NIH Public Access
Author Manuscript
Rev Neurosci. Author manuscript; available in PMC 2014 October 16.

Published in final edited form as:
Rev Neurosci. 2014 ; 25(1): 1–24. doi:10.1515/revneuro-2013-0054.

Cognitive control in alcohol use disorder: deficits and clinical relevance

Claire E. Wilcox[*],
Claire E. Wilcox, Department of Psychiatry, 1 University of New Mexico, MSC 09-5030, Albuquerque, NM 87131, USA

Charlene J. Dekonenko,
School of Medicine, 1 University of New Mexico, MSC 09-5040, Albuquerque, NM, USA

Andrew R. Mayer,
The Mind Research Network, 1101 Yale Boulevard NE, Albuquerque, NM, USA; Department of Neurology, University of New Mexico, MSC 10 5620, Health Sciences Center, 1 University of New Mexico, Albuquerque, NM, USA; and Department of Psychology, University of New Mexico, MSC 03 2220, 1 University of New Mexico, Albuquerque, NM, USA

Michael P. Bogenschutz, and
Department of Psychiatry, 1 University of New Mexico, MSC 09-5030, Albuquerque, NM, USA

Jessica A. Turner
The Mind Research Network, 1101 Yale Boulevard NE, Albuquerque, NM, USA; and Department of Psychology and Neuroscience, Georgia State University, Atlanta, GA, USA

Abstract

Cognitive control refers to the internal representation, maintenance, and updating of context information in the service of exerting control over thoughts and behavior. Deficits in cognitive control likely contribute to difficulty in maintaining abstinence in individuals with alcohol use disorders (AUD). In this article, we define three cognitive control processes in detail (response inhibition, distractor interference control, and working memory), review the tasks measuring performance in these areas, and summarize the brain networks involved in carrying out these processes. Next, we review evidence of deficits in these processes in AUD, including both metrics of task performance and functional neuroimaging. Finally, we explore the clinical relevance of these deficits by identifying predictors of clinical outcome and markers that appear to change (improve) with treatment. We observe that individuals with AUD experience deficits in some, but not all, metrics of cognitive control. Deficits in cognitive control may predict clinical outcome in AUD, but more work is necessary to replicate findings. It is likely that performance on tasks requiring cognitive control improves with abstinence, and with some psychosocial and medication treatments. Future work should clarify which aspects of cognitive control are most important to target during treatment of AUD.

[*]Corresponding author: cewilcox@salud.unm.edu.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Keywords

alcohol dependence; alcohol use disorder; cognitive control; functional MRI; inhibition; working memory

Introduction

Alcohol use disorders (AUD) are characterized by a persistent desire or unsuccessful efforts to cut back or control alcohol use, and continued use despite negative physical, psychological, occupational, or social consequences (DSM-V). Maladaptive choices around alcohol use are understood to be mediated by impairments in brain function, and in particular in circuits underlying motivation, working memory, attention, performance monitoring, learning, and decision making (Baler and Volkow, 2006).

Addiction involves associative learning of unhealthy habitual drug-seeking behaviors that become progressively more and more reflexive with repeated use (Robinson and Berridge, 2003). Over time, the semiautomatic stimulus-driven (e.g., drug-cue-triggered) habitual behaviors become less and less amenable to cognitive interference (Robinson and Berridge, 2003; Everitt and Robbins, 2005; Baler and Volkow, 2006). Addiction has been described as a disorder with two components: (i) an overwhelming impulsive and compulsive ‘drive’ toward drug alcohol consumption (often accompanied by the subjective experience of craving, and the desire to relieve the distress of craving); (ii) an inability to ‘hit the brakes’, or inhibit drug or alcohol consumption (Baler and Volkow, 2006; Crews and Boettiger, 2009; Koob and Volkow, 2009; Camchong et al., 2013). In the neuroimaging literature, these two components also correspond to (i) increased involvement of regions that mediate appetitive drive within ‘bottom-up’ (or stimulus-driven) networks and (ii) reduced involvement of regions that mediate cognitive control, within ‘ top-down ’ networks (Ridderinkhof et al., 2004a; Everitt and Robbins, 2005; Li et al., 2009; Camchong et al., 2013). An imbalance in these circuits is believed to contribute to maladaptive decision making around drug or alcohol use and relapse. The second component, cognitive control, will be the focus of this article.

Cognitive control refers to the internal representation, maintenance, and updating of context information in the service of exerting control over thoughts and behavior (Braver and Barch, 2002). It refers to the subset of executive functions that guide a behavior toward or away from a particular task, optimizing adaptive decision making by setting goals and inhibiting habitual acts (Braver and Barch, 2002; Ridderinkhof et al., 2004b). An emerging view considers impaired cognitive control as both a determinant and a consequence of addictive behaviors (Dalley et al., 2011). Brain regions implicated in cognitive control include the dorsolateral prefrontal cortex (DLPFC), lateral orbitofrontal cortex (OFC), anterior cingulate cortex (ACC)/paracingulate cortex, pre-supplementary motor area (pre-SMA), parietal cortex (superior and inferior lobes), dorsal striatum, and thalamus (Ridderinkhof et al., 2004a,b; Dosenbach et al., 2008; Crews and Boettiger, 2009; Feil et al., 2010; Crowe et al., 2013).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

The functional integrity of these regions is critical for addicted individuals to inhibit relapse behaviors (Crews and Boettiger, 2009; Feil et al., 2010; Volkow et al., 2013). Equally important for self-control in the context of interoceptive or external cues triggering craving are connections between these networks and with limbic and other motivational circuits (likely comprising the ventral striatum, amygdala, and hippocampus, for example) regulating goal-directed behavior (Baler and Volkow, 2006; Volkow et al., 2013).

In this article, we summarize the literature on the role of impairments in cognitive control in perpetuating AUD, with our underlying objective to determine which aspects, if any, might best be targets of future treatment approaches. To do so, first we will provide the reader with some background and some context for the cognitive processes on which we will be focusing our review. Then, we will define the three subgroups of cognitive control processes that we have chosen to focus on in our review, and the tasks that can be used to measure these processes, namely (i) response inhibition [e.g., Go No-Go (GNG), Stop-signal, and Continuous Performance tasks (CPT)], (ii) distractor interference control (e.g., Stroop, flanker, Simon and Hayling tasks), and (iii) working memory (e.g., n-back, alpha-span, WAIS letter-number sequencing, and digit-ordering tasks). We will spend some time reviewing the neural circuitry involved in these processes, and the similarities and differences between these subgroups. We will then review how performance on these tasks and the integrity of the brain circuits and brain functions driving these processes differ between AUD patients and healthy controls. Finally, we will identify the evidence for how impairments in these processes may be important (especially in the context of relapse) in AUD, reviewing to what degree these impairments either predict outcomes or moderate treatment effects, and what interventions and treatments for AUD might produce improvements in cognitive control. Finally, we will review the implications this information has for future studies of treatment for AUD, both with medications and psychosocial interventions.

Scope

While this article focuses on cognitive control, there are a variety of important cognitive and psychological processes that may contribute to maladaptive decision making in AUD that we will not discuss extensively. For example, individuals with AUD demonstrate deficits in processing speed, facial recognition, learning, memory, social cognition, and emotion regulation (Blume et al., 2005; Rupp et al., 2006; Pitel et al., 2007; Heffernan, 2008; Uekermann and Daum, 2008; Kopera et al., 2012; Montgomery et al., 2012; Noel et al., 2012; Thoma et al., 2013). In addition, impairments in executive functions (other than the cognitive control processes we will be focusing on), such as attention, visuospatial abilities, decision making, abstract thinking, rule acquisition, rule shifting, flexibility, planning, verbal fluency, and initiation of goal-directed behavior, have been demonstrated (Brown et al., 2000; Sullivan et al., 2000b; Ratti et al., 2002; Sullivan et al., 2002; Blume et al., 2005; Goudriaan et al., 2006; Rupp et al., 2006; Chanraud et al., 2007; de Wit, 2009; Kopera et al., 2012; Montgomery et al., 2012; Noel et al., 2012; Wollenweber et al., 2012; Thoma et al., 2013). Two domains even more directly related to cognitive control are error monitoring (Ridderinkhof et al., 2004b; Mayer et al., 2011) and oculomotor inhibition (Weafer et al., 2011; Noel et al., 2013), which we will not be covering in any detail in this article either.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

'Impulsivity' is a commonly used term in both everyday speech and in clinical settings, referring to a variety of processes as they relate to a wide range of psychiatric diagnoses. However, it is a multidimensional construct for which there is little consensus on its definition (Congdon and Canli, 2005; de Wit, 2009; Dick et al., 2009; Dalley et al., 2011). For example, this term is used to refer to a variety of behaviors, including responding before instructions are given or completed, responding without considering all options, inability to refrain from responding to an inappropriate stimulus, acting without considering the full set of consequences and without forethought or planning, risky decision making/risk taking, urgency (both positive and negative), impatience, carelessness, difficulty paying attention, novelty seeking, pleasure seeking, greater reward sensitivity, an underestimated sense of harm, lack of perseverance, impairments in time estimation, impairments in learning from negative consequences or punishment, and extroversion (Patton et al., 1995; Whiteside and Lynam, 2003; Congdon and Canli, 2005; Crews and Boettiger, 2009; Dick et al., 2009; Dalley et al., 2011; Weafer et al., 2011). Impulsivity also refers to the concept of overvaluing short-term rewards and undervaluing greater long-term rewards, showing impairments in delaying gratification, and delay discounting (Kirby and Petry, 2004; Crews and Boettiger, 2009; de Wit, 2009; Dalley et al., 2011). Although scores on self-report scales and performance on tasks measuring many of these components of impulsivity may indeed have clinical relevance in distinguishing individuals with AUD from controls and predicting outcomes (Mitchell et al., 2005; Dalley et al., 2011), not all of these components are all related to one another, nor are they necessarily related to inhibition or cognitive control (de Wit, 2009; Broos et al., 2012). Because we feel the term impulsivity is overinclusive for the purposes of the goals for this review, we chose to focus our review by including only studies incorporating tasks designed to directly measure cognitive control (in particular response inhibition, distractor interference control, and working memory) and studies using the Barratt Impulsivity Scale (BIS). The BIS is a scale that has three subscales measuring cognitive impulsiveness (making quick decisions), motor impulsiveness (acting without thinking), and non-planning impulsiveness (lack of forethought), and scores on this scale appear to correlate with performance on tasks of response inhibition (reviewed in the next section); however, it does not directly measure constructs such as extroversion, sensation seeking, or delay discounting (Patton et al., 1995). We excluded studies focused more on delay discounting and studies using scales measuring facets of impulsivity less directly related to cognitive control.

That said, our decisions about which measures to include versus exclude from this review were made somewhat arbitrarily, and are based on insufficient evidence. We alert the reader to the fact that the degree to which impairments in the domains mentioned in the preceding two paragraphs, and the ones on which we are focusing in our review are overlapping or separate from one another has not been determined in many cases. For example, performance during tasks such as the GNG task (a response inhibition task) may be correlated with novelty seeking (Fallgatter et al., 1998) and memory may be correlated with flexibility and response inhibition (Noel et al., 2012) in AUD. While meta-analytic approaches can tease apart both commonalities and distinctions among the circuitries underlying these processes (Niendam et al., 2012), further combinations of individual neuroimaging and neuropsychological testing need to be done to better understand how

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

these processes, and impairments in these processes in neuropsychiatric disease states, cluster together or separate out from one another.

In addition, there is a wide literature supporting the fact that dysfunctional cognitive control is both a potential risk factor for (Saunders et al., 2008; Silveri et al., 2011; Mackiewicz Seghete et al., 2013) or a potential consequence of (Pfefferbaum et al., 1998) AUD. In this article, exploring 'which came first ' and the relationships of family history of inhibitory control and genetics will not be a focus. Rather, we will emphasize the nature of the deficits in cognitive control in individuals who have already developed AUD, with our goal to establish ways that this information can be used to improve available treatments.

We now move on to discuss in more detail the relevant three cognitive control processes of interest for this review: response inhibition, distractor interference control, and working memory.

Cognitive control processes of interest

Response inhibition

Response inhibition is also known as inhibitory control or behavioral inhibition, and it requires attention, the ability to inhibit a prepotent response, action restraint, and action cancellation (Congdon and Canli, 2005). Tasks that measure the integrity of these systems include Stop-signal tasks (SST) (on which reaction time and errors of commission are used as markers of deficient performance), and CPT or GNG (on which errors of commission in particular are used as markers of deficient performance). These tasks are similar in that they require the individual to withhold from following through on an otherwise reflexive action (Nigg, 2000; Bjork et al., 2004; Congdon and Canli, 2005).

These tasks also differ from one another in subtle ways. In the case of the GNG paradigms, 'Go' stimuli are presented more frequently than ' No-Go ' stimuli. Therefore, neural response to a No-Go stimulus may involve activation of attentional processes involved in detecting infrequent stimuli, in addition to processes mediating behavioral inhibition. A CPT tests both the ability to perform a repetitive task and to inhibit prepotent responses. The CPT can be presented as high demand, where errors of commission are important, and in this case it is like the GNG task; however, there are also low-demand versions of the CPT where the ratios are reversed, the target is rare, and it is sustained attention that is put to the test (Conners, 2000). In a SST, by contrast, a 'Stop' signal appears after the onset of a 'Go' signal on a subset of trials, requiring the participant to interrupt a response to the Go signal that has already been triggered, and the primary dependent measure is the Stop-signal reaction time (SSRT) (Rubia et al., 2001, 2003; Congdon and Canli, 2005). Although some claim the SST is, by its design, believed to invoke more inhibitory control processes than the GNG task (Rubia et al., 2001, 2003; Congdon and Canli, 2005), others argue that it may actually be measuring a slightly different process. The GNG and CPT may be measuring 'action restraint' processes (or stopping the movement before it starts), whereas the SST gets more at 'action cancellation ' processes (or the modulation of already initiated behaviors) (Eagle et al., 2008; Rogers et al., 2010). In fact, one review concluded that manipulation of serotonergic neurotransmission affected GNG but not SST (as measured by SSRT)

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

performance (Eagle et al., 2008), implying that these tasks are testing two different processes.

Finally, the BIS (mentioned above) deserves mention (Patton et al., 1995), as scores on this measure appear to correlate with performance on tasks of response inhibition in many cases. For example, total BIS score was found, in 504 participants, to be correlated with errors on the GNG, but not with Stroop interference scores (using a German color-word version) or SSRT (Aichert et al., 2012). In another work, the total score on the BIS and on the motor subscale and cognitive subscales were found to be significantly correlated with impaired GNG performance, and the non-planning subscale was correlated with 'Log Beta' on the D-Prime CPT (a measure of the tendency to tolerate higher commission error rate in pursuit of higher hit rate), whereas Stroop interference was not associated with BIS (Keilp et al., 2005). In a third study, the BIS total score was correlated with both GNG errors of commission and errors in the setting of conflict (which involved having to do something opposite of what the examiner is doing repeatedly), whereas the BIS motor subscale score correlated significantly with errors of commission, and the BIS cognitive subscale score was associated with conflict scores (Spinella, 2004). A fourth study showed that although there was no correlation between BIS score and performance on a GNG task, there was a negative correlation between BIS motor score and right DLPFC activation during inhibition relative to non-inhibition trials of a GNG task during fMRI (Asahi et al., 2004). However, in recent work, using principal components, BIS (using the three subscales but not the total score) and response inhibition (as measured by SSRT and the ratio of commission errors to correct detections on a CPT, specifically an immediate and delayed memory task) loaded on different factors, indicating that BIS may not always be measuring the same process as tasks of response inhibition (Broos et al., 2012). We still felt it useful to include BIS in this article, as it is probably the self-report scale with the most evidence for some association with cognitive control, and in particular with response inhibition.

Distractor interference control

Distractor interference control involves resolving response conflict (Ridderinkhof et al., 2004b), and it classically involves resolving stimulus incompatibility, processing conflicting information, and carrying out a response that competes with the prepotent, or 'natural' response (Roberts and Hall, 2008; Dick et al., 2009). These tasks require intact response inhibition processes, but also require intact selective attention networks, and are more complex than pure response inhibition tasks, as they require carrying out competing responses (e.g., suppressing a response in favor of 'alternative stimulus-response mapping') rather than just withholding a prepotent one (Nigg, 2000; Roberts and Hall, 2008).

Tasks used to measure interference control processes include the Stroop (Golden, 1976), Simon, flanker (Roberts and Hall, 2008), and Hayling tasks (Burgess and Shallice, 1996; Noel et al., 2012, 2013). In a task of interference control, there are generally trials where the distractor encourages the same response as the target (congruent) and other trials where the distractor encourages a different response as the target (incongruent), and performance is often measured as a difference measure between congruent and incongruent trials. One of the most commonly known tasks, the color-word Stroop task, requires individuals to say the

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

color that a word is written in, while ignoring what the word itself spells (also a color). The main performance measure of interest in the color-word Stroop is either an accuracy measure, or an 'interference score', which is a measure of the speed of performance during the interference condition, relative to a non-interference condition such as reading the color that a series of Xs are written in (Stroop, 1935; Treisman and Fearnley, 1969; Golden, 1976; Nigg, 2000). The Hayling task, testing similar processes, involves inhibiting a tendency to finish a sentence with a natural ending that makes sense, and instead inserting a nonsense word at the end of a sentence. In this task, the time it takes to insert the nonsense word relative to finishing a sentence with a word that makes sense is used as a marker of performance (Burgess and Shallice, 1996; Noel et al., 2012, 2013). Another series of Stroop tasks are growing in number, including the emotional Stroop (threat words) and the drug Stroop (Nigg, 2000; Hester et al., 2006), and indicate the potential involvement of limbic systems in moderating interference control, which may have particular relevance in addictive disorders. The Erikson flanker task also has low conflict and high conflict trials, with the high conflict trials either requiring individuals to identify one letter out of two different letters (each written in a different target color) or requiring individuals to press a button corresponding to a letter on the opposite side of the screen as the response hand. Low-conflict trials use the same letters, or require a button press corresponding to a letter on the same side of the screen as the response hand (Padilla et al., 2011). The Simon task is also a classic task that tests for reaction times to incongruent versus congruent stimuli, although we found no studies investigating performance on this task in AUD, and therefore will not describe it further.

Working memory

The third category is that of working memory. Although somewhat ill defined, it has been said to refer to the functionally opposing computations of (i) 'on-line' stabilization of task-relevant representations and (ii) flexible updating of those representations in response to novel information (Cools and D'Esposito, 2011). Although working memory is classically considered to refer to the system that buffers information that may become relevant for future behavior, tasks testing working memory often also require an intact supervisory system, requiring inhibitory control (response inhibition) and error correction (Hildebrandt et al., 2004). The degree to which response inhibition and working memory are separate processes or part of one system is still an area of debate (Braver and Barch, 2002; Friedman and Miyake, 2004; Hildebrandt et al., 2004; Cools and D' Esposito, 2011; Noel et al., 2013). However, most working memory tasks indeed generally require intact inhibitory functions, as might be tested in response inhibition or distractor interference control, such as suppression of unwanted thoughts, and resistance to intrusion of external and internal distractors (Nigg, 2000; Braver and Barch, 2002; Friedman and Miyake, 2004; Hildebrandt et al., 2004; Cools and D 'Esposito, 2011). Moreover, they usually require an ability to resist memory intrusions from information that was previously relevant to the task but has since become irrelevant, dubbed 'resistance to proactive interference', which may be a different process from response inhibition and distractor interference control (Friedman and Miyake, 2004; Noel et al., 2013). In addition, most of the working memory tasks test the integrity of memory systems and executive functions such as flexibility and complex reasoning, holding

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

multiple pieces of transitory information in the mind, and the ability to focus or switch attention (Nigg, 2000; Braver and Barch, 2002; Hildebrandt et al., 2004).

There are several tasks that test working memory. During the WAIS letter-number sequencing test, the examiner presents combinations of two to nine letters and numbers. The subject is asked to repeat the numbers in ascending order and then the letters in alphabetical order (Wechsler, 1981). In the alpha-span task, the subject is asked to repeat word sequences by direct recall and alphabetical recall and these two conditions are compared to assess the subject's performance (Belleville et al., 1998). During the WAIS digit-ordering task, the subject is asked to recall digit sequences both forward and backward and the score is the difference between the digit span forward and backward (Joos et al., 2013b). The delay alternation task requires the subject to decide under which picture the target is lying based on a specific alternating pattern that the subject would have ideally learned, over time, in previous trials (Ambrose et al., 2001). The Sternberg task is a verbal, numeric, or spatial working memory task. In the verbal version, subjects are asked to remember various letters, and then they are shown a letter on a screen, and press a button if the letter matches a remembered letter (Desmond et al., 2003). During a computation span task, subjects solve a series of math problems and are asked to recall the second digit of each answer in order, while the number of problems increases (Montgomery et al., 2012). The self-ordered pointing task is a visuospatial working memory task in which subjects are presented with a series of cards with 6– 12 abstract designs that are positioned differently on each card. The subjects are then asked to point to a different design on each card and they are scored based on number of errors (Goudriaan et al., 2006). Finally, the n-back test is a measure of complex working memory that is largely free of the effects of differences in vocabulary ability (Quinette et al., 2003; Pitel et al., 2007; Noel et al., 2012). During the n-back task, the subject is presented with a sequence of stimuli, and the task consists of indicating when the current stimulus matches the one from n steps earlier in the sequence. The load factor n can be adjusted to make the task more or less difficult (Quinette et al., 2003; Pitel et al., 2007; Noel et al., 2012). The proactive interference component of working memory has been tested by the Brown-Peterson task and the cued recall task (Kane and Engle, 2000; Noel et al., 2013). During the Brown-Peterson and cued recall tasks, the subject is asked to recall lists of words or individual words, portions that are subject to interference (because they are, for example, from a similar category as a previously read list), whereas others are not subject to such interference (Kane and Engle, 2000; Noel et al., 2013).

Brain circuitry of cognitive control

General cognitive control brain circuitry

The large-scale brain circuitry mediating cognitive control has been studied extensively. The prefrontal cortex (PFC) is defined as the area that receives projections from the medial dorsal thalamus, and includes the DLPFC, the medial PFC (MPFC; includes the ACC and pre-SMA), and the orbitofrontal cortex (Bonelli and Cummings, 2007; Crews and Boettiger, 2009). The MPFC plays a significant role in the evaluative component of decision making. For example, the rostral and dorsal ACC and pre-SMA are critical for response conflict and feedback or error monitoring (Garavan et al., 2002; Ridderinkhof et al., 2004a,b; Crews and

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Boettiger, 2009; Mayer et al., 2011). The MPFC and ACC are also critical for motivation (Bonelli and Cummings, 2007; Crews and Boettiger, 2009). The MPFC projects to the lateral PFC, and the to ventral striatum, which then projects to multiple brain regions for additional influence on behavioral output (Ridderinkhof et al., 2004a,b; Bonelli and Cummings, 2007; Crews and Boettiger, 2009). The DLPFC is more involved in regulative or inhibitory processes, and is believed to be essential to draw attention to important factors and to actively select or inhibit goals (Ridderinkhof et al., 2004a,b; Crews and Boettiger, 2009). Along with the regulative ventrolateral PFC (VLPFC) (Ridderinkhof et al., 2004a,b), the DLPFC projects to areas involved in motor planning and action adjustment (SMA motor cortex, dorsal striatum, and thalamus) (Ridderinkhof et al., 2004a,b), as well as to the parietal cortex (which plays a significant role in adaptation of behavior and rule shifting during cognitive control) (Dosenbach et al., 2008; Crowe et al., 2013). The OFC plays a combined evaluative and regulative role, in that it responds to outcomes but also signals outcome expectancies (Schoenbaum et al., 2009). In particular, the lateral OFC responds to negative reinforcers (influencing future action) and may play a particular role in inhibition, whereas the medial OFC responds to positive reinforcers and rewards, and, therefore, may be more involved in signaling positive outcome expectancies (Kringelbach, 2005; Bonelli and Cummings, 2007; Elliott et al., 2010). The cerebellum and its extensive circuitry also support these prefrontal circuits during cognitive control (Sullivan and Pfefferbaum, 2005; Schmahmann, 2010). A recent meta-analysis of 193 published studies of ‘executive function’ found that the common regions for cognitive control included not only the frontal cortex regions such as the DLPFC and ACC, but also the superior and inferior parietal lobes, precuneus, and pre-central gyrus (Niendam et al., 2012).

Some effort has been undertaken to identify the roles played by the different neurotransmitter systems during cognitive control. In particular, much attention has been given to the influence of dopamine (DA), and it has been observed that performance (e.g., on working memory tasks) is quite sensitive to changes in PFC DA levels. It is believed that there is an optimal DA level in the PFC that follows an ‘inverted U’ pattern, such that too little or too much DA is associated with impaired performance (Cools and Robbins, 2004; Arnsten, 2009; Cools and D’Esposito, 2011). DA also enhances signal-to-noise ratio and could thereby influence the salience of particular stimuli, and the likelihood that an action will be taken, or not taken, depending on the strength of transmitted signal (Bilder et al., 2004; Goto and Grace, 2005). Similarly, PFC noradrenaline (NA) fine tunes cognitive control (Arnsten, 2009). In fact, similar to the case for DA, there is an optimal NA level in the PFC in which the relationship between performance and cognitive function follows an ‘ inverted U ’ pattern (Arnsten, 2009). Both DA and NA are released during stress, which could further provide a mechanism by which the environment and emotional state influence decision making and the ability to inhibit a reflexive action (Arnsten, 2009). Similarly, serotonin (Eagle et al., 2008; Arnsten, 2009) may play an important role in cognitive control, as evidenced by studies showing that serotonergic stimulation may lead to decreased PFC neuronal firing during a cognitive control task, as may the balance between GABA and glutamate systems that fine tune prefrontal cortical neuronal firing (Arnsten, 2009).

Both overlapping and separate circuits may be responsible for the three categories of cognitive control we are addressing in this article (response inhibition, distractor

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

interference control, and working memory). While the Niendam et al. (2012) meta-analysis mentioned previously distinguished inhibition, flexibility, and working memory components in their studies of cognitive control, the authors conflated inhibition and distractor interference control into one domain, combining GNG with Simon, flanker, and Stroop studies, and thus does not completely serve our purposes (Niendam et al., 2012). Although more work needs to be done to determine the relative involvement of the different circuits in the three different processes, perhaps through future neuroimaging meta-analyses, we felt it useful to review in a general way how these processes are currently understood to both overlap and differ from one another at the circuit level.

Response inhibition brain circuitry

Response inhibition tasks commonly activate many of the regions involved in cognitive control in general. In particular, these tasks tend to activate bilateral DLPFC, VLPFC (BA 44/45), inferior parietal lobe, MPFC (ACC/pre-SMA), SMA, dorsal striatum, and thalamus, although activation in cortical areas tends to be more extensive and reliably seen on the right compared with the left during these tasks (Braver et al., 2001; Rubia et al., 2003; Asahi et al., 2004; Ridderinkhof et al., 2004a; Congdon and Canli, 2005; Nakata et al., 2008; Roberts and Hall, 2008). The right VLPFC in particular may be most specific to response inhibition, relative to the other brain regions (Congdon and Canli, 2005). Even more specifically, the right VLPFC may be especially important in the process of action cancellation (Aron et al., 2003, 2004; Chambers et al., 2006; Chevrier et al., 2007; Schachar et al., 2007), as demonstrated by studies showing a more right lateralized pattern for the SST, as opposed to the GNG task, which is associated with more left DLPFC activation (Rubia et al., 2001; Congdon and Canli, 2005).

Distractor interference control brain circuitry

Although tasks of distractor interference control classically activate many of the same brain networks mediating response inhibition mentioned above (Nigg, 2000; Roberts and Hall, 2008), there are some differences, and, not surprisingly given the higher complexity of the tasks, more widespread brain activation is generally seen. During these tasks, studies generally report activation in the bilateral ACC, DLPFC, VLPFC, anterior insula, pre-SMA, SMA, motor cortex, and parietal lobes (Nigg, 2000; Gruber et al., 2002; Ridderinkhof et al., 2004a; Marsh et al., 2006; Roberts and Hall, 2008; Mayer et al., 2011), without evidence of the same degree of right lateralization as is seen in most studies using tasks of response inhibition.

Working memory brain circuitry

Working memory tasks are classically thought to invoke DLPFC, more reliably and extensively than the other two aforementioned categories of tasks. In addition to the other functions mentioned, the DLPFC is believed to play a key role in actively holding representations of either emotional objects or other task-relevant information in awareness (Smith and Jonides, 1999; Dosenbach et al., 2008). However, this more extensive activation of the DLPFC during working memory tasks relative to the other tasks may be related to the fact that working memory tasks are more complex and abstract. Some theories posit that there is a hierarchy of representations such that the DLPFC may be involved in more

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

abstract goal representations, whereas the VLPFC (which is often activated during tasks of response inhibition, for example) may play a greater role in concrete goal representations (Badre, 2008). In addition, it is not surprising, given the complexity of most working memory tasks, that most of the other regions involved in response inhibition and distractor interference control, such as the MPFC, parietal cortex, ACC, striatum, thalamus, and insula, are also often activated during working memory tasks (Smith and Jonides, 1999; Badre, 2008; Dosenbach et al., 2008).

Individuals with AUD compared with controls

Self-report and neuropsychological testing

Having established the cognitive processes of greatest interest for this review, and the tests that we feel most adequately represent these processes, we now move on to review the studies that investigate differences in cognitive control in individuals with AUD compared with controls. First, it is worth mentioning that scores on the BIS appear to be higher in individuals with AUD compared with controls in adolescents (Soloff et al., 2000) and adults (Bjork et al., 2004; Mitchell et al., 2005; Chen et al., 2007; Rubio et al., 2008), indicating, in a general sense, that individuals with AUD probably have some impairments in cognitive control.

More specifically, performance on tasks of response inhibition has been demonstrated to be impaired in individuals with AUD compared with controls in most studies. Using a Go-No-Go task during measurement of event related potentials (ERP), one study demonstrated no differences in reaction time and no increases in ‘ No-Go’ errors, but significant increases in total Go and No-Go errors in individuals with AUD compared with controls (Kamarajan et al., 2005). In addition, greater numbers of errors of commission on a GNG have been found to be related to greater drinking quantities in social drinkers (Weafer et al., 2011). Individuals with AUD (Goudriaan et al., 2006; Maurage et al., 2011; Joos et al., 2013b) and heavy drinkers (Rubio et al., 2008) have demonstrated increased SSRT compared with controls in a number of studies. Although one study did not see a significant difference in errors of commission or omission on one version of the CPT in heavy drinkers versus controls, a trend was observed (p=0.059) (Rubio et al., 2008), and increased errors of commission and faster response latencies on a CPT have been demonstrated in individuals with AUD compared with controls in another work (Bjork et al., 2004). Moreover, increased errors of commission on a CPT in adolescent psychiatry individuals with AUD compared with controls have been observed (Pogge et al., 1992). Finally, in a task designed to test working memory, flexibility, and inhibition at the same time (named ‘an alternate response task’), individuals with AUD demonstrated impaired inhibition with normal working memory (Hildebrandt et al., 2004).

Individuals with AUD have also demonstrated impairments in performance on tasks testing distractor interference control compared with controls. Group differences have been perhaps slightly less reliably seen compared with response inhibition tasks, as some studies have shown no group differences on speed-related Stroop interference scores (Noel et al., 2001; Tapert et al., 2001; Chanraud et al., 2007; Pitel et al., 2009) and performance on the Erikson flanker task (Padilla et al., 2011) and others have only shown a trend (Ratti et al., 2002).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

However, many studies have demonstrated that individuals with AUD perform more poorly than controls. For example, compared with controls, individuals with AUD show higher interference scores (Dao-Castellana et al., 1998; Goudriaan et al., 2006; Pitel et al., 2007) and number of errors (Dao-Castellana et al., 1998; Tedstone and Coyle, 2004; Noel et al., 2012). Individuals with both bipolar disorder and AUD had higher Stroop interference scores compared with controls (no bipolar disorder and no AUD), whereas there were no significant differences between individuals with bipolar disorder without AUD and controls (Sanchez-Moreno et al., 2009). Individuals with AUD have also been found to be slower in response inhibition on the Hayling task given more related words (errors of commission) (Noel et al., 2001, 2012, 2013).

Finally, individuals with AUD show impairments on tasks of working memory, but these impairments are even less consistent than impairments seen in the other categories. However, some studies have shown that individuals with AUD perform more poorly than controls. Poor performance has been demonstrated on an n-back task (Pitel et al., 2007, 2009) and on a spatial working memory task (Kopera et al., 2012) in individuals with AUD versus controls. Additionally, on an alpha-span task, AUD patients performed more poorly than controls on alphabetical compared with direct recall, indicating poor ability to manipulate information (Noel et al., 2001, 2012). Moreover, poorer performance on a delay alternation task has been demonstrated in individuals with AUD, which worsens with greater load (Ambrose et al., 2001). Finally, WAIS letter-number sequencing has also been shown to be impaired in individuals with AUD versus controls (Chanraud et al., 2007; Thoma et al., 2013). By contrast, a number of studies comparing individuals with AUD to controls have not shown a group effect. For example, using a computation span task where heavy social drinkers were compared with light social drinkers, there was no significant group difference in computation span (Montgomery et al., 2012). In a two-back task (Hildebrandt et al., 2004) or an n-back task (Brokate et al., 2003; Noel et al., 2013), there was no evidence of group differences or evidence of a change in group differences with increases in load. Finally, a composite measure including a number of working memory tasks (WAIS digit span backward, visuospatial working memory task) showed no group differences (Goudriaan et al., 2006).

We have discussed ways in which impairments in cognitive control might theoretically be contributing to persistent relapse. We have defined and discussed specific cognitive control constructs, and the neurobiology and neuroanatomy of the healthy performance of tasks requiring cognitive control. We have discussed how individuals with AUD differ from controls in performance on a variety of tasks mediating cognitive control. Now, we will consider how particular brain changes in AUD may be mediating the aforementioned performance problems.

Anatomical and functional brain changes in cognitive control networks

In vivo structural neuroimaging studies in AUD have confirmed the presence of brain volume loss, including gray matter in the frontal lobes, insula, basal ganglia (thalamus, caudate, putamen), temporal lobes, brainstem, cerebellum, and hippocampus (Harper and Matsumoto, 2005; Sullivan and Pfefferbaum, 2005; Chanraud et al., 2007). Larger ventricles

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

and brain tissue volume loss correlate with the amounts of alcohol consumed (Ding et al., 2004). The notion of compromised fronto-cortico-cerebellar functional networks in AUD appears to be a well-replicated construct, and there is evidence that deficits in a variety of executive functions, and in particular in performance on tasks of cognitive control, are associated with volume loss in the frontal, cerebellar, and subcortical (striatum and thalamus) regions, in particular (Sullivan, 2003; Scheurich, 2005; Chanraud et al., 2007).

Abnormalities in metabolites (*n*-acetylaspartate and choline) using proton magnetic resonance spectroscopy, cerebral blood flow using single photon emission computed tomography, perfusion weighted MRI, and metabolism using PET have been consistently demonstrated in AUD, especially in the frontal areas (Adams et al., 1993; Nicolas et al., 1993; Moselhy et al., 2001; Parks et al., 2002; Clark et al., 2007). Furthermore, mediofrontal hypometabolism was associated with interference time, and dorsolateral prefrontal hypometabolism correlated with the number of errors in both individuals with AUD and controls on a Stroop task (Dao-Castellana et al., 1998). Animal studies suggest that volume loss and metabolite changes in these areas may be related to direct alcohol toxicity on neurons that cause neuronal cell death and prevent neuronal proliferation and neurogenesis and decrease dendritic branching (e.g., direct alcohol neurotoxicity) (Crews and Nixon, 2009).

Excessive alcohol consumption can adversely affect white matter fibers, thereby disrupting transmission of information between brain sites, which is important because executive control likely requires intact connectivity between regions (Chanraud et al., 2009; Pfefferbaum et al., 2010; Schulte et al., 2010). Alcohol toxicity may cause changes in myelination and axonal integrity and dendritic neuropil function (Harper, 1998; Sullivan and Pfefferbaum, 2005). Abnormalities in posterior cingulum fibers (Schulte et al., 2012), the genu, and splenium (Sullivan and Pfefferbaum, 2005) have been measured in AUD, as have a relationship between working memory scores and diffusivity in the genu (Sullivan and Pfefferbaum, 2005).

Neurophysiology studies using EEG to measure ERP have also been done to try to establish markers of impairments in cognitive control. Specific components of ERP have been implicated in various cognitive tasks. For example, the N2 (a negative deflection at 200 ms) and P3 or P300 (a positive deflection at 300 ms) components have been identified as markers for response inhibition during the No-Go condition of GNG tasks (Kopp et al., 1996). The N400 component (a negative deflection at 400 ms) occurs after presentation of an incongruent semantic stimulus (Ganis et al., 1996), which may have particular relevance for tasks of distractor interference control. Several ERP studies examining these components have been conducted in AUD. The P3 or P300 component has often been the focus of studies cognitive control in AUD (Kamarajan et al., 2005; Petit et al., 2012), and it has been thought to represent inhibition involving the VLPFC (Chiu et al., 2008). The N2 component is thought to represent conflict monitoring and effortful processing involving the rostral ACC (Chiu et al., 2008). During tasks of response inhibition, a delayed or blunted No-Go P3/P300 component, with a mostly normal N2 component, has been observed in heavy social drinkers (Petit et al., 2012) and individuals with AUD (Cohen et al., 1997; Fallgatter et al., 1998; Kamarajan et al., 2005). Moreover, a blunted N400 ERP response has been

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

observed in individuals with AUD compared with controls during a Stroop-like reading task (Nixon et al., 2002). A blunted or delayed P3/P300 component during response inhibition may be a relatively consistent marker distinguishing individuals with AUD from controls.

Finally, fMRI studies using tasks from all three aforementioned categories of cognitive control support altered function in cognitive control networks in individuals with AUD. Four studies have been performed using response inhibition tasks. The first found decreased left DLPFC activation in individuals with AUD during an SST during behavioral inhibition, and decreased right DLPFC activation during post-error slowing (a measure of post-error behavioral adjustment) but increased visual and frontal (anterior cingulate gyri, occipital lobes, parietal lobes, pre-central gyri) activity during errors compared with controls (Li et al., 2009). A second study showed decreased activation in the putamen in individuals with AUD compared with controls during an SST when stop success versus stop error trials were contrasted (Schmaal et al., 2013). A third study showed no significant differences between individuals with AUD and controls during an auditory GNG task but, when comparing individuals with AUD with high trait anxiety to those with low trait anxiety, observed increased activation in the middle frontal gyrus, superior frontal gyrus, right inferior frontal gyrus, and temporo-parietal brain regions (Karch et al., 2008). Finally, another study comparing more severe AUD to less severe AUD during a GNG task found reduced neural response with increasing AUD severity in the right insula, inferior frontal gyrus, pregenual ACC, and inferior parietal lobe during response inhibition (Claus et al., 2013). In general, AUD or greater AUD severity may be associated with decreased activation during response inhibition.

Two studies have been done using tasks testing distractor interference control. The first study used a Stroop-like task where participants were asked to match color cues with colors of targets, and, during incongruent trials, targets spelled-out distractor color words written in colored (matching or non-matching) ink. Compared with controls, who demonstrated posterior cingulate cortex (PCC) deactivation during conflict, individuals with AUD demonstrated activation in the PCC. Moreover, AUD patients demonstrated greater task-related activation during response repetition than during response switching in the PCC and midbrain (substantia nigra and subthalamic nucleus), whereas in controls, the PCC and midbrain were activated during response switching but deactivated in response repetition. These two PCC patterns (deactivation/activation) were both correlated with the quantity of alcohol consumption (Schulte et al., 2012). The second study demonstrated increased activation in the DLPFC, thalamus, basal ganglia, and other sensorimotor cortical areas in individuals with AUD compared with controls when both incongruent and congruent trials were combined but no significant group-by-condition interactions (in a small sample size; total n=16) (Wilcox et al., under review).

The majority of fMRI studies of cognitive control in AUD have been performed using working memory tasks. Greater activation in the left PFC (BA 44/45) and right superior cerebellum during a Sternberg task has been observed in individuals with AUD compared with controls to maintain similar levels of performance (individuals with AUD activated appropriate regions more widely than controls), and the authors hypothesized that the hyperactivation represented a compensatory response to frontocerebellar network

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

compromise (Desmond et al., 2003). During a two-back versus rest study of working memory, individuals with AUD exhibited decreased activation in the bilateral DLPFC compared with controls (Pfefferbaum et al., 2001). In addition, in the center versus rest contrast (which was the motor control for this study), the control group demonstrated increased activation in the PFC (BAs 9,10,45) compared with individuals with AUD, whereas individuals with AUD demonstrated increased activation in the posterior VLPFC (BA 47) compared with controls (Pfefferbaum et al., 2001). Another study using a two-back task showed decreased activation in individuals with AUD compared with controls in the bilateral frontal and pre-central cortex, and left superior temporal, superior parietal, and cerebellar cortex; however, this work did not report any performance metrics (Park et al., 2011). A study in adult women demonstrated significantly less spatial working memory-associated BOLD response in individuals with AUD compared with controls in the right inferior and superior parietal lobule, postcentral gyrus, and middle frontal gyrus, as well as the left superior frontal gyrus, ventral lateral thalamus, and cerebellar anterior lobe, individuals with AUD demonstrating poorer performance on the task compared with controls (Tapert et al., 2001). The same task was used to compare adolescent individuals with AUD and controls, and demonstrated similar performance between groups, with greater BOLD response in individuals with AUD compared with controls during the spatial working memory task in bilateral parietal cortices and diminished response in other regions, including the left precentral gyrus and bilateral cerebellar areas (Tapert et al., 2004a). Finally, a task designed to elicit activation in networks responsible for resistance to proactive interference demonstrated increased activation in controls in the ventromedial OFC, pons, lingual gyrus, and ventromedial nuclei of the thalamus, but increased activation in individuals with AUD in the lateral PFC, ACC, and ventral striatum (De Rosa et al., 2004).

During the aformentioned tasks designed for use during fMRI to test cognitive control, differences in behavior (accuracy and reaction time) between individuals with AUD and controls have not been consistently demonstrated (Pfefferbaum et al., 2001; Desmond et al., 2003; Tapert et al., 2004a; Karch et al., 2008; Schmaal et al., 2013) despite differences in some cases in activation patterns. This absence of an effect on performance is not surprising, as it is generally considered optimal in a scanner task for group differences in performance to be minimized, as it minimizes noise from error commission-related brain activation (Yarkoni et al., 2009). The exceptions to this are listed below. In one of the aforementioned response inhibition studies, individuals with AUD demonstrated longer go trial reaction time and higher stop success rate compared with controls. However, controls and individuals with AUD were indistinguishable in SSRT and post-error slowing, indicating similar response inhibition function (Li et al., 2009). In the studies of distractor interference control, controls outperformed individuals with AUD in reaction time differences between incongruent and congruent stimuli (Schulte et al., 2012). In the task testing similar processes, but specifically testing the ability to focus on particular modalities while ignoring distraction from a different modality (auditory versus visual distractors), controls also outperformed individuals with AUD (Wilcox, under review). Finally, in the aforementioned studies of working memory, controls outperformed individuals with AUD (accuracy) during a spatial working memory task (Tapert et al., 2001).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

As can be seen above, a clear pattern of hyper- or hypofunction in expected prefrontal and subcortical regions in individuals with AUD during tasks requiring cognitive control has not been supported by the findings. This lack of consistency has also been observed in other substance use disorders (e.g., cocaine use disorders), as has been discussed in previous work (Mayer et al., 2013). The inconsistencies also persist within subclasses of cognitive control, as we have approached them, with slightly more consistency for tasks of response inhibition compared with the other classes. Factors such as small subject numbers, length of sobriety and absence or presence of withdrawal (Tapert et al., 2004b), task difficulty and type of task (Simmonds et al., 2008), age (D'Esposito et al., 2003), sex (Bell et al., 2006), concurrent medications (Del-Ben et al., 2005), comorbid psychiatric disorders (Karch et al., 2008), and AUD severity and quantity of use (Claus et al., 2011a,b) could all theoretically influence the BOLD response. Even studies comparing higher-risk participants to lower-risk participants (either level of response to alcohol or family history) are contradictory, one showing that higher-risk participants have greater activation in the DLPFC and posterior parietal cortex during a working memory task (Paulus et al., 2006) and another showing that higher-risk participants had less activation in the right DLPFC compared with lower-risk participants (Mackiewicz Seghete et al., 2013).

Functional connectivity analyses allow for measurement of intrinsic low-frequency brain oscillations in the BOLD response, and provide more information about spatially distributed networks (Fox and Raichle, 2007). There have been a number of investigations of functional connectivity in cognitive control networks, comparing AUD with controls. One study found greater AUD severity to be associated with weaker functional connectivity between the putamen and prefrontal regions (e.g., the anterior insula, ACC, and MPFC) during response inhibition during an SST (Courtney et al., 2013). Connectivity measurements during performance of a Stroop task demonstrated decreased functional connectivity between PCC and middle cingulate in individuals with AUD but increased connectivity between the midbrain and middle cingulate/SMA, as well as between the midbrain and putamen, compared with controls. Further analyses demonstrated greater cortico-cortical connectivity among middle cingulate, posterior cingulate, and medial prefrontal cortices in controls compared with individuals with AUD, whereas individuals with AUD exhibited greater midbrain-orbitofrontal cortical network connectivity (Schulte et al., 2012). In another study, individuals with AUD exhibited less synchrony and lower efficiency indices (using graph theory analysis) between the PCC and cerebellum compared with controls at rest (Chanraud et al., 2011) but greater connectivity between these regions during a working memory task to achieve similar performance, indicating compensatory networking to achieve normal performance (Chanraud et al., 2011). A final study was done showing that long-term abstinent alcohol-dependent individuals had decreased synchrony between a subgenual ACC seed region and caudate and thalamus, decreased synchrony between a nucleus accumbens seed region and caudate and thalamus, but increased synchrony between the DLPFC and both the ACC seed and the nucleus accumbens seed compared with controls during resting state; this was argued to be a compensatory mechanism associated with decreased connectivity between regions involved in bottom-up appetitive drive, and increased connectivity within inhibitory control regions theoretically improving the ability to maintain abstinence (Camchong et al., 2013).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Connectivity studies in AUD focused on other networks (stress reactivity, cue reactivity, motor, sensory processing) have shown decreased connectivity between cortical structures (dACC, VLPFC, OFC, occipital gyrus, middle frontal gyrus, parietal lobule, DLPFC, premotor cortex, insula) and other regions in individuals with AUD compared with controls and in individuals with more severe AUD (O'Daly et al., 2012; Rogers et al., 2012). In summary, AUD may be associated with decreased connectivity between cortical structures (dACC, VLPFC, OFC, occipital gyrus, middle frontal gyrus, parietal lobule, DLPFC, premotor cortex) and between striatum and ACC/MPC/PFC, but increased connectivity between the midbrain and limbic structures (amygdala), middle cingulate, OFC, and striatum (cue processing or reward regions). Finally, in a study of individuals with AUD treated with modafinil, reduced connectivity between the thalamus and the primary motor cortex accompanied improvements in SSRT (Schmaal et al., 2013), indicating the thalamocortical connectivity may deserve more focus in studies of AUD and response inhibition deficits. In general, studies contrasting functional connectivity metrics between controls and individuals with AUD may provide more reliable findings from study to study than some of the studies using metrics of evoked BOLD response.

Some work has also been done to investigate neurochemical differences (at the level of neurotransmitter systems) in individuals with AUD compared with controls, although to what degree these changes contribute to the impairments in cognitive control in individuals with AUD needs further study. Of note, D2 receptors have been shown to play a role in cognitive control. Specifically, models of action selection and goal-directed behavior posit that D2 agonism leads to less spontaneous firing and more PFC stability, perhaps leading to more cognitive control (Seamans and Yang, 2004; Goto and Grace, 2005). Compared with controls, AUD patients exhibit decreases in D2/D3 availability in the ventral striatum and putamen (Heinz et al., 2004). Changes in striatal DA synthesis capacity may also be associated with alcohol dependence as measured by FDOPA (Heinz et al., 2005). Low serotonin in the OFC is linked to poor response inhibition (Logue and Gould, 2013), and low serotonin activity overall is associated with early-onset alcoholism and a low response to alcohol (a well-established predictor for AUD) (Kreek et al., 2005). By contrast, postmortem studies of AUD have demonstrated upregulation of certain subtypes of opioid receptors (Bazov et al., 2013). Most likely, imbalances in a variety of central neurotransmitter systems may contribute both to deficits in cognitive control and maintenance of AUD and loss of control.

Clinical significance of deficits in cognitive control

Cognitive control as an outcome predictor or moderator

Although it is difficult to rank the most consistent markers of impairment in cognitive control in AUD with any degree of accuracy, through our review thus far, it appears that the more promising markers include response inhibition task performance and associated brain activation, BIS scores, and volume loss, followed by distractor interference control task performance, neurophysiological changes, and fcMRI, whereas working memory performance, and fMRI task-evoked activation during tasks of distractor interference control and working memory show less consistent findings. We now move on to explore the clinical

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

significance of these deficits, and in particular whether any of them predict drinking outcomes and future AUD severity.

There have been few longitudinal studies investigating the clinical relevance of particular deficits in cognitive control in AUD. A handful of studies have indicated that the BIS score, particularly the cognitive component (Charney et al., 2010), can predict drinking outcomes at 4 weeks (Charney et al., 2010) and 12 months (Evren et al., 2012) in AUD. Moreover, slower SSRTs in heavy drinkers significantly predict alcohol consumption at 4 years follow-up, and the risk of development of AUD, whereas errors of omission on the CPT and BIS scores are also predictive in the expected direction, but non-significant (Rubio et al., 2008). However, neither Stroop performance (as measured by the number of colors named during the interference condition) nor working memory performance on a verbal and spatial span task have been found to predict outcome in individuals with AUD when comparing returners to non-returners and abstainers to non-abstainers (Pitel et al., 2009). In another study, slowed reaction time on a modified Stroop (which involved identifying if a colored word was the ‘same’ or ‘different’ than the ink in which the word was printed) was found to be neither a moderator of the effect of cognitive bias retraining on alcohol consumption in AUD (Eberl et al., 2013) nor a predictor of overall outcomes. A recent study was performed in early abstinent individuals with AUD using seed-based connectivity analysis in which some (but not all) of the seeds were placed in brain regions mediating cognitive control such as the subgenual ACC and insula. This study found that for all seeds, decreased synchrony with other brain regions was associated with higher relapse risk (Camchong et al., 2013). These works indicate that higher BIS scores, impaired performance on tasks of response inhibition, and decreased functional connectivity deserve further exploration as potential outcome predictors in AUD.

A much more extensive body of work has explored risk factors for the development of future AUD in non-clinical populations, and it has indicated that impairments in response inhibition (Porjesz et al., 1998; Crean et al., 2002; Nigg et al., 2006; Saunders et al., 2008; Schuckit et al., 2012), distractor interference control (Silveri et al., 2011), and working memory (Trim et al., 2010; Mackiewicz Seghete et al., 2013) systems are associated with a higher risk of future development of AUD. However, there is a paucity of literature on the topic in clinical populations who have already developed AUD. Clearly, more studies are needed to identify predictors of outcome using markers of cognitive control in clinical AUD populations.

When trying to identify predictors of outcome in any longitudinal study of AUD, it is important to consider the fact that AUD is a heterogeneous disorder, made up of subtypes (Bogenschutz et al., 2009). There are a variety of proposed methods for subtyping, although no single method has emerged as superior (Penick et al., 1999). The ‘age of onset ’ dimension appears to span multiple subtyping methods, and to account for overlap between subtypes, including that of Babor (type A/type B), Cloninger (type 1/type 2), or based on timing of illness onset alone [(early onset alcoholics (EOA)/late onset alcoholics (LOA)] (Chick et al., 2004; Roache et al., 2008; Bogenschutz et al., 2009). Type A alcoholics (which overlap with the type 1 and LOA groups) are characterized by later onset and lesser severity, whereas type B (which overlap with type 2 and EOA) are characterized by an

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

earlier-onset, antisocial personality disorder (ASPD), family history, and co-occurring other substance use (Bogenschutz et al., 2009). Different subtypes may have different clinical trajectories. For example, although the aforementioned categories may not predict drinking outcome overall, there is growing evidence that they may moderate response to clinical outcome for AUD during pharmacotherapeutic treatment for relapse prevention, with the direction of the effects varying by medication (Chick et al., 2004; Roache et al., 2008; Bogenschutz et al., 2009). For example, EOA may have a better clinical response to ondansetron, whereas type 1/A alcoholics may have a better clinical response to selective serotonin reuptake inhibitors and naltrexone (Chick et al., 2004; Roache et al., 2008; Bogenschutz et al., 2009). Subtyping by other methods, such as the presence or absence of psychiatric diagnosis, may also predict different treatment outcomes, as seen by the fact that cluster B personality disorder diagnosis may predict worse outcome to general ‘addiction treatment’ at 12 months (Charney et al., 2010).

For this reason, we felt it useful to review, briefly, below, what is known about the differences in cognitive control between different subtypes of AUD. Type 2 alcoholics may do more poorly on tests of response inhibition as evidenced by a study showing that, on a CPT, they had more errors of commission and faster response latencies compared with type 1 alcoholics (Bjork et al., 2004) (with no differences on a delay discounting task or risk taking task by typology). This is supported by work showing that initiation of alcohol use during adolescence (before 18 years) is associated with higher rates of commission errors on a CPT in social drinkers (Dougherty et al., 2004) and that EOA have higher BIS scores, and higher rates of attention deficit hyperactivity disorder (ADHD) and ASPD compared with LOA (Joos et al., 2013b). By contrast, LOA, not EOA, had a lower Stroop interference score and greater digit span errors (Joos et al., 2013b), indicating that deficits in cognitive control may not be uniformly deficient in one typology subgroup compared with another. When investigators have subtyped by co-occurring psychiatric diagnosis, AUD with ADHD demonstrated no worse impairment on response inhibition tasks than those without ADHD (Weafer et al., 2011). However, AUD with cluster B diagnoses had higher BIS scores than AUD without cluster B diagnoses, as well as greater numbers of errors of commission on a GNG (with no differences in reaction time) (Dom et al., 2006). However, no significant differences on Stroop interference scores between AUD with co-occurring cluster B diagnoses have been observed (Dom et al., 2006). In summary, impairments in response inhibition may both differentiate AUD subtype and predict clinical outcomes. Further work is needed to see if response inhibition and typology interact to predict outcomes in general, and in response to particular treatments for AUD.

Cognitive control as a mediator

Demonstration of a mediational chain first involves establishing significant relations between the independent factor (in our case, treatment group assignment or baseline factor) and outcome of interest (in our case, alcohol use outcomes), between the independent factor and mediator (in our case, cognitive control), and between the mediator and the outcome. Moreover, the path from independent factor to outcome through the mediator needs to account for the relationship between the independent factor and outcome (Baron and Kenny, 1986). Little work has been done to identify whether changes in cognitive control, and in

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

particular in response inhibition, distractor interference control, or working memory mediate the effect of a predictor or particular treatment on alcohol use outcomes. However, to this end, we review work demonstrating that potentially effective interventions and treatments for AUD also appear to improve certain elements of cognitive control, thereby deserving exploration in mediational analyses in the future.

Abstinence—Current abstinence predicts future abstinence in large longitudinal studies, which is mediated, in part, by increases in self-efficacy (Maisto et al., 2008). Improvements in cognitive control may also mediate the effect of abstinence on future abstinence and deserves attention in treatment studies examining mediators of drinking outcomes.

There is an abundance of evidence that abstinence results in improved general cognitive function (Fein et al., 2006). It has been proposed that, in AUD, there may be both a subacute effect of alcohol on cerebral microcirculation, related to recent alcohol use, and a more chronic effect on cortical and subcortical structures, related to total lifetime consumption (Nicolas et al., 1993). However, studies have demonstrated stronger associations between cognitive deficits and recent alcohol consumption but weaker and inconsistent associations with lifetime quantities (Scheurich, 2005; Sullivan and Pfefferbaum, 2005). In fact, abstinence results in neurogenesis and brain regrowth (Crews and Nixon, 2009), and even with 1 month of sobriety, brain volume can begin to normalize (Pfefferbaum et al., 1995; Sullivan and Pfefferbaum, 2005), whereas volume loss recurs with relapse (Pfefferbaum et al., 1995; Sullivan and Pfefferbaum, 2005). Functional connectivity studies in AUD also support compensatory changes and normalization of brain function with time abstinent (Chanraud et al., 2011). Moreover, the longer an individual with AUD stays abstinent, the greater the recovery in general cognitive functioning (Bates et al., 2002, 2004; Kopera et al., 2012).

Abstinence is also particularly associated with improvements in cognitive control. For example, a cross-sectional study showed associations between abstinence for > 1 year and improved performance on a spatial working memory task (Kopera et al., 2012). A more convincing longitudinal study showed that, in individuals with AUD who were able to maintain 6 months of abstinence, working memory performance (as measured by accuracy and reaction time on a two-back task) was statistically lower in the abstinent subgroup compared with controls at baseline, but equal to controls at 6 months follow-up (Pitel et al., 2009). Multiple episodes of alcohol withdrawal (experiencing withdrawal symptoms) and binge drinking, but not blackouts, may also have a particularly significant effect on cognitive function, and in particular on working memory function (Glenn et al., 1988; Duka et al., 2004; Maurage et al., 2012; Wollenweber et al., 2012). This emphasizes the importance of treating alcohol withdrawal (e.g., with benzodiazepines), in addition to helping patients maintain abstinence.

Not all of the impairments in cognitive control may be reversible with abstinence. In one study, difficulties in working memory were found to linger into long-term sobriety while some of the other cognitive functions improved (Sullivan et al., 2000a; Sullivan and Pfefferbaum, 2005) and, in another work, on a spatial working memory task, individuals with long-term abstinence performed better than individuals with short-term abstinence, but

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

controls performed the best (Kopera et al., 2012). Of course, impairments in cognitive control may, in some cases, precede AUD onset, and therefore would not be expected to reverse with cessation of alcohol use (Porjesz et al., 1998; Crean et al., 2002; Nigg et al., 2006; Saunders et al., 2008; Trim et al., 2010; Silveri et al., 2011; Schuckit et al., 2012; Mackiewicz Seghete et al., 2013). In addition, medical problems and older age (Bates et al., 2004) predict less improvement in general cognitive function, and older age predicts less improvement in working memory performance (Pitel et al., 2009) on alcohol abstinence.

In summary, given the clear effects of abstinence on general cognitive recovery, and the likely effects on improvement in working memory, cognitive control deserves exploration as a potential mediator of the effect of abstinence on future abstinence. Furthermore, to maximize chances of cognitive recovery, and potentially thereby minimize chances of relapse, clinicians should strongly encourage abstinence, and make reasonable efforts to minimize alcohol withdrawal severity and frequency.

Psychotherapeutic—A variety of psychotherapeutic interventions are known to be effective in improving drinking outcomes for individuals with AUD, and theoretically may work by, among other mechanisms, improving cognitive control. In particular, given that emotional triggers may decrease response inhibition (Euser and Franken, 2012), it makes theoretical sense to imagine that improving affect regulation (a common goal in many forms of psychotherapy) may improve response inhibition, thereby contributing to improved drinking outcomes.

In particular, mindfulness training may both decrease drinking and improve cognitive control. Research suggests that mindfulness training may be an effective intervention for AUD, as evidenced by results from an observational study of medical students in which significant inverse correlations were found between current meditation practice and alcohol use and AUDIT scores (Black et al., 2011), and, more convincingly, from a randomized controlled trial of mindfulness-based relapse prevention for the treatment of AUD (Bowen et al., 2009) that demonstrated the efficacy of an 8-week mindfulness-based relapse prevention training. Mindfulness training is also associated with improvements in performance on tasks of working memory (Jha et al., 2010; Zeidan et al., 2010) and decreases in stress reactivity (Tang et al., 2007, 2009).

Pharmacological—A variety of medications have been shown to improve drinking outcomes in individuals with AUD, the most established being naltrexone, acamprosate, disulfiram, and topiramate (Galanter and Kleber, 2008). For some medications, there is already evidence that they may be acting through effects on response inhibition. For example, topiramate, which appears to be an effective relapse prevention agent (Johnson et al., 2007), has been found to be associated with improvement in response inhibition as measured by errors of commission and omission on the CPT and SSRT, and changes in response inhibition was correlated with decreases in drinking over a 12-week period (Rubio et al., 2009).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Interventions that generally improve cognitive control and are worthy for study in AUD relapse prevention

Psychotherapeutic/non-pharmacological—Non-invasive brain stimulation, such as with transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), may affect response inhibition. Recent studies have demonstrated faster SSRT after tDCS over the right inferior frontal gyrus (Jacobson et al., 2011) and after TMS over the same area, consistent with established models that the right inferior frontal gyrus plays a significant role in response inhibition. For this and other reasons, tDCS and TMS are also currently being studied for use in AUD to reduce craving, and possibly improve drinking outcomes (Nakamura-Palacios et al., 2012; Nardone et al., 2012).

There is growing interest in developing training focused particularly on improving cognitive function in AUD, with an aim to ultimately help individuals stop drinking. One group performed general cognitive remediation training in AUD (Rupp et al., 2006), which was directed toward attention/executive function and memory domains. The training resulted in significant improvement in attention, working memory, recall, and psychological well-being. In addition, these improvements in cognitive function were also associated with decreased craving. Future development of these kinds of trainings, in particular focused on those cognitive domains most important at predicting better outcomes (like response inhibition), should be pursued.

Pharmacological—The potential utility of medications affecting the adrenergic, cholinergic, dopaminergic, glutamatergic, and GABA-ergic systems for the treatment of addictions has been recently reviewed extensively (Brady et al., 2011); however, this review focused mostly on stimulant use disorders. Interestingly, few of the studies cited in this article were performed in individuals with AUD, indicating a potentially useful area for future research in AUD. Given the known beneficial effects of the GABA agonist/glutamate antagonist on response inhibition and alcohol drinking as discussed in prior sections (Johnson et al., 2007; Rubio et al., 2009), further exploring similar medications (including pregabilin, zonisamide, and tiagabine) may prove useful, but there has been little more done to investigate the effects of these medications on cognitive control. We therefore move on to discuss medications targeting the cholinergic, adrenergic, and dopaminergic systems.

Nicotinic agonists (nicotine, varenicline) have been shown to improve attention and working memory in non-smokers (Ceballos et al., 2005; Brady et al., 2011; Mocking et al., 2013). Moreover, in heavy drinking smokers, varenicline may decrease craving and drinking (McKee et al., 2009). However, two recent placebo controlled studies had opposite findings about the effects of varenicline on drinking in individuals with AUD (Litten et al., 2013; Plebani et al., 2013); thus, the efficacy of varenicline as a pharmacotherapeutic agent for decreasing drinking is still unclear. However, given the likely beneficial effects of nicotine agonists on cognitive function, markers of working memory integrity and other cognitive control systems may be useful as moderators in future clinical trials of varenicline in AUD.

Stimulants (modafinil, atamoxetine, methylphenidate, amphetamine), especially in those with ADHD, tend to enhance function on tests of cognitive control (presumed to be through their effects on DA and NA function in projections to the PFC) (Riccio, 2001; Brady et al.,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

2011) and in particular response inhibition, as measured by performance on the CPT (Riccio, 2001) and SST (Bari et al., 2009; Schmaal et al., 2013). In one study of AUD discussed above, modafinil improved response inhibition in AUD patients with baseline poor performance, but worsened response inhibition in those with better initial performance. Improvement in performance was mediated by activation in the thalamus and SMA, and better performance was associated with decreased connectivity between the thalamus and the motor cortex (Schmaal et al., 2013). In fact, in a randomized placebo controlled trial of modafinil for AUD, modafinil improved response inhibition overall but only improved drinking outcomes in individuals with slower baseline SSRT, whereas it worsened drinking in those with faster SSRT (Joos et al., 2013a). Baseline response inhibition may be a key moderator of response to treatment for AUD with stimulants.

In a similar manner, pure dopaminergic agonists may have opposite effects on cognitive control and alcohol use, depending on the individual. As discussed previously, there is growing evidence that the relationship between DA or NA and working memory/cognitive control is somewhat complex in that some individuals get worse and others get better with agonists at these receptors. There may be an 'inverted U' relationship between DA or NA function and cognitive performance (Arnsten, 2009; Cools and D'Esposito, 2011). Regarding DA, DA receptor agonists (bromocriptine and pergolide) given to healthy volunteers appear to improve performance on working memory tasks (Gibbs and D 'Esposito, 2005; Cools and D 'Esposito, 2011) but improvement is based on baseline performance (e.g., those with initial good performance do not improve as much, or may even get worse). To our knowledge, only one large randomized trial of a DA agonist (long-acting bromocriptine) in AUD has been done, and showed no effect on drinking outcomes, but baseline working memory performance was not investigated as a moderator of response (Narano et al., 1997). However, future investigations into such medications by focusing on individuals with baseline poor cognitive control could prove to be worthwhile.

Atypical antipsychotics (which transiently block D2 receptors) have looked promising in the past, as evidenced by combined work showing that quetiapine improves response inhibition in AUD patients (Moallem and Ray, 2012), and appears to decrease drinking in type B alcoholics (Kampman et al., 2007) in a larger, multisite study. However, typology did not predict response to quetiapine in a second study attempting to replicate the findings from Kampmen et al. (Litten et al., 2013), and therefore studies within this drug class may not be highest on the priority list in future mediational studies focused on cognitive control.

Relationship between alcohol cues and cognitive control

Although this article is not focusing on cue reactivity *per se*, there is growing evidence that cognitive control and cue processing may be associated with one another. On the one hand, alcohol context and cues may worsen response inhibition in AUD. One study using a GNG task using both neutral and alcohol cues showed that AUD have impaired GNG performance, with greater numbers of errors of commission and omission overall, and slower reaction time compared with controls during presentation of alcohol cues in particular (Noel et al., 2007). Another study designed for use with ERP monitoring noted that heavy social drinkers make more commission errors on the GNG than light drinkers do,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

but only in an alcohol context (Petit et al., 2012). These studies imply that alcohol contexts may cause further deterioration in response inhibition in AUD, putting them at heightened risk of acting on a habitual response, and relapsing.

On the other hand, impairments in response inhibition and prefrontal cortical function may predispose an individual to higher levels of cue reactivity. For example, impaired response inhibition (BIS total and motor score, and SSRT) was found to be related to cue-induced alcohol craving in AUD (Papachristou et al., 2013).

Psychological strategies to improve the prepotent response inhibition in the setting of alcohol cues may be particularly important to help individuals with AUD abstain from drinking. In fact, one study has found that training designed to do so (Houben et al., 2011) decreases craving and subsequent drinking behavior in heavy drinking students. It is difficult to know if this training decreased craving through an improvement in general inhibitory control, or just through a change in response to alcohol cues. Still, it remains possible that training individuals to divert attention away from alcohol cues (attentional bias modification training) (Schoenmakers et al., 2010) may not only help decrease cue reactivity but may also enhance general cognitive control, by minimizing the deteriorating effect of alcohol cues on cognitive control.

Discussion

AUD is defined by, among other qualities, a ‘loss of control’ of alcohol use, and this may be, in part, caused by deficits in cognitive control. Individuals with AUD appear to have deficits in inhibitory functions as measured through performance on tasks of response inhibition and distractor interference control, whereas the evidence for deficits in working memory is less consistent. Although anatomical changes (and, in particular, volume loss in a variety of brain areas) are well established, more work is needed to define the particular functional neuroimaging markers associated with these deficits in AUD. As we have seen in our review, studies using metrics of functional connectivity and neurophysiological studies (such as ERP) may prove especially reliable to define the deficits in cognitive control network function in AUD, and to aid in predicting outcome; however, again, more work is needed in this area. Task-evoked activation during tasks of cognitive control may prove useful in the future; however, most likely related to the heterogeneity in task design or population characteristics from study to study, findings have not thus far established a particular activation pattern that distinguishes AUD patients from controls or that predicts outcome. The exception is that in most cases, AUD patients demonstrate hypoactivation during tasks of response inhibition compared with controls.

In particular, it would be useful for future work defining deficits in AUD to use larger sample sizes, account for clinical differences within AUD groups (such as typology, co-occurring psychiatric disorder, and stage of abstinence) (Camchong et al., 2013), and to compare groups using more than one domain of cognitive control at a time (e.g., a GNG, a task of distractor interference control, and a working memory task) perhaps, also, with varying cognitive loads. As we move forward, it will be very important to identify the most sensitive and reliable markers for deficits in cognitive control in AUD, including metrics of

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

task performance and those derived from functional neuroimaging, as well as the deficits that are most important clinically (e.g., may directly contribute to difficulty maintaining abstinence).

There are few longitudinal studies that have identified predictors of outcome for AUD using metrics of cognitive control, although scores on the BIS and performance on tasks of response inhibition certainly appear to hold promise. There are also few studies that have directly investigated whether baseline levels of cognitive control moderate drinking outcomes during particular treatments for AUD. Therefore, it will be important to identify moderators of particular treatments such that treatment can be targeted to individuals most likely to respond. As discussed, cognitive profiles may differ by AUD typology, and AUD heterogeneity may have particular relevance in predicting treatment outcomes (Chick et al., 2004; Roache et al., 2008; Bogenschutz et al., 2009). Ignoring this heterogeneity, and in particular in the cognitive control domains, may be causing us to miss medications with clinical utility, for example, as seen in studies of modafinil, which only was associated with improved response inhibition (Schmaal et al., 2013) and drinking outcomes (Joos et al., 2013a) in AUD with initial poor response inhibition.

Furthermore, it will also be of utmost importance to identify and develop treatments whose effects are mediated by improvement in cognitive control. By doing so, this will inform investigations of newer medications and help us identify the most clinically important metrics of cognitive control. Although little work in this area has been done, there are some promising candidates for future study. For example, abstinence is associated with improvement in cognitive control and predicts decreases in future drinking. Moreover, both topiramate and mindfulness training may increase cognitive control and improve drinking outcomes. Finally, a variety of medications and therapeutic interventions (such as TMS and tDCS) are being explored for their effects on cognitive function; these deserve more attention in treatment studies of AUD, and potentially in related meditational analyses.

Another factor deserves mention for future work. Higher sensitivity to alcohol cues and affect dysregulation may both increase relapse risk (Berking et al., 2011) and be linked closely with deficits in cognitive control. As discussed previously, alcohol cues may acutely impair inhibitory control (Petit et al., 2012), and increases in cognitive control may be associated with decreased cue reactivity (Papachristou et al., 2013). Similarly, affect dysregulation may acutely impair cognitive control (Euser and Franken, 2012), and neurocognitive impairment and prefrontal dysfunction may be associated with impaired emotional processing and problems with affect regulation (Johnson-Greene et al., 2002; Salloum et al., 2007). By testing cognitive control globally (independent of context), we may be missing important information. Medications and cognitive-behavioral techniques aimed at reducing craving and attentional bias (Schoenmakers et al., 2010) or improving affect regulation (Stasiewicz et al., 2013) could work in part by indirectly improving cognitive control at critical decision-making times. This could be emphasized more (and explored) in future work as well.

In summary, cognitive control is altered in AUD, and it may influence clinical outcomes, especially deficits in inhibitory functions. Future work could aim to identify the most

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

reliable and valid markers for the deficits, the deficits that most predict problematic drinking, and the degree to which deficits or changes in cognitive control moderate or mediate response to particular treatments.

Acknowledgments

The writing of this article was supported by the National Institute on Alcohol Abuse and Alcoholism-funded grant K23 AA021156-01A1, awarded to Dr. Claire Wilcox, who is being mentored by, among others, Drs. Michael Bogenschutz and Andrew Mayer, both co-authors on this work.

References

Adams KM, Gilman S, Koeppe RA, Kluin KJ, Brunberg JA, Dede D, Berent S, Kroll PD. Neuropsychological deficits are correlated with frontal hypometabolism in positron emission tomography studies of older alcoholic patients. Alcohol Clin Exp Res. 1993; 17:205–210. [PubMed: 8488956]

Aichert DS, Wostmann NM, Costa A, Macare C, Wenig JR, Moller HJ, Rubia K, Ettinger U. Associations between trait impulsivity and prepotent response inhibition. J Clin Exp Neuropsychol. 2012; 34:1016–1032. [PubMed: 22888795]

Ambrose ML, Bowden SC, Whelan G. Working memory impairments in alcohol-dependent participants without clinical amnesia. Alcohol Clin Exp Res. 2001; 25:185–191. [PubMed: 11236831]

Arnsten AF. Stress signalling pathways that impair prefrontal cortex structure and function. Nat Rev Neurosci. 2009; 10:410–422. [PubMed: 19455173]

Aron A, Fletcher P, Bullmore E, Sahakian B, Robbins T. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nat Neurosci. 2003; 6:115–116. [PubMed: 12536210]

Aron A, Robbins T, Poldrack R. Inhibition and the right inferior frontal cortex. Trends Cogn Sci. 2004; 8:170–177. [PubMed: 15050513]

Asahi S, Okamoto Y, Okada G, Yamawaki S, Yokota N. Negative correlation between right prefrontal activity during response inhibition and impulsiveness: a fMRI study. Eur Arch Psychiatry Clin Neurosci. 2004; 254:245–251. [PubMed: 15309395]

Badre D. Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. Trends Cogn Sci. 2008; 12:193–200. [PubMed: 18403252]

Baler R, Volkow N. Drug addiction: the neurobiology of disrupted self-control. Trends Mol Med. 2006; 12:559–566. [PubMed: 17070107]

Bari A, Eagle DM, Mar AC, Robinson ES, Robbins TW. Dissociable effects of noradrenaline, dopamine, and serotonin uptake blockade on stop task performance in rats. Psychopharmacology (Berl). 2009; 205:273–283. [PubMed: 19404616]

Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986; 51:1173–1182. [PubMed: 3806354]

Bates ME, Bowden SC, Barry D. Neurocognitive impairment associated with alcohol use disorders: implications for treatment. Exp Clin Psychopharmacol. 2002; 10:193–212. [PubMed: 12233981]

Bates ME, Barry D, Labouvie EW, Fals-Stewart W, Voelbel G, Buckman JF. Risk factors and neuropsychological recovery in clients with alcohol use disorders who were exposed to different treatments. J Consult Clin Psychol. 2004; 72:1073–1080. [PubMed: 15612853]

Bazov I, Kononenko O, Watanabe H, Kuntic V, Sarkisyan D, Taqi MM, Hussain MZ, Nyberg F, Yakovleva T, Bakalkin G. The endogenous opioid system in human alcoholics: molecular adaptations in brain areas involved in cognitive control of addiction. Addict Biol. 2013; 18:161–169. [PubMed: 21955155]

Bell EC, Willson MC, Wilman AH, Dave S, Silverstone PH. Males and females differ in brain activation during cognitive tasks. Neuroimage. 2006; 30:529–538. [PubMed: 16260156]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Belleville S, Rouleau N, Caza N. Effect of normal aging on the manipulation of information in working memory. Mem Cognit. 1998; 26:572–583.

Berking M, Margraf M, Ebert D, Wupperman P, Hofmann SG, Junghanns K. Deficits in emotion-regulation skills predict alcohol use during and after cognitive-behavioral therapy for alcohol dependence. J Consult Clin Psychol. 2011; 79:307–318. [PubMed: 21534653]

Bilder RM, Volavka J, Lachman HM, Grace AA. The catechol-*O*-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacology. 2004; 29:1943–1961. [PubMed: 15305167]

Bjork JM, Hommer DW, Grant SJ, Danube C. Impulsivity in abstinent alcohol-dependent patients: relation to control subjects and type 1-/type 2-like traits. Alcohol. 2004; 34:133–150. [PubMed: 15902907]

Black DS, Semple RJ, Pokhrel P, Grenard JL. Component processes of executive function – mindfulness, self-control, and working memory – and their relationships with mental and behavioral health. Mindfulness (N Y). 2011; 2:179–185. [PubMed: 22013495]

Blume A, Schmaling K, Marlatt G. Memory, executive cognitive function, and readiness to change drinking behavior. Addict Behav. 2005; 30:301–314. [PubMed: 15621401]

Bogenschutz MP, Scott Tonigan J, Pettinati HM. Effects of alcoholism typology on response to naltrexone in the COMBINE study. Alcohol Clin Exp Res. 2009; 33:10–18. [PubMed: 18828797]

Bonelli RM, Cummings JL. Frontal-subcortical circuitry and behavior. Dialogues Clin Neurosci. 2007; 9:141–151. [PubMed: 17726913]

Bowen S, Chawla N, Collins SE, Witkiewitz K, Hsu S, Grow J, Clifasefi S, Garner M, Douglass A, Larimer ME, et al. Mindfulness-based relapse prevention for substance use disorders: a pilot efficacy trial. Subst Abus. 2009; 30:295–305. [PubMed: 19904665]

Brady KT, Gray KM, Tolliver BK. Cognitive enhancers in the treatment of substance use disorders: clinical evidence. Pharmacol Biochem Behav. 2011; 99:285–294. [PubMed: 21557964]

Braver TS, Barch DM. A theory of cognitive control, aging cognition, and neuromodulation. Neurosci Biobehav Rev. 2002; 26:809–817. [PubMed: 12470692]

Braver T, Barch D, Gray J, Molfese D, Snyder A. Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. Cerebral Cortex. 2001; 11:825–836. [PubMed: 11532888]

Brokate B, Hildebrandt H, Eling P, Fichtner H, Runge K, Timm C. Frontal lobe dysfunctions in Korsakoff's syndrome and chronic alcoholism: continuity or discontinuity? Neuropsychology. 2003; 17:420–428. [PubMed: 12959508]

Broos N, Schmaal L, Wiskerke J, Kostelijk L, Lam T, Stoop N, Weierink L, Ham J, de Geus EJ, Schoffelmeer AN, et al. The relationship between impulsive choice and impulsive action: a cross-species translational study. PLoS One. 2012; 7:e36781. [PubMed: 22574225]

Brown SA, Tapert SF, Granholm E, Delis DC. Neurocognitive functioning of adolescents: effects of protracted alcohol use. Alcohol Clin Exp Res. 2000; 24:164–171. [PubMed: 10698367]

Burgess PW, Shallice T. Response suppression, initiation and strategy use following frontal lobe lesions. Neuropsychologia. 1996; 34:263–272. [PubMed: 8657357]

Camchong J, Stenger A, Fein G. Resting-state synchrony in long-term abstinent alcoholics. Alcohol Clin Exp Res. 2013; 37:75–85. [PubMed: 22725701]

Ceballos NA, Tivis R, Lawton-Craddock A, Nixon SJ. Visual-spatial attention in alcoholics and illicit stimulant abusers: effects of nicotine replacement. Prog Neuropsychopharmacol Biol Psychiatry. 2005; 29:97–107. [PubMed: 15610951]

Chambers CD, Bellgrove MA, Stokes MG, Henderson TR, Garavan H, Robertson IH, Morris AP, Mattingley JB. Executive "brake failure" following deactivation of human frontal lobe. J Cogn Neurosci. 2006; 18:444–455. [PubMed: 16513008]

Chanraud S, Martelli C, Delain F, Kostogianni N, Douaud G, Aubin HJ, Reynaud M, Martinot JL. Brain morphometry and cognitive performance in detoxified alcohol-dependents with preserved psychosocial functioning. Neuropsychopharmacology. 2007; 32:429–438. [PubMed: 17047671]

Chanraud S, Reynaud M, Wessa M, Penttila J, Kostogianni N, Cachia A, Artiges E, Delain F, Perrin M, Aubin HJ, et al. Diffusion tensor tractography in mesencephalic bundles: relation to mental

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

flexibility in detoxified alcohol-dependent subjects. Neuropsychopharmacology. 2009; 34:1223–1232. [PubMed: 18615012]

Chanraud S, Pitel AL, Pfefferbaum A, Sullivan EV. Disruption of functional connectivity of the default-mode network in alcoholism. Cereb Cortex. 2011; 21:2272–2281. [PubMed: 21368086]

Charney DA, Zikos E, Gill KJ. Early recovery from alcohol dependence: factors that promote or impede abstinence. J Subst Abuse Treat. 2010; 38:42–50. [PubMed: 19632079]

Chen AC, Porjesz B, Rangaswamy M, Kamarajan C, Tang Y, Jones KA, Chorlian DB, Stimus AT, Begleiter H. Reduced frontal lobe activity in subjects with high impulsivity and alcoholism. Alcohol Clin Exp Res. 2007; 31:156–165. [PubMed: 17207114]

Chevrier AD, Noseworthy MD, Schachar R. Dissociation of response inhibition and performance monitoring in the stop signal task using event-related fMRI. Hum Brain Mapp. 2007; 28:1347–1358. [PubMed: 17274022]

Chick J, Aschauer H, Hornik K. Efficacy of fluvoxamine in preventing relapse in alcohol dependence: a one-year, double-blind, placebo-controlled multicentre study with analysis by typology. Drug Alcohol Depend. 2004; 74:61–70. [PubMed: 15072808]

Chiu PH, Holmes AJ, Pizzagalli DA. Dissociable recruitment of rostral anterior cingulate and inferior frontal cortex in emotional response inhibition. Neuroimage. 2008; 42:988–997. [PubMed: 18556218]

Clark CP, Brown GG, Eyler LT, Drummond SP, Braun DR, Tapert SF. Decreased perfusion in young alcohol-dependent women as compared with age-matched controls. Am J Drug Alcohol Abuse. 2007; 33:13–19. [PubMed: 17366242]

Claus ED, Ewing SW, Filbey FM, Sabbineni A, Hutchison KE. Identifying neurobiological phenotypes associated with alcohol use disorder severity. Neuropsychopharmacology. 2011a; 36:2086–2096. [PubMed: 21677649]

Claus ED, Kiehl KA, Hutchison KE. Neural and behavioral mechanisms of impulsive choice in alcohol use disorder. Alcohol Clin Exp Res. 2011b; 35:1209–1219. [PubMed: 21676001]

Claus ED, Feldstein Ewing SW, Filbey FM, Hutchison KE. Behavioral control in alcohol use disorders: relationships with severity. J Stud Alcohol Drugs. 2013; 74:141–151. [PubMed: 23200160]

Cohen HL, Porjesz B, Begleiter H, Wang W. Neurophysiological correlates of response production and inhibition in alcoholics. Alcohol Clin Exp Res. 1997; 21:1398–1406. [PubMed: 9394110]

Congdon E, Canli T. The endophenotype of impulsivity: reaching consilience through behavioral, genetic, and neuroimaging approaches. Behav Cogn Neurosci Rev. 2005; 4:262–281. [PubMed: 16585800]

Conners, CK. Conners' Continuous Performance Test II: Computer Program for Windows Technical Guide and Software Manual. North Tonawanda, NY: Multi-Health Systems; 2000.

Cools R, Robbins TW. Chemistry of the adaptive mind. Philos Trans A Math Phys Eng Sci. 2004; 362:2871–2888. [PubMed: 15539374]

Cools R, D'Esposito M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry. 2011; 69:e113–e125. [PubMed: 21531388]

Courtney KE, Ghahremani DG, Ray LA. Frontostriatal functional connectivity during response inhibition in alcohol dependence. Addict Biol. 2013; 18:593–604. [PubMed: 23240858]

Crean J, Richards JB, de Wit H. Effect of tryptophan depletion on impulsive behavior in men with or without a family history of alcoholism. Behav Brain Res. 2002; 136:349–357. [PubMed: 12429396]

Crews F, Boettiger C. Impulsivity, frontal lobes and risk for addiction. Pharmacol Biochem Behav. 2009; 93:237–247. [PubMed: 19410598]

Crews FT, Nixon K. Mechanisms of neurodegeneration and regeneration in alcoholism. Alcohol Alcohol. 2009; 44:115–127. [PubMed: 18940959]

Crowe DA, Goodwin SJ, Blackman RK, Sakellaridi S, Sponheim SR, Macdonald AW 3rd, Chafee MV. Prefrontal neurons transmit signals to parietal neurons that reflect executive control of cognition. Nat Neurosci. 2013; 16:1484–1491. [PubMed: 23995071]

D'Esposito M, Deouell LY, Gazzaley A. Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. Nat Rev Neurosci. 2003; 4:863–872. [PubMed: 14595398]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. Neuron. 2011; 69:680–694. [PubMed: 21338879]

Dao-Castellana MH, Samson Y, Legault F, Martinot JL, Aubin HJ, Crouzel C, Feldman L, Barrucand D, Rancurel G, Feline A, et al. Frontal dysfunction in neurologically normal chronic alcoholic subjects: metabolic and neuropsychological findings. Psychol Med. 1998; 28:1039–1048. [PubMed: 9794011]

De Rosa E, Desmond JE, Anderson AK, Pfefferbaum A, Sullivan EV. The human basal forebrain integrates the old and the new. Neuron. 2004; 41:825–837. [PubMed: 15003180]

de Wit H. Impulsivity as a determinant and consequence of drug use: a review of underlying processes. Addict Biol. 2009; 14:22–31. [PubMed: 18855805]

Del-Ben CM, Deakin JF, McKie S, Delvai NA, Williams SR, Elliott R, Dolan M, Anderson IM. The effect of citalopram pretreatment on neuronal responses to neuropsychological tasks in normal volunteers: an FMRI study. Neuropsychopharmacology. 2005; 30:1724–1734. [PubMed: 15827569]

Desmond JE, Chen SH, DeRosa E, Pryor MR, Pfefferbaum A, Sullivan EV. Increased frontocerebellar activation in alcoholics during verbal working memory: an fMRI study. Neuroimage. 2003; 19:1510–1520. [PubMed: 12948707]

Dick DM, Smith G, Olausson P, Mitchell SH, Leeman RF, O'Malley SS, Sher K. Understanding the construct of impulsivity and its relationship to alcohol use disorders. Addict Biol. 2009; 15:217–226. [PubMed: 20148781]

Ding J, Eigenbrodt ML, Mosley TH Jr, Hutchinson RG, Folsom AR, Harris TB, Nieto FJ. Alcohol intake and cerebral abnormalities on magnetic resonance imaging in a community-based population of middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. Stroke. 2004; 35:16–21. [PubMed: 14657449]

Dom G, De Wilde B, Hulstijn W, van den Brink W, Sabbe B. Behavioural aspects of impulsivity in alcoholics with and without a cluster-B personality disorder. Alcohol Alcohol. 2006; 41:412–420. [PubMed: 16782972]

Dosenbach NU, Fair DA, Cohen AL, Schlaggar BL, Petersen SE. A dual-networks architecture of top-down control. Trends Cogn Sci. 2008; 12:99–105. [PubMed: 18262825]

Dougherty DM, Mathias CW, Tester ML, Marsh DM. Age at first drink relates to behavioral measures of impulsivity: the immediate and delayed memory tasks. Alcohol Clin Exp Res. 2004; 28:408–414. [PubMed: 15084898]

Duka T, Gentry J, Malcolm R, Ripley TL, Borlikova G, Stephens DN, Veatch LM, Becker HC, Crews FT. Consequences of multiple withdrawals from alcohol. Alcohol Clin Exp Res. 2004; 28:233–246. [PubMed: 15112931]

Eagle DM, Bari A, Robbins TW. The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks. Psychopharmacology. 2008; 199:439–456. [PubMed: 18542931]

Eberl C, Wiers RW, Pawelczack S, Rinck M, Becker ES, Lindenmeyer J. Approach bias modification in alcohol dependence: do clinical effects replicate and for whom does it work best? Dev Cogn Neurosci. 2013; 4:38–51. [PubMed: 23218805]

Elliott R, Agnew Z, Deakin JF. Hedonic and informational functions of the human orbitofrontal cortex. Cereb Cortex. 2010; 20:198–204. [PubMed: 19435707]

Euser AS, Franken IH. Alcohol affects the emotional modulation of cognitive control: an event-related brain potential study. Psychopharmacology (Berl). 2012; 222:459–476. [PubMed: 22371302]

Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci. 2005; 8:1481–1489. [PubMed: 16251991]

Evren C, Durkaya M, Evren B, Dalbudak E, Cetin R. Relationship of relapse with impulsivity, novelty seeking and craving in male alcohol-dependent inpatients. Drug Alcohol Rev. 2012; 31:81–90. [PubMed: 21450046]

Fallgatter AJ, Wiesbeck GA, Weijers HG, Boening J, Strik WK. Event-related correlates of response suppression as indicators of novelty seeking in alcoholics. Alcohol Alcohol. 1998; 33:475–481. [PubMed: 9811199]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Feil J, Sheppard D, Fitzgerald PB, Yucel M, Lubman DI, Bradshaw JL. Addiction, compulsive drug seeking, and the role of frontostriatal mechanisms in regulating inhibitory control. Neurosci Biobehav Rev. 2010; 35:248–275. [PubMed: 20223263]

Fein G, Torres J, Price LJ, Di Sclafani V. Cognitive performance in long-term abstinent alcoholic individuals. Alcohol Clin Exp Res. 2006; 30:1538–1544. [PubMed: 16930216]

Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007; 8:700–711. [PubMed: 17704812]

Friedman NP, Miyake A. The relations among inhibition and interference control functions: a latent-variable analysis. J Exp Psychol Gen. 2004; 133:101–135. [PubMed: 14979754]

Galanter, M.; Kleber, HD., editors. Textbook of Substance Abuse Treatment. Washington, DC: American Psychiatric Publishing Inc; 2008.

Ganis G, Kutas M, Sereno MI. The search for “common sense” : an electrophysiological study of the comprehension of words and pictures in reading. J Cogn Neurosci. 1996; 8:89–106. [PubMed: 23971417]

Garavan H, Ross TJ, Murphy K, Roche RAP, Stein EA. Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. Neuroimage. 2002; 17:1820–1829. [PubMed: 12498755]

Gibbs SE, D’Esposito M. A functional MRI study of the effects of bromocriptine, a dopamine receptor agonist, on component processes of working memory. Psychopharmacology (Berl). 2005; 180:644–653. [PubMed: 16001111]

Glenn SW, Parsons OA, Sinha R, Stevens L. The effects of repeated withdrawals from alcohol on the memory of male and female alcoholics. Alcohol Alcohol. 1988; 23:337–342. [PubMed: 3228455]

Golden CJ. Identification of brain disorders by the Stroop Color and Word Test. J Clin Psychol. 1976; 32:654–658. [PubMed: 956433]

Goto Y, Grace AA. Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. Nat Neurosci. 2005; 8:805–812. [PubMed: 15908948]

Goudriaan AE, Oosterlaan J, de Beurs E, van den Brink W. Neurocognitive functions in pathological gambling: a comparison with alcohol dependence, Tourette syndrome and normal controls. Addiction. 2006; 101:534–547. [PubMed: 16548933]

Gruber SA, Rogowska J, Holcomb P, Soraci S, Yurgelun-Todd D. Stroop performance in normal control subjects: an fMRI study. Neuroimage. 2002; 16:349–360. [PubMed: 12030821]

Harper C. The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? J Neuropathol Exp Neurol. 1998; 57:101–110. [PubMed: 9600202]

Harper C, Matsumoto I. Ethanol and brain damage. Curr Opin Pharmacol. 2005; 5:73–78. [PubMed: 15661629]

Heffernan TM. The impact of excessive alcohol use on prospective memory: a brief review. Curr Drug Abuse Rev. 2008; 1:36–41. [PubMed: 19630703]

Heinz A, Siessmeier T, Wrase J, Hermann D, Klein S, Grusser SM, Flor H, Braus DF, Buchholz HG, Grunder G, et al. Correlation between dopamine D(2) receptors in the ventral striatum and central processing of alcohol cues and craving. Am J Psychiatry. 2004; 161:1783–1789. [PubMed: 15465974]

Heinz A, Siessmeier T, Wrase J, Buchholz HG, Grunder G, Kumakura Y, Cumming P, Schreckenberger M, Smolka MN, Rosch F, et al. Correlation of alcohol craving with striatal dopamine synthesis capacity and D2/3 receptor availability: a combined [18F]DOPA and [18F]DMFP PET study in detoxified alcoholic patients. Am J Psychiatry. 2005; 162:1515–1520. [PubMed: 16055774]

Hester R, Dixon V, Garavan H. A consistent attentional bias for drug-related material in active cocaine users across word and picture versions of the emotional Stroop task. Drug Alcohol Depend. 2006; 81:251–257. [PubMed: 16095852]

Hildebrandt H, Brokate B, Eling P, Lanz M. Response shifting and inhibition, but not working memory, are impaired after long-term heavy alcohol consumption. Neuropsychology. 2004; 18:203–211. [PubMed: 15099142]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Houben K, Nederkoorn C, Wiers RW, Jansen A. Resisting temptation: decreasing alcohol-related affect and drinking behavior by training response inhibition. Drug Alcohol Depend. 2011; 116:132–136. [PubMed: 21288663]

Jacobson L, Javitt DC, Lavidor M. Activation of inhibition: diminishing impulsive behavior by direct current stimulation over the inferior frontal gyrus. J Cogn Neurosci. 2011; 23:3380–3387. [PubMed: 21452949]

Jha AP, Stanley EA, Kiyonaga A, Wong L, Gelfand L. Examining the protective effects of mindfulness training on working memory capacity and affective experience. Emotion. 2010; 10:54–64. [PubMed: 20141302]

Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K, McKay A, Ait-Daoud N, Anton RF, Ciraulo DA, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. J Am Med Assoc. 2007; 298:1641–1651.

Johnson-Greene D, Adams KM, Gilman S, Junck L. Relationship between neuropsychological and emotional functioning in severe chronic alcoholism. Clin Neuropsychol. 2002; 16:300–309. [PubMed: 12607143]

Joos L, Goudriaan AE, Schmaal L, Fransen E, van den Brink W, Sabbe BG, Dom G. Effect of modafinil on impulsivity and relapse in alcohol dependent patients: a randomized, placebo-controlled trial. Eur Neuropsychopharmacol. 2013a; 23:948–955. [PubMed: 23141152]

Joos L, Schmaal L, Goudriaan AE, Fransen E, Van den Brink W, Sabbe BG, Dom G. Age of onset and neuropsychological functioning in alcohol dependent inpatients. Alcohol Clin Exp Res. 2013b; 37:407–416. [PubMed: 23025636]

Kamarajan C, Porjesz B, Jones KA, Choi K, Chorlian DB, Padmanabhapillai A, Rangaswamy M, Stimus AT, Begleiter H. Alcoholism is a disinhibitory disorder: neurophysiological evidence from a Go/No-Go task. Biol Psychol. 2005; 69:353–373. [PubMed: 15925035]

Kampman KM, Pettinati HM, Lynch KG, Whittingham T, Macfadden W, Dackis C, Tirado C, Oslin DW, Sparkman T, O'Brien CP. A double-blind, placebo-controlled pilot trial of quetiapine for the treatment of Type A and Type B alcoholism. J Clin Psychopharmacol. 2007; 27:344–351. [PubMed: 17632217]

Kane MJ, Engle RW. Working-memory capacity, proactive interference, and divided attention: limits on long-term memory retrieval. J Exp Psychol Learn Mem Cogn3. 2000; 26:336–358.

Karch S, Jager L, Karamatskos E, Graz C, Stammel A, Flatz W, Lutz J, Holtschmidt-Taschner B, Genius J, Leicht G, et al. Influence of trait anxiety on inhibitory control in alcohol-dependent patients: simultaneous acquisition of ERPs and BOLD responses. J Psychiatr Res. 2008; 42:734–745. [PubMed: 17826793]

Keilp JG, Sackeim HA, Mann JJ. Correlates of trait impulsiveness in performance measures and neuropsychological tests. Psychiatry Res. 2005; 135:191–201. [PubMed: 15996748]

Kirby KN, Petry NM. Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. Addiction. 2004; 99:461–471. [PubMed: 15049746]

Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2009; 35:217–238. [PubMed: 19710631]

Kopera M, Wojnar M, Brower K, Glass J, Nowosad I, Gmaj B, Szelenberger W. Cognitive functions in abstinent alcohol-dependent patients. Alcohol. 2012; 46:665–671. [PubMed: 22703992]

Kopp B, Mattler U, Goertz R, Rist F. N2, P3 and the lateralized readiness potential in a nogo task involving selective response priming. Electroencephalogr Clin Neurophysiol. 1996; 99:19–27. [PubMed: 8758967]

Kreek M, Nielsen D, Butelman E, LaForge K. Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. Nat Neurosci. 2005; 8:1450. [PubMed: 16251987]

Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci. 2005; 6:691–702. [PubMed: 16136173]

Li CS, Luo X, Yan P, Bergquist K, Sinha R. Altered impulse control in alcohol dependence: neural measures of stop signal performance. Alcohol Clin Exp Res. 2009; 33:740–750. [PubMed: 19170662]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Litten RZ, Ryan ML, Fertig JB, Falk DE, Johnson B, Dunn KE, Green AI, Pettinati HM, Ciraulo DA, Sarid-Segal O, et al. A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. J Addict Med. 2013; 7:277–286. [PubMed: 23728065]

Logue SF, Gould TJ. The neural and genetic basis of executive function: attention, cognitive flexibility, and response inhibition. Pharmacol Biochem Behav. 2013 Epub ahead of print.

Mackiewicz Seghete KL, Cservenka A, Herting MM, Nagel BJ. Atypical spatial working memory and task-general brain activity in adolescents with a family history of alcoholism. Alcohol Clin Exp Res. 2013; 37:390–398. [PubMed: 23078615]

Maisto SA, Clifford PR, Stout RL, Davis CM. Factors mediating the association between drinking in the first year after alcohol treatment and drinking at three years. J Stud Alcohol Drugs. 2008; 69:728–737. [PubMed: 18781248]

Marsh R, Zhu H, Schultz RT, Quackenbush G, Royal J, Skudlarski P, Peterson BS. A developmental fMRI study of self-regulatory control. Hum Brain Mapp. 2006; 27:848–863. [PubMed: 16421886]

Maurage P, Callot C, Chang B, Philippot P, Rombaux P, de Timary P. Olfactory impairment is correlated with confabulation in alcoholism: towards a multimodal testing of orbitofrontal cortex. PLoS One. 2011; 6:e23190. [PubMed: 21858026]

Maurage P, Joassin F, Speth A, Modave J, Philippot P, Campanella S. Cerebral effects of binge drinking: respective influences of global alcohol intake and consumption pattern. Clin Neurophysiol. 2012; 123:892–901. [PubMed: 22055841]

Mayer AR, Teshiba TM, Franco AR, Ling J, Shane M, Stephen JM, Jung RE. Modelling conflict and error in the medial frontal cortex. Hum Brain Mapp. 2011; 33:2843–2855. [PubMed: 21976411]

Mayer AR, Wilcox CE, Teshiba TM, Ling JM, Yang Z. Hyperactivation of the cognitive control network in cocaine use disorders during a multisensory Stroop task. Drug Alcohol Depend. 2013; 133:235–241. [PubMed: 23735613]

McKee SA, Harrison EL, O'Malley SS, Krishnan-Sarin S, Shi J, Tetrault JM, Picciotto MR, Petrakis IL, Estevez N, Balchunas E. Varenicline reduces alcohol self-administration in heavy-drinking smokers. Biol Psychiatry. 2009; 66:185–190. [PubMed: 19249750]

Mitchell JM, Fields HL, D'Esposito M, Boettiger CA. Impulsive responding in alcoholics. Alcohol Clin Exp Res. 2005; 29:2158–2169. [PubMed: 16385186]

Moallem N, Ray LA. Quetiapine improves response inhibition in alcohol dependent patients: a placebo-controlled pilot study. Pharmacol Biochem Behav. 2012; 100:490–493. [PubMed: 22037407]

Mocking RJ, Patrick Pflanz C, Pringle A, Parsons E, McTavish SF, Cowen PJ, Harmer CJ. Effects of short-term varenicline administration on emotional and cognitive processing in healthy, non-smoking adults: a randomized, double-blind study. Neuropsychopharmacology. 2013; 38:476–484. [PubMed: 23072834]

Montgomery C, Fisk JE, Murphy PN, Ryland I, Hilton J. The effects of heavy social drinking on executive function: a systematic review and meta-analytic study of existing literature and new empirical findings. Hum Psychopharmacol. 2012; 27:187–199. [PubMed: 22389083]

Moselhy H, Georgiou G, Kahn A. Frontal lobe changes in alcoholism: a review of the literature. Alcohol Alcohol. 2001; 36:357–368. [PubMed: 11524299]

Nakamura-Palacios EM, de Almeida Benevides MC, da Penha Zago-Gomes M, de Oliveira RW, de Vasconcellos VF, de Castro LN, da Silva MC, Ramos PA, Fregni F. Auditory event-related potentials (P3) and cognitive changes induced by frontal direct current stimulation in alcoholics according to Lesch alcoholism typology. Int J Neuropsychopharmacol. 2012; 15:601–616. [PubMed: 21781352]

Nakata H, Sakamoto K, Ferretti A, Gianni Perrucci M, Del Gratta C, Kakigi R, Luca Romani G. Somato-motor inhibitory processing in humans: an event-related functional MRI study. Neuroimage. 2008; 39:1858–1866. [PubMed: 18083602]

Naranjo CA, Dongier M, Bremner KE. Long-acting injectable bromocriptine does not reduce relapse in alcoholics. Addiction. 1997; 92:969–978. [PubMed: 9376779]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Nardone R, Bergmann J, Christova M, Lochner P, Tezzon F, Golaszewski S, Trinka E, Brigo F. Non-invasive brain stimulation in the functional evaluation of alcohol effects and in the treatment of alcohol craving: a review. Neurosci Res. 2012; 74:169–176. [PubMed: 22951276]

Nicolas JM, Catafau AM, Estruch R, Lomena FJ, Salamero M, Herranz R, Monforte R, Cardenal C, Urbano-Marquez A. Regional cerebral blood flow-SPECT in chronic alcoholism: relation to neuropsychological testing. J Nucl Med. 1993; 34:1452–1459. [PubMed: 8355063]

Niendam TA, Laird AR, Ray KL, Dean YM, Glahn DC, Carter CS. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. Cogn Affect Behav Neurosci. 2012; 12:241–268. [PubMed: 22282036]

Nigg JT. On inhibition/disinhibition in developmental psychopathology: views from cognitive and personality psychology and a working inhibition taxonomy. Psychol Bull. 2000; 126:220–246. [PubMed: 10748641]

Nigg J, Wong M, Martel M, Jester J, Puttler L, Glass J, Adams K, Fitzgerald H, Zucker R. Poor response inhibition as a predictor of problem drinking and illicit drug use in adolescents at risk for alcoholism and other substance use disorders. J Am Acad Child Adolesc Psychiatry. 2006; 45:468–475. [PubMed: 16601652]

Nixon SJ, Tivis R, Ceballos N, Varner JL, Rohrbaugh J. Neurophysiological efficiency in male and female alcoholics. Prog Neuropsychopharmacol Biol Psychiatry. 2002; 26:919–927. [PubMed: 12369267]

Noel X, Van der Linden M, Schmidt N, Sferrazza R, Hanak C, Le Bon O, De Mol J, Kornreich C, Pelc I, Verbanck P. Supervisory attentional system in nonamnesic alcoholic men. Arch Gen Psychiatry. 2001; 58:1152–1158. [PubMed: 11735844]

Noel X, Van der Linden M, d'Acremont M, Bechara A, Dan B, Hanak C, Verbanck P. Alcohol cues increase cognitive impulsivity in individuals with alcoholism. Psychopharmacology (Berl). 2007; 192:291–298. [PubMed: 17279375]

Noel X, Van der Linden M, Brevers D, Campanella S, Hanak C, Kornreich C, Verbanck P. The contribution of executive functions deficits to impaired episodic memory in individuals with alcoholism. Psychiatry Res. 2012; 198:116–122. [PubMed: 22377577]

Noel X, Van der Linden M, Brevers D, Campanella S, Verbanck P, Hanak C, Kornreich C, Verbruggen F. Separating intentional inhibition of prepotent responses and resistance to proactive interference in alcohol-dependent individuals. Drug Alcohol Depend. 2013; 128:200–205. [PubMed: 22980674]

O'Daly OG, Trick L, Scaife J, Marshall J, Ball D, Phillips ML, Williams SS, Stephens DN, Duka T. Withdrawal-associated increases and decreases in functional neural connectivity associated with altered emotional regulation in alcoholism. Neuropsychopharmacology. 2012; 37:2267–2276. [PubMed: 22617355]

Padilla ML, Colrain IM, Sullivan EV, Mayer BZ, Turlington SR, Hoffman LR, Wagstaff AE, Pfefferbaum A. Electrophysiological evidence of enhanced performance monitoring in recently abstinent alcoholic men. Psychopharmacology (Berl). 2011; 213:81–91. [PubMed: 20941595]

Papachristou H, Nederkoorn C, Havermans R, Bongers P, Beunen S, Jansen A. Higher levels of trait impulsiveness and a less effective response inhibition are linked to more intense cue-elicited craving for alcohol in alcohol-dependent patients. Psychopharmacology (Berl). 2013; 228:641–649. [PubMed: 23508556]

Park MS, Sohn S, Park JE, Kim SH, Yu IK, Sohn JH. Brain functions associated with verbal working memory tasks among young males with alcohol use disorders. Scand J Psychol. 2011; 52:1–7. [PubMed: 21054421]

Parks MH, Dawant BM, Riddle WR, Hartmann SL, Dietrich MS, Nickel MK, Price RR, Martin PR. Longitudinal brain metabolic characterization of chronic alcoholics with proton magnetic resonance spectroscopy. Alcohol Clin Exp Res. 2002; 26:1368–1380. [PubMed: 12351932]

Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol. 1995; 51:768–774. [PubMed: 8778124]

Paulus M, Tapert S, Pulido C, Schuckit M. Alcohol attenuates load-related activation during a working memory task: relation to level of response to alcohol. Alcohol Clin Exp Res. 2006; 30:1363–1371. [PubMed: 16899039]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Penick EC, Nickel EJ, Powell BJ, Liskow BI, Campbell J, Dale TM, Hassanein RE, Noble E. The comparative validity of eleven alcoholism typologies. J Stud Alcohol. 1999; 60:188–202. [PubMed: 10091957]

Petit G, Kornreich C, Noel X, Verbanck P, Campanella S. Alcohol-related context modulates performance of social drinkers in a visual Go/No-Go task: a preliminary assessment of event-related potentials. PLoS One. 2012; 7:e37466. [PubMed: 22616012]

Pfefferbaum A, Sullivan EV, Mathalon DH, Shear PK, Rosenbloom MJ, Lim KO. Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. Alcohol Clin Exp Res. 1995; 19:1177–1191. [PubMed: 8561288]

Pfefferbaum A, Sullivan EV, Rosenbloom MJ, Mathalon DH, Lim KO. A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. Arch Gen Psychiatry. 1998; 55:905–912. [PubMed: 9783561]

Pfefferbaum A, Desmond J, Galloway C, Menon V, Glover G, Sullivan E. Reorganization of frontal systems used by alcoholics for spatial working memory: an fMRI study. Neuroimage. 2001; 14:7–20. [PubMed: 11525339]

Pfefferbaum A, Rosenbloom MJ, Fama R, Sassoon SA, Sullivan EV. Transcallosal white matter degradation detected with quantitative fiber tracking in alcoholic men and women: selective relations to dissociable functions. Alcohol Clin Exp Res. 2010; 34:1201–1211. [PubMed: 20477772]

Pitel AL, Beaunieux H, Witkowski T, Vabret F, Guillery-Girard B, Quinette P, Desgranges B, Eustache F. Genuine episodic memory deficits and executive dysfunctions in alcoholic subjects early in abstinence. Alcohol Clin Exp Res. 2007; 31:1169–1178. [PubMed: 17511749]

Pitel AL, Rivier J, Beaunieux H, Vabret F, Desgranges B, Eustache F. Changes in the episodic memory and executive functions of abstinent and relapsed alcoholics over a 6-month period. Alcohol Clin Exp Res. 2009; 33:490–498. [PubMed: 19120052]

Plebani JG, Lynch KG, Rennert L, Pettinati HM, O'Brien CP, Kampman KM. Results from a pilot clinical trial of varenicline for the treatment of alcohol dependence. Drug Alcohol Depend. 2013; 133:754–758. [PubMed: 23916324]

Pogge DL, Stokes J, Harvey PD. Psychometric vs. attentional correlates of early onset alcohol and substance abuse. J Abnorm Child Psychol. 1992; 20:151–162. [PubMed: 1593024]

Porjesz B, Begleiter H, Reich T, Van Eerdewegh P, Edenberg HJ, Foroud T, Goate A, Litke A, Chorlian DB, Stimus A, et al. Amplitude of visual P3 event-related potential as a phenotypic marker for a predisposition to alcoholism: preliminary results from the COGA Project. Collaborative Study on the Genetics of Alcoholism. Alcohol Clin Exp Res. 1998; 22:1317–1323. [PubMed: 9756048]

Quinette P, Guillery B, Desgranges B, de la Sayette V, Viader F, Eustache F. Working memory and executive functions in transient global amnesia. Brain. 2003; 126:1917–1934. [PubMed: 12876141]

Ratti MT, Bo P, Giardini A, Soragna D. Chronic alcoholism and the frontal lobe: which executive functions are impaired? Acta Neurol Scand. 2002; 105:276–281. [PubMed: 11939939]

Riccio C. Effects of stimulants on the continuous performance test (CPT): implications for CPT use and interpretation. J Neuropsychiatry Clin Neurosci. 2001; 13:326–335. [PubMed: 11514638]

Ridderinkhof K, van den Wildenberg W, Segalowitz S, Carter C. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. Brain Cognit. 2004a; 56:129–140. [PubMed: 15518930]

Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The role of the medial frontal cortex in cognitive control. Science. 2004b; 306:443–447. [PubMed: 15486290]

Roache JD, Wang Y, Ait-Daoud N, Johnson BA. Prediction of serotonergic treatment efficacy using age of onset and Type A/B typologies of alcoholism. Alcohol Clin Exp Res. 2008; 32:1502–1512. [PubMed: 18565156]

Roberts KL, Hall DA. Examining a supramodal network for conflict processing: a systematic review and novel functional magnetic resonance imaging data for related visual and auditory Stroop tasks. J Cogn Neurosci. 2008; 20:1063–1078. [PubMed: 18211237]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Robinson T, Berridge K. Addiction. Ann Rev Psychol. 2003; 54:23–53.

Rogers RD, Moeller FG, Swann AC, Clark L. Recent research on impulsivity in individuals with drug use and mental health disorders: implications for alcoholism. Alcohol Clin Exp Res. 2010; 34:1319–1333. [PubMed: 20528825]

Rogers BP, Parks MH, Nickel MK, Katwal SB, Martin PR. Reduced fronto-cerebellar functional connectivity in chronic alcoholic patients. Alcohol Clin Exp Res. 2012; 36:294–301. [PubMed: 22085135]

Rubia K, Russell T, Overmeyer S, Brammer MJ, Bullmore ET, Sharma T, Simmons A, Williams SC, Giampietro V, Andrew CM, et al. Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. Neuroimage. 2001; 13:250–261. [PubMed: 11162266]

Rubia K, Smith AB, Brammer MJ, Taylor E. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. Neuroimage. 2003; 20:351–358. [PubMed: 14527595]

Rubio G, Jimenez M, Rodriguez-Jimenez R, Martinez I, Avila C, Ferre F, Jimenez-Arriero MA, Ponce G, Palomo T. The role of behavioral impulsivity in the development of alcohol dependence: a 4-year follow-up study. Alcohol Clin Exp Res. 2008; 32:1681–1687. [PubMed: 18631324]

Rubio G, Martinez-Gras I, Manzanares J. Modulation of impulsivity by topiramate: implications for the treatment of alcohol dependence. J Clin Psychopharmacol. 2009; 29:584–589. [PubMed: 19910725]

Rupp CI, Fleischhacker WW, Drexler A, Hausmann A, Hinterhuber H, Kurz M. Executive function and memory in relation to olfactory deficits in alcohol-dependent patients. Alcohol Clin Exp Res. 2006; 30:1355–1362. [PubMed: 16899038]

Salloum JB, Ramchandani VA, Bodurka J, Rawlings R, Momenan R, George D, Hommer DW. Blunted rostral anterior cingulate response during a simplified decoding task of negative emotional facial expressions in alcoholic patients. Alcohol Clin Exp Res. 2007; 31:1490–1504. [PubMed: 17624997]

Sanchez-Moreno J, Martinez-Aran A, Colom F, Scott J, Tabares-Seisdedos R, Sugranyes G, Torrent C, Daban C, Benabarre A, Goikolea JM, et al. Neurocognitive dysfunctions in euthymic bipolar patients with and without prior history of alcohol use. J Clin Psychiatry. 2009; 70:1120–1127. [PubMed: 19758523]

Saunders B, Farag N, Vincent AS, Collins FL Jr, Sorocco KH, Lovallo WR. Impulsive errors on a Go-NoGo reaction time task: disinhibitory traits in relation to a family history of alcoholism. Alcohol Clin Exp Res. 2008; 32:888–894. [PubMed: 18373725]

Schachar R, Logan GD, Robaey P, Chen S, Ickowicz A, Barr C. Restraint and cancellation: multiple inhibition deficits in attention deficit hyperactivity disorder. J Abnorm Child Psychol. 2007; 35:229–238. [PubMed: 17351752]

Scheurich A. Neuropsychological functioning and alcohol dependence. Curr Opin Psychiatry. 2005; 18:319–323. [PubMed: 16639156]

Schmaal L, Joos L, Koeleman M, Veltman DJ, van den Brink W, Goudriaan AE. Effects of modafinil on neural correlates of response inhibition in alcohol-dependent patients. Biol Psychiatry. 2013; 73:211–218. [PubMed: 22858150]

Schmahmann JD. The role of the cerebellum in cognition and emotion: personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy. Neuropsychol Rev. 2010; 20:236–260. [PubMed: 20821056]

Schoenbaum G, Roesch MR, Stalnaker TA, Takahashi YK. A new perspective on the role of the orbitofrontal cortex in adaptive behaviour. Nat Rev Neurosci. 2009; 10:885–892. [PubMed: 19904278]

Schoenmakers TM, de Bruin M, Lux IF, Goertz AG, Van Kerkhof DH, Wiers RW. Clinical effectiveness of attentional bias modification training in abstinent alcoholic patients. Drug Alcohol Depend. 2010; 109:30–36. [PubMed: 20064698]

Schuckit MA, Tapert S, Matthews SC, Paulus MP, Tolentino NJ, Smith TL, Trim RS, Hall S, Simmons A. fMRI differences between subjects with low and high responses to alcohol during a stop signal task. Alcohol Clin Exp Res. 2012; 36:130–140. [PubMed: 22003983]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Schulte T, Muller-Oehring EM, Pfefferbaum A, Sullivan EV. Neurocircuitry of emotion and cognition in alcoholism: contributions from white matter fiber tractography. Dialogues Clin Neurosci. 2010; 12:554–560. [PubMed: 21319499]

Schulte T, Oberlin BG, Kareken DA, Marinkovic K, Muller-Oehring EM, Meyerhoff DJ, Tapert S. How acute and chronic alcohol consumption affects brain networks: insights from multimodal neuroimaging. Alcohol Clin Exp Res. 2012; 36:2017–2027. [PubMed: 22577873]

Seamans JK, Yang CR. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog Neurobiol. 2004; 74:1–58. [PubMed: 15381316]

Silveri MM, Rogowska J, McCaffrey A, Yurgelun-Todd DA. Adolescents at risk for alcohol abuse demonstrate altered frontal lobe activation during Stroop performance. Alcohol Clin Exp Res. 2011; 35:218–228. [PubMed: 21073483]

Simmonds DJ, Pekar JJ, Mostofsky SH. Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. Neuropsychologia. 2008; 46:224–232. [PubMed: 17850833]

Smith EE, Jonides J. Storage and executive processes in the frontal lobes. Science. 1999; 283:1657–1661. [PubMed: 10073923]

Soloff PH, Lynch KG, Moss HB. Serotonin, impulsivity, and alcohol use disorders in the older adolescent: a psychobiological study. Alcohol Clin Exp Res. 2000; 24:1609–1619. [PubMed: 11104107]

Spinella M. Neurobehavioral correlates of impulsivity: evidence of prefrontal involvement. Int J Neurosci. 2004; 114:95–104. [PubMed: 14660071]

Stasiewicz PR, Bradizza CM, Schlauch RC, Coffey SF, Gulliver SB, Gudleski GD, Bole CW. Affect regulation training (ART) for alcohol use disorders: Development of a novel intervention for negative affect drinkers. J Subst Abuse Treat. 2013; 45:433–443. [PubMed: 23876455]

Stroop J. Studies of interference in serial verbal reactions. J Exp Psychol. 1935; 18:643–662.

Sullivan EV. Compromised pontocerebellar and cerebellothalamocortical systems: speculations on their contributions to cognitive and motor impairment in nonamnesic alcoholism. Alcohol Clin Exp Res. 2003; 27:1409–1419. [PubMed: 14506401]

Sullivan E, Pfefferbaum A. Neurocircuitry in alcoholism: a substrate of disruption and repair. Psychopharmacology. 2005; 180:583–594. [PubMed: 15834536]

Sullivan EV, Rosenbloom MJ, Lim KO, Pfefferbaum A. Longitudinal changes in cognition, gait, and balance in abstinent and relapsed alcoholic men: relationships to changes in brain structure. Neuropsychology. 2000a; 14:178–188. [PubMed: 10791858]

Sullivan EV, Rosenbloom MJ, Pfefferbaum A. Pattern of motor and cognitive deficits in detoxified alcoholic men. Alcohol Clin Exp Res. 2000b; 24:611–621. [PubMed: 10832902]

Sullivan EV, Fama R, Rosenbloom MJ, Pfefferbaum A. A profile of neuropsychological deficits in alcoholic women. Neuropsychology. 2002; 16:74–83. [PubMed: 11853359]

Tang YY, Ma Y, Wang J, Fan Y, Feng S, Lu Q, Yu Q, Sui D, Rothbart MK, Fan M, et al. Short-term meditation training improves attention and self-regulation. Proc Natl Acad Sci USA. 2007; 104:17152–17156. [PubMed: 17940025]

Tang YY, Ma Y, Fan Y, Feng H, Wang J, Feng S, Lu Q, Hu B, Lin Y, Li J, et al. Central and autonomic nervous system interaction is altered by short-term meditation. Proc Natl Acad Sci USA. 2009; 106:8865–8870. [PubMed: 19451642]

Tapert SF, Brown G, Kindermann S, Cheung E, Frank L, Brown S. fMRI measurement of brain dysfunction in alcohol-dependent young women. Alcohol Clin Exp Res. 2001; 25:236–245. [PubMed: 11236838]

Tapert SF, Brown GG, Baratta MV, Brown SA. fMRI BOLD response to alcohol stimuli in alcohol dependent young women. Addict Behav. 2004a; 29:33–50. [PubMed: 14667419]

Tapert SF, Schweinsburg AD, Barlett VC, Brown SA, Frank LR, Brown GG, Meloy MJ. Blood oxygen level dependent response and spatial working memory in adolescents with alcohol use disorders. Alcohol Clin Exp Res. 2004b; 28:1577–1586. [PubMed: 15597092]

Tedstone D, Coyle K. Cognitive impairments in sober alcoholics: performance on selective and divided attention tasks. Drug Alcohol Depend. 2004; 75:277–286. [PubMed: 15283949]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Thoma P, Winter N, Juckel G, Roser P. Mental state decoding and mental state reasoning in recently detoxified alcohol-dependent individuals. Psychiatry Res. 2013; 205:232–240. [PubMed: 22995039]

Treisman A, Fearnley S. The Stroop test: selective attention to colours and words. Nature. 1969; 222:437–439. [PubMed: 5768618]

Trim RS, Simmons AN, Tolentino NJ, Hall SA, Matthews SC, Robinson SK, Smith TL, Padula CB, Paulus MP, Tapert SF, et al. Acute ethanol effects on brain activation in low- and high-level responders to alcohol. Alcohol Clin Exp Res. 2010; 34:1162–1170. [PubMed: 20477775]

Uekermann J, Daum I. Social cognition in alcoholism: a link to prefrontal cortex dysfunction? Addiction. 2008; 103:726–735. [PubMed: 18412750]

Volkow ND, Wang GJ, Tomasi D, Baler RD. Unbalanced neuronal circuits in addiction. Curr Opin Neurobiol. 2013; 23:639–648. [PubMed: 23434063]

Weafer J, Milich R, Fillmore M. Behavioral components of impulsivity predict alcohol consumption in adults with ADHD and healthy controls. Drug Alcohol Depend. 2011; 113:139–146. [PubMed: 20863628]

Wechsler, D. Wechsler Adult Intelligence Scale-Revised. San Antonio: The Psychological Corporation; 1981.

Whiteside SP, Lynam DR. Understanding the role of impulsivity and externalizing psychopathology in alcohol abuse: application of the UPPS impulsive behavior scale. Exp Clin Psychopharmacol. 2003; 11:210–217. [PubMed: 12940500]

Wollenweber FA, Halfter S, Brugmann E, Weinberg C, Cieslik EC, Muller VI, Hardwick RM, Eickhoff SB. Subtle cognitive deficits in severe alcohol addicts – do they show a specific profile? J Neuropsychol. 2012 Epub ahead of print.

Yarkoni T, Barch DM, Gray JR, Conturo TE, Braver TS. BOLD correlates of trial-by-trial reaction time variability in gray and white matter: a multi-study fMRI analysis. PLoS One. 2009; 4:e4257. [PubMed: 19165335]

Zeidan F, Johnson SK, Diamond BJ, David Z, Goolkasian P. Mindfulness meditation improves cognition: evidence of brief mental training. Conscious Cogn. 2010; 19:597–605. [PubMed: 20363650]