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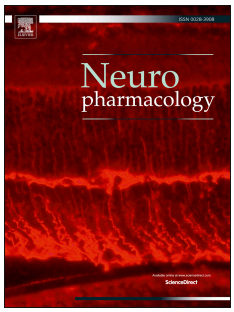

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Perspectives on Fronto-fugal Circuitry from Human Imaging of Alcohol Use Disorders

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ABSTRACT

Descriptions of the cognitive functions affected by alcohol use disorders (AUD) often highlight dysfunction of executive processes such attention, inhibitory control, working memory, and cognitive flexibility. Such complex cognitive functions have historically been ascribed to the prefrontal cortex. AUD, however, disrupts extensive areas of the brain. Structural and functional MRI studies suggest a central role for degradation of circuitry originating in the prefrontal cortex including nodes in widespread brain regions. This review features fronto-fugal circuits affected by AUD including frontocerebellar, frontolimbic, and frontostriatal networks and their relations to the salient, enduring, and debilitating cognitive and motor deficits reported in AUD.

Keywords: cerebellum, limbic system, hippocampus, striatum, circuitry, networks

INTRODUCTION

In the Diagnostic Statistical Manual of Mental Disorders 5th Edition (DSM-5) published in 2013, the biaxial distinction between alcohol abuse and alcohol dependence defined in the DSM-IV was replaced with an umbrella diagnosis of alcohol use disorder (AUD) with continua of symptoms. In the DSM-5 revision, the criterion of alcohol-related legal problems was dropped and a new craving criterion was added (**Table 1**). The criterion, "continued use despite untoward consequences," a form of perseveration, present in both DSM-IV and DSM-5, also characterizes behavior in patients with frontal lobe lesions. Our work is based on the hypothesis that some people consume alcohol to excess, even though it interferes knowingly with their wellbeing, because alcohol changes the brain. Acute alcohol intoxication reversibly affects brain while continued consumption causes brain structural and functional brain changes, or neuroadaptations that can promote the need for further alcohol consumption. In this way, AUD is a self-perpetuating disorder.

Here we focus on neural nodes, networks, and functions damaged and potentially reparable in AUD based on findings from neuroimaging and neuropsychology and organize them according to three structural and functional brain systems: frontocerebellar, frontolimbic, and frontostriatal networks.

Prefrontal Cortex Anatomy and Function

The prefrontal cortex (PFC), delimited by the presence of a granular layer IV, has been subdivided based on Brodmann areas to include dorsolateral (Brodmann areas 8, 9, 46), ventrolateral (Brodmann areas 44, 45, lateral 47), orbitofrontal (also known as ventromedial, basal, or orbital and includes Brodmann areas orbital 47 and 11), and

frontopolar (also known as anterior or rostral and includes Brodmann area 10) regions (Jacobsen, 1936). The PFC integrates information from other cortical and subcortical regions (Wilson et al., 2010): its principal role, as defined from a neuropsychological perspective, is executive functioning, which includes attentional and inhibitory control, working memory, and cognitive flexibility (Fuster, 1985; Goldman-Rakic, 1996; Mangels, 1997; Rezai et al., 1993; Zald and Andreotti, 2010).

Pattern of Neuropsychological Changes in AUD

Neuropsychological tests conducted in lesion (e.g., stroke, focal injury, surgery) studies identify disruptions in select functions associated with specific brain structures (e.g., Caramazza et al., 1990; Markowitsch, 1984; Vaina, 1989). The use of similar tests in AUD not only establishes a pattern of neuropsychological impairment and sparing, but also permits the investigation of brain structures potentially underlying the pattern of observed behaviors. Neuropsychological tests commonly administered to AUD subjects include tests of executive functions, working memory, declarative memory, visuospatial abilities, emotion, and motor ability. From these tests, AUD subjects relative to healthy controls have been found to have mild to moderate impairments of component processes involving executive function, working memory, declarative memory, visuospatial abilities, upper limb motor ability, and gait and balance (**Fig. 1**) (Bechara et al., 2001; Chanraud et al., 2007; Ellis and Oscar-Berman, 1989; Fama et al., 2009; Fernandez-Serrano et al., 2010; Maurage et al., 2014; Oscar-Berman and Marinkovic, 2007; Sullivan et al., 2002; Sullivan et al., 2000b; Sullivan et al., 2000c; Van Horn et al., 2006; Weafer and Fillmore, 2015). The pattern of neuropsychological deficits in AUD has been used to guide where to look in the brain for compromise.

Prefrontal Cortex in Normal Aging and AUD

Normal aging has profound effects on brain structure including expansion of the ventricles and decreases in tissue volume (e.g., Ge et al., 2002; Pfefferbaum et al., 1994; Pfefferbaum et al., 2013; Symonds et al., 1999; Tang et al., 2001). Relevant to the current discussion, the PFC naturally atrophies with age (Calso et al., 2016; Mander et al., 2013; Schretlen et al., 2000). Data from normal aging permits modeling of age-related brain changes (Cabeza and Dennis, 2013) and permits detection of age-disease interactions. Older individuals with AUD, for example, have disproportionate volume deficits in frontal gray and white matter relative to their younger counterparts, independent of age of AUD onset (Pfefferbaum et al., 1997).

Postmortem evaluation of AUD brains has noted biochemical disturbances in frontal regions including effects on gene, protein, and receptor expression (e.g., Alexander-Kaufman et al., 2006; Henriksson et al., 2008; Lewohl et al., 2000; Mayfield et al., 2002; Mitsuyama et al., 1998; Watanabe et al., 2009). Synaptic loss (i.e., Brodman's area 10, Brun and Andersson, 2001), changes in neuronal morphology, and decreases in neuronal density have also been reported in the AUD frontal cortex (Harper and Kril, 1989; Harper et al., 1987; Kril et al., 1997). Indeed, neuronal loss in the frontal lobes in AUD might explain cognitive deficits that persist with abstinence.

Magnetic resonance imaging (MRI) tools have confirmed postmortem findings of a specific vulnerability of frontal regions in AUD relative to healthy control individuals including volume deficits (Cardenas et al., 2011; Chanraud et al., 2007; Fein et al., 2002; Jernigan et al., 1991; Kubota et al., 2001; Makris et al., 2008; Pfefferbaum et al., 1998; Sullivan et al., 1998), low rates of glucose metabolism (Moselhy et al., 2001;

Volkow et al., 1990; Volkow et al., 2008), and depressed BOLD responses (e.g., during inhibition tasks Cservenka and Nagel, 2012; Li et al., 2009; Marinkovic et al., 2012; O'Daly et al., 2012), possibly related to altered resting state activity of executive control networks (Krmpotich et al., 2013; Weiland et al., 2014; Zhu et al., 2015). Additionally, MR spectroscopy (MRS) studies with voxels placed in frontal regions report lower levels of the brain metabolite, N-acetylaspartate (NAA) in recently sober AUD subjects relative to healthy controls (Bendszus et al., 2001; Durazzo et al., 2004; Durazzo et al., 2010; Fein et al., 1994; Jagannathan et al., 1996; Meyerhoff et al., 2004; Schweinsburg et al., 2003; Seitz et al., 1999). Although the frontal lobes are considered a primary site of pathology in AUD (Moselhy et al., 2001; Oscar-Berman and Hutner, 1993), expected correlations between relatively simple measures such as volumes of frontal lobes and performance on relevant neuropsychological tests in AUD have not always been forthcoming. Instead, circuitry originating and moving away from the frontal cortex (i.e., fronto-fugal) has been proposed to underlie some of the distinct cognitive and motor functions shown in behavioral studies to be impaired in AUD (Geschwind and Kaplan, 1962; Sullivan et al., 2003a; Sullivan and Pfefferbaum, 2005; Thiebaut de Schotten et al., 2015).

Frontocerebellar Systems

The frontocerebellar network includes efferent pathways from frontal lobes to cerebellum via pons and afferents to frontal lobes from cerebellum via thalamus (**Fig. 2)** (Ramnani and Miall, 2001). To our knowledge, the anatomy linking frontal brain regions with the cerebellum was first proposed by Dr. Henrietta C. Leiner (Leiner et al., 1986, 1989; Leiner et al., 1993a; Leiner et al., 1993b; Leiner et al., 1993c; Leiner et al.,

1993d). Connections between the frontal cortex and cerebellum were confirmed by careful anatomic work in monkeys using viral tracing methods to identify parallel closed loops forming frontocerebellar circuits that support dissociable behaviors (Kelly and Strick, 2003; Middleton and Strick, 1994). Neuroimaging studies confirmed the presence of segregated corticocerebellar loops (Habas et al., 2009; Krienen and Buckner, 2009; Schmahmann and Pandya, 1997). Examples of these divergent but parallel loops include: (1) the motor network, involving motor lobules of the cerebellar vermis (e.g., IV, V, VI) and motor cerebral cortices (Biswal et al., 1995) (2) the executive network, involving the cerebellar neocortex (e.g., lobule VII, lobule VIII, Crus I, and Crus II) and PFC sites (e.g., Brodmann areas 9 and 46).

There is some initial evidence that a family history of AUD is associated with altered frontocerebellar connectivity in alcohol naïve youth (Herting et al., 2011). In adults with AUD, structural MRI has demonstrated that relative to healthy controls, the volumes of the pons, thalamus, cerebellar hemispheres, and cerebellar vermis are smaller (**Fig. 3)** (Chanraud et al., 2007; Pfefferbaum et al., 1992; Sullivan et al., 2000a; Sullivan et al., 1998; Sullivan et al., 2003b). These findings are apparently generalizable as AUD cohorts in both the US and France relative to healthy control individuals show similar volume deficits (i.e., smaller volumes of pons, thalamus, cerebellar hemispheres and vermis, and frontal lobes (**Fig. 4)** (Le Berre et al., 2014).

In addition to identifying volume compromise in nodes of the frontocerebellar circuit, further support for the involvement of this network in AUD (Sullivan et al., 2003a; Sullivan and Pfefferbaum, 2005) emerged from work seeking a neural substrate for ataxia. Body sway, measured with posturographical recordings from a force platform, is

far greater in AUD individuals, even after 1 month of sobriety, than in age-matched, low drinking individuals (e.g., Bauer, 1993; Diener et al., 1984a; Ledin and Odkvist, 1991; Scholz et al., 1986; Sullivan et al., 2000a). Correlational analyses revealed that a longer sway path during quiet standing in AUD is associated with a smaller volume of the anterior superior vermis of the cerebellum (Sullivan et al., 2000a; Sullivan et al., 2010a), recapitulating findings observed in patients with lesions of the cerebellar vermis (Diener et al., 1984b). Whereas those with lesions of the vermis do not benefit from visual cues (Diener et al., 1984b), those with AUD successfully used vision to normalize sway (Sullivan et al., 2006). These findings are in contrast to healthy aging men and women, wherein greater postural sway was associated with ventricular and sulcal enlargement and white matter hyperintensity burden (Sullivan et al., 2009). Truncal tremor, measured by analyzing the temporal frequency of the sway path, is also evident in individuals with AUD: tremor at 3-5 Hz (Koller et al., 1985) and 5-7 Hz has been reported (Sullivan et al., 2010b; Sullivan et al., 2015). As with sway path, tremor (both low- (i.e., 3-5 Hz) Sullivan et al., 2006 and high- (i.e., 5-7 Hz)) in AUD is associated with vermian volume (Sullivan et al., 2015). Tremor elicited in these two frequency bands by cognitive challenge during quiet standing showed degradation of separate brain systems: the lower frequency tremor was associated with integrity of the cerebellar hemispheres and superior cingulate bundles, whereas higher frequency tremor correlated with motor cortex and internal capsule integrity (Sullivan et al., 2015).

Further evidence indicates that recruitment of functionally intact cerebellar loops in AUD can compensate for otherwise impaired performance on tasks requiring, for example, visuospatial or working-memory skills (Sullivan and Pfefferbaum, 2005). A

biological interpretation is that the recruitment of an unaffected loop parallel to the affected one leads to rapid changes in connectivity, which depend on already present but “silent” connections rather than the creation of new ones (Nakayama et al., 2005). For example, in AUD, equivalent performance on a verbal working memory task is associated with increased, bilateral activation of Brodmann areas 44/45 (left frontal) and right superior cerebellum (**Fig. 5**) (Desmond et al., 2003; Desmond et al., 1997). In further investigation of verbal working memory, individuals with AUD activate frontal and cerebellar regions, a task accomplished by controls with only the frontal system (Desmond et al., 2003). Similarly, exploratory analysis of language skills revealed that, even though individuals with AUD show comparable performance in terms of error rates and response time relative to controls, they exhibit greater fMRI response in the left middle frontal gyrus, right superior frontal gyrus, and cerebellar vermis relative to controls (Chanraud-Guillermo et al., 2009). During an impulsivity task, AUD subjects with compromised frontocerebellar functional circuitry recruited an alternative network, including the premotor cortex, to perform well under low-risk, unambiguous conditions (Jung et al., 2014). In summary, the positive outcome of *shift and expansion* in functional anatomy can be apparently normal performance, but this comes at the price of usurping reserve that reduces processing capacity for conducting multiple tasks simultaneously and efficiently (e.g., De Rosa et al., 2004; Desmond et al., 2003; Jung et al., 2014; Pfefferbaum et al., 2001; Sullivan and Pfefferbaum, 2005; Tapert et al., 2001).

Connectivity analyses of fMRI data collected at rest has identified intrinsic functional connectivity networks that are more activated and synchronous at rest than while engaged in a task (Biswal et al., 1995; Raichle and Snyder, 2007; Van Dijk et al.,

2010). The initially identified network, referred to as the default mode network (DMN), has as a seed – the start point of the correlation between that region and the activity in the rest of the brain – the posterior cingulate cortex: its activity is correlated with medial PFC and other sites, making a functional network. DMN integrity may provide an index of neural health and flexibility (Chanraud et al., 2011). Individuals with AUD showed the same pattern of activation synchrony as controls but had less robust synchrony between posterior cingulate and cerebellar regions (Chanraud et al., 2011). During a spatial working memory task, whereas controls recruited prefrontal-cerebellar regions VI/Crus I known to subserve working memory, individuals with AUD recruited two other parallel frontocerebellar loops: dorsolateral PFC-cerebellar VIII system during rest and dorsolateral PFC-cerebellar VI system while task-engaged. Greater synchronous activity between cerebellar lobule VIII and dorsolateral PFC at rest and greater activation within cerebellar lobule VI and dorsolateral PFC while preforming a task predicted better working memory performance. Thus, higher intrinsic cerebellar activity in AUD was an adequate condition for triggering task-relevant activity in the frontal cortex required for normal working memory performance (Chanraud et al., 2013). Together, these findings suggest that despite equivalence in behavioral performance, either a functional reorganization of brain systems or an invocation of inappropriate brain systems has occurred as a consequence of AUD.

Frontolimbic Systems

Herein, the frontolimbic network includes connections between the PFC and the insula, anterior cingulate, amygdala, hippocampus, mammillary bodies, and thalamus (**Fig. 6**) (Broca, 1878; Newman and Harris, 2009; Papez, 1937). Although the limbic

system is highly interconnected with the nucleus accumbens (Morgane et al., 2005), this and other basal ganglia structures will be discussed in the section on Frontostriatal Systems. Frontolimbic circuitry was identified as relevant to AUD (e.g., Harris et al., 2008; Lingford-Hughes et al., 2012; Wrase et al., 2008) in the search of a neural substrate for mild memory impairment (Cermak, 1987; Fama et al., 2009; Goldman et al., 1991; Oscar-Berman and Ellis, 1987). This circuitry is also relevant to allostatic load (e.g., Herman, 2012) and negative emotions (e.g., irritability, anxiety, depression, the so-called, “dark side of addiction”) that emerge when alcohol is not available (Koob and Le Moal, 2005; Lu and Richardson, 2014).

The sequelae of ‘uncomplicated” AUD marked by mild to moderate memory impairment has been compared with individuals with AUD that have Korsakoff’s syndrome (KS), which is marked by dense anterograde amnesia, the result of thiamine deficiency and Wernicke’s encephalopathy (WE) (Dreyfus and Victor, 1961). Classically, WE is characterized by the detection of three clinical signs: ophthalmoplegia, ataxia, and confusion. In “uncomplicated” AUD, however, the incidence of neuropathological signs of WE seen postmortem remains higher than recognized in vivo (Harper, 1983; Harper et al., 1986). In an attempt to diagnose WE using objective in vivo criteria, a chart review of postmortem cases evaluated 4 general operational markers in place of the 3 traditional, clinical signs: signs of oculomotor abnormalities in place of ophthalmoplegia, any indication of cerebellar dysfunction in place of ataxia, altered mental state in place of confusion, and additionally noting evidence for dietary deficiency. Having only 2 of 4 of these more generalized indicators correlated with presence of neuropathology indicative of WE (Caine et al., 1997). Using operationalized

definitions of the 4 signs, we evaluated 56 AUD subjects relative to 38 healthy controls and found that although none of the AUD subjects presented with the 3 classical signs, a large proportion of this group met 1 (>50%) or 2 (16%) criteria; only about one quarter of the group were free of signs. The pattern of functional impairments quantified using neuropsychological tests across the AUD group, without consideration of the criteria, indicated only mild to moderate deficits in a few functional domains. However, when the AUD group was divided by the number of criteria met, AUD individuals meeting no criteria performed at normal levels in all domains, those meeting 1 criterion showed modest selective compromise, and those meeting 2 criteria were the most widely and severely impaired (Pitel et al., 2011). This AUD cohort was also used to demonstrate that poor memory performance was related to lower blood levels of the biologically relevant form of thiamine, thiamine diphosphate (TDP) (Pitel et al., 2011).

Although amnesic disorders are often attributed to disturbances of the hippocampus (Sullivan et al., 2000a; Sullivan et al., 2002), the classical neuropathology of KS has been primarily linked to atrophy of the mammillary bodies (Bigler et al., 1989). Compared with controls, KS subjects show profound bilateral volume deficits of the mammillary bodies: uncomplicated, non-amnesic individuals with AUD also have mammillary bodies volume deficits, but to a milder degree. The thalamus and hippocampus likewise show graded volume deficits in these study populations (**Fig. 7**) (Le Berre et al., 2014; Sullivan et al., 1999; Sullivan and Pfefferbaum, 2009). Although the mammillary bodies appear to be the primary site of damage in KS, input from other brain regions, including the frontal cortex, hippocampus, cerebellum, and amygdala,

may have a modulatory role on memory function in AUD (Kril and Harper, 2012; Poldrack and Gabrieli, 1997).

As was discussed for the frontocerebellar systems, there is evidence of sparing of particular structures of the frontolimbic system. For example, inferior cingulate cortical volume appears to be relatively spared in AUD and may compensate for compromised frontal regions and contribute to successful recall (Rosenbloom et al., 2009). In a face-name associative learning task, those with AUD had preserved limbic activation but lower cerebellar (Crus II) activation than controls (Pitel et al., 2013). This finding could be the result of functional reorganization: functional connectivity analysis at rest showed that in controls, the left hippocampus and left Crus II are positively synchronized, while in AUD these two regions are negatively synchronized (Pitel et al., 2013).

In addition to its role as a substrate for memory, the frontolimbic system is involved with emotional regulation. In social drinkers, acute alcohol attenuates the response to fearful stimuli in limbic regions (Gilman and Hommer, 2008). In another fMRI study, control subjects showed stronger activation in the amygdala and hippocampus when viewing faces with emotional relative to neutral expressions, whereas individuals with AUD responded in an undifferentiated manner to all facial expressions (Marinkovic et al., 2009). The observation that individuals with AUD respond to emotionally-valenced stimuli in an undifferentiated manner is consistent with clinical evidence of their interpersonal difficulties and may constitute a relapse factor (Kornreich et al., 2002). In the AUD participants, amygdala activity was inversely correlated with an increase in lateral PFC activity as a function of behavioral deficits (Marinkovic et al., 2009). PFC activity as a compensation for blunted limbic activity is in

agreement with distributed network engagement and suggests that in AUD, the brain relies on frontal rather than temporal areas to maintain behavioral adequacy when faced with emotionally or socially challenging situations.

Frontostriatal Systems

The frontostriatal circuits connect frontal lobe regions with the basal ganglia (**Fig. 8**) (Alexander et al., 1986; Tekin and Cummings, 2002). Interest in the frontostriatal system in AUD emerged from the rich literature on dopaminergic activity in substance dependence (e.g., Noble, 1996). Single photon emission computed tomography (SPECT) and Positron Emission Tomography (PET) studies have quantified and reported disrupted dopamine transmission in AUD (Boileau et al., 2003; Ebert et al., 2002; Guardia et al., 2000; Heinz et al., 2004; Laine et al., 1999a; Laine et al., 1999b; Martinez et al., 2005; Repo et al., 1999; Tiihonen et al., 1995; Tiihonen et al., 1998; Volkow et al., 1996; Yoder et al., 2005).

Nodes of the frontostriatal system are affected by AUD (e.g., Namura and Hishikawa, 1997). Volumes of the caudate, putamen, and nucleus accumbens are smaller in AUD men than age-matched control men, regardless of length of sobriety (**Fig. 9**) (Makris et al., 2008; Sullivan et al., 2005; Wrase et al., 2008). Whether smaller volumes (Benegal et al., 2007) or altered activation patterns (Acheson et al., 2009; Andrews et al., 2011; Casement et al., 2015; Heitzeg et al., 2008; Heitzeg et al., 2010; Nees et al., 2012; Yau et al., 2012) in reward-related regions can predict higher risk for AUD remains equivocal. While there are inherent difficulties in resolving brain volumes as a function of premorbid condition or outcome of alcohol exposure, another confounding factor may be sex: binge drinking men showed smaller prefrontal, striatal,

and medial temporal lobe volumes relative to non-binge drinking men, but binge drinking women showed the inverse pattern of larger volumes of these areas relative to non-binge drinking women (Kvamme et al., 2016). A recent study of 872 Mexican-American individuals evaluating subcortical volumes suggested that amygdala volume, but not volumes of hippocampus, caudate, putamen, pallidum, or thalamus, is sensitive to genetic predisposition for AUD (Dager et al., 2015). In an fMRI study, adolescents that were family history positive for AUD showed a pattern of nucleus accumbens connectivity to supplementary sensorimotor area and precuneus that correlated positively with and mediated the relationship with sensation seeking and also with total volume of alcohol consumed (Weiland et al., 2013). This latter finding indicates that a number of logistical and scientific challenges, including the use of prospective, longitudinal neuroimaging data from alcohol-naïve pre-adolescents, remain to be addressed to distinguish clearly neurodevelopmental precursors from the consequences of alcohol exposure (Fishbein et al., 2016).

One of the first relevant fMRI studies showed that alcohol-associated visual stimuli activated the ventral putamen in AUD but not control subjects (Braus et al., 2001). This was followed by several visual cue-reactivity fMRI studies in AUD showing brain regions, particularly the basal ganglia (Wrase et al., 2002), including the putamen, nucleus accumbens, and medial PFC, responding more intensely to images of alcohol vs. other images (Grusser et al., 2004; Ihssen et al., 2011; Myrick et al., 2004; Myrick et al., 2008; Seo et al., 2011; Wrase et al., 2006). Olfactory (Bragulat et al., 2008; Kareken et al., 2010; Kareken et al., 2004; Schacht et al., 2013; Schacht et al., 2011) and taste cues (Claus et al., 2011; Feldstein Ewing et al., 2010; Filbey et al., 2008a; Filbey et al.,

2008b; Myrick et al., 2010) resulted in similar activation patterns in mesocortical structures. It appears that brain activation in individuals with AUD is biased towards responding to alcohol-associated cues, as the ventral striatum shows greater activation in response to alcohol cues but lower activation during anticipation of monetary gain in AUD relative to control individuals (Beck et al., 2009; Wrase et al., 2007). Additional non-drug, monetary incentive, reward-task based fMRI studies also demonstrate altered basal ganglia functioning in AUD relative to healthy subjects (Bjork et al., 2012; de Greck et al., 2009; Forbes et al., 2014).

One theory of the neural correlates of the transition from casual to compulsive, uncontrolled consumption of alcohol is a shift from goal-directed behaviors executed by regions of the PFC to more automatic, habitual behaviors driven by appetitive regions such as the caudate and putamen (Camchong et al., 2014; Everitt and Robbins, 2005; Sjoerds et al., 2013). Indeed, tests of this hypothesis using implicit tasks (Ames et al., 2014; Virag et al., 2015) support a dual processing framework: habits are mediated through neural circuitry dependent on the striatum, while more controlled behaviors are mediated through neural circuitry more dependent on the PFC (Fein and Cardenas, 2015). Another way disturbances to these systems have been reported is by demonstrating greater synchrony in executive control networks (including regions such as the anterior cingulate cortex and dorsolateral PFC) and lower synchrony in appetitive drive networks (including regions such as the nucleus accumbens, thalamus, and caudate) in abstinent AUD relative to healthy control individuals (Camchong et al., 2013a; Camchong et al., 2013b, c). Other studies evaluating the neural substrate of compulsive alcohol use have reported a shift in alcohol-cue reactivity from ventral to

dorsal striatum (Vollstadt-Klein et al., 2010). A more refined framework suggests that the shift from goal-directed to habitual behaviors is mediated via subtly different cortical to subcortical circuitry: dorsal prelimbic PFC to nucleus accumbens *core* playing a role in the acquisition of goal-directed actions while the more ventral infralimbic PFC to nucleus accumbens *shell* circuitry plays a role in the expression of habitual behavior (Barker et al., 2015). Indeed, in nonhuman primates, the nucleus accumbens shell and core subregions are organized in a series of parallel circuits linked in an ascending spiral to the dorsal striatum in a manner that could account for the transition from goal-directed to habitual behaviors during the development of addiction (Renteria et al., 2016). Whether these bidirectional nucleus accumbens circuits are relevant to human addiction will require further evaluation and the development of imaging methods with higher resolution and greater detection capabilities for microstructure and neurochemistry (Lucas-Neto et al., 2015).

Highlighting the relevance of frontostriatal systems to behavioral regulation in AUD, abnormal connectivity (e.g., between the dorsolateral PFC and striatum) predicts impairments in learning (Park et al., 2010) and response inhibition (Courtney et al., 2013; Muller-Oehring et al., 2013; Schulte et al., 2012). Impaired functional connectivity may in fact be due to compromised anatomical integrity of corticostriatal fibers (Yeh et al., 2009).

Summary and Conclusions

For exposition, the three systems described herein were represented as independent and non-overlapping and as mediating specific neuropsychological deficits in AUD. Our work and much of the literature cited includes data from normal aging to

permits detection of age-disease interactions. In other words, the deficits in brain and behavior described are a function of AUD and not merely aging. The literature reviewed herein suggests that frontocerebellar systems mediate motor and working memory deficits, frontolimbic systems mediate semantic memory impairments and emotional dysregulation, and frontostriatal systems mediate the transition from goal-directed to habitual behaviors in AUD. These frontally-based networks, however, are highly interconnected and whether a certain brain region (e.g., thalamus) is included in one system or another can depend on the scope and perspective of the work (e.g., psychology or imaging) (e.g., Fein and Cardenas, 2015; Yan and Li, 2009) or the behavior evaluated (e.g., affect may be subserved by frontolimbic or frontostriatal systems) (Alexander et al., 1986; Schmahmann and Pandya, 2008). Although we have described fronto-fugal pathways, the cerebellum, limbic system, and basal ganglia are also interconnected. For example, the output of the cerebellum, the dentate nucleus, projects to the input structure of the basal ganglia, the striatum (Hoshi et al., 2005). The ventral tegmental area can act as a mediator of dialogue between these systems because dopamine projections target, among other regions, the cerebellum, thalamus, hypothalamus, nucleus accumbens, amygdala, hippocampus, and prefrontal cortices (Oades and Halliday, 1987). Information from these subcortical regions may also be integrated in regions not discussed herein, such as the inferior parietal lobule, which has inputs from the hippocampus and cerebellum and subserves functions including attention and calibration of eye-hand coordination (Clower et al., 2001). Together, current data demonstrate that the cognitive and motor impairments noted in AUD are the result of disturbances in the coordinated activity of a number of regions interacting

with frontal structures, rather than a single area in the PFC. We speculate that a more refined knowledge of the structures and functions that are compromised and which are spared in AUD could enhance therapeutic efforts to redirect neural recruitment from the usual but disrupted paths and networks to functional alternatives, possibly through behavioral therapy. This knowledge might also inform pharmacological efforts for initiating sobriety, maintaining abstinence and promoting recovery.

Conflict of interest: The authors declare no competing financial interest in relation to the work described here.

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Figure Legends

Fig. 1. Profile of cognitive and motor deficits in men and women with Alcohol Use Disorders (AUD) relative to healthy control individuals. Apart from balance, AUD men and women show a similar pattern of impairment. Modified from Sullivan, E. V., Rosenbloom, M. J., Pfefferbaum, A., 2000c. Pattern of motor and cognitive deficits in detoxified alcoholic men. Alcohol Clin Exp Res 24, 611-621.

Fig. 2. The frontocerebellar network with key nodes highlighted including the prefrontal cortex (PFC), thalamus (T), pons (P), and cerebellm (Cbl).

Fig. 3. Mean ± SE of volumes (expressed as standardized *Z*-scores, adjusted for normal variation in intracranial volume and age) of pons, cerebellar hemispheres, and cerebellar vermis (quantified as areas V1-V4) in healthy control subjects (black), subjects with Alcohol Use Disorders (AUD, blue), and those with Korsakoff's syndrome (KS, red). The expected value of the controls is 0 with a standard deviation = 1; low values of volume in AUD and KS groups reflect volume deficits. The pons, cerebellar hemispheres, and vermis each demonstrate a trend toward a graded effect from AUD to KS. Modified from Sullivan, E. V., Pfefferbaum, A., 2009. Neuroimaging of the Wernicke-Korsakoff syndrome. Alcohol Alcohol 44, 155-165.

Fig. 4. Results from a large-scale study pooling MRI data across 2 French sites (Orsay and Caen) and our US site, resulting in normative data from 287 healthy controls. Here, the age-corrected Z-scores derived from the common control group are now coded by color shading and the volumes of the regions of interest were identified with parcellation of selective brain structures—the green represents frontocerebellar regions and mustard represents nodes of the limbic system that showed volume deficits in AUD compared with controls. The brighter colors indicate even greater severity and extent of deficits in KS than AUD or controls, again indicative of the graded deficit concept. From e Berre, A. P., Pitel, A. L., Chanraud, S., Beaunieux, H., Eustache, F., Martinot, J. L., Reynaud, M., Martelli, C., Rohlfing, T., Sullivan, E. V., Pfefferbaum, A., 2014. Chronic alcohol consumption and its effect on nodes of frontocerebellar and limbic circuitry: comparison of effects in France and the United States. Hum Brain Mapp 35, 4635-4653.

Fig. 5. AUD activated frontal and cerebellar regions to maintain verbal material in working memory, a task accomplished by controls with the frontal system only.

Fig. 6. The frontolimbic network with key nodes highlighted including the prefrontal cortex (PFC), insula (ins), anterior cingulate (AC), amygdala (amy), hippocampus (hip), mammillary bodies (MB), and thalamus (T).

Fig. 7. Mean ± SE of volumes (expressed as standardized *Z*-scores, adjusted for normal variation in intracranial volume and age) of thalamus and hippocampus in healthy control subjects (black), subjects with Alcohol Use Disorders (AUD, blue), and those with Korsakoff's syndrome (KS, red). The thalamus and hippocampus both demonstrate a trend toward a graded effect from AUD to KS. Modified from Sullivan, E.

V., Pfefferbaum, A., 2009. Neuroimaging of the Wernicke-Korsakoff syndrome. Alcohol Alcohol 44, 155-165.

Fig. 8. The frontostriatal network with key nodes highlighted including the prefrontal cortex (PFC), striatum (Str), globus pallidus (GP), and ventral tegmental area (VTA).

Fig. 9. Volume measures (expressed as age- and intracranial volume -corrected *Z* scores) for mean bilateral volumes of caudate, putamen, and nucleus accumbens for 51 control subjects, 6 AUD subjects who had been drinking in the past 3 weeks, and 19 AUD subjects with a median sobriety of 1 year. Modified from Sullivan, E. V., Deshmukh, A., De Rosa, E., Rosenbloom, M. J., Pfefferbaum, A., 2005. Striatal and forebrain nuclei volumes: Contribution to motor function and working memory deficits in alcoholism. Biological Psychiatry 57, 768-776.

Table 1. DSM-IV versus DSM-5 criteria for Alcohol Abuse, Dependence, or Use Disorder

DSM-IV Alcohol Abuse or Alcohol Dependence	DSM-5 Alcohol Use Disorder
Two distinct but hierarchical constucts: alcohol abuse only diagnosed in absence of alcohol dependence	*A single, unitary construct, with moderate and severe diagnoses based on number of criteria endorsed.*
alcohol abuse: 1+ abuse criteria required	*moderate AUD: 2-3 criteria required*
alcohol dependence: 3+ dependence criteria required	*severe AUD: 4+ criteria required*
Abuse Criteria:	**Use Disorder Criteria:**
recurrent use resulting in failure to fulfill work, school, home obligations.	recurrent use resulting in failure to fulfill work, school, home obligations.
recurrent use when physically hazardous	recurrent use when physically hazardous
recurrent use despite social or interpersonal problems	recurrent use despite social or interpersonal problems
recurrent use despite legal problems	-
Dependence Criteria	
tolerance	tolerance
withdrawal or use to relieve/avoid withdrawal	withdrawal or use to relieve/avoid withdrawal
drinking in larger amounts or for longer than intended	drinking in larger amounts or for longer than intended
persistent desire or unsucessful attempts to reduce or stop drinking	persistent desire or unsucessful attempts to reduce or stop drinking
inordinate time spent obtaining alcohol	inordinate time spent obtaining alcohol
societal, occupational, recreational activites reduced	societal, occupational, recreational activites reduced
continued use despite physiological or psychological problems	continued use despite physiological or psychological problems
	craving

Fig. 1

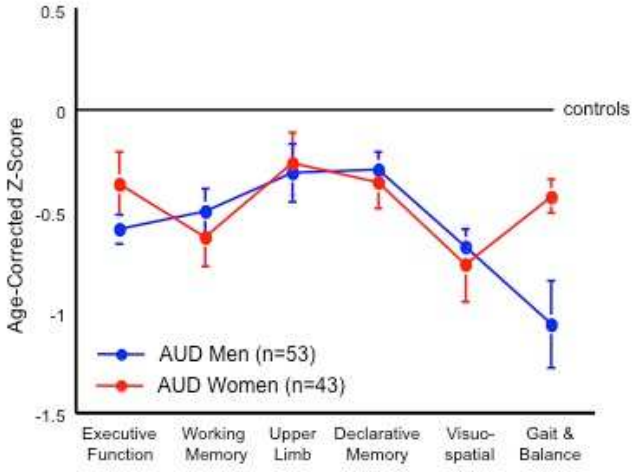


Fig. 2

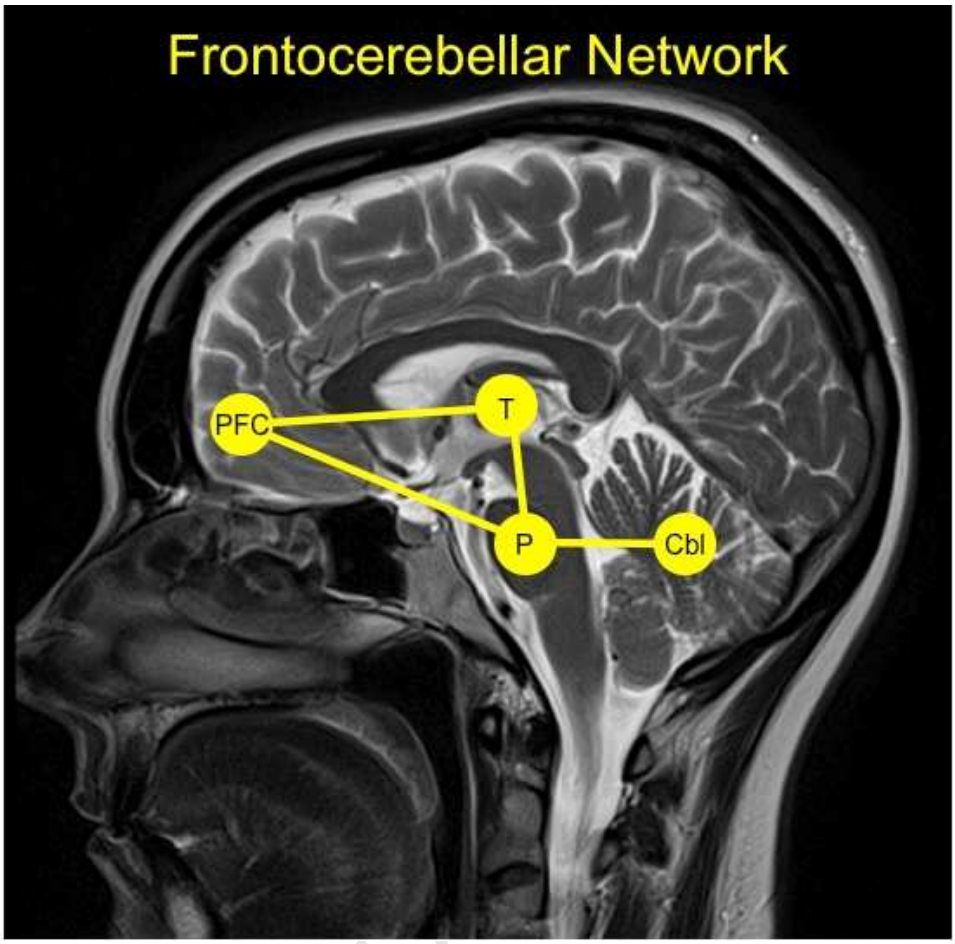


Fig. 3

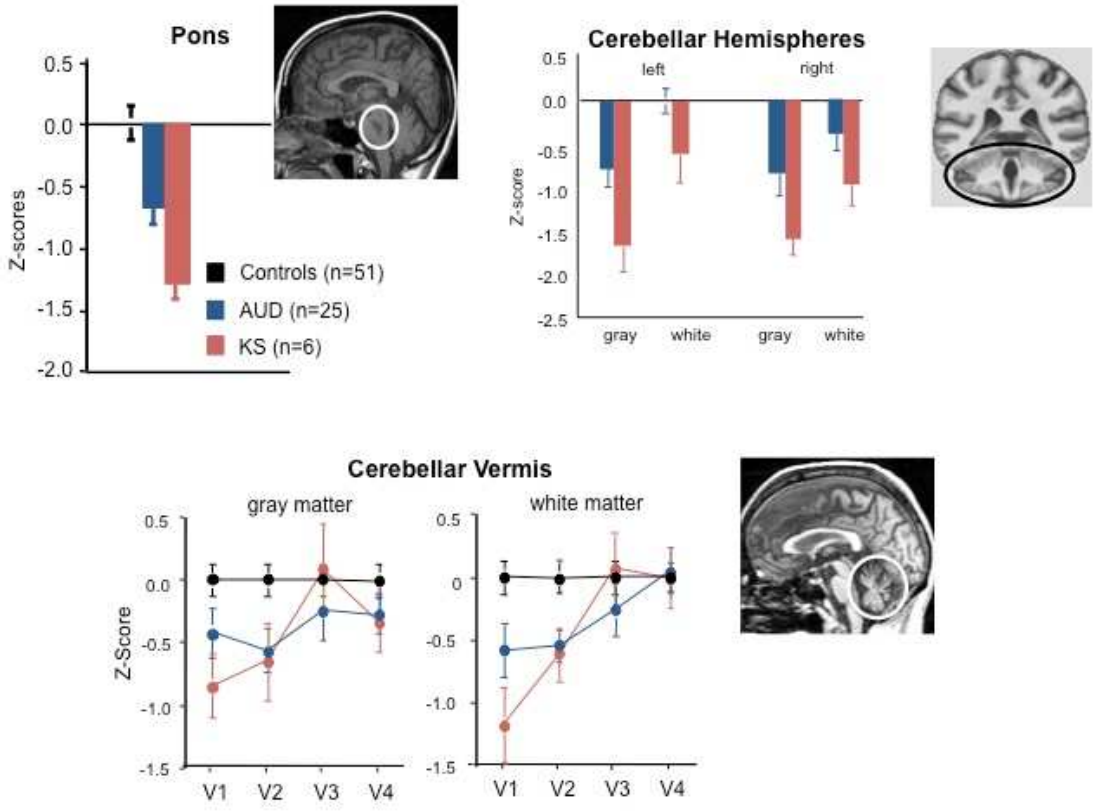


Fig. 4

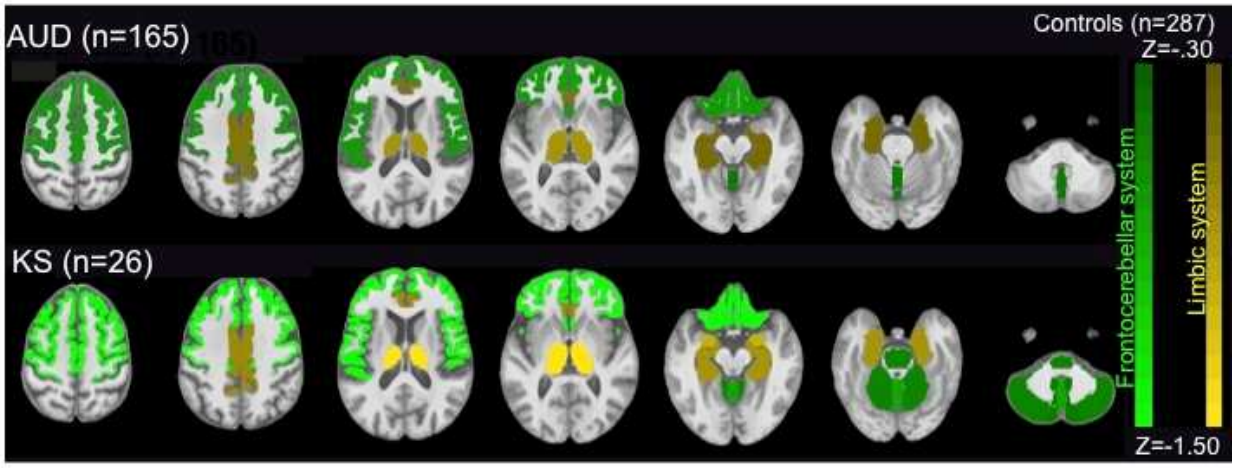


Fig. 5

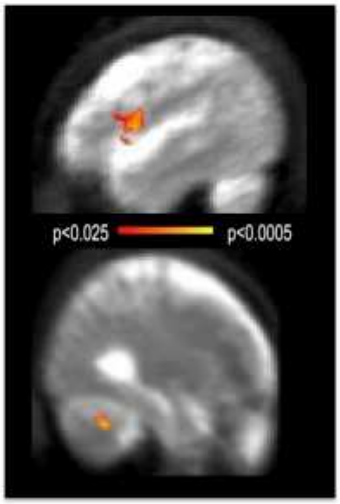


Fig. 6

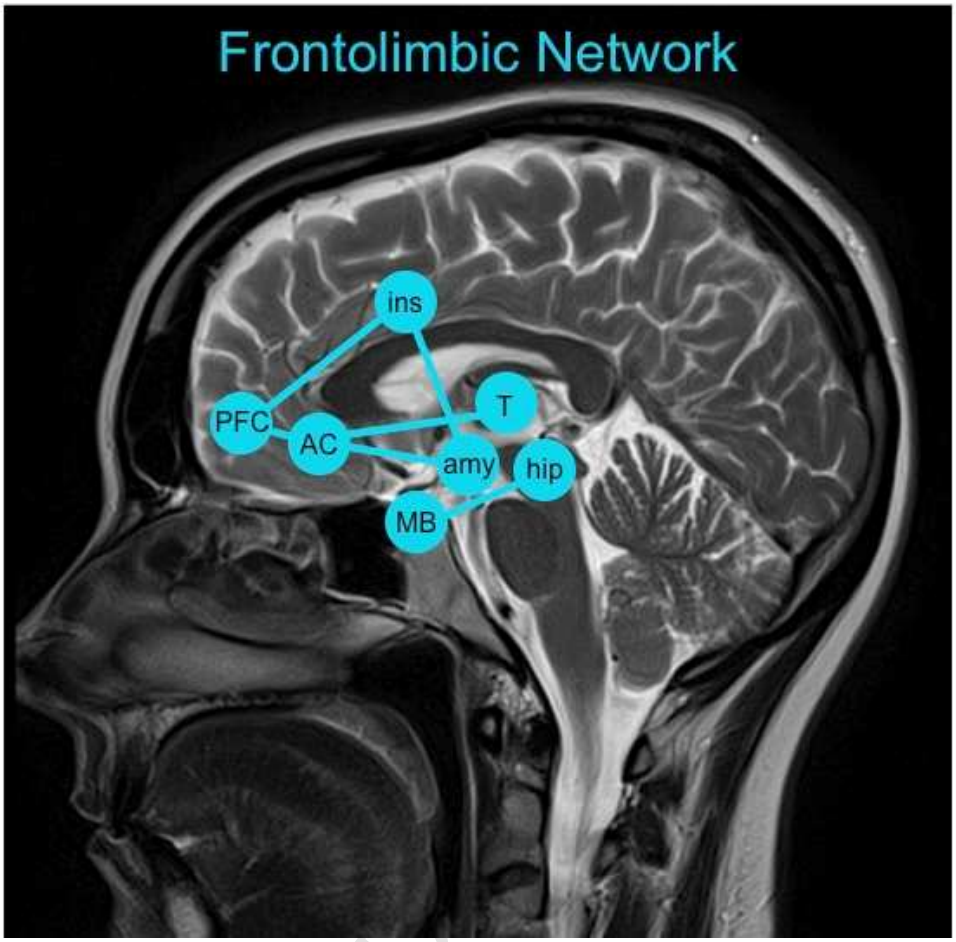


Fig. 7

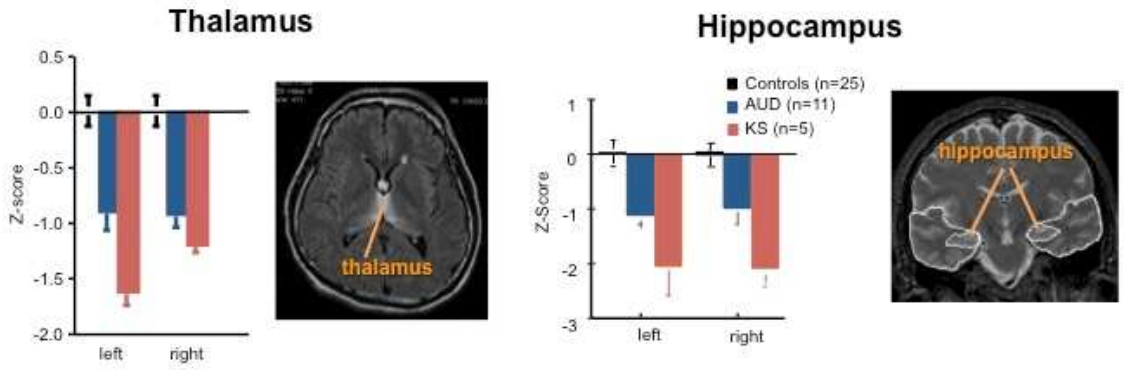


Fig. 8

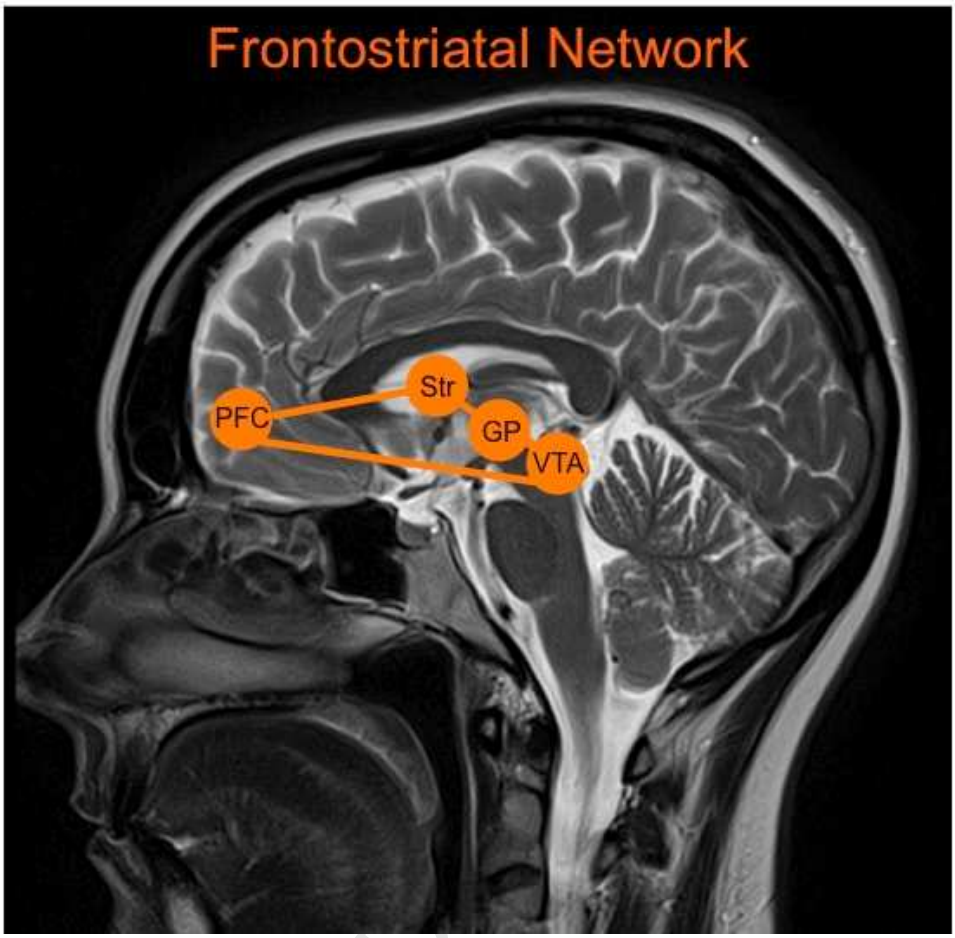
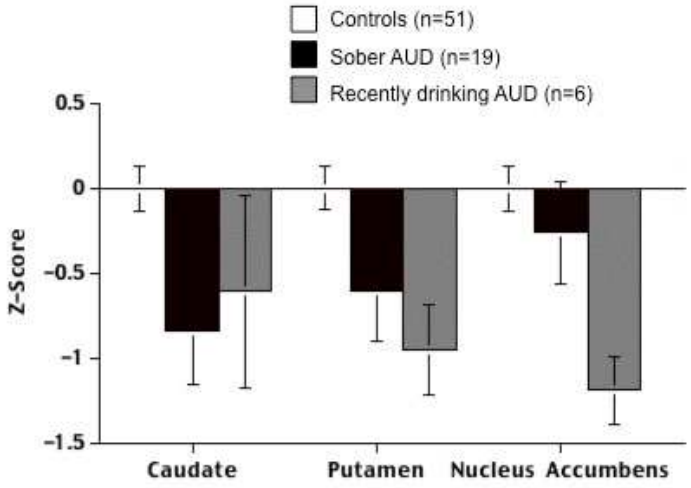


Fig. 9



Highlights

- Brain structures and functions damaged in Alcohol Use Disorders (AUD) are presented based on findings from neuroimaging and neuropsychology studies.
- Compromised networks are organized according to three structural and functional brain systems: frontocerebellar, frontolimbic, and frontostriatal.
- Frontocerebellar systems underlie motor and working memory deficits in AUD.
- Frontolimbic systems underlie declarative memory and emotional regulation deficits in AUD.
- Frontostriatal systems are involved in the transition from casual to compulsive alcohol consumption.