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Chapter 28

Modeling neurocognitive and neurobiological recovery in addiction

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MODELING NEUROCOGNITIVE AND NEUROBIOLOGICAL RECOVERY IN ADDICTION

Neurocognitive dysfunction associated with alcohol and substance use disorders (SUDs) has been well-established and is the topic of most chapters in this book. However, neurocognitive changes occurring during abstinence from alcohol and substances have been less frequently described. This chapter first summarizes the main neurocognitive and neurobiological abnormalities associated with alcohol and SUDs, before reviewing more extensively the neurocognitive and neurobiological changes that occur with abstinence from alcohol and other substances. As a recent review focused on findings from functional magnetic resonance imaging (fMRI) and positron emission tomography studies during abstinence from alcohol (Charlet et al., 2018), the neurobiological descriptions here focus on brain morphological and spectroscopic MR studies of individuals with alcohol and/or SUDs. While the neurocognitive and neurobiological abnormalities associated with addiction increase mortality and morbidity for the afflicted individual and the society, there is also clear evidence of adaptive and variable recovery from these abnormalities. A better understanding of the specific changes associated with abstinence, their trajectories over time, and of their potential mechanisms will inform more efficacious interventions for alcohol and SUDs in future. Additionally, a better understanding of the course of neurobiological changes associated with abstinence can ultimately serve as powerful psychoeducational information for those considering and seeking treatment for alcohol and SUDs.

NEUROCOGNITIVE DEFICITS IN ADDICTION

Alcohol and SUDs in general (cocaine, methamphetamine, cannabis, or tobacco) are associated with dysfunction, primarily in the domains of learning/memory, working memory, and other executive-based skills, including cognitive/inhibitory control (extensively reviewed in previous chapters). Persons with alcohol use disorder (AUD) have been studied most, with the nature and level of impairment showing considerable variability (for recent reviews, see Stavro et al., 2013; Bernardin et al., 2014; Oscar-Berman et al., 2014; Le Berre, Fama et al., 2017). Approximately 55% of AUD manifest clinically significant neurocognitive deficits after acute detoxification (i.e., >1.5 standard deviations below the level in healthy controls), but some degree of recovery from these deficits is apparent with short-term (i.e., ≤1 month), intermediate-term (i.e., 1–12 months), and long-term (i.e., >1 year) abstinence from alcohol (Rourke and Grant, 2009; Durazzo et al., 2014b). Some dysfunction has been reported to persist into long-term abstinence from alcohol, particularly in the domains of executive and visuospatial skills, learning and memory, and postural stability (Durazzo and Meyerhoff, 2007; Rourke and Grant, 2009; Stavro et al., 2013; Le Berre, Fama et al., 2017). The degree of cognitive dysfunction and the rate of recovery during abstinence appear to be influenced by many factors such as age, sex, family history of AUD, treatment history, pretreatment alcohol consumption level, number of detoxifications, nutritional status, comorbid

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psychiatric and biomedical conditions, and comorbid SUD (Durazzo and Meyerhoff, 2007; Oscar-Berman and Marinkovic, 2007; Rourke and Grant, 2009; Schulte et al., 2014).

Most treatment-seeking substance users today concurrently and/or simultaneously consume more than one illicit/licit compound, so-called polysubstance users (PSU) (Hasin and Grant, 2015). Among PSU, comorbid tobacco use disorder is most prevalent in AUD (Durazzo and Meyerhoff, 2007; Weinberger et al., 2016), and chronic cigarette smoking itself is associated with significant neurocognitive deficiencies (e.g., visuospatial memory, motor impulsivity) in both AUD and non-AUD cohorts (e.g., Brody, 2006; Glass et al., 2005; Durazzo et al., 2006b; Gazdzinski et al., 2006; Durazzo and Meyerhoff, 2007; Almeida et al., 2008; Durazzo et al., 2010a; Durazzo et al., 2011; Durazzo et al., 2012; Morales et al., 2012; Pennington et al., 2013; Durazzo et al., 2014b; Durazzo et al., 2015a,b). Smoking AUD performed worse than their nonsmoking counterparts on domains of auditory verbal learning and memory, processing speed, cognitive efficiency, and working memory during the first month of abstinence from alcohol (Durazzo et al., 2006b; Pennington et al., 2013). Smoking AUD also demonstrated poorer neurocognition with increasing age than never-smoking AUD, and the performance of former-smoking AUD on several domains was intermediate to that of never-smoking and actively smoking AUD (Durazzo et al., 2013b; Pennington et al., 2013).

Particularly common among PSU is the simultaneous and/or concurrent abuse of alcohol, tobacco, and psychostimulants (Moss et al., 2015). Therefore, in many published research reports on the neurobiological and neurocognitive consequences of AUD, many individuals were also likely nicotine-dependent, and in studies of cocaine use disorder, participants were also likely heavy drinkers. This was both likely and most apparent in literature before about 2010, when polysubstance abuse had not been attended to more widely in substance abuse research, and other substance use was largely treated as a nuisance variable. More recently, poorer health outcomes and greater treatment resistance have been reported for PSU compared to monosubstance users (Walitzer et al., 2015; Weinberger et al., 2017). Despite its prevalence, however, few studies have directly examined the neuropsychological or neurobiological consequences of polysubstance abuse. In early studies, cocaine-dependent individuals with and without AUD showed cognitive deficits at 3 months of abstinence (Di Sclafani, Bloomer et al., 1998), and decision-making was still impaired in similar individuals abstinent for 8 months (Verdejo-Garcia et al., 2007). Even after several years of abstinence, psychostimulant-related deficits of episodic memory, planning, and cognitive flexibility were persistent in PSU (Fernandez-Serrano et al., 2011). These relatively persistent cognitive deficits were associated with the amount of cocaine and cannabis consumed (Fernandez-Serrano et al., 2010; Schmidt et al., 2017) as well as with relapse risk (Verdejo-Garcia et al., 2007; Verdejo-Garcia et al., 2012). Cognitive efficiency, processing speed, and visuospatial learning were less impaired in 1-month-abstinent PSU who continued to abstain versus those who subsequently relapsed between 1 and 4 months of abstinence (Schmidt et al., 2017); similarly, 1-month-abstinent AUD with the lowest processing speed showed a significantly increased risk for relapse following treatment (Durazzo et al., 2008a,b). In comparisons to 1-month-abstinent AUD, 1-month-abstinent PSU performed worse on measures of auditory verbal memory and learning and general intelligence (Schmidt et al., 2017), suggesting a diminished capacity (compared to ALC) of learning, memorizing, and integrating new skills presented in clinical treatment settings. In addition, PSU exhibited worse decision-making and higher self-reported impulsivity than AUD, potentially placing them at a greater relapse risk during early recovery. Finally, PSU between the ages of 25 and 70 years showed greater age-related declines in processing speed, general intelligence, cognitive efficiency, and global intelligence than controls, indicating the detrimental cumulative effects of polysubstance use on neurocognition (Schmidt et al., 2017).

As described, the degree and nature of neurocognitive deficits varies considerably among substance-using groups investigated, critically related to the combination of both illicit and licit substances abused and their use histories. However, it is noteworthy that even mild neurocognitive deficits can impact quality of life and relapse risk (Goldstein et al., 2004; Bates et al., 2013). Impaired neurocognition and inhibition may adversely affect maintenance of abstinence during treatment and long-term treatment efficacy (Aharonovich et al., 2006; Passetti et al., 2008; Streeter et al., 2008; de Wit, 2009; Bates et al., 2013; Stevens et al., 2014; Rupp et al., 2016); specifically, neurocognitive deficits can interfere with treatment efficacy by reducing the individual's ability to encode, process, recall, integrate, and apply program information during and following treatment (Durazzo et al., 2008a,b; Dominguez-Salas et al., 2016; Rezapour et al., 2016). As such, assessment of cognitive abilities during treatment may improve treatment outcomes by providing clinicians an understanding of the individual's capabilities during treatment and inform appropriate posttreatment follow-up care (Bates et al., 2013).

Neurocognitive changes during abstinence

Studies of longitudinal neurocognitive changes during abstinence from alcohol and other substances are far less common than cross-sectional studies (e.g., Fernandez-Serrano et al., 2011). Most longitudinal studies assessed neurocognition several weeks after detoxification and then 6–12 months later; they demonstrated several neurocognitive functions improve at least partially during sustained abstinence, whereas some cognitive dysfunction persists for years after detoxification (for recent reviews, see Bernardin et al., 2014; Oscar-Berman et al., 2014; Le Berre et al., 2017). Psychological changes in AUD during a residential rehabilitation program have recently been documented and include significant decreases in anxiety, depression, and psychological distress within about 1 month of detoxification in those with substance-induced mood disorders (Giorgi et al., 2015). In studies on the effects of comorbid tobacco use on neurocognitive recovery in AUD (Durazzo et al. 2006a, 2007b; Durazzo et al., 2010a; Pennington et al., 2013), we found that smoking was associated with significantly diminished improvement of visuospatial learning and processing speed within the first year of abstinence from alcohol (Pennington et al., 2013; Durazzo et al., 2014b).

We analyzed neurocognition across three different time points during abstinence from alcohol (1 week, 1 month, and 8 months) and as a function of smoking status (never-smoking, former-smoking, and actively smoking AUD) (Durazzo et al., 2014b). Over 8 months of abstinence, AUD as a group showed significant improvements of visuospatial learning and memory, processing speed, and working memory, with less pronounced changes in executive functions, postural stability, and auditory verbal learning and memory. Overall, the recovery rates were nonlinear over time, showing faster recovery between 1 and 4 weeks than between 1 and 8 months of abstinence. Improvements in the foregoing domains in AUD were driven by never-smoking AUD, where both former-smoking and actively smoking AUD showed significantly less recovery than never-smoking AUD. Additionally, active smokers showed significantly less improvement with increasing age than never-smoking AUD over 8 months on measures of processing speed and learning and memory. At 8 months of abstinence, currently smoking AUD remained inferior to controls and never-smoking AUD on multiple measures, former smokers performed worse than never-smoking AUD on several tests, but never-smoking AUD were not significantly different from controls on any measure. Thus, in this AUD cohort over 8 months of abstinence from alcohol, smoking status interacted with both abstinence duration and age to robustly moderate recovery on measures of auditory verbal and visuospatial learning and memory, as well as processing speed. The above findings were adjusted for education, estimated premorbid verbal intelligence, lifetime drinking severity, and medical, psychiatric, and substance misuse comorbidities. Importantly, in actively smoking AUD, more lifetime years of tobacco use were related to poorer recovery of auditory verbal memory over 8 months of abstinence (Durazzo et al., 2014b). For a discussion of smoking-related neurobiological mechanisms potentially underlying the differential recovery observed in AUD subgroups, see Durazzo et al. (2010a) and Durazzo et al. (2014a).

In studies of neurocognitive recovery during abstinence from substances, neurocognition was largely unchanged over 1 month of abstinence from methamphetamine (Simon et al., 2010), but improved somewhat over longer periods of sustained abstinence (Iudicello et al., 2010). Attention, working memory, declarative memory, and executive functions in cocaine users improved in those who decreased their cocaine use over a 1-year interval and normalized in those who were abstinent for 1 year (Vonmoos et al., 2014). Decline of working memory over 1 year was associated with increased cocaine use in these individuals and with younger age of onset of cocaine use. In abstinent PSU, cross-sectional studies with different durations of abstinence did (Verdejo-Garcia et al., 2004; Fernandez-Serrano et al., 2011) or did not (Medina et al., 2004) suggest recovery from neurocognitive dysfunction. The additive detrimental effects of concurrent cocaine and alcohol dependence persisted over 1 month of abstinence (Bolla et al., 2000). However, over 6 months of abstinence, individuals with comorbid alcohol and stimulant use disorders demonstrated improvements on measures of immediate memory (Fein et al., 2002), and improvements in verbal short-term memory were also observed over 3–4 months of abstinence from substances (Block et al., 2002). Concurrent use of substances in those with AUD (i.e., PSU) hampered neurocognitive recovery (Schulte et al., 2014), consistent with the detrimental effects of comorbid tobacco use in AUD. Nevertheless, in treatment-seeking PSU who maintained abstinence (other than tobacco) for 3 months after their baseline assessment at 1 month of sobriety (Schmidt et al., 2017), we observed significant improvements in executive functions, cognitive efficiency and processing speed, working memory, and reductions in self-reported impulsivity (Dominguez-Salas et al., 2016; Rezapour et al., 2016). These improvements likely aid in treatment adherence and reduce relapse risk. Fine motor skills, learning, and memory, however, remained deficient after 4 months of abstinence, especially in smoking PSU. During abstinence, self-reported impulsivity decreased in PSU, whereas performance on a measure of decision-making/risk-taking did not improve, commensurate with findings for long-term abstinent AUD (Fein et al., 2004) (but see Loeber et al., 2010). Thus, although some deficits appear to be more enduring (and may be

potentially premorbid and serve as risk factors for development of an addictive disorder (Rezapour et al., 2016)), PSU showed significant recovery across multiple neurocognitive domains over 3 months of sustained abstinence, despite decades of substance abuse.

Taken together, significant neurocognitive improvements are generally observed beyond about 1 month of abstinence in those with SUD, whereas abstinent individuals with AUD appear to show a more rapid recovery trajectory. However, the research dedicated to studying the short-term and long-term neurocognitive recovery in AUD is considerably greater than that in SUD, and more longitudinal research is required to more fully explicate the course of neurocognitive recovery with abstinence in those with SUD. These neurocognitive recoveries during abstinence suggest that the deficits are largely a consequence of chronic alcohol and/or substance use and the associated maladaptive lifestyle (i.e., poor diet/nutrition, physical activity, sleep); some persistent deficits may be premorbid and may have contributed to initiation of alcohol or substance abuse in the first place or are related to clinically significant comorbid conditions. The neurocognitive changes during abstinence suggest parallel adaptive neuroplasticity, which may present a critical window of opportunity for augmenting recovery in AUD and SUD with plasticity-based neurocognitive remediation, magnetic/electric stimulation methods, or targeted pharmacology (Rabin et al., 2015; Klein, 2016; Rezapour et al., 2016), in particular during the initial months of abstinence (Durazzo et al., 2014b). The corresponding neurocognitive improvements in these individuals (and neurobiology, discussed next) will likely promote better treatment response—as demonstrated for AUD (Bates et al., 2013)—and ultimately longer abstinence.

Neurobiological abnormalities in addiction

Underlying the neurocognitive deficits in AUD and SUD as well as their changes with abstinence from alcohol and/or substances are neurobiological adaptations and their changes during abstinence. Here, we first review MR-based studies of brain alterations in addiction, followed by review of serial MR studies performed to better understand the neuroadaptations associated with recovery during abstinence. We focus on descriptions of MR structural and spectroscopic findings in addiction, with the vast fMRI field not covered (but see Charlet et al., 2018).

Magnetic resonance (MR)–based neuroimaging studies of individuals with use disorders of alcohol, cocaine, amphetamines, marijuana, or tobacco have revealed regional brain atrophy as correlates of neurocognitive dysfunction (for reviews, see Goldstein and Volkow, 2011; Wang et al., 2015; Buhler and Mann, 2011; Sneider et al., 2013; Xiao et al., 2015; Sullivan et al., 2018). Atrophy is observed throughout the brain with a prefrontal preference and is likely driven by loss of, or damage to, neuronal cell bodies, dendrites (including dendritic spines, axons/teledendria/terminal endings as demonstrated neuropathologically), and/or glial cells (Crews and Boettiger, 2009; Zahr et al., 2011). However, abused substances may affect brain structures differentially, potentially related to the distribution of specific receptors (such as cannabinoid or cholinergic receptors) throughout the brain and/or to the heterogeneity of substance use severities across the different brain imaging studies published. In addition to variable and regionally varying cortical atrophy, psychostimulant studies describe enlargement of subcortical structures: For example, methamphetamine users (Chang et al., 2007), heavy cannabis users (Moreno-Alcázar et al., 2018; Nader and Sanchez, 2018), and cocaine-dependent individuals (Ersche et al., 2011) (as well as their unaffected siblings (Ersche et al., 2013)) have all been shown to have enlarged striatal volumes. Additionally, prescription opioid analgesics are associated with both decreases and increases of regional brain volumes after only 1 month of opioid administration, with many of the changes persisting for 5 months after discontinuation (Younger et al., 2011).

Consistent with the above reports on (ostensibly) monosubstance users, structural brain abnormalities have also been described in PSU, who are the largest but most understudied SUD group. Greater years of polysubstance use were related to lobar cortical and thalamic gray matter volume loss (Noyan et al., 2016). In comparison to AUD, PSU had larger lobar white matter volumes in the absence of the widespread gray matter volume loss typically observed in AUD with comparable lifetime drinking and smoking histories (Pennington et al., 2015). Furthermore, PSU exhibited distinct relationships between regional brain volumes and processing speed, cognitive efficiency, working memory, and inhibitory control, which were not observed in AUD or controls; this suggests potential alterations/compensations in neural circuits of PSU that are classically associated with the above functional domains. Taken together, neuronal atrophy in PSU may be countered by the adverse effects of reactive gliosis and neuroinflammation (as reflected in the subcortical volume enlargements of psychostimulant users), possibly masking atrophy typically observed in AUD.

Other neuroimaging methods help assess functional alterations or neurobiological mechanisms underlying brain structural alterations in addiction. They include functionally relevant low cerebral blood flow (Rogers et al., 1983; Tunving et al., 1986; Volkow et al., 1988; Nicolas et al., 1993; Oishi et al., 1999; Ernst et al., 2000a,b; Gansler et al.,

2000; Chang et al., 2002; Hwang et al., 2006; Heinz et al., 2009; Murray et al., 2018), altered brain glucose metabolism (Volkow et al., 1993; Volkow et al., 1994; Volkow et al., 2001; Eldreth et al., 2004; Kim et al., 2005), and altered brain metabolite levels measured by proton magnetic resonance spectroscopy (MRS). MRS studies revealed regional metabolic abnormalities in those with alcohol and SUDs that are consistent with abnormal markers of neuronal integrity (as measured by lower concentrations of N-acetylaspartate [NAA] or glutamate [Glu]), cellular bioenergetics (as indicated by lower concentrations of creatine-containing metabolites, Cr), glial or cell membrane turnover/synthesis (as indicated by altered levels of choline-containing metabolites, Cho), and glial content/gliosis or osmoregulation (as reflected in altered levels of myo-inositol [mI]) (Meyerhoff et al., 1994; Fein et al., 1995; Meyerhoff et al., 1999; Ernst et al., 2000a,b; O'Neill et al., 2001; Parks et al., 2002; Durazzo et al., 2004; Ke et al., 2004; Meyerhoff et al., 2004; Nordahl et al., 2005; Chang et al., 2007; Hermann et al., 2007; Durazzo et al., 2008a,b; Durazzo et al., 2010b; Sailasuta et al., 2010; Prescot et al., 2011; Prescot et al., 2013; Murray et al., 2016) (also reviewed by Meyerhoff et al., 2013). These studies indicate that alcohol and illicit substances alter regional neuronal integrity, energy metabolism, membrane synthesis/turnover, the metabolic pools of Glu and gamma-aminobutyric acid (GABA) that are in equilibrium with their neurotransmitter pools, and gliotic/inflammatory processes (Yang et al., 2009; Licata and Renshaw, 2010). In several of the MRS reports cited here, the brain metabolite abnormalities correlated with the duration of substance use and neurocognitive deficits (e.g., Murray et al., 2016).

Furthermore, chronic cigarette smoking compounds and regional brain metabolite abnormalities (and neurocognitive dysfunction, see above) are observed in AUD (Meyerhoff, 2007; Wang et al., 2009; Durazzo et al., 2013). The chronic abuse of different substances is associated with tissue alterations in largely similar brain regions, primarily in the prefrontal cortex (PFC), the underlying white matter, the thalami, and the basal ganglia including striatal structures (Holman et al., 1991; Volkow et al., 1992; Weber et al., 1993; Ernst et al., 2000a,b; Sullivan, 2000; Sullivan et al., 2000; Franklin et al., 2002; Matochik et al., 2003; Eldreth et al., 2004; Thompson et al., 2004; Dom et al., 2005; Matochik et al., 2005; Nordahl et al., 2005; Bae et al., 2006; Hermann et al., 2007; Sorg et al., 2012; Wang et al., 2015; Murray et al., 2016). Specifically, the dorsolateral PFC is implicated in executive functions involving planning and organization, response inhibition, working memory, reasoning, problem solving, set shifting, and goal-directed behavior (e.g., Goldstein and Volkow, 2011). The collective subregions of the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) combine to subserve processing of affective or emotional stimuli or contexts, conflict monitoring, interoceptive-autonomic and reward-processing aspects of reward processing, switching between habitual (overlearned) and goal-directed behavior based on consequences of actions, and reward identification and acquisition (Volkow and Baler, 2014; Williams, 2016; Moorman, 2018). As such, the affected brain regions are all critically important for the initiation and maintenance of addictive behaviors (Volkow et al. 2012, 2013; Volkow and Baler, 2014).

We have also studied the neurobiological consequences of polysubstance use via brain MRS. Early studies suggested that alcohol-dependent individuals with and without cocaine dependence differed in their regional metabolite concentrations and the brain regions primarily affected (Meyerhoff et al., 1999). More recent studies compared 1-month-abstinent PSU to drug-free controls and found lower NAA, Cr, and mI in the dorsolateral PFC of PSU, with lower prefrontal NAA in PSU related to poorer visuospatial learning/memory and working memory (Abé et al., 2013). While prefrontal Glu levels were normal in these PSU, GABA tended to be reduced in the ACC, and lower GABA in the dorsolateral PFC was associated with greater cocaine consumption. In contrast, dorsolateral PFC metabolite levels and prefrontal GABA levels were normal in age-equivalent AUD with similar lifetime drinking histories, and initially low NAA, Cr, and mI levels in the ACC of these AUD had all normalized by 1 month of abstinence from alcohol (Mon et al., 2012). As such, metabolite alterations appear to be regionally different in abstinent PSU and AUD, more pronounced in the dorsolateral PFC of PSU, which may signal more enduring brain injury during abstinence in PSU. The detected metabolite abnormalities in PSU were unrelated to age, alcohol consumption, body mass index, smoking status, as well as comorbid depression and anxiety symptomatologies; the abnormalities were likely related to the misuse of illicit drugs in PSU. Such cross-sectional comparisons of brain alterations across different substance-using groups suggest slightly different brain injuries and recovery dynamics that suggest better targeted approaches for optimal treatment.

Neurobiological changes during abstinence

The cross-sectional neuroimaging abnormalities described above were reported to either relate or not relate to abstinence duration (e.g., Hanlon et al., 2013; Yucel et al., 2016); thus, they could be a consequence of alcohol/substance abuse and the associated lifestyle, a premorbid risk factor for its development, or both. Only serial studies focusing on neurobiological recovery during sustained abstinence can distinguish between these interpretations by providing evidence

of recovery from brain abnormalities during abstinence. Poor subject retention, however (Morales et al., 2012; Salo and Fassbender, 2012; Hanlon et al., 2013; Mackey and Paulus, 2013), has limited the execution of longitudinal neuroimaging studies in treatment seekers during abstinence, especially in illicit substance abusers.

The best evidence for beneficial neuroadaptation during sobriety is available from longitudinal morphometric neuroimaging studies of treatment seekers abstinent from alcohol (see reviews by Buhler and Mann, 2011; Meyerhoff, 2014; Zahr, 2014; Durazzo et al., 2015a,b; Charlet et al., 2018). Brain volume increases can be demonstrated by quantitative MRI within as few as 14 days of abstinence (van Eijk et al., 2013; Durazzo et al., 2015a,b; Zou et al., 2018), driven by increases in regional frontal, occipital, and parietal cortical thickness but not surface area (Wang et al., 2016); reduced subcortical volumes did not recover over the first 2 weeks of abstinence (van Eijk et al., 2013). Volume increases were also observed over a 6-month follow-up period in a few select brain regions (including cerebellar vermis and cingulate gyrus) in those who did not manage to achieve complete abstinence (i.e., those who engaged in some low-level drinking after treatment with no resumption of heavy consumption) (Segobin et al., 2014), supporting the harm reduction theory in AUD treatment. Hippocampal volume recovery within the first month of alcohol abstinence was a function of brain-derived neurotrophic factor genotype (Hoefer et al., 2014) and associated with improvements in visual short- and long-term memory (Gazdzinski et al., 2008). When investigated, repeat studies in abstinent individuals often indicate positive associations between volumetric and neurocognitive recoveries (Durazzo and Meyerhoff, 2007; Meyerhoff, 2008).

Almost all longitudinal neuroimaging studies in addiction involved one follow-up examination after a few weeks of abstinence; only a few studies used at least three assessment points (Pfefferbaum et al., 1995; Agartz et al., 2003; Gazdzinski et al., 2005a,b; Yeh et al., 2007; Hoefer et al., 2014; Durazzo et al., 2015a,b; Zou et al., 2018) to investigate the trajectory of brain volume recovery over a longer period of abstinence from alcohol. In an early study of the temporal dynamics of volume recovery (Gazdzinski et al., 2005a,b), we observed that approximately 50% of the tissue volume recovery of the entire brain over 7–12 months of continuous abstinence occurred during the first month of abstinence. We also showed that a nonlinear mathematical formula predicted very well the experimentally observed data for lobar gray and white matter volume changes (Mon et al., 2011). Further analyses of structural imaging data from a similar cohort (Durazzo et al., 2015a,b) revealed that gray matter volumes increased significantly in the frontal, parietal, and occipital lobes of AUD between 1 week and 7.5 months of abstinence. However, the monthly gray matter volume change rates of the frontal and parietal lobes were significantly greater between 1 week and 1 month of abstinence than between 1 and 7.5 months of abstinence, suggesting a nonlinear gray matter volume recovery trajectory with faster recovery in earlier phases of sobriety. In a follow-up study, we observed that the functionally distinct dorsolateral PFC, OFC, and insula had nonlinear volume recovery trajectories over long-term abstinence, whereas the trajectories for the ACC and hippocampus were linear over the entire observation period (Zou et al., 2018). This gray matter plasticity apparent during alcohol abstinence and its timing may have important treatment implications. Specifically, the degree of regional structural recovery during early and later phases of abstinence may identify those at increased risk for relapse and inform the type and timing of interventions that promote the most efficient adaptive neuroplasticity during early recovery (Seo and Sinha, 2015; Seo et al., 2015; Durazzo and Meyerhoff, 2017).

Methamphetamine-dependent individuals showed volume increases in inferior frontal, angular, and superior temporal gyri, precuneus, insula, and occipital pole over 4 weeks of abstinence (Morales et al., 2012). In cocaine-dependent treatment seekers, PFC volume recovered between months 5 and 9 of abstinence; increases in inferior frontal gyrus as well as ventromedial PFC volumes were associated with improvements in cognitive flexibility and decision-making, respectively (Parvaz et al., 2017). In this study, lapses did not necessarily impede cortical volume recovery. Similarly, reducing (not ceasing) cocaine use in heavy users over 19 months was associated with thickening of the lateral frontal cortices that related to better attention (Hirsiger et al., 2019). These latter studies lend initial support for a harm reduction model also in cocaine use disorder treatment.

In unpublished neuroimaging studies of 20 PSU patients between 1 and 4 months of abstinence (a subgroup of individuals described in the cross-sectional PSU neuroimaging analyses above) (Pennington et al., 2015), we found evidence for widespread volumetric change also in individuals who co-abused alcohol and stimulants for more than 20 years: an increase in left caudate volume, a decrease in right superior temporal lobe volume, and trends to decreasing insula and entorhinal cortex volumes (unpublished). These changes, however, were much less dramatic than observed in short-term abstinent AUD described above. Given that abnormalities in PSU involved both smaller and larger regional tissue volumes (purportedly from competing neural mechanisms—see cross-sectional review above), observing both volume increases and decreases across different brain regions during sustained abstinence is not surprising and may relate to the competing morphometric processes and altered functional connectivity postulated among these brain regions.

Longitudinal MRS studies have been used to try to further understand the tissue changes that underlie volume changes during recovery. We showed in a series of studies in recovering AUD that after correcting for parallel tissue volume changes, NAA and Cho concentrations throughout the brain recovered significantly, but variably over 5 weeks of abstinence, with some of the metabolite changes related to improvements in specific neurocognitive domains (Durazzo et al., 2006a, Gazdzinski et al. 2008). The brain metabolite recovery was generally greater in nonsmoking than smoking AUD (Meyerhoff, 2007), with less frontal white matter NAA recovery related to longer smoking duration (Durazzo et al., 2006a). In an MRS study of recently abstinent methamphetamine abusers, low Glu in ACC recovered over 5 months of abstinence, together with a reduction of craving (Ernst and Chang, 2008). Over just 4 weeks of abstinence, however, prefrontal NAA and Cho in intravenous methamphetamine users did not change significantly (Yoon et al., 2010), in contrast to observations in short-term abstinent AUD. In our small cohort of abstinent PSU, regional metabolite concentrations recovered between 1 and 3 months of abstinence to levels commensurate with controls (unpublished). Specifically, NAA and Cho in the dorsolateral PFC and GABA and NAA in the ACC significantly increased, while Glu and mI in the ACC and mI in the parieto-occipital gray matter decreased; the NAA increases in ACC and dorsolateral PFC correlated with improvements in visuospatial learning and working memory, respectively.

The observed brain tissue volume and metabolite level changes during abstinence from alcohol and/or substances may partially reflect the reversal of maladaptive neuroplastic processes associated with chronic long-term alcohol/substance abuse (Koob, 2009). While initial significant neurobiological changes have been observed within the first month of abstinence in AUD, fewer studies describe such early processes in illicit substance users, reminiscent of the dynamics of potentially related neurocognitive improvements (see above). Neurobiological improvements are observable over many months, even years after initiation of abstinence. They are likely not the result of a single neural process but of several different processes involving different cell types and populations to various degrees—sometimes potentially with opposing effects on regional MR-based outcome measures and with various temporal dynamics. Given the demonstrated associations between neurobiological and neurocognitive measures, this may give rise to the relatively large variability observed for neurocognitive recovery across different substance-using groups and among individuals in the same substance-using group during abstinence. Data from humans and animal models suggest the tissue volume recovery in AUD during early and extended abstinence is related to increases in neuronal dendritic arbor, soma/cell volume, synaptic density, nonreactive glial proliferation (particularly microglia), and remyelination (e.g., Dlugos and Pentney, 1997; Sullivan and Pfefferbaum, 2005; Crews and Nixon, 2009; Anderson, 2011; Zatorre et al., 2012), which are all intrinsic neuroadaptations that are also instrumental in experience-based learning and memory (Anderson, 2011; Zatorre et al., 2012). The metabolite concentration changes that often accompany morphometric changes during abstinence may also be related to these mechanisms.

Clinically relevant modulators of the degree of regional volume reduction in adult AUD and of the extent of structural recovery during abstinence have been identified; they include age, gender, family history of problem drinking and genetic factors, degree of baseline atrophy, number of detoxifications, and comorbid medical (hepatitis C and hypertension), psychiatric (depression, anxiety), and SUDs including tobacco use disorder (Duka et al., 2003; Cardenas et al. 2005, 2007; Gazdzinski et al., 2005a,b; Durazzo et al., 2007a,b; Demirakca et al., 2011; Mon et al., 2013; Hoefer et al., 2014; Pennington et al., 2015; Durazzo and Meyerhoff, 2017; Sullivan et al., 2018). The same factors as well as stress and stress response (Blaine and Sinha, 2017) also modulate metabolic and functional brain injury and recovery in AUD. Finally, a critical determinant of brain injury is the age of onset of substance use, with substance-associated brain changes in adolescents being different both qualitatively and quantitatively from those in adults, as they likely interact with brain development. Studying the effects of substance use cessation in the developing brain is in its infancy, with the current Adolescent Brain Cognitive Development (ABCD) Study, a longitudinal, observational study of over 10,000 youth recruited throughout the United States, promising to address this issue.

CONCLUSIONS AND OUTLOOK

Given these many modulators of neurobiology in alcohol and SUDs, some of which are also risk factors for relapse (Durazzo et al., 2010b; Rando et al., 2011; Seo and Sinha, 2015; Seo et al., 2015; Durazzo and Meyerhoff, 2017), neurobiological and neurocognitive recovery with abstinence from alcohol and other substances is complex and not trivial to study and interpret in a meaningful way. Even more challenging will be to incorporate some of these research findings into clinical practice. One successful example of such development is the now much more widespread integration of smoking cessation into substance abuse treatment: tobacco use, a significant but modifiable health risk for both relapse and common psychiatric comorbidities in AUD, has a greater annual mortality than SUD and AUD

combined, and we can ill afford to continue ignoring it in addiction treatment (Weinberger et al., 2015). It has been demonstrated that treating tobacco use effectively in those seeking treatment for their (other) substance abuse may promote better long-term outcomes (Kalman et al., 2010; Cavazos-Rehg et al., 2014; Durazzo and Meyerhoff, 2017). But our efforts cannot end here, as newer forms of nicotine delivery (e.g., vaping/e-cigarettes) also need to be considered carefully regarding their addictive and brain-altering potentials.

Despite the seemingly overwhelming complexities in studying brain function, morphometry, and recovery in human addiction, demonstrating specific neuroadaptations after detoxification, their time courses, and their dependence on critical modulators are important for several reasons: (1) There might be an optimal window of opportunity for augmenting such intrinsic neurobiological repair processes (neuroplasticity) via interventions such as plasticity-based cognitive remediation, magnetic/electrical stimulation, or pharmacotherapy; (2) many neurocognitive deficits and/or their neurobiological correlates are not premorbid/risk factors of abuse, but rather consequences of abuse, and brain function and tissue integrity can improve with sustained abstinence; and (3) relapse risk likely decreases over time with abstinence as brain neurobiology and functions recover from injury (adaptive neuroplasticity). Identifying the specific neurobiological mechanisms associated with such improvements, their mitigating factors, time courses, and trajectories can critically inform interventions aimed at facilitating brain repair and recovery processes, such as strengthening prefrontal neural connectivity or employing GABAergic therapy to improve inhibitory control. A recent opinion piece (Humphreys and Bickel, 2018) calls for "expanding and deepening the neuroscience of recovery from addiction" to improve addiction-focused clinical care and public policy. In that spirit, we hope that this chapter contributes to describing a critical part of the current state of addiction recovery research.

Finally, it is noteworthy that all recovery research described in this chapter has been conducted in individuals having (ostensibly) achieved complete abstinence from alcohol and other substances. Research has rarely examined psychological or physical functioning in moderation-focused treatment approaches (see, e.g., Witkiewitz et al., 2019). Given the increasing consideration of treatment outcome endpoints other than complete abstinence, future research will almost certainly be conducted to better understand the degree of neurobiological recovery associated with reduced substance use (harm reduction from nonabstinence-based recovery). Additional research might focus on recovery processes that go beyond the standard treatment durations of several months described here, to better understand neuropsychological and neurobiological factors associated with sustained recovery in later years when treated individuals remain at some degree of relapse risk.

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