

Review

Impulsivity, frontal lobes and risk for addiction

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ABSTRACT

Alcohol and substance abuse disorders involve continued use of substances despite negative consequences, i.e. loss of behavioral control of drug use. The frontal-cortical areas of the brain oversee behavioral control through executive functions. Executive functions include abstract thinking, motivation, planning, attention to tasks and inhibition of impulsive responses. Impulsiveness generally refers to premature, unduly risky, poorly conceived actions. Dysfunctional impulsivity includes deficits in attention, lack of reflection and/or insensitivity to consequences, all of which occur in addiction [Evenden JL. Varieties of impulsivity. *Psychopharmacology* (Berl) 1999;146:348–361.; de Wit H. Impulsivity as a determinant and consequence of drug use: a review of underlying processes. *Addict Biol* 2009;14:22–31]. Binge drinking models indicate chronic alcohol damages in the corticolimbic brain regions [Crews FT, Braun CJ, Hoplight B, Switzer III RC, Knapp DJ. Binge ethanol consumption causes differential brain damage in young adolescent rats compared with adult rats. *Alcohol Clin Exp Res* 2000;24:1712–1723] causing reversal learning deficits indicative of loss of executive function [Obernier JA, White AM, Swartzwelder HS, Crews FT. Cognitive deficits and CNS damage after a 4-day binge ethanol exposure in rats. *Pharmacol Biochem Behav* 2002b;72:521–532]. Genetics and adolescent age are risk factors for alcoholism that coincide with sensitivity to alcohol-induced neurotoxicity. Cortical degeneration from alcohol abuse may increase impulsivity contributing to the development, persistence and severity of alcohol use disorders. Interestingly, abstinence results in bursts of neurogenesis and brain regrowth [Crews FT, Nixon K. Mechanisms of neurodegeneration and regeneration in alcoholism. *Alcohol Alcohol* 2009;44:115–127]. Treatments for alcoholism, including naltrexone pharmacotherapy and psychotherapy may work through improving executive functions. This review will examine the relationships between impulsivity and executive function behaviors to changes in cortical structure during alcohol dependence and recovery.

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1. Introduction: executive function and impulsivity

Executive functions in cognitive psychology control abstract thinking, rule acquisition, planning and flexibility in responses including rule shifting, as well as initiating appropriate actions and inhibiting inappropriate actions. Impulsivity has a range of definitions that generally include actions that are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation that often result in undesirable consequences (Evenden, 1999; de Wit, 2009). At times, impulsivity in personality is valuable for rapid decisions at opportune times. Components of impulsivity include attention, suppressing responses, poor evaluation of consequences and/or an inability to forgo immediate small rewards in favor of greater delayed rewards. Decision-making reflects a process in which attention is focused and a choice is made after reflecting on the expected outcomes of possible actions and/or inactions. This process requires attention, whereas impulsivity may not require attention. With repetition, decisions require less attention and may be rapid, learned, but not impulsive. Impulsivity assessments have included urgency, lack of premeditation, lack of perseverance and sensation seeking (Congdon and Canli, 2008). Urgency motivating impulsive behaviors overlaps with concepts of addiction that suggest chronic substance abuse increases reward value while decreasing inhibitory control (Jentsch and Taylor, 1999; Robinson and Berridge, 2003). Executive functions are often invoked to override responses that have been automatically elicited. The frontal lobe executive functions receive input from all sensory modalities, integrate memories and using working memory of temporary information, assemble reward and valuation information with timing of events to carry out planned behaviors. An individual's activity can be altered by environmental factors that change directed goals. For example, smelling popcorn will distract individuals, draw them to the source, induce hunger and automatically stimulate eating. This is normal; however, not all will be distracted. People, who are dieting, activate executive functions drawing attention to the distracting smell and block eating, often through a strategy of leaving the area and avoiding further distraction. Similar factors may be involved in alcoholic cues promoting drinking and causing relapse. Attention and impulse inhibition can block the movement to and eating of the popcorn or responding to alcoholic cues. Impulsivity leads to rapid responses without reflection. Impulsivity can include weak inhibitory control, lack of attention, or bad decisions. Thus, executive functions oppose impulsivity.

The multiple components of executive function are difficult to study in humans and animals, however, specific definitions such as dysfunctional impulsivity and impulsive choice have made determinations of deficits in executive psychopathology and frontal brain structure–function studies possible (Congdon and Canli, 2005; de Wit, 2009). Experimental studies suggest that specific frontal corticostriatal circuits work as stop signals (Aron et al., 2007). Deficits in impulse control are associated with adolescence, alcohol use disorders (AUD, alcoholism), other drug addiction, attention deficit/hyperactivity disorder (ADHD), anti-social personality disorder and other neuropsychiatric and neurological conditions (Congdon and Canli, 2008; Evenden, 1999). Impulsive choice is one aspect of impulsivity that involves the choice of small, sooner rewards over larger, delayed rewards (Cardinal et al., 2004). Psychological testing has used delay discounting, procedures designed to assess reward value and the ability to delay for greater rewards or to discount the greater reward for smaller immediate rewards. Delayed discounting has been used to assess impulsive choice of small, sooner rewards over larger, delayed rewards. Thus, the present value of a reward decreases as a function of duration of the delay required to receive the reward. This involves executive working memory components reducing impulsive choices, delaying responses for later greater reward (Petry, 2001). Human alcohol and drug abusers compared to never-users or ex-users show consistent deficits in delayed discounting (de Wit, 2009; Petry, 2001).

Reciprocal connections between frontal-cortical brain regions, hippocampal–amygdala limbic brain areas and striatal regions regulate goal-directed behavior (Winstanley, 2007). A fundamental aspect of addiction is continued use of alcohol or other substances. Alcoholics have deficits in working memory and decision-making that are similar to deficits found in individuals with frontal-cortical damage (Bechara, 2005; Bechara et al., 1994). Multiple components of impulsivity, including delay discounting, behavioral inhibition and poor attention, show deficits in alcohol and substance abusing individuals (de Wit, 2009). This review will relate chronic drug-induced changes in the brain to changes in behavior that underlie alcohol use disorder and other addictions. In addition, mechanisms of successful treatment involve change in behavior and brain structure during abstinence. This review will examine the relationships between drug and abstinence induced changes in impulsivity, executive function and cortical structure.

2. Frontal lobes and goal-directed activity

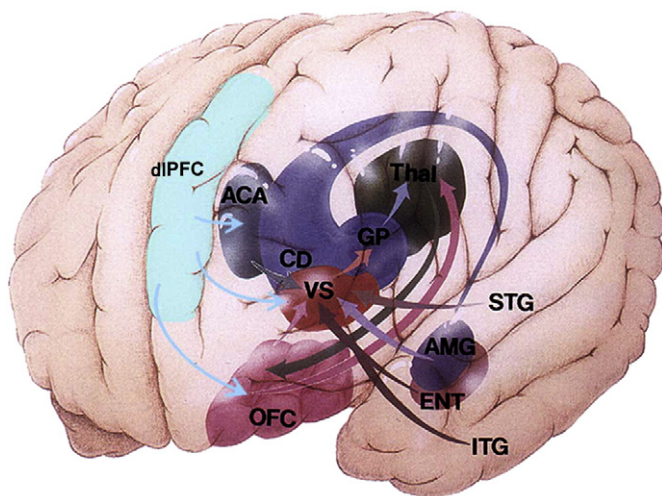
The prefrontal cortex (PFC), including orbitofrontal gyri and the anterior cingulate cortex, are important for executive functions. The PFC is defined as the projection region of the medial dorsal thalamus that includes the dorsal lateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), and orbital frontal cortex (OFC). When properly functioning, the frontal lobes equip individuals with the capacity to use past experience and knowledge to make sense of current behavior and to guide future selection of responses from their behavioral repertoire (Stuss et al., 2001). The frontal lobes are commonly divided into five parallel, though interacting, subcircuits: motor, oculomotor, dorsolateral, orbitofrontal, and anterior cingulate (Alexander et al., 1986). The dorsolateral prefrontal circuit underlies executive function, which includes the control of attention, as well as the sustained organization of behavior to solve complex problems (Cummings, 1993; Stuss and Alexander, 2000). The dlPFC is essential to draw attention to important factors and to actively select goals (Abe and Hanakawa, 2009). The medial prefrontal/cingulate circuit is critical for feedback monitoring and motivation, with lesions producing profound apathy (Bonelli and Cummings, 2007). The dlPFC and OFC is associated with behavioral regulation owing to its unique capacity to maintain and integrate sensory, affective, and associative information (Carmichael and Price, 1995a,b). These functions allow representation of expected outcomes, information that can in turn be used to guide behavior (Schoenbaum et al., 2006).

Damage to the OFC results in loss of this critical behavioral guide, producing profound deficits in self-regulation, as was first documented in the famous case of Phineas Gage (Harlow, 1848, 1868), a railway worker who survived the passage of a tamping rod through his OFC. While the personality changes, especially disinhibition, that Gage experienced are the most frequently cited consequence of his injury, the physician who documented Gage' case, John Harlow, also noted that Gage lost his ability to assign appropriate monetary value to objects (MacMillan, 2000). This deficit is consistent with the view that an essential function of the OFC is the flexible assignment of value to environmental stimuli, which critically determines how such stimuli influence our actions (Schoenbaum et al., 2006). Other consequences of OFC lesions include impulsive or perseverative behaviors (Bechara et al., 1994; Berlin et al., 2004; Rolls et al., 1994). Cases of frontotemporal dementia with OFC pathology are also marked by compulsive consummatory behaviors, including hyperphagia, gambling, and substance abuse (Gorno-Tempini et al., 2004; Ikeda et al., 2002; Rosen et al., 2005; Thompson et al., 2003; Whitwell et al., 2007; Williams et al., 2005; Woolley et al., 2007). Thus, the pattern of behavior seen with OFC damage in humans, as well as in non-human primates and rodents (Bechara, 2005; Schoenbaum et al., 2006), is highly reminiscent of addictive behavior.

The frontal lobes supervise cognitive tasks, such as memory, attention, and response selection. Intact control of response selection fundamentally underpins adaptive decision-making. Thus, decision-making impairments may be considered evidence of executive function impairment (Fig. 1). One theorized anatomical basis for such impairments is a relative dominance of signaling with an amygdala-driven impulsive system (AMG), relative to a prefrontal cortex (PFC) reflective system (Bechara, 2005). The amygdala's ability to drive impulsive, non-reflective response selection (or decision-making) is thought to stem from the amygdala's key role in conditioned responding (Balleine and Killcross, 2006), whereby appetitive or aversive stimuli (or contexts) come to trigger automatic responding to those stimuli. The product of such conditioning in the amygdala (AMG) is thought to underlie the craving triggered by people, places, and things associated with drug use, which may precipitate relapse to drug-seeking behavior (Weiss, 2005). Studies in animals have found that repeated drinking and withdrawal–abstinence cycles causes a progressive adaptive change to increase anxiety and negative affect,

apparently through amygdala activation (Breese et al., 2005). Recruitment of brain stress amygdala activation has been suggested to cause the negative motivational state that drives addiction (Koob, 2009). This is supported by human neuroimaging data showing amygdala hyperactivation in response to stimuli that induce craving (Breiter et al., 1997; Childress et al., 1999; Kilts et al., 2001). Thus, a weakness in executive function tips the decisional balance from dlPFC-OFC-ACC controlled responses, particularly if AMG to drive creates urgency that promotes impulsive, automatic responding to dominate behavior (Fig. 1).

The frontal regions of the brain weigh consequences of future actions with the decisional balance requiring attention and activation of multiple brain circuits. The prefrontal cortex (dlPFC), includes as well as projects to anterior cingulate cortex (ACC) and the OFC with all 3 projecting to the ventral striatum (VS) a dopamine rich area important for expression of behaviors (Fig. 1). dlPFC, ACC and OFC all contribute to executive functions and inhibition of impulses. Limbic regions including the AMG and entorhinal cortex (ENT) also project to VS, which projects to globus pallidus (GP) and thalamus (Thal), which then projects to multiple brain regions for expression of behaviors. Impulsive behaviors are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation that often results in undesirable consequences. Expression of impulsive behaviors results from a deficit in suppressing responses, poor evaluation of consequences and an inability to forgo immediate small rewards in favor of greater delayed rewards. Craving drugs is a learned behavioral repertoire, possibly learned early in life and strengthened through repetition. Likely craving represents limbic subconscious drives. Thus, addiction is likely due, in part, to increased impulsiveness from the loss of frontal-cortical inhibition of impulses and increased limbic drive (Fig. 1).



Adapted from Salloway S et al.

Fig. 1. A simplified schematic of the frontal-cortical and limbic brain region circuitry that contributes to addictive behavior. Shown is a diagram of a human brain with internal structures highlighted with projections indicated by arrows with the structure color. Frontal-cortical areas are involved in reflection, attention, goal setting and planning as well as impulse inhibition. The dorsal lateral prefrontal cortex (dlPFC), projects to anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) with all 3 projecting to the ventral striatum (VS) a dopamine rich area important for expression of behaviors. Although all 3 structures are within the PFC. Recent studies have indicated that the dlPFC is a key brain region for executive functions, particularly to select attention, monitoring and planning (Abe and Hanakawa, 2009). The dlPFC receives inputs from all sensory systems and association cortex that projects to other PFC areas and premotor areas. The dlPFC appears to be sensitive to behavioral costs of attention selection of goal related information (Liu et al., 2006). Thus, the dlPFC must be activated to attend to decisions. Without the dlPFC addictive behavior can proceed as a cue induced semi-automatic learned behavioral repertoire. The dlPFC projects to ACC and OFC with all contributing to executive functions and inhibition of impulses. The ACC likely plays a key role in maintaining attention. The OFC projects to the amygdala and contributes to evaluation of outcomes and particularly unexpected outcomes, key elements for successful reversal learning (Schoenbaum et al., 2007). Once dlPFC focuses attention on activity it activates OFC to use associative information and project future outcomes (Schoenbaum et al., 2006). Limbic regions including the amygdala (AMG) and entorhinal cortex (ENT) also project to VS, which projects to globus pallidus (GP) and thalamus (Thal), which then projects to multiple brain regions for expression of behaviors. Impulsive behaviors reflect poor executive function since they include actions that are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation that often results in undesirable consequences. Expression of impulsive behaviors result from a deficit in suppressing responses, poor evaluation of consequences and an inability to forgo immediate small rewards in favor of greater delayed rewards. Thus, adolescent impulsivity due to poor development of executive functions is a risk period for addiction due to the high experimentation, risk-taking and active learning of associations. After initiation of drinking, progressive increased drinking may damage frontal areas leading to a progressive loss of executive function that may ultimately lead to loss of control over substance use, i.e. addiction.

3. Frontal lobes and addiction

Addiction is simply defined as engaging in the continued use of substances or activities in the face of negative consequences. Addiction appears to result from a combination of precipitating environmental factors and underlying biological risk factors, similar to other neurobehavioral disorders, like schizophrenia or depression. The biological mechanisms of addiction have been explored in great detail, uncovering much about the neurobiology of drug self-administration and effects of chronic drug exposure (Everitt et al., 2007; Jentsch and Taylor, 1999; Robinson and Berridge, 2003). However, the cognitive aspects of addiction remain relatively unexplored despite converging evidence that perturbation of cognitive control is a hallmark of addiction (Ersche et al., 2005; Garavan and Stout, 2005; Wilson et al., 2007). As cognitive control is commonly considered the domain of the frontal lobes, there is growing interest in frontal lobe investigations in the context of addiction. Moreover, there are similarities in behavior between addicted individuals and patients with PFC damage. For example, damage to the human OFC (Berlin et al., 2004), but not the ventromedial frontal lobe (Fellows and Farah, 2005), increases the tendency to choose immediate rewards over larger, delayed rewards. Similar results are seen in rats with lesions of the OFC (Mobini et al., 2002; Rudebeck et al., 2006). Such bias towards immediate rewards may be viewed as a form of impulsivity (Evenden, 1999), and a phenotype important for the neural bases of addiction (Reynolds, 2006). After injury to the prefrontal cortex, patients recover normal intelligence, memory and other cognitive functions, but emotional, affect and social behavior change (Bechara, 2005). Furthermore, damage to the OFC impairs the ability to refrain from responding to formerly rewarding cues that are no longer reinforced (Dias et al., 1996; McAlonan and Brown, 2003; Mishkin, 1964; Ostlund and Balleine, 2007; Rahman et al., 1999; Rolls et al., 1994; Schoenbaum and Roesch, 2005; Schoenbaum et al., 2007; Tait and Brown, 2007). Rule shifting is an executive function that can be tested using reversal learning models in animals. The ability to change responding to a previously rewarded activity relates to addiction,

because addiction is an inability to change, i.e. loss of control, when alcohol or other drugs cause negative consequences. Reversal learning, which is impaired in cocaine addicts and animals that have chronically self-administered cocaine (Schoenbaum and Shaham, 2008) or alcohol (Obernier et al., 2002b) provides an experimental approach to investigating drug-induced changes in cognition. A circuit including orbitofrontal cortex, basolateral amygdala and striatum subserves reversal learning, specifically orbitofrontal cortex loses the ability to signal expected outcomes, and basolateral amygdala becomes fixed emotional memories of reward. Executive cognitive flexibility must bring attention and working memory to inhibit learned responses that are currently wrong. The lack of rule shifting is consistent with the loss of control that is characteristic of addiction. Thus, the hallmark of addiction, i.e. continued drug taking with negative consequences, represents increased impulsivity and an inability to reverse previously learned rewarding activities.

Consistent with the data described above is the fact that numerous neuroimaging studies have found abnormal OFC function associated with substance abuse (Boettiger et al., 2007; Dom et al., 2005; Ersche et al., 2005; London et al., 2000; Volkow and Fowler, 2000). The OFC is thought to moderate impulsive choice (Mobini et al., 2002; Rudebeck et al., 2006), and to represent subjective value during decision-making (Izquierdo et al., 2004; Padoa-Schioppa and Assad, 2006; Roesch and Olson, 2004; Schoenbaum and Roesch, 2005). Alcoholics have decreased densities of neurons and glia in OFC (Miguel-Hidalgo et al., 2006) and ethanol drinking in rats alters glia in frontal prefrontal cortex (Miguel-Hidalgo, 2006). Recently, we have found that reduced OFC activity during decision-making among abstinent alcoholics is correlated with their tendency to choose immediate over delayed rewards (Boettiger et al., 2007), indicating a dysfunction of the OFC that may contribute to the persistence of addictive disorders. The dysfunction in delayed discounting reward tests involves learning initial rewards and continually assessing outcomes to improve results. This requires a form of relearning that initial learned rewards can be delayed for bigger rewards. Alcoholics have difficulty with these tasks. Interestingly, we have found that the non-selective opioid antagonist

naltrexone (NTX), one of the few drugs approved to treat alcoholism in the U.S., significantly elevates activity in the OFC during decision-making (Fig. 2) (Boettiger et al., 2009-this issue). Moreover, the effect of NTX on OFC activity predicted the effect of NTX on decision-making (Boettiger et al., 2009-this issue). These results suggest that a therapeutic action of NTX may be to support the long-term decision-making critical to recovery from alcoholism by increasing activity in the OFC. It is likely that frontal-cortical dysfunction contributes to the impulsive–compulsive aspects of addictive behavior and effective addiction therapies may reverse the frontal-cortical dysfunction.

4. Alcoholic neurodegeneration and executive dysfunction

Heavy drinking and high blood alcohol levels induce neurodegeneration and frontal-cortical dysfunction. As mentioned above, frontal-cortical dysfunction and impulsivity likely contribute to the consumption of dangerous amounts of alcohol despite the knowledge that problems occur as a result of drinking, the key characteristic of alcohol use disorders. Alcohol use disorder is in part due to a heavy drinking environment. High alcohol consumption causes neurodegeneration that contributes to loss of executive functions. In general, human alcoholics, both men and women, have lower brain volume of cortical and subcortical brain structures that include both widespread grey and white matter volumes below age-matched averages (Crews and Nixon, 2009). This occurs in the absence of major nutritional deficiencies, although nutritional deficiencies can cause neurodegeneration and could contribute to alcoholic degeneration (Bowden et al., 2001). Both post-mortem and in vivo imaging studies of alcoholic brain morphology find abnormal reduced brain volumes of grey and white matter across multiple regions of the brain. However, neuronal loss, likely, does not account for all the volume loss, although the superior frontal cortex (Harper and Kril, 1989) and orbital frontal cortex (Miguel-Hidalgo et al., 2006) show neuronal loss. The frontal lobes are the most insulted region in the alcoholic brain (Rosenbloom and Pfefferbaum, 2008; Sullivan and Pfefferbaum, 2005). Chronic alcoholism is associated with impaired judgment, blunted affect, poor

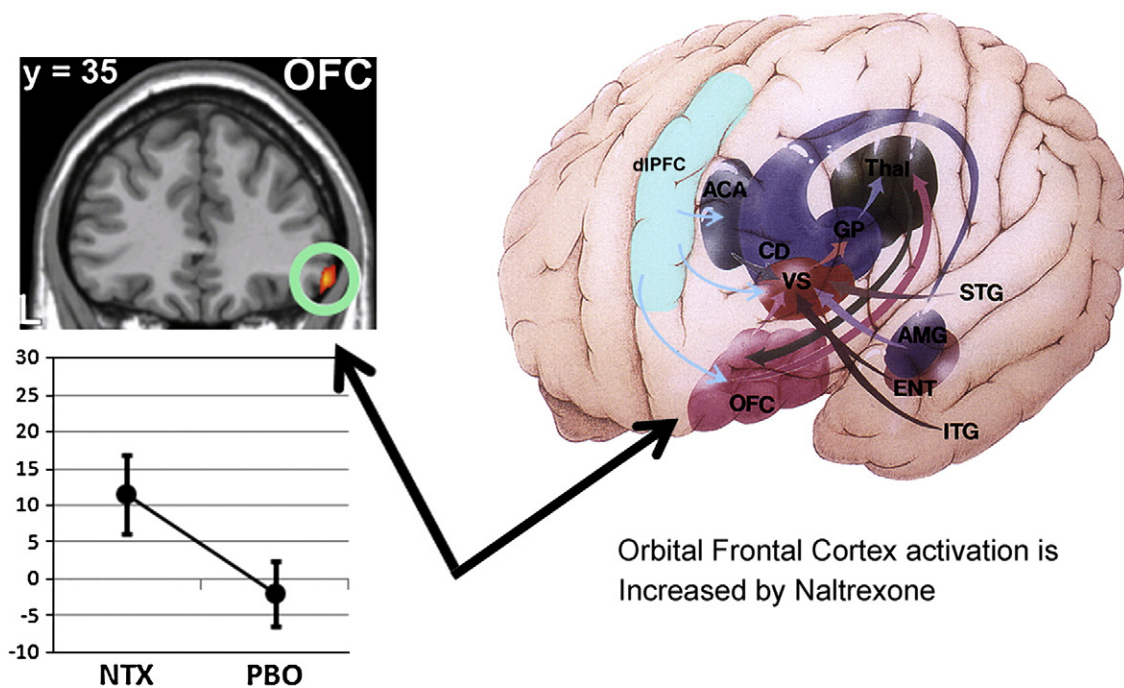


Fig. 2. Naltrexone increases activation of the orbital frontal cortex. The left panel shows the effect of naltrexone on brain activity, as measured by fMRI, during decisions between small, immediate and larger, delayed rewards. Activity was increased following acute administration of 50 mg of Naltrexone (NTX) relative to administration of placebo (PBO; adapted from Boettiger et al., 2009-this issue). The lower plot shows the mean activity in the orbitofrontal cortex (OFC) site indicated by the green circle in the image above as a function of drug condition. The right panel provides orientation as to the location of the orbitofrontal cortex within the brain. The plot reflects mean \pm S.D. L, left hemisphere.

insight, social withdrawal, reduced motivation, distractability, attentional and impulse control deficits (Oscar-Berman and Hutner, 1993; Parsons, 1987). It has been proposed that progressive increases in ethanol consumption lead to alterations in the brain structure that reduce behavioral control promoting further alcohol abuse and neurodegeneration (Crews et al., 2004). Drug- and ethanol-induced frontal-cortical degeneration and loss of executive function contribute to an imbalance between reflective, attention-controlled decision-making, frontal-cortical functions, and a hyperactive limbic system that drives impulsive behavior through involuntary signals (Bechara, 2005) (Fig. 1) driving both the progressive and persistent nature of addiction (Crews et al., 2005).

Basic animal model studies have established that high blood levels of alcohol can induce brain damage (Crews et al., 2004). Many studies of alcohol-induced brain damage have used a multiday binge induced brain damage model in rats. This model involves high blood ethanol levels ($\cong 250$ mg %) that are similar to the blood alcohol levels commonly found among hospital emergency room patients (Teplin et al., 1989). In the binge model alcohol-induced brain damage occurs during intoxication in limbic and frontal cortex, including agranular insular cortex, anterior

piriform cortex, perirhinal cortex, entorhinal cortex and hippocampal dentate gyrus, particularly ventral dentate gyrus (Fig. 3). Dark cell degeneration, a necrotic form of cell death with shrunken soma is the predominant form of neuronal death (Obernier et al., 2002a). In addition, ethanol inhibits brain neural stem cell proliferation and neurogenesis (Fig. 3) (Nixon and Crews, 2002), possibly contributing to deficits in learning and alterations in mood (Crews et al., 2003; Stevenson et al., 2008). In general the diffuse degeneration and loss of neurogenesis found in the rat binge model mimics the diffuse mild degeneration reported in human alcohol abusers (Crews et al., 2005). In addition to alcohol-induced neuronal cell loss and inhibition of neurogenesis, there is likely a cellular shrinkage that contributes to the loss of brain size in alcoholics. Alcohol reduces the size, length and branches of the dendrites in new developing adult neurons (Fig. 4), possibly reflecting broad changes in neuronal size and structure. Thus, the reduced size of alcoholic human brain likely represents alcohol neurotoxicity.

Alcoholic cognitive impairments may be linked to alcoholic neurodegeneration. Investigations into the persistent behavioral effects of binge induced brain damage found that two weeks after the last dose of ethanol, binge treated rats exhibited perseverative responses in

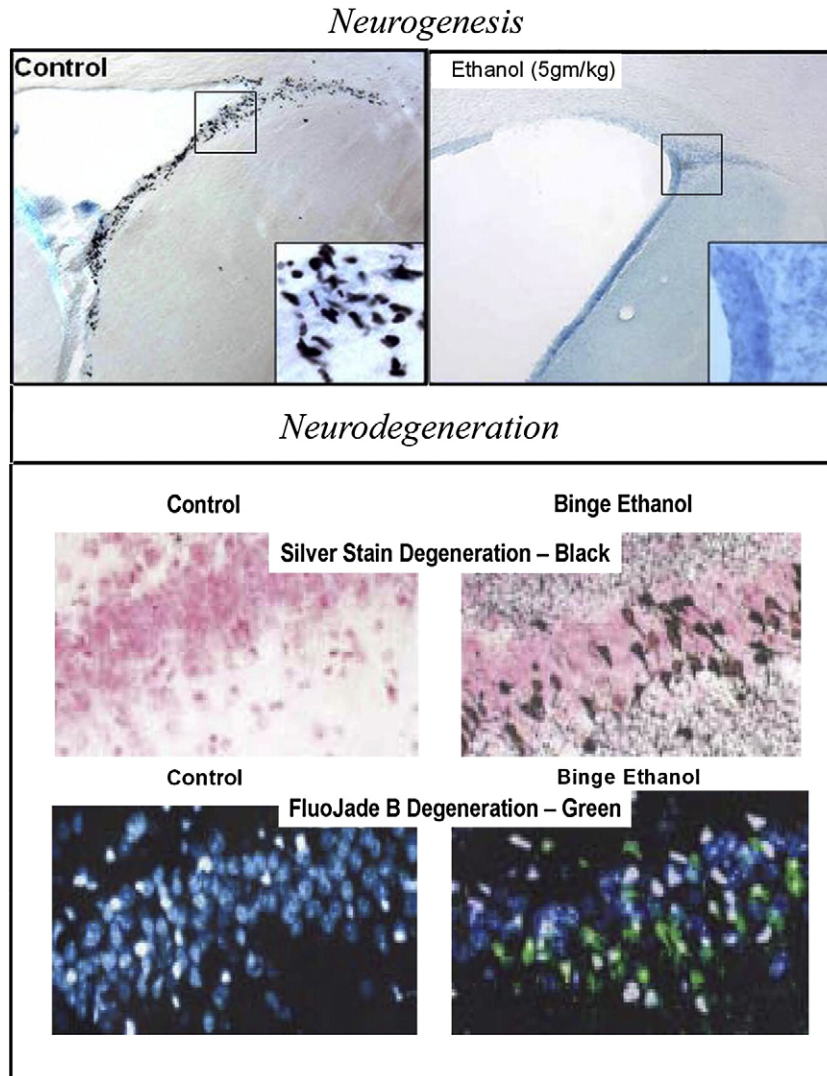


Fig. 3. Ethanol induced brain damage and inhibition of neurogenesis. Shown are brain sections of control and alcohol treated animals. Neurogenesis as indicated by BrdU + histochemistry (black cells on the edge of the ventricle). Top left – Control brain, right – ethanol (5 g/kg). Note control on left has many black dots that represent newly forming neuroprogenitors that will migrate to the forebrain. Note one dose of ethanol completely eliminated the stem cells (adapted from Crews et al., 2006a). Pictures middle and bottom show binge alcohol-induced brain damage. BIBD ethanol induced necrotic degeneration in hippocampus visualized by agyrophilic amino cupric silver stain (black – middle photo) or Fluoro-Jade B (green – bottom) (Obernier et al., 2002a). Note only binge treated brains show black silver stain neuronal death and green FluoroJade neuronal death stains. The neuronal cell death and loss of neurogenesis are forms of alcoholic neurodegeneration.

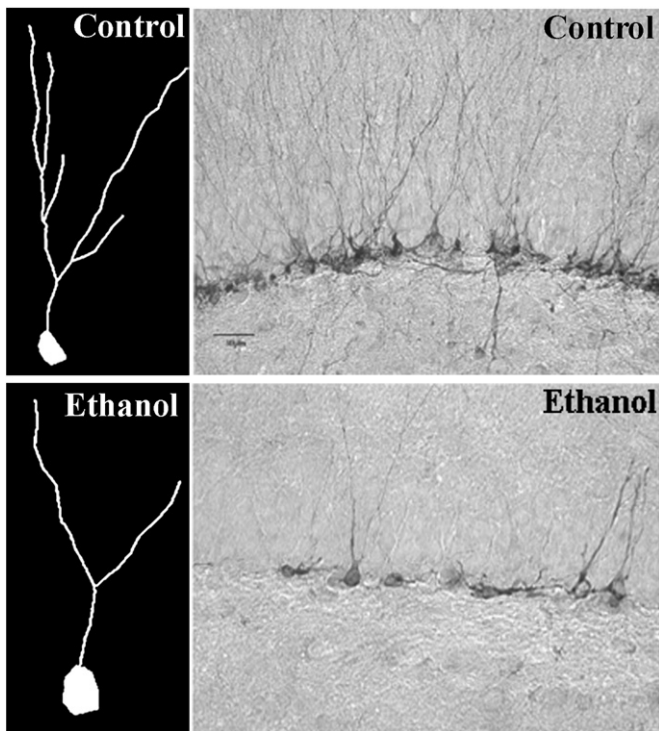


Fig. 4. Alcohol reduces new neuron dendritic growth. Progenitors in hippocampus progress from dividing progenitors that exit cell cycle to grow and differentiate into neurons that are synaptically linked and appear to become fully functional integrated neurons. Doublecortin is a structural protein only expressed in differentiating neuronal progenitors during dendritic elongation and arborization. Immunohistochemistry for doublecortin provides an index of neurogenesis, the formation of new neurons, as well as allowing analysis of the effects of ethanol on neuroprogenitor growth. Left: Representative dendritic trees from traced immunohistochemistry for doublecortin in hippocampus of control (top) or ethanol treated animal (bottom). Right: Doublecortin histochemistry from control or ethanol treated animals. Note how ethanol reduced new neuron formation as well as the branching and size of dendritic trees.

reversal learning trials (Fig. 5). (Obernier et al., 2002b). Although learning was not altered by binge treatment, Morris Water maze reversal learning, e.g. relearning tasks, showed deficits in trials to criterion, time in wrong quadrant, and entries in the wrong quadrant, that are consistent with disrupted frontal lobe function and perseveration (Obernier et al., 2002b). Animals and people with OFC lesions show reversal learning deficits (Schoenbaum and Roesch, 2005; Schoenbaum and Shaham, 2008). In addition, persistent increases in markers of microglial density, a sign of neurodegeneration, were elevated by binge rat treatment (Obernier et al., 2002b) similar to findings in post-mortem alcoholic human brain of increased microglial density (He and Crews, 2008). Thus, animal models have established that high blood alcohol levels cause neurotoxicity in cortical and limbic regions that induce reversal learning deficits that mimic the perseverative behaviors consistent with frontal-cortical dysfunction in alcohol use disorders.

5. Genetic regulation of impulsiveness and risk for addiction

Polymorphisms in several genes in the dopaminergic system, which targets the frontal and limbic brain structures that regulate impulsive behavior, have been identified as likely contributors to impulsivity (Kreek et al., 2005). For example, recent results indicate that genetic variation at the Val158Met polymorphism of the catechol-O-methyltransferase (COMT) gene influences decision-making behavior and underlying activity in brain activity associated with impulsive choice (Boettiger et al., 2007). The COMT enzyme plays a significant role in regulating frontal DA (Chen et al., 2004), and individuals homozygous for the enzymatically more active 158^{Val} allele show an increased tendency to choose immediate over delayed rewards. Such

genetic variation in COMT function may also contribute to other forms of impulsive behavior (Congdon and Canli, 2005; Cools and Robbins, 2004; Kreek et al., 2005). Studies linking COMT to alcoholism are equivocal (Ishiguro et al., 1999; Kauhanen et al., 2000; Kim et al., 2006; Samochowiec et al., 2006; Sery et al., 2006). However, some data suggest that alcoholic sub-phenotypes may associate with specific COMT diplotypes (Enoch et al., 2006; Kweon et al., 2005; Tiihonen et al., 1999; Wang et al., 2001). Thus, genes that alter impulsivity contribute to risk for alcoholism and other mental diseases that have overlapping psychopathology.

The genetics of alcoholism, impulsive behavior and neurodegeneration may overlap. Proinflammatory genes appear to be involved in alcoholic neurodegeneration and the genetics of alcoholism. The human alcoholic brain shows increased NF- κ B gene transcription (Okvist et al., 2007), a key proinflammatory transcription factor. Similarly the human alcoholic brain shows increased proinflammatory cytokine and microglial protein expression (He and Crews, 2008). Animal studies find alcohol induced proinflammatory gene expression with neurodegeneration (Crews et al., 2006a; Qjin et al., 2008). Human genetic variations in NF- κ B genes have been associated with increased risk for human alcoholism, particularly early onset alcoholism (Edenberg et al., 2008). Proinflammatory cytokines found in alcoholic human brain (He and Crews, 2008) increase the reward value of alcohol drinking in mice (Blednov et al., 2005). Animal models of genetic high risk for alcoholism, e.g. the “P-alcohol preferring rat” that was bred for heavy alcohol drinking, have increased risk for alcoholic brain damage corresponding with increased genetic risk for alcoholism (Crews and Braun, 2003). High impulsivity has also been found in families with alcoholism, suggestive of a genetic link (Saunders et al., 2008). Thus, the genetics of impulsivity overlaps with genetic risks for alcohol use disorder and possibly alcoholic neurodegeneration.

6. Adolescent brain development represents a critical risk period for addiction

Adolescence is an important period of development during the transition from childhood to adulthood. Adolescence is best defined by characteristic behaviors such as high social interaction, high levels of risk-taking, high exploration, impulsivity, novelty and sensation seeking, high activity and play behaviors. These are shared across species from humans (12 to 20–25 years of age), to rats (post-natal days 28 to 42) and many other species (Spear, 2000). The characteristic behaviors of adolescence likely represent continued cortical development of complex functions that include sensory motor systems, but also limbic and frontal-cortical brain structures (Crews et al., 2007; Spear, 2000). Adolescent neuroplasticity allows environmental shaping of complex skills for development of adult behaviors appropriate for the environment and good for the survival of the family, group or herd. In mammals, complex behaviors are important for group interactions. Adolescents develop the social skills needed for independence, and appropriate adult behavioral repertoires, including becoming leaders and/or followers. The high impulsivity of adolescence likely represents an important risk factor for binge drinking and initiation of drinking experiences (de Wit, 2009). Major changes occur in the brain during adolescence with absolute PFC volume declines during adolescence in both humans (Sowell et al., 2001, 1999) and rats (van Eden et al., 1990). Changes occur in brain regional volumes, chemistry and circuitry. For example, dopamine and serotonin (5-HT) inputs to PFC increase during adolescence to peak levels well above those seen earlier or later in life (Kalsbeek et al., 1988; Rosenberg and Lewis, 1994). Similarly, cholinergic innervation of PFC also increases in adolescence to reach mature levels in both rats (Gould et al., 1991) and humans (Kostovic, 1990). Neuronal circuitry as investigated by stress-induced Fos-like immunoreactivity in cortical and amygdaloid nuclei differs between adolescent and adults (Kellogg et al., 1998; Waters et al., 1997), as do cortisol responses (Walker et al., 2001). Thus,

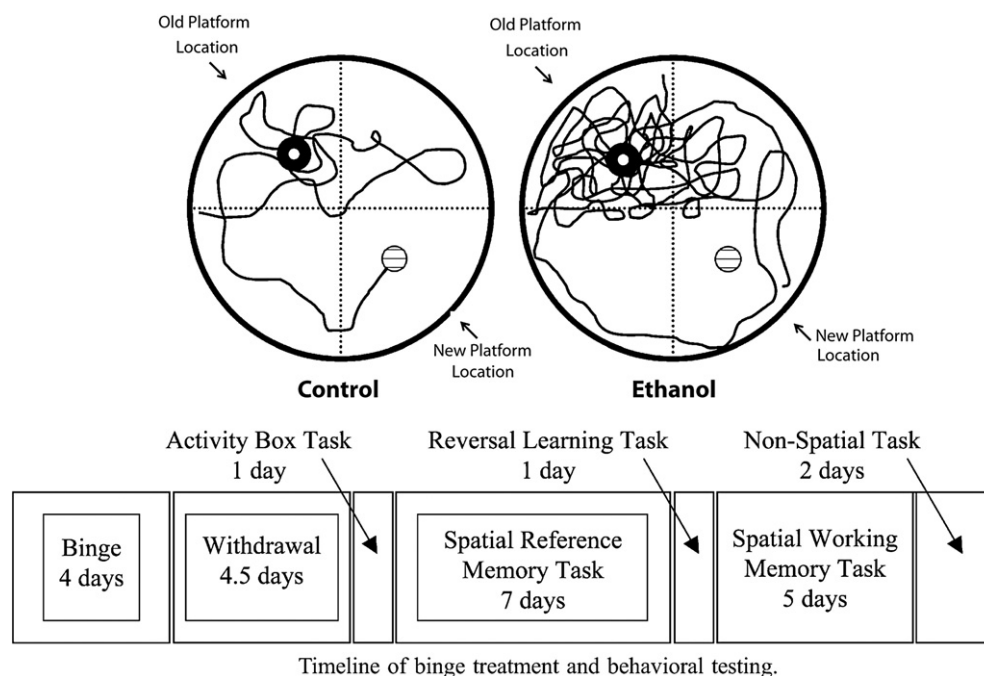


Fig. 5. Perseverative repetitive behaviors due to binge induced brain damage. The Morris water maze is a round water bath with a hidden platform that tests learning the location of the hidden platform just under the water using visual cues. The experimental time line on the bottom shows that tests were done long after behavioral withdrawal was complete, e.g. 5–6 days after the last dose of alcohol. Learning (decreased time to find the platform) was not altered in animals known to have binge ethanol induced brain damage. Both controls and sober binge treated rats readily learned the platform location. However, they differed in the reversal learning task of the Morris water maze. The submerged platform was placed in the quadrant opposite that in which it had been placed during the learning memory task (moved from upper left to lower right quadrant). Circles on the top represent a vertical view of the track taken by a control and binge ethanol treated rat during the first trial of the reversal learning task. Binge ethanol treated animals show deficits in relearning. Note the perseverative circling behavior shown by the binge ethanol treated animal with numerous re-entries into the original goal quadrant. The binge treated rat failed to reach the new platform location within the maximum time allowed and was removed. Thus, binge treatment induced brain damage induces cognitive deficits that mimic human alcoholism. Relearning deficits could contribute to the difficulty alcoholics have in learning to live in abstinence. (Adapted from Obernier et al., 2002b).

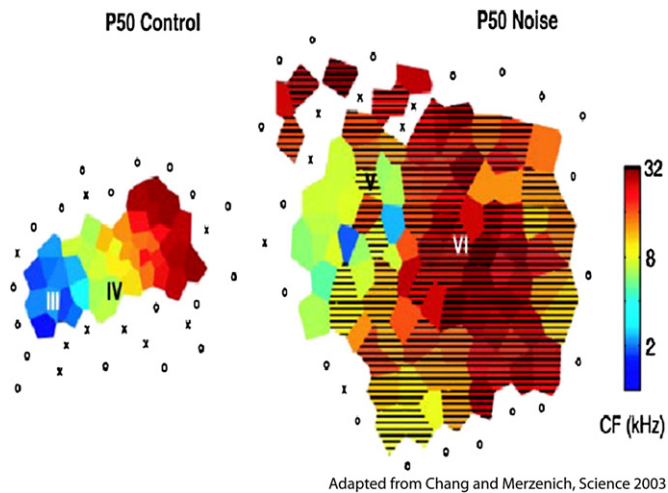
remodeling of the adolescent brain is associated with high impulsivity, high plasticity, and development of more complex adult behaviors.

Studies of cortical development and function have established critical periods, e.g. specific windows in time, during development when the environment can remodel, under genetic influences, to establish adaptive functional characteristics that persist into adulthood (Crews et al., 2007). In humans, cortical development occurs over the first 3 decades of life with changes in grey matter and myelination during the transitions from childhood to adolescence to adulthood. Cortical areas develop at different ages with dorsal parietal and primary sensorimotor regions increasing function during ages 4–8, followed by parietal areas of language and spatial orientation around 11–13 years of age and frontal areas involved in integrating information from senses, reasoning, and other “executive functions” maturing last, during late adolescence (Gogtay et al., 2004; Toga et al., 2006). Age-related changes in cortical structure are associated with improved function. Cortical thinning in the left dorsal frontal and parietal lobes correlate with improved performance on a test of general verbal intellectual functioning between the ages of 5–11 (Sowell et al., 2004). Other studies following individuals from age 6 through 19 found that individuals with superior intelligence show the greatest changes in frontal-cortical thickness compared to individuals with high or average intelligence (Shaw et al., 2006). Environmental experiences and training are known to induce changes in cerebral cortex including neurochemical, altered cortical thickness, size of synaptic contacts and dendritic structure as well as improving performance on learning tests (Rosenzweig and Bennett, 1996). Learning in humans during studying for exams (Draganski et al., 2006) or practicing juggling (Draganski et al., 2004) alters cortical structure consistent with use contributing to structural changes in the brain. Thus, brain structural changes are pronounced in adolescents and the high learning abilities in adolescence are associated with structural changes in the brain during this important period of development.

The development illustrates the increased brain efficiency through focusing of cortical activity as brain circuits develop. The auditory cortex undergoes a developmental process that involves a progressive sharpening of frequency receptive fields during the maturation of the auditory cortex (Chang and Merzenich, 2003)(Fig. 6). The focal sharpening of cortical activation by sound likely corresponds with improved ability to identify specific tones essential for music and sequences of sounds essential for language. Thus, cortical development leads to increased efficiency and focus that is modified by the environment. Normal development allows the auditory cortex to focus sound and tonal discrimination. However, excessive white noise during the critical period of cortical development disrupts auditory cortex focal sharpening (Fig. 6). Excessive noise during the critical period of auditory cortex development leads to persistent changes in cortical responsiveness, lack of tonal and temporal sharpening of responses and loss of higher order discrimination function, e.g. sounds do activate cortex, but focal specificity is lost (Chang and Merzenich, 2003; Zhou and Merzenich, 2008). These findings indicate that environmental factors during adolescent critical periods of cortical development regulate the long-term complex function of cortex. High alcohol consumption during adolescence may disrupt frontal-cortical development similar to sound disruption of auditory cortex development.

A critical period for frontal cortex plasticity has not been defined, but behavioral studies show that performance on tasks including inhibitory control, decision-making and processing speed continues to develop during adolescence. During adolescence tasks of selective attention, working memory and problem solving improve, consistent with frontal-cortical synaptic pruning and myelination improving performance (Blakemore and Choudhury, 2006). Inhibitory control involves executive functions that improve from adolescence to adulthood. Studies measuring behavioral inhibition on a Go-NoGo task and fMRI data reveal greater activation of DLPFC and OFC in children than in adolescents, and greater in adolescents than in adults,

Noise during adolescence disrupts response selectivity of adult auditory Cortex



Adapted from Chang and Merzenich, *Science* 2003

Fig. 6. Representative cortical frequency maps of characteristic frequency (CF) defined cortical responses. Shown are CF maps of adult, post-natal age 50 (P50) controls or animals exposed to noise during the auditory cortex critical period (P7–P35). Note the sharply defined frequency responses of receptive fields during the maturation of the auditory cortex (control left). Noise during the critical period of auditory cortex development disrupts the sharpening of sound tone specific auditory cortex activation. The focal sharpening of cortical activation by sound likely corresponds with improved ability to identify specific tones essential for music and sequences of sounds essential for language (Chang and Merzenich, 2003; Zhou and Merzenich, 2008). The disruption of the focal sharpening of sound activation of auditory cortex represents an example of environmental disruption of normal cortical development. Adolescent binge drinking may disrupt frontal-cortical sharpening resulting in loss of executive and control functions.

with the adults showing the lowest dorsolateral, but equal orbito-frontal activation and greater inhibitory control performance (Casey et al., 1997; Tamm et al., 2002). These studies support the concept that the immature brain has more extensive and less efficient frontal activation and lower performance compared to adults, who have a more focused pattern of frontal activation, faster reaction times, and better performance (Blakemore and Choudhury, 2006). Taken together these studies suggest that remodeling of the cortex during the transitions from youth to adolescence to adulthood have functional implications for the entire adult life.

Adolescent high impulsivity, risk-taking, thrill and novelty-seeking behaviors promote heavy drinking and other drug experimentation. Adolescent individuals drink their heaviest in their late teens and early to mid-twenties and are more likely to drink large amounts of alcohol when drinking. 44% of college students binge drink every two weeks and 19% have more than 3 binge drinking episodes per week (Wechsler et al., 2000). Adolescents are less sensitive to the sedative effects of alcohol (Monti et al., 2005; Silveri and Spear, 1998), which allows them to stay awake to drink more alcohol. However, they are more vulnerable to alcohol-induced neurotoxicity (Crews et al., 2000, 2006b; Monti et al., 2005). Interestingly, the parts of the brain undergoing highly plastic changes in adolescence are sensitive to alcohol neurotoxicity in adolescence (Crews et al., 2000) (Fig. 7). Studies of adolescent individuals with alcohol use disorder have found smaller prefrontal grey and white matter volumes than age-matched controls. Lower prefrontal volumes correlated with a higher maximum number of drinks per drinking episode (De Bellis et al., 2005). Studies of social drinkers have found that the heaviest binge drinkers have more negative moods and performed worse on executive function tasks (Townshend and Duka, 2003; Weissenborn and Duka, 2003). Thus, adolescence

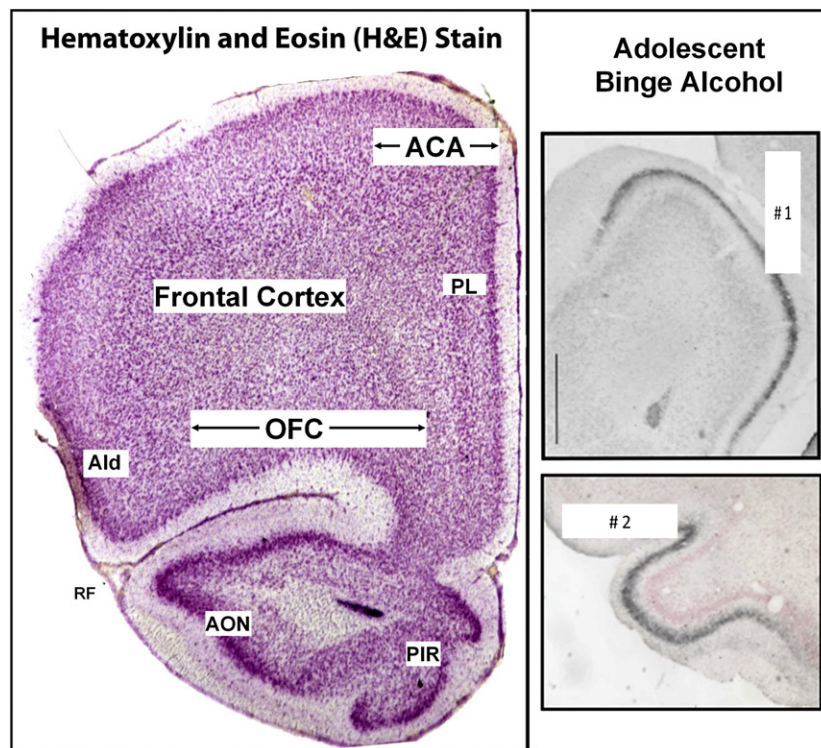


Fig. 7. Binge drinking in adolescent rats damages frontal brain regions. The frontal cortex of a rat is a heterogeneous mixture of cortical layers. On the left is shown the left half of a coronal section of the rat brain stained for cellular nuclei and cytoplasm (H&E) stain. The midline (right side) of the left picture is the medial part of the frontal cortex. Note the rhinal fissure (RF) is an indentation from the left side (lateral) of the brain moving inside. This separates the anterior olfactory nucleus (AON) and anterior piriform cortex (PIR) from the orbital frontal cortex (OFC) and agranular insular cortex, dorsal part (Ald). Arrows show OFC medial (right) and lateral (left). The prelimbic area (PL) and anterior cingulate area (ACA) are part of the medial frontal cortex. On the right are sections from 2 adolescent rats exposed to binge ethanol treatment (Crews et al., 2000) that have been stained with the neurodegeneration silver stain. The black regions in the pictures at the right represent binge induced neuronal cell death. Note the degeneration looping in the frontal cortex (#1 – upper right) and over orbital frontal cortex, the anterior olfactory nucleus (AON) and anterior piriform cortex (PIR) (#2 – lower right). These images are representative of the significant frontal-cortical degeneration found following binge treatment in adolescent rats (Crews et al., 2000).

impulsivity and poor executive function is a risk for initiation of drinking and enhanced learning of drug reward, possibly linked to socially rewarding experiences. This initial risk is enhanced during drinking induced cortical disruption and neurotoxicity further disrupting development of executive functions and possibly leading to persistent loss of inhibitory control (Crews et al., 2007). Taken together these findings suggest that the unique developing limbic and cortical regions in adolescent brain may be a critical period of risks for disruption of frontal-cortical development (Crews et al., 2007).

7. The frontal cortex and stages of change in recovery from addiction

Recovery from addiction involves a significant change in behavior. The factors that regulate the persistence of dependence and motivation to control addictive behavior reflect aspects of the decisional balance between reflective and impulsive systems. Psychological changes that occur during recovery from addiction involve motivation and have been modeled as “Stages of Change” as an aid to therapists with a diversity of clients in various phases of recovery (Fig. 8) (DiClemente, 2007). Addicted individuals often fluctuate from *precontemplation*, e.g. no interest in changing their drug use and likely denial of problems, to *contemplative*, e.g. risk-reward analysis of the benefits of recovery vs. the negatives of addiction. These stages are consistent with an increasing involvement of the frontal-cortical function in behavior. The stages of *preparation* and *action*, taking specific steps to implement behavioral change, likely involve frontal-subcortical balance with increasing attention shifting to directed motivation and socially responsive behaviors. Lack of executive function leads to normal repetitive addictive behavior. This model of behavioral change has been criticized for focusing on conscious decision-making and planning (West, 2005), when addiction involves associative learning of unhealthy habit patterns that become entrenched and semi-automatic through repetition (Robinson and Berridge, 2003). Executive function likely is essential for effective reversal of addictive behavior learned earlier in life, likely during adolescence when unique learning abilities predominate cortical

development. Lost executive function likely reduces attention and motivation allowing learned substance seeking behaviors to become semi-automatic. Increased attention due to negative consequences can motivate addicted individuals to seek treatment. Thus, the transition from precontemplation to contemplation, preparation, action and maintenance all are dependent on executive function attention, analysis of outcomes of actions, planning actions and sustaining attention to reverse habitually learned addictive behavior. The two most commonly used psychotherapeutic approaches to addiction therapy are motivation interview therapy (Hettema et al., 2005) and cognitive behavioral therapy (Clay et al., 2008). These therapies through counselor promoted processes increase use of the frontal cortex through discussions of motivation and attention to actions as well as planning and setting of goals on how to maintain non-addictive behavior. The counseling sessions themselves activate frontal-cortical executive functions that through use and activation likely help promote maintenance of controlled behavior. This activation of executive functions increases attention and frontal lobe function reducing impulsivity and preventing relapse (Fig. 8). Motivation is a key component of the behavioral change needed for recovery and is related to frontal-cortical function, particularly prefrontal/cingulate areas (Bonelli and Cummings, 2007). As mentioned previously, naltrexone pharmacotherapy for alcohol dependence increases frontal-cortical activation (Boettiger et al., 2009-this issue). Thus, the neurobiology of behavioral change in recovery from addiction may represent levels of frontal-cortical involvement in regulating behavioral change and psychotherapy tends to use frontal-cortical activation through motivated attention and goal setting and pharmacotherapy also enhances frontal activation consistent with successful addiction therapy using frontal circuits to motivate and attend to negative consequences and long-term goals.

8. Summary

The fundamental problem in addiction is the destructive nature of the substance abuse and the inability to stop. The frontal regions of the brain control behaviors including planning and organization, motivation for goal-directed activity, weighing consequences of future actions and impulse inhibition, known collectively as executive functions. The PFC projects to ACC and OFC, with all 3 projecting to the VS, a dopamine rich area important for expression of behaviors. Frontal-cortical damage occurs with binge drinking intoxication. Dysfunction in specific regions of the brain contributes to an imbalance between craving-limbic drive and frontal-cortical attention and executive functions, particularly reflection and inhibitory control. PFC, ACC and OFC all contribute to executive functions and inhibition of impulses. Impulsive behaviors result from impaired executive functions since they include actions that are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation, which often result in undesirable consequences. Thus, addiction is likely due in part to increased impulsiveness from the loss of frontal-cortical inhibition of impulses and increased limbic drive.

The discovery of a key role of the frontal cortex in addiction provides new approaches to therapy. Adolescent age and genetics are clear risk factors for neurodegeneration that could inform strategies to reduce drinking in high-risk populations and thereby prevent the progressive neurodegeneration and impulsive-addictive changes. Further, existing therapies for addiction involve frontal-cortical activation. Naltrexone, a pharmacotherapy for alcoholism, increases OFC activity. Abstinence from alcohol induces brain regrowth and return of some cognitive abilities. Addiction therapies focused on enhancing abstinent brain activity and growth could become new approaches to treating addiction. In any case, there is substantial evidence that addiction is related to loss of frontal lobe function and increased impulsivity.

Stages of Change

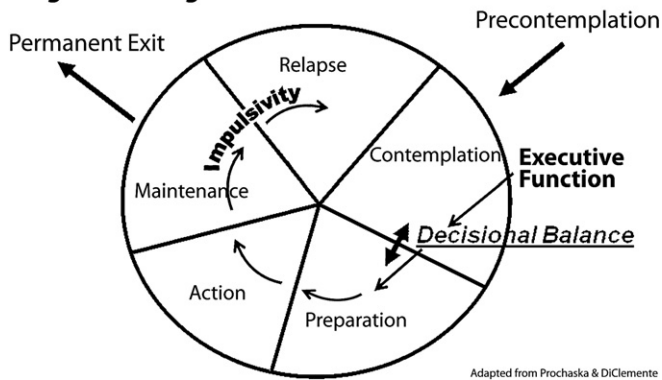


Fig. 8. Impact of executive functions and impulsiveness on stages of change associated with treatment, recovery and relapse during addiction. Psychological changes that occur during recovery from addiction likely involve alterations in the frontal-cortical function. Behavioral change during recovery from addiction can be modeled as “Stages of Change” (DiClemente, 2007). Addicted individuals can be in a state of precontemplation, e.g. no interest in changing behavior and likely denial of drug problems, or may enter into the first stage of change, contemplation, e.g. risk-reward analysis. Preparation, involving planning and committing is consistent with increased activation of the frontal cortex. As mentioned earlier, naltrexone, which increases orbitofrontal activation in recovering alcoholics can improve recovery. Recovery may represent frontal-subcortical activation of directed motivation and socially responsive behaviors. Increased impulsivity during maintenance of recovery could underlie relapse and return to the limbic driven behaviors of addiction. Thus, the neurobiology of the psychology of stages of recovery may represent levels of frontal-cortical involvement in behavior and regulation of impulsivity.

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