Addictions NeuroImaging Assessment (ANIA): towards an integrative framework for alcohol use disorder

Short title: Addictions Neuroimaging Assessment

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Abstract

Alcohol misuse and addiction are major international public health issues. Addiction can be characterized as a disorder of aberrant neurocircuitry interacting with environmental, genetic and social factors. Neuroimaging in alcohol misuse can thus provide a critical window into underlying neural mechanisms, highlighting possible treatment targets and acting as clinical biomarkers for predicting risk and treatment outcomes. This neuroimaging review on alcohol misuse in humans follows the Addictions Neuroclinical Assessment (ANA) that proposes incorporating three functional neuroscience domains integral to the neurocircuitry of addiction: incentive salience and habits, negative emotional states, and executive function within the context of the addiction cycle. Here we review and integrate multiple imaging modalities focusing on underlying cognitive processes such as reward anticipation, negative emotionality, cue reactivity, impulsivity, compulsivity and executive function. We highlight limitations in the literature and propose a model forward in the use of neuroimaging as a tool to understanding underlying mechanisms and potential clinical applicability for phenotyping of heterogeneity and predicting risk and treatment outcomes.

Key words: neuroimaging, alcohol use disorder, alcohol dependence, binge drinking, MRI, PET

1. Introduction

Alcohol misuse and addiction are major international public health issues with high associated morbidity and mortality (Kwako *et al.*, 2016). Alcohol addiction can be characterized as a disorder of neurocircuitry interacting with environmental and social factors. Treatment interventions are only moderately effective and underutilized. Critically, neuroimaging can provide important mechanistic insights and act as potential clinical biomarkers for predicting risk and therapeutic outcomes and define novel treatment targets.

This review adheres to the Addictions Neuroclinical Assessment (ANA) (Kwako *et al.*, 2016) focusing on a neuroimaging review of alcohol misuse, as an exemplar of neuroimaging in addictions neuroscience. Thus, we do not include the many neuroimaging studies on other drugs of abuse or on process addictions, e.g., gambling. Here, we review multiple imaging modalities (task-based functional magnetic resonance imaging (fMRI) and the neuropharmacology of positron emission tomography imaging and integrate with both resting state network and anatomical approaches) focusing on the neurocircuitry of alcohol misuse in the human brain examining macrostructure and neurochemical modulators and cognitive processes that underlie functional network impairments. We address the stages of alcohol misuse including binge drinkers who are at elevated risk for developing subsequent alcohol dependence (AD), heavy alcohol users, non-treatment seeking AD and abstinent AD along with unaffected subjects with a family history of AD.

We focus on a prominent theoretical framework (Koob and Le Moal, 1997) elaborated in the ANA (Kwako *et al.*, 2016) where addiction is conceptualized as a process comprised of 3 stages i.e., binge/intoxication, withdrawal/negative and preoccupation/anticipation. Using this framework, the pathophysiology of addiction is thought to reflect as an increase in the incentive salience of alcohol-related stimuli and pathological habits in the *binge/intoxication* stage, negative emotional states in the *withdrawal/negative affect* stage, and executive function deficits in the *preoccupation/anticipation* stage, which together provide a

powerful impetus for compulsive drinking (See Fig. 1 for proposed integration of cognitive domains and addiction cycle).

Insert Figure 1 here

These domain dysfunctions correspond to allostatic neuroadaptations in three key neurocircuits, respectively: basal ganglia, extended amygdala, and prefrontal cortex (Koob and Volkow, 2016). Allostatic adaptations maintain stability via changes in the brain but in a non-homeostatic manner. An eventual transition into an allostatic state suggests a chronic disequilibrium in a regulatory system from its 'normal' homeostatic state, for example, threshold changes for certain hedonic mood states reach low allostatic points following repeated drug use (Koob *et al.*, 2014). Interacting with these allostatic neural and functional adaptations are developmental (exposure to abuse, stress, or alcohol), genetic, and epigenetic factors that convey vulnerability to the initiation and maintenance of addiction and relapse. Thus, alcohol use disorder can be considered as a neural-network disorder with abnormalities primarily in basal ganglia, extended amygdala and prefrontal cortex which are also reported in macrostructural and functional imaging studies. (See Fig. 2 for an extended neural-circuit model and integration of functional and structural imaging studies in alcohol misuse).

Insert Figure 2 here

The neuroimaging literature mostly focuses on cognitive domains, (e.g., compulsivity and executive function); here we emphasize the importance of negative affect and the allostatic shift (where alcohol becomes a negative reinforcer) in understanding addiction mechanisms, (Koob *et al.*, 2014) as motivational, affective and cognitive processes are indeed interconnected. These allostatic neuroadaptations can functionally lead to higher tolerance, reduced rewarding responses to alcohol, and increased withdrawal-related negative affect (Koob and Volkow, 2016), which in turn lead to compulsive alcohol consumption. We further address the imaging-related dimensional

neuropsychological constructs of addiction highlighted in a recent international expert consensus study (Yücel *et al.*, 2019) including aspects of reward processing (expectancy, cue value, associative learning), cognitive control (including impulsivity and compulsivity constructs) and executive dysfunction (including working memory). A critical question is how cognitive processes underpinning the task-based fMRI studies might underlie the stages of alcohol misuse. Each of the addiction cycle components is discussed in the next sections and we conclude by highlighting the neuroimaging limitations to date and here we propose a model for the use of neuroimaging in addictions neuroscience. Although we propose that specific cognitive processes may be associated with particular stages of the addiction cycle, we note that this proposed model requires further systematic evaluation of the specificity of the association. We also emphasize that these processes are not necessarily only confined to the proposed cycle component but as discussed below may be more relevant within specific components of the addiction cycle.

2. Methodology

The following Medline search strategy was used and updated to October 2019: (alcohol dependence or alcohol abuse or alcohol use disorder or binge drinking) in the following combinations: AND PET; AND (connectivity or resting state or diffusion tensor imaging or MRS or spectroscopy or SPECT or voxel based morphometry or cortical thickness or perfusion or ASL); AND (incentive or salience or emotion or reward or punishment or monetary incentive delay or inhibition or discounting or impulsivity or compulsivity or reversal or habit or set shifting or attentional bias or stroop or cue reactivity or effort or motivation or relapse or abstinence or endophenotype) AND MRI]; AND (delay discounting or premature responding or go no go or ssrt or stop signal or stroop or impulsivity or response inhibition or waiting impulsivity or reflection impulsivity or risk taking or uncertainty) AND MRI; AND MRI NOT (previous specific search terms for imaging techniques or cognitive processes); limited to Human research and English articles. A search specifically for abstracts from the IMAGEN data set was also conducted. The abstracts were screened and limited to

sample sizes of at least 25 target and 25 healthy controls although lower sample sizes for PET imaging were allowed and if few studies were available for the category. Magnetic resonance spectroscopy studies were not included. After abstract screening at least 2 coauthors reviewed and approved further selection of articles. In cases where a meta-analysis or mega-analysis had been published, the smaller publications on the same topic were not included. Table 1 summarizes the task-based fMRI papers discussed in this review (not including genetic studies).

Insert Table 1 here

3. Stages of the Addiction cycle

We organize this review within the context of a model of correspondence between stages of the addiction cycle and cognitive mechanisms and representative imaging modalities. We note that further studies are required to assess the specificity and overlap of these mechanisms and addiction stage in human studies.

3.1 Stage 1: Binge/ Intoxication

3.1.1 *Reward anticipation*

Alcohol consumption has rewarding properties in both animals and humans driven by enhanced dopamine and opioid transmission in the basal ganglia and extended amygdala (Koob and Volkow, 2016). Human imaging studies of acute alcohol administration demonstrate direct evidence of a release of dopamine (Martinez *et al.*, 2005) and opioid peptides (Mitchell *et al.*, 2012) in the nucleus accumbens (NACC), that reflect the initial hedonic and subjective positive effects. In non-treatment seeking AD subjects, intravenous alcohol increased dopamine release in the right ventral striatum (VS) compared to social drinkers (Yoder *et al.*, 2016). Incentive salience, the process by which a neutral stimulus gains incentive value, is mediated by ventral striatal dopaminergic transmission. This conditioned reinforcement of alcohol consumption engenders a behavioral approach response that may represent maladaptive craving in alcohol

dependence (George and Koob, 2017). We propose here that reward anticipation may be highly relevant to triggering or facilitating bingeing behaviors. We further note that reward anticipation may be relevant across the addiction cycle. For example, reward anticipation may be secondary to negative emotionality driving compensatory behaviors to manage the reduced reward from alcohol, or may be related to cue- or stress-induced relapse or reactivity driving secondary reward anticipation. In this section we focus on reward anticipation including the context of the risk towards developing binge drinking behaviors in adolescents.

A very commonly used paradigm to assess reward anticipation is the monetary incentive delay (MID) task. The MID has been extensively studied in healthy controls and substance use disorders with a meta-analysis across substance use disorders (including 5 studies with 4 abstinent AD studies) showing decreased striatal activity during reward anticipation and increased VS activity during reward outcome (Luijten *et al.*, 2017). Neural activity to the MID has been used as a biomarker for pharmacological response in abstinent AD: the D3 antagonist GSK598809 normalized the blunted VS response and enhanced response in the D3 receptor rich ventral pallidum and substantia nigra (Murphy *et al.*, 2017). Notably these studies have predominantly used monetary reward as the anticipated reward outcome; however, in a study using alcohol sips as the anticipated outcome, there were no differences observed between light, heavy and non-treatment seeking AD subjects (Groefsema *et al.*, 2019). Whether protracted abstinence might influence the anticipation of alcohol outcome remains to be investigated.

The relative role of reward-related ventral striatal activity and threat-related amygdala activity has been investigated in the initiation of drinking. Adolescents with early drinking initiation have greater lifetime stress and greater amygdala activity but not VS activity (Elsayed *et al.*, 2018). Undergraduate students who develop problem drinking in the context of stress, show either high VS and low amygdala reactivity mediated by impulsivity and greater delay discounting or

low VS and high amygdala reactivity mediated by anxious-depressive symptomatology (Nikolova *et al.*, 2016).

Studies with large sample sizes have started to elucidate the population heterogeneity factors predicting aberrant alcohol-related behaviors using a hypothesis-free statistical approach. The IMAGEN multi-site study investigated 2000 14 year olds with re-testing at age 16 and 19 to develop predictive psycho-neurobiological models of the development of psychiatric disorders (Schumann *et al.*, 2010). In the IMAGEN cohort, factor analysis including neural activity related to reward anticipation using the MID, personality and behavioural variables such as impulsivity, extraversion, risk-taking and delay aversion predicted an acceptable proportion of variance in the initiation of early drinking. However, the contribution of neural markers alone to the predictive accuracy of the model was marginal relative to that of personality variables. The authors thus concluded that the initiation of alcohol misuse is primarily guided by personality variables, whereas aberrant neural responses to reward anticipation might play a bigger role in the establishment of an addiction (Nees *et al.*, 2012). In a comparison of adolescents with or without a positive family history of AD, an alternate means of assessing trait risk, there were also no differences in neural activity to reward anticipation on the MID task (Müller *et al.*, 2015). Similarly, in a separate analysis of the IMAGEN cohort focusing on predicting binge drinking behaviours, subject history (defined as important life events) turned out to be the most important predictor relative to neuroimaging markers (Whelan *et al.*, 2014).

The neural regions discriminating between current versus predicted binge drinking were dissociable in the IMAGEN data. Current binge drinkers at age 14 showed both reductions in grey matter volume and aberrant functional activity during reward processing and processing of negative stimuli in the ventromedial prefrontal cortex (vmPFC) and left inferior frontal gyrus. In contrast, future binge drinkers at age 16 showed aberrant grey matter volumes and neural activation to reward outcomes and inhibition failures in bilateral superior frontal and the right middle/precentral gyri, respectively (Whelan *et al.*, 2014).

The anticipation of reward highlighted four distinct nodes implicated in early visual processing, somatomotor, occipital-parietal-cerebellum, with a role for caudate and visual processing activity shown to be associated with alcohol usage (Jia *et al.*, 2016). Several IMAGEN studies have further investigated the relationship with alcohol use, genetics and the MID task implicating the RASGRF2 (Stacey *et al.*, 2012) (Stacey *et al.*, 2016), KALRN (Peña-Oliver *et al.*, 2016), DRD1 (Baker *et al.*, 2019) and the BDNF genes (Nees *et al.*, 2015).

3.1.2 Summary

A combination of neural factors including volumetric and functional (reward, negative affect and inhibition) differentiates current and predicted adolescent binge drinkers. These neural markers combined with subject history, personality variables and behavioral profile together can predict the initiation of adolescent binge drinking. Neural factors alone however appear to play less of a predictive role relative to history and personality factors. Reward-related neural activity in adolescent alcohol use is also modulated by genetic factors. In undergraduates, a balance between reward-related VS and threat-related amygdala activity mediated by impulsivity or an anxious-depression phenotype predicts stress-related problem drinking. In abstinent AD adults, neural activity to the anticipation of monetary rewards appears to be hypoactive similar to other abstinent substance use disorders. Reward type may be particularly relevant highlighting the role of non-drug or non-alcohol rewards (e.g. monetary reward acting as a conditioned reinforcer or a non-drug reward or natural rewards such as social, food or sexual rewards), potentially narrowing the behavioral repertoire of environmental interactions and interests.

3.2 Stage 2: Withdrawal

3.2.1 Negative emotionality

Myriad forms of negative emotionality play a role in the development and maintenance of AD. For example, dysphoria is associated with withdrawal and protracted abstinence (Koob and Le Moal, 1997), and chronic and acute stress are known to act as risk factors for the development, maintenance and relapse of

AD (Sinha, 2008). Indeed, mood and anxiety disorders are highly comorbid with dependence (Swendsen *et al.*, 2010). Changes in the hypothalamic pituitary adrenal axis and brain stress systems using corticotropin-releasing factor play a major role in the upregulation of stress systems (Koob, 2010) during the progression of addiction. Here we emphasize that negative emotionality is a critical factor in the withdrawal stage of the cycle but also note its likely relevance in the anticipatory craving stage characterized by dysphoria, its role in stress-induced relapse and negative reinforcement and as a potential risk factor for the development of disorders of addiction.

Neural responses to negative information are disturbed in AD. In a series of early smaller imaging studies, similar findings were observed to negative affective stimuli in abstinent AD. During the anticipation of a negative event such as an unpredictable threat stressor, abstinent AD males demonstrated reduced activation in corticolimbic striatal regions (pregenual cingulate cortex, medial PFC, medial orbitofrontal cortex (OFC)) (Yang *et al.*, 2013). Similarly, in response to negative facial expression, abstinent AD show reduced activation in the rostral affective anterior cingulate cortex (ACC) (Salloum *et al.*, 2007), right dorsomedial frontal gyrus (Padula *et al.*, 2015), OFC and insula (O'Daly *et al.*, 2012) with the hypoactivity correlating with greater severity. Negative contexts further decreased neural activity during behavioral control tasks. For example, higher binge drinking in university age adults correlated with greater hypoactivity to negative emotional contexts during response inhibition and delay discounting (Herman *et al.*, 2018). The cingulate cortex has been suggested to play a critical role: abstinent AD show lower intrinsic cingulate connectivity to alcohol and stress cues with longer times to relapse associated with weaker dACC connectivity to neutral cues and a stronger posterior cingulate cortex connectivity to alcohol compared to stress cues (Zakiniaeiz *et al.*, 2017). Craving in response to negative emotional stimuli dissociated between higher order cortical and limbic activity with craving positively correlating with dorsolateral PFC (dlPFC) and inferior parietal activity and negatively correlating with amygdala activity in abstinent AD (Lee *et al.*, 2013).

Genetic variation appears to play a role in modulating such brain activity. Imaging studies suggest involvement of CRF1 variation in the development of alcoholism and negative emotionality, through reduced negative emotionality and increased ventrolateral PFC activation in response to negative emotional stimuli (Glaser *et al.*, 2014). Additionally, NMDA genetic variation impacts the development of alcoholism, through reduced fear acquisition capacity and insula activation during fear acquisition (Cacciaglia *et al.*, 2013). A genetic variation of the recently identified risk variant for major depression (rs10514299) has also been shown in AD to be associated with greater putaminal activity to rewards and losses and greater depression symptom severity (Muench *et al.*, 2018).

Although these findings highlight a decrease in activity or intrinsic connectivity in abstinent AD in response to negative emotionality, the role of changes in grey matter structure on findings of hypoactivity has been also been emphasized. For example, a study in abstinent AD subjects showed that multiple regions hypoactive to aversive faces were explained by grey matter differences, whereas greater activity in left rostral ACC and medial frontal gyrus unrelated to grey matter differences was a resiliency factor associated with less lifetime drinking history, longer abstinence and less subsequent binge drinking (Charlet *et al.*, 2014b). Negative affect during early withdrawal in recently detoxified AD was shown to be positively correlated with medial OFC volume with lower OFC volumes predicting a greater risk of relapse (Zois *et al.*, 2017).

Neural activity to affective faces has also been investigated as a biomarker of pharmacological responses. For instance, varenicline, an α4β2-nicotinic partial agonist, decreases the enhanced amygdala activity to fearful faces in heavy drinkers (Gowin *et al.*, 2016) but pexacerfont, a corticotropin releasing hormone 1 receptor antagonist, did not appear to influence neural activity to fearful faces in abstinent AD (Kwako *et al.*, 2015).

In addition to negative stimuli, aberrant responses to positive and neutral stimuli also appear to be clinically relevant to AD. Greater VS and thalamic activity to positive stimuli in abstinent AD has been associated with lower

relapse risk suggesting a protective role (Heinz *et al.*, 2007). However, another study in early abstinent AD showed that increased vmPFC and ACC activation during presentation of a personalized, relaxing stimulus correlated with greater stress- and alcohol-induced craving, and, critically, this greater activity predicted a greater risk of relapse with a hazards ratio greater than eight (Seo *et al.*, 2013).

3.2.2 *Dopaminergic and Opioidergic function: positron emission tomography (PET)*

In terms of alcohol withdrawal symptoms, overwhelming preclinical data from animal models show a compromised dopamine system during acute and protracted withdrawal (Koob and Le Moal, 1997; Nestler, 2005). Alterations of the dopamine system have been found consistently, with lower baseline striatal D2/3 receptor (D2/3R) availability in abstinent AD (Martinez *et al.*, 2005) which correlates with alcohol craving (Heinz *et al.*, 2004) with no clear improvement with abstinence (Volkow *et al.*, 2002). 18F-fallypride imaging showed lower D2/3R availability in thalamus, hippocampus, insula and temporal cortex, indicating a mixed striatal picture (Grusser *et al.*, 2004; Heinz *et al.*, 2005b; Rominger *et al.*, 2012). In response to psychostimulant challenges, which normally increase striatal dopamine release, abstinent AD show blunted VS dopamine release (Martinez *et al.*, 2005; Volkow *et al.*, 2007). In contrast, unaffected subjects with an alcohol family history showed either no differences or enhanced baseline striatal D2/3R availability and no differences in dopamine release to amphetamine challenge (Munro *et al.*, 2006; Alvanzo *et al.*, 2017) (Volkow *et al.*, 2006). The expectation of alcohol administration however appears to enhance VS dopamine release in unaffected subjects with a positive family history suggesting a potential role of hyper-responsivity of the dopaminergic system to alcohol expectation (Kegeles *et al.*, 2018).

Presynaptic striatal dopamine synthesis capacity as measured using 18F-DOPA has not shown differences in abstinent AD (Heinz *et al.*, 2005b; Deserno *et al.*, 2015), although craving correlated with lower pre-synaptic capacity (Heinz *et al.*, 2005b). In detoxified AD, ventral striatal coding of reward prediction error is intact, but the negative correlation normally observed in healthy controls

between ventral striatal prediction error activity and striatal dopamine synthesis capacity is absent (Deserno *et al.*, 2015). AD was also associated with lower striatal dopamine transporter (DAT) binding levels (Tiihonen *et al.*, 1995) in early abstinence with substantial recovery within the first 4 days (Laine *et al.*, 1999b) and normalization within a month (Laine *et al.*, 1999a). These changes in dopaminergic transmission may drive underlying neuroadaptations. During normal aversive processing, presynaptic dopamine function in the amygdala is associated with amygdala and anterior cingulate blood oxygen level dependent functional connectivity. However, in abstinent AD, this functional connectivity is decreased and there appears to be no relationship between dopamine transmission and neural circuit connectivity (Kienast *et al.*, 2013).

Beyond the dopaminergic system, the μ-opioid receptor is also implicated in hedonic tone, motivation and impulse control and interacts with dopamine release. AD has been associated with higher striatal μ-opioid receptor availability as measured using 11C-carfentanil in early (Weerts *et al.*, 2011) and mid-abstinence in some but not all studies (Turton *et al.*, 2018) with this increase negatively correlated with craving (Heinz *et al.*, 2005a; Weerts *et al.*, 2011). Similar to studies of blunted psychostimulant-induced dopamine release, AD subjects also show blunted dexamphetamine-induced opioid release (Turton *et al.*, 2018).

3.2.3 Summary

Negative emotions during early withdrawal in AD is positively correlated with medial OFC volume. Negative imagery and stress cues generally appear to decrease limbic and prefrontal activity and intrinsic connectivity in abstinent AD subjects. However, differences in grey matter as a function of AD may influence these findings: after controlling for grey matter volume, enhanced prefrontal activity to negative imagery in AD was shown to act as a marker of resilience. Reactivity to positive and relaxing stimuli appears also to be clinically relevant in predicting AD outcomes.

Following chronic alcohol exposure in AD, abstinence is associated with lower striatal D2/3 and enhanced μ-opioid receptor availability along with blunted amphetamine-induced dopamine and dexamphetamine-induced opioid striatal release. The lower striatal D2/3 receptor and blunted amphetamine-induced dopamine release appears to persist into late abstinence.

3.3 Stage 3: Preoccupation/Anticipation ("craving")

Craving is a hallmark feature of the preoccupation/anticipation stage as the latter represents protracted abstinence when subjects are most vulnerable to relapse. At this stage, enhanced cue reactivity and impulsivity co-exist with deterioration of functional circuits underlying inhibitory control, behavioral flexibility and executive function coinciding with and strengthening circuits associated with craving.

3.3.1 *Cue- Reactivity*

Cue reactivity, a learned response to substance-related stimuli, can be modulated not only by disease-related factors (such as treatment status and abstinence, severity, exposure to stressors, availability of substances) but also task-related features (such as treatment sensory modality, type of cue and implicit and explicit regulation)(Jasinska *et al.*, 2014). Multiple drug cue reactivity meta-analyses identify common activity in the connections associated with the mesocorticolimbic dopamine system, including the ventral tegmental area and VS, as well as salience detection and regulation systems including amygdala, ACC, OFC, dlPFC, insula and hippocampus(Chase *et al.*, 2011) (Engelmann *et al.*, 2012) (Kuhn and Gallinat, 2011). An activation likelihood estimation based meta-analysis focusing on alcohol cues with a cohort of 679 heavy drinkers, treatment seeking or abstinent AD, and 174 controls showed common activation of VS, ventral ACC, vmPFC, posterior cingulate, precuneus, insula, temporal cortex and visual processing regions (Schacht *et al.*, 2013a).

Studies have also focused on deconstructing the cognitive processes underlying cue reactivity studies and the influence of alcohol cues on motivational and

approach processes. Attempts to assess the role of the conditioned cue versus the outcome showed increased VS dopamine release in heavy drinkers (Oberlin *et al.*, 2015b) to both the conditioned stimulus (beer flavor) and the outcome (intravenous alcohol) with responsivity to the beer cue correlating with family history of AD (Oberlin *et al.*, 2013),(Oberlin *et al.*, 2016). Detoxified AD subjects show enhanced pavlovian-instrumental-transfer (PIT), a process in which classically conditioned stimuli enhances motivational instrumental responses, a potential mechanism underlying how contextual alcohol cues might enhance instrumental alcohol seeking or intake behaviors (Garbusow *et al.*, 2016). PIT-related NAcc activity predicted subsequent relapse behaviors. In this same cohort, alcohol cues inhibited previously learned instrumental approach behaviors. This inhibition was associated with NAcc activation in those who subsequent abstained and had milder illnesses (Schad *et al.*, 2019). This observation was interpreted as a marker of resilience: in AD subjects that maintain abstinence or have milder illness, the alcohol cue may act as a salient signal to inhibit approach behaviors.

Genotype, including variants of the OPRM 1 (Heilig *et al.*, 2011; Ramchandani *et al.*, 2011), DAT 1 (Schacht *et al.*, 2013b) and GABRA2 (Kareken *et al.*, 2010) genes also appear to modulate responses to alcohol and alcoholic cues. Amygdala reactivity to alcohol has also been used to track progress in avoidance cognitive bias training in abstinent AD subjects, which decreased both elevated cue reactivity and craving (Wiers *et al.*, 2015).

3.3.2 *Impulsivity*

Impulsivity, defined as rapid, poorly considered disinhibited responses, is associated with enhanced risk for the development of substance use disorders and affected by substance exposure (Voon and Dalley, 2016). Impulsivity consists of heterogeneous subtypes with discrete but overlapping neural substrates and can be divided into motor and decisional forms (See Fig. 3 for frontostriatal circuitry parcellation and integration with impulsive-compulsive subtypes and other cognitive processes)(Voon and Dalley, 2016). Abstinent AD subjects show blunted VS and ACC activity during anticipation of monetary

rewards associated with elevated questionnaire-based impulsivity (Beck *et al.*, 2009) thus linking reward anticipation and impulsivity.

Insert Figure 3 here

A meta-analysis of response inhibition behavioural outcomes from the stop signal task and go/nogo task demonstrated impaired response inhibition in heavy users and AD subjects, and similarly in other stimulant and nicotine dependent subjects and pathological gamblers (Smith *et al.*, 2014). A review of response inhibition imaging studies showed consistent findings across alcohol and substance dependent groups with hypoactivity of an inhibitory network (ACC, inferior frontal gyrus, dlPFC and parietal cortices) (Luijten *et al.*, 2014) with evidence for differences in neural correlates to response inhibition as a pre-existing risk factor (Schweinsburg *et al.*, 2004; Norman *et al.*, 2011; Whelan *et al.*, 2012; Kareken *et al.*, 2013; Hardee *et al.*, 2014; Heitzeg *et al.*, 2014). Using the stop signal task, the IMAGEN study differentiated between underlying risk versus compensatory mechanisms secondary to drug state effects in adolescents showing OFC hypoactivity with drug initiation and inferior frontal cortex hyperactivity with excessive drug use (Whelan *et al.*, 2012). In a cross-translational IMAGEN study of the ubiquitously expressed GTPase Arf6 and Efa6, mutant flies showed differential sensitivity to alcohol preference, tolerance and sedation; the human ortholog, the PSD3 haplotype associated with AD was localized within the prefrontal cortex associated with response inhibition (Gonzalez *et al.*, 2018). Acute administration of modafanil improved response inhibition and thalamic and supplementary motor area activity in abstinent AD but only in those with underlying baseline inhibitory impairments (Schmaal *et al.*, 2013). AD and binge drinkers also display impaired waiting impulsivity (or the tendency to response prematurely) along with reduced resting state functional connectivity between the subthalamic nucleus, VS and subgenual cingulate cortex (Sanchez-Roige *et al.*, 2014; Morris *et al.*, 2016b).

Enhanced delay discounting, or the preference for smaller immediate rewards over larger delayed rewards, is also very commonly observed in AD (Lim *et al.*,

2017; Swan *et al.*, 2018; Gowin *et al.*, 2019). The few imaging studies in heavy drinkers and subjects with a mixed range of alcohol severity report enhanced activity in a diverse range of regions (supplementary motor area, insula, OFC, inferior frontal gyrus and precuneus; dlPFC and parietal cortex)(Claus *et al.*, 2011) (Amlung *et al.*, 2014). In a study designed to dissociate delay and magnitude, abstinent AD showed lower activity to delay in the anterior insula, dACC, dlPFC and inferior parietal lobule and greater activity to magnitude in medial PFC, rostral ACC, left posterior parietal and right precuneus (Dennis *et al.*, 2020). The delay discounting process has been linked with dopaminergic function with AD and social drinkers showing lower right ventral striatal 11C-raclopride binding potential correlating with greater delay discounting (Oberlin *et al.*, 2015a). Cue reactivity appears to be modulated by delay discounting: in heavy drinkers, greater delay discounting was associated with lower frontoparietal alcohol cue taste reactivity and sensation seeking with greater fronto-striatal cue reactivity (Burnette *et al.*, 2019) . Acute modafanil decreases delay discounting in abstinent AD and enhances frontoparietal activity and decreases vmPFC activity (Schmaal *et al.*, 2014)

AD individuals are also impaired across several measures of risky decision making (Lim *et al.*, 2017; Swan *et al.*, 2018; Gowin *et al.*, 2019). By contrasting risk-taking (speeded trials) to risk-aversion (slowed trials) in the Stop Signal Task, abstinent AD show reduced putaminal, insula and amygdala activity (Li *et al.*, 2009) and heavy drinkers showed lower superior frontal gyrus and left caudate activity (Bednarski *et al.*, 2012). In AUD subjects, greater hazardous drinking was associated with lower activity in the insula, dACC and striatum to risky choices on the Balloon Analogue Risk Task (Claus and Hutchison, 2012). Preliminary evidence also suggests a potential role for neural correlates of risk taking as an underlying endophenotype. For instance, adolescents with a positive family history show lower right dlPFC activity to risky choices compared to those without a family history (Cservenka and Nagel, 2012). Similarly adolescents who make more risky choices and have greater NAcc and precuneus activity to risky and rewarding choices develop earlier binge drinking (Morales *et al.*, 2018).

In the evaluation of risk, the anticipation of the negative outcome and sensitivity to loss aversion is also highly relevant: greater activity in dlPFC, OFC and superior parietal activity when anticipating risky large losses was observed in binge drinkers (Worbe *et al.*, 2014) but critically, the capacity to decrease risk taking behavior by learning from loss feedback was intact and associated with enhanced inferior frontal activity, a region involved in stopping behaviours (Worbe *et al.*, 2014). Similarly, abstinent AD and pathological gamblers (PG) showed decreased loss sensitivity in a mixed gamble study. Whereas healthy controls showed dlPFC hypoactivity to losses, AD showed increasing dlPFC activity with rising losses suggesting enhanced recruitment of cognitive resources (Genauck *et al.*, 2017) In contrast, PG showed a different neural profile with altered prefrontal-amygdala connectivity. Binge drinkers further show enhanced reflection impulsivity, or the tendency to make rapid decisions with limited evidence accumulation during probabilistic decisions, correlating with lower dlPFC volumes (Banca *et al.*, 2016b).

Resting state synchrony in reward and executive function-related regions, associated with impaired inhibitory control shows clinical relevance in differentiating relapsers from abstainers (Camchong *et al.*, 2013a). In a large scale resting state fMRI (rs-fMRI) general population study cross-validated across the Human Connectome Project and IMAGEN datasets, heavy drinking subjects showed general increases in functional connectivity and more specifically within reward-related medial-OFC and cingulate cortex correlating with impulsivity (Cheng *et al.*, 2019). This contrasted with lower functional connectivity in smokers specifically in the lateral-OFC, inferior frontal cortex and precuneus also correlating with impulsivity.

3.3.3 *Compulsivity or behavioural inflexibility*

Compulsivity can be defined as behavioural inflexibility despite changes in environmental context or negative outcomes and consists of multiple subtypes implicating fronto-striatal circuitry. Such compulsivity can range from more complex behaviors including goal-directed and habit control, exploration and

exploitation, set shifting and reversal learning, to simpler forms of behavioral inflexibility including switching and perseveration (Voon and Dalley, 2016).

Within the basal ganglia, an influential hypothesis of the transition to addiction with chronic substance exposure argues that repeated NACC activation recruits ventral-to-dorsal spiraling projections, eventually engaging the dorsal striatum and representing a shift from initial goal-directed behavioral control (VS/NACC) to automatic habitual behavior (dorsal striatum) (Everitt and Robbins, 2005). Findings in human studies suggest diminished goal-directed reward-related learning and potentially increased habitual strategies influenced by recency of use, bingeing and abstinence (Voon *et al.*, 2017). These behavioral pathological changes are absent in social drinkers (Nebe *et al.*, 2018). As a function of increasing severity of alcohol use, goal-directed control becomes impaired as shown in a large online population study (Gillan *et al.*, 2016). Abstinent AD subjects show an over-reliance on stimulus-response habit learning associated with an decrease in engagement of regions implicated in goal-directed learning such as the ventromedial prefrontal cortex and anterior putamen and an increase in activity in habit learning regions such as the posterior putamen (Sjoerds *et al.*, 2013a). Heavy drinkers also show enhanced compulsive actions to earn alcohol points despite experiencing aversive painful consequences associated with greater activity and functional connectivity in mesial prefrontal, anterior insula and striatal activity (Grodin *et al.*, 2018). These behavioural changes with alcohol exposure highlight the chronicity required for longer-term allostatic neuroadaptations that drive dependence. The impairment in goal-directed control appears to improve rapidly within days of discontinuation of binge drinking (Doñamayor *et al.*, 2018) and early abstinence in AD subjects (Voon *et al.*, 2015). In detoxified AD, mesial prefrontal impairments in goal-directed control and behavioural measures of high alcohol expectancies associated with impaired model-based control predict subsequent relapse (Sebold *et al.*, 2017).

In response to dynamically changing contingencies in a probabilistic reward task, abstinent AD also show lower right dlPFC activity to positive prediction

error and lower left dlPFC activity to negative prediction error (Beylergil *et al.*, 2017). As abstinent AD do not show any differences in VS coding of prediction error for probabilistic tasks with limited change in contingencies (Deserno *et al.*, 2015), this lower dlPFC coding of prediction error suggests a potential impairment in the adaptive control of action selection with changing environmental contingencies (Beylergil *et al.*, 2017). Exploration tendencies in the context of uncertainty, or the tendency to sample alternate unknown options, has also been shown to be decreased in abstinent AUD subjects (Morris *et al.*, 2016a).

Set-shifting, another form of behavioural inflexibility which measures the capacity to switch attention towards previously irrelevant stimuli, is also commonly impaired in AD (Kwako *et al.*, 2016). Imaging studies in AD show that set shifting impairments correlate with medial prefrontal glucose hypometabolism (Adams *et al.*, 1993) and lower inferior frontal cortex volumes (Trick *et al.*, 2014). Intrinsic network connectivity changes in abstinent AD show reduced synchrony of a reward and limbic network (caudate, thalamus, VS and ACC) but increased connectivity between VS and ACC with the executive network (dlPFC), during set shifting (Camchong *et al.*, 2013b), suggesting a shift in networks with greater flexible behaviours.

In contrast, reversal learning impairments, in which subjects must learn to switch choices following a contingency change and which implicates the OFC, are less prominent in AD (Vanes *et al.*, 2014; Banca *et al.*, 2016a). The tracking of prediction error in reversal learning can involve updating of the chosen or unchosen action. Unlike healthy controls, AD subjects predominantly tracked the chosen action rather than both options and further showed decreased mesial PFC activity when making inferences about the unchosen action, relating to increased drinking habits in AD (Reiter *et al.*, 2016).

3.3.4 *Executive deficits: working memory*

Executive processes such as working memory implicating lateral prefrontal cortices are very commonly impaired in AD (Kwako *et al.*, 2016). In rodent binge

drinking models, acute abstinence is associated with impaired working memory along with activation of mesial prefrontal GABAergic interneurons and disruptions in medial prefrontal and amygdala functional connectivity (George *et al.*, 2012). Similarly, in humans, working memory deficits in AD show lower activity in prefrontal regions (medial, middle and inferior frontal gyri) (Pfefferbaum *et al.*, 2001; Tapert *et al.*, 2001; PARK *et al.*, 2011) with increased activity in alternate regions (ACC and superior cerebellar activation) (Desmond *et al.*, 2003; Vollstadt-Klein *et al.*, 2010), possibly representing compensatory mechanisms. Similarly, adolescents who transitioned to heavy drinking had less baseline medial frontal activation compared to continued abstainers (Squeglia *et al.*, 2012). In contrast, AD subjects who maintained abstinence showed greater prefrontal activation to a working memory task suggesting a potential predictor of outcome (Charlet *et al.*, 2014a). However, gender differences exist in the degree of prefrontal activation in relation to working memory impairments in binge drinkers and adolescents (Caldwell *et al.*, 2005; Squeglia *et al.*, 2011).

3.3.5 Summary

These studies emphasize a shift in balance of executive function with hyperactivity to alcohol cues and hypoactivity in behavioural control and executive networks. AD is characterized by a hyperactive alcohol cue reactivity network interacting with genotype, mediated by enhanced dopaminergic release. Alcohol cues enhance pavlovian-instrumental transfer in AD, a potential explanatory model for how contextual alcohol cues might enhance motivational instrumental alcohol seeking behaviors. In AD subjects who maintain abstinence, alcohol cues can also act as markers of resilience by acting as salient signals inhibiting approach behaviors.

In contrast to the hyperactivity observed to alcohol cues, measures of impulsivity (with studies particularly in response inhibition and risk taking), compulsivity (impaired goal-directed control, set shifting and tracking of the alternate option in reversal learning) and working memory generally showing hypoactivity of relevant networks with some evidence of abnormal compensatory activity in other networks. The cognitive processes underlying delay discounting are

potentially dissociable in AD with lower activity to the delay process and greater activity to magnitude. Risk taking appears to be in part related to impaired loss aversion during anticipation and associated with greater recruitment of cognitive resources.

Evidence supports a role for habit theories in AD. Multiple levels of behavioral flexibility appears to be impaired in chronic alcohol misuse captured through behavioral and computational models and reflected in aberrant neural activity. These processes are integral to flexible responding to an uncertain changing environment and include a shift from goal-directed to habitual control, decreased aversion to losses, decreased exploration of unknown options, impaired adaptation to changing reward contingencies, decreased set shifting and impaired tracking of alternative options.

4. Resting state functional MRI (rsfMRI) and structural imaging

Although rsfMRI and structural imaging outcomes in alcohol disorders may reflect multiple stages in the addiction cycle, critically, the neural substrates particularly of structural imaging overlap with the task-based fMRI findings of cognitive processes (Fig. 2).

Resting state functional MRI

In addition to resting state functional connectivity studies in impulsivity(Morris *et al.*, 2016b; Cheng *et al.*, 2019) and compulsivity(Camchong *et al.*, 2013b) measures in AD, network analyses have also focused on its predictive capacity to classify disorders using machine learning techniques. Functional connectivity of the subthalamic nucleus has been shown to discriminate between alcohol misuse and healthy controls related to impairments in waiting impulsivity (Morris *et al.*, 2016b). In a study comparing the classification capacity of differing imaging modalities, resting state connectivity between networks predicted 33% of the variance of alcohol use severity in adults with problem drinking patters, and outperformed the predictive capacity of structural MRI or task-based functional

MRI (monetary incentive delay and face matching) (Fede *et al.*, 2019). Epigenetic factors have also been examined with dopamine receptor D2 methylation associated with severity of alcohol problems and negatively associated with functional connectivity of the executive control network (Hagerty *et al.*, 2018).

4.1 Structural changes: grey matter

Grey matter structural differences have been shown in multiple studies between AD and healthy controls (Momenan *et al.*, 2012; Grodin *et al.*, 2013; Mole *et al.*, 2014; Kvamme *et al.*, 2016; Grodin *et al.*, 2017). A mega-analysis from the ENIGMA Addictions consortium examining 2140 individuals with substance dependence including those with AD highlighted across all substances decreased subcortical volumes in bilateral hippocampus, amygdala and right nucleus accumbens and decreased cortical thickness across multiple regions including bilateral insula, precentral gyrus, supramarginal gyrus and right medial OFC (Mackey *et al.*, 2018). AD in particular was also associated with lower thickness more specifically in bilateral putamen, right thalamus, right globus pallidus and left NACC along with bilateral posterior cingulate and superior frontal cortex. Furthermore, AD subjects could be classified from healthy controls using support vector machine approaches. Similarly, a meta-analysis of voxel-based morphometry studies (Xiao *et al.*, 2015) from 296 AD subjects and 359 healthy controls highlighted decreased volumes in the ACC, dorsomedial PFC, insula and putamen, regions associated with functional cognitive impairments. The insular findings were corroborated in a parallel rodent and human study which showed lower insular and higher amygdalar volumes in AD subjects along with a 60% decrease in von Economo neurons in the anterior insula in postmortem AD subjects (Senatorov *et al.*, 2015).

These large-scale studies highlight cross-sectional differences whereas prospective studies and comparisons with unaffected family members point towards potential trait related effects. Healthy subjects with a positive family history, show reduced volumes within prefrontal cortices (middle and inferior frontal and orbitofrontal gyrus), mid-cingulate, right insula and bilateral nucleus accumbens (Filippi *et al.*, 2019) and the right parahippocampal gyrus (Sjoerds *et*

al., 2013b). In adolescents with limited alcohol exposure, a positive family history was associated with lower cortical thickness in orbitofrontal and superior parietal cortices in additional to greater impulsivity and impaired memory (Henderson *et al.*, 2018). These findings suggest the decrease in prefrontal regions and particularly the OFC, cingulate, insular and nucleus accumbens volumes might be a trait risk factor for alcohol dependence rather than secondary to ongoing alcohol use. In contrast, in the large scale IMAGEN study of healthy adolescents, higher caudate and cerebellar volumes at age 14 predicted greater alcohol consumption over 5 years (Kühn *et al.*, 2019). The predictors for risk for AD might indeed also differ from those for increasing use in adolescence.

These decreases in brain volumes have been shown to be clinically relevant in predicting relapse outcomes. At baseline, future relapsers had reduced grey matter volumes within OFC, medial PFC and ACC compared to both healthy controls and future abstainers (Beck *et al.*, 2012), with smaller medio-frontal and parieto-occipital volumes predicting shorter time to relapse (Rando *et al.*, 2011). Lower medial OFC volumes have been particularly highlighted as a risk factor for subsequent relapse, with larger medial OFC volumes associated with greater negative affect during withdrawal states (Zois *et al.*, 2017). The lower ACC and anterior insula volumes observed in AD subjects have also been shown to be associated with greater self-reported impulsivity and compulsivity measures (Grodin *et al.*, 2017).

Recent studies have also focused on the aging hypothesis and gender effects. Accelerated aging across multiple regions has been shown in AD with volumetric analyses (Guggenmos *et al.*, 2017) and also in white matter cerebellar volumes with a brain age increase of 11.7 years relative to healthy controls (Zhao *et al.*, 2019). A role for gender effects has been highlighted in the IMAGEN cohort followed from 14 to 19 years old with heavy drinking associated with decreased grey matter volume across multiple brain regions with greater prominence in females compared to males (Seo *et al.*, 2019).

4.2 Structural changes: diffusion tensor imaging (DTI)

Diffusion MRI provides an index of white matter integrity. A large study examining whole brain fractional anisotropy (FA) in AD demonstrated reduced FA throughout the brain, including in the corpus callosum, cingulum and superior longitudinal fasciculus (Pfefferbaum *et al.*, 2014). Persistent lower FA in cortico-striatal and frontal fibres was observed in both early abstinence (Yeh *et al.*, 2009) and later abstinence (Wang *et al.*, 2009). Later abstinence was also associated with reduced tract integrity between midbrain and pons in AD, associated with cognitive flexibility impairments (Chanraud *et al.*, 2009). Lower FA has also acted as a predictive marker: lower frontal FA predicted subsequent relapse in AD (Sorg *et al.*, 2012) and lower accumbofrontal FA in adolescents predicted earlier binge drinking mediated by greater NACC activation in risk-reward decision making (Morales *et al.*, 2019).

White matter FA further interacts with gender and age. Decreases in FA in the corpus callosum and tracts connecting anterior and posterior brain regions such as the superior longitudinal fasciculus and arcuate fasciculus were shown to be decreased in male AD but increased in female AD (Sawyer *et al.*, 2018). FA reduces with age in healthy volunteers but in AD who subsequently abstain from alcohol intake, show a reduced slope, indicating some recovery (Pfefferbaum *et al.*, 2014).

Neurite Orientation Dispersion and Density Imaging (NODDI) is a recently developed diffusion MRI technique, which provides higher specificity of microstructural characteristics than conventional DTI (Zhang *et al.*, 2012). NODDI uses a model-based procedure with geometric modelling of water diffusion to reflect microstructure and to explicitly represent the dispersion of axon orientations expected in grey matter, detailing grey matter complexity. NODDI microstructural modeling has a more direct relationship with axonal orientation distribution, neurite density and dendritic architecture. While this technique is relatively new, it has been used to demonstrate that binge drinkers have reduced cortical dorsolateral prefrontal and parietal neurite complexity

and increased ventral striatal complexity, the latter associated with the severity of bingeing (Morris *et al.*, 2018).

5. Conclusion

Together these findings suggest that alcohol misuse is associated with widespread alterations in brain structure and function, especially in terms of processing reward, emotions and substance-related stimuli. Neural factors appear to dissociate between current and predicted adolescent binge drinkers. Neural factors, history and personality factors in combination predict the initiation of adolescent binge drinking but neural factors alone may play less of a predictive role relative to history and personality. In adults with AD, we observe aberrant neural activity to a wide range of impaired cognitive processes underlying monetary reward anticipation, multiple impulsivity and compulsivity domains and working memory. Both a decrease in activity or aberrant hyperactivity has been observed reflecting dysfunction and potential compensatory function. These findings parallel observations of aberrant resting state networks, lower brain volumes and impaired white matter integrity in regions implicated in these cognitive processes. Similarly, impairments in dopaminergic and opioidergic function at baseline and in response to classical challenges underscore the capacity to regulate and optimize optimal function. In response to bottom-up conditioned alcohol cues that might underlie triggers to cue-induced relapse states, we observe enhanced dopamine release along with enhanced neural activity suggesting a need for greater cognitive demand and resources. In contrast, negative emotional stimuli that might underlie emotional stress-induced triggers appear to be associated with lower neural activity suggesting different neural pathways towards stress or negative emotional relapse triggers. Together these findings suggest aberrant function at all stages of the addiction cycle. Further studies investigating the exact correspondence between the stages of the addiction cycle, cognitive measures and imaging are indicated.

Despite the wealth of imaging data in alcohol misuse, the field is not without limitations. Some of these are known issues with imaging (Poldrack *et al.*, 2017), while some issues are specific to that of alcohol misuse. Mixed findings in individual studies highlight key issues underlying neuroimaging studies in AD including that of statistical error from small sample sizes, weak mechanistic effects or heterogeneity of mechanisms underlying differing cognitive phenotypes, or disease or task-related effects. By increasing statistical power, meta-analyses across cue studies show commonalities of enhanced activity across reward and salience networks in alcohol misuse, although notably appropriate study inclusion is needed for robust conclusions from meta-analyses. Mega-analyses of grey matter volume have further highlighted similarities and differences between substance types with AD being most likely to be associated with lower volumetric differences. Population heterogeneity can be also addressed in large sample sizes and statistical techniques to identify clinically meaningful phenotypes.

A major issue in the field is that of disease-based and task-based heterogeneity (including differences in imaging acquisition, task type and analysis such as region of interest or whole brain analyses and necessity for replication) which can result in inconsistent findings. Issues further contributing to heterogeneity include the role of gender, stage in the addiction cycle of testing, genetic vulnerabilities, treatment status and other comorbidities including other substance use. Teasing out state versus trait effects of alcohol, vulnerability versus resilience and the role of compensatory mechanisms is critical and can be achieved with integration with genetics and longitudinal studies. Notably, studies comparing unaffected subjects with and without family histories suggest some of these decreases in brain volumes and thickness may be risk factors rather than consequences of AD. Further integration of findings across cognitive processes, longitudinal studies in multiple imaging modalities, and postmortem studies are indicated.

Here we highlight the critical need for further studies addressing the neurocircuitry dysfunctions in AD but in the context of the heuristic domains of

the ANA: incentive salience/pathological habits, reward deficits/ stress surfeit and impaired executive, impulsivity and behavioural flexibility function. The marked comorbidity with dysphoria, depression, anxiety and stress prevalent in both premorbid and withdrawal states and the need to understand the interactions between negative emotionality, aversive learning and stress and the relevant neurochemical and network substrates, the hypothalamic-pituitary axis and the risk for the development of and relapse risk underlying alcohol misuse is an area largely neglected in imaging studies (Koob and Le Moal, 1997; Koob *et al.*, 2014). Recent studies on the role of microglial activation in AD have not replicated the enhanced neuroinflammation observed in pre-clinical studies but rather, lower activation of microglia in AD which may reflect an interaction with cholesterol binding (Kalk *et al.*, 2017; Kim *et al.*, 2018). Further studies into the role of inflammation and alcohol misuse are indicated. Spectroscopy studies at ultrahigh MR resolution and PET imaging ligands with novel targets including those from the "dark side of addiction" such as brain stress/dysphoria systems, neuroinflammatory markers and even beta-amyloid might provide further mechanistic insights and novel treatment targets. Understanding mechanisms underlying these aberrant processes and their contribution to the heterogeneity underlying alcohol misuse is particularly critical to the development of novel and appropriate treatment targets.

We thus propose a body of omnibus MR imaging data collection in line with that of the ANA as a starting point to investigate and determine the neural substrates of addiction subtypes and the development of neural markers as predictors for alcohol misuse and treatment outcomes and as novel treatment targets. These would include structural measurements, rsfMRI, and task driven fMRI for the investigation of neural alterations at various stages of alcohol use and misuse. We highlight the need for multiple cross-sectional cohort studies to collect large numbers using consistent criteria and measures. Along these lines, the collection of large data sets such as ABCD (https://www.addictionresearch.nih.gov/abcd-study) and ENIGMA are currently underway (Thompson *et al.*, 2014). Reconciliation and harmonization of collected data sets is required to develop a research data commons that is open source to qualified investigators. Research

questions and the application of computational techniques can be both theoretical hypothesis-driven to define underlying cognitive, neurochemical and micro- or macro-structural network-based processes or data-driven based on the application of new computational analytics for predictive modeling applied to large databases. Similar to the concept of a stress test as a predictor of cardiovascular function, we envision that imaging, in combination with other cognitive or physiological measures, may one day have clinical applicability to phenotype heterogeneity and predict individualized risk and treatment outcome to psychological, pharmacological and neuromodulation approaches with high predictive value. Utilizing new methodologies in determining and understanding neuroimaging fingerprints (Finn *et al.*, 2015) improves our ability to establish and evaluate individual variations of addiction. This in turn, in conjunction with innovative approaches such as neurofeedback and biofeedback (deCharms *et al.*, 2005; Hanlon *et al.*, 2013; Young *et al.*, 2017), real time fMRI can be used to examine non-invasive manipulation of affected neural networks in order to verify these findings, and perhaps alter the state of the use disorder or its withdrawal symptoms in favor of abstinence or reduction in consumption. Neuroimaging thus provides a critical window into human neurocircuitry underlying alcohol misuse and serves converging roles as a tool for mechanistic exploration and potential for precision medicine.

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Table 1. Summary of the functional task-based imaging studies reviewed

Legend: AD=alcohol dependence; MID=Monetary Incentive Delay Task; VS=ventral striatum; BD=binge drinkers; HC=healthy controls; DLPFC=dorsolateral prefrontal cortex; AUD=alcohol use disorder; PCC=posterior cingulate cortex; ACC=anterior cingulate cortex; OFC=orbitofrontal cortex; vmPFC=ventromedial prefrontal cortex; NAcc=nucleus accumbens; FHx+=family history of alcohol dependence; FHx-=no family history of alcohol dependence

Reward Anticipation	**Summary**
(Luijten *et al.*, 2017)	Meta-analysis of substance use disorders and gambling disorder (including 4 abstinent AD studies and 1 mixed abstinent AD study): lower ventral striatal activity to anticipation of Monetary Incentive Delay (MID) task and greater activity to monetary reward outcome across substance use disorders
(Groefsema *et al.*, 2019)	No differences between light, heavy and non-treatment seeking AD (N=39;64;47) groups in anticipating, obtaining or tasting beer in Beer Incentive Delay task
(Murphy *et al.*, 2017)	In abstinent AD, acute administration of the D3 antagonist GSK598809 normalized the blunted VS activity and enhanced the D3 receptor rich ventral pallidal and substantia nigra activity during reward anticipation in the MID task
(Elsayed *et al.*, 2018)	Early alcohol initiators in adolescents (N=330) followed prospectively showed greater lifetime stressful events and greater threat-related amygdala but not reward-related VS activity.
(Nikolova *et al.*, 2016)	Stress-related problem drinking in 759 undergraduate students showed were related to either high reward-related VS and low threat-related amygdala reactivity mediated by impulsivity or low VS and high amygdala reactivity mediated by anxious-depression phenotype
(Nees *et al.*, 2012)	IMAGEN: Neural activity to MID and reward-related behaviour variables contributed to 26% of explained variance in initiation of binge drinking in healthy adolescents (N=324) but neural activity less important than other variables
(Müller *et al.*, 2015)	IMAGEN: No group differences in MID task in adolescents with (N=256) and without (N=256) family history of AD
(Whelan *et al.*, 2014)	IMAGEN: Adolescent current (age 14: 115 BD; 150 non-BD) and predicted binge drinkers (age 16: 121 future BD)

	dissociable in grey matter volume and brain activity during reward anticipation (MID task), inhibitory and emotional processing. Subject history (or important life events) most important predictor of binge drinking relative to neural activity
(Heinrich *et al.*, 2016; Jia *et al.*, 2016)	IMAGEN: Caudate and early visual processing activity during reward anticipation of MID associated with adolescent alcohol use (N=1544)
Negative emotionality	
(Yang *et al.*, 2013)	Decreased activity to unpredictable painful threatening versus predictable non-painful conditioned stimuli in pregenual ACC, medial PFC, mOFC cortex in abstinent male AD versus HC
(Salloum *et al.*, 2007)	Decreased rostral anterior cingulate activity particularly to negative facial affective images (fearful, disgust versus neutral) in abstinent male AD versus HC
(Padula *et al.*, 2015)	Decreased right dorsomedial frontal cortex to fearful versus neutral affective faces in abstinent AD versus HC
(Herman *et al.*, 2018)	Greater binge drinking in university age subjects correlated with greater hypoactivity to fearful images during response inhibition and delay discounting
(Lee *et al.*, 2013)	Negative emotional stimuli-induced craving correlated with lower DLPFC and inferior parietal lobule and higher amygdala activity in abstinent AD versus HC (N=17;25)
(Zakiniaeiz *et al.*, 2017)	Relative to HC (N=30), AUD (N=45) show lower cingulate intrinsic connectivity to both alcohol and stress imagery scripts. Longer times to relapse were predicted by greater difference in PCC connectivity to alcohol versus stress cues and lower ACC connectivity to neutral cues
(Charlet *et al.*, 2014b)	Abstinent AD relative to HC (N=33,33) showed hypoactivity of multiple regions to aversive faces related to grey matter differences. Greater left rostral ACC and medial frontal hyperactivity unrelated to grey matter differences was a resiliency factor predicting lower binge drinking
(Zois *et al.*, 2017)	Lower grey matter volumes were observed in 95 recently detoxified AD versus 85 HC in PFC (including medial OFC), ACC and insula. Greater negative affect during withdrawal positively correlated with medial OFC volumes. Lower medial OFC predicted greater relapse risk.
(Gowin *et al.*, 2016)	Varenicline, an α4β2-nicotinic partial agonist, decreased the enhanced amygdala activity to fearful faces in heavy drinkers
(Kwako *et al.*,	Pexacerfont, a corticotropin releasing hormone 1 receptor

2015)	antagonist, did not have any effect on neural activity to fearful faces in abstinent AD
(Heinz *et al.*, 2007)	Negative, positive and alcohol images increased activity in PFC (BA 10) in abstinent AD versus HC (N=12,12) with other regions increased with alcohol and positive images. Only greater VS and thalamic activity to positive versus neutral images predicted relapse.
(Seo *et al.*, 2013)	Early abstinent AD compared to HC (N=45,30) showed increased vmPFC and ACC activation to personalized, relaxing stimuli which correlated with greater stress- and alcohol-induced craving, and, predicted a greater relapse with a hazards ratio greater than eight
Cue reactivity	
(Schacht *et al.*, 2013a)	Meta-analysis of alcohol cue reactivity (679 heavy drinkers, treatment seeking or abstinent AD, and 174 controls) showed common activation of VS, ventral ACC, vmPFC, posterior cingulate, precuneus, insula, temporal cortex and visual processing regions
(Garbusow *et al.*, 2016)	Detoxified AD subjects compared to HC (N=31,24) showed enhanced pavlovian-instrumental-transfer (PIT) (classically conditioned stimuli enhances motivational instrumental responses) associated with NAcc activity which predicted relapse
(Schad *et al.*, 2019)	Alcohol cues in detoxified AD subjects compared to HC (N=31,24) inhibited previously learned instrumental approach behaviors. Inhibition was associated with NAcc activation in those who subsequent abstained and had milder illnesses
(Wiers *et al.*, 2015)	32 abstinent AD subjects underwent a randomized controlled study of avoidance cognitive bias training. Amygdala activity to alcohol cues was elevated pre-training with decreased activity in the active relative to sham control and correlating with craving.
Impulsivity	
(Beck *et al.*, 2009)	19 detoxified AD versus 19 HC showed blunted VS and ACC activity during anticipation of monetary rewards on MID task correlating with elevated impulsivity on Barratt Impulsiveness Scale-Version 10
(Smith *et al.*, 2014)	Meta-analysis of stop signal task and Go/NoGo task across heavy substance users and dependent groups. Inhibitory impairments in heavy users or alcohol dependence with similar impairments in stimulant and nicotine dependence

	and pathological gambling.
(Luijten *et al.*, 2014)	Review of stop signal task and Go/NoGo imaging studies showed consistent findings across alcohol and substance dependent groups with hypoactivity of an inhibitory network (ACC, inferior frontal gyrus, dlPFC and parietal cortices)
(Heitzeg *et al.*, 2014)	45 9-12 year olds scanned with a Go/NoGo task were followed over 5 years. Problem users showed blunted left middle frontal gyrus activity to failed versus correct inhibition
(Hardee *et al.*, 2014)	43 children with positive family history (FHx+) and 30 with negative history (FHx-) followed between 7 to 12 years scanned repeatedly with Go/NoGo task. Baseline activity was blunted in FHx+ with increase in mid-cingulate activity with age whereas FHx- showed decreased right caudate, mid-cingulate and mid frontal with age
(Schweinsburg *et al.*, 2004)	12 FHx+ 12 to 14 year olds showed lower left mid frontal gyrus activity to Go/NoGo task compared to 12 FHx-
(Norman *et al.*, 2011)	38 12-14 year olds followed longitudinally with subsequent heavy users showing lower activity on NoGo trials (left IFG, left dorsomedial frontal gyrus, bilateral motor, cingulate, left putamen)
(Kareken *et al.*, 2013)	During acute alcohol challenge, 18 FHx- young adults showed greater reduction of right PFC to successful inhibition versus Go trials in the Stop Signal Task compared to 22 FHx+ consistent with lower sensitivity to alcohol in FHx+
(Whelan *et al.*, 2012)	IMAGEN: In adolescents (N=1896), the stop signal task differentiated between underlying risk versus compensatory mechanisms secondary to drug state: OFC hypoactivity was associated with drug initiation and inferior frontal cortex hyperactivity with excessive drug use
(Schmaal *et al.*, 2013)	Acute modafanil improved response inhibition and supplementary motor area and thalamic activity in 16 abstinent AD with baseline poor inhibitory control compared to 16 HC
(Morris *et al.*, 2016b)	36 abstinent AUD and 32 BD showed greater premature responding on a 4-Choice Serial Reaction Time task versus 55 HC. Greater waiting impulsivity correlated with lower connectivity of the subthalamic nucleus with VS and subgenual cingulate.
(Claus *et al.*, 2011)	151 individuals with social drinking to severe AD were scanned with a delay discounting task. Severe AD associated with greater discounting and greater activity in supplementary motor area, insula/orbitofrontal cortex,

	inferior frontal gyrus, and precuneus
(Amlung *et al.*, 2014)	Heavy drinking men with AUD as compared to those without AUD (N=13,12) showed greater activity in DLPFC and posterior parietal cortex during delayed choices
(Dennis *et al.*, 2020)	Using a probabilistic delay discounting task to dissociate delay and magnitude, 39 abstinent AD compared to 46 HC showed lower activity to delay in the anterior insula, dACC, dlPFC and inferior parietal lobule and showed greater activity to magnitude in medial PFC, rostral ACC, left posterior parietal and right precuneus
(Burnette *et al.*, 2019)	In 55 heavy drinkers, greater delay discounting was associated with lower frontoparietal alcohol cue taste reactivity and sensation seeking with greater frontostriatal cue reactivity
(Schmaal *et al.*, 2014)	Acute modafanil decreased delay discounting in 14 abstinent AD along with enhancing frontoparietal and decreasing vmPFC activity relative to 16 HC
(Li *et al.*, 2009)	By comparing risky (speeded trials) to risk-averse (slowed trials) in the Stop Signal Task, 24 abstinent AD compared to 24 HC showed lower putaminal, insular and amygdala activity
(Bednarski *et al.*, 2012)	By comparing risky (speeded trials) to risk-averse (slowed trials) in the Stop Signal Task, 20 heavy alcohol users compared to 20 light users showed lower right superior frontal gyrus and left caudate activity
(Claus and Hutchison, 2012)	In 79 AUD, greater hazardous alcohol use was associated with lower activity in the insula, striatum and dACC to risky choices in the Balloon Analogue Risk Task
Compulsivity	
(Cservenka and Nagel, 2012)	18 adolescents with FHx+ compared to 13 FHx- showed lower right dlPFC activity during risky choices in a Wheel of Fortune task
(Morales *et al.*, 2018)	In 47 adolescents, greater risk taking and greater NAcc and precuneus activity to risky and rewarding choices was associated with earlier binge drinking
(Worbe *et al.*, 2014)	In 40 BD and 70 HC, subjects chose between risky gambles and safe choices. BD made greater risky anticipatory choices to high risk losses. In 20 BD and 20 HC, BD showed greater dlPFC, OFC and superior parietal activity to high risk loss anticipation. Explicit exposure to loss feedback decreased risk taking in BD associated with greater right inferior frontal gyrus activity suggesting enhanced inhibitory control over risk taking.

(Genauck *et al.*, 2017)	Using mixed gambles, abstinent AD and pathological gamblers (PG) showed decreased loss sensitivity with no difference in gain sensitivity. AD showed increasing dlPFC activity with rising losses suggesting enhanced recruitment of cognitive resources whereas HC showed decreased activity. PG showed altered prefrontal-amygdala connectivity.
(Banca *et al.*, 2016b)	BD showed less evidence prior to a probabilistic decision on the Beads task with both behavioural and computational models compared to HC (N=60) with greater reflection impulsivity correlating with lower DLPFC and inferior parietal volumes
(Grodin *et al.*, 2018)	Heavy drinkers compared to light drinkers (N=42) showed greater selection of actions to earn alcohol points despite experiencing aversive painful shocks associated with greater mesial PFC, anterior insula and striatal activity and greater ventral striatal and insular functional connectivity
(Sjoerds *et al.*, 2013a)	31 abstinent AD subjects compared to 19 HC show an over-reliance on stimulus-response habit learning associated with an decrease in engagement of regions implicated in goal-directed learning such as the ventromedial prefrontal cortex and anterior putamen and an increase in engagement of regions implicated in habit learning such as the posterior putamen
(Sebold *et al.*, 2017)	90 detoxified AD and 96 HC were scanned using the two-step task. AD who subsequently relapsed showed decreased medial PFC activity to model-based control and behaviourally showed high alcohol expectancies associated with low model-based control
(Beylergil *et al.*, 2017)	In response to a dynamically changing probabilistic reward task, 34 abstinent AD compared to 26 HC showed lower right dlPFC activity to positive prediction error and lower left dlPFC activity to negative prediction error suggesting potential impairments in adaptive control of action selection with changing environmental contingencies
(Reiter *et al.*, 2016)	43 detoxified AD and 35 HC were scanned using a reversal learning task and modelled using a double update model. Unlike HC, AD subjects tracked the chosen action rather than both options and showed decreased mesial PFC activity when making inferences about the unchosen action related to greater alcohol severity

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Figure Legends

Figure1. Addiction theories and processes: The figure illustrates the concepts of vulnerability and resistance with the binge-intoxication-withdrawal cycle and the stages at which relevant addiction theories and cognitive processes are proposed to be implicated.

Figure2. Summary illustration of neural regions implicated in cognitive processes, functional connectivity and volumetric differences associated with alcohol misuse. Here we illustrate a summary of commonly observed regions and processes in alcohol misuse discussed in this review. The closed colored circles and open grey circle represent impaired cognitive processes and volumetric differences and their associated neural regions relevant to studies of alcohol misuse. Note that the positioning of the circle represents the relevant brain region and not the peak activity.
Abbreviations: vmPFC: ventromedial prefrontal cortex: OFC: orbitofrontal cortex; lPFC: lateral prefrontal cortex; IFC: inferior frontal cortex

Figure3. Fronto-striatal connectivity and cognitive processes relevant to alcohol misuse. The images show fronto-striatal functional connectivity maps based on functionally defined prefrontal seeds (left) and connectivity to striatal subregions in healthy controls. The upwards arrow in the middle image is intended to reflect ventral to dorsal striatal spiraling loops. Cognitive processes mapped to relevant fronto-striatal circuitry are shown on the right. The columns on the right represent constructs of impulsivity, compulsivity and other cognitive processes relevant to the addiction process. The processes are colour-coded to match colour coding of the fronto-striatal region implicated in the cognitive process. The images and fronto-striatal maps of the cognitive constructs for impulsivity and compulsivity processes are adapted from (Morris *et al.*, 2016c; Voon and Dalley, 2016).
Abbreviations: dlPFC: dorsolateral prefrontal cortex; vlPFC: ventrolateral PFC; iPFC: inferior PFC; lOFC: lateral orbitofrontal cortex; SMA: supplementary motor area; PMC: premotor cortex; pre-SMA: pre-supplementary motor area; Ant PFC:

anterior prefrontal cortex; D cing: dorsal cingulate; SG cing: subgenual cingulate; vmPFC: ventromedial PFC; mOFC: medial OFC