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Alterations in resting-state functional connectivity in substance use disorders and treatment implications

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Abstract

Substance use disorders (SUD) are diseases of the brain, characterized by aberrant functioning in the neural circuitry of the brain. Resting state functional connectivity (rsFC) can illuminate these functional changes by measuring the temporal coherence of low-frequency fluctuations of the blood oxygenation level-dependent magnetic resonance imaging signal in contiguous or non-contiguous regions of the brain. Because this data is easy to obtain and analyze, and therefore fairly inexpensive, it holds promise for defining biological treatment targets in SUD, which could help maximize the efficacy of existing clinical interventions and develop new ones. In an effort to identify the most likely "treatment targets" obtainable with rsFC we summarize existing research in SUD focused on 1) the relationships between rsFC and functionality within important psychological domains which are believed to underlie relapse vulnerability 2) changes in rsFC from satiety to deprived or abstinent states 3) baseline rsFC correlates of treatment outcome and 4) changes in rsFC induced by treatment interventions which improve clinical outcomes and reduce relapse risk. Converging evidence indicates that likely "treatment target" candidates, emerging consistently in all four sections, are reduced connectivity within executive control network (ECN) and between ECN and salience network (SN). Other potential treatment targets also show promise, but the literature is sparse and more research is needed. Future research directions include data-driven prediction analyses and rsFC analyses with longitudinal datasets that incorporate time since last use into analysis to account for drug withdrawal. Once the most reliable biological markers are identified, they can be used for treatment matching, during preliminary testing of new pharmacological compounds to establish clinical potential ("target engagement") prior to carrying out costly clinical trials, and for generating hypotheses for medication repurposing.

Keywords

treatment target; substance use disorder; biomarker; resting state; connectivity

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Introduction

Substance use disorders (SUD) continue to be a major global public health problem. Many of the criteria required for a diagnosis of a SUD, including loss of control of substance use, continued use despite negative consequences and craving (American Psychiatric Association, 2013) can be explained by abnormalities in brain function. Specifically, addictive behavior is, to a significant degree, driven by abnormal functioning in the neural circuitry of decision making, impulse control, emotion regulation, stress mitigation, and reward learning and seeking (Courtney *et al.*, 2016; Kwako *et al.*, 2015; Tiffany & Wray, 2012; Wilcox *et al.*, 2014; Wilcox *et al.*, 2016). For this reason, identification of biological markers ("biomarkers") for substance use disorders and other forms addictive behavior that are targetable with treatment ("treatment targets") are important and will focus efforts to develop more efficacious therapeutic interventions.

Although there are available treatments to help individuals with SUD reduce their use or maintain abstinence, the effects are usually modest. Treating withdrawal (which for most drugs lasts only days) is important but does not necessarily prevent relapse or qualify as addiction treatment. Repeated relapses are due to long-lasting neurobiological changes in decision-making networks, and, to be effective, relapse prevention agents need to restore functioning in this circuitry (Kalivas & Volkow, 2005; Koob & Volkow, 2010; Wilcox & Bogenschutz, 2013). Treating withdrawal is helpful but not enough. Reviews of available relapse prevention medications and evidence-based psychosocial interventions are available and outside the scope of this article (Wilcox & Bogenschutz, 2013).

Recent research efforts have focused on identification of treatment targets in the SUD and wider mental health field (Insel, 2013; Kwako *et al.*, 2015; Sofuoglu, 2010; Tiffany & Wray, 2012). A treatment target also furthers understanding of the pathophysiology of the disorder. For something to be deemed a treatment target, it would ideally demonstrate several qualities: 1) measurable deficits in functionality in a particular domain (e.g. excessive craving) would predict later deficits in clinical function (e.g. relapse), 2) it needs to be a state rather than a trait measure (needs to be alterable with an intervention) 3) changes in these quantifiable measures (e.g. normalization) of the target in the short term with an intervention would predict better clinical response (e.g. less relapse) at later time points (Insel, 2013, 2018; Kwako *et al.*, 2015; Tiffany & Wray, 2012). Successful target engagement with an intervention (i.e., modulation of craving) but with no change in substance use suggests that the proposed mechanism is not related to outcome (Tiffany & Wray, 2012).

Establishing how treatments work (with an objective marker from functional magnetic resonance imaging (fMRI)) can provide essential guidance for treatment development (Cabrera *et al.*, 2016; Volkow & Baler, 2013b). For one, once a target is established, effects of potential novel treatments can be measured ("target engagement") in smaller, shorter-term trials to determine likelihood of efficacy before running more expensive, and costly large-scale clinical trials, which is a major push within National Institutes of Mental Health (NIMH) (Insel, 2013). In theory, since target engagement is measured closer to the time of the intervention, and in the case of neuroimaging, measures underlying physiological changes, the target would be altered with greater effect sizes than downstream clinical

outcome measures. Second, if a particular target is present in several types of SUD [e.g. both in nicotine use disorder (NUD) and alcohol use disorder (AUD)], such knowledge can inform hypotheses about whether treatments that work in one SUD (NUD) but are untested in another (AUD) are likely to be worthwhile. Although biomarkers have not yet been deployed for use in clinical settings in mental health, establishing targets may prove helpful for informing clinical decision-making. Once these targets are identified, they can first help in risk stratification, assigning individuals that are at higher risk of relapse to more intensive treatments or to individualized treatment plans. Furthermore, identification of engagement of these markers with a particular treatment could facilitate "treatment matching" or "precision medicine", which is a major priority within the mental health and substance use disorder research fields (Dishman, 2018; MATCH, 1997). Knowing which treatments work best on which deficits can maximize the efficacy of existing treatments, as, once harnessed with that information, providers could recommend treatments targeting an individual's vulnerabilities.

Resting state functional connectivity (rsFC) is an especially attractive tool to measure underlying brain function as it is short, inexpensive, and data-collection methods are easily replicable. Recent research has focused on this area within the last ten years utilizing rsFC to understand the brain circuitry of SUD (Fedota & Stein, 2015; Sutherland *et al.*, 2012). For these reasons, rsFC also holds promise for identification of treatment targets. Other advantages of rsFC over task-based fMRI paradigms include 1) data collection is more straightforward and easily replicable across sites, 2) subject participation does not require intact cognition, and 3) the data is not as susceptible to interference by changes in motivation or performance (Fedota & Stein, 2015; Lu & Stein, 2014; Pandria *et al.*, 2016; Pariyadath *et al.*, 2016; Sutherland *et al.*, 2012; Wilcox & Claus, 2017). rsFC has advantages over genetics (although not necessarily epigenetics) and other more static imaging measures like structural imaging because it changes over time and can be utilized to look at treatment mechanisms (Lu & Stein, 2014; Pariyadath *et al.*, 2016).

The first goal of this review is to review the rsFC literature to identify targets for SUD.

Biological treatment targets in research can be identified with several different methods. One common approach throughout the mental health field is to compare individuals with a diagnosis with individuals matched on important characteristics to those without a diagnosis (healthy comparisons (HC)) (or simply correlating measures of disease severity with measures of brain function) to try to understand underlying functional deficits. Studies like this have been done extensively and in a variety of SUD populations as well [for some excellent reviews see (Fedota & Stein, 2015; Ieong & Yuan, 2017; Lu & Stein, 2014; Moeller *et al.*, 2016; Pandria *et al.*, 2016; Pariyadath *et al.*, 2016; Sutherland *et al.*, 2012; Wilcox *et al.*, 2014; Wilcox *et al.*, 2016)]. However, there is a problem with using these data when collected in a cross-sectional design if the goal is to identify treatment targets, as identified group differences may or may not be causing behavior change. Although some of the brain changes observed at a particular time point in someone with a SUD could potentially be causing the disorder, they could also simply be a result of the SUD and therefore may or may not have anything to do with future perpetuation of the substance use, for example resulting from neurotoxic effects of chronic alcohol or drug use, and/or the

many downstream negative effects of the lifestyle associated with SUD (e.g. trauma or stress exposure). Just because there is a change in brain function does not necessarily provide insight into the underlying cause of pathological behaviors that contribute to aberrant decision-making and relapse risk. Therefore, we propose to review the literature using a variety of alternative angles.

Our first approach will be to focus on the relationships between rsFC and functionality within psychological domains that are believed to contribute to vulnerability to relapse or excessive use (subjective withdrawal severity, craving, cue reactivity, cognitive and impulse control, and anxiety, depression and emotion regulation) within SUD. These domains fall into the research domain criteria (RDoc) (positive valence, cognitive systems, negative valence) and are widely considered to be important potential targets in SUD (Kwako *et al.*, 2015). A word of caution about this approach is that, since many of these studies are also cross-sectional, they will have some of the same problems as those observed in the SUD vs. HC literature, because identified neural markers could simply be due to effects of previous substance use (either toxic or environmental exposure), and may not be contributing to the underlying behavior driving the disorder, so positive findings will be over inclusive. Results will also not indicate the degree to which the identified markers are alterable with an intervention; they could be static or dynamic. Finally, whether the psychological constructs are definitively linked with future clinical behavior (e.g. relapse) is not yet definitively established for these domains, even though they are assumed to be important (Kwako *et al.*, 2015; Tiffany & Wray, 2012). With these caveats in mind, we felt it useful to review them since, to our knowledge, a synthesis of the literature in this area has not been done in the past in a review article. If findings from these analyses also carry through into longitudinal datasets, they could be given more attention in future hypothesis-driven work.

The second approach will be to identify brain changes associated with the withdrawal state or abstinence, relative to the satiated state. Although treatment of withdrawal is only the first step for treatment of a SUD, it is still a very important step (Wilcox & Bogenschutz, 2013). Treatment of withdrawal not only relieves discomfort, but also helps individuals restrain from using their substance of abuse to relieve that discomfort and during the early days of treatment-seeking is an important part of helping someone get stabilized. Therefore, identifying the neural markers associated with this more vulnerable state could be very informative for identifying treatment targets to maximize this aspect of treatment.

Our third and fourth approaches will focus on longitudinal studies which follow patients over time. These studies are likely to have more clinical relevance and results will be more specifically related to clinical outcome, given that measures of both the hypothetical target and clinical outcome are obtained in the same population, and because they are longer term studies (weeks), especially important for relapse prevention agents. *Our third approach* will be to summarize the literature with studies that use rsFC and related metrics at a baseline time-points to find correlates of future overall relapse vulnerability or treatment outcome. Although this approach has an advantage in that markers identified are linked to future behavior, these studies will not indicate whether these rsFC markers are alterable with treatment. If they are static, and not alterable with any intervention, the marker would not be a treatment target. *The fourth approach* will be to review studies which overcome that

limitation by administering an intervention, thus getting at alterable biomarkers, and with this we will summarize the effects of interventions (both established and novel) on rsFC.

The second goal of this review will be to discuss future strategies to identify reliable treatment targets, and how this information might be used

In this section, we will discuss future research directions. First, we will highlight the need for more advanced prediction methods that utilize multivariate, data-driven approaches. Second, longitudinal datasets that link treatment outcomes with targeted engagement will confirm the translational significance and clinical relevance of this research. Third, we will emphasize the importance of controlling for withdrawal state and length of abstinence, and of using rsFC to identify moderators of treatment outcome to supplement precision medicine and treatment matching efforts.

In summary, this review is distinguishable from previous reviews in this subject area for several reasons. For one, we cover a broad range of SUD, not just NUD (Fedota & Stein, 2015) AUD (Wilcox *et al.*, 2014) or opiate use disorder (OUD) (Ieong & Yuan, 2017; Pandria *et al.*, 2016). Second, the majority of previous reviews have included cross-sectional studies focused on finding differences between SUD and HC populations (Fedota & Stein, 2015; Ieong & Yuan, 2017; Lu & Stein, 2014; Moeller *et al.*, 2016; Pandria *et al.*, 2016; Pariyadath *et al.*, 2016; Sutherland *et al.*, 2012; Wilcox *et al.*, 2014; Wilcox *et al.*, 2016). In this review, by contrast, we only include studies which investigate associations between rsFC and behavior within important psychological domains, withdrawal state, and treatment outcome in individuals with SUD. By doing so, we aim to more precisely identify potential treatment targets and to isolate markers contributing to perpetuation of the disorder from those caused by substance use.

Definitions

Resting state fMRI:

FMRI measures the blood oxygenation-level dependent (BOLD) signal in the brain. During a resting state scan, participants are asked and to relax and think about nothing in particular, usually over 5–12 minutes. It can be obtained during eyes open or eyes closed, but most studies use eyes open. New data indicates longer (up to 20 minutes) is better for control of motion artifact, and delineation of resting state networks for example, but most published data are on shorter scans (Glasser *et al.*, 2013). Data acquired at rest have been shown to correlate with both subsequent behavioral performance on a task and activation of brain regions that support task performance (Fedota & Stein, 2015).

Connectivity:

Connectivity analyses utilize information about fluctuation in the BOLD signal at low frequency over time and identify the degree of synchrony between regions (Fox & Raichle, 2007; Fox *et al.*, 2005). There are three major types of rsFC analysis: seed-based analyses, independent component analysis (ICA), and graph-theoretical analyses (Fedota & Stein, 2015). Seed-based analyses look at the correlation strength in the BOLD time courses between an a priori seed (either the size of a voxel or many voxels) over a particular area of

interest and the rest of the brain. Seed based analyses are usually hypothesis driven and anatomically-based (Fedota & Stein, 2015). ICA is a data-driven computational method to decompose an overall signal into independent, orthogonal components, segmenting the brain into large-scale components or networks that are generally well conserved across individuals and over time (Calhoun & Adali, 2012; Calhoun *et al.*, 2001). This can be a helpful step to reduce the many hundred thousand voxels to a more digestible number of components (typically 30, 75, or 100), which are based on functional similarities rather than anatomical ones (Calhoun & Adali, 2012; Fedota & Stein, 2015; Sutherland *et al.*, 2012). Correlation strengths between time series within these networks can be measured in the same fashion as they are done with seed based analyses (often called functional network connectivity rather than rsFC) providing analogous information (Allen *et al.*, 2010; Arbabshirani *et al.*, 2013; Wilcox, Calhoun, *et al.*, 2017). Analyses using ICA can be hypothesis driven as well as exploratory. For both seed-based and network-based analyses, synchrony between two regions or networks is usually represented by a positive value, and anticorrelation (or negative coupling) by a negative value. Therefore, in cases where there is an positive relationship between connectivity and a behavior, that could either indicate greater synchrony between two regions, or reduced anticorrelation. This is important because during normal brain functioning both correlation and anticorrelation is observed, depending on the networks being examined (Fox *et al.*, 2005). Graph-theoretical analyses can be performed at the voxelwise or seed-based level, or after parsing the brain activation into components (through ICA), and seek to characterize brain network topology to identify how connectivity density varies between a region or network and close or far regions of the brain (Fedota & Stein, 2015; Konova *et al.*, 2015; Morris *et al.*, 2018; J. Wang *et al.*, 2010). However, interpreting the somewhat abstract network parameters (e.g., modularity, small worldness, partition coefficient) from graph theory analyses, and relating them to brain systems that underlie known cognitive processes can be a challenge (Fedota & Stein, 2015). Global brain connectivity gets at a similar underlying process as graph theory analyses, analyzing connectivity between a particular region or network and some derived method, like averaging, to combine voxels in the whole brain (K. Wang *et al.*, 2014).

Methods:

We used PubMed to perform an extensive literature search using combinations of the following search terms: [substance OR cocaine OR methamphetamine OR stimulant OR opiate OR opioid OR alcohol OR nicotine OR marijuana OR cannabis OR smoking] AND [resting state OR connectivity OR fMRI]. Any intervention study that was either open label or placebo-controlled (including medication trials, neurostimulation trials, therapy trials), longitudinal studies, repeated measurement studies (i.e. during abstinent or deprived vs. satiated states), and studies which were cross sectional but also included in their study a measure of cognitive control (neuropsychological testing), impulsivity, anxiety, depression and emotion regulation, craving, subjective withdrawal, or evoked BOLD activity during a cognitive, cue reactivity, or emotional task) were included in this review. For the cross-sectional studies relating rsFC with functionality in important psychological domains, we focused on articles that have looked within SUD only, instead of including non-SUD, as rsFC changes associated with deficits in these domains can differ in SUD compared to HC

(Muller-Oehring *et al.*, 2014; Zhai *et al.*, 2015). Moreover, in this section we include subjective withdrawal with the craving and cue reactivity constructs because these are subjective composite measures of various symptoms which often include questions about craving. This is to be distinguished from the ensuing section in which we discuss effects of abstinence or deprivation vs. satiety on rsFC, which are different in that this next section involves within subjects analyses, and are objectively through an intervention (rather than subjectively) in a deprived state. For the studies examining effects of abstinence versus satiety, only studies performed in NUD were included (effects of nicotine on rsFC in brain function in healthy controls were excluded). To our knowledge, there are no studies in other SUD which have examined rsFC alterations during abstinent versus satiated states.

Important brain regions that underlie addictive behavior include the amygdala, hippocampus, parahippocampal gyrus, insula, cingulate cortex, prefrontal cortex, posterior cingulate cortex, striatum (dorsal and ventral, including caudate, putamen and nucleus accumbens) and ventral tegmental area (VTA) (Cabrera *et al.*, 2016; Kalivas & Volkow, 2005; Moeller *et al.*, 2016; Pandria *et al.*, 2016; Volkow & Baler, 2013a, 2013b; Wilcox *et al.*, 2014; Wilcox *et al.*, 2016). These regions also fall within particular brain networks including the default mode network (DMN), the executive control network (ECN), the salience network (SN) and the limbic and reward networks. The DMN is centered on nodes in the medial prefrontal cortex (mPFC) and the midline posterior cingulate cortex (PCC), and has been implicated in ruminations, mind wandering, planning the future, and reflections on the past (Anticevic *et al.*, 2012). The ECN is centered on nodes in the dorsolateral prefrontal cortex (dlPFC) and the lateral posterior parietal cortex, has been associated with attending to and processing exogenous, attentionally driven executive functions (Lerman *et al.*, 2014). The salience network (SN) is centered on nodes in the dorsal anterior cingulate cortex (dACC) and mid cingulate cortex (MCC) and the insular cortex and has been implicated in the facilitation of attentional orientation to internal or external stimuli (Lerman *et al.*, 2014; Muller-Oehring *et al.*, 2014). DMN is generally anticorrelated with the SN and ECN (Fox *et al.*, 2005; Lerman *et al.*, 2014; Wilcox, Claus, *et al.*, 2017). The reward network for the sake of this review will be defined as within striatum (nucleus accumbens, caudate and putamen), midbrain (VTA) or subgenual ACC (sgACC)/medial orbitofrontal cortex (mOFC), as has been defined in previous work (Janes *et al.*, 2012; Muller-Oehring *et al.*, 2014; Zhai *et al.*, 2015) (M.O-2014, Zhai 2015). Also, the sgACC/mOFC often falls into the DMN (Taylor *et al.*, 2013; Wilcox *et al.*, 2016) so for the sake of this review when findings are observed in the sgACC/mOFC we will label it both as a finding for the DMN network as well as for the reward network. Limbic networks will include amygdala, hippocampus, and parahippocampus. In Tables 1–4 (where results are presented), we report findings that occur either in one of our networks of interest, or, if the findings occur in a particular region, we simply report them as occurring within one of the networks of interest. For example, if there is a finding in the insula, we simply put it in our table as a finding relating to the SN. Likewise, we will also utilize the term “rsFC” in the text when grouping both seed-based rsFC and FNC measures, but the table indicates which studies utilized which approach.

Studies showing less anticorrelation or “reduced negative coupling” will be listed as “increased connectivity” in the tables, as this would be defined by a less negative number during connectivity analyses. This approached allowed for pooling of studies that did not

explicitly report whether a positive result came from reduced negative coupling or increased connectivity with those that were explicit. Therefore, when explicitly defined as reduced anticorrelation in a paper, we report this simply in the table as “Up”. When many results are reported (Muller-Oehring *et al.*, 2014; Zhu *et al.*, 2017), we only report the significant findings after correction for multiple comparisons.

We excluded studies which included only adolescents, and results related to task-related connectivity changes, non-connectivity based measures of resting state fMRI [for example fractional amplitude of low-frequency fluctuations (fALFF)], or within region connectivity. We did not review the literature on rsFC-based deficits which predate substance use, which has been reviewed in other work (Squeglia *et al.*, 2017). Finally, we only focused on graph-theory analysis in the text (no tabular representation) secondary to the paucity of studies.

Results:

Relationships between rsFC and functionality in relevant psychological domains (Table 1)

Cognitive control and impulsivity (Table 1):

Studies that examined relationships between self-reported impulsivity and concentration (Cole *et al.*, 2010; Contreras-Rodriguez *et al.*, 2016; Hobkirk *et al.*, 2018; Kohno *et al.*, 2016; McHugh *et al.*, 2013; Zhai *et al.*, 2015; Zhu *et al.*, 2017) performance on tasks of cognitive control (Berlingeri *et al.*, 2017; Camchong *et al.*, 2013b; Camchong *et al.*, 2013c; Contreras-Rodriguez *et al.*, 2015; McHugh *et al.*, 2017; Motzkin *et al.*, 2014; Muller-Oehring *et al.*, 2014; Pujol *et al.*, 2014; Whitfield-Gabrieli *et al.*, 2017), delay discounting (Contreras-Rodriguez *et al.*, 2015; Zhu *et al.*, 2017) activation during cognitive control tasks (Lerman *et al.*, 2014) or activation during risky decision making (Kohno *et al.*, 2014) were reviewed. Reduced within ECN connectivity (Camchong *et al.*, 2013c; Cole *et al.*, 2010; McHugh *et al.*, 2017; Zhai *et al.*, 2015) was found to relate to impaired functioning in these domains. Furthermore, elevated connectivity between DMN and both SN and ECN (Camchong *et al.*, 2011; Cole *et al.*, 2010; Lerman *et al.*, 2014; Muller-Oehring *et al.*, 2014; Whitfield-Gabrieli *et al.*, 2017; Zhu *et al.*, 2017) was observed. That elevated connectivity between DMN and ECN was associated with impairment is important because anticorrelation between DMN and ECN occurs during cognitive tasks, and reduced anticorrelation or impaired “negative coupling” would be reflected by a more positive connectivity value reflecting reduced functionality (Sutherland *et al.*, 2012). Furthermore, results show that reduced SN-ECN connectivity (Lerman *et al.*, 2014; Muller-Oehring *et al.*, 2014) was also associated with impairment, which is supported by findings from an additional study that did not fit criteria for inclusion in our review but, utilizing seed-regions derived from a group (NUD vs. healthy controls) contrast during a cognitive control task, also demonstrated reduced connectivity between insula (SN) and DLPFC (ECN) in smokers compared to controls (Fedota *et al.*, 2016). Finally elevated within reward network, within DMN, and between reward network and DMN connectivity (Berlingeri *et al.*, 2017; Camchong *et al.*, 2013c; Contreras-Rodriguez *et al.*, 2015; Contreras-Rodriguez *et al.*, 2016; Kohno *et al.*, 2014; Kohno *et al.*, 2016; Pujol *et al.*, 2014; Whitfield-Gabrieli *et al.*, 2017; Zhai *et al.*, 2015) was associated with higher levels of impairment. The only study that

conflicted, was a study in AUD (Zhu *et al.*, 2017), which showed reduced connectivity between mOFC (DMN and reward network in our methods) and both DMN and ECN, as well as elevated connectivity between SN and ECN in more impulsive individuals. However, this was a fairly small sample of AUD (n=25) and participants had been abstinent for a much shorter period of time (mean 16 days) compared to the other studies of AUD in this table (months of abstinence) (Camchong *et al.*, 2013b; Camchong *et al.*, 2013c; Muller-Oehring *et al.*, 2014).

Subjective withdrawal, craving and cue reactivity (Table 1):

Several studies have examined relationships between rsFC and subjective withdrawal severity (Cole *et al.*, 2010; Hobkirk *et al.*, 2018; Wilcox, Calhoun, *et al.*, 2017), craving (Bi *et al.*, 2017; Janes *et al.*, 2014; Kohno *et al.*, 2017; Lerman *et al.*, 2014; Sutherland, Carroll, Salmeron, Ross, & Stein, 2013; Yang *et al.*, 2017) and degree of drug cue reactivity while undergoing fMRI (Janes *et al.*, 2015). Elevated connectivity between ECN and both limbic and reward networks (Hobkirk *et al.*, 2018; Kohno *et al.*, 2017; Wilcox, Calhoun, *et al.*, 2017; Yang *et al.*, 2017) during higher levels of subjective craving or withdrawal is probably the most replicated finding. Except for one study (Sutherland, Carroll, Salmeron, Ross, & Stein, 2013) elevated connectivity of SN to both reward network and DMN is also associated with craving and subjective withdrawal (Bi *et al.*, 2017; Janes *et al.*, 2014; Kohno *et al.*, 2017; Lerman *et al.*, 2014; Wilcox, Calhoun, *et al.*, 2017), which would fit nicely with posited models that during craving or withdrawal states, the SN biases attention away from networks involved in staying on task (ECN) and towards other networks involved in processing interoceptive experience, (DMN), or wanting (reward network) (Lerman *et al.*, 2014; Sutherland *et al.*, 2012).

Emotion regulation, anxiety and depression (Table 1):

Very few studies have been done in this area. Reduced connectivity between ECN and SN (similar to the impulsivity and cognitive control literature summarized in Table 1) (Muller-Oehring *et al.*, 2014) and reduced connectivity between reward and limbic networks, between SN and reward, and between SN and DMN (Muller-Oehring *et al.*, 2014; Sutherland, Carroll, Salmeron, Ross, & Stein, 2013) are associated with impaired emotion regulation (alexithymia) (Sutherland, Carroll, Salmeron, Ross, & Stein, 2013) or higher levels of depression and anxiety (Muller-Oehring *et al.*, 2014). More work in this area needs to be done to draw any definitive conclusions about the rsFC correlates of emotion regulation and anxiety/depression within SUD.

Effects of nicotine abstinence on rsFC in smokers (Table 2)

Many studies have been performed in smokers to determine how rsFC changes during nicotine abstinence vs. satiety, by comparing individuals receiving nicotinic receptor agonists (such as nicotine or varenicline) with those receiving placebo (Cole *et al.*, 2010; L. Hong *et al.*, 2009; Sutherland, Carroll, Salmeron, Ross, Hong, *et al.*, 2013), by comparing individuals who have recently smoked a cigarette with those who were in a deprived state (Bi *et al.*, 2017; Cole *et al.*, 2010; Ding & Lee, 2013; Hobkirk *et al.*, 2018; Huang *et al.*,

2014; Lerman *et al.*, 2014; Sweitzer *et al.*, 2016), or through correlating changes in craving and changes in connectivity from abstinence to satiety (Cole *et al.*, 2010; Janes *et al.*, 2014).

There appear to be some common themes across studies. Abstinent states are associated with reductions in connectivity between SN and ECN or within ECN (Cole *et al.*, 2010; Ding & Lee, 2013; L. Hong *et al.*, 2009; Lerman *et al.*, 2014) and increases in connectivity between ECN and DMN (Cole *et al.*, 2010; Ding & Lee, 2013; Hobkirk *et al.*, 2018; Huang *et al.*, 2014) (the latter, perhaps, again, reflecting impaired anti-correlation). Moreover, abstinence is associated with elevated connectivity within the reward network and DMN networks, as well as between reward network and DMN (Cole *et al.*, 2010; Ding & Lee, 2013; Hobkirk *et al.*, 2018; Huang *et al.*, 2014; Janes *et al.*, 2014). These findings mirror those observed in the "cognitive control and impulsivity" section above. The only exception was seen in a study showing increases in connectivity between anterior and posterior hubs (sgACC/frontal pole/rostral ACC and PCC) of the DMN (L. Hong *et al.*, 2009) on nicotine compared to placebo, which could just have been spurious as it was a relatively small study (19 smokers). Finally, elevated connectivity between SN and both DMN and reward network is observed in numerous studies (Bi *et al.*, 2017; Ding & Lee, 2013; Hobkirk *et al.*, 2018; Huang *et al.*, 2014; Janes *et al.*, 2014; Lerman *et al.*, 2014; Sutherland, Carroll, Salmeron, Ross, Hong, *et al.*, 2013), again, nicely mirroring those observed in the "subjective withdrawal, craving and cue reactivity" section above. That rsFC changes associated with nicotine abstinence are similar to those seen with impaired cognitive control, impulsivity, craving or subjective withdrawal are not surprising, given the known beneficial effects of nicotine agonists on functioning within these psychological domains (Ashare & McKee, 2012; Atzori *et al.*, 2008; Barr *et al.*, 2008; Heishman *et al.*, 2010; L. E. Hong *et al.*, 2011; Kleykamp *et al.*, 2011; McClernon *et al.*, 2016; Rhodes *et al.*, 2012), and given that many of the studies in Table 1 were also in Table 2. Still, it is reassuring to see patterns replicate, and indicates we may be tapping into a true signal with these rsFC measurements.

On the whole, findings summarized in this section nicely support a theory that was proposed in the literature some years before much of these data were published, which posits that, during abstinence "…the insula" (SN) "interacts with DMN regions in the service of orienting attention to resolve this inner tumult and return the system to homeostasis, thereby shifting network dynamics and biasing processing towards the DMN and away from the ECN. This hypothesized shift in network dynamics during abstinence would result in one or more of the following observable changes in rsFC: 1) enhanced rsFC between insula and DMN; 2) reduced rsFC between insula and the ECN; 3) enhanced rsFC within the DMN; 4) reduced rsFC within the ECN; and 5) a breakdown in negative coupling between the DMN and ECN" (Sutherland *et al.*, 2012). In summary, these would seem to be important potential candidates for treatment targets for nicotine withdrawal. Whether these are also targets in other SUD remains to be explored.

One other study deserves mention whose methods were not directly applicable to those utilizing more traditional analysis approaches. This study indicated that withdrawal states were associated with higher global brain connectivity in the insula and superior frontal gyrus (K. Wang *et al.*, 2014). Future work could also explore this as a biomarker marker of withdrawal.

Baseline correlates of clinical outcome (Table 3)

Many studies have measured whether or not rsFC relates to treatment outcome at later time points, in an effort to find risk markers for increased lapse or relapse (Addicott *et al.*, 2015; Adinoff *et al.*, 2015; Berlingeri *et al.*, 2017; Camchong *et al.*, 2013a; Contreras-Rodriguez *et al.*, 2015; Janes *et al.*, 2010; Li *et al.*, 2015; McHugh *et al.*, 2014; McHugh *et al.*, 2017; Sweitzer *et al.*, 2016; Wilcox, Calhoun, *et al.*, 2017) greater substance use following treatment (Wilcox, Calhoun, *et al.*, 2017) or treatment dropout (Kohno *et al.*, 2017; Vaughn R Steele *et al.*, 2017), for example. These studies show that reduced connectivity within ECN or between SN and ECN relates to worse treatment outcome in a few studies (Camchong *et al.*, 2013a; Janes *et al.*, 2010; McHugh *et al.*, 2017; Wilcox, Calhoun, *et al.*, 2017). This mirrors what we saw in our section on “cognitive control and impulsivity” and “effects of nicotine abstinence on rsFC in smokers” above, which could indicate that this (reduced connectivity within ECN or between SN and ECN) might be a treatment target at various stages of recovery (during acute withdrawal and longer-term relapse prevention). Several studies have also found that lower connectivity between reward network (primarily striatum) and ECN correlate with worse treatment outcome (Berlingeri *et al.*, 2017; Kohno *et al.*, 2017; Sweitzer *et al.*, 2016). However, a single study found the opposite to be true, but only when measured in individuals with heightened subjective withdrawal at the time of the scan (Wilcox, Calhoun, *et al.*, 2017), highlighting the possibility that state effects may sometimes trump or override the trait effects from being properly measured, and should always be properly controlled for. Only a single study in SUD has used truly state of the art “prediction methods” (machine learning with cross validation), which is more likely to give accurate information on how the model will generalize to an independent dataset (Vaughn R teele *et al.*, 2017) but its results did not easily fit into the patterns from the other studies. One study which utilized methods precluding it from inclusion in the table demonstrated that relapse was associated with higher levels of eigenvector centrality in the DLFPC and cerebellum (Shen *et al.*, 2017). In summary, low connectivity within ECN and between SN and ECN could be explored further as possible markers.

rsFC changes as markers of treatment mechanisms in SUD treatment (Table 4)

Probably the most definitive way to determine whether something is a treatment target is to identify markers which, when altered, result in beneficial changes in behavior. Changes in rsFC in response to interventions which also cause reductions in clinically significant endpoints (substance use, dropout, or even craving) may indicate treatment targets. Many of the treatments which act as relapse prevention agents are also agonists at the same receptors on which the drug of abuse acts (or they act with the same directionality on the neurotransmitter systems of interest), and alleviate withdrawal Examples of these include many of the relapse prevention treatments for nicotine use disorder (varenicline, nicotine replacement therapy) and opioid use disorder (methadone). Therefore, several of the studies which were reviewed in Table 2 are brought back down here into this section if they were studies looking at effects of either nicotine replacement or varenicline on rsFC. Other relapse prevention medications and interventions work via different mechanisms, and these are included in this table as well.

Pooling together studies measuring effects of treatments (Wilcox & Bogenschutz, 2013) which are either established relapse prevention agents (in these cases nicotine replacement therapy or varenicline) (Cole *et al.*, 2010; L. Hong *et al.*, 2009; Sutherland, Carroll, Salmeron, Ross, Hong, *et al.*, 2013) or which are under investigation (Froeliger *et al.*, 2017; Karch *et al.*, 2015; Konova *et al.*, 2013; X. Li *et al.*, 2017; Wilcox *et al.*, 2015; Yang *et al.*, 2017) nicely mirror some of our previous findings and models. When identified, treatment was consistently associated with increases in connectivity within ECN and between ECN and SN (Cole *et al.*, 2010; L. Hong *et al.*, 2009; Karch *et al.*, 2015). Furthermore, reduced connectivity between DMN and ECN was observed in two studies in NUD (Cole *et al.*, 2010; X. Li *et al.*, 2017). These consistent with theoretical models that reduced connectivity in ECN and between ECN and SN and reduced anticorrelation between DMN and ECN are treatment targets (Sutherland *et al.*, 2012). Although by no means definitive, converging evidence support the possibility that changes in these particular markers in these directions may also portend clinical improvement.

Two additional studies to mention here are those looking at effects of long-term abstinence. Abstinence breeds abstinence, such that recovery in brain function contributes to greater ease staying abstinent or maintaining control (Wilcox *et al.*, 2014) and could in a sense be considered an intervention promoting recovery. In AUD and StimUD abstinence is also associated with increasing connectivity within ECN (Camchong *et al.*, 2013c; McHugh *et al.*, 2017) and decreasing connectivity within reward network (Camchong *et al.*, 2013c) or between nodes of the DMN (Ipser *et al.*, 2018) consistent with many the treatment effect findings mentioned above.

Two studies using alternative analysis approaches did not make it into the table. One was a study of the effect of naltrexone in AUD, and showed that treatment normalized heightened local efficiency (clustered and segregated network processing) associated with an AUD diagnosis (Morris *et al.*, 2018). Another study using similar methods in cocaine use disorder (Konova *et al.*, 2015) utilized global and local connectivity. Across participants, methylphenidate decreased short-range (local) functional connectivity density (FCD) in the thalamus/putamen, and decreased long-range (global) FCD in the supplementary motor area and postcentral gyrus. Therefore both of these studies indicate reductions in local efficiency to be associated with treatment, and [now bringing down a third study from the withdrawal section (K. Wang *et al.*, 2014)] combined with our knowledge that heightened global connectivity is associated with withdrawal these three studies together indicate that heightened global and local connectivity may be treatment targets across SUD.

Unfortunately too few studies have been done looking at effects of efficacious treatments on rsFC, and more work linking brain changes during treatment with downstream clinical effect of treatments is sorely needed. The field would benefit greatly from studies looking at changes in rsFC resulting from treatments which are known to work (naltrexone in AUD, varenicline in NUD, suboxone or methadone in OUD as examples) (Wilcox & Bogenschutz, 2013) and which also measure whether these rsFC changes mediate the effects of treatments on clinical outcome. This would establish which rsFC markers should be utilized in target engagement studies to test the potential efficacy of new compounds (e.g. which changes are true treatment targets).

Summary

In conclusion, we have found many studies that replicate important findings which can be used to focus future work in developing rsFC as a biomarker to inform addition treatment studies and perhaps (one day) deploying for use in clinical practice. First, deficits in cognitive control and impulsivity are associated with reduced connectivity within ECN and between ECN and SN, elevated connectivity between DMN and ECN (perhaps reflecting reduced anticorrelation), elevated connectivity between SN and both reward network and DMN, and elevated within reward network, within DMN and between reward network and DMN. Second, craving and subjective withdrawal are associated with elevated connectivity between ECN and both the reward and limbic networks, and elevated connectivity between SN and both DMN and reward network. Except for elevated ECN to limbic/reward network connectivity, these same findings are observed during abstinent or deprived states in individuals with NUD compared to satiated states, which is consistent with the known fact that nicotine withdrawal is associated with impairments in cognitive control and impulsivity as well as craving. Third, reduced connectivity within ECN and between SN and ECN at baseline also correlate with poorer treatment outcome in longitudinal studies. Finally, relapse prevention treatments which reduce substance use also tend to increase connectivity within the ECN, between the ECN and SN, and reduce (possibly reflecting increased anticorrelation) connectivity between the ECN and DMN. Converging evidence indicates that increasing connectivity within ECN, between SN and ECN, and possibly increasing anticorrelation between ECN and DMN could be associated with a healthier brain in SUD and better treatment outcomes. These patterns are consistent with the known roles of these networks in mediating cognitive control (Anticevic *et al.*, 2012; Lerman *et al.*, 2014).

Future directions

More robust prediction models needed for risk stratification:

The studies reviewed in Table 3 have advantages over cross sectional correlational analyses or group comparisons for treatment target identification and risk stratification because they are time-lagged, with the target being measured antecedent to the outcome. However these studies are still essentially correlational in nature and not true “prediction” studies (Abbott *et al.*, 2016). In the mental health field at large, studies which use standard regression or correlation analyses to investigate relationships between baseline signals and treatment outcomes, dubbed “post correlation” studies, are being called into question because they may inflate relationships if they are not retested in independent samples and are known to be overly optimistic about how a finding in a given data set will generalize to a new data set (for example, another set of patients), thereby lacking adequate sensitivity and specificity for clinical use (Abbott *et al.*, 2016; Vaughn R Steele *et al.*, 2017). The goal of cross validation is to define a dataset to “test” a predictive model in the training phase (i.e., the *validation set*), and then to investigate the predictive value of the model in a different sample, in order to limit problems like overfitting, and give an insight on how the model will generalize to an independent dataset. Testing generalizability can be accomplished by having larger patient groups in which a model developed for one group transfers usefully to a second, independent group (out of sample cross validation) (Whitfield-Gabrieli *et al.*, 2016).

However, this can be inefficient and requires large sample sizes. More efficient methods such as those that utilize leave one out cross-validation are gaining popularity. Leave-one out cross-validation loops through a sample and each subject is involved in both the model building and the testing phase (Vaughn R Steele *et al.*, 2017). Random forest methods achieve similar goals (Gowin *et al.*, 2015). Machine learning, support vector machine Gaussian process classification, and support vector regression are multivariate approaches that can be used in combination with cross validation (Kim *et al.*, 2015; Vaughn R Steele *et al.*, 2017). Studies using these kinds of state-of-the-art methods to predict substance use treatment outcomes are few (V. R. Steele *et al.*, 2014; Vaughn R Steele *et al.*, 2017), whereas other areas of mental health research have done much more work using these kinds of methods (Abbott *et al.*, 2016; Drysdale *et al.*, 2017; Jiang *et al.*, 2018; Kim *et al.*, 2015; Whitfield-Gabrieli *et al.*, 2016).

Data driven and multimodal approaches:

Most of the studies cited in this review employed seed-based analyses and are often hypothesis-driven. This leaves out significant amounts of data from analyses, and this excluded data may have predictive importance. In future studies using resting state analyses, more whole brain and data-driven approaches should be utilized. When done so, in combination with true “predictive” models as described above like with multivariate pattern analysis (Vaughn R Steele *et al.*, 2017; Thijssen *et al.*, 2017; Whitfield-Gabrieli *et al.*, 2016) we are likely to identify more reliable and generalizable markers, with a higher potential for clinical utility. Integrating other measures in with self-report, neurocognitive, DTI, structural, task-based fMRI and/or task-based functional connectivity or task-based network analyses (multimodal approaches) could also improve accuracy of prediction models (Drysdale *et al.*, 2017; Kim *et al.*, 2015) although the more data-collection is necessary, the less clinical applicability it may have, due to increasing complexity. Genetic markers may influence rsFC, and so interaction effects may need to be taken account to optimize predictive models (S. Li *et al.*, 2017; Zhu *et al.*, 2015).

Other ways to analyze resting state data:

Other analysis approaches which have not been utilized in SUD can also be explored, which may reveal different underlying functional changes. These kinds of analyses include fALFF (X. Li *et al.*, 2017) power spectra (Thijssen *et al.*, 2017) and dynamic FNC (Pariyadath *et al.*, 2016; Vergara *et al.*, 2018).

More longitudinal datasets:

The argument to use healthy controls to understand pathological brain function in psychiatric disease is to control for rsFC variability and to establish a normal reference range. However, cross-sectional studies comparing healthy controls to SUD are problematic for treatment target identification because findings are over-inclusive. However, studies comparing SUD to HC could provide more important insights especially if they utilize longitudinal designs, by assessing several SUD groups at different time points since last use, as has been done in some studies (K. Wang *et al.*, 2014). Many investigations have assessed the relationship between changes in NUD deprivation state and rsFC. However, the literature linking these changes with treatment outcomes or relapse risk is still sparse. Furthermore,

aside from a few studies in the each of the other SUD drug classes, few studies have investigated the impact of withdrawal treatment or relapse prevention treatment on rsFC or focused on defining the rsFC markers which relate most strongly to treatment outcome.

rsFC for precision medicine in SUD:

In other medical fields, such as internal medicine, laboratory tests (objective markers) can be used to guide treatment decision making. For this reason, internists can identify people more likely to respond to one treatment over another and stratify risk. Furthermore, the sensitivity and specificity of these tests are often well-established. Within mental health, biomarkers have yet to be useful for clinical decision making. Precision medicine is now a major priority within NIH and the general psychiatry and SUD treatment fields (Dishman, 2018). Within other mental health disorders, simply finding a biomarker to help determine diagnosis may be all that is needed to guide treatment selection and improve efficacy. However, SUD are heterogeneous, even within drug categories. Biomarkers that identify an overall vulnerability for relapse, or relapse risk for a specific treatment, will inform and individualize treatment plans. What might be a treatment target for one SUD subtype may not be for another (Kwako *et al.*, 2015). Several studies in SUD using non-rsFC based markers have been published and show some success in identifying possible treatment matching characteristics (Bogenschutz *et al.*, 2009; Haass-Koffler *et al.*, 2017; Mann *et al.*, 2014; Roos *et al.*, 2017; Wilcox & Bogenschutz, 2013), although validation of these findings in independent samples and determination of sensitivity and specificity is needed before deployment into clinical practice. Future work might employ methods that have been performed previously, such as investigating whether rsFC moderates response to a medication relative to placebo (Wilcox, Calhoun, *et al.*, 2017) or define subtypes by using a clustering procedure on rsFC to then see whether membership in a particular cluster predicts differential response to one medication over another (Drysdale *et al.*, 2017). Continued efforts to identify biological mechanisms of treatment (Table 4) will contribute to future treatment matching study hypotheses as well. For example, a medication that improves cognitive control or related biomarkers (i.e. within ECN rsFC) would hypothetically work best in someone with impaired executive control (reduced within-ECN rsFC) at baseline.

Controlling for withdrawal state and length of abstinence:

As we have seen in this review, abstinence, or the withdrawal state, in NUD is associated with changes in rsFC, and these changes are remarkably consistent across studies. Therefore, our review shows that withdrawal state *absolutely* needs to be controlled for during scanning in NUD, and whenever possible homogeneous groups with specific criteria regarding time since last use should be recruited, as connectivity is clearly altered between abstinent and satiated states and these effects may obscure important treatment targets (Wilcox, Calhoun, *et al.*, 2017). Unfortunately, other than in NUD, none of the other SUD neuroimaging research has explored this relationship between withdrawal state and changes in rsFC. In many of the other SUD (e.g. alcohol, stimulant) individuals are often some days or weeks abstinent or score low on withdrawal scales at the time of their scans. However, studies in AUD show that not only withdrawal but also time abstinent (over weeks) should be taken into account as rsFC changes over longer time periods as well (Camchong *et al.*, 2013c). Regarding the similarity between rsFC during deprived states in NUD and impaired

functioning within psychological domains like impulsivity, cognitive control, and craving, it is reasurring to see findings converge. However, because of the overlap, it will still be essential to control for withdrawal state when trying to isolate the rsFC markers of craving, cue reactivity, cognitive control and impulsivity in future work, which only some studies in this area have done up to now. In order to be methodical about developing new treatments, neural changes related to acute withdrawal (and easily reversible with either time abstinent or with available treatments like the nicotine patch in NUD or methadone in OUD and other direct agonists) will need to be distinguished from those that persist following treatment of withdrawal and requiring treatment with a longer-term relapse prevention agent.

rsFC to parse one SUD drug class from another and to identify characteristics that bridge drug classes:

Certain aspects of susceptibility to addiction are independent of the type of drug (Agrawal & Lynskey, 2008) and the mesocorticolimbic system may play a similar role in the development of SUDs involving all classes of drugs (Koob & Volkow, 2010; Pariyadath *et al.*, 2016). This is mirrored in the treatment literature, in that some medications appear to work in several SUD (topiramate/zonisamide, varenicline) whereas others are drug-specific (methadone) (Litten *et al.*, 2013; Wilcox & Bogenschutz, 2013). Acknowledging that there may be neural alterations both unique to each drug class and that span drug classes, there has been a growing push to both compare individuals with different SUD profiles to one another, while also looking at overlapping effects (Vergara *et al.*, 2017; Vergara *et al.*, 2018). Results from work in this area indicate hypo-connectivity among salience, sensory, and visual networks in both AUD and NUD, but increased connectivity in AUD compared to controls within the reward system, and hypo-connectivity between thalamus and putamen and hyper-connectivity between precuneus and left angular gyrus in NUD compared controls (Vergara *et al.*, 2017). Doing a similar type of analysis but to predict treatment outcome rather than diagnostic category alone could help inform hypotheses about treatment targets that are cross-class versus unique to one class, and could inform treatment development.

Issues of clinical applicability:

Whether imaging results provide additional predictive value above and beyond that available with clinical data remains to be seen, and this is necessary to justify the additional cost of imaging. For example, although higher connectivity between dACC and insula had been identified in several studies as a marker of better treatment outcome if NUD severity was controlled for using the Fagerstrom test of nicotine dependence, when baseline smoking quantity was used as a covariate instead (Addicott *et al.*, 2015; Heatherton *et al.*, 1991; Janes *et al.*, 2010; Wilcox, Calhoun, *et al.*, 2017), the relationship between dACC to insula rsFC and treatment outcome disappeared, indicating that the imaging did not add additional predictive value.

Limitations

There are several limitations to note regarding our approach. First, in order to try to simplify and identify replicating patterns, we chose to group regional findings into particular networks. Some of our choices were necessarily somewhat arbitrary (this was not a meta-

analysis) and could be challenged. For example, including mOFC/sgACC into both DMN and reward networks may not have been an approach that others would have advocated (other research has considered this region its own network) (Zhu *et al.*, 2017). However, in the end, our approach identified replicating patterns across sections of the paper, and for this reason was probably a successful strategy and provided some insight into our main questions of interest. Furthermore, we did not focus on some potentially important regions and regions including the primary and premotor cortex, primary somatosensory cortex, cerebellum, visual areas, inferior frontal gyrus and thalamus which may play important roles in SUD severity (Addicott *et al.*, 2015; Janes *et al.*, 2010; Moeller *et al.*, 2016; Muller-Oehring *et al.*, 2014; Pandria *et al.*, 2016).

Conclusions

In summary, through our review of the literature, reduced ECN-SN connectivity and within ECN rsFC show promise as being treatment targets for SUD. Furthermore, although less consistent, elevated within DMN, within reward network, and DMN to reward network rsFC, elevated DMN-SN connectivity, as well as reduced anticorrelation between DMN and ECN, are possible treatment targets. Replication and validation of findings in independent datasets, more longitudinal studies in all SUD, more state-of-the-art data-driven and generalizable prediction analyses, and consistent controlling for withdrawal state and time abstinent are needed to move the field forward.

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Highlights

- Resting state functional connectivity (rsFC) is altered in substance use disorder
- Reduced rsFC within executive control network (ECN) may be a treatment target
- Reduced rsFC between ECN and salience network (SN) may be a treatment target
- Withdrawal state profoundly affects rsFC and needs to be controlled for in research
- More research using data-driven longitudinal prediction analyses are needed

Table 1.

Relationships between rsFC and functionality in relevant psychological domains Impaired function/high vulnerability is associated with …

				Within				Between								
	Dx	**Study**	**N/|Effect Sizes|**	**Rew**	**DMN**	**SN**	**ECN**	**Lim and ECN**	**Rew and Lim**	**Rew and ECN**	**Rew and SN**	**DMN and SN**	**DMN and Rew**	**DMN and Lim**	**DMN and ECN**	**SN and ECN**
Low Cognitive Contro l/ High Impulsive	NUD	Lerman 2014	37/r=0.7[2]									Up				Down
		Cole 2010	17/r=0.6[2]				Down								Up	
		Hobkirk 2018	9/r=0.7–0.8[2]							Up			Up			
	AUD	*Muller-O. 2015*	27/r=0.5													Down
		Zhu 2017	25/r=0.5–0.7							Down		Up	Down		Down/Up	Up
		Camchong 2013c	27/rho= 0.4	Up			Down									
		Camchong 2013b	23/r=0.6							Up						
	StUD	Contreras-R. 2015	20/r=0.7–0.8	Up						Up			Up			
		Contreras-R. 2016	20/r=0.6		Up								Up			
		McHugh 2013	66[1]/r=0.3								Down					
		McHugh 2017	58[1]/r=0.4–0.5				Down									
		Berlingeri 2017	18/not avail.	Up							Up					
		Kohno 2016	19/r=0.3	Up												
		Camchong 2011	27/r=0.3–0.4							Up					Up	
		Kohno 2014	25 not avail.	Up						Down						
	CaUD	Whitfield-G. 2017	12/r=0.6		Up										Up	
		Pujol 2014	28/r=0.9		Up											
	OUD	Zhai 2015	20/r=0.6	Up			Down						Up			
	SUD	Motzkin 2014	40[1]/r=0.4–0.5							Down						
High Cue Reactivity	NUD	Janes 2015	17/not avail.			Up										
High Craving/Subjective W/d	NUD	Wilcox 2017 *	144/rho= 0.2							Up	Up	Up				
		Sutherland 2013	24/r=0.6								Down	Down				
		Yang 2017	32/r=0.5[2]					Up								
		Hobkir k 2018	9/r=0.7–0.8[2]							Up			Up			
		Cole 2010	17/r=0.6[2]				Down								Up	
		Bi 2017	33/r=0.5[2]									Up				

				Within				Between								
	Dx	**Study**	**N/|Effect Sizes|**	**Rew**	**DMN**	**SN**	**ECN**	**Lim and ECN**	**Rew and Lim**	**Rew and ECN**	**Rew and SN**	**DMN and SN**	**DMN and Rew**	**DMN and Lim**	**DMN and ECN**	**SN and ECN**
		Janes 2014	17/not avail.[2]	Up	Up						Up	Up	Up	Up		
		Lerman 2014	37/r=0.7[2]									Up				Down
	AUD	Kohno 2017	27/0.5–06					Up			Up					
		Kohno 2017	18/0.5													Up
High Anx/High Dep/Impaired ER	NUD	Sutherland 2013	24/r=0.5								Down	Down				
	AUD	*Mueller O. 2015*	27/r=0.5–0.6						Down							Down

Studies listed in italics did not utilize network based approaches but performed regions of interest/seed-based analyses instead. For these studies, results applying to particular brain regions which fell anatomically within one of these networks (as defined in the “Definitions” section of this paper) are displayed in this table as if they occurred in a network.

*This study used functional network connectivity rather than functional connectivity.

[1]Both healthy controls and individuals with cocaine use disorder were included in these correlation analyses. In all other studies sample and effect sizes are reported for the SUD groups only.

[2]These effect sizes were derived from change scores (over time). All other studies utilized a single time point.

N=sample size

r=Pearson’s correlation coefficient

rho=Spearman’s rho

Rew=reward

Lim=limbic

ECN=executive control network

SN=salience network

DMN=default mode network

Dx=diagnosis

NUD=nicotine use disorder

AUD=alcohol use disorder

StUD=stimulant use disorder

CaUD=cannabis use disorder

OUD=opiate use disorder

SUD=substance use disorder (poly substance use disorder)

Up=elevated connectivity in these circuits were reported

Down=reduced connectivity in these circuits were reported

W/d=withdrawal

High Anx=high anxiety

High Dep=high depression

ER=emotion regulation

Ambiguous citations:

Wilcox 2017 = Wilcox CE, Claus, ED, Calhoun, VD, Rachakonda, S, Littlewood, RA, Mickey, J, Arenella, PB, Goodreau, N, & Hutchison, KE (2017) Default mode network deactivation to smoking cue relative to food cue predicts treatment outcome in nicotine use disorder. Addict Biol.

Sutherland MT, Carroll, AJ, Salmeron, BJ, Ross, TJ, & Stein, EA (2013) Insulas' functional connectivity with ventromedial prefrontal cortex mediates the impact of trait alexithymia on state tobacco craving. Psychopharmacology (Berl) 228(1): 143–155.

Table 2.

Resting state functional connectivity during abstinence vs. satiated states Abstinence is associated with…

			Within				Between									
Dx	**Study**	**N**	**Rew**	**ECN**	**SN**	**DMN**	**Rew and ECN**	**DMN and ECN**	**ECN and Lim**	**SN and Lim**	**SN and Rew**	**DMN and SN**	**SN and ECN**	**Rew and Lim**	**DMN and Rew**	**DMN and Lim**
NUD	Sutherland 2013	24			Up					Up	Up	Up				
	Janes 2014	17	Up			Up					Up	Up			Up	Up
	Lerman 2014	37										Up	Down			
	Hobkirk 2018	9	Up				Up	Up			Up	Up				
	Bi 2017	33										Up				
	Hong 2009	19				Down							Down			
	Cole 2010	17		Down		Up	Up	Up					Down			
	Huang 2014	11				Up		Up				Up				
	Sweitzer 2016	37												Down	Down	
	Ding 2013	21			Up	Up		Up	Up			Up	Down			

Studies listed in italics did not utilize network based approaches but performed regions of interest/seed-based analyses instead. For these studies, results applying to particular brain regions which fell anatomically within one of these networks (as defined in the “Definitions” section of this paper) are displayed in this table as if they occurred in a network.

Rew=reward

Lim=limbic

ECN=executive control network

SN=salience network

DMN=default mode network

Dx=diagnosis

NUD=nicotine use disorder

Up=elevated connectivity in these circuits were reported

Down=reduced connectivity in these circuits were reported

Ambiguous Citations:

Sutherland 2013 = Sutherland MT, Carroll, AJ, Salmeron, BJ, Ross, TJ, Hong, LE, & Stein, EA (2013) Down-regulation of amygdala and insula functional circuits by varenicline and nicotine in abstinent cigarette smokers. Biol Psychiatry 74(7): 538–546.

Table 3.

Baseline correlates of clinical outcome. Worse outcome is associated with…

			Within				Between								
Dx	**Study**	**N/|Effect size|**	**Rew**	**ECN**	**SN**	**DMN**	**ECN and Lim**	**Rew and ECN**	**Rew and SN**	**SN and ECN**	**DMN and Rew**	**DMN and SN**	**DMN and Lim**	**SN and Lim**	**DMN and ECN**
NU D	Wilcox 2017 ***	144/beta=0.2			Down *										
	Wilcox 2017 *** Hi wd	72/beta=0.4						Up	Up						
	Wilcox 2017 *** Lo wd	71/beta=0.2		Down											
	Addicott 2015	85/r=0.4			Down				Down						
	Janes 2010	21/r=0.5	Down		Down					Down	Down	Down			
	Sweitzer 2016 **	37/r=0.5	Down					Down	Down		Down				
StU D	Contreras-R. 2015	20/r=0.7	Up								Up				
	McHugh 2014	45/r=0.3											Down		
	Adinoff 2015	40/r=0.7											Up		
	McHug h 2017	43/r=0.3–0.4		Down						Down					
	Berlingeri 2017	18/not reported						Down	Down						
AU D	Kohno 2017	43/r=0.1	Up				Up	Down	Up						
	Camchong 2013a	69/r=0.4	Down	Down					Down		Down				Down
OUD	Li 2015	26/r=0.7				Up/Down									
SUD	Steele 2017 ***	139/not reported			Up				Down		Down		Down	Down	

Studies listed in italics did not utilize network based approaches but performed regions of interest/seed-based analyses instead. For these studies, results applying to particular brain regions which fell anatomically within one of these networks (as defined in the “Definitions” section of this paper) are displayed in this table as if they occurred in a network.

*This association was only significant if baseline smoking was not included as a covariate.

**This study was unique from the others in that the predictor was change in functional connectivity rather than functional co nnectivity at a particular time point.

***This study used functional network connectivity rather than functional connectivity.

Rew=reward

Lim=limbic

ECN=executive control network

SN=salience network

DMN=default mode network

Dx=diagnosis

NUD=nicotine use disorder

StUD=stimulant use disorder

AUD=alcohol use disorder

OUD=opioid use disorder

SUD=substance use disorder

lo wd=individuals self-reporting low levels of withdrawal

hi wd=individuals self-reporting high levels of withdrawal

Ambigouos citations:

Camchong 2013a = Camchong J, Stenger, A, & Fein, G (2013a) Resting-state synchrony during early alcohol abstinence can predict subsequent relapse. Cereb Cortex 23(9): 2086–2099.

Wilcox 2017 = Wilcox CE, Claus, ED, Calhoun, VD, Rachakonda, S, Littlewood, RA, Mickey, J, Arenella, PB, Goodreau, N, & Hutchison, KE (2017) Default mode network deactivation to smoking cue relative to food cue predicts treatment outcome in nicotine use disorder. Addict Biol.

Table 4:

Pre-Post Treatment (in treatments that show clinical benefit). Treatment causes.…

			Within			Between								
Dx	**Study/Intervention**	**N**	**Rew**	**ECN**	**DMN**	**ECN and Lim**	**Rew and ECN**	**DMN and ECN**	**SN and Lim**	**DMN and SN**	**SN and ECN**	**DMN and Rew**	**DMN and Lim**	**Rew and Lim**
NUD	*Froeliger 2017/Mindfulness*	18	Up		Up							Up		
	Yang 2017/tDCS	32				Down								
	Sutherland 2013/Varen&NRT *	24							Down	Down				
	Hong 2009/NRT *	19			Up						Up			
	Cole 2010/NRT *	17		Up	Down		Down	Down			Up			
	Li 2017/rTMS	10						Down						
AUD	*Wilcox 2014/Loraz&Disu lf*	7					Down							
	Karch 2015/Neurofeedbk	13		Up		Up	Up			Up	Up			
StUD	*Konova 2013 Methylphen*	18	Up/Down			Up			Down	Up		Up	Up	Up/Down

Studies listed in italics did not utilize network based approaches but performed regions of interest/seed-based analyses instead. For these studies, results applying to particular brain regions which fell anatomically within one of these networks (as defined in the “Definitions” section of this paper) are displayed in this table as if they occurred in a network.

*Thesee are studies which utllized a well-established relapse prevention agent (as opposed to a novel/experimental relapse prevention agent).

Rew=reward

Lim=limbic

ECN=executive control network

SN=salience network

DMN=default mode network

Dx=diagnosis

NUD=nicotine use disorder

StUD=stimulant use disorder

AUD=alcohol use disorder

tDCS=transcranial direct current stimulation

Varen=varenicline

NRT=nicotine replacement therapy

Loraz=lorazepam

Disulf=disulfiram

Methylphen=methylphenidate

Nerurofeedbk=neurofeedback

Ambiguous Citations:

Li 2017 =Li X, Du, L, Sahlem, GL, Badran, BW, Henderson, S, & George, MS (2017) Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex reduces resting-state insula activity and modulates functional connectivity of the orbitofrontal cortex in cigarette smokers. Drug Alcohol Depend 174: 98–105.

Sutherland 2013 = Sutherland MT, Carroll, AJ, Salmeron, BJ, Ross, TJ, Hong, LE, & Stein, EA (2013) Down-regulation of amygdala and insula functional circuits by varenicline and nicotine in abstinent cigarette smokers. Biol Psychiatry 74(7): 538–546.