Bouncing back: Brain rehabilitation amid opioid and stimulant epidemics

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ABSTRACT

Recent methamphetamine and opioid use epidemics are a major public health concern. Chronic stimulant and opioid use are characterized by significant psychosocial, physical and mental health costs, repeated relapse, and heightened risk of early death. Neuroimaging research highlights deficits in brain processes and circuitry that are linked to responsivity to drug cues over natural rewards as well as suboptimal goal-directed decision-making. Despite the need for interventions, little is known about (1) how the brain changes with prolonged abstinence or as a function of various treatments; and (2) how symptoms change as a result of neuromodulation. This review focuses on the question: What do we know about changes in brain function during recovery from opioids and stimulants such as methamphetamine and cocaine? We provide a detailed overview and critique of published research employing a wide array of neuroimaging methods – functional and structural magnetic resonance imaging, electroencephalography, event-related potentials, diffusion tensor imaging, and multiple brain stimulation technologies along with neurofeedback – to track or induce changes in drug craving, abstinence, and treatment success in stimulant and opioid users. Despite the surge of methamphetamine and opioid use in recent years, most of the research on neuroimaging techniques for recovery focuses on cocaine use. This review highlights two main findings: (1) interventions can lead to improvements in brain function, particularly in frontal regions implicated in goal-directed behavior and cognitive control, paired with reduced drug urges/ craving; and (2) the targeting of striatal mechanisms implicated in drug reward may not be as cost-effective as prefrontal mechanisms, given that deep brain stimulation methods require surgery and months of intervention to produce effects. Overall, more studies are needed to replicate and confirm findings, particularly for individuals with opioid and methamphetamine use disorders.

1. Brain recovery from stimulant and opioid use disorders

Methamphetamine and opioid use epidemics have resulted in chronic relapse, early death, and millions of life years lost (Gomes et al., 2018; Gonzales et al., 2010; Oquendo and Volkow, 2018; Schuckit, 2016; Turner et al., 2018), warranting novel therapeutic interventions to lessen the personal and societal burdens of these addictions. Although a substantial literature highlights aberrant brain circuitry and processes in the presence versus absence of substance use disorders (Goldstein et al., 2009; Goldstein and Volkow, 2011; Koob and Volkow, 2016; Volkow et al., 2016) much less is known about how the brain changes as a function of various therapeutic interventions or prolonged abstinence from drugs. According to the Oxford English Dictionary, recovery is defined as "a return to a normal state of health, mind or strength" or "the action or process of regaining possession or control of something stolen or lost." Within the context of addiction, cognitive control over drug craving and urges is lost, along with responsivity to non-drug rewards, resulting in a chronic cycle of habitual drug consumption despite negative consequences. Recovery can be thought of as breaking this cycle. This review provides a detailed overview and critique of published studies employing neuroimaging methods to: (1) directly manipulate brain mechanisms implicated in addiction maintenance/relapse; (2) track addiction treatment outcome; and/or (3) predict individual differences in abstinence versus relapse. This review is focused solely on studies of opioid and stimulant (cocaine and amphetamine) use disorders, given the drastic escalation of mortality due to these drug classes in the United States over the past forty years (Ellis et al., 2018; Jalal et al., 2018).

Table 1 lists key search terms and article selection processes used in compiling data for this review. We intentionally focused on individuals with a clinical diagnosis of stimulant and/or opioid 'dependence' or 'use disorder' as opposed to a diagnosis of 'abuse', which requires

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Table 1
Search terms and article selection for this review.

Key Words	
Drugs	methamphetamine, amphetamine, cocaine, heroin, oxycodone, opioid, prescription opioid, stimulant, dependence, use disorder
Brain	electroencephalography, EEG, event related potentials, ERP, magnetic resonance imaging, MRI, brain stimulation, repetitive, magnetic, transcranial, deep, direct current, TMS, DBS, tDCS, diffusion tensor imaging, DTI
Recovery	abstinence, relapse, recovery, treatment, methadone maintenance, therapy, outcome, naltrexone, buprenorphine, pharmacotherapy, longitudinal, follow-up
Modality	Human
Journal Articles	
# Evaluated	151
# Included	EEG/ERP = 19; MRI = 44; DTI = 8; neuromodulation = 29
Reasons for Exclusion	arterial spin labeling ($n = 2$); review papers ($n = 12$); vaccine ($n = 1$); antisocial personality disorder ($n = 1$); brief post-surgical opioid use ($n = 1$); one dose of medication ($n = 4$); no brain imaging ($n = 6$); chronic pain patients without opioid use disorder ($n = 1$); no recovery outcome ($n = 6$); electrical nerve stimulation ($n = 1$); side effects ($n = 2$); polysubstance use not focusing on stimulants or opioids ($n = 2$); positron emission tomography ($n = 2$); no active user group directly compared to MMT group ($n = 8$)

Note. TMS = transcranial magnetic stimulation. DBS = deep brain stimulation. tDCS = transcranial direct current stimulation.

endorsement of only one symptom and can be considered less severe; as the key word 'addiction' can be construed as a broader term encompassing 'abuse', 'dependence' and 'use disorder' we did not include 'addiction' as a search term. In addition, we included cross-sectional neuroimaging studies in our review only when they compared two or more user groups with differing treatment or abstinence characteristics (e.g., active illicit opioid users versus individuals on six months of stable methadone maintenance treatment), as they facilitate conclusions that can be drawn with respect to recovery as opposed to third variables (e.g., presence or absence of substance use history). Our primary goal is to identify whether brain functioning can improve during the process of recovery, increasing responsivity to natural rewards over drug cues and optimizing goal-directed decision-making. Our secondary goal is to evaluate whether consistent patterns emerge as a function of drug or treatment type. Our third goal is to determine whether modulation of various brain regions is associated with reduced drug craving/urges and increased abstinence. Lastly, we provide future research recommendations that we hope will improve brain resilience and restoration for individuals who are struggling with these use disorders.

In the sections below, we first explain each of several neuroimaging tools, including electroencephalography (EEG), event related potentials (ERPs), structural and functional magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS). We then review cross-sectional and longitudinal intervention and abstinence literature relevant to opioid and stimulant recovery organized as a function of neuroimaging modality and/or technique employed in each study. The most common interventions that researchers have investigated are cognitive behavioral therapy (CBT), methadone maintenance therapy (MMT), residential treatment, and brain stimulation, although neuroimaging researchers are beginning to evaluate links between brain circuitry and naltrexone treatment as well as EEG neurofeedback. Two interrelated brain circuits repeatedly appear in this review, demonstrating changes

as a function of recovery: (1) frontocingulate regions including anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), inferior frontal gyrus (IFG), dorsolateral prefrontal cortex (DLPFC), and ventromedial prefrontal cortex (VMPFC, or more generally, medial prefrontal cortex, MPFC) that are involved in aspects of self-relevance, cognitive control, working memory, decision-making, and attention; and (2) components of the basal ganglia such as the striatum (caudate, putamen, nucleus accumbens) along with the globus pallidus, ventral pallidum, substantia nigra, and subthalamic nucleus, regions involved in reward learning and responsivity.

2. Electroencephalography (EEG)

EEG data are comprised of electrical voltages per electrode over time while participants are either resting or engaged in an active task; as EEG waveforms can be analyzed in the frequency and/or time domain, we review findings for each domain separately. Table 2 illustrates significant relationships between frequency and time domain EEG patterns and abstinence/treatment.

2.1. Frequency bands

EEG signal in the time domain is subjected to a Fast Fourier Transform, which separates it into frequency components comprised of sine waves with various amplitudes and phases, typically compiled together in specific ranges or 'bands'. Power within a frequency band, defined as signal amplitude squared, is the most common metric employed in analysis. EEG power is traditionally examined as a function of particular frequency bands measured in Hertz (Hz, or cycles per second), such as delta (1–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), and beta (13–30 Hz); delta, theta and alpha are linked to global brain processing, whereas faster beta signals suggest more specialized, localized processing (Knyazev, 2012). With respect to function: (1) delta is associated with sleep (Knyazev, 2012); (2) theta is related to MPFC working memory sequencing and action monitoring (Cavanagh et al., 2012; Gevins et al., 1997; Ishii et al., 1999; Pizzagalli et al., 2003; Roux and Uhlhaas, 2014); (3) alpha is involved in suppression of task-irrelevant responses (Klimesch, 2012; Roux and Uhlhaas, 2014); and (4) beta involves active concentration and motor preparation localized to somatosensory and motor regions (Jurkiewicz et al., 2006). As individuals with substance use disorders show impairments in sleep, working memory, error monitoring, and goal-directed behavior (Angarita et al., 2016; van der Plas et al., 2009), study of these frequency bands may shed light on the degree to which these functions improve during abstinence and positive treatment response.

2.2. EEG activity and recovery from substance use

With respect to cocaine recovery, four longitudinal resting EEG studies show mixed results. Higher baseline alpha power over the frontal lobe predicts longer residential treatment retention ($\geq$ 21 weeks; Prichep et al., 1999), whereas higher baseline delta and theta power predict successful cocaine abstinence three months later (Levin et al., 2007). However, other research suggests that baseline delta, theta, alpha, and beta power do not significantly predict future successful completion of a nine-week medication trial (Venneman et al., 2006); furthermore, attenuated delta and theta power evident in cocaine users during detoxification does not appear to change as a function of one- or six-month abstinence within the same individuals (Alper et al., 1998). Of the two studies evaluating resting EEG patterns as a function of opioid recovery, one cross-sectional report indicates that individuals on stable MMT show similar EEG frequency profiles as active illicit opioid users, with both groups showing greater alpha, theta, and beta power than healthy controls; moreover, this heightened EEG activity in previous and current users is also linked to poorer attention and executive functioning performance (Wang et al., 2015a). In

Table 2
Electroencephalography Results as a function of Abstinence and/or Treatment for Stimulant and/or Opioid Use Disorders ($n = 20$).

Cocaine	Increases	Decreases	Recording Type	Design	Abstinence/Treatment
Alper et al. (1998)	None	None	Resting EEG (Eyes-Closed)	Longitudinal	Abstinence (5–10 days versus 1 month versus 6 months)
Bauer (1997)	↑ frontal non-target P3a amplitude	None	ERP (Visual Three-Stimulus Oddball)	Longitudinal	Abstinence (6 months)
Levin et al. (2007)	↑ low beta and delta absolute power (temporal region)	None	Resting EEG (Eyes-Closed)	Longitudinal	Abstinence (3 months)
Marhe et al. (2013b)	↑ ERN amplitude	None	ERP (Eriksen Flanker)	Longitudinal	Abstinence (3 months)
Parvaz et al. (2017b)	↑ LPP amplitude to pleasant non-drug images	None	ERP (Passive picture viewing of Drug vs. Pleasant Images)	Longitudinal	Baseline (post-detoxification) compared to follow-up Abstinence (6 months)
Prichep et al. (1999)	↑ anterior alpha power	None	Resting EEG (Eyes-Closed)	Longitudinal	Treatment stay
Venneman et al. (2006)	None	None	Resting EEG (Eyes-Closed)	Longitudinal	Medication treatment completion (8 weeks)
Wan et al. (2010)	↑ parietal target P3b amplitude	None	ERP (Visual Head Rotation)	Longitudinal	Residential treatment completion (6 months)
Methamphetamine	*Increases*	*Decreases*	*Recording Type*	*Design*	*Abstinence/Treatment*
Haifeng et al. (2015)	None	↓ P3b amplitude	ERP (Stroop: Drug > Neutral Words)	Longitudinal	Abstinence (3 months)
Opioids	*Increases*	*Decreases*	*Recording Type*	*Design*	*Abstinence/Treatment*
Fingelkurts et al. (2007)	↑ delta and theta oscillations	↓ alpha and beta oscillations	Resting EEG (Eyes-Closed)	Longitudinal	≥6 months MMT treatment (versus current active use and withdrawal)
Garland et al. (2015, 2018)	↑ LPP amplitude to natural reward images (compared to neutral images)	None	ERP (Picture Viewing)	Longitudinal	Treatment (post- minus pre- 8-week mindfulness versus support)
Lubman et al. (2009)	None	↓ P3 amplitude to startle-induced pleasant images (compared to drug images)	ERP (Picture Viewing during Auditory Startle Probes)	Longitudinal	Abstinence (6 months)
Wang et al. (2015a)	None	None	Resting EEG (Eyes-Closed and Eyes-Open)	Cross-Sectional	MMT (versus active opioid users)
Wang et al. (2015b)	↑ frontal target P3b amplitude	None	ERP (Auditory Two-Stimulus Oddball)	Cross-Sectional	MMT (versus active opioid users and controls)
Yang et al. (2015)	↑ N2 nogo versus go differentiation	None	ERP (Visual Go/NoGo)	Cross-Sectional	MMT (versus active opioid users)
Stimulants and Opioids	*Increases*	*Decreases*	*Recording Type*	*Design*	*Abstinence/Treatment*
Anderson et al. (2011)	↑ midline non-target P3a amplitude	None	ERP (Auditory Three-Stimulus Oddball)	Longitudinal	Treatment completion (3 months)
Fink et al. (2016)	↑ non-target P3a amplitude	↓ (smaller) non-target N2 amplitude	ERP (Visual Three-Stimulus Oddball)	Longitudinal	Treatment completion (3 months)
Kouri et al. (1996)	↑ target P3b amplitude	None	ERP (Auditory Two-Stimulus Oddball)	Longitudinal	Treatment (buprenorphine versus placebo)
Steele et al. (2014)	↑ nogo P2 amplitude; ↑ ERN amplitude	↓ Pe amplitude	ERP (Go/NoGo)	Longitudinal	Treatment completion (CBT)

Note. ERN = error related negativity. LPP = late positive potential. ERP = event related potential. EEG = electroencephalography. MMT = methadone maintenance therapy. CBT = cognitive behavioral therapy. ERN = error related negativity. Pe = error positivity.

3

contrast, the second study, which utilized a within-subjects design, suggests that delta and theta oscillations increase as a function of the transition from current opioid use to withdrawal to six months of MMT, while alpha and beta oscillations decrease (Fingelkurts et al., 2007). Findings from these six studies are inconsistent and do not point toward a clear biomarker of recovery. It is important to emphasize that residential and drug treatment retention may depend on other economic (e.g., health insurance coverage) or biological (e.g., side effects) factors specific to an individual. Thus, leaving treatment earlier than others does not necessarily mean that an individual has relapsed, which complicates interpretation of treatment retention findings. In addition, the two studies best able to control for individual differences by collecting three EEG timepoints within the same participants during their recovery process (Alper et al., 1998; Fingelkurts et al., 2007) do not show consistent results for changes in delta and theta patterns; these two studies are also limited by relatively small sample sizes and warrant replication.

2.3. Event related potentials (ERPs)

EEG data are analyzed in the time domain by time-locking electrical signals to a stimulus or response and then averaging over multiple trials to produce event-related potentials (ERPs), amplifying signals to a repeated event while cancelling out random noise. ERP differences in amplitude and latency are often compared between stimulus conditions and/or groups. ERP amplitude is traditionally defined as the difference between a pre-stimulus baseline and the largest waveform peak within a window of time, whereas ERP latency reflects the time from stimulus onset to peak amplitude (Fabiani et al., 2000; Polich, 2007). Overall, EEG possesses significantly greater temporal resolution (on the order of milliseconds) than spatial resolution, enabling researchers to document the timing of a cognitive, emotional, and/or motor process.

2.4. ERP components and individual differences in treatment outcome or abstinence

Many ERP researchers use oddball tasks to evaluate the timing (latency) and/or amount of neural resources (amplitude) allocated to stimulus evaluation in substance users. The oddball task elicits P2, N2, and P3 ERPs, and involves pressing a button to an infrequent target while ignoring a frequent standard (and sometimes an infrequent novel non-target as an added distraction). Oddball tasks can be presented with auditory stimuli, visual stimuli, or both. Visual oddball task designs may also incorporate aspects of a go/no-go task, where participants are explicitly instructed to press a button when they see one type of stimulus, but withhold a button press when they see another type of stimulus.

Whereas frontocentral P2 (150–200 ms) is linked to selective attention (Dunn et al., 1998; Paulmann and Pell, 2009), frontocentral N2 (200–300 ms) is thought to detect stimulus deviance within oddball paradigms or conflict within go/no-go tasks (Downes et al., 2017; Enriquez-Geppert et al., 2010; Fabiani et al., 2000; Falkenstein et al., 1999; Hugdahl, 1995). The ability to discern between various types of stimuli associated with divergent outcomes or task demands may benefit users in recovery who are trying to figure out what stimuli in their environments lead to positive as opposed to negative real-life consequences away from substance use. P2 findings are scant with respect to recovery; although auditory P2 target amplitude does not differentiate active opioid users from those on MMT (Wang et al., 2015b), greater baseline visual P2 target amplitude does appear to predict future successful CBT completion for opioid/stimulant users, even above and beyond years of drug use (Steele et al., 2014). N2 findings linked to recovery are also minimal. For instance, one cross-sectional report indicates that individuals on stable MMT show more adaptive N2 amplitude differentiation between visual go and no-go stimuli than active opioid users (Yang et al., 2015); a longitudinal study demonstrates that

smaller visual oddball non-target N2 amplitudes at baseline predict future successful treatment completion in stimulant/opioid users (Fink et al., 2016). It is possible that heightened attention to goal-relevant stimuli paired with reduced attention to distractors may predict successful treatment, but again these findings require replication.

While P2 and N2 reflect earlier voluntary attention, P3 follows these components during oddball, go/no-go, and other tasks and is thought to reflect memory updating of task-relevant stimulus characteristics (Fabiani et al., 2000; Hugdahl, 1995; Polich, 2007). P3 is divided into two subdivisions, P3a and P3b; centroparietal P3b amplitude is largest to auditory and visual targets, whereas frontocentral P3a amplitude is largest to auditory and visual non-targets (distractors) that require either no response or inhibition of a prepotent response (Comerchero and Polich, 1999; Downes et al., 2017). First, five studies investigating P3b amplitude as a function of recovery show results consistent with improved neural resources devoted to non-drug goal-directed stimuli. More specifically, with respect to research employing oddball tasks, higher visual target P3b amplitude at baseline predicts six-month residential cocaine treatment completion (Wan et al., 2010), and individuals on stable MMT exhibit higher auditory target P3b amplitude than both active illicit opioid users and healthy controls (Wang et al., 2015b). Furthermore, opioid and stimulant users exhibit larger auditory P3b amplitude after buprenorphine treatment as opposed to placebo (Kouri et al., 1996).

In another study, a modified color-word Stroop task was used to elicit ERPs in response to methamphetamine-relevant and neutral words (Haifeng et al., 2015). In the standard Stroop paradigm, participants view words printed in one of four colors (red, yellow, blue, and green) and are asked to press a button corresponding to the color of the word. However, they are presented with two conditions of stimuli: (1) congruent, wherein the color of the word (red) matches the content of the word ('red'); and (2) incongruent, wherein the color of the word (red) is inconsistent with the content of the word ('blue'). As participants experience more conflict in the incongruent condition than the congruent condition, reaction times tend to be longer for incongruent than congruent stimuli; to obtain a measure of this increased conflict, the Stroop effect is typically measured by subtracting reaction times (and ERP amplitudes) of the congruent from the incongruent condition. In a modified Stroop task, drug-related (e.g., 'pipe') and neutral (e.g., 'chair') words are presented in the four colors, in place of actual color words; in this scenario there is no direct conflict between the color and meaning of each word, but it is argued that longer reaction times (or P3b amplitudes) to drug than neutral words reflect an attentional bias toward drug-related cues. Consistent with this attentional bias theory, this study demonstrates that lower baseline P3b amplitude to methamphetamine-related words (when compared to neutral words) predicts successful three-month abstinence (Haifeng et al., 2015). Another study asked opioid users to view pleasant and drug-relevant images while they experienced auditory startle probes during some but not all of the trials (Lubman et al., 2009); the greater the startle-induced attenuation of P3b amplitude for a particular condition is thought to reflect greater attentional bias toward those particular stimuli. Lower P3b amplitude to startle-induced pleasant images (compared to drug images) at baseline predicted future six-month abstinence from opioids (Lubman et al., 2009). These findings point to better recovery outcomes for individuals who allocate more neural resources to updating non-drug, goal-relevant stimuli in working memory.

With respect to P3a amplitude, three oddball studies (two visual, one auditory) suggest that larger baseline amplitudes to non-target distractors predict future six-month cocaine abstinence (Bauer, 1997), three-month stimulant/opioid treatment completion requiring drug-abstinent urines (Anderson et al., 2011), and completion of manualized treatments (addictions counseling, relapse prevention, and substance expectation therapy) in stimulant and opioid users (Fink et al., 2016). Does P3 fare better as a marker of recovery than P2 and N2? Results indicate that yes, larger P3a and P3b responses to non-drug stimuli can

predict future abstinence and treatment success; individuals who, at the outset, allocate greater brain resources devoted to stimulus deviance, memory updating, and novelty show more success during recovery.

Three additional ERPs relevant to addiction recovery are: (1) the late positive potential (LPP), associated with the motivational salience of a stimulus (Brown et al., 2012); (2) the error related negativity (ERN), related to monitoring for errors/conflict (Holroyd and Coles, 2002); and (3) the error positivity (Pe), associated with the strength of a conscious belief that an error has been committed (Boldt and Yeung, 2015; Orr and Carrasco, 2011; Steinhauser and Yeung, 2010). The LPP onsets after the P3 (400–1000 ms post-stimulus) to visual stimuli; as LPP amplitude increases to images that are motivationally relevant for a particular person, examining LPP amplitudes can help determine whether individuals show heightened salience of drug-related cues when compared to other types of emotional stimuli at various points in the recovery process. A novel study testing LPP amplitude at two timepoints shows that: (1) after detoxification, treatment-seeking cocaine users display higher LPP amplitudes to drug than pleasant images, but (2) the difference in LPP amplitude between drug and pleasant cues diminishes six months later, driven by an increase in responses to pleasant cues, not a change in responses to drug cues (Parvaz et al., 2017b). Moreover, two crucial individual differences in LPP amplitude emerge, such that: (1) users who report greater drug craving and lower cocaine abstinence at follow-up still show LPP amplitudes biased toward drug cues at follow-up; and (2) users with baseline higher LPP amplitudes to pleasant images report lower baseline cocaine liking/wanting (Parvaz et al., 2017b). Similarly, a treatment study in pain patients with opioid use disorder indicates that a mindfulness intervention provides greater enhancement of LPP amplitudes to naturally rewarding (as opposed to neutral) images than a support group, a pattern linked to decreased pain severity and increased pain coping (Garland et al., 2015; Garland, 2018).

While LPP reflects elaborative stimulus processing, the fronto-cingulate ERN is elicited about 150 ms after a person makes an error and is thought to reflect monitoring for conflict/mistakes (Holroyd and Coles, 2002). The Eriksen Flanker task is often employed to elicit ERN responses; similar to the Stroop task, participants encounter congruent and incongruent conditions, but instead of words, they are asked to press a button to indicate the direction of a central arrow stimulus amidst similarly directed arrows (congruent) or arrows pointed in the opposite direction (incongruent). As stimuli are presented for only a brief duration, individuals tend to make mistakes, particularly during incongruent trials that possess higher conflict than congruent trials. One study utilizing this paradigm demonstrates that cocaine users with larger baseline ERN amplitudes during error trials report less cocaine use at three-month follow-up than users with smaller ERN amplitudes (Marhe et al., 2013b). The go/no-go task mentioned earlier can also elicit ERN responses to errors; consistent with Flanker results, another study indicates that higher ERN amplitude at baseline predicts future CBT completion in a sample of stimulant and opioid users (Steele et al., 2014). This study also measures the Pe response, a positive ERP deflection elicited 100–200 ms after a person commits an error (Orr and Carrasco, 2011); research suggests that higher Pe amplitude tracks the degree of conscious certainty that an error has been made (e.g., Boldt and Yeung, 2015; Steinhauser and Yeung, 2010). Steele et al. (2014) report that lower baseline Pe amplitude significantly predicts future CBT treatment completion above and beyond other ERP and self-report measures; these findings suggest that individuals who allocate fewer neural resources to error awareness may benefit from cognitive-behavioral techniques that explicitly connect and test links between beliefs, actions, and feeling states to outcomes.

Taking LPP, ERN, and Pe results together, there is evidence that ERP components can track individual differences, i.e. the LPP and the ERN relate to abstinence/treatment outcome and the Pe is associated with treatment outcome. The LPP successfully indexes individual differences in reward salience that predict treatment success, and it can also track

group-level reward-related changes linked to treatment. Conversely, individuals with attenuated ERN amplitude likely show problems learning from mistakes that forecast continued drug use despite negative consequences and replication of ERN/Pe amplitude findings are warranted to confirm utility of these ERPs in tracking recovery.

2.5. Conclusions for EEG/ERP findings

In summary, out of the 20 studies presented in Table 2, six measured electrical activity at least twice within the same individuals to effectively track mean-level changes as a function of successful treatment/abstinence (Alper et al., 1998; Fingelkurts et al., 2007; Garland et al., 2015, 2018; Kouri et al., 1996; Parvaz et al., 2017b). In addition to comparing mean ERP differences across two timepoints, Parvaz et al. (2017b) also related individual differences in cocaine liking/wanting to ERP amplitude at each of the two timepoints, highlighting the importance of person-level variables in recovery prediction. Another 11 out of the remaining 14 studies used individual differences in baseline EEG/ERP metrics to predict future treatment outcomes (Anderson et al., 2011; Bauer, 1997; Fink et al., 2016; Haifeng et al., 2015; Levin et al., 2007; Lubman et al., 2009; Marhe et al., 2013b; Prichep et al., 1999; Steele et al., 2014; Venneman et al., 2006; Wan et al., 2010), while the final three studies examined cross-sectional mean-level differences between MMT and current illicit opioid use groups (Wang et al., 2015a, 2015b; Yang et al., 2015). Overall, published ERP results suggest that more successful recovery is associated with heightened attentional resources devoted to the processing of: (1) goal-relevant and salient non-drug stimuli (P3b and LPP amplitudes); (2) distractors (P3a amplitude); and (3) mistakes (ERN amplitude). No discernable differences are present as a function of drug of choice or treatment method.

3. Structural magnetic resonance imaging (sMRI)

MRI uses magnetic field gradients and radio frequency signals to manipulate hydrogen atoms within water molecules, resulting in sMRI images contrasting tissue types with high spatial resolution (typically on the order of 1 mm³). Table 3 illustrates significant relationships between MRI signals and stimulant and/or opioid abstinence/treatment. Gray matter contains most neuronal cell bodies as well as dendrites, unmyelinated axons, and synapses that facilitate information processing, whereas white matter consists of long-range myelinated axon fibers that coordinate signals between these regions. With respect to sMRI analysis, voxel-based morphometry segments and quantifies gray matter volume across the cortex, distinguishing it from white matter and cerebrospinal fluid (Whitwell, 2009). Structural impairments in specific brain regions at the outset of rehabilitation efforts may limit the degree of functional changes we can expect in the long-term.

3.1. What does sMRI research tell us about recovery?

A total of seven studies in Table 3 evaluate relationships between gray matter volume and recovery, two employing cross-sectional designs (Connolly et al., 2013; He et al., 2018) and five employing longitudinal designs (Brooks et al., 2016; Fahmy et al., 2018; Parvaz et al., 2017a; Ruan et al., 2018; Xu et al., 2014). Cross-sectional findings suggest that individuals with approximately 30–35 weeks of abstinence show higher gray matter volume than early-abstinent users, as well as healthy controls, in insular, cingulate, superior frontal, middle temporal and cerebellar regions (Connolly et al., 2013), suggesting that brain recovery processes may go above and beyond "normal" levels, perhaps to compensate for prior deficits developed during past cocaine use; however, additional longitudinal studies tracking gray matter changes within-subjects during recovery are warranted to test this hypothesis. A second cross-sectional study also demonstrates that cocaine users abstinent for 12 months (approximately 48 weeks) or longer exhibit larger frontal gray matter volume than active cocaine users (He

Table 3
Neuroimaging Results as a function of Abstinence and/or Treatment for Stimulant and/or Opioid Use Disorders ($n = 44$).

Cocaine	Increases	Decreases	MRI Scan Type	Design	Abstinence/Treatment
Balodis et al. (2016)	↑ thalamus, precuneus, striatum, midbrain, substantia nigra, posterior cingulate	None	Functional (MID: Anticipation Win)	Longitudinal	Post- minus pre-treatment
		↓ ventral striatum	Functional (MID: Anticipation Loss)	Longitudinal	Higher abstinence (negative urine screens)
	↑ IFG and superior temporal gyrus	None	Functional (MID: Anticipation Win and Loss)	Longitudinal	Post- minus pre-treatment
Berlingeri et al. (2017)	↑ ventral striatum and DLPFC connectivity	None	Functional (Resting-State)	Longitudinal	Abstinence (8 months)
Brewer et al. (2008)	↑ VMPFC, posterior cingulate, dorsal striatum*; ↑ DLPFC**	None	Functional (Stroop: Incongruent > Congruent contrast)	Longitudinal	*Abstinence during various treatments (8 weeks); **Treatment retention
Connolly et al. (2013)	↑ insula, cingulate gyrus, superior frontal gyrus, cuneus, culmen, and middle temporal gyrus	↓ cuneus and precuneus	Structural (Gray Matter Volume)	Cross-Sectional	Abstinence (0.7–102 weeks)
DeVito et al. (2012)	None	↓ thalamus, basal ganglia, IFG, ACC, middle/superior frontal gyrus, middle/superior temporal gyrus, cuneus	Functional (Stroop: Incongruent > Congruent contrast)	Longitudinal	Post- minus pre-treatment (8-week TAU +/- Computer CBT)
DeVito et al. (2017)	None	↓ precentral/postcentral gyrus, inferior parietal lobule, middle/medial frontal gyrus	Functional (Stroop: Incongruent > Congruent contrast)	Longitudinal	Post- minus pre-treatment changes correlating with better CBT attendance and greater earned CM prizes
DeVito et al. (2019)	None	↓ medial frontal gyrus, cingulate gyrus, thalamus, midbrain, culmen	Functional (Stroop: Incongruent > Congruent contrast)	Longitudinal	Abstinence during treatment (MMT with 8-week TAU +/- Computer CBT)
Geng et al. (2017)	↑ VMPFC and temporal pole connectivity	None	Functional (Resting-State)	Longitudinal	Abstinence (6 months)
Goudriaan et al. (2013)	↑ ACC and dorsal striatum	↓ VTA	Functional (Passive Picture Viewing: Drug > Neutral Cues contrast)	Longitudinal	Treatment (modafinil versus placebo)
He et al. (2018)	↑ frontal pole and DLPFC	↓ striatum and insula	Structural (Gray Matter Volume)	Cross-Sectional	Abstinence (>1 year sober versus active users)
	None	↓ DLPFC, thalamus, basal ganglia, insula, frontal pole	Functional (Passive Picture Viewing: Drug > Neutral Cues contrast)	Cross-Sectional	Abstinence (>1 year sober versus active users)
Jia et al. (2011)		↓ dorsal striatum and thalamus*; ↓ amygdala and parahippocampal gyrus**	Functional (MID Reward Anticipation: Gain > Non-Gain contrast)	Longitudinal	*Abstinence (8 weeks); **Treatment retention
		↓ ventral striatum, thalamus, culmen	Functional (MID Reward Outcome: Gain > Non-Gain contrast)	Longitudinal	Abstinence
Kosten et al. (2006)	None	↓ precentral gyrus, posterior cingulate	Functional (Passive Picture Viewing: Drug Cue > Baseline contrast)	Longitudinal	Abstainers/Treatment Completers (versus Relapsers)
Luo et al. (2013)	Women: ↑ thalamus and dorsal ACC; Men: ↑ insula and dorsal ACC	None	Functional (Stop Signal: Stop Error > Stop Success contrast)	Longitudinal	Abstinence (3 months)
Marhe et al. (2013a)	None	↓ dorsal ACC	Functional (Stroop: Cocaine word > Neutral word contrast)	Longitudinal	Abstinence (3 months)
Moeller et al. (2010)	↑ thalamus	None	Functional (Working Memory: Delayed > Immediate contrast)	Longitudinal	Treatment success
Moeller et al. (2012)	↑ VTA, substantia nigra, thalamus, precuneus	↓ medial frontal gyrus, pre-SMA, inferior parietal lobule, inferior occipital gyrus, lingual gyrus	Functional (Stroop: Cocaine word > Neutral word contrast)	Longitudinal	Abstinence (6 months) minus Baseline
Moeller et al. (2018)	None	↓ VTA	Functional (Choice: Cocaine > Food contrast)	Cross-Sectional	Abstainers (>1 month) versus current users
Parvaz et al. (2017a)	↑ IFG and VMPFC	None	Structural (Gray Matter Volume)	Longitudinal	Abstinence (6 months)

Table 3 (*continued*)

Cocaine	Increases	Decreases	MRI Scan Type	Design	Abstinence/Treatment
Patel et al. (2013)	None ↑ VTA	↓ frontal pole None	Functional (MID Anticipation: Loss > No Loss contrast) Functional (MID Outcome: Loss > No Loss contrast)	Cross-Sectional Cross-Sectional	Abstainers (~46 months) versus current users Abstainers (~46 months) versus current users
Stewart et al. (2014a)	↑ IFG and striatum during decision-making; ↑ DLPFC and anterior insula to reward learning	None	Functional (Reward Learning: Decision > Outcome contrast)	Longitudinal	Abstinence (1 year)
Worhunsky et al. (2013)	↑ IFG, VMPFC, thalamus, striatum, amygdala, and hippocampus connectivity	None	Functional (Stroop: Incongruent > Congruent contrast)	Longitudinal	Abstinence during treatment (8- or 12-week CBT alone, with CM, or with disulfiram/placebo versus TAU)
		↓ frontocingulate connectivity	Functional (Stroop: Incongruent > Congruent contrast)	Longitudinal	Treatment retention (8- or 12- week CBT alone, with CM, or with disulfiram/placebo compared to TAU)
Xu et al. (2014)	None	↓ hippocampus	Structural (Gray Matter Volume)	Longitudinal	Treatment success (Behavior therapy +/- CM) and Abstinence
Yip et al. (2016)	None	↓ IFG, posterior insula, angular gyrus, and middle/superior temporal gyrus	Functional (Monetary Incentive Delay: Loss Anticipation > Baseline)	Cross-Sectional	MMT (versus non-MMT)
	None	↓ dorsal striatum	Functional (Monetary Incentive Delay: Win Anticipation > Baseline)	Longitudinal	Abstinence within MMT during treatment (8-week CBT or TAU)
Methamphetamine	***Increases***	***Decreases***	***Scan Type***	***Design***	***Abstinence/Treatment***
Brooks et al. (2016)	TAU and CT: ↑ dorsal striatum CT: ↑ amygdala and hippocampus	TAU and CT: ↓ cerebellum	Structural (Gray Matter Volume)	Longitudinal	Post- versus pre-treatment (TAU +/- computer CT)
Harlé et al. (2019)	↑ IFG, anterior insula, temporoparietal junction	None	Functional (Stop Signal: Bayesian Prediction Error contrast)	Longitudinal	Abstainers (1 year) versus Relapsers
Gowin et al. (2014/2015)	↑ insula and striatum	None	Functional (Risky Gains: Risky Reward > Safe Reward)	Longitudinal	Abstinence (1 year)
Kohno et al. (2018)	None	↓ ventral striatum, hippocampus, midbrain and amygdala connectivity	Functional (Resting-State)	Longitudinal	Treatment (naltrexone versus placebo)
Paulus et al. (2005)	↑ insula, dorsal striatum, inferior parietal lobule, and middle temporal gyrus	None	Functional (Two-Choice Prediction: Prediction > Response contrast)	Longitudinal	Abstinence (~1 year)
Ruan et al. (2018)	↑ cerebellum	↓ cingulate gyrus	Structural (Gray Matter Volume)	Longitudinal	Abstinence (6 months vs. 1 year)
Stewart et al. (2014b)	↑ IFG, insula, striatum and ACC	None	Functional (Reward Learning: Outcome > Decision contrast)	Longitudinal	Abstinence (1 year)
	None	↓ IFG and dorsal striatum	Functional (Reward Learning: Decision > Outcome contrast)	Longitudinal	Abstinence (1 year)
Opioids	***Increases***	***Decreases***	***Scan Type***	***Design***	***Abstinence/Treatment***
Chang et al. (2016)	↑ precuneus/lingual gyrus, parahippocampal gyrus, middle temporal gyrus	↓ medial OFC, dorsal striatum, and cerebellum	Functional (Resting-State)	Longitudinal	MMT plus Abstinence (1 year)
Fahmy et al. (2018)	↑ striatum-insula and frontal-cingulate connectivity	None	Structural (Gray Matter Volume)	Longitudinal	Treatment (4 weeks of mindfulness versus TAU)
Gradin et al. (2014)	↑ midbrain and parahippocampal gyrus	None	Functional (Reward Learning: Loss > Loss Avoidance)	Cross-Sectional	MMT post-methadone ingestion (versus pre-)
Langleben et al. (2008)	None	↓ insula, amygdala, and hippocampus	Functional (Drug Cues)	Longitudinal	MMT post-methadone ingestion (versus pre-)
Q. Li et al. (2013)	None	↓ ACC, medial prefrontal cortex, dorsal striatum, inferior parietal lobule, precuneus, middle occipital gyrus	Functional (Picture Viewing: Drug Cue > Neutral Cue contrast)	Cross-Sectional	Long-Term Abstainers (150–300 days) compared to Short-Term Abstainers (7–72 days)
Q. Li et al. (2015)	None	↓ nACC, subcallosal cortex, and cerebellum	Functional (Picture Viewing: Drug Cue > Neutral Cue contrast)	Longitudinal	MMT abstainers (versus relapsers)

Table 3 (continued)

Cocaine	Increases	Decreases	MRI Scan Type	Design	Abstinence/Treatment
W. Li et al. (2015)	↑ superior occipital gyrus and inferior temporal gyrus connectivity	↓ precuneus and cingulate gyrus connectivity	Functional (Resting-State)	Cross-Sectional	MMT abstainers (versus relapsers)
Li et al. (2018)	↑ DLPFC and VMPFC connectivity	↓ dorsal ACC and VMPFC connectivity	Functional (Resting-State)	Longitudinal	Abstinence after onset of stable MMT (3 months)
Lou et al. (2012)	↑ occipital and temporal	↓ parietal, frontal, cerebellum, posterior cingulate, insula, thalamus, and dorsal striatum	Functional #(Picture Viewing: Drug > Neutral contrast)	Cross-Sectional	Abstinence (1 year)
Shi et al. (2018)	None	↓ ventral striatum and medial OFC	Functional #(Picture Viewing: Drug > Control contrast)	Longitudinal	Treatment (post- versus pre-naltrexone)
Wang et al. (2014)	None	↓ dorsal striatum	Functional (Picture Viewing: Drug > Neutral contrast)	Cross-Sectional	MMT (at least 2 years versus under 1 year)
Wang et al. (2018)	None	↓ thalamus and ventral striatum	Functional (Baby Schema: High > Low Cuteness contrast)	Longitudinal	Treatment (post- versus pre-naltrexone)
Stimulants	*Increases*	*Decreases*	*Scan Type*	*Design*	*Abstinence/Treatment*
Clark et al. (2014)	↑ ventral ACC, posterior cingulate, and insula to novel non-targets	None	Functional (Visual Three-Stimulus Oddball)	Longitudinal	Abstinence (6 months)
Stimulants and Opioids	*Increases*	*Decreases*	*Scan Type*	*Design*	*Abstinence/Treatment*
Steele et al. (2018)	↑ rostral ACC, amygdala, hippocampus, striatum, DLPFC, thalamus, inferior temporal, posterior insula, hypothalamus, and parahippocampal connectivity	↓ caudal ACC, superior temporal, culmen, insula, and precuneus connectivity	Functional (Go/NoGo)	Longitudinal	Treatment retention

Note. DLPFC = dorsolateral prefrontal cortex. ACC = anterior cingulate cortex. VMPFC = ventromedial prefrontal cortex. IFG = inferior frontal gyrus. OFC = orbitofrontal cortex. VTA = ventral tegmental area. CBT = cognitive behavioral therapy. CT = cognitive training. MMT = methadone maintenance therapy. CM = contingency management. TAU = treatment-as-usual. MID = monetary incentive delay task.

et al., 2018); in contrast to findings from Connolly et al. (2013), however, He and colleagues (2018) demonstrate that cocaine abstainers actually show lower insula, as well as striatum, gray matter volume than active users. At this point it is unclear which individual difference metrics, such as drug craving/urges or other personality/drug use variables, might explain these attenuations. Longitudinal studies may provide clarity on the direction of brain changes due to treatment and/ or abstinence. A study collecting sMRI twice within the same individuals indicates that six-month cocaine abstinence is associated with frontal volume increases when compared to baseline (Parvaz et al., 2017a) findings consistent with He et al. (2018). With respect to other brain regions, lower hippocampus volume at baseline predicts greater cocaine abstinence and behavior therapy success with or without added contingency management (Xu et al., 2014); in addition, methamphetamine users show hippocampus and amygdala volume increases post- as opposed to pre-computer therapy (Brooks et al., 2016). As Xu et al. (2014) only measure sMRI volume at baseline and not again at the end of therapy, it is unclear whether behavioral therapy treatment success would have also shown hippocampal volume increases like those reported by Brooks et al. (2016).

Methamphetamine users also show dorsal striatum increases and cerebellar decreases post- as opposed to pre-treatment as usual with added computer therapy (Brooks et al., 2016), but it is unclear whether heightened striatal volume is specifically related to greater response to natural as opposed to drug-related rewards. In contrast, sMRI scans within the same cohort of opioid users suggest that 12-month abstinence is associated with increases in cerebellar volume paired with decreases in cingulate gyrus volume when compared to 6-month abstinence (Ruan et al., 2018); as the recovery timeframe from 6–12 months abstinence in Ruan et al. (2018) does not overlap with the shorter treatment timeframe in the work of Brooks et al. (2016), it may be the case that directionality of cerebellar changes may not actually be at odds with each other. Finally, within a sample of opioid-dependent individuals, those assigned to four weeks of mindfulness treatment show increased connectivity within striatum-insula and frontal-cingulate regions than those assigned to four weeks of treatment as usual; within users completing mindfulness treatment, frontal-cingulate connectivity increases are related to individual reductions in negative urgency, a type of impulsivity associated with urges to use drugs (Fahmy et al., 2018).

3.2. Conclusions for sMRI findings

Taken together, sMRI research does not provide a clear picture of recovery, as directionality of findings and brain regions implicated do not replicate across studies. As treatment completion is not synonymous with abstinence, it is reasonable to expect that brain changes as a function of one may not be identical as a function of the other. Only two out of the seven studies focused on within-subject individual differences in abstinence/treatment response, whereas the other five centered on mean group or time differences, limiting conclusions that can be drawn as a function of person-based characteristics associated with recovery.

4. Functional magnetic resonance imaging (fMRI)

In contrast to sMRI scans, fMRI scans measure cerebral blood flow changes (e.g., blood oxygenation level dependent, or BOLD contrast) as a proxy of neural activity, revealing brain regions more active in one condition than another. In addition to quantifying BOLD signal during various tasks, characterization of spontaneous (or intrinsic) brain signals during a resting state is important, as these measurements are thought to reflect energy required for the individual to maintain default functioning (Raichle, 2009; Snyder and Raichle, 2012). fMRI offers good spatial resolution (on the order of a few mm³) but possesses lower temporal resolution (on the order of seconds) than EEG/ERP. Most research outlined below and in Table 3 focuses on baseline fMRI scans

predicting future clinical outcomes, with some studies investigating functional connectivity (temporal correlations in BOLD signal) between brain regions. Task-based fMRI studies employ drug cue reactivity, reward sensitivity, attention, working memory, and cognitive control paradigms to forecast and/or track recovery.

4.1. fMRI research on brain responsivity to drug rewards as a function abstinence

There is a surprisingly consistent pattern of findings showing that in eight out of eight studies, abstinence is linked to attenuated brain activation in response to drugs; four studies employ cross-sectional designs (He et al., 2018; Q. Li et al., 2013; Lou et al., 2012; Moeller et al., 2018) to show this effect, while four utilize longitudinal designs (Kosten et al., 2006; Q. Li et al., 2015; Marhe et al., 2013a; Moeller et al., 2012). Cross-sectional work shows that brain regions involved in reward processing, including areas within the basal ganglia and midbrain, respond less to drug than neutral cues as a function of abstinence duration. For example, individuals abstinent from stimulants for 12 + months exhibit lower striatal, thalamus, frontal, and insular BOLD signal to drug images (compared to neutral images) than active stimulant users (He et al., 2018). Similarly, individuals abstinent from opioids for at least a year exhibit fewer opioid withdrawal symptoms and lower dorsal striatum, insula, posterior cingulate, and thalamus BOLD signal to drug images than individuals with only one month of sobriety (Lou et al., 2012). Another study partly replicates this research, demonstrating that long-term abstainers (for 150–300 days) show lower MPFC and dorsal striatum BOLD signal, among other regions, to drug images compared to neutral images than short-term abstainers (for 7–72 days; Q. Li et al., 2013). Finally, in a novel study comparing brain responses to drug as opposed to food images, cocaine abstainers (>1 month) show lower ventral tegmental area BOLD signal than active cocaine users (Moeller et al., 2018). As meta-analyses demonstrate that alcohol/drug cue reactivity is linked to heightened BOLD signal in insula, MPFC/IFG, and/or striatal regions (e.g., Engelmann et al., 2012; Noori et al., 2016; Schacht et al., 2013), attenuated signal in these areas as a function of recovery suggests that the brain is becoming less responsive to drug rewards as opposed to other types of stimuli.

Longitudinal studies also indicate that individuals with longer cocaine abstinence show lower baseline BOLD signal responses to drug than neutral images in precentral gyrus and posterior cingulate (Kosten et al., 2006) as well as ACC (Marhe et al., 2013a). Meta-analytic work demonstrates that heightened posterior cingulate cortex, ACC, and precuneus responses are elicited by drug and alcohol cues (e.g., Engelmann et al., 2012; Noori et al., 2016; Schacht et al., 2013). As posterior cingulate is thought to be involved in internally-focused cognition, attention, and arousal (Leech and Sharp, 2014), lower BOLD signal to drug versus neutral words suggest that less self-focus is triggered by cocaine as a function of recovery. Similarly, precuneus, like posterior cingulate, is considered a core region involved in the brain's default mode network, thought to be involved in the manifestation of self-consciousness and self-relevant mental representations (Cavanna and Trimble, 2006); lower precuneus responses to drug than neutral words with abstinence may reflect reduced perception of drug use as a part of the self. Moreover, research collecting fMRI scans twice within the same individuals demonstrates that six-month cocaine abstinence is associated with higher VTA, substantia nigra, thalamus, and precuneus responses to drug-related words (as opposed to neutral words) in a modified Stroop task when compared to baseline (Moeller et al., 2012); in addition, abstinence is marked by decreases in MPFC, premotor, parietal/occipital BOLD signal to drug versus neutral words in this study.

In contrast to the cross-sectional studies above that demonstrate decreases in reward-related BOLD signal to drug cues, Moeller et al. (2012) instead show increases in signal; inconsistent findings may be related to differences in word versus image-based stimuli as well as

divergent task designs (fMRI measured at multiple timepoints to track abstinence versus only one timepoint). Lastly, within individuals on MMT, abstainers from illicit opioids exhibit lower ventral striatum and MPFC BOLD signal to drug than neutral images than relapsers, consistent with cross-sectional studies showing striatal reductions to drug images with sobriety (Q. Li et al., 2015). In summary, while lower basal ganglia/midbrain responses to drug cues linked to abstinence may reflect lowered appetitive salience as a function of recovery, whereas attenuated MPFC, precuneus, and cingulate responses to drug-relevant cues as opposed to other types of stimuli might reflect decreased pairing of drug use as a core component of self.

4.2. fMRI and changes in drug responsiveness as a function of pharmacotherapy

Treatment studies show that: (1) cross-sectionally, longer MMT duration is associated with lower dorsal striatum BOLD signal to drug images, even when controlling for illicit opioid use history (Wang et al., 2014); (2) longitudinally, acute post-methadone ingestion in MMT users is linked to decreased insula, amygdala, and hippocampus BOLD responses to opioid images when compared to pre-methadone ingestion (Langleben et al., 2008); (3) longitudinally, post-naltrexone is associated with lower ventral striatum and MPFC signals to opioid images when compared to pre-naltrexone in recently detoxified users (Shi et al., 2018); and (4) within-subjects, modafinil is linked to lower VTA but higher ACC and dorsal striatum responses to cocaine pictures than placebo, a pattern associated with lower drug craving (Goudriaan et al., 2013). In summary, many but not all studies point to brain regions implicated in drug salience and craving (e.g., striatum/basal ganglia, insula, frontocingulate areas) becoming less responsive to drugs with abstinence and treatment. It is helpful when BOLD signal patterns are correlated with other measures of craving/urges, reward processing, or cognitive control to help explain the potential functionality of brain attenuations or hyperactivations.

4.3. fMRI studies of non-drug reward and future abstinence or treatment response

Individual differences in BOLD signal to rewards are correlated with future stimulant abstinence and/or treatment response, although the directionality of brain findings may depend upon the drug of choice or the specific paradigm used. Four studies, three longitudinal (Balodis et al., 2016; Jia et al., 2011; Yip et al., 2016) and one cross-sectional (Patel et al., 2013) employ a monetary incentive delay (MID) task to evaluate how users' responses during anticipation and receipt of monetary win (versus no-win) and loss (versus no-loss) conditions relate to recovery. First, cross-sectional research indicates that cocaine abstainers (for ~ 46 months) show lower MPFC BOLD signal than active cocaine users during MID loss anticipation, but higher VTA BOLD signal to loss outcomes than current users (Patel et al., 2013). As MPFC and basal ganglia regions are implicated in the development and maintenance of action-outcome associations leading to reward (Hampton and O'Doherty, 2007), these results suggest a shift in resources potentially devoted to learning from stimuli leading to negative consequences. Second, longitudinal research demonstrates that individuals with cocaine use disorder show increased thalamus, posterior cingulate, striatum, substantia nigra, and precuneus BOLD signal during win anticipation for fMRI scans recorded post- as opposed to pre-treatment; in addition, lower ventral striatum BOLD signal during MID loss anticipation predicts a greater number of drug-negative urine screens during treatment (Balodis et al., 2016). Increases in brain regions involved in self-referential (posterior cingulate, precuneus) and/or reward processing (basal ganglia) during anticipation of wins may reflect increased responsiveness to non-drug reward. Additional longitudinal research shows that greater cocaine abstinence over an eight-week period is predicted at baseline by lower dorsal striatum and thalamus BOLD

signal during MID win anticipation, as well as lower ventral striatum, thalamus, and cerebellum BOLD signal during MID win outcome (Jia et al., 2011). Inconsistent findings in directionality between Jia et al. (2011) and Balodis et al. (2016) may be related to reporting fMRI findings collected at the start of recovery as opposed to changes documented as a function of post- minus pre-treatment. Lastly, within a sample of cocaine users, Yip et al. (2016) demonstrate that those on stable MMT exhibit lower inferior frontal and posterior insula BOLD signal during MID loss anticipation than those not on MMT; furthermore, lower dorsal striatum BOLD signal during MID win anticipation at baseline predicts future abstinence during MMT paired with eight-week CBT or treatment as usual (Yip et al., 2016). Taken together, two out of four studies relate (1) attenuated frontal responses during loss anticipation to successful abstinence/treatment (Patel et al., 2013; Yip et al., 2016); and (2) attenuated dorsal striatum responses during win anticipation to successful abstinence/treatment (Jia et al., 2011; Yip et al., 2016). Lack of consistency in basal ganglia, frontal, and midbrain findings across the four studies may be associated with study design (e.g., one baseline fMRI scan predicting future outcomes as opposed to two fMRI scans comparing pre- and post-treatment within-subjects); these findings warrant replication in methamphetamine and opioid users, as research thus far focuses on cocaine users.

Other fMRI studies examining non-drug reward employ reward learning paradigms, risky decision-making tasks involving wins and losses, and viewing of other types of pleasant stimuli such as baby faces. For instance, Stewart et al. (2014a, 2014b) record fMRI responses during decision and outcome phases of a paper scissors rock task to evaluate whether brain responses involving the learning of decision-outcome contingencies leading to wins, or responses to outcomes (wins, ties, and losses) forecasts abstinence versus relapse. For cocaine users, higher baseline striatum, insula, IFG, and DLPFC BOLD signal during reward learning predicts cocaine abstinence 12 months later (Stewart et al., 2014a), whereas lower striatum and IFG signal during the same task predicts methamphetamine abstinence across the same timeframe (Stewart et al., 2014b). Similarly, cocaine and methamphetamine abstainers diverge from relapsers when they receive win/loss outcomes, with cocaine abstainers showing frontostriatal differentiation of wins and losses, but methamphetamine abstainers exhibiting heightened frontocingulate and insula responses to both wins and losses (Stewart et al., 2014a, 2014b). The same sample of methamphetamine users from Stewart et al. (2014b) completed a risky gains task at baseline, which instructs participants to either press a button to earn a safe reward (20 cents) or wait to see if they can win a high-risk, high-reward option (either 40 or 80 cents); during this risk task, methamphetamine abstainers show greater insula and striatum differentiation between safe and risky rewards at baseline than relapsers (Gowin et al., 2015, 2014), suggesting that brain patterns linked to abstinence may change as a function of task parameters and requirements.

While the aforementioned longitudinal work focuses on stimulant users, one cross-sectional study compares reward learning outcomes in two groups of opioid users on MMT, those assigned to take their daily methadone dose before an fMRI scan, and those assigned to take it after an fMRI scan (Gradin et al., 2014); those taking methadone post-scan exhibit higher midbrain and parahippocampal gyrus BOLD signal to loss than those ingesting methadone pre-scan, suggesting that state factors are important to consider when studying brain responses during reward processing. An additional study in opioid users indicates that naltrexone treatment (as opposed to baseline) is associated with lower striatum responses to baby pictures paralleled by decreased craving, but BOLD signals are unrelated to opioid abstinence duration (Wang et al., 2018); as no placebo condition or group is included for comparison in this study, brain attenuations could be due, at least in part, to habituation to pleasant stimuli. In summary, although individual differences in pre-treatment striatum, insula, and prefrontal cortex predict the ability to remain abstinent, directionality of these results (increases versus decreases) are inconsistent, limiting a clear-cut directive for

screening likelihood of positive rehabilitation outcomes.

4.5. fMRI studies of attention, memory, or cognitive control and recovery

Whereas ERP studies focus mainly on oddball and go/no-go tasks to study these processes, fMRI studies tend to contrast two conditions of the color-word Stroop task: incongruent trials (conflict between word color and word meaning, such as 'blue' presented in red font) versus congruent trials (no conflict between word color and meaning, such as 'red' presented in red font). As individuals engaged in the Stroop task are instructed to press a button indicating the word color, not the word meaning, incongruent trials require an override of a prepotent response (word reading) to respond correctly to word color; as a result, participants show longer reaction times when correctly responding to incongruent than congruent trials due to differences in overriding, or controlling, responses to conflict. Five longitudinal studies of cocaine users relate recovery metrics to BOLD signal that is greater for incongruent than congruent trials (termed 'the Stroop effect') to determine how higher-order cognitive control processes correlate with abstinence/treatment. First, with respect to baseline BOLD signal predicting treatment response, two studies employing the Stroop task demonstrate that lower frontocingulate connectivity during incongruent (compared to congruent) trials predicts future cocaine treatment retention (Brewer et al., 2008; Worhunsky et al., 2013). Second, for BOLD signal tracking brain changes linked to interventions, incongruent (compared to congruent) Stroop trials are associated with: (1) striatum/basal ganglia BOLD signal decreases as a function of two-month cocaine treatment (DeVito et al., 2012); and (2) thalamus, cingulate, hippocampus, precentral/postcentral gyrus, and cerebellum decreases after three months of cocaine rehabilitation, with more frequent treatment attendance further associated with VMPFC, precentral, and inferior parietal decreases (DeVito et al., 2017). Third, BOLD signals at baseline or over the course of treatment appear to predict future sobriety. For instance, higher VMPFC, posterior cingulate, and striatum BOLD signal and heightened subcortical and striatal-prefrontal network connectivity (thalamus, striatum, amygdala, hippocampus, IFG, VMPFC) to incongruent (compared to congruent) trials predict future cocaine sobriety (Brewer et al., 2008; Worhunsky et al., 2013). Moreover, decreased insula, precentral/postcentral gyrus, inferior parietal, and superior temporal BOLD signal changes to incongruent (as opposed to congruent) trials as a function of rehabilitation correlate with longer abstinence in cocaine users on stable MMT (DeVito et al., 2019).

In addition to Stroop tasks, researchers evaluating recovery processes also employ visual oddball, go/no-go, stop signal, and other types of decision-making paradigms. Using a three-stimulus oddball task like those used in ERP studies, Clark et al. (2014) demonstrate that higher insula, ACC, and posterior cingulate BOLD signal to non-target distractors at baseline predicts six-month abstinence from stimulants. Within the context of a go/no-go paradigm, where individuals are instructed to press a button when viewing one stimulus but withhold their button response when viewing a second stimulus, higher baseline connectivity between ACC, DLPFC, thalamus, insula, striatum, and other regions predicts successful treatment retention for opioid and stimulant users (Steele et al., 2018). Similar to the go/no-go paradigm, the stop signal task requires either an activation or inhibition of a behavioral response (go versus stop) but the stimulus context is slightly different: participants press a button when they see a series of stimuli (go) unless an additional auditory or visual stimulus is presented (stop signal), which cues them to inhibit the button press (stop). In addition, stop trial difficulty can be manipulated by varying how close in time the stop signal is to the go stimulus, with greater difficulty associated with higher response conflict, leading to more errors.

Two longitudinal studies examine whether stop signal responses at baseline predict future recovery, with the first reporting that greater dorsal ACC BOLD signal to stop error trials (compared to stop success trials) predicts three-month cocaine abstinence (Luo et al., 2013); this

work also notes gender differences in prediction, with men remaining abstinent showing heightened insula BOLD signal at baseline, and women maintaining abstinent showing heightened thalamus BOLD signal (Luo et al., 2013). The second stop signal study applies concepts from Bayes Theorem by calculating the difference between each methamphetamine user's prediction error, defined as the predicted versus actual need to stop on a given trial, on a trial-by-trial basis, and then correlating this probability of stopping, or P(Stop), with BOLD signal for each trial during the task (Harlé et al., 2019). Findings show that users remaining abstinent 12 months later showed higher insula and inferior frontal gyrus BOLD signal associated with P(Stop) prediction errors at baseline than users relapsing within this timeframe (Harlé et al., 2019). Lastly, two studies use baseline fMRI metrics during other types of decision-making to predict recovery; Moeller et al. (2010) demonstrate that higher thalamus BOLD signal responses during delayed as opposed to immediate memory processing forecasts future cocaine treatment success, whereas Paulus et al. (2005) indicate that higher insula, dorsal striatum, inferior parietal, and middle temporal BOLD signal during the decision phase of a two-choice prediction task (compared to the outcome phase) predicts future 12-month methamphetamine abstinence.

4.6. What do resting-state fMRI scans reveal about engagement in recovery efforts?

Of the six resting-state studies included in Table 3, one employs a cross-sectional design, comparing relapsers and abstainers from heroin use while enrolled in MMT (W. Li et al., 2015), whereas the other five employ longitudinal designs, four of these focused on connectivity, or functional correlations involved with frontal and/or striatal brain regions (Berlingeri et al., 2017; Chang et al., 2016; Geng et al., 2017; Kohno et al., 2018; Li et al., 2018). For instance, within cocaine users, greater baseline VMPFC-temporal pole connectivity predicts future six-month abstinence (Geng et al., 2017), whereas greater baseline ventral striatum-DLPFC connectivity predicts future eight-month abstinence (Berlingeri et al., 2017). Similarly, higher DLPFC-VMPFC connectivity and lower dorsal ACC-VMPFC connectivity at baseline predict three-month illicit opioid abstinence after the onset of stable MMT (Li et al., 2018). Furthermore, within a sample of methamphetamine users, naltrexone treatment is associated with decreased ventral striatal connectivity with hippocampus/amygdala when compared to placebo; this attenuated connectivity, in turn, is linked to lower past-month methamphetamine use (Kohno et al., 2018). Individual differences in brain responses also relate to abstinence for opioid users on MMT, wherein higher middle temporal gyrus, parahippocampal gyrus, precuneus, and lingual gyrus BOLD signal, as well as lower OFC, striatum, and cerebellum BOLD signal, predict greater sobriety one year later (Chang et al., 2016). Furthermore, cross-sectional work indicates that within a cohort of opioid users on MMT, abstainers from illicit opioids show greater occipital-temporal connectivity and weaker precuneus-cingulate gyrus connectivity than chronic relapsers (W. Li et al., 2015). Thus, individual differences in prefrontal cortex connectivity are associated with differential outcomes in cocaine users. However, there is no clear consistency regarding the brain regions and directionality of findings when examining the relationship between stimulant and opioid drugs and specific treatment outcomes.

4.7. Conclusions for fMRI findings

Interpreting fMRI studies across resting-state and task contexts, it appears that those individuals whose brain activity is under tighter control by the prefrontal cortex, or those who show greater brain activation in regions such as ACC, MPFC, insula and striatum when making decisions at the outset of treatment are also those individuals who can maintain abstinence. Similarly, individuals who show less striatal drug reactivity tend to succeed in recovery efforts. However, it

is unclear whether this initial assessment is a sign of trait characteristic of the individual or whether this is a consequence of limited impairment by chronic drug use.

5. Diffusion Tensor Imaging (DTI)

According to the laws of physics, properties of material can range from isotropic (uniform in all directions) to anisotropic (different as a function of direction/orientation). DTI maps water molecule movement in various tissues (Alexander et al., 2007), differentiating anisotropic patterns within white matter fibers from isotropic patterns elsewhere in the brain. During DTI, magnetic field changes during MRI recording sensitize water diffusion to a particular direction, resulting in a diffusion tensor matrix containing three eigenvalues for each brain voxel. Mean diffusivity is the average of these three eigenvalues, reflecting the total amount of water diffusion within each voxel. Fractional anisotropy (FA) is the normalized variance of the three eigenvalues, measuring the fraction of the diffusion that is anisotropic (O'Donnell and Westin, 2011). Axial diffusivity (reflecting diffusion parallel to a white matter tract) is the largest of the three eigenvalues, whereas radial diffusivity (reflecting diffusion perpendicular to a white matter tract) is the average of the two smaller eigenvalues (O'Donnell and Westin, 2011). White matter pathology causes FA to decrease, which may result from either reduced axial diffusivity or increased radial diffusivity (Alexander et al., 2007). Whereas axial diffusivity is thought to be linked to axon degeneration, radial diffusivity is thought to be related to white matter pathology involving decreased myelin (Alexander et al., 2007). In other words, higher FA and lower diffusivity suggest greater structural integrity of the brain. Table 4 illustrates significant relationships between DTI metrics and abstinence/treatment response.

5.1. DTI and clinical outcomes

The limited number of DTI studies focus primarily on pre-treatment scans predicting future clinical outcome in cocaine users as well as opioid users enrolled in MMT. Two cross-sectional studies demonstrate that individuals who have longer cocaine abstinence display higher baseline FA than those with shorter abstinence durations (Bell et al., 2011; van Son et al., 2016). Similarly, two longitudinal studies of cocaine users report that higher baseline FA predicts better outcomes, as measured by treatment retention (Ma et al., 2017) and two-month abstinence (Xu et al., 2010). With respect to opioid users, two out of four longitudinal studies also report that higher baseline FA predicts future abstinence (one month: Wang et al., 2011; six months: Li et al., 2016), whereas one finds no relationship between FA and nine-month abstinence for opioid users not on pharmacotherapy (Ivers et al., 2018), and the other indicates that lower baseline FA predicts longer duration of MMT (Lin et al., 2012). Although five out of the eight DTI studies link increased FA with recovery, substantial variability exists with respect to the location of white matter impairments, warranting further research and replication before any strong conclusions can be drawn. For instance, greater white matter integrity implicated in successful cocaine sobriety covers many brain regions, including but not limited to: (1) longitudinal fasciculus, an association fiber tract connecting frontal and parietal regions; (2) uncinate fasciculus, a tract connecting hippocampus/amygdala to IFG/OFC; (3) posterior cingulum and fornix, which both connect to hippocampus; and (4) splenium, the posterior section of the corpus callosum that connects inferior and medial temporal regions, including posterior cingulate, as well as parietal and occipital cortices.

6. Neuromodulation treatment approaches and their implications for recovery

Multiple neuroimaging-informed brain stimulation techniques are more frequently being applied to the treatment of substance use

disorders. While EEG and fMRI neurofeedback involve training each person to up- or down-regulate brain activity in the hope of reducing drug craving/urges, methods such as deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS) apply electrical or magnetic currents to specific brain regions to produce similar effects. Table 5 highlights results of brain stimulation studies targeting stimulant and opioid addiction and we briefly describe utility of each method thus far.

6.1. EEG neurofeedback

EEG neurofeedback paradigms involve recording brainwaves, displaying signals from a frequency band in real-time to participants, and instructing these participants to engage in cognitive, emotional, and/or motor strategies to increase or decrease amplitude/power of these signals, a change that participants can monitor themselves on a computer screen. This process is typically repeated across multiple sessions in attempts to train individuals to regulate particular brain functions, thereby reducing clinical symptoms. EEG frequency band studies of treatment prediction and response are quite limited, with two studies reporting symptom relief (lower anxiety, higher quality of life), or improved cognitive performance (increased attention), and longer rates of abstinence, as a result of targeted EEG neurofeedback. The first EEG neurofeedback study focuses on parietal alpha/theta and frontocentral/parietal beta power training in methamphetamine users abstinent for at least one month (Rostami and Dehghani-Arani, 2015), whereas the second study targets central beta power in stimulant and opioid users also enrolled in psychotherapy (Keith et al., 2015). Findings from these two studies suggest that beta band neurofeedback training, while extremely time intensive (15–30 sessions), appears to reduce psychological distress, improve cognitive control, and extend periods of abstinence. It would be helpful for future EEG neurofeedback studies to determine whether: (1) upregulation of beta band activity also increases drug-free urines and decreases self-reported craving; and (2) positive results can be gained with a lower number of sessions.

6.2. Direct brain stimulation (DBS)

DBS in stimulant/opioid use disorders focuses on implantation of electrodes within nucleus accumbens (striatum) to deliver electrical impulses and alter synaptic transmission relevant to chronic drug-seeking behaviors (Peisker et al., 2018). Only one case study reports DBS success in increasing abstinence and reducing symptoms of cocaine use disorder; however, this DBS protocol took 30 months to complete, and found no differences in symptoms when the DBS electrodes were turned on versus off (Goncalves-Ferreira et al., 2016). Moreover, three DBS studies that together comprise ten opioid users report mixed outcomes: although six users maintained abstinence greater than two years

after DBS onset, the other four relapsed, with one person overdosing within five months of DBS onset (Chen et al., 2019; Zhang et al., 2018a; Zhou et al., 2011). Finally, six-months of DBS for treatment-refractory opioid and alcohol users results in no improvement in impulsivity and reward responsivity (Peisker et al., 2018). It appears that individual differences in opioid use chronicity and/or detoxification status could play a role in the success of DBS in enhancing recovery. Given the substantial time as well as invasive surgery required for DBS treatment, along with inconsistent findings, we do not foresee DBS as a cost-effective treatment that can be widely implemented.

6.3. Repetitive transcranial magnetic stimulation (rTMS)

While DBS is an invasive method of applying electrical currents to the brain, (rTMS) applies a fluctuating magnetic field, usually at frequencies between 0–10 Hz, to provide noninvasive stimulation of specific cortical regions, reaching depths of 1.5–2 cm (Liang et al., 2018a, 2018b). The majority of rTMS studies target DLPFC activity in individuals with stimulant use disorder, given a substantial literature showing that cocaine and methamphetamine users show impairments in cognitive control associated with this region (Garavan and Hester, 2007; Goldstein and Volkow, 2011; Nestor et al., 2011). Overall, these studies vary in sample size, duration of stimulant abstinence at the outset of treatment (e.g., one day up to three months), and rTMS protocol parameters (e.g., number of sessions, stimulation frequency). Five out of six rTMS studies report reductions in craving and/or improvement in cognitive/emotional function in methamphetamine users following multiple sessions of left DLPFC stimulation (Liang et al., 2018a, 2018b; Liu et al., 2017; Su et al., 2017; Zhang et al., 2018b); one of these studies also demonstrates the utility of right DLPFC stimulation in reducing methamphetamine craving (Liu et al., 2017). Moreover, research targeting left DLPFC rTMS in cocaine users demonstrates its effectiveness in reducing craving and producing fewer positive urine drug screens (Terraneo et al., 2016); another study is underway that includes an eight-week follow-up assessment of cocaine use outcomes, which is longer than most rTMS follow-up durations (Scarpino et al., 2019). Although one study reports increased methamphetamine craving as a function of left DLPFC rTMS (X. Li et al., 2013), study design differences related to stimulation frequency (e.g., low as opposed to high), timing/number of sessions, and craving ratings may have influenced findings. More specifically, left DLPFC rTMS increased users' behavioral responsiveness to negative images over time (Zhang et al., 2018b) as well as decreasing response times during a selective attention task (Liang et al., 2018a). Additional rTMS studies with longer follow-up durations are warranted to determine if these short-term behavioral improvements also translate to paying attention to the negative consequences of drug use and effectively reducing drug intake. Finally, the sole study of left DLPFC rTMS in opioid users also demonstrates reduced craving as a

Table 4
Diffusion Tensor Imaging Results as a function of Abstinence and/or Treatment for Stimulant and/or Opioid Use Disorders (*n* = 8).

Cocaine	Increases	Decreases	Design	Abstinence/Treatment
Bell et al. (2011)	↑ thalamic, cingulum, precentral gyrus FA	↓ superior/inferior longitudinal fasciculus FA	Cross-Sectional	Abstinence (0.7 to 102 weeks)
Ma et al. (2017)	↑ change in splenium FA	None	Longitudinal	Treatment (2.5 months)
van Son et al. (2016)	↑ uncinate fasciculus, posterior cingulum, and fornix-striatum FA	None	Cross-Sectional	Abstinence (weeks)
Xu et al. (2010)	↑ longitudinal fasciculus and cerebellum FA	↓ frontal, temporal, parietal, occipital diffusivity	Longitudinal	Abstinence (2 months)
Opioids	**Increases**	**Decreases**	**Design**	**Abstinence/Treatment**
Ivers et al. (2018)	None	None	Longitudinal	Abstinence (9 months)
Li et al. (2016)	↑ internal capsule, anterior corona radiata, and external capsule FA	↓ internal and external capsule diffusivity	Longitudinal	Abstinence (6 months)
Lin et al. (2012)	None	↓ superior longitudinal fasciculus and parahippocampal FA	Longitudinal	Longer MMT treatment duration
Wang et al. (2011)	↑ frontocingulate FA	None	Longitudinal	Abstinence (1 month)

Note. FA = fractional anisotropy. MMT = methadone maintenance therapy.

Table 5
Neuromodulation Results as a function of Abstinence and/or Treatment for Stimulant and/or Opioid Use Disorders (n = 29).

Cocaine	Outcomes	Targeted Brain Region	Type	Intensity	Design	Abstinence/Treatment
Bolloni et al. (2016)	↓ cocaine intake	Bilateral PFC	rTMS	10 Hz	Randomized, double-blind	Treatment (6 months)
Conti et al. (2014)	↓ P3 current intensity in frontal areas to drug cues	Bilateral DLPFC	tDCS	2 mA	Randomized	Abstinence (≤ 31 days)
Conti & Nakamura-Palaciso(2014)	↓ N2 component of ACC	Bilateral DLPFC	tDCS	2 mA	Not reported	Abstinence (≤ 39 days)
Gonçalves-Ferreira et al. (2016)	↓ severity of use > 2.5 years post-surgery	nACC, BNST	DBS	130 Hz	Longitudinal case study, double-blind, cross-over	Treatment-refractory
Gorini et al. (2014)	RDLPFC: ↑ safe behaviors LDLPFC: ↑ risky behaviors	L/R DLPFC	tDCS	1.5 mA	Single-blind, sham-controlled	Abstinence (≥ 2 weeks)
Hanlon et al. (2015)	↓ craving, ↓ striatum/AI BOLD	Left MPFC	cTBS (rTMS)	5 Hz	Single-blind, sham-controlled pilot study	Non-treatment seeking
Hanlon et al. (2017)	↓ caudate, nACC, ACC, OFC, PC BOLD	Left MPFC	cTBS (rTMS)	5 Hz	Single-blind, sham-controlled, cross-over	Non-treatment seeking
Kearney-Ramos et al. (2018)	↓ functional connectivity to drug cues	Left VMPFC	rTMS	5 Hz	Single-blind, sham-controlled, cross-over	Non-treatment seeking
Klauss et al. (2018)	No change in craving or relapse	DLPFC	tDCS	2 mA	Randomized, double-blind, sham-controlled, clinical trial	Treatment-seeking
X. Li et al. (2013)	↑ cue-induced craving	Left DLPFC	rTMS	1 Hz	Single-blind, sham-controlled, cross-over	Non-treatment seeking
Liu et al. (2017)	↓ craving	R/L DLPFC	rTMS	1/10 Hz	Randomized	Abstinence (2 months)
Martinez et al. (2018)	↓ choice for cocaine in 10 Hz condition	Medial PFC/ACC	dTMS	1/10 Hz	Randomized, pilot study	Non-treatment seeking
Rapinesi et al. (2016)	↓ craving	Left DLPFC	dTMS	20 Hz	Pilot Study	Treatment-seeking
Scarpino et al. (2019)	N/A – proposed study protocol	Left PMC/DLPFC	rTMS	15 Hz	Randomized, placebo-controlled, pilot	Treatment-seeking
Terraneo et al. (2016)	↓ cocaine intake	Left DLPFC	rTMS	15 Hz	Between-subject, open-label, randomized clinical trial	Treatment-seeking
Methamphetamine	**Outcomes**	**Targeted Brain Region**	**Type**	**Intensity**	**Design**	**Abstinence/Treatment**
Liang et al. (2018a)	↓ post-error RT slowing	Left DLPFC	rTMS	10 Hz	Double-blind, randomized parallel-group	Abstinence (≥1 month)
Liang et al. (2018b)	↓ craving, sleep problems, depression, anxiety	Left DLPFC	rTMS	10 Hz	Double-blind, randomized parallel-group	Abstinence (1–15 days)
Rostami & Dehghani-Arani (2015)	↓ anxiety, ↑ life quality	N/A	EEG neurofeedback (30 sessions)	12–15 Hz (SMR); 15–18 Hz (low beta)	Randomized control trial	Treatment (2 months)
Shahbabaie et al. (2018a)	↓ craving	Bilateral DLPFC	tDCS	2 mA	Double-blind, sham-controlled, cross-over	Abstinence (≥1 week)
Shahbabaie et al. (2018b)	↓ attentional bias to drug cues	Left DLPFC	tDCS	2 mA	Double-blind, sham-controlled, cross-over	Early abstinence
Su et al. (2017)	↓ craving	Left DLPFC	rTMS	10 Hz	Double-blind, randomized control trial	Abstinence (~3 months)
Zhang et al. (2018b)	↑ emotional attention	Left DLPFC	rTMS	10 Hz	Single-blind	Abstinence (≤ 2 months)
Opioids	**Outcomes**	**Targeted Brain Region**	**Type**	**Intensity**	**Design**	**Abstinence/Treatment**
Chen et al. (2019)	↑ length of abstinence, ↓ craving	nACC, ALIC	DBS	130–185 Hz	Longitudinal	Treatment-refractory
Peisker et al. (2018)	No effect on delay-discounting behaviors	nACC	DBS	130 Hz	Double-blind, randomized, cross-over	Treatment-refractory
Shen et al. (2016)	↓ craving	Left DLPFC	rTMS	10 Hz	Randomized, sham-controlled, cross-over	Not reported
Wang et al. (2016)	↓ cue-induced craving	Bilateral FPT	tDCS	1.5 mA	Randomized, sham-controlled, single-blind	Abstinence (≥ 1.5 years)
Zhang et al. (2018a)	Relapse, Overdose, Death	VC/VS	DBS	130 Hz	Case Study	Treatment-refractory, no detoxification
Zhou et al. (2011)	↑ length of abstinence	nACC	DBS	145 Hz	Case Study	Treatment-refractory, rapid detoxification
Stimulants and Opioids	**Outcomes**	**Targeted Brain Region**	**Type**	**Intensity**	**Design**	**Abstinence/Treatment**
Keith et al. (2015)	↑ cognitive control performance	N/A	EEG neurofeedback (15 sessions)	12–15 Hz (SMR); 15–18 Hz (low beta)	Randomized	Treatment (1.5 weeks)

Note. EEG = electroencephalography. nACC = nucleus accumbens. ALIC = anterior limb of the internal capsule. VC/VS = ventral capsule and ventral striatum. PC = parietal cortex. FPT = frontal-parietal-temporal areas. SMR = sensory motor rhythm.

result of stimulation (Shen et al., 2016). Taken together, the majority of rTMS findings suggest that repeated stimulation of left DLPFC, a brain region implicated in cognitive control and goal-directed decision-making, is associated with short-term improvements in drug craving. What we still do not know is whether these short-term improvements persist in the long-term and help individuals maintain sobriety, or what the optimal stimulation parameters are to achieve desired effects.

6.4. Theta burst stimulation (cTBS)

In addition to DLPFC, other frontal regions are thought to play a role in maintaining chronic addiction. For example, MPFC may also be a potential treatment target, as users show heightened MPFC responses to drug cues that could serve to maintain drug-seeking behaviors. As dysfunction between MPFC and DLPFC circuitry with other cortical and subcortical regions may contribute to continued use (Hanlon et al., 2015), a variation of rTMS, cTBS, is used to target regions of PFC and their connecting networks in cocaine users. cTBS delivers a constant current within the theta band frequency range in a time frame shorter than regular rTMS, producing a comparable effect (Hanlon et al., 2015). Two cTBS studies attempting to decrease MPFC activation demonstrate its effectiveness in reducing self-reported cocaine craving, as well as lowering striatum, insula, and ACC activity linked to drug craving (Hanlon et al., 2015, 2017; Kearney-Ramos et al., 2018). Furthermore, greater change in connectivity between MPFC-striatum is associated with longer cocaine use chronicity and higher pre-cTBS craving (Kearney-Ramos et al., 2018). Like standard rTMS, cTBS shows promise in targeting brain circuitry implicated in drug salience, but more studies are needed with longer follow-up durations to determine whether these effects are transient or persistent.

6.5. Deep TMS (dTMS)

dTMS allows for noninvasive brain stimulation like rTMS, but it delivers current layers deep within the cortex, up to 6 cm below the skull, resulting in a wider electrical field change (Zangen et al., 2005). This deeper and wider distribution allows for greater modulation of connective networks across the brain (Martinez et al., 2018). As addiction is characterized by impaired cognitive control over drug cravings and urges that are thought to drive relapse, dTMS targeting frontal regions may change neurotransmission within PFC circuitry, reducing craving. Preliminary results show that: (1) left DLPFC dTMS reduces cocaine craving (Rapinesi et al., 2016); (2) high but not low frequency MPFC/ACC dTMS decreases cocaine self-administration up to two weeks post-stimulation (Martinez et al., 2018); and (3) bilateral DLPFC dTMS decreases cocaine use at three- and six-month follow-up assessments (Bolloni et al., 2016). Like rTMS, dTMS findings are encouraging for stimulant use recovery, but replications with longer follow-up assessments are needed.

6.6. Transcranial direct current stimulation (tDCS)

Lastly, tDCS is a noninvasive tool, like rTMS and dTMS, delivering low frequency direct electrical currents to alter cortical activity; tDCS is achieved by placing electrodes over the brain region of interest to induce intracerebral current flow (Stagg and Nitsche, 2011). Neuronal activity can be increased by applying positive stimulation via an anodal electrode or decreased by delivering negative stimulation via a cathodal electrode. tDCS currents are delivered for 10–20 min, ranging in intensity from 1–2 milliamps (mA). Preliminary results indicate that tDCS aimed at increasing left DLPFC activity reduces methamphetamine craving (Shahbabaie et al., 2018a), changes methamphetamine users' resting-state functional connectivity in default mode, executive control, and salience networks (Shahbabaie et al., 2018a), and decreases attentional bias to methamphetamine cues (Shahbabaie et al., 2018b). In contrast, tDCS findings are less consistent for cocaine users, showing:

(1) no significant improvements in craving or relapse specific to left DLPFC stimulation (Klauss et al., 2018); (2) lower frontal N2 and P3 amplitudes to cocaine cues after bilateral DLPFC stimulation (Conti et al., 2014; Conti and Nakamura-Palacios, 2014); and (3) reduced risky behavior on two decision-making tasks with increased right DLPFC stimulation, with mixed results for left DLPFC increases (Gorini et al., 2014). Overall, differences in the number of tDCS sessions as well as outcome metrics limit integration of findings across studies and warrant replication. Finally, one study shows that bilateral frontal, temporal and parietal tDCS reduces craving in individuals with 5–25 years of opioid use (Wang et al., 2016).

6.7. Conclusions for neuromodulation techniques

Overall, methods of TMS, including rTMS, cTBS and dTMS, show the most promise as a potential brain stimulation technique to be used as a treatment for substance use disorders. On the other hand, DBS does not appear to be a promising treatment given inconsistent findings and the required invasive surgery, while interpretation of tDCS findings at this point is difficult given the variation in methods and contradictory findings. Future research should examine the potential for long-term change following TMS methods to further determine its effectiveness in improving substance use outcomes.

7. What does neuroimaging tell us about recovery and where do we go from here?

Fig. 1 illustrates the degree various neuroimaging techniques have been applied to the study of abstinence and treatment within stimulant and opioid use disorders. ***Taken together, what do these studies tell us about processes in the brain that may undergo or contribute to recovery?*** Not enough. First, there is little distinction between brain mechanisms indexing pre-existing individual differences versus changes linked to sobriety and/or successful interventions. It makes intuitive sense that people who have more intact brain structure and function at the start of treatment, particularly within the executive domain, do better at maintaining abstinence and completing treatment, but what is the recourse for people who have structural and functional impairments attempting recovery? Second, there is almost no evidence for differential brain patterns of recovery within and across stimulant and opioid drug classes; often comorbidities are not explicitly considered within analyses, which complicate the clinical picture even further. Longitudinal neuroimaging designs of recovery allow everyone to serve as their own within-subjects control, enabling us to separate out variance associated with trait characteristics (e.g., history of depression/anxiety disorders, years of opioid chronicity) from state changes in recovery over time. Unfortunately, this type of longitudinal research is expensive, particularly for MRI scanner costs, as well as time-intensive and challenging with respect to keeping in touch with people who relapse during follow-up. In an ideal world, individuals would come in for neuroimaging visits before and multiple times after starting interventions (e.g., naloxone, MMT, buprenorphine, CBT, residential treatment), regardless of abstinence or relapse status at each timeframe, so that we can better characterize acute differences in brain/structure and function within the person and how they relate to percentage of days sober, or number of drug-negative urine screens. In the Adolescent Brain Cognitive Development (ABCD) study funded by the National Institute on Drug Abuse, twenty-one research sites across the United States use a standardized neuroimaging battery along with various self-report and behavioral metrics to examine longitudinally how the brain changes during development from childhood, before the onset of most substance use disorders, into adolescence and adulthood; is it impossible to develop a similar study for tracking brain changes in individual patterns of drug abstinence/relapse and treatment success across various sites starting in late adolescence and early adulthood? As opposed to youth entering the ABCD study who start out relatively
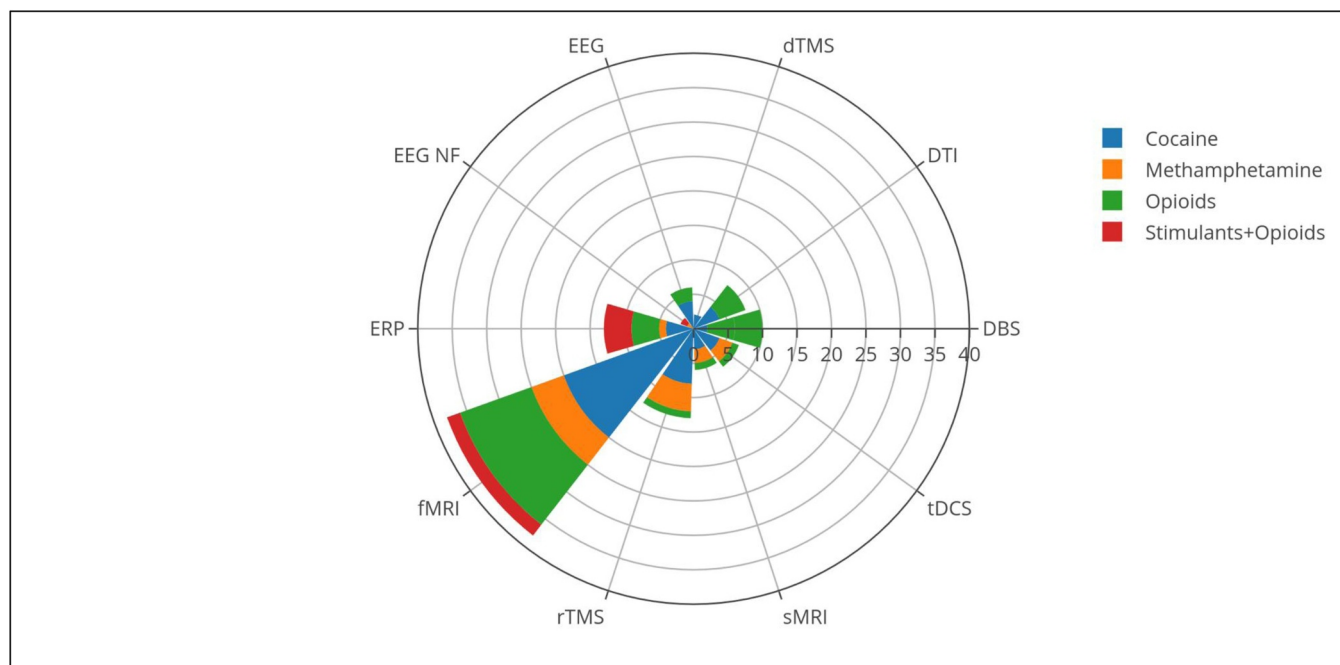
Fig. 1. Applications of neuroimaging approaches to examine recovery in stimulant and opioid use disorders. The graph indicates the qualitative prevalence of the technique as a function of cocaine, methamphetamine, and opioid use. Numbers indicate the number of included publications on each topic. DBS = deep brain stimulation. DTI = diffusion tensor imaging. dTMS = deep transcranial magnetic stimulation. EEG = electroencephalography. EEG NF = electroencephalography neurofeedback. ERP = event related potential. fMRI = functional magnetic resonance imaging. rTMS = repetitive transcranial magnetic stimulation. sMRI = structural magnetic resonance imaging. tDCS = transcranial direct current stimulation.

clean from severe psychopathology, people using stimulants and/or opioids by late adolescence/early adulthood likely will present with comorbid clinical diagnoses and adverse life events that researchers perceive as potential confounds, but we need to accept that substance use disorders are complicated. Large scale longitudinal studies at multiple timepoints allow us to statistically model relationships between and within factors contributing to brain change. It is easy for us to propose this research trajectory, but ridiculously ambitious to enact in practice.

Overall, what do these studies convey about brain regions to target for improving sobriety?

It appears that engaging activity in prefrontal areas helps to reduce drug craving in the short-term, but more research is needed to determine whether these brain interventions persist in long-term craving reductions as well as prolonged abstinence. At this point, there is little evidence for substance-specific effects, although Fig. 1 illustrates that much more work has focused on cocaine use disorder than opioid use disorder. Clearly, there is limited scalability of deep brain stimulation efforts, although this has the potential to change with the current development of ultrasonic stimulations (Monti et al., 2016). Finally, there is no consensus within various brain stimulation literatures with respect to target parameters and number of sessions needed to achieve reductions in drug craving/urges, and what individual differences in brain structure or function (e.g., measured by EEG/ERP and/or MRI) might contribute to stimulation success in decreasing drug-seeking behaviors.

Overall, there are five general problems in the literature limiting interpretations of brain recovery as a function of stimulant and opioid use disorders. First, many studies consist of small sample sizes that limit generalizability as well as statistical power to identify effects. Second, there are short, if any, follow-up intervals and lack of repeated brain measurements. Third, there are no systematic intervention studies that include neuroimaging. Fourth, and perhaps most importantly, there is not a clear standard on how to measure recovery, which makes comparability of studies difficult. Finally, while longitudinal studies predicting recovery often relate individual differences in brain function to outcomes, cross-sectional and treatment outcome studies with imaging collected at two timepoints tend to report group mean differences that do not speak to individual-level prediction of recovery.

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