abuse other substances) described gray matter volume/density reductions in prefrontal, anterior cingulate, parietal, occipital, and temporal cortices, insula, striatal nuclei, thalami and the cerebellum [22]. A large voxel-based morphometry (VBM) study of MRI data from nearly 1000 current and never-smokers revealed gray matter volume loss in the prefrontal and anterior cingulate cortices, the insula, and the olfactory gyrus, with white matter volumes being not significantly affected [23]. The gray matter loss in current smokers was related positively to lifetime use of cigarettes (pack-years). In non-treatment seeking individuals with AUD, we found smaller total and temporal gray matter volumes in cigarette smokers vs. non-smokers [24], consistent with parietal and temporal gray matter atrophy in smoking vs. non-smoking treatment seeking alcoholics [25]. More pack-years in individuals in their sixth decade were associated with smaller left nucleus accumbens area volume and larger left putamen volume [26]. Larger putaminal volume was also associated with a lower age at smoking initiation.

Chronic marijuana use by itself is related to volumetric alterations within the mesial temporal lobe (i.e., hippocampus and amygdala) and subregions of the prefrontal cortex and the cerebellum. The findings, however, were not always consistent across studies and both volume increases and decreases were reported, with some evidence of persistent alterations

in longterm abstinent marijuana users [27]. Teens who used both marijuana and alcohol had relatively normal hippocampal volumes, whereas teens who used alcohol only had smaller hippocampi [28], suggesting that alcohol-related atrophy may be offset by marijuana-related glial proliferation, a mechanism proposed for greater white matter density in marijuana users [29].

Note that the regions of gray matter volume affected by chronic tobacco and marijuana use are similar to those affected by AUD and stimulant use. Although rarely indicated in the participants section of the relevant papers (even when other comorbid substance use is listed), it is likely that most substance users involved in these 'mono'-substance use studies were also chronic cigarette smokers and, additionally, that the majority of drug-free control participants were not chronic cigarette smokers (the prevalence of chronic smoking in non-clinical samples is generally much lower than in substance using populations). Thus, the observed structural abnormalities in these chronic substance users may be confounded by the effects of comorbid tobacco and/or marijuana use. Very few studies have tried to disentangle the effects from different substances abused, including tobacco, most likely because 'pure' mono-substance abusers are difficult to find, especially among chronic users. Therefore, the variability in the type and amount of substances abused, including tobacco and marijuana, across the different studies may have contributed to discrepancies in study results. As such, several of the studies cited above that ostensibly describe mono-substance users may in fact have described individuals with PSU, who have a drug of choice they may be dependent on, but more commonly than not also abuse or use other substances concurrently.

Polysubstance Use Studies by Name

Polysubstance use was first addressed by MR-based structural neuroimaging more than 20 years ago by demonstrating no difference of the ventricle-to-brain ratio in relatively young polysubstance abusers compared to drug-free healthy controls [30]. This coarse structural measure, that essentially reflects the amount of brain tissue, may have foreshadowed more recent reports of cortical volume loss and concomitant subcortical volume increases described in studies of stimulant abusers. Gray matter volume loss in the prefrontal lobe in the absence of white matter loss was found in 2-week abstinent PSU who reported cocaine as their substance of choice, used cannabis regularly, alcohol moderately, while a third also used >2 grams heroin/week [31]. Polysubstance users dependent on two or more substances (mainly cocaine, alcohol, amphetamines and cannabis) compared to drug-free controls showed less gray matter volume bilaterally in the medial orbitofrontal cortex (OFC), a metric that correlated with the persistence in playing 'bad' cards, a measure of impaired decision making [32]. While these studies established structural abnormalities related to PSU, a few additional studies compared poly- to monosubstance users. One study compared treatment-seeking individuals with alcohol dependence alone to those with either comorbid alcohol and cocaine use disorders or comorbid alcohol and marijuana use disorders: both comorbid groups showed whole brain gray and white matter volumes similar to the group dependent on alcohol alone, despite their more severe lifetime drinking severities and additional substance use [33]. In addition, the age-related decline in gray matter volume was larger across the alcohol dependent group than the comorbid groups. The comorbid groups also had a higher prevalence of anterior white matter hyper-intensities than the group

dependent on alcohol alone [33]. When evaluating different brain regions, we found that gray matter loss was greater in the frontal lobe of treatment-seeking individuals with comorbid alcohol and cocaine dependence compared to those with alcohol dependence alone, controlling for differences in drinking severity [34, 35]. The comorbid group had similar gray matter volume reduction in the prefrontal cortex than individuals dependent on cocaine only [34, 36]). Furthermore, frontotemporal atrophy was still observed in alcohol dependent cocaine addicts who remained abstinent for 1 to 3 years [34, 36]. In a more recent study, all assessed subcortical volumes were normal in 3-month-abstinent alcoholics with a comorbid stimulant disorder (cocaine and/or methamphetamine), whereas their hippocampal, caudate, and thalamic, amygdala, and nucleus accumbens volumes were significantly larger than those of alcoholics without a stimulant disorder [37]. Similarly, Grodin et al. reported comparable prefrontal gray matter volume reductions in individuals with AUD and PSU, but subcortical volume reductions in AUD only [38], consistent with the reports of larger subcortical volumes in ‘pure’ stimulant users versus controls (see above).

These cross sectional MRI studies indicate that comorbid substance use is associated with frontal gray matter atrophy, but the studies do not suggest additive or synergistic effects from multiple concurrently abused substances. Specifically, chronic alcohol consumption in illicit substance users does not further decrease whole brain or frontal gray matter volumes, but comorbid cocaine dependence appears to be associated with greater frontal cortical atrophy than AUD. Furthermore, most studies cited above, in addition to accounting for drinking severity differences between substance using groups, also controlled for potential differences in abstinence duration, acknowledging the potential for structural changes during abstinence.

In a recent study performed at 1.5T magnetic field strength, we found gray matter reductions only in the temporal lobe, thalami and lenticular nuclei of 1-month-abstinent individuals with PSU (alcohol dependent individuals with at least one psychostimulant disorder, mostly cocaine and methamphetamine, with and without marijuana and tobacco use disorder) [39]. This was surprising, because 1-month-abstinent alcohol dependent individuals with similar lifetime alcohol and cigarette smoking histories did have widespread lobar gray matter atrophy. Compared to normal lobar white matter volumes in the ‘pure’ alcoholics, the PSU individuals had *larger* lobar white matter volumes than both controls and alcoholics, and the parietal white matter volume correlated positively with cocaine use in the prior year [39], suggesting a drug-related white matter expansion also reported in methamphetamine dependence [40], chronic cigarette smoking [25], and heavy marijuana use [29]. These observations are consistent with and reminiscent of the potential effects of neuroinflammation associated with stimulant use described above for the striatum or of glial proliferation described in marijuana users. As such, gliosis may mask and thereby underestimate regional gray matter atrophy in alcohol dependent individuals with comorbid illicit substance use [7].

In a similar PSU cohort examined at 4T, we were able to examine regional gray matter morphometry with finer volumetric parcellation. Regional volumes, surface areas, and cortical thickness were obtained for dorsal prefrontal cortex (PFC), ACC, OFC, and insula [41]. While the PSU group had smaller left OFC and right dorsal PFC volumes and surface

areas than controls, they did not differ significantly from ‘pure’ alcoholics on these measures; instead, they had thinner right ACC and left dorsal PFC. These morphometric abnormalities in subregions of the frontal lobe of PSU individuals correlated with poorer cognitive efficiency, executive function, intelligence, processing speed, higher self-reported impulsivity, and risk-taking. Chronic cigarette smoking in the PSU group was associated with trends to thinner cortices in dorsolateral PFC and OFC, consistent with significant smoking-related thinning observed in both alcoholics and controls [42]. Smoking PSU individuals also had greater age-related volume losses in parietal gray and white matter than their non-smoking counterparts, consistent with findings in AUD [25].

Conclusions and Future Studies

Taken together, the rather small body of brain structural studies in PSU suggests both regional gray matter atrophy and regional tissue volume expansion in individuals with PSU. However, gray matter loss from concurrent use of multiple substances is not additive or synergistic. Mechanisms of cortical gray matter loss may include oxidative stress, mitochondrial degradation, vasoconstriction, neuroinflammation, and glutamate-mediated excitotoxicity, while volume expansion may be related to widespread altered glial function or myelination and neuroinflammation. By contrast, individuals with AUD, who have lifetime drinking and smoking histories similar PSU individuals, have somewhat more widespread cerebral atrophy but no regions of tissue expansion.

Any structural brain alterations (both volume reductions and subcortical enlargements) are either the result of substance use and/or they could predate substance use in a population at-risk (see e.g., [9]). Longitudinal and familial risk studies can distinguish between these possibilities. However, they are almost non-existent in stimulant users and PSU (except for [9] and references cited therein), likely because of challenges with recruitment and retention of this difficult-to-study population.

It has been shown that volume, surface areas, and cortical thickness of various top-down regions in AUD affect the ability to control future alcohol consumption [43] and that these measures are differentially sensitive to relapse and post-treatment alcohol use [44, 45]. In contrast to our AUD cohort, our PSU individuals, who relapsed within 6 to 12 months after structural MRI, compared to those who stayed abstinent, had *thicker* ACC and OFC at one month of abstinence (unpublished); these thicker cortices may reflect increased glial volume and/or neuroinflammation specific to PSU and future relapse or more active use of ACC/OFC function. Studies are useful to identify future relapsers and predict relapse based on neurobiological biomarkers.

To the best of our knowledge, no published reports in PSU addressed the question of structural recovery with abstinence. From the cross-sectional 4T PSU sample described above, we re-studied 20 PSU individuals who remained abstinent for 3 months after their baseline assessment: Preliminary evidence indicates some widespread volumetric changes in cortical and subcortical structures, as opposed to widespread volume increases commonly reported in abstinent AUD (e.g., [21, 46]). The volume changes in PSU were significant for left caudate (increase) and right superior temporal lobe (decrease). These structural changes

may underlie the significant cognitive improvements measured in these PSU individuals during abstinence, including in the clinically relevant domains of executive function, working memory, and cognitive efficiency [47]. The demonstration that the brain recovers after chronic polysubstance use by effectively engaging neuroplasticity suggests a critical window of opportunity for intervention with plasticity-based cognitive remediation methods. The corresponding improvement of function and overall brain health will likely promote long term abstinence in PSU individuals, and future studies should clarify the behavioral correlates of improved neurobiology and overall health with abstinence from PSU.

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Highlights

- The concurrent abuse of several substances is common among substance users today
- Both alcohol and stimulant abuse are associated with cortical gray matter volume loss
- Brain tissue loss is not simply additive in concurrent abuse of multiple substances
- Gliosis in polysubstance users may offset cortical volume loss and increase subcortical volume
- Some structural abnormalities in substance users may predate chronic abuse