The Effects of Stress and Placebo Alcohol on Cognitive Activation and Inhibitory Control in Male Problem Gamblers and Problem Gamblers with Alcohol Use Disorder

by

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A thesis submitted in conformity with the requirements
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This experiment studied relapse by assessing the separate/combined effects of two instigators: alcohol cues and stress on the salience of alcohol/gambling target stimuli and inhibitory control in twelve male problem gamblers and twelve male comorbid drinker-gamblers.

Our study day consisted of two test sessions. Subjects received alcohol (non-alcoholic beer) and/or stress (uncontrollable noise) in a counterbalanced method. Hypotheses were tested using computer-based tasks, including the modified Stroop, gambling-word Shift Task, and the conventional and modified Stop-Signal Tasks.

Stimuli with incentive value divert attention (i.e., are salient) selectively based on their clinical relevance to the subject and the nature of the instigating factor – stress (expected negative reinforcement) vs. anticipation of alcohol (expected positive reinforcement).

Results suggest that alcohol cues and stress have differing effects on incentive salience, and disinhibit behaviour in both pathological populations. These findings have the potential to facilitate treatment and improve understanding for relapse prevention in these subjects.
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1. INTRODUCTION

1.1 Background and Rationale

a) Problem of Relapse

Relapse is a critical challenge in the treatment of addiction. Chronic use of alcohol, drugs, and (potentially) compulsive behaviours such as gambling can induce long-lasting changes in brain function that render individuals vulnerable to the effects of motivational instigating stimuli long after they have achieved abstinence. Exposure to the abused substance or situation and stress are two of the most important instigators of relapse. Animal research indicates that the effects of these stimuli are mediated by different neurochemical systems: one that regulates approach behaviour (i.e. seeking); and another that regulates avoidance. It is thought that the avoidance system exerts a tonic inhibitory effect on the approach system to ensure that the sought after reinforcement does not occur in the face of undue risk. The regulatory process described above seems to be defective in addicted individuals. As a result, exposure to stimuli can instigate seeking of addictive reinforcers despite their negative consequences. The present study investigated the effects of stress and placebo alcohol on cognitive activation and inhibition in four distinct populations: alcohol dependent individuals (AD), pathological gamblers (PG), comorbid subjects with both disorders (PGAD) and healthy controls. The findings reported and discussed here pertain to the PG and PGAD groups.

1.2 Review of the Literature

1.2.1 Cognitive Inhibition

A number of investigators have hypothesized a critical association between drug and alcohol addiction and deficits in impulse control (Ernst and Paulus, 2005; Everitt and
Robbins, 2005; Goldstein and Volkow, 2002, Volkow and Li, 2005). Psychological comparison of non-abusing and abusing individuals has revealed a pattern of “neurobehavioral disinhibition” (Tarter et al., 2003) consisting of increased sensation seeking, risk-taking, aggressiveness, and anti-social behavior.

The Dual-Process Theory has been used widely to explain behaviour. It is thought to be determined by the interplay of two qualitatively different systems: a fast, associative, implicit, impulsive system, which includes the automatic appraisal of stimuli in terms of their affective and motivational significance, and a slower rule-based, explicit, reflective system, including controlled processes related to conscious deliberations, emotion regulation and expected outcomes (Duetsch and Strack, 2006; Evans, 2003, Evans and Coventry, 2006; Strack and Deutsh, 2004; Wiers and Stacy, 2006; Wiers et al., 2007). The ability of controlled processes to moderate the impact of spontaneous impulsive processes is a central element of executive functioning, which can be defined as a set of cognitive control mechanisms that are relevant to goal-directed behavior. Individual differences in executive functioning determine whether automatic impulses to drink alcohol can be controlled or not. Individual differences in this ability may pose as a risk factor for developing an alcohol abuse problem. It has been suggested that the impulsive system can become sensitized with repeated alcohol use, which can increase the appetitive motivation to use alcohol (Wiers et al., 2007). A study conducted by Houban & Wiers examined whether individual differences in response inhibition moderate the influence of implicit alcohol associations on drinking behavior. Inhibition processes appear to be a family of functions, rather than a single unitary construct,
including pre-potent response inhibition, resistance to distracter interference, and resistance to proactive interference (Friedman and Miyake, 2004).

1.2.1.1 Action Inhibition, Action Restraint, & Action Cancellation

Inhibitory control is a component process subsumed under the broader construct of Impulsivity. Impulsivity can be a trait – a stable tendency to act without regard for the consequences or without planning (Moeller et al., 2001); it can also be a state – such as the purchase of a magazine at the checkout counter – an “impulse buy.” In general, trait impulsivity is a strong risk factor for addictive behaviour (Evenden, 1999; Goudriaan et al. 2006; Karch et al. 2008). In its extreme form, Impulsivity may even be considered the core pathology of a particular disorder or class of disorders. PG is an example of the latter, falling under the formal classification of Impulse Control Disorders in the Diagnostic and Statistical Manual of Mental Disorders IV-TR (APA, 2000). Thus, impulsivity is a central construct to consider when investigating PG-related symptoms and, in this particular study, relapse. In this clinical sense, impulsivity may manifest as a failure to delay gratification or decision to pursue short-term gratification despite long-term adversity.

Addictive drug seeking behavior may result from two distinct, but inter-related, phenomena that involve impulsivity. The disorder could be characterized by the enhancement of the potency of the impulse (increased salience of the rewarding and/or reinforcing qualities of the desired drug/stimulus). Alternatively, the ability to actively inhibit the impulse at the cognitive level may be diminished (Aron 2007; Chamberlain & Sahakian, 2007; Eagle et al., 2007).
Humans and animals, whether experienced drug users or not, are subject to behavioral control by internal or motivational states (“impulses”) that are either innate or conditioned (Eagle et al., 2008). There appears to be an active inhibitory control mechanism in the brain to modulate this type of pre-potent responding to allow the suppression of rapid, conditioned responses and reflexes so that slower cognitive mechanisms can guide behavior (Fillmore et al., 1999). This inhibitory control appears to be a function of the frontostriatal system. A dysfunction of this system can produce extreme impulsivity, as seen in a number of pathological states (Goldstein & Volkow, 2002). Damage to the frontal cortical regions has led to impairments in inhibitory control, specifically disinhibition (Aron et al., 2003; Bechara et al., 1994; Cools et al., 2004; Gansler et al., 2000; Goldstein & Volkow, 2002).

The generalized term “inhibition” has been widely used in neuroscience for over 100 years (Smith 1992 in Aron 2007), and can be viewed as a critical executive-control mechanism, regulating a wide range of cognitive and motor processes required to prevent execution of an action. Current literature proposes that there are three different forms of inhibition that reflect different neural processes in the brain (Miyake et al., 2000; Noel et al., 2005; Shuster, in press). Evidence that translates from rodent to human tasks shows that forms of inhibition are mediated via different anatomical and neurochemical substrates within the brain. This may have significant implications for the development of novel therapies for disorders in which action-inhibition deficits are pronounced (Chamberlain and Sahakaian 2007; Robinson et al. 2007; Winstanley et al. 2004a; Winstanley et al. 2006).
Firstly, action inhibition reflects a set of subtly different processes that are dissociable at the neural level; attending to, and interpreting, signals to inhibit; making decisions based on those signals and other internal and external cues; selecting an appropriate inhibitory action and successfully executing a motor action that counteracts the pre-planned motor response.

A second form of inhibition, called action restraint, involves pre-empting of the motor response before that response has been started (Schachar et al., 2007). It has been studied using the go/no-go task, which focuses on the ability or failure to withhold a key press response based on a learned correspondence between that response and a target stimulus. In this case, inhibitory control is operationally defined by the percentage of successfully withheld responses to No-Go stimuli vs. unsuccessfully withheld responses to No-Go stimuli, i.e., commission errors, which are sometimes referred to as “false alarms.”

A final form of inhibition is action cancellation, which entails overriding a motor response during its execution. This type of inhibition can be studied using the stop-signal task. This task involves countermanding an already initiated key press response to a visual stimulus when unexpectedly signaled to do so by a subsequent auditory stimulus (the stop signal). Stop signal reaction time (SSRT) is the key component (the estimate of the time taken for a subject to attend to, process and complete an inhibitory response to the stop signal) evaluated by this task.

The Go/No-Go and Stop Signal Tasks of behavioral inhibition are well-validated tools for translational research as the basic forms of these tasks are appropriate for testing
human, primate and rodent subjects without significant changes in experimental design (Eagle et al., 2008).

1.2.1.2 Animal and Human Studies of Inhibition

a) Animal Studies

Response inhibition is an active process for modulating stimulus-reward-response associations, allowing animals to shift between old and new contingencies and inhibit inappropriate ones (Chamberlain and Sahakian 2007). Action inhibition deficits have been documented as resulting from dysfunction of the frontostriatal system (Chamberlain and Sahakian 2007; Yajeya 1988; Mar 2007). Early primate studies showed that lesions of the dorsolateral prefrontal cortex, lateral orbitofrontal cortex or the ventromedial or limbic frontal cortex in monkeys resulted in increased perseveration and inhibitory deficits measured by the go/no-go paradigm and other tasks after frontal cortex lesions (Butter et al., 1973; Jodo et al., 1992; Iversen and Mishkin 1970; Menon et al., 2001). In go/no-go discrimination tasks, subjects learn to respond to one discriminative stimulus and withhold their response to another. Lesions of the inferior prefrontal convexity of the monkey produce impairments on an asymmetric version of the task in that subjects “go” on the “no-go” trials (Iversen and Mishkin 1970; Butters et al. 1973). This area is comparable to the inferior frontal gyrus in humans.

b) Human Studies

Many neuroimaging studies of response inhibition (Rubia et al., 1999, 2003; Menon et al., 2001) and neuroimaging studies of go/no-go switching or strategy (Cools et al., 2002) have reported activation within the right hemisphere of the inferior frontal gyrus (IFG). A combined EEG/functional MRI study investigating go vs. wait factors
and switch vs. non-switch factors suggested the right inferior frontal cortex (IFC) was related to switching to a suppression mode (Aron et al., 2004). A study conducted by Aron et al. 2004 which looked at patients with excisions of the frontal cortex using MRI-based methods, highlighted the involvement of the dorsolateral prefrontal cortex, inferior frontal cortex and the dorsal anterior cingulated cortex in behavioral inhibition tasks. They concluded that the IFC (more notably the right IFC) was critical to inhibition. Another study focused on the patients with lesion damage to the frontal cortex as they performed the stop-signal task. Lesion size and performance on the task was strongly correlated within the right IFC, with the patients having an increased SSRT (Aron et al, 2003; Rubia et al., 2003). Thus, frontal cortex and striatal dysfunction may both play a role in impulsivity resulting from a deficit in response inhibition. For these reasons, frontal cortical cognitive dysfunction may be extremely relevant to drug abuse (Jentsch & Taylor 1999).

1.2.2 Neurochemical Basis of Impulsivity

Just as there are multiple components to Impulsivity, and multiple sub-components to inhibition, so too are there multiple neurochemical systems that are engaged by these different processes. Three neurochemical systems in particular have been found to mediate performance on the tasks and animal paradigms described above, namely the monoamines, dopamine, norepinephrine and serotonin (5-hydroxytryptamine; 5-HT).

Dopamine (DA) is involved in the regulation of inhibitory control. The anterior cingulated gyrus and the lateral orbitofrontal cortex are two structures that are believed to influence inhibitory processes. These structures have consistently been documented as
having decreased activity in imaging studied of drug-addicted individuals (Volkow, Fowler et al. 2004). Since DA receptor availability is associated with activity levels in these regions, it is expected that poor inhibitory control is mediated in part by disturbances in DA transmission (Volkow, Fowler et al. 2004).

As well as a clear role for DA, impulsivity may also be linked with norepinephrine (NE) (Kuczenski & Segal 1997). NE has been implicated in the modulation of prefrontal cortical function and serotonin. Knowledge of catecholeminergic mediation of inhibition has come from studying the action of psychostimulants, which act in general as indirect catecholamine agonists. By blocking DA reuptake and promoting the release of DA from axon terminals, the subsequent increase in DA may underlie the therapeutic effects of these drugs (Eagle 2008).

Whereas work on catecholamine systems (DA, NE) has provided recent insights into the neurochemistry of inhibition, the early neurochemical research on impulsivity focused on serotonin (Soubrie, 1986 Bizot J et al, 1988). Correlational evidence by Bergh et al 2006 showed that there was a direct relationship in rats between aggression towards intruders and a form of behavioural disinhibition, mainly, impulsive choice (delayed gratification). This indirectly supports the lack of effect of serotonin in the control of stopping because there are links between serotonin and some forms of aggression. For example, 5-HT depletion using acute tryptophan depletion (ATD) may increase aggression in subjective assessment and in lab tests such as the Point Subtraction Aggression Paradigm (Moeller et al. 1996).

The role of 5-HT on cognitive processes is less well characterized (Cools et al., 2004). The orbitofrontal cortex (OFC) is involved in emotion-cognition interactions, and
5-HT drugs modulate response to feedback and decision making within this region (Clarke et al., 2005). 5-HT has been implicated in response inhibition; a function linked with the right inferior frontal gyrus (Aron et al., 2003). Literature, translating across rodent, primate and human studies, suggests serotonin may be responsible for only some of the behavioral subtypes of inhibition (Clark et al. 2005; Clarke et al, 2005; Dalley et al, 2002; Winstanley et al. 2004). Rubia et al, 2005 tested the hypothesis that 5-HT modulates neurocognitive brain activation during inhibitory control by examining the effect of ATD (which decreases 5-HT synthesis in the brain) on functional brain activation during a go/no-go task. ATD significantly reduced right orbitofrontal prefrontal activation during the task and increased activation in the superior and medial temporal cortices, although there was no significant alteration in inhibitory performance on the task. These findings provide neuro-functional evidence of serotonergic modulation of the right inferior prefrontal gyrus during inhibitory motor control.

Global 5-HT depletion has been found to disrupt the acquisition of action restraint in response to a no-go signal in rats and also to impair ability of previously trained rats to subsequently inhibit correctly to a no-go signal (Harrison et al., 1997). Serotonin also appears to be specific to the initiation and maintenance of inhibition as seen by the 5-HT depleted rats showing unimpaired acquisition of conditional visual discriminations where both correct choices involve active responses (Graham et al, 1994; Ward et al, 1999). Eagle et al. (2008) have shown that in a no-delay version of the stop signal task, rats with global serotonin depletion are unable to withhold inhibition in an extended limited hold challenge.
Human neuroimaging studies implicate the OFC in relation to the effects of 5-HT on action restraint inhibition. There is also evidence for a negative correlation between commission errors and 5-HT synthesis capacity in some cortical sites (Leyton et al., 2001). The precise mechanism by which serotonin exerts its influence over performance via the OFC is not clear. Recently, it has been proposed that a polymorphism in the promoter of the 5-HT2A receptor gene may underlie some forms of behavioral inhibition and there is evidence that this receptor plays a role in action restraint (Nomura and Nomura 2006). Subjects with the A-1438A allele of the 5-HT(2A) receptor gene make more commission errors in a go/no-go task (Nomura and Nomura 2006).

1.2.3 Pathological Gambling

1.2.3.1 Definition

The act of “gambling” involves placing something of value at risk with the hope of gaining something of greater value in return (Potenza, 2001).

Pathological gambling (PG) was first included in the third edition of the Diagnostic and Statistical Manual for Mental Disorders (American Psychiatric Association, 1980) as a disorder of impulse control. As an impulse control disorder, PG is currently classified in DSM-IV with kleptomania, pyromania, intermittent explosive disorder, and trichotillomania. Unlike other impulse control disorders, however, the criteria for PG were borrowed from substance dependence criteria. For this reason, many consider PG to be a ‘behavioral’ addiction (Grant and Kim, 2003). The essential feature of PG is a pattern of “maladaptive gambling behavior that disrupts personal, family, or vocational pursuits” (APA, 1994 p. 615). It is characterized by gambling behavior that significantly impairs occupational, interpersonal and financial functioning (National

Table 1 criterion for pathological gambling across versions of the DSM

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Item number in versions</th>
<th>DSM-III</th>
<th>DSM-III-R</th>
<th>DSM-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronically unable to resist gambling impulses</td>
<td></td>
<td></td>
<td>8*</td>
<td></td>
</tr>
<tr>
<td>Across for (admits to*) illegal acts to obtain gambling money</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fails to honor debts or other financial responsibilities</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family or spouse relationship difficulties related to gambling</td>
<td>3</td>
<td></td>
<td>8*</td>
<td></td>
</tr>
<tr>
<td>Borrows money from illegal sources to gamble</td>
<td>4</td>
<td></td>
<td>8*</td>
<td></td>
</tr>
<tr>
<td>Not able to account for money</td>
<td>5</td>
<td></td>
<td>8*</td>
<td></td>
</tr>
<tr>
<td>Absences from work because of gambling</td>
<td>6</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Relies on others to provide money for desperate financial situations</td>
<td></td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Preoccupied with gambling or with ways to obtain money to gamble</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gambles more money or wagers over a longer period of time than intended</td>
<td>2</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Needs to increase the amount of frequency of gambling to obtain</td>
<td>3</td>
<td></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Feels restless or irritable if not able to gamble</td>
<td>4</td>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Consistently losing money and going back again to try and win back losses</td>
<td>5</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Tries repeatedly to reduce or stop gambling</td>
<td>6</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Often gamble when expected to meet social or occupational obligations</td>
<td>7</td>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Sacrifices or jeopardizes important social or occupational or recreational activities to gamble</td>
<td>8</td>
<td></td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Continues gambling even though unable to pay debts, regardless of social, occupational, or legal problems that the person knows to be exacerbated by gambling</td>
<td>9</td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Gambles to escape from problems or to relieve negative moods</td>
<td></td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lies to family members, therapist, or others to conceal the extent of involvement with gambling</td>
<td>7</td>
<td></td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

1.2.3.2 Prevalence

Research suggests that the prevalence of pathological gambling has increased along with the growing availability of gambling opportunities. The percentage of adults who ever gambled increased from 35% in 1975 to 80% in a 1998 national survey. Rush, Veldhuizen, and Adlaf (2007) found that the proximity to gambling venues predicts the risk for PG. Gambling involvement and gambling pathology are not uniform across
demographic groups. The 1998 National Opinion Research Center study showed more pathological and problem gambling among men (2.5%) than women (1.7%). Pathological gambling is diagnosed in individuals if they score $\geq 5$ on the South Oaks Gambling Screen (SOGS) (i.e., a tool used to measure the severity of gambling) whereas problem gambling is a less severe form of the disorder with scores on the SOGS ranging between 3 and 4. Rates of PG were found to decline with age, from 3.1% among respondents ages 18-29 to 0.3% for those 65 or older. Rates were also found to be lower among those with higher incomes and more education. It is estimated that 10% of adult gamblers meet criteria for the diagnosis of problem gambling (Shaffer et al., 1999) and as many as 70-90% of North Americans have engaged in some form of gambling activity (Raylu and Oei, 2002). However, only approximately 1-2% of the general population meets criteria for pathological gambling (PG) (Petry, 2005). The discrepancy between these numbers suggest that most people who gamble do not develop PG, leading researchers to search for risk factors related to this disorder (Raylu and Oei, 2002).

1.2.3.3 Pathological Gambling and Impulse Control

The pathophysiology of PG is still unclear; however, it is thought that progression of the disorder might include environmental factors coupled with a genetic vulnerability and the dysfunction of different brain areas and their neurotransmitters (Marazziti et al., 2008). Indeed, disorders of substance abuse (SA) provide a model for looking at the impulsive and self-destructive behaviours seen in PG. Recent neurobehavioural research has shown that a connection between pathological gambling and impulsivity exists (Petry, 2001). Published studies indicate that impulsivity, disinhibition, sensation seeking, risk taking, and novelty seeking are associated with PG. In fact, impulsivity is
related to the actual severity of gambling behaviour and predicts the development of PG
(Slutske et al., 2005 & Vitaro et al., 1997). The connection with impulsivity is most
likely related to functional brain changes as well as neuropsychological and personality
anomalies. Different hypotheses have been drawn: a genetic vulnerability involving
dopamine receptors, biochemical dysfunctions at the level of serotonin and dopamine
systems or alterations of different brain areas.

1.2.3.4 Neurobiology of Pathological Gambling

Up to one half of PG subjects report that direct presentation of gambling stimuli is
a trigger to gamble (Grant and Kim 2001), with men reporting a greater likelihood to
gamble than women. As identifying cues/triggers for gambling are reported as essential
in the idea of relapse prevention, understanding neurobiological correlates would be a
priority (Crockford et al., 2005). However, many of the clinical trials in PG subjects are
hard to interpret due to very large placebo effects.

1.2.3.4.1 Neurochemical aspects of impulsivity in PG

Two neurotransmitter systems are thought to play a role in the neurocognitive
mechanisms that underlie behavioural initiation, disinhibition and reward and
reinforcement in PGs: the dopaminergic and serotonergic system. Studies investigating
these neurotransmitters are limited. Work examining these systems has looked at them as
discrete circuits however, it is likely that these circuits are inter-related and communicate
through feedback mechanisms. Dopamine and NE may be involved in go-related
(approach) processes; whereas serotonin may be involved in inhibition (avoidance)
processes.
a) Dopamine

The brain dopaminergic system, particularly the dopamine D2 receptor, plays a role in the behavioural reward system in both humans and animals. Recent reports have linked DA receptor agonist toxicity with de novo PG in Parkinson’s disease (Black and Friedman 2006). Ibanez et al. 2002 showed that the D2 receptor gene DRD2 could be a genetic liability factor for psychiatric co-morbidity in PG. Pharmacological approaches have also demonstrated that low D2 receptor availability induced by a drug enhances the reinforcing effects of slot machine gambling in PGs (Zack and Poulos 2007). These findings suggest that other DA substrates modulated by D2 could be important for gambling reinforcement (Zack and Poulos 2004).

fMRI studies to date suggest that gambling may activate the brain’s dopaminergic reward system. Gambling and responses to monetary consequences in healthy volunteers has been reported to activate the OFC, striatum, and limbic areas believed to be part of the extended dopamine reward pathway (Goldstein and Volkow 2002; Kalivas, 2001). The frontal lobes (prefrontal cortices) are involved in mediating reward expectancy from the direct presentation of rewards or conditioned cues (Hikosaka and Watanabe 2000). fMRI studies of PGs to date (Potenza et al 2003, Reuter et al 2005) have identified relative decreases in OFC and ventromedial prefrontal cortex (VMPFC) activity. Patients with ventromedial prefrontal cortex abnormalities show impairment in decision making. This has been assessed by the Iowa Gambling Task which explores the subject’s ability to balance immediate rewards against long-term consequences (Bechara et al., 1994; Bechara et al., 2002). PG patients, as well as people suffering from obsessive compulsive disorder (OCD), cocaine, opiate, or alcohol abuse, present similar problems when
presented with this task. The subjects continue to make choices based on immediate reward rather than long term consequences (Goudriaan et al., 2006). This abnormality can be linked to a dysfunctional ventromedial prefrontal cortex.

b) Norepinephrine

Interestingly, in another study, Volkow et al (2003) found that methyphenidate-induced increased in blood pressure were highly correlated with plasma NE and with increases in striatal DA. The drug’s effects were partly mediated by peripheral epinephrine. Other studies have shown an elevation in gambling induced blood pressure under haloperidol may reflect elevations in striatal DA with corresponding effects on epinephrine (Zack and Poulos 2007).

c) Serotonin

Serotonin function is acknowledged as an important mediator of behavioural inhibition and response control. Open label and double-blind studies have shown selective serotonin reuptake inhibitors (SSRIs) to be effective in the treatment of PG. Pettinati et al. (2000) in a prospective, open-label trial, demonstrated that Nefazadone, a novel SSRI which is a specific 5-HT 2 antagonist was effective in reducing gambling urges and gambling behaviour. This is interesting, since there is evidence that 5-HT2 receptors may play a role in disorders of impulse control as well.

Moreno et al. 1991 found some evidence of a hypoactive serotonin system in gamblers. Two other studies (Blanco et al., 1996; Carrasco., 1994) reported decreased platelet monoamine oxidase activity, and another found low CSF levels of a serotonin metabolite (Nordin et al., 1999). While these data suggest the possibility of a serotonin
deficiency, and possibly a post-synaptic hypersensitivity of serotonin receptors, other studies have found no serotonin abnormalities in gamblers (Potenza, 2008).

1.2.3.5 Pathological Gambling and Inhibitory Control

There is a broad spectrum of neuropsychological deficits in PG – in some cases, even more extreme than those seen in subjects who have chronically used a known neurotoxin, methamphetamine (Kalechstein et al. 2007).

The go/no-go task (Goudriaan et al., 2005; Fuentes et al., 2006) has been used for the assessment of “response inhibition” ability in PG. PG subjects’ performance on the task was impaired relative to healthy control subjects (Goudriaan et al., 2005; Fuentes et al., 2006). In the go/no-go task, the relatively decreased frequency of the go/no-go events enhances expectation that the next stimulus will be a go stimulus. Therefore, this design provides a useful test for evaluating inhibitory control and action monitoring (Menon et al., 2001) in which an inaccurate response to the no-go event is assumed to reflect impaired inhibition (Berwid, 2005). More specifically, errors of commission would be interpreted as failures of inhibitory control.

A study conducted by Kertzman et al. (2008) proceeded to show that PG patients were significantly slower than controls and showed more commission errors in the go/no-go condition. The number of commission errors is a direct measure of the ability to delay automatic responses. Therefore, PG subjects appear to have difficulty suppressing an automatic response when a conflicting response is required (Spreen and Strauss, 1998). This is consistent with the “response conflict monitoring” hypothesis (Botvinick et al. 2001; Carter et al. 1998). In PG, dysfunction of cognitive regulatory processes may impair ability to inhibit self-defeating urges or desires. With frustration, the inhibitory
system in PG is overwhelmed by intense motivational drives, resulting in disinhibition of behaviour that is run by stimulus-driven tendencies. This leads to impulsivity a consequence also seen in compulsive drug-taking.

In PG Ss, inhibitory control as measured by the stop-signal task is strongly linked with the clinical process under investigation in this study, namely relapse. Based on race model principles, the ability to inhibit an action in this paradigm depends on the outcome of competing activating and inhibiting processes (Fillmore and Rush 2002). Neurocognitive markers of decision-making and disinhibition, such as the card playing task and stop signal reaction time respectively seem to play a role in predicting relapse in PG (Goudriaan et al., 2007). The inability to inhibit irrelevant information might explain the decision-making impairment shown in PG. An fMRI study of PG subjects (Potenza 2003) employed the Stroop test. The study concluded that there was a decrease in ventromedial prefrontal cortex activity in these subjects. In another study by Kertzman et al., 2006, performance on the reverse Stroop task, which demonstrates the ability to inhibit interferences, was significantly impaired in PG patients vs. controls. As deficits in the regions aligned with the OFC have been reported to be associated with decreased response inhibition and a tendency to seek immediate gratification (Bechara et al. 1997, 1998) the studies suggest that PG subjects may be more prone to PG behaviour via differential response compared with control subjects to emotional/motivational cues and decreased response inhibition (Crockford et al., 2005).
1.2.4 Alcohol Dependence

1.2.4.1 Prevalence

Alcohol dependence and abuse cause substantial morbidity and mortality. Alcohol related mortality contributes to 2-4% of all deaths in adults, with the highest rate in the first decade after treatment (Shuckit, 2009). The disorder is common in all developed countries, and is more prevalent in men than in women (Shuckit MA, 2006; Teeson et al., 2006; Saxena, 1997). Currently, as many as 80% of men and 60% of women, in developed countries, drink at some point during their lives. About 30-50% of people who drank in the previous year will experience at least one adverse alcohol-related problem during their lifetime. The lifetime risk for an alcohol-use disorder (AD) for men is more than 20%, with a risk of about 15% for alcohol abuse and 10% for alcohol dependence. The risk of developing AD in the previous year is about 10% overall (Schuckit, 2009). The criteria for diagnosis of AD according to the Diagnostic and Statistical Manual (DSM-IV) has been characterized by a preoccupation with obtaining and drinking alcohol despite devastating physical, social and occupational consequences. Table 1 lists the criteria for alcohol dependence. About 40-60% of the risk of AD is explained by genes and the rest through gene x environment interactions (Schuckit et al., 2006). The environment can influence the availability of alcohol, attitudes towards drinking, peer pressure, stress levels and related coping strategies, and laws and regulatory framework. Gene forms associated with impulsivity, disinhibition and sensation seeking contribute to vulnerability to both drug abuse and AD. Perhaps through an impaired learning of mistakes and bad judgment these individuals have a reduced control over their alcohol intake (Babor et al., 1992; Enoch et al., 2006). It is also
possible that these individuals are aware of the consequences of their actions but persistently fail to heed them due to deficits in impulse control that lead to precipitous actions or intolerance for delay of reward.

Table 1: DSM-IV Criteria for Alcohol Dependence

1. Tolerance, as defined by either of the following:
   - A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
   - Markedly diminished effect with continued use of the same amount of alcohol.
2. Withdrawal, as defined by either of the following:
   - The characteristic withdrawal syndrome for alcohol (refer to DSM-IV for further details).
   - Alcohol is taken to relieve or avoid withdrawal symptoms.
3. Alcohol is often taken in larger amounts or over a longer period than was intended*
4. There is a persistent desire or there are unsuccessful efforts to cut down or control alcohol use.
5. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
7. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the alcohol (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Alcohol Dependence is defined as three or more of these criteria in a 12-month period.

*For example, exceeding set limits

1.2.4.2 AD and Impulse Control

1.2.4.2.1 Response Activation/Inhibition

Response inhibition can be defined as the capacity to inhibit pre-potent responses and interference when engaged in goal-directed action (Miyake et al., 2000).

Consequently, if executive functioning ability indeed moderates the impact of automatic impulses on drinking behavior, this could carry important implications for intervention strategies.

AD patients demonstrate deficits in response inhibition (Noel et al., 2005, 2007). Altered inhibitory control specifically, has been studied in AD patients by Anderson et al., (2005); Karch et al., (2008); and Schweinsburg et al., (2004) among others. These
various experiments have concluded that functional deficits in frontal areas in AD individuals exist (Gilman et al., 1990; Martin et al., 1995; Gansler et al., 2000).

Alcohol related cues tend to grab attention and elicit approach responses in heavy drinkers compared to light drinkers. For example, the ability to inhibit pre-potent responses was measured by using the Stroop task (Stroop, 1935). The Stroop task has been demonstrated to tap pre-potent response (i.e., automatic tendency to read a word) inhibition and is exceptionally sensitive to attentional bias (Friedman and Miyake, 2004). The Alcohol Stroop task contains Alcohol related and Neutral words. Both AD and heavy social drinkers show attentional bias for the Alcohol stimuli (Cox et al., 2005).

Further studies conducted on this phenomenon demonstrate that heavy drinkers, but not light drinkers, are slow to name the colour in which Alcohol related words are printed (Field, 2007; Stormark et al., 2000; Sharma et al., 2000).

1.2.4.2.2 Neurochemistry of acute and chronic alcohol-related disinhibition/impulsivity

Administration of alcohol has been associated with alterations in dopamine, NE, GABA and serotonin (Koob & Weiss, 1992). In a review by Markou et al. (1998), acute ethanol administration was reported to influence the function of ligand gated ion channels and signal transduction mechanisms. Alteration of these devices bears a direct relationship with changes in neurotransmission. More specifically, DA, NE, GABA and serotonergic neurotransmission are enhanced while glutamatergic neurotransmission is reduced (Koob et al., 1998).
a) Dopamine

The initial reinforcing effects of drugs of abuse are widely believed to result from a large and rapid increase in DA within the nucleus accumbens (Baler and Volkow 2006). Previously addicted individuals can relapse when exposed to drug cues months or years after quitting, and hyper-reactivity of DA to these instigating factors has been critically implicated in this process. In line with these accounts, animal studies using DA D1 and D2 receptor antagonists have shown that DA blockade can reduce cue-induced reinstatement of alcohol seeking (Liu and Weiss 2002).

b) GABA

Alcohol activates the GABA-mediated increase in chloride ion flow resulting in neuronal inhibition. A GABAergic anti-anxiety effect was shown by Kushner et al (1996) showing that low doses of alcohol act acutely to reduce panic and anxiety. This finding lends support to the view that drinking by those with stress and anxiety is reinforced by this GABAergic effect. A mechanism has been posited in which GABAergic inhibition results in the activation of opioid receptors that ultimately activate behaviourally rewarding DA neurons (Julien 2005).

c) Serotonin

There is growing literature on the role of serotonin in the actions of alcohol. Evidence from animal studies suggests that serotonin plays an important role in relapse. Models of reinstatement to alcohol seeking have shown local infusions of 5-HT1A agonist 8-OH-DPAT into the median raphe nucleus (MRN), a major site of cell bodies for the 5-HT neuronal system, can induce alcohol reinstatement in rats (Le, Funk et al. 2008).
Evidence has shown that chronic alcohol consumption results in deficits in serotonin transmission and this dysfunction may play a role in the pathogenesis of some types of alcoholism. Both excessive and deficient 5-HT transmission has been implicated in AD, and these deviations appear to be linked with genetic risk factors. Today, important serotonin receptors have been identified, specifically, 5-HT2 and 5-HT3 in the central effects of ethanol. The receptors are located on dopaminergic neurons in the nucleus accumbens (Julien 2005).

1.2.5 Comorbidity of PG and Alcohol Use Disorders

Alcohol and AD can be characterized as “state” and “trait” moderating factors, respectively, on behaviour in gamblers. Acute alcohol doses have been shown to affect gambling behaviour. This may involve differing inhibitory processes. The possibility that synergistic effects of state x trait factors partially explain the high comorbidity between PG and AD is the rationale for our specific investigation and hypotheses. One reason why co-morbidity may be so high is that deficits related to avoiding alcohol carry over to impact on inhibition of gambling behaviour. i.e., if you cannot resist drinking alcohol, you will incur the effects of alcohol (or alcohol cues); these in turn may undermine efforts to resist gambling (in this case through a conditioned associative process rather than a pharmacological one).

Presently, literature suggests that higher rates of AD are present among individuals with PG as compared to the general population (Cunningham-Williams et al. 1998; Maccallum and Blaszczynski, 2002; Toneatto et al., 2002). PG is more common among individuals with AD as compared to those without disorders (Grant et al., 2002), alcohol use is a risk factor for PG (Welte et al., 2004), and gambling and excessive
alcohol consumption are co-occurring activities (Elia and Jacobs, 1993). Sher and Slutsker (2003) have reported that the most robust findings on the comorbidity of problem gambling are community-based findings of elevated rates of AD among individuals with PG. Looking at a genetic level, 12-20% of the genetic variation in the risk for disordered gambling is accounted for by genetic variation in common with the risk for alcohol dependence (Slutske et al. 2003). A linear relationship was also observed between AD and the severity of disordered gambling in a sample of 6718 male members of the Vietnam Era Twin Registry. Also notably, impulsivity reliably predicts both of these disorders (Vitaro, Arsenault, & Tremblay, 1999; Colder & Chassin, 1997). Rates of alcohol use present among individuals with PG have been reported to range as high as 44% to 72% (Petry, 2005). More recently, Pietrzak et al. (2007) reported that older adult problem and pathological gamblers, compared to recreational and non-gamblers, experienced higher rates of lifetime AD. Welte et al. (2001) specifically examined substance related comorbidity in relation to gambling pathology using a nationally represented sample of rural and urban households including 2638 adults in the US. Pathological gamblers were 23 times more likely to be alcohol dependent, although this estimate was based on a small sample size. The 1998 NORC study found that pathological or problem gamblers had approximately 7 times the rate of AD found among non-gamblers and low-risk gamblers. Another study examined data from the St. Louis Epidemiologic Catchment Area Site and found a significant positive relationship between problem gambling and AD (Cunningham-Williams et al., 1998). Despite the pervasive correspondence between PG and AD, relatively little is known about the processes or
mechanisms that underlie this association, especially as it relates to gambling treatment outcome and relapse.

Recent research shows that the enhancement of positive affect and coping with negative affect represent discrete motivational states in individuals with PG (Stewart, S. et al, 2002) as they do in AD (Cooper et al., 1992). In addition, like alcohol concepts (Stetter et al., 1995), gambling concepts are over-represented (i.e. highly salient) in semantic memory networks in problem gamblers, as evidenced by increased Stroop interference to gambling-related words (e.g. “wager”) (McCusker & Gettings, 1997). Addiction specific networks have the potential to become more defined and susceptible to cue-induced activation as the severity of the addiction increases (Rather & Goldman, 1994). These findings suggest that words that denote gambling positively (e.g., jackpot) or negatively (e.g., bankrupt) may activate alcohol concepts in problem gamblers who drink alcohol while gambling (Zack et al., 2005).

1.2.5.1 Comorbidity and Inhibitory Control

Co-morbid PGAD patients show impairment in a range of executive functioning tasks including response inhibition, time estimation, and cognitive flexibility and planning tasks (Goudriaan et al., 2006). As noted earlier, such deficits are also linked with faster rates of relapse to gambling in PG samples (Goudriaan et al., 2007). In a study by Kertzman et al., 2006, performance on the reverse Stroop task, which demonstrates the ability to inhibit interferences, was significantly impaired in PG patients vs. controls.
1.2.6 Alcohol Cues

1.2.6.1 Cue-induced craving in Alcohol Dependence & PG

The incentive-sensitization theory (Robinson & Berridge 1993) states that these cognitive biases occur as a result of chronic exposure to drugs of abuse, including alcohol. As noted earlier, the increased incentive salience of gambling cues on the Stroop task has been reported in PG subjects (Crockford et al. 2005) Such priming effects have also been directly linked with motivation to engage in addictive behaviour (Zack et al. 2001) and with actual rates of addictive behaviour outside the laboratory (Wiers et al. 2002).

In co-morbid populations, it is conceivable that cues for one disorder might “cross-prime” the other due to conditioned or conceptual associations between these classes of stimuli. Accordingly, negative affect words (e.g., tense) have been found to improve response time to alcohol words (e.g., beer) in high but not low anxious AD subjects (Zack, Toneatto and MacLeod, JAP 1999). Such improvement in response time is referred to as ‘semantic priming’ and is believed to indicate an association between the corresponding concepts in memory (Meyer and Shvaneveldt, 1971; Neely, Keefe and Ross, 1989). Using a similar word-association paradigm in PG subjects, words denoting positive aspects of gambling (jackpot) were found to prime (speed response time to) alcohol words (beer) relative to negative aspects of gambling (bankrupt). Notably, this effect was significantly greater in co-morbid PGAD than non-comorbid PG subjects; and a history of drinking to celebrate gambling wins (i.e., Pavlovian association) coincided with significantly greater gambling-alcohol priming, regardless of other factors. These findings indicate a functional linkage between gambling (or its positive effects) and
alcohol that distinguishes co-morbid vs. non-co-morbid PG subjects. They also raise the possibility that activation of these processes by relevant cues could contribute to relapse in PGAD subjects.

Non-alcoholic beer – a pharmacologically neutral cue for alcohol - has also been found to activate beliefs about alcohol in social drinkers (Martin and Sayette 1993). Fillmore and Blackburn, 2002 found that social drinkers who consumed placebo alcohol showed greater disinhibition overall on a stop-signal choice reaction time task, compared to subjects who did not consume any beverage. Therefore, non-alcoholic beverages that provide conditioned cues for alcohol can significantly influence alcohol-related cognition and inhibitory control processes.

1.2.7 Stress

The role of stress in precipitating drug relapse has been investigated in numerous studies. Brain stress and reward systems have been shown to interact in response to cues for drugs or alcohol in animals with a history of exposure to these substances (Breese et al., 2005; Koob, 2004). This process has formed the basis of reinstatement models of conditioned “craving” and relapse in animals (Shaham et al.). In animals, unpredictable and uncontrollable foot-shock is the most commonly used form of stress induction. In humans, uncontrollable, unpredictable aversive stimuli (e.g., loud noise) have been found to reliably activate the hypothalamic-pituitary axis – the primary stress pathway in human subjects (Breier et al., 1987).
1.2.7.1 Animal and Human Studies of Stress Exposure

a) Animal Studies

Reinstatement models in animal studies have shown stress exposure, cue exposure and combined stress and cue exposure increase alcohol seeking in alcohol experienced and dependent lab animals (Le et al., 2002, 2005).

b) Human Studies

Human studies on stress and craving have focused on negative reinforcement including desires, positive expectancies, obsessions, compulsions, reduction in withdrawal, and intent to drink (Anton, 2000). Healthy volunteers who have undergone the C/UC paradigm have reported higher ratings of stress, helplessness, lack of control, tensions, and anxiety following exposure to uncontrollable noise (Breier, Albus et al., 1987). Research has shown that stress/anxiety brought on by stress as well as negative mood states can increase alcohol consumption (Chiang et al., 2002). In a study conducted by Sinha et al (2009), alcohol-dependent individuals (AD), as compared to social drinkers (SD), showed a marked increase in basal heart rate and salivary cortisol levels in response to a stressful personalized situation. The stress and alcohol cue exposure each produced a significant and lasting craving state marked by an increase in anxiety, negative emotion, and systolic blood pressure in the AD group. These results suggest stress and cue exposure induce a negative emotion related alcohol craving state, accompanied by a dysregulated HPA and physiological arousal responses. (Sinha, R et al., 2009).

In our current experiment, this negative mood state induced by stress was generated as a result of a controllable/uncontrollable (C/UC) noise task (Richell and
Anderson 2004). The uncontrollable noise task thus represents a reliable and ethically acceptable procedure to temporarily induce stress, which in turn should increase motivation to engage in addictive behaviour. The specificity of this motivation (gambling vs. alcohol) and the respective impact of stress vs. alcohol cues on this process are clearly important matters for investigation.

1.3 Restatement of Purpose

Based on a review of the literature – it appears that the nature of the relationship between approach (incentive motivation) and avoidance (inhibitory control) tendencies has yet to be systematically studied in subjects with PG or AD. Furthermore, the extent to which these processes vary in PG only vs. co-morbid PGAD subjects remains unknown.

1.4 Hypotheses

1: Compared to controllable noise (non-stress control), exposure to uncontrollable noise (active stress) will increase the relative salience of Alcohol and Gambling words vs. Neutral words on a modified Stroop task.

2: Compared to soft drink, placebo alcohol will increase the relative salience of Gambling vs. Neutral words on a modified Go/No-Go Task (increasing commission errors), and differentially impair inhibitory control (increasing SSRT) to Alcohol vs. Neutral words on a Lexical version of the Stop Signal Task.

3: If co-morbidity involves additive or synergistic disturbances in salience/inhibitory control, these effects will be more pronounced in PGAD than in PG only subjects.
2. METHODS

2.1 Study Design

This study employed a single-blind, fully counterbalanced repeated measures 2 (Group: Problem Gambler [PG], Comorbid Drinker-Gambler [PGAD]) x 2 (Stress Sequence: Uncontrollable Noise on Day 1, Uncontrollable Noise on Day 2) x 2 (Drink Sequence: Beer on Day 1, Beer on Day 2) x 2 (Session) design. For this initial validation study, the sample was restricted to men since effects of stress can vary significantly with the female menstrual cycle (Kudielka and Kirschbaum 2005).

The study was designed to assess the individual and combined effects of stress and placebo alcohol. Therefore each subject received each level of noise: Controllable (no stress), and Uncontrollable (active stress) as well as each level of alcohol cue (placebo, de-alcoholized beer versus the soft drink). Due to habituation, uncontrollable noise stress can only be effectively administered once to each subject. Hence, half of the subjects received stress (uncontrollable noise) in combination with placebo beer; the other half received stress in combination with soft drink. Table 3 outlines the fully-crossed, stress and drink sequence design for the two groups. As noted earlier, the PG and PGAD groups formed part of a larger, 4-group sample (which included AD and control groups). Thus, the group size (n = 12) was somewhat smaller than in a 2-group study. The minimum number of observations for each outcome measure was: 12 x 2 x 2 = 48.
Table 3 Stress-Drink sequences for problem gamblers (PG; n = 12) and problem gamblers with alcohol use disorder (PGAD; n = 12).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test Session 1</th>
<th>Test Session 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stress + soft drink</td>
<td>No stress + placebo alcohol</td>
</tr>
<tr>
<td>2</td>
<td>Stress + placebo alcohol</td>
<td>No stress + soft drink</td>
</tr>
<tr>
<td>3</td>
<td>No stress + soft drink</td>
<td>Stress + placebo alcohol</td>
</tr>
<tr>
<td>4</td>
<td>No stress + placebo alcohol</td>
<td>Stress + soft drink</td>
</tr>
</tbody>
</table>

2.2 Recruitment

Subjects were recruited through multiple avenues. Recruitment advertisements, approved by the Center for Addiction and Mental Health’s (CAMH) Research Ethics Board (REB), appeared in weekly public newspapers, an Internet advertising site, and on bulletin boards within CAMH itself. Additional advertisements were posted at a nearby hospital. Volunteers were instructed to call a study number, and were contacted by an experimenter who administered a telephone pre-screening assessment.

2.3 Screening

The telephone screening evaluated drinking, and other substance use, as well as diagnostic scales for AD, drug abuse and PG.

Using a modified Timeline Followback procedure (Sobell and Sobell, 1992) subjects reported the number of standard alcoholic drinks they consumed per week (PG ≤ 12; PGAD > 20); based on norms for moderate drinking levels in treatment-seeking AD subjects [Wilkinson and LeBreton – see Zack et al JAP 1999 for citation]) the number of cigarettes smoked (≤ 20 per day to minimize nicotine withdrawal effects during the test sessions). Volunteers who met these inclusion criteria then received the three main symptom scales:

a) Alcohol Dependence Scale (ADS): (Skinner & Allen, 1982) The ADS provides a quantitative measure of the severity of alcohol dependence consistent with the DSM concept of the alcohol dependence syndrome. Its 25 items cover alcohol
withdrawal symptoms, impaired control over drinking, awareness of a compulsion to drink, increased tolerance to alcohol and salience of drink-seeking behaviour.

b) South Oaks Gambling Screen (SOGS): (Lesieur & Blume, 1987) The SOGS is a psychometrically validated 16-item self-report questionnaire that asks respondents to describe their lifetime gambling habits (i.e. “have you ever gambled more than you intended to” or “have you ever borrowed money from someone and not paid them back as a result of your gambling”). Eleven items are scored, and SOGS scores ≥ 5 are used to identify “probable pathological gamblers.” The content of the SOGS was derived from Gamblers Anonymous’ 20 questions and from DSM-III (APA, 1980) criteria. SOGS scores correlate well with scores on a DSM-IV based symptom checklist for PG (Beaudoin and Cox, 1999).

c) Beck Depression Inventory (BDI-sf): (Beck & Beck, 1972). The BDI-sf is a 13-item self-report instrument designed to detect depression in a primary care population. In the present study, a score is as follows: <10, indicating at most low-level depressive symptoms, were considered acceptable.

2.4 Subjects

Twenty-five subjects, 12 PG (mean age = 36.42 years, SD = 7.83) and 13 PGAD (mean age = 38.85 years, SD = 12.55) were recruited. PG subjects, on average consumed 7.25 (SD = 2.99) standard drinks of alcohol per week whereas PGAD subjects consumed 27.62 (SD = 8.35) standard drinks per week. To ensure equal weighting for all experimental cells in the Stress Sequence x Drink Sequence x Session design, only the first 12 PGAD subjects (of 13 completers) were included in the analyses.
Subjects were informed they would receive $300 compensation for participation, $150 for each test session, as well as transit tokens for travel to and from the laboratory on each test session.

2.5 Inclusion Criteria

The study was open to physically healthy males, aged 19-65 yrs. PG subjects scored ≤8 on the ADS (Ross, Gavin, Skinner, 1990), ≥5 on the SOGS (Lesieur and Blume, 1987) and ≤10 on the BDI-sf (Furlanetto, LM, J Affect Disorders, 2005, 86 (1): 87-91). PGAD subjects scored ≥13 on the ADS; ≥5 on the SOGS; and ≤10 on the BDI-sf. All subjects had to have a grade 7 level of education to ensure comprehension of study requirements. They were required to be fluent in the English language, as determined by the understanding of the telephone screening, to ensure comprehension of the verbal stimuli on the computer tasks. They had to have normal or corrected-to-normal vision to ensure ability to see the stimuli correctly on the experimental tasks.

2.6 Exclusion Criteria

Subjects were excluded if they currently were diagnosed with a physical or mental illness, apart from PG, AD or nicotine dependence; if they were currently using any psychoactive medication; currently in treatment for PG or AD, currently abstinent or wished to be abstinent from alcohol or if they drank > 70 drinks/week on average in order to avoid alcohol withdrawal symptoms during the test sessions.

2.7 Apparatus/Materials

A JX4-ALERT (Alcohol Countermeasures Inc., Mississauga, ON, Canada) handheld breathalyzer verified that blood alcohol concentration (BAC, %) was 0 at the start of both test sessions for all subjects. The breathalyzer was administered again at the
end of the placebo session before the subjects left the lab, to ensure they did not think they might still be intoxicated.

A mock breathalyzer designed to closely resemble the ALERT was also used during the placebo session. It was administered approx. 10 minutes after subjects completed their second drink. The device registered a false BAC of 0.041% to strengthen subjects’ belief that they had actually consumed alcohol. The reading of .041% is the highest credible value for placebo manipulations of this kind (Martin & Sayette, 1993).

During placebo alcohol test days, the beer consumed by subjects was Labatt Nordic (Labatt Brewing Co., Toronto, ON, Canada), which contains <0.05% alcohol content. It was poured into a 355ml frosted, plastic cup in order to blind the subject from the brand of drink, and chilled thoroughly to make it difficult to detect the absence of alcohol.

On the soft drink test days, an equal volume of Fresca (Diet Fresca, Coca-Cola Ltd., Toronto, ON, Canada) was administered in the same 355 ml frosted plastic cup. This soft drink is not usually mixed with alcohol, minimizing potential associative cues for alcohol.

During both test sessions subjects’ heart rate and blood pressure was tested at selected intervals, starting at baseline (arrival), and ending just before departure from the lab. The first half of the sample was tested with a Wrist cuff (HEM-601, Omron Inc., Vernon Hills, IL). A standard upper-arm cuff device was introduced for the second half of subjects for more precise readings - The Dinamap 100 Monitor with DURA-CUF (GE healthcare Clinical systems, Mississauga, ON.).
All computer-based experimental tasks were administered on a PC equipped with MicroExperimental Laboratories (MEL) Professional version 2.01 with an integrated microphone. A serial response box was used to code the accuracy of responses for the computer tasks (MEL and Box from Psychology Software Tools, Inc., Pittsburgh, PA).

2.8 Questionnaires

2.8.1 State Scales

On three occasions during each test session (pre-test baseline, immediately after the stressor but before drink 1, and ~20 min after drink 2, upon completion of the Lexical Stop Signal Task; LSST) state questionnaires were administered. These included:


A VAS was used to quantify the subjects’ desire for alcohol and desire to gamble. The scale endpoints, 100 = “extremely high” and 0 = “not at all” were connected by a 100mm line. Subjects circled the point on the line at the position that best reflected their current desire to drink alcohol or gamble.

b) Profile of Moods States-short form (POMS-sf):

This questionnaire measures a range of subjective states (anger/hostility, confusion, depression, vigor, fatigue and tension/anxiety) at a specific point in time. It consists of 37 mood-related adjectives (e.g., tired, excited, happy), rated on a scale from 0-4 or (“not at all” to “extremely”).


The uncontrollable noise stressor is designed to induce a sense of helplessness and frustration. Subjects, especially males, may be reluctant to acknowledge feelings of helplessness or stress, but may be more willing to acknowledge feelings of anger. The
State portion of the State-Trait Anger Scale was used to test this possibility. The scale is composed of 15 anger-related statements (i.e., “I am mad” or “I feel angry”) that subjects rate on a 4-point scale ranging from “not at all” to “very much so,” based on the intensity of their anger at that moment. Total scores are calculated by summing all 15 items (range: 15-60).

2.8.2 Trait Scales

At the end of test session 2 after all other measures had been taken, subjects receive an additional questionnaire package examining stable background or personality characteristics (traits), which they completed before debriefing. The package included the following questionnaires:

a) Drinking Motives Questionnaire (DMQ): (Cooper, Russell et al. 1992)

The questionnaire is divided into 3 factors: Enhancement, Coping and Social motives for drinking. The sum of these items yields the subscale score. Respondents estimate how often they are motivated to drink for the 15 reasons specified on a 4 point Likert scale from “Never or almost never” to “almost always”. The total value for a subscale can range from 5-20 points. This scale enabled direct assessment of the extent to which negative affect (e.g., stress) or positive affect was a discriminative stimulus for drinking, which could contribute to conditioned motivation to drink in the presence of the uncontrollable noise task.

b) Gambling Motives Questionnaire (GMQ): (Stewart & Zack, 2007):

This measures gambling motives and was modeled after the psychometrically validated DMQ. Specifically, the GMQ assesses gamblers’ relative frequency of gambling for each of 15 reasons. All items on the GMQ, except one, were adapted
directly from the DMQ; the remaining item was reworded from the DMQ to make it appropriate to the gambling context. As with the DMQ there are 5 items per subscale, and the measure consists of 3 subscales: Social, Coping, and Enhancement gambling motives. Relative frequency of gambling is rated on the same 4-point scale used for the DMQ.


The EPI was used to assess Extraversion, Neuroticism, Impulsivity and tendency to Lie (i.e., respond in a socially desirable manner). It is composed of 57 “yes” or “no” questions about individuals’ usual way of acting or feeling. Extraversion scale scores range from 0-24; Neuroticism scale scores ranged from 0-24; Impulsivity scale scores ranged from 0-9; and the Lie scale also ranged from 0-9.

2.9 Other Measures


Subjects must repeat increasingly longer strings of one-digit numbers first forwards (test of short term memory) and then in reverse order (test of working memory). Digits backwards can tap this central executive aspect of working memory (Stout, 1995), and is a behavioural index closely linked with impulse control (Bobova, L. et al., 2009 Exp Clin Psychopharm 17(1): 51-61).

b) Drink Strength Rating Scale (DSRS; Vogel-Sprott, 1992):

At the end of the placebo alcohol test day, subjects were asked to rate approximately how many standard 5% bottles of beer they thought they consumed during
the session on a scale ranging from 0 to >8.5, with half-point intervals. It is used in order to assess whether or not the drink manipulation (placebo alcohol) was successful.

c) Alcohol Timeline Followback: (TLFB; Sobell & Sobell, 1992).

At the end of test session 2 subjects completed a history of their drinking behavior over the last three months starting with their most recent drinking episode and working backward. This enabled confirmation of the drinking levels reported in the initial phone screening with the full validated version of the TLFB. Mean drinks per week serves as a global index of alcohol use.

2.10 Experimental (Computer Based) Tasks

Subjects completed several computer-based tasks, the results of which constitute the primary outcome measures for this experiment. These procedures assess cognitive activation and sub-types of inhibition, as outlined in the Introduction. The computer tasks included:


The modified Stroop task assessed the effects of the stress manipulation on the salience of motivationally relevant vs. neutral word stimuli. Salience is measured by interference (increased latency to name the colour of motivationally relevant vs. neutral stimuli).

The Stroop task was administered on a PC and run entirely within MS-DOS (the procedure is identical to that of Zack et al (2007)). Subjects faced the screen at a distance of 60cm and responded vocally to the stimuli. A microphone attached to the computer by
a cable and positioned approx. 3cm from the subject’s mouth registered vocal response
time (RT) to each stimulus with millisecond (ms) accuracy. Subjects were instructed not
to read the word stimuli but instead to name the colour the word was printed in as quickly
and accurately as possible. During the task, the experimenter coded response accuracy
(correct response; error: incorrect name or reading the word) after each trial using the
button box, also attached to the computer by a cable. There were two procedurally
identical versions of the task: a practice version that used neutral words only and
familiarized the subject with the task before the experimental manipulations, and a test
version containing words from motivationally relevant and neutral categories. The 8
word categories for the test version of the task were: Physical Threat (e.g., death), Social
Threat (e.g., embarrassed), Depression (e.g., hopeless), Positive Affect (e.g., happy),
Anger (e.g., destroy), Alcohol (e.g., whisky), Gambling (e.g., jackpot), and Neutral (e.g.,
trombone). Positive, Physical Threat and Social Threat items were taken from Stewart et
items were taken from Cox et al. (1999). Gambling items were taken from Zack and

The practice and test versions of the task began with 20 warm-up trials made up
of neutral word stimuli only. The sequence of each trial was identical. The stimulus
appeared in the center of the screen (1cm in height) in 1 of 4 colours (red, yellow, green
or blue) and remained there until a vocal response was made. The response extinguished
the word, after which the screen remained blank for 1000ms when another stimulus
appeared in the same location. There were 20 items per category, and categories and
items were distributed randomly over trials. The task lasted approximately 10 minutes.
b) Shift Task (Go/No-Go): (Newman & Kosson, 1986)

This task, adapted from Newman and Kosson (1986) and again by Noel et al. (2007), involves the serial presentation of words on a computer screen (750 ms duration). There are 10 blocks which include 2 practice blocks at the start of the computer task. Each block is divided into 2 categories including gambling related words (G) or neutral words (N). For each block, one of the two word categories is selected as a target (go) and the other a distracter (no/go). Subjects have to learn when to go (press the “/” computer key with their right index finger as quickly as possible) or not go (withhold their key press response). The target order for the 10 blocks was NNGGNNGGNN or GGNNGGNNGG. Subjects with odd subject numbers received this sequence on test days 1 and 2, respectively. Individuals with even subject numbers received these sequences on day 2 and day 1, respectively.

‘Shift’ trials are those for which the response rule (go vs. no-go) changes, i.e., when G stimuli shift from being designated as targets to being designated as distracters, and likewise when N stimuli shift from being targets to distracters. Subjects only learn of the shift from post-response feedback (correct/incorrect), indicating that the stimulus (G/N) response (go-no/go) mapping has changed. Therefore, as indicated in the two block sequences above, 4 test blocks were non-shift blocks (NN or GG), and the remaining 4 test blocks are shift blocks (NG or GN).

Each trial is identical: the stimulus word appears in the middle of the screen for 750ms. Then there is a 1000ms interval during which time a fixation point of (++++) is presented in the same location. If the “/” key is pressed for a distracter (no/go) word a 450 Hz tone sounds (indicating an incorrect response, i.e., key press instead of no key
press) for 500ms and the screen appears blank. There were a total of 30 G and 30 N words, taken from Zack and Poulos (2004). The total number of commission errors to G and N words for shift and non-shift trials was the primary dependent measure.


The conventional SST follows that of Logan et al. 1997 and was run in Quick Basic within MS-DOS. The task assesses the time required to stop a response that is already in the process of being executed (i.e., action cancellation, as described above). During this task subjects are asked to perform a series of trials in which they are to make a choice between pressing either one of two keys as quickly as possible depending on the stimulus that appeared on the screen. The subject is instructed to press the “z” key with their left index finger when the letter X appears on the screen or the “/” key when the letter O appears on the screen as quickly as possible without making any mistakes. Different letters (a, b; c, d) were used for each administration of the task to minimize practice effects. The letters act as the “go” signal. Thus, all go stimuli in this task are conceptually meaningless and are motivationally neutral.

A tone (stop-signal) occurs briefly after the onset of the visual cue during 25% of the trials, which indicates that subjects are to withhold their key press for that trial. Choice decisions to visual cues as well as the inhibition of key pressing in response to a tone are used as a measure of inhibitory control. The sequence of events for each trial is identical. A total of 256 trials are administered, split into 3 blocks with two 40-second rest periods in between. The subjects receive 2 practice blocks before the test trials. Stop
signal tones are split evenly between “x” and “o” trials. The entire task lasts approximately 10 minutes.

The primary outcome measure on this task is stop-signal response time; SSRT (the time taken, after a stop signal is presented, for inhibition to be effected). SSRT is a measure derived from the difference between RT to visual cues and the delay or interval between the onset of the visual (go) stimuli and the onset of the auditory stop-signal. This interval is initially set at 250 ms and modulated by the program based on a subject’s inhibitory success. After trials where the stop signal sounds and the response is inhibited, the program increases the interval between the go and stop stimuli by 50 ms, making it harder for the stop process to catch up with the go process and cancel the key press response. After trials where the stop signal sounds but the response is committed (inhibitory failure), the program decreases the go-stop signal interval, making it easier to inhibit the response on the next stop trial. Over the course of trials, this program converges on the go-stop delay associated with 50% successful inhibition. The difference between mean RT to the go stimuli and the delay associated with 50% successful inhibition equals SSRT, which provides a unitary estimate of inhibitory proficiency.

d) Lexical Stop Signal Task (LSST):

This exploratory task, adapted from Logan et al. (1997), was run in MEL within MS-DOS. It provides an independent measure of salience (through go reaction times) and disinhibition (through stop signal reaction times) to stimuli that are motivationally relevant versus neutral. This task requires the subject to press one of two keys as quickly as possible depending on whether a string of letters that is displayed on the computer
screen is a real English word or if it is just nonsense. The “z” key is pressed for a nonsense word, and the “/” key for a real English word. An equal number of real words and nonsense words were administered in random order on each trial block. Of the real words, 50% were alcohol-related and the other half were neutral. On 25% of the trials for each stimulus type (Alcohol word, Neutral word, Non-word), a tone (stop signal) sounds and the subject must inhibit his response. Using the same procedure as described for the conventional SST, the program yields separate mean SSRT values for Alcohol word trials and Neutral word trials, enabling comparison of inhibitory efficiency as a function of the ‘salience’ of go stimuli. As in standard lexical decision tasks, RT to non-word stimuli was not analyzed.

The sequence of events on a trial was as follows: A 500 ms fixation stimulus (++++) appeared in the middle of the screen, followed by a blank screen for 1000ms. The letter string (go signal) appeared on the screen for 1000ms immediately thereafter. On stop-signal trials, a 1000 Hz tone (stop-signal) sounded for 100 ms at varying delays after the string appeared. Throughout the task, the interval between the go signal and the stop signal varied. Initially, it was set at 350 ms (as opposed to 250 ms in the conventional task, reflecting the longer processing time required for lexical stimuli) and was automatically adjusted to the subject’s performance as described above. There were 120 Alcohol words, 120 Neutral words and 240 Nonsense letter strings presented, with stimuli taken from Zack et al. (1999). All items were presented in a random order and the task was divided into 8 blocks with 30-sec rest periods in-between. Twenty practice trials preceded the test trials. This task lasted approximately 20 minutes.
2.11 Stress-Manipulation – Noise Task

Richell et al. (2004) validated the stressor procedure used in this experiment, which was originally used to induce stress in healthy controls. A separate computer (using Microsoft Windows) was used for the stress task. The stimulus was a 110db burst of white noise, delivered through headphones in random durations of 2-20 sec. Uncontrollable noise at this volume has been shown to activate the hypothalamic-pituitary axis in healthy controls (Brier, Albus et al. 1987).

Subjects are instructed that they must find a way to stop the noise generated by the computer by using the correct sequence/timing of mouse clicks on a circular target in the middle of the computer screen. There are 2 noise conditions. In the controllable condition the noise can be terminated by pressing the right mouse button consecutively 4 separate times on the target. The screen then flashes “Subject-Out”, meaning the subject stopped the noise himself. In the uncontrollable (active stress) condition, the green circular target on the screen cannot be extinguished, regardless of whether or how often the subject clicks on it. The target disappears from the computer screen at random intervals (longer than those required to extinguish the target in the controllable condition), and the noise remains on during the entire time the target is displayed. When the target does extinguish the message “Time-out” appears, informing the subject he was unable to stop the noise and the computer automatically timed out. Subjects are led to believe that they can in fact terminate the noise themselves (even in the uncontrollable condition) when they actually cannot. Feelings of stress and negative moods have been shown to develop under this uncontrollable noise manipulation in healthy subjects (Richell et al., 2004).
The no-stress test session consisted of 2 blocks of controllable noise (4 mouse clicks on the visual target extinguishes the noise). Each block was made up of 25 trials, lasting 5 minutes. The controllable condition leaves the subject feeling that he has successfully solved the problem for the task. Richell and Anderson (2004) have shown that (un)controllability of the noise rather than its duration is the critical factor for the emergence of stress.

In the active stress condition, the subject completes 1 block of controllable noise trials, which makes him believe the noise can be successfully extinguished, followed by a second block that is uncontrollable. This uncontrollable condition is made up of 15 trials, lasting 10 minutes.

2.12 Procedure for Experimental Sessions

Eligible subjects attended two procedurally identical (apart from stress/drink condition) test sessions, at least 2 days apart, at the Clinical Neuroscience laboratory of CAMH. Each session lasted approximately 4 hours. Together with travel time, the total commitment was about 10 hours. Subjects received a reminder phone-call the night before coming in for the experiment. They were instructed to consume a light meal no more than 2 hours before coming in for the experiment to ensure even absorption of their drinks during the test phase. As well, subjects were asked to refrain from drinking any alcoholic beverages for at least 12 hours before the start of testing on each day to ensure a baseline BAC of 0.

The experimenter read from a script throughout both test sessions to ensure that instructions and procedures were standardized. Both sessions began promptly at 11am. The timeline for the test session can be found in Table 4. Upon arrival on test day 1, a
consent form was administered outlining all of the study requirements and subjects had an opportunity to ask any questions before providing written consent. They were told which drink they would be receiving that day (i.e. beer vs. soft drink) and underwent an initial breathalyzer measure to ensure a baseline reading of 0. Their baseline heart rate (HR) and blood pressure (BP) were then checked to confirm a systolic reading of $\leq 140$ mm Hg, since the stress manipulation could be dangerous for such borderline hypertensive subjects. HR and BP were checked seven times throughout the test session at pre-determined intervals.
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1100</td>
<td>Arrival&lt;br&gt;Consent&lt;br&gt;Baseline Measures&lt;br&gt;  - Breathalyzer (BAC = 0)&lt;br&gt;  - BP/HR (1)&lt;br&gt;  - State Questionnaire Package (1)</td>
</tr>
<tr>
<td>1115</td>
<td>Digit Span Task&lt;br&gt;Neutral Stroop Task&lt;br&gt;SST (XO version)</td>
</tr>
<tr>
<td>1140</td>
<td>Stress Manipulation (Controllable vs. Uncontrollable)</td>
</tr>
<tr>
<td>1155</td>
<td>Test Stroop</td>
</tr>
<tr>
<td>1205</td>
<td>BP/HR (2)&lt;br&gt;State Questionnaire Package (2)</td>
</tr>
<tr>
<td>1210</td>
<td>Drink 1 (Beer or Soft Drink)</td>
</tr>
<tr>
<td>1220</td>
<td>Shift Task</td>
</tr>
<tr>
<td>1230</td>
<td>Drink 2 (Beer or Soft Drink)</td>
</tr>
<tr>
<td>1235</td>
<td>BP/HR (4)&lt;br&gt;Mock Breathalyzer (Beer day only)</td>
</tr>
<tr>
<td>1240</td>
<td>Lexical Stop Signal Task</td>
</tr>
<tr>
<td>1300</td>
<td>BP/HR (5)&lt;br&gt;State Questionnaire Package (3)</td>
</tr>
<tr>
<td>1305</td>
<td>Stop Signal Task (a/b version session 1, c/d version session 2)</td>
</tr>
<tr>
<td>1315</td>
<td>BP/HR (6)&lt;br&gt;Drink Strength Rating Scale (Beer day)&lt;br&gt;Timeline Followback (session 2 only)</td>
</tr>
<tr>
<td>1330</td>
<td>Lunch</td>
</tr>
<tr>
<td>1400</td>
<td>BP/HR (7)&lt;br&gt;Breathalyzer&lt;br&gt;Debriefing and Payment (session 2 only)&lt;br&gt;Dismissal</td>
</tr>
</tbody>
</table>

State questionnaire package: visual analog scale, state anger scale, profile of mood state, biphasic alcohol effects scale, state measures desire for alcohol and state measures desire for gambling.<br>Trait questionnaire package: alcohol expectancy questionnaire, gambling expectancy questionnaire, drinking motives questionnaire, gambling motives questionnaire, Eysenck personality inventory, inventory of drinking situations, inventory of gambling situations, social phobia and anxiety inventory, trait anger scale, state-trait anxiety inventory, Penn alcohol craving scale, Penn gambling craving scale and South Oaks gambling screen. Timeline followback of standard alcoholic drinks per day for preceding 90 days; BP, Blood Pressure; HR, Heart Rate.
Baseline Self-Report measures were then administered (M-VAS, SAS, POMS, BAQ, DAQ, DAQ-g). The same package of questionnaires was administered two more times during the test session: once after exposure to noise (right after the Stroop test) and again after the LSST (~20 min after the second drink).

After the baseline self-report measures subjects were escorted into the computer lab and completed the Digit Span task. Subjects then performed their baseline computer tasks: the neutral Stroop task and the conventional SST (X-O visual stimuli), in order to familiarize themselves with the procedure before the test phase. Following the familiarization tasks, subjects were led into a different room for the noise task. Upon completion of the noise task, subjects were escorted back to the original computer room for the test-phase, which began with the modified Stroop task. After the Stroop, subjects were led back to the waiting room and were asked to complete their post-computer task questionnaires (state measures). Next, they received their first drink (~355 ml placebo beer or soft drink) which they were instructed to consume steadily over a 5-min interval. After completion of the first drink, subjects were escorted to the computer lab and completed the modified gambling go/no-go (‘Shift’) task. Upon completion of this task, subjects consumed their second drink over the course of 5 minutes.

Approximately 10 minutes after the second drink (during the placebo beer day) subjects were lead to the computer lab where they received their false 0.041% BAC reading on the “mock” breathalyzer. Subjects then completed the LSST. This computer test was followed by another HR and BP reading and the third state questionnaire package. Subjects then completed their final computer task, the conventional SST (visual stimuli were a / b on test session 1 and c / d on test session 2). If subjects had received
beer, they were asked to fill out the Drink Strength Rating Scale, as the last element of the test phase, after which lunch was served. Prior to departure on beer days, subjects also got a final breathalyzer showing that their BAC was 0. On test session 2 the trait questionnaire package was administered with lunch (AEQ, GEQ, DMQ, GMQ, EPQ, IDS-42, IGS, SPAI, TAS, STAI-T, PACS, PGCS, and the SOGS). Subjects were then debriefed, given their payment and dismissed.

2.13 Data Analysis

Performance data were analyzed using SPSS (v. 15.0) software. Experimental effects were assessed with 2 Group (PG, PD-PG) x 2 Drink Sequence (Beer Day 1/Soft Drink Day 2 vs. Soft Drink Day 1/Beer Day 2) x 2 Stress Sequence (Uncontrollable Noise Day 1/Controllable Noise Day 2 vs. Controllable Noise Day 1/Uncontrollable Noise Day 2) x 2 (Session) repeated measures analyses of variance (ANOVAs). Within-subject variables (e.g., word condition – in Stroop, Shift or LSST) were added into the analysis when appropriate. Background measures and trait characteristics were analyzed using a multivariate analysis of variance (MANOVAs). The Bonferroni procedure controlled for inflation of family-wise $\alpha$ with multiple comparisons in the MANOVA.

To control for intrinsic variation and isolate treatment effects when there were baseline differences between groups, repeated measure analyses of covariance (ANCOVAs) were conducted using the pre-experimental baseline scores as covariates in the analysis (cf. Sayette et al., 2001). If no significant baseline effects were observed, baseline scores were included, as the first level of the repeated measures comparison (e.g., time of test), in the ANOVA. For all analyses (self-report data, cognitive computer tasks, and physiological measures), if a significant interaction was observed in the
ANOVA/ANCOVA, tests of simple effects were conducted using the appropriate MS-
error term and degrees of freedom from the variance analysis to compute a “standard
effect of the mean” (SEM) (Winer 1971). In cases where hypothesized effects were
marginally significant (p ~ .10) in the variance analyses, simple effects were computed to
compare the specific means to which the hypotheses pertained (see Howell, 1992).
3. RESULTS

3.1 Background Characteristics

3.1.1 Subject Eligibility

A total of 485 calls were made to potential subjects who had responded to study advertisements over a 1-year period. Of these, 377 subjects were successfully contacted. Out of the 377 contacted, 346 were ineligible for inclusion in the study. The most common reasons for exclusion during the telephone screening were: score >10 on the BDI-sf, score < 5 on the SOGS, score = 9-12 on the ADS in PG-only subjects, or drinks per week < 20 in the PGAD group. The final eligible sample consisted of 31 (17 PG, 14 PGAD) subjects, of which 25 completed testing (12 PG, 13 PGAD). The last PGAD subject was dropped from the analysis in order to ensure equal weighting of scores (n = 12/group) in the stress/drink/session cells (3 per cell) for both groups.

3.1.2 Subject Characteristics and Procedural Check

A 2 (Group) x 2(Drink Sequence) x 2(Stress Sequence) MANOVA of subjects’ background characteristics yielded a main effect of Group. There were no significant between-group differences in the average age of subjects (p > .57). Mean (SD) age was 36.4 (7.8) years in Group PG and 39.7 (12.7) years in Group PGAD. The mean (SD) sample value on the SOGS at intake was 9.8 (3.6) for Group PG and 10.7 (4.6) for Group PGAD. These means were well above the cutoff of 5 for ‘probable pathological gambling’, indicating a substantial gambling problem.

Univariate ANOVA’s with Bonferroni control of family-wise alpha, revealed a significant main effects of Group (see Table 5), on the ADS, F (1, 22) = 77.00, p < .001), and drinks consumed per week, F (1, 22) = 63.64, p < .001). These differences
confirmed that the two groups differed significantly with respect to AD-related but not PG related symptoms.

A significant group difference was also observed on the BDI-sf, $F(1, 22) = 5.81$, $p = .025$, where Group PGAD had a significantly higher mean score than Group PG (Table 5).

Table 5 MANOVA of background characteristics in Problem Gamblers (PG; n=12) and Problem Gamblers with Alcohol Use Disorder (PGAD; n=12)

<table>
<thead>
<tr>
<th>Source</th>
<th>Dependent Variable</th>
<th>Type III Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Subject's age</td>
<td>63.375</td>
<td>1</td>
<td>63.375</td>
<td>.567</td>
<td>.459</td>
</tr>
<tr>
<td></td>
<td>The # of standard drinks of alcohol in an average week</td>
<td>2542.042</td>
<td>1</td>
<td>2542.042</td>
<td>60.269</td>
<td>.000*</td>
</tr>
<tr>
<td></td>
<td>Alcohol Use Questionnaire Score</td>
<td>1148.167</td>
<td>1</td>
<td>1148.167</td>
<td>77.882</td>
<td>.000*</td>
</tr>
<tr>
<td></td>
<td>Beck Depression Inventory Score</td>
<td>48.167</td>
<td>1</td>
<td>48.167</td>
<td>5.812</td>
<td>.025*</td>
</tr>
<tr>
<td></td>
<td>South Oaks Gambling Screen Score - telephone screening</td>
<td>4.167</td>
<td>1</td>
<td>4.167</td>
<td>.248</td>
<td>.624</td>
</tr>
<tr>
<td></td>
<td>South Oaks Gambling Screen Score – Post test session #2</td>
<td>8.167</td>
<td>1</td>
<td>8.167</td>
<td>.596</td>
<td>.448</td>
</tr>
<tr>
<td></td>
<td>Timeline Followback - Drinks per week</td>
<td>2641.592</td>
<td>1</td>
<td>2641.592</td>
<td>30.106</td>
<td>.000*</td>
</tr>
<tr>
<td></td>
<td>Timeline Followback - Drinks per month</td>
<td>49223.255</td>
<td>1</td>
<td>49223.255</td>
<td>28.480</td>
<td>.000*</td>
</tr>
</tbody>
</table>

* represents statistically significant differences between subject groups

Table 6 shows mean (SD) scores for Groups PG and PGAD on the other trait questionnaires. A 2 x 2 x 2 MANOVA of these scores showed a Group x Stress Sequence interaction on the DMQ Enhancement subscale, $F(1, 16) = 9.22$, $p = .008$, with PGAD > PG, and reflecting a higher score in subjects who received stress on session 1 vs. session 2. A main effect of Stress Sequence was also observed on the EPI-neuroticism scale, $F(1, 16) = 6.18$, $p = .024$, reflecting a higher score in subjects who received stress
on session 1 vs. session 2. A main effect of Group (PGAD>PG) was also found on the DMQ – Coping subscale, F (1, 16) = 5.92, p = .027.

Table 6 Mean (SD) background characteristics in Problem Gamblers (PG; n=12) and Problem Gamblers with Alcohol Use Disorder (PGAD; n=12)

<table>
<thead>
<tr>
<th>Variable</th>
<th>PG Mean (SD)</th>
<th>PGAD Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>36.42 (7.83)</td>
<td>38.85 (12.55)</td>
</tr>
<tr>
<td><strong>ADS</strong></td>
<td>4.33 (2.39)</td>
<td>17.85 (4.81)*</td>
</tr>
<tr>
<td><strong>BDI-SF</strong></td>
<td>4.83 (3.04)</td>
<td>7.38 (2.79)*</td>
</tr>
<tr>
<td><strong>SOGS</strong></td>
<td>9.83 (3.56)</td>
<td>10.31 (4.57)</td>
</tr>
<tr>
<td>Screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Post-test session #2</strong></td>
<td>10.00 (4.67)</td>
<td>8.54 (2.50)</td>
</tr>
<tr>
<td><strong>Drinks</strong></td>
<td>7.25 (2.99)</td>
<td>27.62 (8.35)*</td>
</tr>
<tr>
<td>per week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>per month</td>
<td>28.76 (27.23)</td>
<td>125.25 (54.27)*</td>
</tr>
<tr>
<td><strong>DMQ – Enhancement</strong></td>
<td>13.17 (4.2)</td>
<td>15.08 (2.71)</td>
</tr>
<tr>
<td><strong>DMQ – Coping</strong></td>
<td>10.42 (3.55)</td>
<td>14.00 (3.89)*</td>
</tr>
<tr>
<td><strong>DMQ – Social</strong></td>
<td>15.00 (4.05)</td>
<td>16.67 (1.92)</td>
</tr>
<tr>
<td><strong>GMQ – Enhancement</strong></td>
<td>12.75 (4.59)</td>
<td>12.58 (4.70)</td>
</tr>
<tr>
<td><strong>GMQ – Coping</strong></td>
<td>10.83 (3.49)</td>
<td>10.50 (4.15)</td>
</tr>
<tr>
<td><strong>GMQ – Social</strong></td>
<td>15.00 (2.95)</td>
<td>15.75 (3.52)</td>
</tr>
<tr>
<td><strong>EPI – Extraversion</strong></td>
<td>13.92 (2.39)</td>
<td>14.83 (2.48)</td>
</tr>
<tr>
<td><strong>EPI – Neuroticism</strong></td>
<td>10.08 (4.87)</td>
<td>12.42 (4.03)</td>
</tr>
<tr>
<td><strong>EPI – Lie Scale</strong></td>
<td>5.83 (2.08)</td>
<td>5.25 (1.06)</td>
</tr>
<tr>
<td><strong>EPI – Impulsivity</strong></td>
<td>4.92 (1.68)</td>
<td>5.00 (1.65)</td>
</tr>
<tr>
<td><strong>TAS – Anger Temperament</strong></td>
<td>5.92 (3.32)</td>
<td>7.17 (2.86)</td>
</tr>
<tr>
<td><strong>TAS – Anger Reaction</strong></td>
<td>8.75 (3.96)</td>
<td>9.33 (3.20)</td>
</tr>
<tr>
<td><strong>TAS - Total</strong></td>
<td>27.00 (9.78)</td>
<td>29.83 (7.88)</td>
</tr>
<tr>
<td><strong>STAI – State</strong></td>
<td>32.83 (9.81)</td>
<td>33.17 (9.81)</td>
</tr>
<tr>
<td><strong>STAI - Trait</strong></td>
<td>37.25 (9.58)</td>
<td>40.33 (8.93)</td>
</tr>
</tbody>
</table>

Drinks/week, mean standard alcoholic drinks per week for preceding 12 months; ADS, Alcohol Dependence Scale; BDI-SF, Beck Depression Inventory-Short Form; SOGS, South Oaks Gambling Screen. DMQ, Drinking Motives Questionnaire; GMQ, Gambling Motives Questionnaire; EPI, Eysenck Personality Inventory; TAS, Trait Anger Scale; STAI, State-Trait Anxiety Inventory.

* Significant Group Differences, Bonferroni p < .05.

The effects involving Stress Sequence indicate that, despite random assignment, differences emerged in DMQ drinking to enhance positive affect as well as Neuroticism across the experimental cells. The main effect of Group indicated that co-morbid subjects were more likely to drink to cope with negative affect than were non-comorbid subjects.
3.1.3 Digit Span Task

Table 7 reports mean (SD) Digit Span scores for groups PG and PGAD. A 2 x 2 x 2 x 2 x 2 ANOVA revealed a main effect of Subscale, F (1, 16) = 23.03, p < .001. As usual, subjects in both groups scored higher on the forward recall than the backward recall sub-test. The lack of effects between groups emphasizes their similarity in working memory and helps to ensure that group differences in response to the experimental manipulations do not reflect differences in basic cognitive function.

Table 7  Mean (SD) scores for Problem Gamblers (PG; n=12) and Problem Gamblers with Alcohol Use Disorder (PGAD; n=12) on the digit span task

<table>
<thead>
<tr>
<th></th>
<th>Test Session 1</th>
<th></th>
<th>Test Session 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>forward score</td>
<td>backward score</td>
<td>total score</td>
<td>forward score</td>
</tr>
<tr>
<td>GROUP</td>
<td>score *</td>
<td>score</td>
<td></td>
<td>score *</td>
</tr>
<tr>
<td>PG</td>
<td>9.4(2.7)</td>
<td>7.9(2.5)</td>
<td>17.3(4.9)</td>
<td>8.8(2.2)</td>
</tr>
<tr>
<td>PGAD</td>
<td>9.2(1.5)</td>
<td>7.4(1.0)</td>
<td>16.5(2.0)</td>
<td>9.1(1.0)</td>
</tr>
</tbody>
</table>

* Significant effect of sub-scale (Forward > Backward), p < .05

3.1.4 Drink Strength Rating Scale

Table 8 reports the mean (SD) drink strength rating scores for the PG and PD-PG subjects when beer was administered. A 2 x 2 ANOVA yielded no significant effects. A single sample t-test confirmed that the overall sample mean rating, 3.26 differed significantly from 0 (p<0.001), supporting the credibility of the manipulation. Thus, on average, subjects reported that their 2 cups of beer contained an equivalent of ~3 standard alcoholic drinks.
3.2 Experimental Effects

As noted earlier, the groups here are part of a larger study, whose statistical power and sample N are based on 4 rather than 2 groups. Therefore, effects of p ≤ .10 involving Session (i.e., a manipulation effect) are presented in the Results. Complete results for each analysis are available in Appendix A.

3.2.1 Self-Report Data

3.2.1.1 M-VAS Desire to Gamble

An ANOVA was conducted on the MVAS rating of subjective desire to gamble. The within subject factors were Session (2 levels) and Time (3 levels; baseline, post-stress, post-drink), using the question “right now, I desire or feel like going gambling” as the dependent variable. The between subject factors were Group, Stress Sequence and Drink Sequence. A significant interaction of Session x Time x Stress Sequence was observed, F (1, 16) = 3.53, p = .041). Inspection of the mean scores indicated that this interaction reflected a significant decline in Desire to Gamble score from baseline to post-stress under the Stress alone condition in both PG and PGAD subjects. Aggregated over groups, mean (SD) scores decreased from 32.39 (17.75) at baseline to 23.14 (19.56) post-noise task when stress (alone) was delivered on day 1; and from 42.00 (30.33) at baseline to 36.00 (33.62) post-noise when stress (alone) was delivered on day 2. In contrast, the mean (SD) scores were 22.86 (22.52) for baseline and 25.71 (27.75) post-
noise in the absence of stress on day 1; and 56.00 (13.87) for baseline and 54.00 (13.87) post-noise in the absence of stress on day 2. Thus, subjects who received the uncontrollable noise manipulation alone (stress) report a decrease in desire to gamble.

Figure 1, panels A-D, illustrates the mean desire to gamble scores across all conditions split by test session.

A simple effects analysis comparing desire to gamble scores from baseline to post-stress and post-stress to post-drink was conducted. As seen in panels A and B, in the PG subjects, a significant simple effect was found from baseline to post-uncontrollable noise (stress) task in the Stress and the Stress + Beer condition. There was a significant reduction in desire to gamble when these subjects were exposed to the stressful noise task, $t(32) = 6.26; 3.80 p<.001$, from baseline to post-stress. There was no other consistent effect in PG subjects on desire to gamble when stress was absent.

For the PGAD subjects, panels C and D highlight the significant simple effect found from baseline to post-uncontrollable noise (stress) task in the Beer and Beer + Stress condition. There was a significant reduction in desire to gamble scores from baseline to post-stress when these participants had anticipated they would be receiving the alcohol $t(32) = 2.14; 2.37 p< .05$.

The results suggest that the introduction of a stressor in PG subjects has an inhibitory effect on their desire to gamble. In contrast, in PGAD subjects, inhibition of desire to gamble is influenced more heavily by the anticipation of the alcohol versus exposure to the stressor.
Figure 1 Mean (SEM) visual analog scale ratings of Desire for gambling (0-100; Not at all – Extreme) after baseline, after the noise task, and after drink administration across the four test conditions split by test session: (A) PG group, Session 1; (B) PG group, Session 2; (C) PGAD group, Session 1; (D) PGAD group, Session 2. *P < .001, two-tailed for simple effect of baseline vs. post-stress for each session and condition. #P < .05, two-tailed for simple effect of baseline vs. post-stress for each session and condition.
3.2.1.2 Desire for Alcohol

A 2 x 2 x 2 x 2(Session) x 3(Time: baseline, post-stress, post-drink) ANOVA was conducted on the M-VAS rating of subjective Desire for Alcohol. A main effect of Session was found F(1, 16) = 4.95, p = .04. Both PG and PGAD subjects reported higher ratings of their subjective desire for alcohol on session 2 versus session 1. No other significant interactions were found on the M-VAS rating in their desire for alcohol (p > .10). Figure 2, A-D, shows the mean (SD) scores for desire for alcohol in the PG subjects (panels A and B) and the PGAD subjects (panels C and D) across the four test conditions split by test session. Inspection of the Figure, in contrast to the desire to gamble MVAS questionnaire, indicates there is a consistent but non-significant trend (p> .10) of an increase in desire for alcohol after the noise task in both subject groups regardless of whether the task was controllable (no stress) or uncontrollable (stress).
Figure 2 Mean (SEM) visual analog scale ratings of Desire for Alcohol (0-100; Not at all – Extreme) after baseline, after the noise task, and after drink administration across the four test conditions split by test session: (A) PG group, Session 1; (B) PG group, Session 2; (C) PGAD group, Session 1; (D) PGAD group, Session 2. * represents a non-significant trend of an increase in mean scores post-noise task shown in both the PG and PGAD subjects.
3.2.1.3 State Anger Scale

A 2 x 2 x 2 x 2 x 3 ANOVA was conducted on SAS scores for baseline, post-stress and post-drink 2. Groups had similar scores at baseline. Mean (SD) SAS scores are reported in Figure 3, panels A-D, at baseline, post-stress and post-drink for the two groups across conditions. The analysis yielded a significant interaction of Session x Stress Sequence x Drink Sequence, F (1, 16) = 6.01, p = .026.

Simple effects analysis was then conducted to compare baseline to post-stress scores and post-stress scores to post-drink scores for both groups. Inspection of Figure 3 illustrates that for both the PG group, panels A and B, [t(16)=2.5(p<.05) post-noise task to post-drink, test session 1; t(16)=10(p<.001) post-noise task to post-drink, test session 2] and the PGAD group, panels C and D, [t(16)=4.9, 23.3(p<.001) post-stress task to post-drink, test session 1 and 2], placebo beer alone caused a significant and consistent reduction in the subject’s mean (SD) SAS score from post-stress to post-drink administration. Further inspection of panels A and B indicates that for the PG subjects in the beer + stress condition, receiving the placebo alcohol after being exposed to the uncontrollable noise manipulation, significantly reduced their mean (SD) SAS scores post-drink administration [t(16)=6.65,(p<.001)]. Further inspection of panels C and D indicates that for the PGAD subjects, the decline in SAS after drinking was more pronounced on the soft drink session versus the beer session. The result would indicate that the placebo reduced the decline in post-noise anger over the course of the session (kept them angry) relative to soft-drink.

In sum, placebo alcohol reliably decreased self-reported anger in both test groups and may have a stronger effect in PGs than PD-PGs.
Problem Gamblers - SESSION 1

Problem Gamblers - SESSION 2
Figure 3 Mean (SEM) SAS score after baseline, after noise task, and after drink administration across the four test conditions, split by test session. (A) PG group, Session 1; (B) PG group, Session 2; (C) PGAD group, Session 1; (D) PGAD group, Session 2. * Significant within subject change (p < .001) from preceding time point in a given session.
3.2.2 Cognitive Tasks

3.2.2.1 Modified Stroop Task

The Stroop task occurred immediately after the noise task and before administration of the first drink. However, as noted earlier, subjects are informed at the start of each session whether they would receive beer or soft drink that session. Thus, effects of the beer manipulation for the Stroop task represent the anticipation of receiving the alcohol (combined or not combined with stress).

In line with standard procedure in reaction time tasks (Stanovich and West 1983) individual trial scores of less than 200ms (too fast to reflect a decision) or more than 3 SD above the sample mean (too slow – lapse of attention) were excluded from statistical analyses. One subject was also removed from analysis due to a computer malfunction.

A 2 x 2 x 2 x 2 (session) x 6 (word-type: depression, positive affect, anger-aggression, alcohol, gambling, and neural categorized [musical instruments]) ANOVA was conducted for the RT scores of Stroop task. The analysis yielded an interaction that approached significance at the highest order between Session x Word Type x Group x Stress Sequence x Drink Sequence F(1, 75) = 1.86, p = 0.1. PG subjects had faster mean (SD) RT across test sessions to all critical (Gambling, Alcohol and Neutral) word types in comparison to PGAD subjects: [Gambling: 749 (142) < 849 (158)] [Alcohol: 701 (101) < 895 (168) and Neutral: 734 (120) < 842 (153)].

Two simple effects analyses were performed on the higher order interaction effect from the ANOVA: The first compared Gambling vs. Neutral control words; the second compared Alcohol vs. Neutral words.
Figure 4, panels A-D, display Group PG and Group PGAD mean (SEM) colour-naming RT separated by condition for the Alcohol vs. Gambling vs. Neutral word comparison during session 1 and session 2. Inspection of panel A and B shows that, in PG subjects, the only condition that led to a reliable increase in interference for the gambling vs. neutral word comparison was stress alone, as confirmed by a significant simple effect of Word Type \(t(75)>3.44, p<.001\).

In the PG subjects there were no consistent significant simple effects \((p>.10)\) for the Alcohol vs. Neutral Word Type. However, inspection of panels A and B indicate a non-significant trend that emerged regardless of test condition illustrated by a consistent alcohol RT < neutral RT (i.e., alcohol words less salient than neutral words).

Panels C and D show Group PGAD’s mean colour-naming reaction time (ms) for the Alcohol vs. Gambling vs. Neutral Word Type. Inspection of the Figure indicates that, in the PGAD subjects, no consistent simple effects were observed for Gambling vs. Neutral Word Type. A modest but significant simple effect of Alcohol vs. Neutral Word Type was found, however, in the Beer condition \([t(75), p<.05]\). A marginally significant simple effect for Alcohol vs. Neutral words was also found in the No Treatment condition \([t(75), p<.06]\).

The results suggest that anticipation of alcohol increases the salience of alcohol stimuli in the PGAD subjects. In contrast, the stress manipulation and the anticipation of beer have no effect on the salience of alcohol stimuli in PG subjects.
(A) Problem Gamblers - SESSION 1

Mean Colour-naming Reaction Time (ms)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Alcohol Word Type</th>
<th>Gambling Word Type</th>
<th>Neutral Word Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRESS</td>
<td></td>
<td></td>
<td>900.00</td>
</tr>
<tr>
<td>BEER + STRESS</td>
<td>^</td>
<td>^</td>
<td>800.00</td>
</tr>
<tr>
<td>NO TX</td>
<td>^</td>
<td></td>
<td>700.00</td>
</tr>
<tr>
<td>BEER</td>
<td>**</td>
<td>^</td>
<td>600.00</td>
</tr>
</tbody>
</table>

(B) Problem Gamblers - SESSION 2

Mean Colour-naming Reaction Time (ms)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Alcohol Word Type</th>
<th>Gambling Word Type</th>
<th>Neutral Word Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRESS</td>
<td></td>
<td></td>
<td>900.00</td>
</tr>
<tr>
<td>BEER + STRESS</td>
<td>^</td>
<td>^</td>
<td>800.00</td>
</tr>
<tr>
<td>NO TX</td>
<td>^</td>
<td></td>
<td>700.00</td>
</tr>
<tr>
<td>BEER</td>
<td>**</td>
<td>^</td>
<td>600.00</td>
</tr>
<tr>
<td>Condition</td>
<td>Mean Colour-naming Reaction Time (ms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STRESS</td>
<td>1200.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEER + STRESS</td>
<td>1000.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO TX</td>
<td>800.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEER</td>
<td>600.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4 Mean (SEM) colour-naming response time to Alcohol vs. Gambling vs. Neutral words on the modified Stroop task in the 4 test conditions split by test session. (A) PG group, Session 1; (B) PG group, Session 2; (C) PGAD group, Session 1; (D) PGAD group, Session 2. **P<.001, two-tailed for simple effect of Gambling vs. Neutral word response time; *P<.05, two-tailed for simple effect of Alcohol vs. Neutral word response time; #P<.06, two-tailed for simple effect approaching significance of alcohol vs. Neutral word response time; ^ denotes a non-significant trend of faster SSRT to alcohol vs. neutral words;
3.2.2.2 Shift Task
A 2 x 2 x 2 x 2(session) x 2(Trial type: Non-shift vs. shift) x 2(Word-type: Gambling, Neutral) ANOVA of commission errors on the Shift Task found a main effect of session, F (1, 13) =11.66, p=.005. Inspection of mean (SD) commission errors reveals that both groups made a greater number of commission errors on test session 1 than on test session 2. This reflects a strong learning effect for this task.

A significant interaction was also found between Session x Trial Type x Word Type F (1, 13) =7.70, p=.016, reflecting a increased number of commission shift-errors vs. non-shift errors to Gambling vs. Neutral words during test session 1 but not test session 2 in both groups. An interaction that approached significance was found between Session x Trial Type x Drink Sequence F (1, 13) =3.15, p=0.10. This result indicated that subjects made a greater number of commission errors for shift words vs. non-shift words when they received placebo alcohol vs. soft drink.

Figure 5, panels A and B depicts the Session x Shift/Non-shift Trial Type x Word Type interaction in Group PG. The panels show a significant simple effect of beer alone. For non-shift trials, the difference in mean commission errors to Gambling vs. Neutral words was significantly greater when PG subjects received placebo beer vs. soft drink, both on session 1 and session 2 [t(13), p<.01].

Simple effects analyses found a significant difference in mean commission errors to Neutral versus Gambling words [t(13), p<.001] in PG subjects during test session 1, regardless of condition.

As indicated in Figure 5 panels C and D, simple effects analyses also found significantly more errors on shift trials to Gambling than to Neutral words in PGAD subjects on session 1.
As seen in Panels B and D, on Session 2, when the task was well-learned, the word type effect on shift trials was not evident in either group.

In sum, when the task was unfamiliar, Gambling words led to significantly more commission errors than Neutral words in both PG and PGAD subjects, and this effect was more pronounced on shift trials (i.e., when a new stimulus-response mapping was required). In PG-only subjects, placebo beer also increased commission errors to Gambling words on non-shift trials (i.e., when there was no conflicting stimulus-response rule to be implemented). Neither stress nor beer reliably influenced commission errors in PGAD subjects.
(A)  

Problem Gamblers - SESSION 1  

Mean Number of Commission Errors  

Condition  

Non-Shift Neutral Word designated as no-response  
Non-Shift Gambling Word designated as no-response  
Shift to Neutral Word designated as no-response  
Shift to Gambling Word designated as no-response  

(B)  

Problem Gamblers - SESSION 2  

Mean Number of Commission Errors  

Condition  

Non-Shift Neutral Word designated as no-response  
Non-Shift Gambling Word designated as no-response  
Shift to Neutral Word designated as no-response  
Shift to Gambling Word designated as no-response
Figure 5  Mean (SEM) number of commission errors for non-shift neutral vs. gambling words and shift neutral vs/ gambling words designated as no-response in the 4 test conditions split between test sessions. (A) PG group, Session 1; (B) PG group, Session 2; (C) PGAD group, Session 1; (D) PGAD group, Session 2. *P < .001, two-tailed for simple effect of Neutral vs. Gambling word commission errors. # P < .01, two-tailed for simple effect of non-shift to Neutral vs. Gambling word commission errors.
3.2.2.3 Lexical Stop Signal Task

A 2 x 2 x 2 x 2(session) x 2(response type: go RT, SSRT) x 2(Word-type: Alcohol, Neutral) ANOVA was conducted on RT scores. Subjects whose mean SSRT scores were greater than 400 ms (n=3), were excluded from the analyses. Such scores are more than twice the expected value for the stop task and indicate that the subject was likely not complying with the instructions – e.g., responding regardless of whether or not he heard the tone, which would result in an extremely lenient delay and correspondingly large difference scores (go RT – stop signal delay).

For go RT, the analysis yielded a main effect of Word Type, $F(1, 12) = 18.08$, $p = .001$. Simple effects analyses revealed that subjects had a significantly slower mean (SD) go RT to Alcohol, 879 (218) ms, than Neutral words, 850 (212) ms, across sessions, $t(12) > 4.32$, $p < .001$.

Figure 6 shows the scores for the critical variable, SSRT, by Word Type on both sessions. As with go RT, subjects had a slower SSRT to Alcohol vs. Neutral words on session 1, $t(12) = 4.78$, $p < .001$ and session 2 $t(12) = 4.41$, $p < .001$. These results show that Word Type has a consistent effect on go RT and SSRT, regardless of experimental condition, and that alcohol stimuli impair both these indices. There were no other significant interactions for go RT.

Figure 7 shows SSRT to Alcohol and Neutral words for each group, session and condition. The analysis yielded a significant interaction of Session x Drink Sequence, $F(1, 12) = 8.81$, $p = .01$, implying that on days when subjects received placebo alcohol their SSRT was slower for both Alcohol and Neutral words. A significant main effect of
Word Type was also observed, F (1, 12) = 6.60, p=.03. Regardless of condition, both PG and PGAD subjects had slower SSRT to alcohol versus neutral words.

In the PG group (see Figure 7, panel A and B) there was a simple effect of Word Type that approached significance in the combined beer + stress manipulation across both test sessions [t(12) = 1.92, p=.09]. In PG subjects the simple effect of Word Type was only reliably significant in the No-Treatment condition [t(12) = 5.67 p<.001].

Simple effects analysis was conducted on the comorbid PGAD subjects. Figure 7, panels C and D illustrate the significant simple effect observed for these subjects across test conditions. Inspection of the graph reveals a significant effect for every condition excluding stress alone. The beer alone [t(12) = 3.45,  p<.01], combined beer + stress [t(12) = 6.38, p<.001], and no treatment condition [t(12) = 5.72  p<.001] all produced significant effects with respect to their SSRT. On the LSST PGAD subjects were generally less proficient at inhibiting their response to alcohol words vs. neutral words.

---

Figure 6 Mean (SEM) stop signal reaction time for alcohol and neutral words across each session on the Lexical Stop Signal task. *P < .001, two-tailed for simple effect of word type for each session.
Figure 7 Mean (SEM) stop signal reaction time to alcohol and neutral words on the Lexical Stop Signal Task in the 4 test conditions, split between test sessions: (A) PG group, Session 1; (B) PG group, Session 2; (C) PGAD group, Session 1; (D) PGAD group, Session 2. * P < .001, two-tailed for simple effect of word type for each session under each condition. #P < .01, two-tailed for simple effect of word type for each session under each condition.
3.2.2.4 Conventional Stop Signal Task

A 2 x 2 x 2 x 2(session) x 2(time: pre-drink, post-drink) ANOVA was conducted for both go RT and SSRT scores. Subjects were excluded from analysis who had SSRT scores greater than 400 ms (n=3) as this indicates they did not follow instructions.

For go RT, a marginally significant Session x Stress Sequence x Drink Sequence interaction emerged, F (1, 13) = 2.95, p=.10. Simple effects analyses of go RT indicated that on test sessions when subjects received both beer and stress, their mean go RT was faster than when they received neither beer nor stress t(15)>2.13, p < .05.

For SSRT, a marginally significant interaction among all factors was observed, F (1, 13) = 2.88, p=0.1.

For the PG subjects no significant simple effects were found. Inspection of the mean (SD) SSRT scores in Table 9 confirms the inconsistency in reaction time. PGs average stop signal RT before vs. after drink did not differ in a consistent way in any of test conditions.

Figure 8, panels A and B, display mean SSRT for the PGAD subjects across the four test conditions and split by test session. A significant simple effect was observed during the beer alone condition [t(13) = 1.92, p<0.1 beer in test session #1; t(13) = 6.37, p< .001 beer in test session #2]. In comparison to pre-drink administration at post-drink administration, PGAD subjects had a significantly faster SSRT.

Results indicate that in subjects with no drinking pathology, alcohol administration and/or stress together or alone does not seem to differentially affect their inhibitory processes; in contrast, cues for alcohol seem to improve inhibitory response in
comorbid subjects. This may be related to increased cortical arousal or a conditioned drug-opposite (i.e. alcohol-opposite) effect in the presence of a placebo.

Table 9 Mean (SD) SSRT for the conventional stop signal task in problem gamblers (PG; n=12).

<table>
<thead>
<tr>
<th>Group</th>
<th>Condition</th>
<th>Test Session 1</th>
<th>Test Session 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-Drink</td>
<td>Post-Drink</td>
</tr>
<tr>
<td>PG</td>
<td>Stress</td>
<td>210 (88)</td>
<td>241 (75)</td>
</tr>
<tr>
<td></td>
<td>Beer + Stress</td>
<td>274 (163)</td>
<td>206 (138)</td>
</tr>
<tr>
<td></td>
<td>No Treatment</td>
<td>168 (5)</td>
<td>162 (5)</td>
</tr>
<tr>
<td></td>
<td>Beer</td>
<td>256 (158)</td>
<td>263 (134)</td>
</tr>
</tbody>
</table>
Figure 8 Mean (SEM) stop signal reaction time pre-drink vs. post-drink on the conventional stop signal task in the 4 test conditions, split by test session: (A) PGAD group, Session 1; (B) PGAD group, Session 2.

*P<.05, two-tailed for simple effect of beer alone under each condition.
3.2.3 Physiological Measures

3.2.3.1 Systolic Blood Pressure

Baseline systolic blood pressure (SBP) scores for Groups PG and PGAD differed significantly across sessions and conditions. Therefore, baseline SBP was entered as a covariate in a 2 x 2 x 2 x 2 x 6 (Time of Test) ANCOVA. A significant Session x Time x Group x Drink Sequence interaction was found, $F(1, 20) = 2.77$, $p=.023$.

Figure 9, Panels A-D shows the mean SBP measurements across the different time points in Groups PG and PGAD. In the PG subjects (panels A & B) a significant simple effect of beer was found across test sessions, $t(80) > 3.41$, $p<.001$. Relative to soft drink, beer was associated with maximum SBP regardless of whether it was given on session 1 or session 2. In these subjects mean SBP peaked post-drink #2 after receiving the beer manipulation.

In the PGAD subjects (panel C and D) a significant simple effect of beer was found across test sessions [test session 1 ($t(80)>3.41$, $p<.001$); test session 2 ($t(80)>1.99$, $p<.05$)]. The subjects’ mean SBP peaked post-drink #2 after receiving the beer manipulation.

These results suggest that the alcohol cue manipulation alone acted to temporarily increase sympatho-adrenal activity in problem gamblers regardless of whether they had an alcohol use disorder.
Problem Gamblers - BEER SESSION 1

(A)

Problem Gamblers - BEER SESSION 2

(B)
Figure 9 Mean systolic blood pressure across test sessions. (A) PG group, beer on session 1; (B) PG group, beer on session 2; (C) PGAD group, beer on session 1; (D) PGAD group, beer on session 2. *P<.05, two-tailed for simple effect of SBP scores after drink 2 vs. after drink 1 and post LSST. LSST, lexical stop signal task; SST, conventional stop signal task.
3.2.3.2 Diastolic Blood Pressure

A 2 x 2 x 2 x 2 x 7 (Time of Test) ANOVA yielded a significant Session x Time x Stress Sequence x Drink Sequence interaction, $F(1, 20) = 2.71$, $p = .018$. Figure 10, panel A and B shows both groups’ diastolic blood pressure (DBP) across the different time points during each test session. On days when subjects received only the placebo alcohol manipulation and no stress, DBP peaked after both drinks had been consumed. Simple effects analysis revealed a significant effect of beer alone in PG and PGAD subjects’ mean DBP readings. DBP, post-drink #2, differed significantly from the previous as well as the subsequent DBP reading, $t(96) > 3.402$, $p < .001$. These results suggest that the alcohol cue manipulation alone acted to temporarily increase sympato-adrenal activity in both PG and PGAD subjects.
Figure 10 Mean Diastolic blood pressure during the two beer alone test conditions. (A) Subjects who received placebo beer on test session 1 in the absence of stress; (B) Subjects who received placebo beer on test session 2 in the absence of stress. *P<.001, two-tailed for simple effect of DBP after drink 2 vs. after drink 1 and post LSST. LSST, lexical stop signal task; cSST, conventional stop signal task.
3.2.3.3 Heart Rate

There were no significant differences between subjects at baseline. A 2 x 2 x 2 x 2 x 7 (Time of Test) ANOVA was conducted on the subjects’ heart rate (HR) over the course of each session, including pre-test baseline. A significant interaction was found between session x time, F (1, 20) = 2.22, p=.048; reflecting a change in mean HR (SD) across the different time points during each session. A significant interaction was also found between Session x Time x Drink Sequence, F(1, 20)  = 5.12, p<.001; Implying that the administration of placebo alcohol vs. soft drink influenced the subjects change in HR. Figure 11, panels A-D, illustrate the change in subjects HR over the different time points during test session 1 and test session 2 as a function of drink sequence. Inspection of Figure 11 indicates a significant increase in HR post-drink #2 when subjects receive the alcohol manipulation versus when they receive soft-drink.

A simple effects analysis revealed a significant effect post-drink #2 administration for the PG group [t(96) p < .001]. Panel A and B illustrates the peak in subjects’ HR after receiving the beer manipulation. For the PGAD group, there were no significant simple effects; however, as seen in Panel C and D a similar trend emerged post-drink #2 administration during test session 1 and 2. Subjects’ HR increased after receiving the placebo alcohol.
(A) Problem Gamblers - BEER SESSION 1

(B) Problem Gamblers - BEER SESSION 2
Figure 11 Mean Heart Rate (HR) across different time points split by drink sequence. (A) PG group, beer session 1; (B) PG group, beer session 2; (C) PGAD group, beer session 1; (D) PGAD group, beer session 2. *P<.001, two-tailed for simple effect of HR scores after drink 2 vs. post stroop. LSST, lexical stop signal task; SST, conventional stop signal task.
4. DISCUSSION

This study investigated the effects of uncontrollable noise stress and alcohol cues, in the form of placebo beer, on cognitive activation and inhibition in subjects with and without pathological gambling (PG) and an alcohol use disorder (AD). The objective was to assess the interaction among several factors shown to moderate the relapse process in animals to validate an experimental model of these factors for human experimental testing. Three key interactions were considered: (a) the cognitive dimensions of salience (approach) and inhibitory control (avoidance); (b) the instigating factors of stress and exposure to addiction-related cues; and (c) the clinical dimensions of PG and AD.

We hypothesized that exposure to the combination of stress and alcohol cues would have a greater effect on motivation for gambling and alcohol, than either of these instigating factors alone. Moreover, we hypothesized that the influence of stress and alcohol cues on salience and inhibitory control would be greater in comorbid gamblers with an alcohol use disorder (PGAD) than in non-comorbid problem gamblers (PG). These hypotheses were tested with three sets of outcome measures: Self-report, computer-based cognitive tasks, and measures of cardiovascular response.

The most important result for self-report was: stress alone in PG subjects and stress in addition to the placebo beer in the PGAD subjects caused a significant reduction in their desire to gamble. The most important result for the cognitive tasks was: stimuli with incentive value divert attention (i.e., are salient) selectively based on their clinical relevance to the subject and the nature of the instigating factor – stress (expected negative reinforcement) vs. anticipation of alcohol (expected positive reinforcement). The most important result for cardiovascular response was: placebo beer administration increased
SBP, DBP and HR in both PG and PGAD subjects and may have evoked a conditioned drug-opposite effect on physiological reactivity. These results indicate that salient stimuli diverts cognitive resources (attention) required to activate or inhibit overt responses. This distracting effect, rather than simply promoting approach (a presumed consequence of salience; Robinson and Berridge, 2003) impaired both approach-related and avoidance-related responses. The details of these effects and how they relate to the secondary findings are provided below.

4.1 Self-Report

4.1.1 Desire to Gamble:

Stress alone significantly influenced Desire to Gamble. In contrast to our original hypothesis, stress caused a consistent and significant decrease in subjective motivation to gamble, which was evident in the PG group and marginally so in the PGAD group, regardless of whether stress occurred on session 1 or 2. The placebo beer manipulation had no effect on desire to gamble in the PG group nor did it interact with the stress manipulation. For the PGAD subjects, the anticipation of receiving the placebo beer also caused a significant decrease in their subjective motivation to gamble, on both session 1 and session 2.

4.1.2 Desire for Alcohol:

Alcohol dependent individuals have often cited drinking as a means to cope with stress (Li and Sinha 2008). Furthermore, alcohol consumption has been positively associated with stress level (Sinha 2001). Interestingly, analysis of the subjective questionnaire for Desire for Alcohol brought about no significant effects; nonetheless, in
contrast to our findings from Desire to Gamble, a positive trend was found across PG and PGAD subjects showing an increase in desire to drink post-noise task regardless of whether the noise was controllable or uncontrollable. This trend marginally conforms with our original hypothesis that alcohol craving should increase as a result of cue exposure; however, unlike the results from Desire to Gamble, the effect was not more pronounced in the PGAD versus the PG group. Furthermore, there have been inconsistent reports of the effect of stress on craving in the literature. Stress has been found to increase, decrease or have no influence on alcohol craving and consumption depending on stress alcohol intake levels, timing and type of stressor (Fox, Bergquist et al. 2007). It appears from these data that the uncontrollable noise manipulation in this study may not have been sufficiently stressful or the right type of stress to produce a significant conscious change in motivation for alcohol in these subjects. It may also be a matter of statistical power, such that the trend for increased Desire for Alcohol following stress in PG and PGAD subjects becomes significant when data from the full 4-group design (AD and controls) are included in the analysis.

The placebo beer manipulation also did not affect subjects’ desire for alcohol post-drink, which is in contrast to recent research showing alcohol cues increase craving in alcohol-dependent individuals (Reid, Flammino et al. 2006). Since the alcohol cue manipulation is divided into two parts: the anticipatory phase (i.e. subjects are told they will be receiving alcohol during the test session, and the drinking phase (i.e. subjects receive their placebo drink) it’s possible that the separate elements of the manipulation differed in their influence on related cognitive processes in comparison to actual alcohol. These results suggest that the placebo beer may not have been a sufficient replacement
for actual alcohol for these subjects. Alternatively this may indicate that gambling rather than alcohol is the predominant addictive reinforcer for subjects with PG even when they also exhibit symptoms of AD.

4.1.3 State Anger Scale:

The State Anger Scale was used to assess whether or not the uncontrollable noise-task was effective at increasing negative affect in these subjects. Exposure to the uncontrollable noise manipulation should generate a great deal of frustration in our subjects. Frustration is widely believed to lead to aggression (D. Buss). Furthermore, men may be especially unwilling to admit helplessness but may be more willing to acknowledge anger.

Changes in anger levels as a function of stress and cue exposure were evident in both groups. Consumption of placebo beer alone decreased anger levels in comorbid subjects regardless of stress sequence, post-drink. A reduction in anger following placebo beer is in line with previous findings on the effects of actual alcohol (Li and Sinha 2008). Congruent with this data, problem gamblers displayed a decrease in anger levels when consuming beer alone as well and when they had been exposed to the stressful noise task. These findings suggest that the belief that one has consumed alcohol may produce an actual anti-stress effect in PG and PGAD subjects. Thus, the anti-stress effects of drinking in these subjects could result from expected anti-stress properties to alcohol versus, or in addition to, alcohol’s actual pharmacological stress-dampening effects. More research must be conducted to confirm this result.

The combined results of the self-report measures suggest a comparable effect of stress in both groups. One finding that was interesting was that anticipation of beer was
more strongly linked with decreased Desire to Gamble in PGAD subjects, whereas stress was more strongly linked with this decrease in PG-only subjects. This does not necessarily imply a progression so much as an associative linkage – albeit an inhibitory one – between alcohol-related stimuli and gambling in the co-morbid subjects.

The most important, and unexpected, finding was that both groups consciously reported a decrease in desire to gamble following stress exposure. Thus, in male problem gamblers, with and without an alcohol use disorder, experiencing failure on a task believed to measure problem solving skill appears to reduce the incentive value of gambling.

4.2 Cognitive Tasks

The PG and PGAD subjects performed similarly on the Digit Span task. This indicates comparable basic short-term and working memory, which reflects availability of cognitive resources and the ability to voluntarily apply them. Overall, performance was similar to norms for the general population, suggesting that these subjects were not cognitively impaired in a general sense. The lack of group differences also helps to ensure that any group differences on the other cognitive tasks are not readily attributed to deficits in general cognitive function.

4.2.1 Modified Stroop Task

The first experimental task administered to the subjects was the modified Stroop task. The task was performed immediately following the stress manipulation (controllable vs. uncontrollable noise) and before the first drink administration (i.e.
Attentional bias to Gambling stimuli was seen in the PG group, in line with past research (Boyer & Dickerson 2003; McCusker and Gettings, 1997), but was absent in the PGAD group. In the former group, attentional bias to Gambling versus Neutral words was significantly increased by exposure to stress. When stress was combined with the anticipation of alcohol, Stroop interference to Gambling words decreased relative to stress alone. Thus, involuntary attention to Gambling stimuli (salience) is increased by exposure to stress in male PG subjects with no alcohol use disorder. The mitigating effect of anticipating alcohol on salience of Gambling words is consistent with the diversion of attention to alternative reinforcers when these reinforcers are available.

Attentional bias to Alcohol words was evident in the PGAD group (Alcohol RT > Neutral RT) but was absent in the PG group (Alcohol RT< Neutral RT). This general bias in PGAD subjects was evident across sessions and conditions, and was significantly intensified by anticipation of beer, regardless of which session this manipulation was applied. These results suggest that the incentive salience of alcohol stimuli may be more strongly evident when anticipating being able to drink alcohol, but only in subjects with an alcohol use disorder.

Incentive salience toward Gambling stimuli on the Stroop was more strongly evident after exposure to stress. However, contrary to this finding, problem gamblers reported a consistent decrease in their self-reported desire to gamble after the noise task, regardless of whether it was controllable or uncontrollable. Because the effects of the Stroop occur involuntarily whereas self-report measures are voluntary and therefore
susceptible to experimental demand, the Stroop results suggest that problem gamblers may be unaware of their involuntary reactivity to Gambling stimuli. Alternatively they may have modified their self-report to deny (to themselves or the experimenters) that the stressor made them want to gamble. Lastly, the two responses could be functionally distinct – that is, they reflect independent processes. Which of these interpretations is correct is a matter for future investigation.

The findings for the Stroop task (i.e. decrease in interference to Gambling vs. increase in interference to Alcohol) indicate that stimuli with incentive value divert attention (i.e., are salient) selectively based on their clinical relevance to the subject (PG vs. PGAD) and the nature of the instigating factor – stress (expected negative reinforcement) vs. anticipation of alcohol (expected positive reinforcement).

4.2.2 Gambling Shift Task (Go-No/Go Task)

The effects of addictive stimuli, other than alcohol, on inhibitory control were assessed using a Gambling Shift task. Inhibitory control varied as a function of gambling versus neutral stimuli. Consistent with previous research (Kertzman et al. 2006), both the PG and PGAD subjects made significantly more commission errors to Gambling words, regardless of treatment condition, when the response rule (Gambling = Go vs. Gambling = No-Go) changed (i.e., shift trials).

The number of commission errors is a direct measure of bias to commit rather than withhold a response. The subject’s impaired ability to switch responses (go/no-go) to a given class of targets is consistent with other studies showing poor performance on tasks involving executive functions in PG subjects (Petry 2001).
An inherent inhibitory deficit to Gambling stimuli is apparent in both populations; however, this deficit manifested itself only during test session 1. This may reflect an overriding effect of practice – e.g., implementing a strategy – on inhibitory responding. For Group PG, an additional inhibitory deficit was found on both test sessions when subjects received beer rather than soft-drink. The disinhibiting effect of beer was evidenced by an increase in commission errors to Gambling words on the non-shift trials. That is, when the response-rule was consistent from trial to trial, placebo beer led to an increase in key press responses to Gambling words when subjects should have withheld their responses. This effect was seen on both test sessions despite the task’s susceptibility to practice effects, strengthening the claim that PG subjects are heavily influenced by context-specific cues.

4.2.3 Lexical Stop Signal Task

A novel experimental task, the LSST, was utilized in this study to assess the interaction between incentive salience and inhibitory control to Alcohol-related stimuli as measured by overt behaviour (rather than covert attentional responses, per the Stroop). Increased salience (slower go RT) to Alcohol words versus Neutral words was observed in both the PG and the PGAD group, regardless of test condition.

An inherent attentional bias to Alcohol words appears to be present in both study groups. Since this inherent bias was not seen across conditions in the Stroop task, it is likely that the LSST assessed separate attentional process. However, since the Stroop task was administered before the placebo beer manipulation and the LSST given after, it cannot be concluded whether the different results were a consequence of diverse
processes or the influence of other instigating factors. Previous research has documented this lack of relationship between measures of attentional bias. Mogg and Bradley, 2002, concluded that attentional bias in smokers based on a modified Stroop task and a visual probe task were not significantly inter-correlated. Therefore, our study follows previous research that suggests the attentional system is not unitary and must involve a series of distinct cognitive processes (Posner and Peterson 1990; Mogg and Bradley 2002).

Deficits in inhibitory control (measured by SSRT) to Alcohol words on the LSST, as a function of study manipulations were observed in both PG and PGAD subjects. The problem gamblers showed a significant deficit in control in the combined stress plus placebo beer condition as well as in the absence of any manipulation. Due to the beer manipulation, subjects were aware that the study was related to drinking. Therefore, it is possible that the effects of the placebo beer on the salience of Alcohol stimuli in the problem gambler subjects may be due to the experimental context of the study.

The comorbid drinker-gamblers showed a significant deficit in inhibitory control in the combined stress plus placebo beer manipulation, the placebo beer alone manipulation as well as in the no treatment condition. Since the control deficit in PGAD subjects was present during no treatment manipulation, results suggest a general deficit in inhibitory control to Alcohol words in these subjects.

The significant overall main effect of Word Type observed for all subjects, regardless of test condition is noteworthy. This result suggests that both inhibitory control (i.e. SSRT) and activation (go RT) processes were preferentially impaired by Alcohol words. Since the pattern of responses was comparable for SSRT and go RT (values on both indices increased, denoting slowing of both stop and go processes), it
supports the suggestion that salience and inhibitory control are functionally related when the go stimuli are motivationally relevant. This contrasts with the conventional SST where the go and stop processes have been explicitly posited to be independent (Boucher L, et al. 2007 Psychological Review). The present findings suggest that mental resources (attention) required to activate or inhibit overt responses were diverted by the salient stimuli. The distracting effect, rather than simply promoting approach (a presumed consequence of salience; Robinson and Berridge, 2003) impaired both approach-related and avoidance-related responses. This more general impairment could contribute to the cognitive debilitating effects of cue exposure or conditioned reactions on ongoing complex tasks (apart from inhibition) in abstinent addicted individuals.

The possibility that attention mediated Word Type-related effects on the LSST is supported by evidence citing the importance of attention in withholding responses to a stop signal on the c-SST. Electrophysiological studies reveal increased amplitude of P300 (indicating perceived importance of a stimulus) on stop-signal trials where the response is successfully inhibited versus trials when the response is (erroneously) committed (Donchin and Coles 1988; De Jong, Coles et al. 1990). Thus, an overall decrease in successful inhibition on stop-signal trials could explain how distraction by salient Alcohol words could translate into longer SSRT in the present study.

4.2.2 Conventional Stop Signal Task

The conventional SST measures generic inhibitory control and, in particular, response cancellation to motivationally neutral stimuli (letters). This task is sensitive to trait deficits in inhibition, like those found in children with ADHD, and state factors like
stimulant drugs (which improve performance in those with low baseline proficiency); and alcohol (which impairs performance in general; Mulvihill et al 1997). Inhibitory control deficits on this task were absent in PG subjects under exposure to stress and alcohol cues. In contrast, placebo beer alone did significantly affect inhibition in the PGAD subjects. Paradoxically, the effect of the placebo beer in these subjects was to decrease SSRT indicating better inhibition post versus pre-drink. Thus, it appears that placebo alcohol reversed the baseline inhibitory deficit in PGAD subjects. The improvement in inhibitory control from the effects of the placebo may be due to the comorbid subjects trying to compensate for the effects of receiving a drink they believed contained alcohol (Marczinski and Fillmore 2005).

4.3 Physiological Measures

For both groups, changes in physiological function were only observed following alcohol cue exposure (Note – there was no corresponding in vivo exposure to gambling cues – e.g., playing a game of blackjack – so the relative physiological activating effects of gambling in these sub-groups remain unknown). Administration of the placebo beer caused a brief and significant peak in systolic blood pressure in both groups. Diastolic blood pressure also increased post-placebo beer administration in both groups. Previous research has shown a similar increase in DBP in the presence of alcohol related cues in both dependent and non-dependent drinkers (Cox, Yeates et al. 1999; Reid, Flammino et al. 2006; Fox, Bergquist et al. 2007). Other work has shown increased blood pressure in PG subjects compared to controls during a game of blackjack (Myers et al., 2004). Contrary to these sympathomimetic effects, research has documented that acute alcohol
intoxication usually results in a decrease in blood pressure (Bilbao et al. 2008). In-line with the blood pressure findings, the placebo beer manipulation also significantly increased heart rate (HR) post-drink administration. Collectively, these results suggest that placebo beer may have evoked a conditioned drug-opposite effect on physiological reactivity (Seigel et al. 2000 Exp Clin Psychopharm 8(3) 276-93).

Stress exposure did not affect physiological responses in our study, which is in opposition to previously documented research (Fox, Bergquist et al. 2007). This may reflect a ceiling effect on arousal by the sensory cues (i.e., loud noise was present in both the no-stress and active-stress conditions; the primary difference between them was its controllability). In sum, it seems that exposure to alcohol cues has a greater impact on cardiovascular reactivity in PG and PGAD subjects than uncontrollable noise stress.

4.4 General Discussion

The experimental manipulations in our study – stress and placebo beer – had differential effects on self-reported motivation, cognitive activation and inhibitory control. In some cases, these effects were evident in both PG-only subjects and in co-morbid PGAD subjects; in other cases they varied with AD status.

Contrary to expectations, stress alone decreased self-reported desire to gamble in PG subjects with or without AD. In PG-only subjects, this decrease was associated with a (discordant) increase in involuntary attention to Gambling words (salience) on the Stroop task; and in both groups with greater numbers of commission errors to Gambling words (disinhibition; cognitive inflexibility) on the shift task.
Consumption of placebo beer reduced state anger in both groups. In PGAD subjects, the placebo also led to greater involuntary attention to Alcohol words on the Stroop task; and in both groups, to increased commission errors to Gambling words on the shift task. Placebo beer also increased systolic blood pressure, diastolic blood pressure and heart rate in both groups.

When combined, stress and beer interacted to promote non-perseverative inhibitory errors (on non-shift trials) to Gambling words on the shift task; longer SSRT (impaired response cancellation) to Alcohol words on the LSST, and slowed subjects’ go RT to motivationally neutral stimuli on the c-SST. In PG-only subjects, stress plus (anticipation of) beer coincided with decreased Stroop interference to Gambling words relative to stress alone.

Collectively, this complex set of effects indicates that both approach (salience) and avoidance (inhibition) processes seem to be defective in addicted individuals.

Results from the modified Stroop task indicate how stress might contribute to relapse in PG subjects. PG subjects show greater Stroop interference to Gambling words following stress despite reporting a decrease in desire to gamble. This suggests that stress may be playing a subconscious instigating role in their problem gambling behaviour. The null effects of stress alone on interference to Gambling words in the PGAD subjects may be the result of these subjects’ concurrent Alcohol Use Disorder. Specifically, PGAD subjects use alcohol as a coping mechanism when under exposure to a stressful event. Support for this claim comes from the significant differences that were found between the PG and PGAD groups on the coping subscale of the Drinking Motives Questionnaire. Thus, alcohol rather than gambling, may serve as a means to cope with daily life events.
in these comorbid subjects. Interestingly, State Anger Scale scores in comorbid subjects were also most impacted (i.e. decreased) after consuming placebo beer. Therefore stress exposure alone would not trigger PGAD subjects’ motivation to gamble in the same way it would for the PGs and alcohol exposure would not trigger PG subjects’ motivation to drink in the same way it would for PGAD subjects. The apparent lack of insight into this effect at the level of self-report suggests that advising PG subjects of their sub-conscious vulnerability to stress may be an important feature to incorporate into relapse prevention treatment.

Repeated drug use is associated with multiple neuroadaptations in pathways that regulate positive and negative reinforcement aspects (Koob and Le Moal 1997). Greater sensitivity to the reinforcing properties of drugs leading to compulsive drug use, and an increased susceptibility to relapse is a consequence of these changes in brain reward circuitry. The diverse effects of alcohol cues and stress in different pathological subject groups could be the result of the “mediating” role of cognition (i.e. attention and disinhibition) on response to rewarding or aversive stimuli. Results from our study indicate that stress exposure alone has a greater overall influence on these cognitive mediating processes in PG subjects, whereas alcohol cues with or without stress have a greater overall influence on PGAD subjects.

The effects from the interaction seen between alcohol cues and stress exposure in PGAD subjects are consistent with previous animal and human research. Brief exposure to foot shock in rats enhances drug seeking behaviour brought on by drug-related cues following a period of extinction in rats (Liu and Weiss 2002). In humans, research has shown that stress brought on before or during testing has induced alcohol craving
(Rubonis et al. 1994; Stasiewicz et al. 1997; Reid et al. 2006). A recent study by Noel et al. 2007 using an Alcohol word version of the Shift task found that detoxified alcoholics in comparison to controls, made significantly more commission errors when the stimuli were Alcohol versus Neutral words. Further support for the importance of alcohol cues on cognitive impulsivity in PGAD subjects is evident with the increase in salience (go RT) and disinhibition (SSRT) to Alcohol stimuli on the LSST signifying that the act of drinking alcohol rather than its pharmacological effects may activate an automatic alcohol-related sub-routine or action plan (Tiffany 1990; Noel et al. 2007).

Possible neurochemical trait or state factors may be operating to influence the cognitive processes analyzed in our study. However, the specific role of these factors is speculative as there were no direct measurements of neurochemistry in our experiment.

The effects of stress in PG subjects when alcohol was thought to be available are potentially important to the understanding of the neurochemical systems involved in relapse and to the understanding of the high rate of gambling comorbidity with other addictive disorders. Animal studies have shown that stress-induced relapse can be blocked by enhancing the serotonin system, and that cue-mediated relapse can be blocked by opioid receptor antagonists suggesting there are two separate pathways to relapse (Le, Poulos et al. 1999). Findings from our study suggest that these neural systems may interact to enhance vulnerability to relapse and even further the progression of pathology from one addictive disease to many depending on the combination of triggers in the subjects’ surroundings. From our results, it seems on its own, stress exposure could reduce levels of serotonin in PGs thereby increasing their negative reinforcement.
motivation. Serotonin function is acknowledged as an important mediator of behavioural inhibition and response control.

Research has demonstrated that stress exposure interferes with cognitive performance, particularly in the ability to sustain attention and in the inhibition of prepotent responding (Glass et al. 1969, 1971). Animal research has found that chronically stressed infant monkeys have increased levels of corticotrophin-releasing factor (CRF) in their cerebrospinal fluid. Chronic drug exposure is believed to be associated with an increased CRF and noradrenergic activation (Sinha 2001). Meany and colleagues found long lasting changes in the CRF-HPA stress response in animals exposed to a variety of early life environmental manipulations. These changes included increased sensitivity to stressors and an altered HPA and behavioural stress response throughout development and adult life (Meany et al, 1993). In humans, the combination of CRF and catecholamine release to stress increases dopaminergic neurotransmission in mesolimbic regions, an area responsible for the reinforcing effects of abused substances (Sinha 2001). Therefore, differences in response to stressful events and previous experience with stressful events appear to generate an increased vulnerability to engage in addictive behaviour. This vulnerability may be linked to a hyper-responsivity of the CRF-HPA system to stress (Sinha 2001). Therefore implications for our study would suggest a comparable CRF-HPA system dysfunction in both PG and PGAD groups and further validates the importance of triggering relapse instigators (i.e. stress exposure) when treating addiction.
4.5 Conclusions

Stroop and LSST data emphasize the different effects between stress and alcohol cues in PG subjects versus PGAD subjects. The ability of stress to increase the incentive salience of Gambling but not Alcohol words on the Stroop task in problem gamblers could be interpreted as one reason why PG subjects resort to gambling and then use gambling as a means to cope with negative affect. This could simply just be an automatic reaction as well. Further investigation into PG coping motives is required to know for sure; whereas, in PGAD subjects, the ability of the anticipation of alcohol to increase involuntary attention to Alcohol words and not Gambling words together with these subjects’ reported tendency to drink to cope with negative affect, suggests that stress serves as a conditioned trigger for alcohol whose effects are manifest in an increase in the incentive salience of Alcohol stimuli. In sum, results suggest that activation and inhibition processes under the influence of stress predispose gamblers who consciously think they don’t want to gamble, to actually focus attention specifically on gambling stimuli; whereas both stress and alcohol cues together act in a matter that may predispose problem gamblers and comorbid drinker-gamblers to seek alcohol for the purpose of relieving stress. This result strongly supports the idea of a common addictive pathway between gambling and alcohol that contributes to the high comorbidity between these two disorders.

Implications for relapse prevention can be suggested from our findings. Medications that target both cognitive processes of activation and inhibition are likely the best candidates to decrease the incentive value of alcohol and gambling stimuli, enhance attentional control, and improve inhibitory deficits in PG and PGAD subjects.
4.6 Limitations

The small sample size of our study limits the generalizability of our findings to the greater population. In the future, studies will need to increase the size and variety of the sample to incorporate different subgroups of problem gamblers and comorbid drinker-gamblers that have differing levels of dependence and to investigate possible gender differences.

Furthermore, real world exposure to alcohol cues and stress may vary from the manipulations used in the lab. This difference may influence the effect they have on the cognitive processes observed in the experiment. Other relapse triggers (e.g., an actual dose of alcohol) may produce different results in this experimental model as well.

4.7 Future Directions

Alcohol cues and exposure to stress are two important factors that can trigger relapse in addicted individuals. PG and PGAD subjects are likely to be exposed to these as well as many other instigators concurrently. Our study findings provide insight into their relative influence on different cognitive pathways responsible for the development and/or progression of one disorder, in this case problem gambling, to another disorder (i.e. problem gambling with alcohol use disorder). Developing effective therapies against the problem of relapse would benefit from a new approach that could study the effects of both the independent and interactive consequences of relapse triggers since our study findings argue that these factors interact and exert differential effects on various aspects of cognition depending on co-morbidity status. Future research should work towards reproducing our study findings in a larger sample. This would further establish the
reliability and validity of the experimental procedure. A newly validated paradigm would be beneficial for probing the cognitive neurochemistry of relapse and for screening potential anti-relapse medications for single or multi-addicted populations.
5. REFERENCES


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Name of Study: Mental and Behavioural Processes in People Who Gamble and/or Drink Alcohol

Principal Investigator: Martin Zack, Ph. D. Phone: (416) 535-8501 ext. 6052

Purpose: The purpose of this study is to collect information about how alcohol affects various behaviours in heavy gamblers and those who drink alcohol. The study is intended for research purposes only. It is not intended to modify your drinking or gambling habits or otherwise influence your activity. However, the information obtained from this study may lead to improved understanding and treatment of problem gambling and/or problem-drinking in the future. Like all ongoing studies at the Center for Addiction and Mental Health (CAMH), this study is subject to monitoring of records and compliance with agreed-upon procedures by the CAMH Research Ethics Board. Neither the principal investigator nor any of the staff working on this project has any conflict of interest, financial or otherwise, that could influence the results.

Alcohol is a drug that can alter thoughts, feelings and behaviour. Recently, studies have found that many people who have gambling problems also have problems with alcohol. Therefore, it is important to evaluate and compare people who engage in one activity or both activities to identify common features as well as differences.

As one of 80 participants in the study, you will attend two separate sessions. Two identical test sessions (~ 5 hrs each) at CAMH. The test sessions will occur at least 2 days apart. You will receive beer on one of the sessions and a soft drink on the other. Whether you receive beer on the first or second session will be determined randomly. The dose of beer will be equivalent to about 2-3 standard (355 ml) bottles. This dose has been given to people in other studies without adverse effects.

During each test session you will be asked to complete several questionnaires and tests, some on computers. At the start of each session and after consuming beer, your blood alcohol level will be monitored periodically by means of breath samples, which you will provide by blowing into a breathalyser for about 5 seconds.

As part of continuing review of the research, your study records may be assessed on behalf of the Research Ethics Board and, if applicable, by the Health Canada Therapeutic Products Programme. A person from the research ethics team may contact you (if your contact information is available) to ask you questions about the research study and your consent to participate. The person assessing your file or contacting you must maintain your confidentiality to the extent permitted by law.

Subject’s Initials ______
Procedures: The session will begin promptly at 11am. You will be required to abstain from alcohol and all drugs or medication for 12 hours prior to the start of the session. Upon arrival you will provide a breath sample to confirm that there is no alcohol in your bloodstream. The test phase will last approximately 4 hours. Lunch and snacks will be provided for you following the test phase on each session. At the end of the session, you will be given transit fare to return home.

As noted above, the Addictions Medicine Clinic has physicians and nurses who can attend to you in the unlikely event of an emergency during the test sessions. These individuals can also be consulted if you feel unwell. A member of the laboratory staff will escort you to the clinic should this circumstance arise.

Steps of the Study:

1. The procedure on each of your test days will be identical. You will report to the laboratory at 11 AM. You must refrain from drinking alcohol or using any drugs or medication for 12 hours prior to the start of your test session. To ensure even absorption of your drinks, you must not eat or drink anything apart from water for 2 hours prior to the start of your test session.

2. To verify alcohol abstinence, you will provide a breath sample at the beginning of the test session. If you smoke, you will be required not to for about 3 hrs during the test phase.

3. You will complete some paper and pencil questionnaires.

4. You will perform an initial series of computer-based tasks so that you are familiar with them before you receive alcohol.

5. Some of the tasks you perform on the computer may be highly challenging or stressful to you. This is normal. As long as you stay focused on the task you are performing you will do fine.

6. You will receive your assigned beverage – beer or soft drink, split into 2 equal-sized drinks, at 15-minute intervals. You will be asked to consume each drink steadily over a period of 5 minutes.

7. Measures of breath alcohol and perceived effects of alcohol will be taken periodically throughout the test phase, by blowing into the breathalyzer. Basic measures of physical function (heart rate, blood pressure) will also be taken using a wrist cuff that slips over your hand and exerts very mild pressure on your forearm for about 30 seconds. None of these measures will cause discomfort.

8. You will perform one computer task after your first drink and two computer tasks after your second drink. Some tasks ask you to identify briefly presented words, on the screen, others require you to make a rapid decision by pressing a designated key on the keyboard. Each of the tasks will be explained to you. These tasks are derived from standard experimental procedures widely used in cognitive psychology as well as alcohol and drug research.

Subject’s Initials _______
9. You will also be asked to fill out several questionnaires periodically throughout the test session. Some of these will ask you to rate the effects of the drinks on your mood at the time. Others will ask you about background characteristics (e.g., your patterns of alcohol use, the kinds of activities you do and don’t enjoy).

10. On days that you receive beer, upon completion of the tasks, you will remain at the laboratory until your blood alcohol level has declined to .01%. This is an extremely important requirement of the study to ensure your safety.

11. After the completion of the study, we will explain to you why we do the various parts of it.

Eligibility: To participate in this study you must be 19-65 years old, as confirmed by picture identification, and have no physical or mental illness (with the exception of problem drinking, problem gambling or smoking). You may not participate in this study if you are taking any medications that could alter your mental or emotional state. You must not be colour-blind and must have normal vision or vision that is normal when you wear glasses or contact lenses. A trained Research Analyst will carry out the assessment of eligibility.

Confidentiality: Your identity will be kept confidential to the full extent provided by law. In addition, neither your name nor any other personal identifier will be used in any reports or publications arising from this study.

All information you provide will be stored in locked cabinets or in computer files accessible only by password. The information you provide will be given a subject number, which cannot be traced back to you. Data from paper copies will be transcribed to computer within 3 months of testing, after which the paper copies will be destroyed. Information linking your name with your research data will only be available to study personnel or a representative of the CAMH Research Ethics Board in the event of a review.

Compensation: You will receive $300.00 to compensate you for your time plus transit fare for you to get home from the laboratory. You will receive your payment upon completion of the study. If you are forced to drop out of the study before it has completed, you will be paid for the portion you have completed. Payment for Test Session 1: $150. Payment for Session 2: $150.

Risks: The dose of beer may cause you to feel confused or queasy. If this happens, the effect will be short lasting, several hours at most. Food and water will be provided for you after the test phase to minimise possible hangover effects. If you feel unwell during the test session and you wish to see a physician, a member of the laboratory staff will escort you to the medical clinic at the Centre for Addiction and Mental Health.

It is possible you will experience emotional or psychological changes as a result of the study. As noted previously, some of the tasks may be quite challenging or stressful. We would like you to carry them out to the best of your ability. However, should you feel you cannot continue, you can drop out of the study at any time, and receive payment for the part you have completed. Similarly, you can refuse to answer any question in the questionnaires that you do.

Subject’s Initials _______
Benefits: This study has not been planned to influence your use of alcohol or gambling, but it may provide information that will be of interest to you about their effects. It is hoped that the results will be useful for helping others who wish to change their behaviour.

Voluntary Participation: Your participation in this study is voluntary. You may choose to withdraw from the study at any time. In addition, the study investigator or staff responsible for this study may end your participation at any time if you do not act in accordance with the study requirements. Your choice to not participate, your choice to withdraw, or your dismissal by us will in no way affect your right to use the services at The Centre for Addiction and Mental Health.

Additional Information: If you have questions about the study that are not answered in this Information Sheet, please ask them. In addition, if you have questions in the future you may contact the study investigator at the telephone number given on the first page. You will also receive a signed copy of this form with additional contact numbers for other study-related concerns. (see next page)
Agreement to Participate

I, ______________________, have read the information in this Consent Form, for the study named “Mental and Behavioural Processes in People Who Gamble and/or Drink Alcohol.” I understand that my role in the study is as a research participant, to help the investigators collect information about various processes associated with the use of alcohol. This information may or may not be useful in designing better ways to help people with alcohol problems and/or gambling problems in the future. My questions, if any, have been answered to my satisfaction, so that I now understand the procedures to be followed in the study, the risks to me from my participation, and my right to the confidential treatment of the information that is collected about me.

Research Volunteer:

Signature:  ____________________________________
Date:   ____________________________________
Name:   ____________________________________
Please Print

Experimenter (person who administered consent form):

Signature:  ____________________________________
Date:   ____________________________________
Name:   ____________________________________
Please Print

Contact in case of ethical concerns about the study:

Dr. Padraig Darby,
Chair, Research Ethics Board
Centre for Addiction and Mental Health
Dr Darby may be reached by telephone at (416) 535-8501, ext. 6876 by research subjects to discuss their rights

Contact for questions about the procedures used in the study:

Dr. Martin Zack
Scientist
Clinical Neuroscience Section
Centre for Addiction and Mental Health
Phone: 416-535-8501, ext. 6052
Email: martin_zack@camh.net

Subject’s Initials ______
### 5.3 APPENDIX C

**Table 1** ANOVA of colour-naming reaction times on the modified Stroop Task

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Table 3 ANOVA of reaction time scores on the Lexical Stop Signal Task

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