



## Regular Article

# Striatal brain volume linked to severity of substance use in high-risk incarcerated youth

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### Abstract

Substance use disorders among juveniles are a major public health concern and are often intertwined with other psychosocial risk factors including antisocial behavior. Identifying etiological risks and mechanisms promoting substance use disorders remains a high priority for informing more focused interventions in high-risk populations. The present study examined brain gray matter structure in relation to substance use severity among  $n = 152$  high-risk, incarcerated boys (aged 14–20). Substance use severity was positively associated with gray matter volume across several frontal/striatal brain regions including amygdala, pallidum, putamen, insula, and orbitofrontal cortex. Effects were apparent when using voxel-based-morphometric analysis, as well as in whole-brain, data-driven, network-based approaches (source-based morphometry). These findings support the hypothesis that elevated gray matter volume in striatal reward circuits may be an endogenous marker for vulnerability to severe substance use behaviors among youth.

**Keywords:** Antisocial behavior; brain volume; juvenile; MRI; substance use disorders

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### Introduction

The prevalence and consequences of substance use disorders (SUDs) among adolescents constitute a major public health concern. This has recently led to prominent shifts in national funding priorities and an expansion of research efforts cutting across diverse disciplines (Casey et al., 2018; Volkow et al., 2018). Among the many risks associated with SUDs in youth, antisocial behavior is a conspicuous concern. Large-scale epidemiological studies have consistently reported more than half of those in juvenile corrections meet diagnostic criteria for SUDs (CASA, 2010; Teplin et al., 2002), 10 times greater than the roughly 5% prevalence recognized among adolescents in the general population (CBHSQ, 2015). Furthermore, most youth involved with the criminal justice system exhibit a history of misusing multiple substances (McClelland et al., 2004). Longitudinal studies have indicated more than 80% of those in juvenile corrections endure some trajectory of persisting SUDs for more than 10 years following their initial incarceration (Welty et al., 2017). Further, the presence of SUDs remains a prominent predictor of future recidivism among those released from juvenile corrections (Mason & Windle, 2002; Welty et al., 2017). It remains clear that efforts to address mental health and behavioral issues among high-risk youth must consider the powerful role of substance use and addiction.

The neural correlates of SUDs have been well described in various biological models of addiction. Neuronal changes accompanying SUDs prominently affect the structure and function of fronto-striatal reward circuits, but also extend to other parts of the brain involved in executive control and socio-affective systems (Volkow et al., 2010, 2011). Individual differences in susceptibility to SUDs are influenced by a combination of genetic and environmental factors that converge on the physiology of the brain (Conrod & Nikolaou, 2016). Significant heritability in problematic use has been consistently reported in conjunction with shared environmental factors (Kendler et al., 2015; Rhee et al., 2003). One of the most conspicuous physical representations of these effects is in gray matter volume (GMV). In a recent “mega-analysis” of over 3000 individuals, patterns of reduced GMV associated with alcohol and other substance dependence were apparent in the hippocampus, amygdala, nucleus accumbens, putamen, globus pallidus, insula, and orbitofrontal cortex – among other regions (Mackey et al., 2019). This large-scale study reflects many consistent findings in extant literature reporting widespread gray matter decrements associated with SUDs in adults, across many different substances of abuse (Barrós-Loscertales et al., 2011; Ersche et al., 2013; Franklin et al., 2002; Lorenzetti et al., 2010; Makris et al., 2008). Further, patterns linking more severe, protracted substance use with greater decrements in gray matter suggest these effects are at least partially caused by the deleterious effects of prolonged substance misuse on neural structures over many years (Infante et al., 2022; Kaag et al., 2018). A recent large-scale review of neuroimaging findings in SUDs emphasizes apparent abnormalities in cognitive control networks and their

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interaction with subcortical salience-processing networks; however, this review also highlights lingering gaps in our understanding of premorbid vulnerabilities and developmental representations of abnormal brain structure and function (Paulus, 2022).

The effects of SUDs on gray matter commonly reported in adult populations are not as clear or consistent in juveniles. From a developmental perspective, adolescence represents a critical period of change with both social and biological influences that promote more risk-taking and reward-oriented decision-making (Blakemore & Robbins, 2012; Casey et al., 2008). Natural developmental trajectories during these years are accompanied by nonlinear and nonuniform patterns of gray matter change across the brain. In typical development, total gray matter volume (across the whole brain) reaches its global maximum around 12 years old, with regional variation in temporal and occipital regions peaking a few years later, up to about 20 years (Giedd et al., 1999; Giedd, 2008; Sowell et al., 2003). Significant neural pruning results in progressively lower density and volume of gray matter, beginning earlier in posterior brain areas and later in frontal regions (Giedd, 2008). Regionally specific pruning, arborization, and myelination promote changes in impulsivity, novelty-seeking, reward-oriented decision-making, and changes in self-monitoring and behavioral inhibition reflected during these important developmental years (Blakemore & Robbins, 2012; Christakou et al., 2011; Luna & Sweeney, 2004).

These complex developmental patterns may obscure the measurement of neural abnormalities specifically related to substance use in this age group and make interpretation of empirical findings difficult. Certain deleterious effects of substance use recognized in adult populations might be collinear with local developmental changes in several brain regions during adolescence. Concurrently, young substance users may simply not have accumulated as much neural damage from substance use as adults. It is also possible that early-stage vulnerability to substance misuse among juveniles may be represented by neural markers that are distinct from those concomitant with the deleterious effects of long-term substance abuse commonly reported in adults. These challenges undoubtedly contribute to more variability apparent in reported findings among youth.

Some reports have suggested causal relationships between gray matter loss and substance use frequency/severity, such as in binge drinking among adolescents (Infante et al., 2022), while others suggest that gray matter reductions associated with natural maturation processes (i.e., pruning) may drive higher frequency of alcohol use (Robert et al., 2020). Again, individual variation in gray matter may also be interpreted as a premorbid marker for vulnerability to substance misuse. Weiland and colleagues, for example, have reported reductions in frontal cortical gray matter as a marker for early risk of both substance abuse and higher externalizing behaviors, controlling for both family history and current substance use (Weiland et al., 2014).

Beyond the frontal cortex, subcortical and salience-processing networks in the brain are also conspicuous candidates for early vulnerability markers. Striatal dopamine modulation in adolescence naturally increases the risk for initiating substance use/abuse, and individual differences in novelty-seeking and reward sensitivity may play a role in differential risk for substance abuse and maintenance of maladaptive behaviors (Casey & Jones, 2010; Kelley et al., 2004). Correspondingly, increased excitatory activity in striatal dopaminergic pathways accompanying substance use during this critical developmental period may also modify

structure and function while the striatum is undergoing development. It has been consistently noted that impulsivity and hyperactivation in networks involved in reward-related evaluations are reliable predictors of substance use outcomes and vulnerability. These effects are especially apparent in medial orbitofrontal and striatal system hyperexcitability of dopamine receptors in this network (Verdejo-Garcia & Albein-Urios, 2020). Dopaminergic function (e.g., fronto-striatal D2 receptors) has been found to be altered among young adults at risk for SUDs based on family history (Jaworska et al., 2020; Weiland et al., 2017). Lees and colleagues reported markers for substance use vulnerability including hyperactivation of ventral striatal regions during reward feedback and risk evaluation accompanied by distinct patterns of frontal/fronto-parietal hypoactivation (during failures of inhibition) and hyperactivation (during successful trials) (Lees et al., 2021). Also, in children (aged 8–12) at risk for SUDs, early exposure to drug use is associated with hyperactivation of the nucleus accumbens during an incentive delay task (Cope et al., 2019).

Considering corresponding effects in gray matter morphology, several studies have reported increased gray matter in fronto-striatal regions among young substance users and in prospective substance abusers. In a study of adolescents using methamphetamine and cannabis, drug use and novelty-seeking traits were both positively associated with striatal GMV (Churchwell et al., 2012). Young cigarette smokers have shown increased GMV in the left putamen (accompanied by decreased volume in the anterior cingulate) compared with nonsmoking controls (Bu et al., 2016). Girls with alcohol use disorder have exhibited larger putamen and thalamic volumes than non-drinking girls (although the effect was reversed in boys) (Fein et al., 2013). In young recreational cannabis users, gray matter was relatively increased in the left nucleus accumbens and extended subcallosal cortex, hypothalamus, and amygdala, even after controlling for age, sex, alcohol use, and cigarette smoking (Gilman et al., 2014). Early cannabis use (younger than age 16) has been associated with larger left nucleus accumbens and increased thickness in right frontal cortex gray matter (Lisdahl et al., 2016). Further, in a longitudinal study, high novelty-seeking 14-year-olds who eventually developed problematic drug use (by age 16) had relatively increased gray matter density in the left ventral striatum, midbrain, and bilateral dorsolateral prefrontal cortex (Büchel et al., 2017) compared with those who did not develop problematic drug use. In support of these morphometric differences reflecting a possible neuro-cognitive vulnerability predicating substance abuse, increased GMV in the medial temporal lobe and basal ganglia have been reported in both drug-dependent individuals and their non-drug-abusing siblings relative to healthy controls, while non-affected siblings also demonstrated concomitant abnormalities in a topographical task, reflecting impairments in impulse control (Ersche et al., 2012). Lees and colleagues reported larger ventral striatal volume (but smaller fronto-parietal and amygdala volume) were associated prospectively with future substance misuse (Lees et al., 2021).

In sum, neural development supporting reward-seeking, exploratory, and elevated risk-taking behavior is a common feature of adolescence. These developmental patterns may promote risky behaviors that include experimentation with substances of abuse. Less is known about neurobiological features contributing to individual differences in substance use behaviors that distinguish enduring, maladaptive patterns of substance abuse. It may be true that exaggerated proportional differences in gray matter reflect a vulnerability for initiation of substance use, amplifying the rewarding effects of drugs and promoting continued

use, and/or stronger perseverative motivation following initial experimentation. Relatively little research has focused on structural brain correlates of substance use severity among high-risk juveniles, particularly those exhibiting early antisocial behavior. In the current study, we set out to examine morphometric differences in gray matter accompanying histories of substance use in boys incarcerated in a secure correctional facility and treatment program for youth. From a design perspective, data from these individuals may be helpful in ascribing effects to substance use, *per se*, as the sample is relatively more homogeneous on several collateral risk factors related to their incarceration status (e.g., antisocial behavior, psychopathic personality traits, sociodemographic risk factors). These are often difficult factors to eliminate or control for when comparing substance abusing youth with typical healthy controls. We present two complementary data analysis approaches, utilizing both traditional, univariate, voxel-based morphometry (VBM) alongside multivariate source-based morphometry (SBM) using independent component analysis (ICA) of structural MRI data. In the univariate approach, we test differences in a priori regions of interest (ROIs) selected for their roles in reward-motivated decision-making and highlighted in prior studies examining SUDs in juveniles. The SBM analysis is a data-driven approach, organizing whole-brain data into naturally occurring (intrinsic) networks of gray matter with closely covarying volume. As such, this method is ideal for validating the univariate findings and demonstrating the natural organizational structure of affected networks, without constraining analyses to artificially defined ROIs. We hypothesized that more severe substance abuse in juveniles would be associated with hypertrophy of gray matter in fronto-striatal reward circuits, reflected in both univariate a priori regions of interest and corresponding intrinsic structural networks derived from SBM analysis.

## Methods

Participants were  $n = 175$  adolescent males incarcerated at the Mendota Juvenile Treatment Center in Madison, Wisconsin. The facility houses and treats youth who have been transferred from other state juvenile facilities, largely due to unmanageable behavior in traditional corrections programs. This cohort represents a particularly high-risk group, even as compared with more typical juvenile corrections samples. All participants provided their own assent accompanied by their guardian's/representative's consent. Participants were aware that their cooperation with research was completely voluntary and would have no impact on their sentence or status at the facility. Research protocols were conducted in accordance with principles established by the Declaration of Helsinki, approved by local IRB, Ethical and Independent Review Services, and by the National Institutes of Health Office of Human Research Protections with respect to the vulnerable status of incarcerated subjects. Participants were admitted into the study if they had at least a fourth-grade reading level and were able to understand informed assent procedures. Participants were excluded from analysis if their IQ was below 70 ( $n = 18$ ) and for history of head injuries/traumatic brain injury (TBI) resulting in prolonged loss of consciousness (60 min, cumulative) or abnormal radiological report following MRI ( $n = 5$ ). A total of  $n = 152$  boys were included in the final analysis. Based on NIH race classifications, participants self-identified as American Indian or Alaskan Native ( $n = 5$ ), Black or African American ( $n = 81$ ), White ( $n = 46$ ), and more than one race ( $n = 19$ ). One participant chose not to self-disclose their race. Additionally,  $n = 19$  participants identified as Hispanic/Latin@, and  $n = 133$  participants identified

**Table 1.** Descriptive features  $n = 152$  incarcerated male youth

	Min	Max	Mean (SD)
Age (years)	14.11	20.76	16.54 (1.07)
IQ	70	120	87.68 (10.99)
PCL:YV total	10	38	26.85 (5.37)
Substance use severity	0	18.75	2.53 (3.26)
GM + WM	957.95	1549.16	1226.25 (109.90)

as non-Hispanic/Latin@. Descriptive features of this sample are provided in Table 1.

## Assessments

**Substance use severity:** The history of substance use was measured using a modified version of the Addiction Severity Index (McLellan et al., 1992). Participants reported duration of regular substance use in their lifetime based on a structured interview tabulating several categories including alcohol, cannabis, heroin, other opiates (e.g., painkillers, methadone, levacetylmethadol), cocaine/crack, methamphetamine, other amphetamines (e.g., Adderall), anxiolytics (e.g., benzodiazepines, Xanax), hallucinogens, inhalants, and others (e.g., DXM, spice). Regular use was defined as using a non-prescribed substance at least three or more times per week. Cumulative years of regular use were summed and summarized for each category. For neuroimaging analyses, years of regular substance use were divided by the participant's age to account for opportunity for use, and a square root transformation was applied to account for non-normality, similar to a method used in prior publications (Ermer et al., 2012; Sajous-Turner et al., 2020). This approach captures variance attributable to the relative level of severity of multiple periods of use across the lifespan.

## Psychopathic traits

**The Hare Psychopathy Checklist: Youth Version (PCL:YV)** (Forth et al., 2003), an expert-administered rating scale consisting of a semi-structured interview and review of collateral information, including institutional and medical records, was used to assess youth psychopathic traits. The PCL:YV is composed of 20 different items assessing personality traits, emotional factors, interpersonal style, developmental characteristics, and behaviors concomitant with psychopathy. PCL:YV total scores can range from 0 to 40. Four facets are also available as separable features of the total score. In the current analysis, the total score is utilized as a covariate to account for individual variation in antisocial traits and delinquent behavior in this high-risk sample.

**Intelligence:** Full-scale IQ was estimated using the Vocabulary and Matrix Reasoning subtests of the Wechsler Adult Intelligence Scale – 3rd Edition (Wechsler, 1997) for participants 16 years of age or older and from the Wechsler Intelligence Scale for Children – 4th Edition (Wechsler, 2003) for participants younger than 16 years of age. IQ < 70 was an exclusionary criterion for this study. IQ is also entered as a covariate in analyses.

**Head Injury:** A history of prior head injuries was taken using a modified post-head injury symptoms questionnaire (King et al., 1995). A total of  $n = 81$  (46%) self-reported some prior history of head injury ranging from minor sub-concussive events (e.g., fell out of bed) to severe incidents resulting in loss of consciousness and hospitalization. Prolonged loss of consciousness (1 hr or more,

cumulative) or abnormal radiological report was an exclusionary criterion for this study.

### MRI collection and processing

Structural MRI scans were acquired on-site at the correctional facility, using the Mind Research Network Siemens 1.5 T Avanto mobile scanner. High-resolution T1-weighted scans were collected using a multi-echo MPRAGE pulse sequence provided by Massachusetts General Hospital Radiology Department (repetition time = 2530 ms, echo times = 1.64 ms, 3.50 ms, 5.36 ms, 7.22 ms, inversion time = 1100 ms, flip angle = 7°, slice thickness = 1.3 mm, matrix size = 256 × 256). This yielded 128 sagittal slices with an in-plane resolution of 1.0 mm × 1.0 mm. Data were preprocessed and analyzed using Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). T1 images were manually inspected by an operator blind to subject identity and realigned using the anterior and posterior commissures to ensure proper spatial normalization. Images were then spatially normalized to the SPM12 T1 Montreal Neurological Institute template using nonlinear registration, segmented into gray matter, white matter, and cerebrospinal fluid, and modulated with the Jacobian determinants to preserve total volume after normalization (Ashburner & Friston, 2000, 2005); that is, voxelwise parameters are interpreted as gray matter volume. Finally, the images were resampled to 1.5 × 1.5 × 1.5 mm and smoothed with a 10 mm full-width at half-maximum Gaussian kernel. Voxels with a gray matter value of < .15 were excluded to remove possible edge effects between gray matter and white matter. Additional quality assurance on MRI data was verified using the MRIQC pipeline (<https://mriqc.readthedocs.io/en/latest/>). No additional exclusions or modifications were necessary following QA assessment.

Voxelwise multiple regression analysis was performed within a priori ROIs, examining the effects of substance use severity on local gray matter while accounting for covariates of age, race, IQ, PCL:YV total scores, and total brain volume (gray matter + white matter). A robust regression method was applied, which reduces bias from outliers and distribution non-normality using an iteratively reweighted least squares approach (Wager *et al.*, 2005; see also <https://github.com/canlab/RobustToolbox>). Bilateral anatomical masks were calculated for the amygdala, nucleus accumbens, caudate, putamen, pallidum, anterior insula, and orbitofrontal cortex (frontal inferior orbital) using automated anatomical labels (AAL3) atlas and extracted with MATLAB. For each region, the familywise error (FWE) rate was maintained at  $p < .05$  by correcting for the volumes of each mask; we report the FWE corrected  $p$ -values.

As a complementary approach, a multivariate data-driven analysis of brain structure (SBM) was used to define intrinsic networks of gray matter using ICA. Detailed methods for this approach have been described elsewhere (Xu *et al.*, 2009). The complementary value of this analysis strikes a balance between confining analysis to a few circumscribed regions of interest and the problematic multiple comparisons issue introduced by whole-brain, voxelwise (univariate) GLM solutions. The algorithm produces a set of maximally independent components (networks) of covarying voxels and parameter values (loading coefficients) for each subject on each component. Stronger/weaker parameter values scale proportionally with individual gray matter values in each represented network. These parameter values are then carried forward in subsequent analyses and statistical estimates can be made for each component network, rather than on a voxel-by-

**Table 2.** Substance use in  $n = 152$  incarcerated male youth

Category	Count with problematic use
Cannabis	105
Alcohol	27
Opiates/analgesics	16
Benzodiazepines (Xanax)	12
Cocaine/amphetamines	10
Other (DXM, spice)	5

voxel basis (i.e., VBM). In this way, statistical estimates represent individual characteristics of a cohesive network as opposed to properties of a single voxel. Following preprocessing, the Group ICA fMRI Toolbox (GIFT) software (<http://mialab.mrn.org/software/gift>) was used to extract 30 maximally independent components. The resulting components (networks) were then evaluated for their voxelwise overlap with selected ROIs, using a selection criterion of at least 10% overlap with a single mask defining voxels corresponding to the combined a priori ROIs. Subsequent analyses were carried out on properties of naturally derived networks corresponding closely with a priori ROIs. Bivariate and partial correlations were then calculated between component parameters (loading coefficients) and individual factors representing substance use severity, with partial correlations controlling for the same nuisance covariates as in the previous univariate ROI regression models.

### Results

The final analysis included  $n = 152$  boys, excluding  $n = 18$  for low IQ and  $n = 5$  for TBI. Descriptive features of this sample are provided in Table 1. Substance use severity in this sample is described in Table 2, which accounts for those in the sample meeting criteria for problematic use of each substance, defined as three or more times per week for a minimum period of 1 month.

For visualization purposes, whole-brain correlations between GMV and substance use severity, controlling for age, race, IQ, PCL:YV total scores, and brain volume (gray matter + white matter), are represented in axial slices in Figure 1. These effects were thresholded to  $p < .005$ , using a cluster-based threshold of 1387 voxels (3DClusSim, Nearest Neighbor 3, allowing faces touching, edges touching, corners touching). This figure is intended to highlight the whole-brain orientation of significant effects in a priori ROIs, presented in data tables.

#### ROI results

Analyses in a priori regions of interest (amygdala, nucleus accumbens, caudate, putamen, pallidum, anterior insula, and orbitofrontal cortex) revealed significant effects in bilateral amygdala, right putamen, right pallidum, right insula, and right orbitofrontal cortex. Effects in other ROIs did not survive FWE corrections across regional volumes. Coordinates and statistics for significant effects are presented in Table 3.

#### SBM results

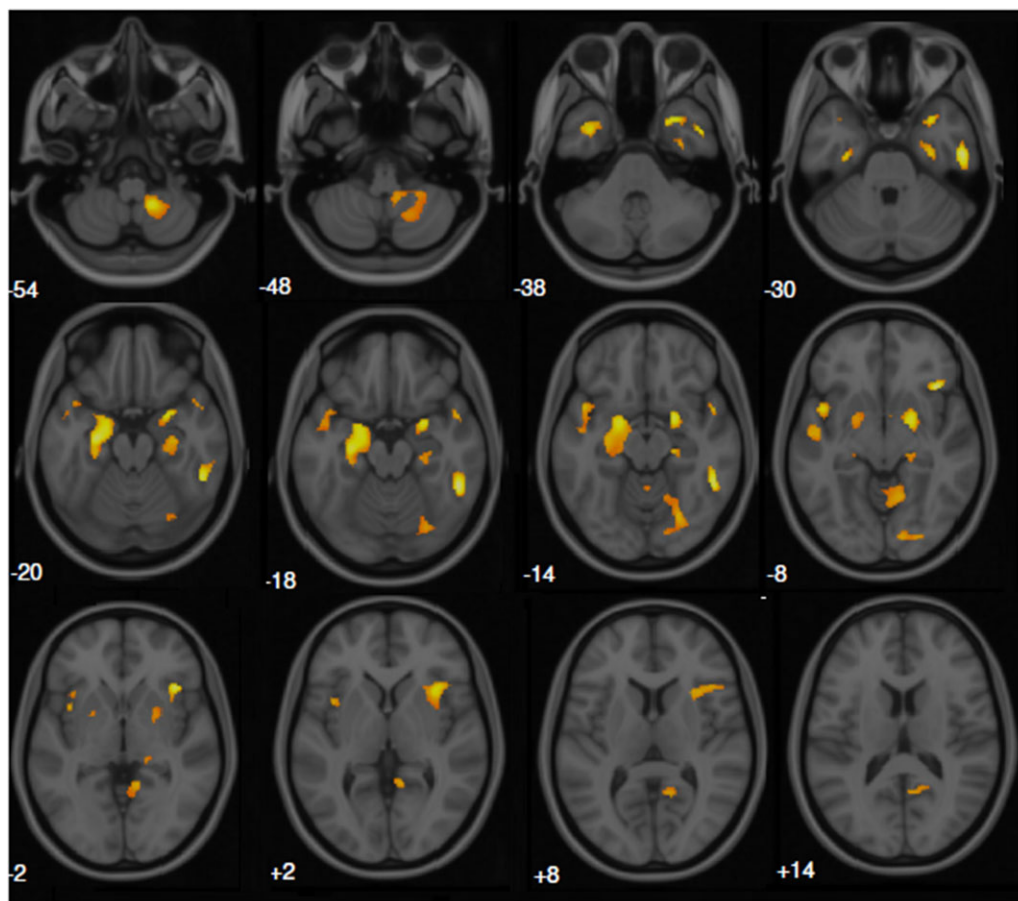
Two structural networks (derived by ICA) exhibited more than 10% overlap with a priori ROIs, together accounting for 80% of voxels examined in the GLM analysis. A network including



**Table 3.** VBM analysis in ROIs: significant effects surviving FWE correction in volume

Region	ROI volume	Cluster size ( $p < .05$ )	Peak coordinates			Z-statistic	p-value (FWE corrected)
			X	Y	Z		
L. amygdala	1846 mm <sup>3</sup>	1782 mm <sup>3</sup>	-21	-3	-15	3.94	<.002
			-21	-7.5	-19.5	3.81	<.004
R. amygdala	2042 mm <sup>3</sup>	1643 mm <sup>3</sup>	19.5	0	-12	4.16	<.001
			25	1.5	-19.5	3.90	<.003
R. putamen	8434 mm <sup>3</sup>	4593 mm <sup>3</sup>	19.5	4.5	-10.5	3.59	<.03
			24	3	-6	3.54	<.03
			28.5	16.5	6	3.45	<.04
			33	12	3	3.43	<.04
R. pallidum	2288 mm <sup>3</sup>	1218 mm <sup>3</sup>	21	0	-7.5	3.84	<.004
R. insula	14,016 mm <sup>3</sup>	4388 mm <sup>3</sup>	39	22.5	-4.5	4.75	<.001
			34.5	15	3	3.91	<.02
R. OFC	7219 mm <sup>3</sup>	1579 mm <sup>3</sup>	40.5	24	-9	4.25	<.002

Note. Significant effects represent increased gray matter associated with more severe substance use in juvenile offenders, supporting our hypotheses. FWE = familywise error correction for multiple comparisons; R. OFC = right orbitofrontal cortex.

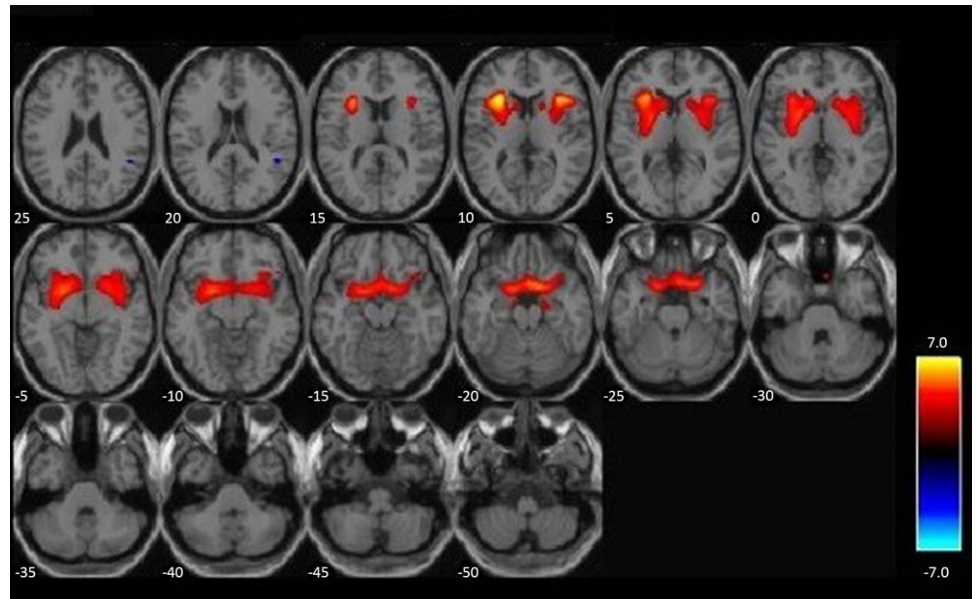


**Figure 1.** Elevated gray matter associated with substance use severity. VBM whole-brain (positive) correlations with substance use severity,  $p < .005$ ,  $K(NN3) = 1387$ , and  $N = 152$ , are highlighted in orange/yellow. More severe substance use is associated with increased gray matter in highlighted regions. Covariates of age, race, IQ, PCL:YV, and total brain volume (GM + WM) are included in this analysis.

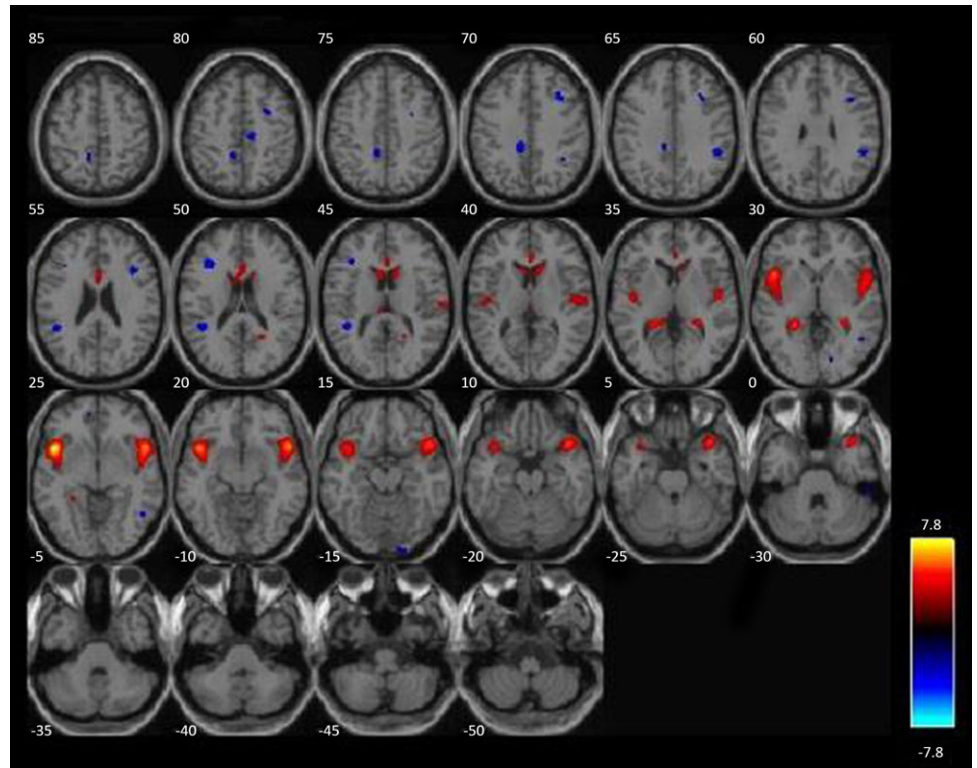
bilateral striatum was positively correlated with substance use severity using bivariate correlations,  $r = .213$ ,  $p = .008$  (see Fig. 2). A second structural network including bilateral insula was also positively correlated with substance use severity,  $r = .166$ ,  $p = .04$

(see Fig. 3). After controlling for other covariates (age, race, IQ, PCL:YV, GM + WM), the striatal component remained significant (partial  $r = .194$ ,  $p = .018$ ), but the insular component only trended in the same direction (partial  $r = .137$ ,  $p = .096$ ). Three additional

**Figure 2.** An intrinsic network with elevated gray matter in those with more severe substance use. A structural network, derived from ICA,  $n = 152$ , positively correlated with substance use severity is highlighted in red/orange. More severe substance use is associated with proportionally more gray matter throughout this intrinsic network, which includes caudate, putamen, nucleus accumbens, ventromedial PFC, and parts of the anterior insula (a priori ROIs). ICA = independent component analysis.



**Figure 3.** A second intrinsic network with increased gray matter associated with more severe substance use. A second structural network, derived from ICA,  $n = 152$ , positively correlated with substance use severity, highlighted in red/orange. More severe substance use is associated with proportionally more gray matter throughout this intrinsic network, which includes bilateral insula (a priori ROIs). ICA = independent component analysis.



components (out of 28 remaining), which did not include a priori regions of interest, also exhibited potentially meaningful relationships with substance use severity. These components included structural networks comprising the posterior cingulate and precuneus (both positively correlated with substance use), and a network including the posterior cerebellum was significantly negatively correlated with substance use severity. These incidental findings are presented for completeness in the [supplementary materials](#); however, these effects do not survive corrections for multiple comparisons if evaluated from an agnostic, whole-brain approach. Nevertheless, they may be of interest in the context of developing new hypotheses for future investigations.

## Discussion

This study reports GMV differences associated with substance use severity among incarcerated juveniles. Consistent with hypotheses, gray matter hypertrophy was apparent in several regions corresponding to salience network, fronto-striatal reward circuits, and basal ganglia. These effects were apparent across two complementary analytic strategies: one prioritizing circumscribed ROIs and another using a data-driven approach for defining naturalistic structural networks across the whole brain. These findings confirmed expectations for abnormal developmental markers associated with early-life substance abuse among high-

risk, antisocial youth in brain areas governing reward/reinforcement learning. Addressing possible limitations of prior studies, these effects were not attributable to variation in antisocial behavior/psychopathic personality traits, nor were they attributable to age, race, IQ, or overall brain size, which were accounted for in statistical models. The direction of effects (increased gray matter associated with greater substance use severity) is consistent with notions that relative hypertrophy and/or neurodevelopmental delays (i.e., pruning) in fronto-striatal reinforcement networks may be a marker for vulnerability to more extreme substance use behaviors. The present findings add support to a growing body of work denoting the importance of altered neurodevelopmental trajectories in early-onset substance misuse. These findings also underscore the relevance of these factors in highly antisocial youth.

The evident patterns of gray matter differences in the present study may be interpreted in more than one way. For instance, these findings may reflect differential rates of development in reward-oriented brain structures. While age is used as a covariate in our analyses, differential developmental trajectories do not perfectly align with chronological age (Kiehl et al., 2018). We know the volume of gray matter in the striatum steadily decreases through adolescence (Giedd et al., 1999; Giedd, 2008) even as youth experience exaggerated dopamine responses and feelings of reinforcement from rewarding stimuli, relative to adults (Galvan, 2010). In this way, if we attribute increased gray matter in high substance users to developmental processes, less mature brains are apparently more susceptible to problematic substance use behaviors in high-risk youth. Alternatively, it is possible that increased substance use (and more frequent, exaggerated stimulation of striatal reward networks) produces a hypertrophic effect on gray matter in these areas, apparent in these younger users, which would hypothetically give way to the well-established deleterious effects of chronic use often reported in adults (Kaag et al., 2018; Mackey et al., 2019). A third possibility is that patterns of increased gray matter reflect some other intrinsic marker for susceptibility to substance abuse, apart from typical maturational variations – fundamentally an endophenotype of vulnerability. This interpretation aligns with prior work recognizing similar patterns of enlarged gray matter in substance abusing youth as well as their non-substance-abusing siblings (Ersche et al., 2012), suggesting some heritable influence independent of substance use. This interpretation also aligns with a prospective, longitudinal study that reported increased gray matter in the striatum, midbrain, and prefrontal cortex of high novelty-seeking youth (pre-exposure to substance use) who went on to develop problematic substance use behaviors years later (Büchel et al., 2017).

As noted in the introduction, there is other prior evidence for positive associations between GMV in the striatum and substance misuse, especially in young populations (Büchel et al., 2017; Bu et al., 2016; Gilman et al., 2014; Lisdahl et al., 2016). Elevated striatal gray matter has also been reported in adult methamphetamine users (Chang et al., 2005), with more exaggerated effects in younger adult users (Jernigan et al., 2005). However, among adults, this has often been attributed to a kind of compensatory response to chronic neuropathological insults to maintain function (Chang et al., 2005). Prior reports also suggest that impulsive, short-term oriented decision-making (e.g., choosing immediate rewards over future larger rewards) is associated with hypertrophy of striatal gray matter in young adult men and women (Tschernegg et al., 2015). In an exploratory analysis from the multisite Adolescent Brain Cognitive Development study, in more than 11,000 children aged 9–10, elevated scores on behavioral activation (as opposed to

inhibition) were positively correlated with GMV in the ventral striatum, and this effect was stronger in monozygotic twins, suggesting a strong genetic influence (Ide et al., 2020). Such findings suggest that, even in the absence of severe substance use behaviors, increased gray matter in striatal areas aligns with personality and behavioral patterns that may promote more drug use/misuse among affected youth.

Several prior studies examining neural correlates of substance use have noted certain limitations in their interpretations related to sampling characteristics (Fein et al., 2013; Schiffer et al., 2011). When comparing substance using individuals with healthy controls, there remain a number of convergent factors that are difficult to control for across cohorts, particularly factors like behavioral disinhibition and antisocial personality traits when comparing substance abusing youth with healthy controls. Also, acute or recent lingering effects of substance use on MRI data are a concern among volunteers from the general population. By studying these effects among highly antisocial youth with varied substance use histories, we have reduced the impact of factors covarying with antisocial behavior and general disinhibitory traits. The boys involved in the correctional program at this particular site are all highly antisocial and indeed matriculated into this program based on unmanageable behavior at other statewide juvenile correctional facilities. Further, as participants are housed in a maximum security/controlled environment, they are under strict enforcement of controlled abstinence, reducing concerns of acute substance use. This study was specifically intended to narrow some of these prior inconsistencies and limitations.

### Limitations

The consequence of studying these effects in this group of high-risk offenders is that it is not yet clear whether these effects reliably generalize to other juvenile samples or whether they exhibit a pathological trend specific to those with prominent risk factors for antisocial behavior. Further, there is scant research examining these effects among girls, but there is some supportive research describing overlapping and gender-specific effects (Fein et al., 2013). Additional research will be necessary to address this with more specificity. As noted above, the present findings align well with other recent research suggesting enlarged gray matter in key brain areas may represent features of an endophenotype for vulnerability to problematic substance use. This interpretation remains uncertain, however. Longitudinal research implementing within-subjects neuroimaging at multiple time points will be necessary to confirm these interpretations, both in high-risk and lower-risk samples.

### Conclusion

Among the approximately seven million individuals under correctional supervision in the United States, more than half meet the criteria for alcohol or other SUDs (CASA, 2010; Glaze & Kaeble, 2014; Mumola & Karberg, 2006), compared to approximately 12% in the general population (Merikangas & McClair, 2012). SUDs also predict maladaptive behavior within the corrections system and remain a risk factor for recidivism following release into the community (Cochran et al., 2014; Henry, 2020). Among those with SUDs, about 60% of those left untreated during incarceration will relapse within 3 years of release, often resulting in parole violations and recidivism (Pearson & Lipton, 1999). Among youth with early encounters in the criminal justice system, it remains a priority to address



known risk factors and neurodevelopmental liabilities with better precision. Periods of incarceration provide us with a valuable opportunity for research and intervention alike, as youth in the correctional system are encountering enforced abstinence, many for the first time. These population characteristics help to reduce the impact of otherwise uncontrollable nuisance factors in general community samples. The present findings may represent a foothold for developing more targeted intervention strategies, which recognize specific neuropathological vulnerabilities influencing the initiation and maintenance of substance misuse at an early age. Continued research in this venue serves both public mental health priorities and addresses humanitarian and practical concerns serving our best interests as a society.

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## References

- Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—the methods. *Neuroimage*, 11(6), 805–821.
- Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *Neuroimage*, 26(3), 839–851.
- Barrós-Loscertales, A., Garavan, H., Bustamante, J. C., Ventura-Campos, N., Llopis, J. J., Belloch, V., Parcet, M. A., & Ávila, C. (2011). Reduced striatal volume in cocaine-dependent patients. *Neuroimage*, 56(3), 1021–1026.
- Blakemore, S. J., & Robbins, T. W. (2012). Decision-making in the adolescent brain. *Nature Neuroscience*, 15(9), 1184–1191.
- Bu, L., Yu, D., Su, S., Ma, Y., Von Deneen, K. M., Luo, L., Zhai, J., Liu, B., Cheng, J., Guan, Y., Li, Y., Bi, Y., Xue, T., Lu, X., & Yuan, K. (2016). Functional connectivity abnormalities of brain regions with structural deficits in young adult male smokers. *Frontiers in Human Neuroscience*, 10, 494. <https://doi.org/10.3389/fnhum.2016.00494>
- Büchel, C., Peters, J., Banaschewski, T., Bokde, A. L. W., Bromberg, U., Conrod, P. J., Flor, H., Papadopoulos, D., Garavan, H., Gowland, P., Heinz, A., Walter, H., Ittermann, B., Mann, K., Martinot, J.-L., Paillère-Martinot, M.-L., Nees, F., Paus, T., Pausova, Z., Poustka, L., Rietschel, M., Robbins, T. W., Smolka, M. N., Gallinat, J., Schumann, G., Knutson, B., & IMAGEN consortium (2017). Blunted ventral striatal responses to anticipated rewards foreshadow problematic drug use in novelty-seeking adolescents. *Nature Communications*, 8(1), 1–11.
- CASA (2010). *Behind Bars II: Substance abuse and America's prison population*. The National Center on Addiction and Substance Abuse at Columbia University. <https://www.ojp.gov/nij/virtual-library/abstracts/behind-bars-ii-substance-abuse-and-americas-prison-population>
- Casey, B., Getz, S., & Galvan, A. (2008). The adolescent brain. *Developmental Review*, 28(1), 62–77.
- Casey, B. J., Cannonier, T., Conley, M. I., Cohen, A. O., Barch, D. M., Heitzeg, M. M., Soules, M. E., Teslovich, T., Dellarco, D. V., Garavan, H., Orr, C. A., Wager, T. D., Banich, M. T., Speer, N. K., Sutherland, M. T., Riedel, M. C., Dick, A. S., Bjork, J. M., Thomas, K. M., Chararani, B., Mejia, M. H., D. J. Hagler Jr., Daniela Cornejo, M., Scat, C. S., Harms, M. P., Dosenbach, N. U. F., Rosenberg, M., Earl, E., Bartsch, H., Watts, R., Polimeni, J. R., Kuperman, J. M., Fair, D. A., & Dale, A. M. (2018). The adolescent brain cognitive development (ABCD) study: Imaging acquisition across 21 sites. *Developmental Cognitive Neuroscience*, 32, 43–54. <https://doi.org/10.1016/j.dcn.2018.03.001>
- Casey, B., & Jones, R. M. (2010). Neurobiology of the adolescent brain and behavior: Implications for substance use disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, 49(12), 1189–1201.
- CBHSQ (2015). *Behavioral health trends in the United States: Results from the 2014 national survey on drug use and health*. Center for Behavioral Health Statistics and Quality. <https://www.samhsa.gov/data/>
- Chang, L., Cloak, C., Patterson, K., Grob, C., Miller, E. N., & Ernst, T. (2005). Enlarged striatum in abstinent methamphetamine abusers: A possible compensatory response. *Biological Psychiatry*, 57(9), 967–974.
- Christakou, A., Brammer, M., & Rubia, K. (2011). Maturation of limbic corticostriatal activation and connectivity associated with developmental changes in temporal discounting. *Neuroimage*, 54(2), 1344–1354.
- Churchwell, J. C., Carey, P. D., Ferrett, H. L., Stein, D. J., & Yurgelun-Todd, D. A. (2012). Abnormal striatal circuitry and intensified novelty seeking among adolescents who abuse methamphetamine and cannabis. *Developmental Neuroscience*, 34(4), 310–317.
- Cochran, J. C., Mears, D. P., Bales, W. D., & Stewart, E. A. (2014). Does inmate behavior affect post-release offending? Investigating the misconduct-recidivism relationship among youth and adults. *Justice Quarterly*, 31(6), 1044–1073.
- Conrod, P. J., & Nikolaou, K. (2016). Annual research review: On the developmental neuropsychology of substance use disorders. *Journal of Child Psychology and Psychiatry*, 57(3), 371–394.
- Cope, L. M., Martz, M. E., Hardee, J. E., Zucker, R. A., & Heitzeg, M. M. (2019). Reward activation in childhood predicts adolescent substance use initiation in a high-risk sample. *Drug and Alcohol Dependence*, 194, 318–325. <https://doi.org/10.1016/j.drugalcdep.2018.11.003>
- Ermer, E., Cope, L. M., Nyalakanti, P. K., Calhoun, V. D., & Kiehl, K. A. (2012). Aberrant paralimbic gray matter in criminal psychopathy. *Journal of Abnormal Psychology*, 121(3), 649–658.
- Ersche, K. D., Jones, P. S., Williams, G. B., Turton, A. J., Robbins, T. W., & Bullmore, E. T. (2012). Abnormal brain structure implicated in stimulant drug addiction. *Science*, 335(6068), 601–604.
- Ersche, K. D., Williams, G. B., Robbins, T. W., & Bullmore, E. T. (2013). Meta-analysis of structural brain abnormalities associated with stimulant drug dependence and neuroimaging of addiction vulnerability and resilience. *Current Opinion in Neurobiology*, 23(4), 615–624.
- Fein, G., Greenstein, D., Cardenas, V. A., Cuzen, N. L., Fouche, J. P., Ferrett, H., Thomas, K., & Stein, D. J. (2013). Cortical and subcortical volumes in adolescents with alcohol dependence but without substance or psychiatric comorbidities. *Psychiatry Research: Neuroimaging*, 214(1), 1–8.
- Forth, A. E., Kosson, D. S., & Hare, R. D. (2003). *Hare psychopathy checklist: Youth version (PCL: YV)*. Multi-Health Systems.
- Franklin, T. R., Acton, P. D., Maldjian, J. A., Gray, J. D., Croft, J. R., Dackis, C. A., O'Brien, C. P., & Childress, A. R. (2002). Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biological Psychiatry*, 51(2), 134–142.
- Galvan, A. (2010). Adolescent development of the reward system. *Frontiers in Human Neuroscience*, 6, 1018. <https://doi.org/10.3389/fnhum.2010.006.2010>
- Giedd, J. N. (2008). The teen brain: Insights from neuroimaging. *Journal of Adolescent Health*, 42(4), 335–343.
- Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., Paus, T., Evans, A. C., & Rapoport, J. L. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*, 2(10), 861–863.
- Gilman, J. M., Kuster, J. K., Lee, S., Lee, M. J., Kim, B. W., Makris, N., van der Kouwe, A., Blood, A. J., & Breiter, H. C. (2014). Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. *Journal of Neuroscience*, 34(16), 5529–5538.
- Glaze, L. E., & Kaeble, D. (2014). *Correctional populations in the United States, 2013*. Bureau of Justice Statistics. <http://www.bjs.gov/index.cfm?ty=pbdetail&iid=5177>
- Henry, B. F. (2020). Adversity, mental health, and substance use disorders as predictors and mediators of rule violations in US prisons. *Criminal Justice and Behavior*, 47(3), 271–289.



- Ide, J. S., Li, H.-T., Chen, Y., Le, T. M., Li, C. S., Zhornitsky, S., & Li, C.-S. R. (2020). Gray matter volumetric correlates of behavioral activation and inhibition system traits in children: An exploratory voxel-based morphometry study of the ABCD project data. *Neuroimage*, 220, 117085. <https://doi.org/10.1016/j.neuroimage.2020.117085>
- Infante, M. A., Ebersson, S. C., Zhang, Y., Brumback, T., Brown, S. A., Colrain, I. M., Baker, F. C., Clark, D. B., De Bellis, M. D., Goldston, D., Nagel, B. J., Nooner, K. B., Zhao, Q., Pohl, K. M., Sullivan, E. V., Pfefferbaum, A., Tapert, S. F., & Thompson, W. K. (2022). Adolescent binge drinking is associated with accelerated decline of gray matter volume. *Cerebral Cortex*, 32(12), 2611–2620.
- Jaworska, N., Cox, S. M., Tippler, M., Castellanos-Ryan, N., Benkelfat, C., Parent, S., Dagher, A., Vitaro, F., Boivin, M., Pihl, R. O., Côté, S. M., Tremblay, R. E., Séguin, J. R., & Leyton, M. (2020). Extra-striatal D 2/3 receptor availability in youth at risk for addiction. *Neuropsychopharmacology*, 45(9), 1498–1505.
- Jernigan, T. L., Gamst, A. C., Archibald, S. L., Fennema-Notestine, C., Mindt, M. R., Marcotte, T. L., Heaton, R. K., Ellis, R. J., & Grant, I. (2005). Effects of methamphetamine dependence and HIV infection on cerebral morphology. *American Journal of Psychiatry*, 162(8), 1461–1472.
- Kaag, A. M., Schulte, M. H. J., Jansen, J. M., Van Wingen, G., Homberg, J., Van Den Brink, W., Wiers, R. W., Schmaal, L., Goudriaan, A. E., & Reneman, L. (2018). The relation between gray matter volume and the use of alcohol, tobacco, cocaine and cannabis in male polysubstance users. *Drug and Alcohol Dependence*, 187, 186–194. <https://doi.org/10.1016/j.drugalcdep.2018.03.010>
- Kelley, A. E., Schochet, T., & Landry, C. F. (2004). Risk taking and novelty seeking in adolescence: Introduction to part I. *Annals of the New York Academy of Sciences*, 1021(1), 27–32.
- Kendler, K. S., Ohlsson, H., Maes, H. H., Sundquist, K., Lichtenstein, P., & Sundquist, J. (2015). A population-based Swedish twin and sibling study of cannabis, stimulant and sedative abuse in men. *Drug and Alcohol Dependence*, 149, 49–54. <https://doi.org/10.1016/j.drugalcdep.2015.01.016>
- Kiehl, K. A., Anderson, N. E., Aharoni, E., Maurer, J. M., Harenski, K. A., Rao, V., Claus, E. D., Harenski, C., Koenigs, M., Decety, J., Kosson, D., Wager, T. D., Calhoun, V. D., & Steele, V. R. (2018). Age of gray matters: Neuroprediction of recidivism. *NeuroImage: Clinical*, 19, 813–823. <https://doi.org/10.1016/j.nicl.2018.05.036>
- King, N., Crawford, S., Wenden, F., Moss, N., & Wade, D. (1995). The rivermead post concussion symptoms questionnaire: A measure of symptoms commonly experienced after head injury and its reliability. *Journal of Neurology*, 242(9), 587–592.
- Lees, B., Garcia, A. M., Debenham, J., Kirkland, A. E., Bryant, B. E., Mewton, L., & Squeglia, L. M. (2021). Promising vulnerability markers of substance use and misuse: A review of human neurobehavioral studies. *Neuropharmacology*, 187, 108500. <https://doi.org/10.1016/j.neuropharm.2021.108500>
- Lisdahl, K. M., Tamm, L., Epstein, J. N., Jernigan, T., Molina, B. S. G., Hinshaw, S. P., Swanson, J. M., Newman, E., Kelly, C., Bjork, J. M., & MTA Neuroimaging Group (2016). The impact of ADHD persistence, recent cannabis use, and age of regular cannabis use onset on subcortical volume and cortical thickness in young adults. *Drug and Alcohol Dependence*, 161, 135–146. <https://doi.org/10.1016/j.drugalcdep.2016.01.032>
- Lorenzetti, V., Lubman, D. I., Whittle, S., Solowij, N., & Yücel, M. (2010). Structural MRI findings in long-term cannabis users: What do we know? *Substance Use & Misuse*, 45(11), 1787–1808.
- Luna, B., & Sweeney, J. A. (2004). The emergence of collaborative brain function: fMRI studies of the development of response inhibition. *Annals of the New York Academy of Sciences*, 1021(1), 296–309.
- Mackey, S., Allgaier, N., Chaarani, B., Spechler, P., Orr, C., Bunn, J., Allen, N. B., Alia-Klein, N., Batalla, A., Blaine, S., Brooks, S., Caparelli, E., Chye, Y. Y., Cousijn, J., Dagher, A., Desrivieres, S., Feldstein-Ewing, S., Foxe, J. J., Goldstein, R. Z., Goudriaan, A. E., Heitzeg, M. M., Hester, R., Hutchison, K., Korucuoglu, O., Li, C.-S. R., London, E., Lorenzetti, V., Luijten, M., Martin-Santos, R., May, A., Momenan, R., Morales, A., Paulus, M. P., Pearson, G., Rousseau, M.-E., Salmeron, B. J., Schluter, Rée, Schmaal, L., Schumann, G., Sjoerds, Z., Stein, D. J., Stein, E. A., Sinha, R., Solowij, N., Tapert, S., Uhlmann, A., Veltman, D., van Holst, R., Whittle, S., Wiers, R., Wright, M. J., Yücel, M., Zhang, S., Yurgelun-Todd, D., Hibar, D. P., Jahanshad, N., Evans, A., Thompson, P. M., Glahn, D. C., Conrod, P., Garavan, H., & the ENIGMA Addiction Working Group (2019). Mega-analysis of gray matter volume in substance dependence: General and substance-specific regional effects. *American Journal of Psychiatry*, 176(2), 119–128.
- Makris, N., Oscar-Berman, M., Jaffin, S. K., Hodge, S. M., Kennedy, D. N., Caviness, V. S., Marinkovic, K., Breiter, H. C., Gasic, G. P., & Harris, G. J. (2008). Decreased volume of the brain reward system in alcoholism. *Biological Psychiatry*, 64(3), 192–202.
- Mason, W. A., & Windle, M. (2002). Reciprocal relations between adolescent substance use and delinquency: A longitudinal latent variable analysis. *Journal of Abnormal Psychology*, 111(1), 63–76. <https://doi.org/10.1037/0021-843X.111.1.63>
- McClelland, G. M., Elkington, K. S., Teplin, L. A., & Abram, K. M. (2004). Multiple substance use disorders in juvenile detainees. *Journal of the American Academy of Child & Adolescent Psychiatry*, 43(10), 1215–1224.
- McLellan, A. T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H., & Argeriou, M. (1992). The fifth edition of the addiction severity index. *Journal of Substance Abuse Treatment*, 9(3), 199–213.
- Merikangas, K. R., & McClair, V. L. (2012). Epidemiology of substance use disorders. *Human Genetics*, 131(6), 779–789.
- Mumola, C. J., & Karberg, J. C. (2006). *Drug use and dependence, state and federal prisoners, 2004*. Bureau of Justice Statistics: Special Report. <https://bjs.ojp.gov/content/pub/pdf/dudsf04.pdf>
- Paulus, M. P. (2022). Neural substrates of substance use disorders. *Current Opinion in Neurology*, 35(4), 460–466.
- Pearson, F. S., & Lipton, D. S. (1999). A meta-analytic review of the effectiveness of corrections-based treatments for drug abuse. *The Prison Journal*, 79(4), 384–410. <https://doi.org/10.1177/0032885599079004003>
- Rhee, S. H., Hewitt, J. K., Young, S. E., Corley, R. P., Crowley, T. J., & Stallings, M. C. (2003). Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Archives of General Psychiatry*, 60(12), 1256–1264.
- Robert, G. H., Luo, Q., Yu, T., Chu, C., Ing, A., Jia, T., Papadopoulos Orfanos, D., Burke-Quinlan, E., Desrivieres, S., Ruggeri, B., Spechler, P., Chaarani, B., Tay, N., Banaschewski, T., Bokke, A. L. W., Bromberg, U., Flor, H., Frouin, V., Gowland, P., Heinz, A., Ittermann, B., Martinot, J.-L., Paillère Martinot, M.-L., Nees, F., Poustka, L., Smolka, M. N., Vetter, N. C., Walter, H., Whelan, R., Conrod, P., Barker, T., Garavan, H., Schumann, G., & for the IMAGEN Consortium (2020). Association of gray matter and personality development with increased drunkenness frequency during adolescence. *JAMA Psychiatry*, 77(4), 409–419.
- Sajous-Turner, A., Anderson, N. E., Widdows, M., Nyalakanti, P., Harenski, K., Harenski, C., Koenigs, M., Decety, J., & Kiehl, K. A. (2020). Aberrant brain gray matter in murderers. *Brain Imaging and Behavior*, 14(5), 2050–2061.
- Schiffer, B., Müller, B. W., Scherbaum, N., Hodgins, S., Forsting, M., Wiltfang, J., Gizewski, E. R., & Leygraf, N. (2011). Disentangling structural brain alterations associated with violent behavior from those associated with substance use disorders. *Archives of General Psychiatry*, 68(10), 1039–1049.
- Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience*, 6(3), 309–315.
- Teplin, L. A., Abram, K. M., McClelland, G. M., Dulcan, M. K., & Mericle, A. A. (2002). Psychiatric disorders in youth in juvenile detention. *Archives of General Psychiatry*, 59(12), 1133–1143.
- Tschernegg, M., Pletzer, B., Schwartenbeck, P., Ludersdorfer, P., Hoffmann, U., & Kronbichler, M. (2015). Impulsivity relates to striatal gray matter volumes in humans: Evidence from a delay discounting paradigm. *Frontiers in Human Neuroscience*, 9, 384. <https://doi.org/10.3389/fnhum.2015.00384>
- Verdejo-García, A., & Albein-Urios, N. (2020). Impulsivity traits and neurocognitive mechanisms conferring vulnerability to substance use disorders. *Neuropharmacology*, 183(108402), 1–9. <https://doi.org/10.1016/j.neuropharm.2020.108402>
- Volkow, N. D., Koob, G. F., Croyle, R. T., Bianchi, D. W., Gordon, J. A., Koroshetz, W. J., Pérez-Stable, E. J., Riley, W. T., Bloch, M. H., Conway, K., Deeds, B. G., Dowling, G. J., Grant, S., Howlett, K. D., Matochik, J. A.,

- Morgan, G. D., Murray, M. M., Noronha, A., Spong, C. Y., Wargo, E. M., Warren, K. R., & Weiss, S. R. B. (2018). The conception of the ABCD study: From substance use to a broad NIH collaboration. *Developmental Cognitive Neuroscience*, 32, 4–7. <https://doi.org/10.1016/j.dcn.2017.10.002>
- Volkow, N. D., Wang, G. J., Fowler, J. S., Tomasi, D., Telang, F., & Baler, R. (2010). Addiction: Decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. *Bioessays*, 32(9), 748–755.
- Volkow, N. D., Wang, G.-J., Fowler, J. S., Tomasi, D., & Telang, F. (2011). Addiction: Beyond dopamine reward circuitry. *Proceedings of The National Academy of Sciences of The United States of America*, 108(37), 15037–15042.
- Wager, T. D., Keller, M. C., Lacey, S. C., & Jonides, J. (2005). Increased sensitivity in neuroimaging analyses using robust regression. *Neuroimage*, 26(1), 99–113.
- Wechsler, D. (1997). *Wechsler adult intelligence scale*. Psychological Corporation.
- Wechsler, D. (2003). *Wechsler intelligence scale for children—Fourth edition*. Psychological Corporation.
- Weiland, B. J., Korycinski, S. T., Soules, M., Zubieta, J.-K., Zucker, R. A., & Heitzeg, M. M. (2014). Substance abuse risk in emerging adults associated with smaller frontal gray matter volumes and higher externalizing behaviors. *Drug and Alcohol Dependence*, 137, 68–75. <https://doi.org/10.1016/j.drugalcdep.2014.01.005>
- Weiland, B. J., Zucker, R. A., Zubieta, J. K., & Heitzeg, M. M. (2017). Striatal dopaminergic reward response relates to age of first drunkenness and feedback response in at-risk youth. *Addiction Biology*, 22(2), 502–512.
- Welty, L. J., Hershfield, J. A., Abram, K. M., Han, H., Byck, G. R., & Teplin, L. A. (2017). Trajectories of substance use disorder in youth after detention: A 12-year longitudinal study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 56(2), 140–148.
- Xu, L., Groth, K. M., Pearlson, G., Schretlen, D. J., & Calhoun, V. D. (2009). Source-based morphometry: The use of independent component analysis to identify gray matter differences with application to schizophrenia. *Human Brain Mapping*, 30(3), 711–724.