

Anticipated Probabilistic Reward: Imaging Reward Processing And Cognitive Control Among Pathological Gamblers

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EXECUTIVE SUMMARY

Our group is currently conducting psychobiological research on Pathological Gambling using functional Magnetic Resonance neuroimaging (fMRI) technology. We are interested in the neurological mechanisms underlying the loss of cognitive control in pathological gamblers, which may generalize to other addicts. This report provides the rationale for our scientific approach (Part I), the details of the current study (Part II), an update on data collection (Part III) and preliminary findings from clinical interview data (Part IV).

Pathological Gambling will soon be recognized as the first non-substance or behavioural addiction. This reclassification is supported by similarities between Pathological Gambling and substance addiction. Increasingly researchers are investigating more fundamental questions of overlap, such as, which *brain processes and structures* are common among addicts?

The study of Pathological Gambling is especially well positioned to answer these questions. In identifying core neurological mechanisms, their interrelationships and influence on behaviour, we will be able to inform the diagnosis and treatment of Pathological Gambling, as well as the substance addictions and such other behavioural addictions as come to be verified in future work.

In the present study we hypothesise that PGs have developed deficits in their capacity to control conditioned reward responses around cues for probabilistic reward. This hypothesis has direct implications for treatment approaches such as Cognitive-Behavioural Therapy (CBT). To test our hypothesis we are administering an established cognitive control of reward paradigm to Pathological Gamblers (PGs) and Healthy Controls (HCs) while their brains are being scanned with a Magnetic Resonance Imaging (MRI) machine.

The process of data collection involves four stages. (1) We recruited potential participants from analysed survey data and targeted newspaper advertisements. (2) We did telephone screening to determine eligibility and suitability for MRI. (3) Face-to-face diagnostic interviews to assess gambling pathology and current and lifetime psychiatric comorbidity were conducted, at which we also administered cognitive and survey assessments to enrich our profile of study participants for later hypothesis testing. (4) We conducted brain scans to collect neuroimaging data. Initially, we have focused data collection on PGs since these are the smaller and more challenging population to obtain. In addition, recruitment of HCs must be matched (with respect to age, sex, and socioeconomic status) to the PG group. To complete data collection we will scan (minimally) 5 more PGs and 15 more HCs.

Given that we screen and interview many more Pathological Gamblers than are suitable for scanning, we are steadily generating comprehensive comorbidity data on PGs, as well as qualitative data on the nature of their gambling problems. Our data suggest distinct groups of disordered gamblers identified by different attributions or reasons for gambling as well as symptom presentation. The average age of interviewed PGs is 43 years and the average monthly income is R9 544. Of the 27 screened PGs 15 (56%) are male. Consistent with international literature, our clinical assessments reveal high rates of comorbidity, especially for Mood, Anxiety and Substance Use Disorders.

PART I

WHY STUDY THE PSYCHOBIOLOGY OF PATHOLOGICAL GAMBLING?

1.1 Introduction

The Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) currently classifies Pathological Gambling (PG) as a disorder of impulse control, along with other disorders such as kleptomania (failure to resist impulses to steal), pyromania (failure to resist fire-setting impulses) and trichotillomania (failure to resist hair-pulling impulses). The DSM is the main tool used by clinicians to diagnose psychological problems and to organise approaches to treatment. However scientists are increasingly discovering evidence of overlap between PG and Substance Use Disorders (drug and alcohol addictions) across natural history (how the disorders develop), phenomenology (how the disorders are experienced), comorbidity (what other disorders co-occur), genetics (what heritable characteristics are involved), neurobiological mechanisms (what brain processes and structures are involved) and response to treatment (see reviews, Hodgins, Stea, & Grant, 2011; Petry, 2006; Potenza, 2006; Potenza, 2008; van Holst, van den Brink, Veltman, & Goudriaan, 2010b; Wareham & Potenza, 2010). These findings have led to a proposed classification revision in the forthcoming diagnostic manual. The revision, tabled for DSM-V, will introduce disordered gambling as the first clinically recognized non-substance or *behavioural addiction*.

While PG has served as the main evidence base for extending the concept of addiction beyond compulsive consumption of drugs or substances (Frascella, Potenza, Brown, & Childress, 2010; Grant, Potenza, Weinstein, & Gorelick, 2010; Holden, 2010; Potenza, 2006; Potenza & Taylor, 2009), there have been very few attempts to clarify and expand contemporary *models of addiction* to incorporate both behavioural and drug based effects or to delimit the boundaries relevant to a consideration of other putative behavioural addictions. Nor have there been efforts to consider how behavioural addictions may shed light on the classification and treatment of more commonly recognised substance addictions, such as alcoholism. This is not merely an intellectual concern. Precisely which behaviour may come to be classified as 'addictive' (e.g., video gaming, fast food eating, sex) will have far-reaching implications for public health policy and consequent industry regulation. Consider for example recent government proposals to ban the advertising of 'fast-foods' to children. Moreover, from a scientific point of view identifying shared mechanisms will inform basic treatment approaches, whether these are ultimately targeting the consumption of toxic substances or of 'high consequence' or 'high-risk' behaviour.

Our group has proposed and is currently investigating a psychobiological theory of addiction based on our work with Pathological Gamblers (originally set forth in Ross, Sharp, Vuchinich, & Spurrett, 2008). Our theory involves a combination of a contemporary model of substance addiction, the Impaired Response Inhibition and Salience Attribution (I-RISA) model (Goldstein & Volkow, 2002) with a neuroeconomic model of reward processing, the Predictor-Valuation Model (PVM) (Montague & Berns, 2002). We hypothesise that the core psychobiological features of addiction such as *craving*, *compulsion* and *loss of control* are due to *reward system hysteresis* in the human midbrain. That is we think addicts are suffering from a brain disorder involving failure of frontal and pre-frontal inhibitory systems that limit the direct influence on behaviour of a neurobiological system involved in seeking out and learning from *surprising* or *novel* events.

To test this psychobiological theory we need to study the workings of addicts' brains. There are a number of neuroimaging techniques available for this. In working with human participants however, functional Magnetic Resonance Imaging (fMRI) is perhaps the most important. fMRI allows us to determine the relative regional activity of the brain when individuals are cognitively engaged (thinking and feeling). This then allows us to compare whether there are specific (hypothesised) regional differences in brain activation between different groups (such as between the addicted and non-addicted), which in turn allows us to identify the neurological *processing* differences underlying variations in behaviour. It is such processing differences that are the target of pharmacological and cognitive-behavioural interventions.

Our research group is fortunate to have access to South Africa's only research dedicated MRI scanner located at the Cross University Brain Imaging Centre (CUBIC), owned jointly by the University of Cape Town and Stellenbosch University. With these resources we are able to examine processing differences between addicted and non-addicted populations. Several other local groups are investigating substance addictions using this technology. However we think that the study of PG provides perhaps the best subject pool to refine and test psychobiological models of addiction. There are at least three reasons for this. Firstly, at the neurobiological level PG is uncomplicated by the exogenous (outside) effects of drugs of abuse. In the methamphetamine addict's brain for example, apart from hypothesised reward processing dysfunction, is actual physical

damage due to the neurotoxic effects of drug use. In the case of the pathological gambler however, the neurobiology represents only the *basic or core form* of processing dysfunction thought to underlie addiction. Second, there is good reason to believe that gambling directly manipulates the main system of interest in addiction, the *dopaminergic reward system*. Indeed the dopamine system is active specifically in response to *positive surprises*, and gambling fundamentally consists in paying for the possibility of a positive surprise. Third, gambling tasks are comparatively easy to replicate in a laboratory environment. Scientific and pragmatic considerations thus converge to place PG at the centre of our research programme.

In summary, psychobiological research on pathological gambling presents a valuable opportunity to study the core mechanisms of addiction. Our understanding of these core mechanisms will directly inform the diagnosis and treatment of pathological gambling, as well as the substance addictions and such other behavioural addictions as turn out to be verified by studies in the years to come. Far from being just a newcomer to the addiction field, pathological gambling could, in a relatively short space of time, come to redefine our understanding of addictions in general.

With the assistance of funding from National Responsible Gambling Foundation (NRGP) our group is currently conducting a neuroimaging study of pathological gamblers focused on a central component of our hypothesis, *loss of control*. As noted above, we hypothesise that PGs have developed deficits in their capacity to control conditioned reward responses around cues for probabilistic reward. To test this hypothesis we are administering an established *cognitive control of reward paradigm* to PGs and controls while their brains are being scanned with a Magnetic Resonance Imaging (MRI) machine. The details of the Cognitive Control study (CCS) are given in Part II.

PART II

THE DESIGN OF THE COGNITIVE CONTROL STUDY (CCS)

2.1 Scientific Rationale and Motivation

People who convince themselves that they would be better off if they changed their behaviour often fail to do so (e.g., to maintain better eating, to exercise more often). In extreme examples, failure to enact and maintain behaviour change in spite of serious consequences (as in addiction) is diagnosed as pathological. Addiction is characterised by extreme *craving, compulsion and loss of control* with respect to consumption of a particular addictive target. *Self-regulation* or cognitive control is thus especially relevant to our understanding of the treatment of addiction.

Cognitively, the *valuation* of environmental cues in terms of expected potential reward is central to motivational and attentional aspects of self-regulatory control. Underlying the valuation process is a functionally and chemically specifiable part of the brain known as the dopamine reward system, which is particularly engaged by surprise, i.e., by a stimulus which is 'better' or 'worse' than predicted (Schultz et al, 1997). Certain exogenous chemicals can recurrently trigger such surprise signals, giving rise to drug specific cravings (Sinha, et al., 2005) and potentially increasing urges for risk-seeking behaviour (Potenza & Winters, 2003). Ross and co-authors (Ross, et al., 2008) refer to such disruptions as 'midbrain mutiny', whereby the striatum usurps the normal personal control apparatus realized by frontal and pre-frontal inhibitory circuits relying on the neurotransmitters *GABA* and *serotonin*, causing the system as a whole to relentlessly pursue reliable cues for surprise (i.e., additive targets). Thus, in addiction, attenuated *GABA* and serotonin signals are thought to lead to *pathological overlearning* of drug related cues, which in turn leads to the valuation of drugs above all other goals, and interferes with ability to attend to predictors of alternative rewards (e.g., social interactions, other entertainment, vocational opportunities) (Montague, Hyman, & Cohen, 2004).

Exogenous chemicals however are not the only route to distinctive pathologies of the reward system. Behavioural and environmental contingencies can also lead to serious self-regulatory failure. For example, disordered gambling is now considered an example of what is known as a behavioural addiction, and there is increasingly interest in purported addictions to food, internet-use and shopping. Since behavioural addictions are not complicated by specific and complex causal effects of particular drugs of abuse, they may present an opportunity to come as close as possible to studying the generic form of extreme self-regulatory failure or addiction (Ross, et al., 2008).

The opportunity to further our understanding of this area with specific implications for treatment approaches such as Cognitive-Behavioural Therapy (CBT) is promising, and is a main motivation for our neuroimaging project focused in particular on *cognitive control in problem gamblers*.

2.2 Problem Identification

Disordered gambling (DG) (encompassing DSM defined 'pathological gambling' as well as sub-threshold 'problem gambling') presents a considerable public health challenge. Studies in the United States (US) estimate lifetime prevalence of pathological gambling at between 0.4% and 2% (Petry, 2009), while problem gambling makes up a further 0.8% to 2.8% (Petry, 2009). Past-year rates are substantially lower at 0.1% to 1.3% and 0.4% to 2.2% for pathological and problem gambling respectively (Petry, 2009). In urban South Africa, past-year prevalence rates are more than double US estimates (Ross, et al., 2010).

However, there is no subthreshold 'problem gambling' condition in the *DSM-IV* (American Psychiatric Association, 1994). For research purposes, various population screen cut-offs have been used, such as the score band for the 'moderate risk group' identified on the Problem Gambling Severity Index (PGSI) (Ferris & Wynne, 2001, February), or some (study-defined) number of items endorsed on the South Oaks Gambling Screen (Lesieur & Blume, 1987). As a result it is difficult to compare information on problem (as opposed to pathological) gambling prevalence. Indeed, very little is known about the number of individuals who lose control in gambling more frequently or heavily than intended, but who claim to encounter moderate, and not severe, gambling-related problems (Petry, 2005).

It is clear that the criteria and presenting problems that characterise disordered gambling, and problem gambling especially, need to be more clearly articulated. That is 'stage one' developmental research (Dodge, 2001) aimed at further describing and clarifying the nature of the problem is implicated. Researchers and clinicians at a recent (2010) conference on disordered gambling (entitled 'redefining diagnosis, treatment and research') made a similar proposal (see e.g., O'Brien, Potenza, & Cottler, 2010; Winters, 2010). Moreover, delegates agreed that our understanding of disordered gambling in the next few years (i.e., prior to the publication of *DSM-V*) could valuably inform approaches to diagnosis and treatment for some time to come.

One approach to refining the diagnostic taxonomy of behavioural addictions (and disordered gambling in particular) is to examine the psychometric properties of commonly used screening measures. Research to this effect is currently underway, focused on testing the validity of different diagnostic subgroups, and the identification of proposed subgroup taxa (e.g., Kincaid, et al., submitted, 2010) and the validity of the PGSI screen in SA (Sharp, et al., in press, 2011). This will no doubt have clinical value. However, we might also consider a more theory-driven approach, with the promise of addressing basic questions about the extent of self-regulatory failure. Thus for example, given current models of the functioning of cortical-basal ganglia reward circuit in classical addictions (Everitt & Robbins, 2005), we might ask if disordered gamblers present with predictable differences in reward processing.

Early neuroscientific work on reward localised brain regions that responded to the presentation of various rewarding stimuli. Consistent with comparative studies, a number of areas innervated by mesolimbic dopamine projections were identified, including the midbrain, ventral striatum (including nucleus accumbens), amygdala, orbital frontal cortex (OFC), and mesial prefrontal cortex (Glimcher & Rustichini, 2004; McClure, York, & Montague, 2004; J. P. O'Doherty, 2004; Schultz, 2004). Recently, more sophisticated theoretical work has sought to disambiguate the dynamic function of the reward circuit. In this respect, the suite of conceptual tools brought forth by economic and computational analysis increasingly provides structure to neuroscientific observations (Daw & Doya, 2006; McClure, Daw, & Montague, 2003; Montague & Berns, 2002; Rutledge, Dean, Caplin, & Glimcher, 2010; Schultz, 2010). At the same time revision of reward paradigms within dynamic and event related designs, as well as the use of new analysis methods, continues to enrich the basic imaging data. Among the many distinctions that have received attention, is the very basic one of separate mechanisms underlying appetitive and consummatory stages of reward processing (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Knutson, Adams, Fong, & Hommer, 2001; Knutson, Fong, Adams, Varner, & Hommer, 2001). Neuroimaging studies experimentally separating reward-processing stages are increasingly common such that *reward anticipation* is now a common focus of investigation (Bjork & Hommer, 2007; Bjork, et al., 2004; Breiter, et al., 2001; Dillon, et al., 2008; Dreher, et al., 2007; Ernst, et al., 2004; Galvan, et al., 2005; Gottfried, O'Doherty, & Dolan, 2003; Jensen, et al., 2003; Kirsch, et al., 2003; Knutson, Adams, et al., 2001; Knutson, Fong, et al., 2001; Knutson, Fong, Bennett, Adams, & Hommer, 2003; Knutson, Taylor, Kaufman, Peterson, & Glover, 2005; Liu, et al., 2007; J. O'Doherty, et al., 2004; J. P. O'Doherty, Deichmann, Critchley, & Dolan, 2002; Rademacher, et al., 2010; Spreckelmeyer, et al., 2009), and is implicated in particular by the role of the *ventral striatum* (VS) (Delgado, 2007). Among addicts, research has consistently revealed drug-cue-related hyperactivity in the

VS, emphasizing reward expectation as a crucial mechanism of addiction (Diekhof, Falkai, & Gruber, 2008). Similarly in disordered gamblers, the limited evidence available, suggests blunted mesolimbic-prefrontal cortex activation to natural rewards, and increased activation when exposed to gambling-related stimuli (van Holst, van den Brink, Veltman, & Goudriaan, 2010a). Less is known about how these differences might affect decision-making. If disordered gamblers show similar VS hyperactivity when placed in a condition of anticipated reward, how might this affect attempts at self-control?

In classical addictions, drug-seeking is thought to be facilitated by impairment of prefrontal cortical "top-down" control mechanisms, which might be expected to inhibit harmful behaviour in healthy individuals (Hyman, Malenka, & Nestler, 2006). Apart from proposed drug specific changes in the functioning of particular areas (such as the orbitofrontal cortex), it is thought that self-regulatory failure might specifically reflect the devaluating of non-drug related goals in prefrontal cortex (PFC) (Montague, et al., 2004). One way to examine the role of PFC in relation to midbrain hyperactivity (such as in the VS) is to test addicts in the utilization of cognitive strategies commonly used in clinical practice. In this respect *emotion regulation strategies* used by non-addicted individuals have been successful in attenuating aversive emotional reactions elicited by various types of negative stimuli (Ochsner & Gross, 2005) and more recently, in regulating positive anticipatory feelings elicited by a conditioned appetitive stimulus (Delgado, Gillis, & Phelps, 2008). It is not clear however, if the same is true for addicts.

In gambling treatment studies, cognitive strategies targeting specific cognitive content have been investigated by Ladouceur (Ladouceur, et al., 2001), with some success. Similarly Petry (Petry, et al., 2006) designed and investigated a Cognitive Behavioural Therapy (CBT) programme focused on 'irrational thinking', and again achieved significant therapeutic gains (and importantly did so against comparison treatments, e.g., Gamblers Anonymous attendance). Thus it appears that facilitated self-regulation through 'top-down' control strategies may be capturing important aspects of the problem. However there is no neuroscientific evidence to this effect.

We are therefore motivated to examine whether and how PGs struggle to control their conditioned reward responses by administering a cognitive control of reward paradigm to PGs while their brains are being scanned. Delgado's (2008) paradigm is especially suited to this purpose.

2.3 Research Aims and Objectives

The aim of the current study is to adapt Delgado's (Delgado, et al., 2008) paradigm to compare brain responses in the cognitive

control of conditioned reward responses between PGs ($n = 20-25$) and matched (age, sex, and SES) normal controls ($n = 20-25$). By using a monetary reward-conditioning procedure with cognitive strategies, Delgado (Delgado, et al., 2008) demonstrated attenuation in both the physiological (skin conductance) and neural correlates (striatum) of reward expectation as participants applied cognitive control strategies (regulation). Against this background, we have two broad hypotheses for the current study: (1) Compared to matched normal controls, PGs will show increased striatum responses when attending to the expectation of reward; and (2) compared to matched normal controls PGs will show decreased prefrontal activation when attempting to regulate conditioned reward responses.

2.4 Research Methods

2.4.1 Overview

All subjects undergo the same fMRI scanning procedures while undertaking a passive reward expectation task (described in more detail below). Subjects lie in an fMRI scanner and observe a presentation of simple conditioned stimuli (coloured blocks), which either predict or do not predict a monetary reward. While engaged in the task subjects are asked to either 'Attend' or 'Regulate' their response to the stimuli paired probabilistically with a reward (a blue square (CS+)) or with no-reward (a yellow square (CS-)). Subjects are also asked to answer a simple question after each trial to ensure attention, and four Likert scale questions between trial blocks to determine subjective ratings of excitement for each of the conditioned stimuli. Responses are made by pressing on a button box in the scanner. The scanner detects changes in regional cerebral blood flow that accompany brain activation during the presentation of the conditioned stimuli. Prior to the scan, subjects are asked to participate in a non-fMRI version of the task, to adequately prepare them for the experimental task they will encounter in the scanner. There is no administration of drugs or placebos or other treatments.

2.4.2 Sampling

Participants are screened for both inclusion and exclusion criteria.

2.4.2.1 Inclusion criteria

For all subjects: 1. right-handed volunteers 2. vision corrected to be able to see the computer display clearly without eyeglasses. For control subjects: 1. Ages 26 to 64 years.

For Pathological Gambling subjects: 1. Ages 26 to 64 years 2. Meet criteria for Problem Gambling as determined by administration of the Canadian Problem Gambling Index (CPGI) (Ferris & Wynne, 2001, February) and Structured Clinical Interview for Pathological

Gambling (SCI_PG) (Grant, Steinberg, Kim, Rounsaville, & Potenza, 2004) by trained research staff.

2.4.2.2 Exclusion Criteria

For all subjects: 1. Left-handed (This is commonly done in fMRI experiments because many brain functions are localized to one hemisphere). 2. Self-reported or diagnosed claustrophobia 3. History of head injury resulting in loss of consciousness for more than 10 minutes 4. Pregnant (through self-report) 5. Contraindications to MRI: pacemaker, aneurysm clips, neurostimulators, cochlear implants, metal in eyes, steel worker, or other metal implants 6. Current Drug dependence/abuse or alcohol dependence 7. Presence of psychotic symptoms including mania (i.e., Bipolar Disorder) 8. Psychoactive medications.

For Controls: 1. Taking psychoactive medications 2. Active medical or neurological disorder 3. Current (last 5 years) DSM-IV Axis I diagnosis as determined by Structured Clinical Interview for the DSM-IV (First, Spitzer, Gibbon, & Williams, 1998) 4. History of drug dependence or abuse, or alcohol dependence or abuse. For Pathological Gambling subjects: 1. Bipolar-I or Bipolar-II 2. Current Drug Dependence or Drug Abuse 3. Current Alcohol Dependence. 4. Psychotic symptoms 5. Claustrophobia.

2.4.3 Procedures

Potential subjects who express interest in research participation and who meet primary inclusion criteria are identified from three main recruitment sources (see sampling below) and contacted telephonically. After verbal consent is obtained subjects complete a screening questionnaire (Participant Screening Questionnaire) that includes demographic variables as well as contraindications to MRI. Thereafter potentially eligible subjects meet with a researcher on the first of two possible testing days. Once written consent is obtained on Day 1, subjects are asked to participate in the assessments described below:

2.4.3.1 Day 1: Structured Interview

All subjects: Participants complete the prevalence questionnaire (see sampling below) in order to acquire demographic information that will be used to assess gender, age and socioeconomic factors influencing task results. Additionally, demographic data is used to appropriately match non-clinical subjects (i.e., participants without clinical diagnosis) to clinical subjects (i.e., participants with a diagnosis of Pathological Gambling).

Individuals with Pathological Gambling: Participants are administered the following measures: the Structured Clinical Interview for the DSM-IV-TR Axis-I (First, et al., 1998), Cognitive Strategies to Control Emotions (CERQ) (Garnefski, Kraaij, &

Spinhoven, 2001) <keywo/, Emotion regulation styles: suppression vs. reappraisal (ERQ) (Gross & John, 2003); Sensation-seeking (SSSV) (Zuckerman, Eysenck, & Eysenck, 1978), Cognitive Control of Thoughts (TCQ) (Wells & Davies, 1994), and Inventory of Erroneous Beliefs related to gambling (Ladouceur, 2004). Assessments are administered by a trained researcher and last approximately 4 hours. Assessments are completed during the Day 1 session prior to scanning, and participants are compensated at a rate of R30/hr, plus transport costs.

Non-clinical participants: Participants are initially screened on the Structured Clinical Interview for the DSM-IV-TR Axis-I. Included participants that match demographic variables (age, sex, SES) of participants with Pathological Gambling are asked to complete the assessments described above, lasting approximately 4 hours. Participants are compensated at a rate of R30/hr, plus transport costs.

2.4.3.2 Day 2: Scanning

Subjects participate in three blocks of 24 trials whilst their brains are being scanned. Each subject observes a sequenced presentation of simple conditioned stimuli (coloured blocks), which either predict (a blue square (CS+)) or do not predict (a yellow square (CS-)) a monetary reward. Conditioning is undertaken by means of detailed instruction prior to commencement of the scanning task. Before presentation of conditioned stimuli in the scanner, subjects are instructed to either 'Attend' or 'Regulate' their response to the stimuli paired probabilistically with a reward (or with no-reward). Subjects are also asked to answer a simple question after each trial to ensure attention, and four Likert scale questions between trial blocks to determine subjective ratings of excitement for each of the conditioned stimuli (see Figure 1 below).

The primary procedure is an MRI scan. The subjects lie still for up to 60 minutes while in the scanner. During each scanning

session, structural scans are acquired during the first 5-10 minutes. Following structural scanning, functional images are acquired for approximately 25 to 30 minutes, followed by more structural scans for 10-15 minutes. The subject in the scanner is in voice-communication with a technician via an intercom and has access to an alert button in case they wish withdraw from the procedure.

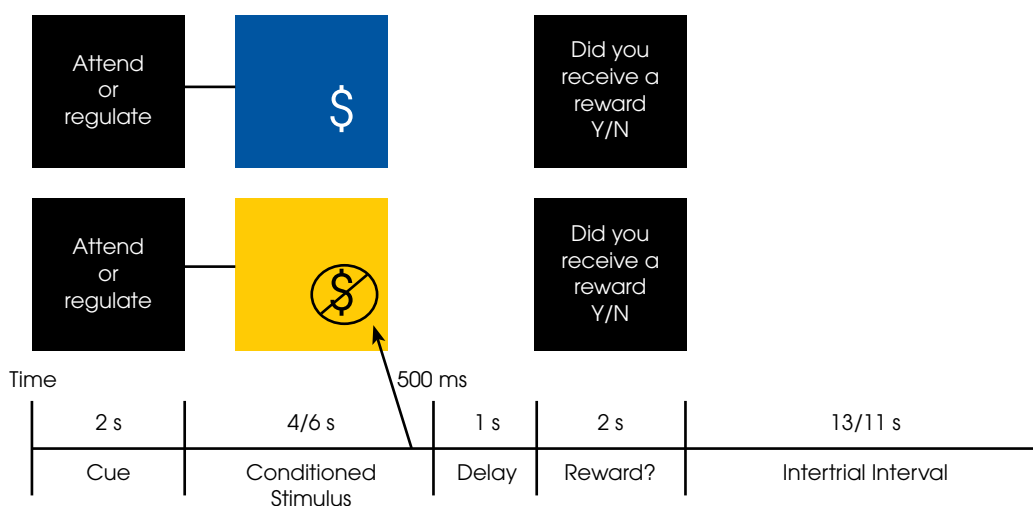
Scanning protocol: Sequence selection is based on the scanning procedures used in the original study using the task by Delgado et al. (2008). Anatomical images are acquired using a T1-weighted protocol (256 X 256 matrix, 176 1-mm sagittal slices). Function images are collected in the same slices using a gradient echo EPI sequences (TR = 2000ms, TE = 20ms, FOV = 192, flip angle = 75 degrees, bandwidth = 4340Hz/px, echo spacing = 0.29 ms, voxel size 3 X 3 X 3). Scanning is divided into three runs corresponding to three blocks of stimulus presentation (programmed in E-prime). Thirty-nine contiguous oblique-axial slices (3 X 3 X 3 mm voxels) parallel to the AC-PC line will be obtained. Each scan takes approximately 60 minutes.

After scanning participants complete a measure of gambling craving (The Gambling Craving Scale) (Young & Wohl, 2009) and provide a cheek swab DNA sample.

2.4.4 Sampling

fMRI studies of standard cognitive activation paradigms typically require 24 subjects in order to achieve statistical significance after correcting for the multiple comparisons characteristic of standard fMRI analysis (Desmond & Glover, 2002). Given this constraint, we expect to include a minimum of 20 - 25 subjects in each group. Note that subjects earn R150-R240 for the scanning session and are reimbursed for transport costs. Subjects are recruited from three main sources.

Figure 1. Scanning Task



Source 1: Researchers involved in the present project conducted a national prevalence study of pathological gambling in South Africa (N=3000) in 2008. Participants in the prevalence study who indicated a willingness to participate in future research, and who resided in the Western Cape (the study site) formed the first pass sampling frame. The questionnaire used in the prevalence study includes two assessments of problem gambling, as well as assessments of depression, anxiety and drug and alcohol problems, which were used to pre-select both clinical and control subjects for potential inclusion in the scanning research (see Part III). As the prevalence of problem gambling in the sample was 3%, additional subjects for the clinical group were also obtained as described below.

Source 2.1: Researchers involved in the present project, are currently conducting a longitudinal study comparing groups of individuals with differing severity of gambling problems over time (N = 300) (The Panel Study). Although subject groups (No risk, Moderate risk, Problem Gamblers) are drawn from the prevalence study described above, additional subjects for the PG group were recruited from advertisements in local newspapers and posters in community centres throughout the Western Cape. PG subjects enrolled in the longitudinal study through this source, and who indicated a willingness to participate in further research, were also screened for inclusion in the scanning study.

Source 3: We regularly top-up both our clinical (Pathological Gambling) and control subject pool via local community newspaper advertisements. In addition NRGPs clinicians have recently agreed to pass on the contact details of treatment-seeking pathological gamblers interested in our research. Potential subjects are screened telephonically for MRI compatibility as well as for severity of pathological gambling. Interviews are arranged for further screening and assessment as is appropriate to the group.

All subjects: Prior to screening, the research project is explained to all potential subjects, and any questions that potential participants have are answered by study staff. If participants continue to express interest in participating initial telephonic screening is conducted by study staff using a screening questionnaire that includes demographic variables as well as contraindications to MRI. If, after screening, participants are eligible for further participation, an appointment is made to meet study staff, where subjects are asked to provide informed consent. The contents of the consent form are reviewed with each potential participant. Following consent, all subjects are screened with the Structured Clinical Interview for the DSM-IV-TR Axis-I.

Controls: Subjects meeting criteria for any Axis-I diagnosis as identified from the Structured Clinical Interview for the DSM-IV-TR Axis-I are excluded from the study scanning.

Problem Gamblers: Subjects meeting criteria for Bipolar-I or II, Current Drug Dependence, Drug Abuse, or for any psychotic symptoms, are excluded from the study scanning

2.4.5 Analysis

Post-processing using the open-source program AFNI will be carried out locally with assistance from study collaborators at the University of Houston and Rutgers University. Group data will be analyzed using a random effects model to determine blood oxygenation level dependent signal (BOLD) for task-specific events. There will be four predictors of interest (Attend CS+, Attend CS-, Regulate CS+, Regulate CS-) and four predictors of no interest (Attend instruction cue, Regulate cue, CS-US trials, US delivery). Trials in which the US was delivered (CS-US trials) will be excluded from analysis. To determine event related BOLD signals in specific brain areas, a general linear model of the experiment will be imposed on the group image to reveal contrast activations when comparing specific trial types. Statistical maps of interest will be created using a threshold of $p < 0.005$ and a cluster threshold of 4 contiguous voxels. Statistical parametric maps will be created based on two specific contrasts which allows the selection of a priori regions of interest (ROIs) in the striatum and PFC, specifically dorsolateral and medial PFC. These contrasts include 1) Attend CS+ /Attend CS- contrast, motivated by previous research on reward expectations and prediction and 2) Regulate/Attend contrast, motivated by previous research on emotion regulation. ANOVAS will be conducted to test main and interaction effects for the 4 conditions of the task, time course and two clinical conditions in order to determine differences between PGs and non-PGs in ROIs.

2.5 Research Activities

- Collate research materials: Complete 2010.
- Design fMRI task in ePrime: Complete 2010.
- Design and pilot subject task briefing: Complete 2010.
- fMRI safety training: Complete 2010.
- Pilot fMRI scanning protocol: Complete 2010.
- Obtain ethics approval: Complete 2010.
- Subject telephone screening: Recruitment source 1: Complete Dec 2010.
- Subject telephone screening: Recruitment source 2: Complete Dec 2010.
- Subject telephone screening: Recruitment source 3: Ongoing, Aug 2010 - Oct 2011.
- SCID recruited subjects: Ongoing, Jul 2010 - Oct 2011.
- Scan subjects: Ongoing, Aug 2010 - Oct 2011.
- Analysis and write up: Jan 2012 - Dec 2012.

3.1 Source 1 and 2 Data (April – September 2010)

As described above the first sampling frame for the CCS was based on the National Prevalence Study dataset, as well as additional recruitment from the Panel Study. The flow chart below (Figure 2) documents the statistical filtering imposed on the data to determine the pool of possible participants in the Western Cape, as well as the details of the recruitment process from telephone screening through to scanning.

Statistical filtering of the prevalence and panel data occurred first by area (Western Cape), followed by age (26 years and older). This resulted in a combined subject pool of 686 possible subjects. We then used the Problem Gambling Severity Index scores (PGSI) to impose threshold criteria for the selection of pathological gambling (≥ 17) and control ($= 0$) groups. On the PGSI a score of 8 and above represents *Pathological Gambling*, while a score of between 1 and 2 places individuals at *Low Risk*. However we deemed it necessary, in light of the high levels of noise to be expected in fMRI data, to maximize cross-sample differences by imposing stricter criteria in both directions. After applying these cut-offs we had 10 potential Pathological Gamblers and 398 potential Controls for inclusion in the study.

Next we used the prevalence study dataset to apply exclusion criteria for Alcohol and Drug Abuse/Dependence for PGs, and for Alcohol and Drug Abuse/Dependence, Depression symptoms and Anxiety symptoms for Controls. 1 PG and 348 Controls remained from the prevalence study data after this process. Supplementing these potential participants with Panel PGs and a small number of NRGP helpline referrals (subsequently discontinued) resulted in a sample frame of 16 PGs and 349 Controls. Potential participants were also organised by socioeconomic status where available data allowed.

The recruitment process occurred by means of telephonic interview. Potential participants learned 1) where we obtained their contact details and 2) the nature of their requested study participation including remuneration. 33.4% of potential participants declined participation while a further 43.8% were not available for screening after repeated call attempts at different times throughout the day (morning, afternoon, evening). 22.7% of the sample frame agreed to the telephone screen, which assessed 1) their suitability for MRI procedures, and 2) their gambling severity group as determined by the PGSI screening

tool. Slightly less than half (44.5%) of screened participants were excluded at this point. Appointments were made for Day 1 interviews with the 46 remaining participants.

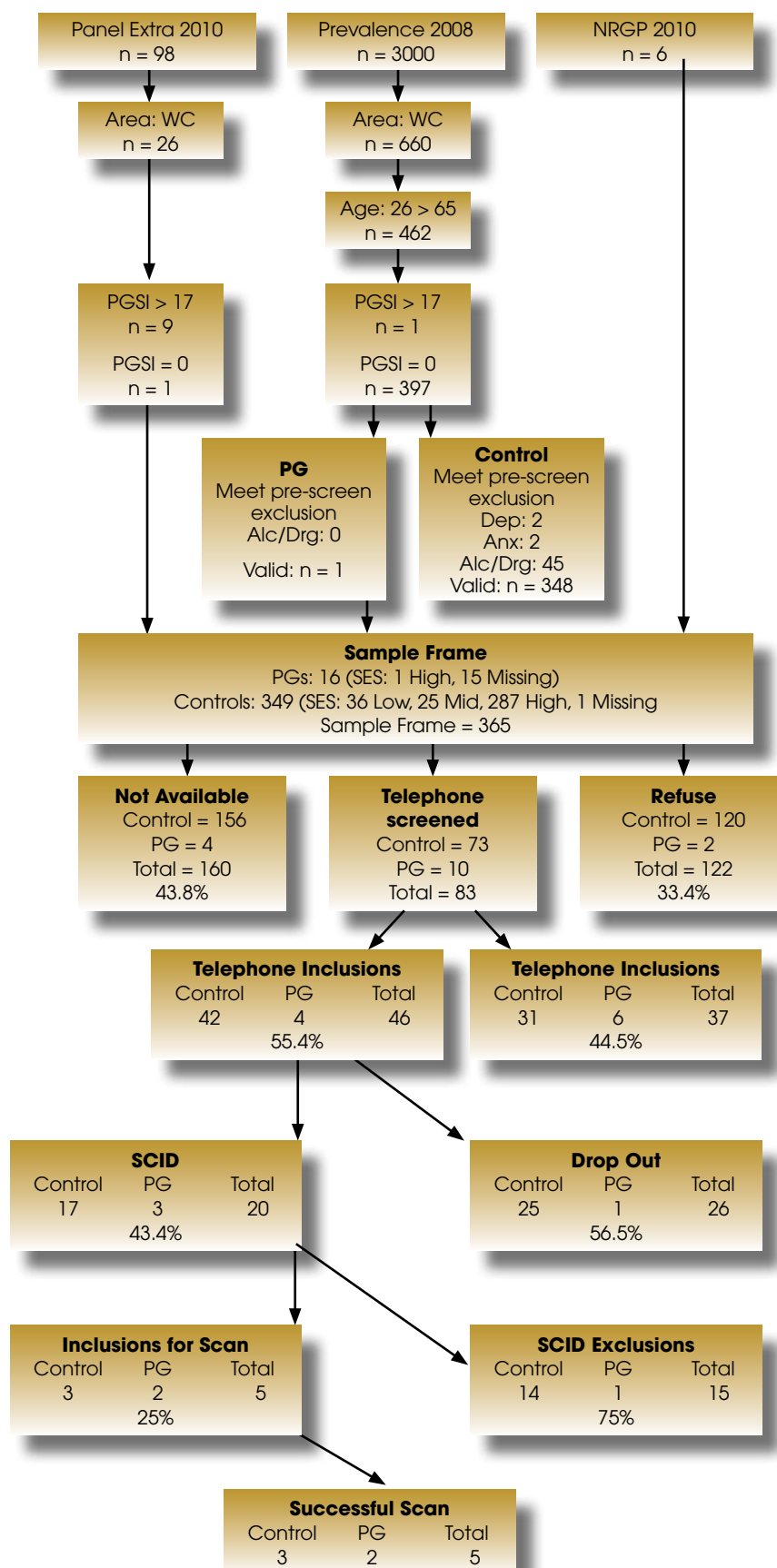
Of those booked for Day 1 interviews 56.5% subsequently dropped out. Every effort was made to interview participants at their convenience (including weekend and after hours interviews as well as re-contacting those who missed appointments), however the length of the interview (4 hours), and the unfamiliarity of South Africans with paid scientific research was clearly a challenge.

Of the 20 subjects from this sample frame who carried out a full SCID interview (3 PGs and 17 Controls), 75% were excluded from scanning. For the most part these were Controls with current alcohol and drug problems (underreported in the prevalence study) or with a history of alcohol and drug problems. Some of the Control participants were also excluded for other psychopathology in the past 5 years (e.g., Depression, Specific Phobias). Only one PG was excluded at this stage (for Alcohol Dependence).

Of the 5 eligible participants for scanning from this sample frame, all 5 completed successful scans. The overall yield from this sample frame was however relatively poor. There is scientific value in employing linked datasets to conduct research, especially data drawn from random probability sampling (such as in the Prevalence Study) or from longitudinal or panel sampling (such as in the Panel Study). The former for example ensures that no self-selection or bias in participation occurs, which then allows us to draw valid inferences from our test subjects to the population at large. However, as detailed above, the pragmatic obstacles of obtaining sufficient subject numbers by drawing on survey data are substantial.

3.2 Source 3 Data (October 2010 – July 2011)

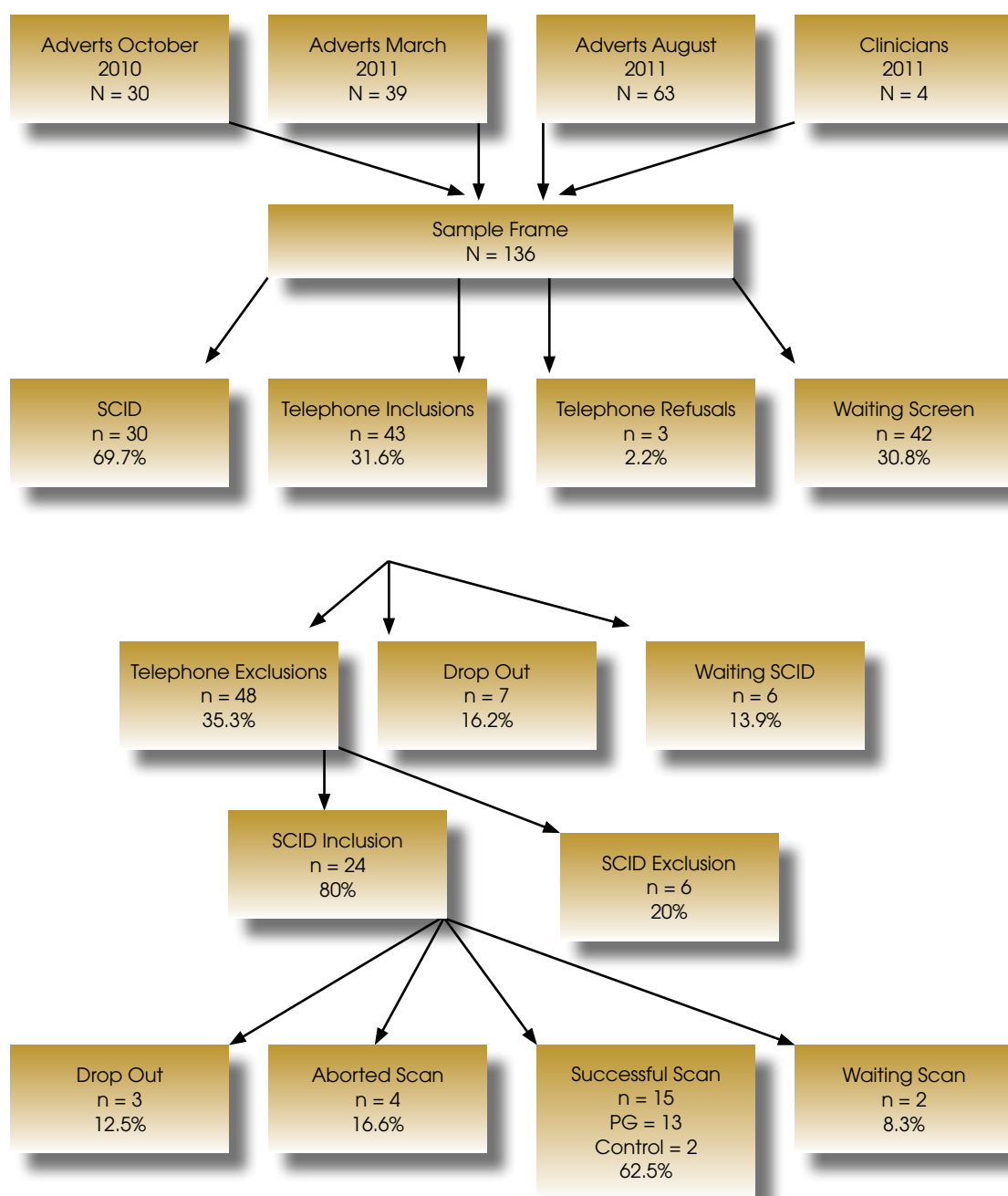
Three newspaper adverts targeting (initially) Pathological Gamblers were released in October 2010, March 2011, and August 2011. In addition NRGP clinicians have recently begun referring treatment-seeking PGs who are interested in research to our group. This kind of recruitment approach means that the sample frame self-selects (i.e., interested potential participants contact us). The sample frame is then interrogated via telephone and face-to-face interview screening to determine eligible

Figure 2. Cognitive Control Study: Flowchart - Recruitment, Assessment and Scanning (April 2010 – September 2010)

participants. This approach has (limiting) implications for how we evaluate the comorbidity data of our participants. However it also greatly improves the size of the potential subject pool. The flow chart below (Figure 3) documents the details of the recruitment process from telephone screening through to scanning for Source 3 Data.

Adverts in various community newspapers throughout Cape Town, as well as clinician referrals provided a sample frame of 136. Almost all potential participants identified themselves as having some problems with gambling as described in the advert, while two contacted us specifically to take part in the study as Controls. Adverts directly targeting controls will be released in early October.

Figure 3. Cognitive control study: Flowchart - Recruitment, Assessment and Scanning (October 2010 - August 2011)



Of the 136 potential participants, 31.6% were considered suitable for Day 1 participation after telephone screen, while 35.3% were excluded. A small number of callers were no longer interested in participating when they learned of the amount of money offered (2.2%). 30.8% of callers from the last round of adverts in August, have not yet fully completed the telephone screen. While almost all of these have been contacted, most have not kept (or agreed to a suitable time for) telephone screen appointments (i.e., we expect many of these to become coded as Refusals). On average it takes 4 calls/call attempts (mean) to take a respondent from initial contact through to booking a Day 1 appointment. Telephone screens take approximately 15 - 20 minutes.

Of the participants meeting telephone screen inclusion criteria 69.7% (n = 30) have been through full Day 1 interviews. These interviews take place during office hours, after hours and on weekends. As it is not uncommon for participants to miss appointments (even with appointment reminders) we continue to reschedule appointments until either an appointment is kept or the subject explicitly drops out. To date 16.2% (n = 7) have dropped out (i.e., repeated no-shows), while 13.9% (n = 6) are scheduled for appointments.

Of the participants completing Day 1 interviews 60% (n = 24) have been eligible for scanning, while 20% (n = 6) have been excluded. Reasons for exclusion among PGs include comorbid Alcohol Dependence and Drug Dependence/Abuse, specific Phobia for closed spaces, and Bipolar I disorder.

Of the participants eligible for scanning 62.5% (n = 15) have successfully completed scanning, 12.5% have dropped out and 16.6% have had to have scans aborted. The reasons cited for drop out include fear of physical abuse should a partner discover participation, fear of harm in the scanner, and unknown (i.e., no-shows, no longer telephone responding). The reasons for scan abortion, include size (n = 2) and anxiety in the scanner (n = 2).

3.3. Data collection summary

Completed Telephone Screen: 174

Completed SCID: 50

Completed Scan: 15 (PGs) + 5 (Controls) = 20

Data collection was scheduled for completion by the end of September. We are targeting at least 5 more PGs and 10 more Controls over the remainder of September but expect data collection will extend until the end of October.

4.1 Overview

An advantage of conducting structured clinical interview based research is the extent and quality of the data that may be obtained. While survey data is typically collected with larger samples, clinical, psychometric and qualitative detail must be sacrificed in order to obtain these large datasets from the field. Since neuroimaging research requires comparisons between relatively small groups of subjects, we have had the opportunity to extensively interview and assess Disordered Gamblers interested in participating in our research. Indeed this has been essential to ensure the neurological systems we are investigating are not complicated by problematic comorbid psychopathology (such as drug dependence, or mania). Although not all interviewed gamblers are thus suitable for scanning, the comorbidity, psychometric and qualitative data obtained with participants over the course of 4-hour long interviews is scientifically and pragmatically valuable.

In what follows we report firstly, on qualitative data from interviews with disordered gamblers, and secondly, on comorbidity data obtained from structured clinical assessments of current and lifetime psychopathology. In order to meaningfully present findings from our psychometric assessments of cognitive control we await comparison data from Control subjects.

4.2 Disordered Gambling Groups: Background

While almost all research groups commonly make the distinction between Pathological Gamblers and Problem Gamblers, the diagnostic criteria for this distinction remain unclear. Presently the most common approach (among researchers as well as practicing clinicians) is to consider Problem Gamblers as a subthreshold group. That is Problem Gamblers are those who demonstrate less than 5 of the 10 diagnostic symptoms recognized for Pathological Gambling. Pathological Gamblers on the other hand are those demonstrating 5 or more of these criteria.

To help inform this issue we may want to arrange or subtype different groups of gamblers based on socio-demographic, personality and motivational characteristics. Indeed, in line with this notion, the wider addiction literature supports the contention of distinct groups of substance abusers who use drugs and alcohol for very different reasons (Conrod, Pihl, Stewart, &

Dongier, 2000). In disordered gambling, as in substance disorders, group differences might be expected to have implications for aetiology, comorbidity and treatment.

Survey research serves as a first approximation for a descriptive project of this sort. Certain demographic characteristics are known to be associated with the development of Disordered Gambling. For example, in US studies, younger age, ethnic minority status, lower socioeconomic standing, marital situation (divorced or separated), and gender (male) are related to disordered gambling behaviour (see review by Petry, 2005). In South Africa, our group has found significant over-representation of Disordered Gambling among males, self-identified black racial status, ages 18-29, the unmarried, those who did not complete high school, the unemployed, and those living in Johannesburg or the East Rand (Ross, et al., 2009). In addition, consistent with findings elsewhere, Disordered Gambling in South Africa is comorbid with depression, anxiety, drug and alcohol problems (Sharp, et al., 2010). While descriptively informative, researchers have preferred to combine Problem and Pathological subgroups when analysing correlates/predictors and comorbidity. As a result survey research does not make clear how these groups might differ, even in broad socio-demographic terms.

There has though been some interest in subtyping individuals based on their motivational attributions or reasons for gambling (Blaszczynski, McConaghy, & Frankova, 1990; Blaszczynski & Nower, 2002; Blaszczynski, Wilson, & McConaghy, 1986; McCormick, 1987; McCormick & Taber, 1988) and recently in relating these subgroups to severity of gambling problems (Stewart & Zack, 2008; Stewart, Zack, Collins, & Klein, 2008). Early research distinguished the 'chronically under-stimulated' or 'bored' from the 'recurrently depressed' (Blaszczynski, et al., 1990; McCormick, 1987). Lesieur (2001) described three characteristic groups ('impulsive escape seekers', 'moderately impulsive action seekers', and 'normal problem gamblers') and Blaszczynski and Nower (2002) described groups of 'emotionally vulnerable', 'antisocial impulsivist', and 'behaviourally conditioned' gamblers. Although the proposed subgroups in each of these studies are subtly different, gambling in response to negative moods (e.g., coping) appears to be commonly distinguished from gambling for excitement (e.g., enhancement or sensation seeking). This distinction, also in the substance abuse literature, is increasingly gaining support in studies of disordered gambling.

For example, Stewart and Zack (2008) have produced a measure of gambling motives, the Gambling Motives Questionnaire (GMQ), modelled after the Drinking Motives Questionnaire (Cooper et al., 1992). This measure similarly identifies 'coping', 'enhancement' and 'social' subgroups. More recently, Stewart, Zack, Collins and Klein (2008) used cluster analyses to subtype reasons provided by probable-pathological and non-pathological gamblers on the Inventory of Gambling Situations (Turner & Littman-Sharp, 2006). Validating derived categories against their own measure of gambling motives they confirmed sub-groups for 'enhancement gambling', 'coping gambling' and 'low emotion-regulation gambling'. Further, these sub-groups showed interesting relationships to gambling problems. For example, 'coping gamblers' scored higher on measures of gambling frequency and gambling problems, consistent with results in the broader addiction literature. This group also had higher rates of comorbid substance disorders compared to 'enhancement' and low 'emotion-regulation' gamblers.

Although attribution research is complicated by recall error and bias, and thus the reasons or motives reported do not necessarily (or even typically) reflect causal influences, findings about perceived internal and external influences may have useful clinical implications. For example, knowledge of common attributions can feature in the design of treatment plans for specific subsets of patients, increasing awareness of erroneous and debilitating beliefs, as well as highlighting areas for enhancing patient motivation. Attributions can also be the focus of public awareness campaigns aimed at encouraging different subsets of disordered gamblers to contemplate behaviour change (Hodgins, Makarchuk, el-Guebaly, & Peden, 2002). Our interviews with Disordered gamblers provided us with the opportunity to describe gambling attributions among individuals with a history of gambling problems.

4.3 Disordered Gambling Groups: Case qualitative data.

For purposes of our research it was important to identify and to distinguish severely pathological gamblers – probable gambling addicts – from people who experience intermittent regret over their occasional over-spend on gambling. We did this by administering three levels of assessment. First we used gambling screens (the PGSI and the Gamblers Anonymous 20 Questions) to ensure participants fell into the High Risk range (a score of 8 and above, and 7 and above respectively). Then we used a prevalence questionnaire focused on assessing the type, frequency and duration of gambling as well as the amount most recently spent and the average monthly gambling spend compared against socio-economic status. Thereafter we administered the Structured Clinical Interview for Pathological Gambling, which allowed us to probe qualitatively across issues such as craving, compulsion and loss of control. In what follows

we describe two cases illustrating both the different disordered gambling groups and attribution subgroups.

Problem Gambler: 'Bart' is a 55 year-old male, married with two adult children. His highest qualification is Grade 12. He used to work as a warehouse manager for a supermarket chain but was given early retirement a year ago. He is currently seeking part time work consulting for his previous employer because his savings are dwindling and his wife is unemployed. He draws about R7600 a month from his retirement savings. His visits the casino 2 – 3 times per week with his wife (and often with a group of friends) and has been doing so for the past 12 years. He plays slots machines and in the past he and his wife usually gambled collectively between R1000 - R2500 per week, though in the last year this has reduced to about R500 per week. He does not think about gambling very often, even now that he can only gamble a smaller amount, though he does not want to give up visiting the casino because of the entertainment (and 'space') it provides for him and his wife. As a result of his weekly visits to the casino, he has recently started to acquire some credit card debt. When asked why he gambles, he responds that he enjoys sitting and chatting to friends whilst gambling and he finds it fun. He has never lied to anyone about his gambling, or done anything illegal to finance his gambling. He is however very worried that his financial situation will mean he can no longer visit the casino, and he feels obliged to keep providing this entertainment for his wife. He feels he has a gambling problem.

Pathological Gambler: 'Calvin' is a 53 year-old male, divorced with two children. His highest qualification is Grade 7. He recently moved back in with his ex-wife to help manage their son's drug addiction. He is employed as a building superintendent and earns R17000 a month. He has gambled for as long as he can remember, though most heavily over the past year. He gambles on Grandslots in bars 3 times per week and is not sure how much he gambles though he estimates that he spent about R6000 in the last month. About a year ago he asked for a bank loan of R50 000 to help with debt and the bank gave him R55 000. Within a few months the entire loan had been spent on gambling. He often thinks about ways to get money to gamble or to pay off his gambling debts. He says he gambles for the 'kicks', and so that he does 'not have to talk with others'. He does not tell anyone about his gambling and regularly gamblers during working hours when moving between building sites. He recently sought treatment for gambling problems though has subsequently dropped out. He feels he is in control of his gambling.

As is evident by comparison of the two cases, both are encountering problems with gambling, but in very different ways. While Bart scored highly on a gambling screen and prevalence questionnaire, clinical interview reveals he does not meet criteria

for pathological gambling. There is little craving, compulsion or loss of control in his behaviour though clearly his budget can no longer afford his gambling activity, and he is reluctant to give up the social enjoyment of gambling. Based on the gambling subtypes discussed above, Bart would be classified as a 'social gambler', who falls in the Problem Gambling range. A number of participants screened either telephonically or during Day 1 assessments present with this kind of gambling. The majority are elderly who view the casino as a safe and accessible outing. They gamble either with friends or family, or see gambling as a way to socialise with others, despite being unable to afford it. The other kind of Problem as opposed to Pathological gambler which we commonly see are those who are very poor, and who gamble as a means of attempting to supplement their income. While not gambling as often or as much, when they do gamble the effects to their budgets are serious, and they commonly experience frustration and regret over their actions.

Calvin on the other hand shows clear loss of control over his gambling, along with poor insight into his gambling problems. Despite serious gambling debt he continues to gamble and is preoccupied with obtaining money to gamble and win back his money. Of the gambling groups discussed above Calvin's reasons for gambling suggest he is an 'enhancement gambler' who falls in the Pathological Gambling range. Most of the pathological gamblers assessed in our study present with either this kind of gambling motive or as 'coping gamblers', who gamble specifically to escape dysphoric mood. The theme of gambling to avoid low mood is very common, as is a focus on the thrill and excitement of winning.

4.4 Psychiatric Comorbidity

Participants who meet criteria for Pathological Gambling undergo full diagnostic interview for lifetime and current psychopathology. While we are still collecting data to reach optimal sample size for comorbidity reporting, we present below the results of assessments for 27 Pathological Gamblers, organised by major DSM disorder groupings. Although our sample does not necessarily represent treatment seekers, the majority of participants did self-select (i.e., they contacted us in response to advertisements). It is therefore not unreasonable to assume these respondents, in being motivated to take part in the research, are more similar to treatment-seekers than to population samples of PGs. For this reason we should expect comorbidity to be higher in our sample than in survey data, as has been found to be the case among treatment-seekers in other research (Heyman 2009). We should therefore also be cautious in generalising these findings to the population of PGs at large.

4.4.1 Mood disorders

These disorders feature a disturbance in mood as the predominant feature. The main mood disorders include Major Depressive Disorder, Dysthymic Disorder and Bipolar disorder. Major Depressive Disorder is characterised by one or more Major Depressive Episodes (i.e., at least 2 weeks of depressed mood or loss of interest accompanied by at least four additional symptoms of depression). Dysthymic Disorder is characterised by at least 2 years of depressed mood for more days than not, accompanied by additional depressive symptoms that do not meet criteria for a Major Depressive Episode. Where Major Depressive Disorder overlaps with Dysthymic Disorder (subject to certain timing conditions), so called 'double depression' is diagnosed. Bipolar disorder (either I or II) features one or more Depressive Episodes accompanied by manic (or mixed) or hypomanic episodes respectively.

Of the 27 PGs interviewed 55.5% (n = 15) had suffered some form of mood disorder at some point in their lives. Major Depressive Disorder occurred in 37% (n = 10) of PGs (lifetime) and was currently present in 14.8% (n = 4) of PGs (current). Dysthymic Disorder was currently present in 29.6% (n = 8) of PGs. Only one participant met criteria for Bipolar disorder (Bipolar 1).

4.4.2 Substance-related disorders

These disorders include those related to the taking of a drug of abuse (including alcohol). DSM defined Substance Use Disorders include Substance Dependence, characterised by a cluster of cognitive, behavioural and physiological symptoms indicating continued use despite significant substance-related problems, and Substance Abuse, characterised by a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to repeated use.

Of the 27 PGs interviewed 70.2% (n = 19) had suffered some Substance Use Disorder at some point in their lives. Alcohol abuse was present in 29.6% (n = 8) of PGs (lifetime, not including dependence) and 11.1% (n = 3) of PGs currently abused alcohol. Dependence was present in 25.9% (n = 7) of PGs (lifetime) and was current in 7.4% (n = 2). A history of Substance Abuse and/or Dependence for various substances (e.g., Mandrax, Cannabis, Cocaine, Methamphetamine) was also common. 11.1% (n = 3) of PGs had a history of Substance Abuse with one or more substances (not including those with substance dependence) and 29.6% (n = 8) had a history of Substance Dependence with one or more substances. Only one subject was excluded for a current Substance Use disorder.

4.4.3 Anxiety disorders

The main anxiety disorders include Panic Disorder, Specific Phobia, Social Phobia, Obsessive-Compulsive Disorder, Posttraumatic Stress Disorder, and Generalized Anxiety Disorder. Panic disorder is characterised by recurrent unexpected panic attacks about which there is persistent concern. Obsessive-Compulsive Disorder is characterised by obsessions (which cause anxiety or distress) and/or by compulsions (which serve to neutralise anxiety). Posttraumatic Stress Disorder is characterised by reexperiencing of an extremely traumatic event accompanied by symptoms of increased arousal and by avoidance of stimuli associated with the trauma. Generalized Anxiety Disorder is characterized by at least 6 months of persistent and excessive anxiety and worry.

Of the 27 PGs interviewed, 55% ($n = 15$) met criteria for some Anxiety Disorder at some time in their lives. In addition 25.9% ($n = 7$) of PGs also met subthreshold criteria for an Anxiety Disorder either in conjunction with full criteria for another disorder or separately. Social Phobia occurred in 7.4% ($n = 2$) of PGs while subthreshold Social Phobia occurred in 11.1% ($n = 3$). Specific Phobia occurred in 33.3% ($n = 9$) of PGs. Unfortunately this commonly included fear of closed spaces, which ruled these participants out for scanning. Obsessive-Compulsive Disorder occurred in 11.1% ($n = 3$) of PGs while a further 7.4% ($n = 2$) were subthreshold for this disorder. Panic Disorder occurred in 7.4% ($n = 2$) of PGs. Finally Anxiety Disorder Not Otherwise Specified occurred in 7.4% ($n = 2$) of PGs.

4.4.4 Other disorders

We also assessed Impulse Control Disorders as well as Eating Disorders. 7.4% ($n = 2$) of PGs had suffered from Anorexia Nervosa (refusal to maintain minimally normal body weight) at some point in their lives, 3.7% ($n = 1$) had suffered from Tourette's Disorder (motor and vocal tics) and 3.7% ($n = 1$) had suffered from Trichotillomania (compulsive hair pulling).

4.5 Conclusion

While the CCS is still in progress, our initial descriptive findings suggest distinct groups of disordered gamblers identified by different attributions or reasons for gambling as well as symptom presentation. In addition, consistent with international literature, clinical assessments have revealed high rates of comorbidity among Pathological Gamblers, especially for Mood, Anxiety and Substance Use Disorders.

REFERENCES

- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders, 4th ed.* Washington, DC: American Psychiatric Association.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders, 4th ed., Text Revision.* Washington, DC: American Psychiatric Association.
- American Psychiatric Association. (2010). DSM-5 development. Proposed revision, pathological gambling. Retrieved December 10, 2010, from <http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=210>
- Bjork, J. M., & Hommer, D. W. (2007). Anticipating instrumentally obtained and passively-received rewards: a factorial fMRI investigation. *Behav Brain Res*, 177(1), 165-170.
- Bjork, J. M., Knutson, B., Fong, G. W., Caggiano, D. M., Bennett, S. M., & Hommer, D. W. (2004). Incentive-elicited brain activation in adolescents: similarities and differences from young adults. *J Neurosci*, 24(8), 1793-1802.
- Blaszczynski, A., McConaghy, N., & Frankova, A. (1990). Boredom proneness in pathological gambling. *Psychol Rep*, 67(1), 35-42.
- Blaszczynski, A., & Nower, L. (2002). A pathways model of problem and pathological gambling. *Addiction*, 97(5), 487-499.
- Blaszczynski, A., Wilson, A., & McConaghy, N. (1986). Sensation seeking and pathological gambling. *Br J Addict*, 81(1), 113-117.
- Breiter, H. C., Aharon, I., Kahneman, D., Dale, A., & Shizgal, P. (2001). Functional imaging of neural responses to expectancy and experience of monetary gains and losses. *Neuron*, 30(2), 619-639.
- Conrod, P. J., Pihl, R. O., Stewart, S. H., & Dongier, M. (2000). Validation of a system of classifying female substance abusers on the basis of personality and motivational risk factors for substance abuse. *Psychol Addict Behav*, 14(3), 243-256.
- Daw, N. D., & Doya, K. (2006). The computational neurobiology of learning and reward. *Curr Opin Neurobiol*, 16(2), 199-204.
- Delgado, M. R. (2007). Reward-related responses in the human striatum. *Ann N Y Acad Sci*, 1104, 70-88.
- Delgado, M. R., Gillis, M. M., & Phelps, E. A. (2008). Regulating the expectation of reward via cognitive strategies. *Nat Neurosci*, 11(8), 880-881.
- Dellis, A., Spurrett, D., Hofmeyr, A., Kincaid, H., Rousseau, J., Sharp, C., et al. (2009, Nov. 14th - 18th). *Gambling prevalence and severity among Rural and peri-urban poor South Africans in Kwa-Zulu Natal*. Paper presented at the 10th Annual National Center for Responsible Gambling (NCRG) Conference on Gambling and Addiction, Las Vegas, Nevada.
- Desmond, J. E., & Glover, G. H. (2002). Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. *J Neurosci Methods*, 118(2), 115-128.
- Diekhof, E. K., Falkai, P., & Gruber, O. (2008). Functional neuroimaging of reward processing and decision-making: a review of aberrant motivational and affective processing in addiction and mood disorders. *Brain Res Rev*, 59(1), 164-184.
- Dillon, D. G., Holmes, A. J., Jahn, A. L., Bogdan, R., Wald, L. L., & Pizzagalli, D. A. (2008). Dissociation of neural regions associated with anticipatory versus consummatory phases of incentive processing. *Psychophysiology*, 45(1), 36-49.
- Dodge, K. A. (2001). The science of youth violence prevention. Progressing from developmental epidemiology to efficacy to effectiveness to public policy. *Am J Prev Med*, 20(1 Suppl), 63-70.
- Dreher, J. C., Schmidt, P. J., Kohn, P., Furman, D., Rubinow, D., & Berman, K. F. (2007). Menstrual cycle phase modulates reward-related neural function in women. *Proc Natl Acad Sci U S A*, 104(7), 2465-2470.
- Ernst, M., Nelson, E. E., McClure, E. B., Monk, C. S., Munson, S., Eshel, N., et al. (2004). Choice selection and reward anticipation: an fMRI study. *Neuropsychologia*, 42(12), 1585-1597.
- Everitt, B. J., & Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci*, 8(11), 1481-1489.

- Ferris, J., & Wynne, H. (2001, February). *The Canadian Problem Gambling Index: Final report*. Ottawa: Canadian Centre on Substance Abuse.
- First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1998). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research version, Patient Edition with Psychotic Screen*. New York: New York State Psychiatric Institute.
- Frascella, J., Potenza, M. N., Brown, L. L., & Childress, A. R. (2010). Shared brain vulnerabilities open the way for nonsubstance addictions: carving addiction at a new joint? *Ann NY Acad Sci*, 1187, 294-315.
- Galvan, A., Hare, T. A., Davidson, M., Spicer, J., Glover, G., & Casey, B. J. (2005). The role of ventral frontostriatal circuitry in reward-based learning in humans. *J Neurosci*, 25(38), 8650-8656.
- Garnefski, N., Kraaij, V., & Spinhoven, P. (2001). Negative life events, cognitive emotion regulation and emotional problems. *Personality and Individual Differences*, 30, 1311-1327.
- Glimcher, P.W. (2003). *Decisions, Uncertainty, and the Brain*. Cambridge, Mass.: MIT Press.
- Glimcher, P.W., & Rustichini, A. (2004). Neuroeconomics: the consilience of brain and decision. *Science*, 306(5695), 447-452.
- Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry*, 159(10), 1642-1652.
- Gottfried, J. A., O'Doherty, J., & Dolan, R. J. (2003). Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science*, 301(5636), 1104-1107.
- Grant, J. E., Potenza, M. N., Weinstein, A., & Gorelick, D. A. (2010). Introduction to behavioral addictions. *Am J Drug Alcohol Abuse*, 36(5), 233-241.
- Grant, J. E., Steinberg, M. A., Kim, S. W., Rounsaville, B. J., & Potenza, M. N. (2004). Preliminary validity and reliability testing of a structured clinical interview for pathological gambling. *Psychiatry Res*, 128(1), 79-88.
- Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *J Pers Soc Psychol*, 85(2), 348-362.
- Hodgins, D. C., Makarchuk, K., el-Guebaly, N., & Peden, N. (2002). Why problem gamblers quit gambling: A comparison of methods and samples. *Addiction Research & Theory*, 10, 203-218.
- Hodgins, D. C., Stea, J. N., & Grant, J. E. (2011). Gambling disorders. *Lancet*.
- Holden, C. (2010). Psychiatry. Behavioral addictions debut in proposed DSM-V. *Science*, 327(5968), 935.
- Hyman, S. E., Malenka, R. C., & Nestler, E. J. (2006). Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci*, 29, 565-598.
- Jensen, J., McIntosh, A. R., Crawley, A. P., Mikulis, D. J., Remington, G., & Kapur, S. (2003). Direct activation of the ventral striatum in anticipation of aversive stimuli. *Neuron*, 40(6), 1251-1257.
- Kincaid, H., Daniels, R., Dellis, A., Hofmeyr, A., Rousseau, J., Sharp, C., et al. (submitted, 2010). A taxometric analysis of the performance of the problem gambling severity index in a south african urban sample. *Addiction*.
- Kirsch, P., Schienle, A., Stark, R., Sammer, G., Blecker, C., Walter, B., et al. (2003). Anticipation of reward in a nonaversive differential conditioning paradigm and the brain reward system: an event-related fMRI study. *Neuroimage*, 20(2), 1086-1095.
- Knutson, B., Adams, C. M., Fong, G. W., & Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci*, 21(16), RC159.
- Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., & Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport*, 12(17), 3683-3687.
- Knutson, B., Fong, G. W., Bennett, S. M., Adams, C. M., & Hommer, D. (2003). A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. *Neuroimage*, 18(2), 263-272.
- Knutson, B., Taylor, J., Kaufman, M., Peterson, R., & Glover, G. (2005). Distributed neural representation of expected value. *J Neurosci*, 25(19), 4806-4812.

- Ladouceur, R. (2004). Perceptions among pathological and nonpathological gamblers. *Addict Behav*, 29(3), 555-565.
- Ladouceur, R., Sylvain, C., Boutin, C., Lachance, S., Doucet, C., Leblond, J., et al. (2001). Cognitive treatment of pathological gambling. *J Nerv Ment Dis*, 189(11), 774-780.
- Lesieur, H. R. (2001). *Cluster analysis of types of inpatient pathological gamblers*. Unpublished Dissertation Abstracts International, 62B, 2065.
- Lesieur, H. R., & Blume, S. B. (1987). The South Oaks Gambling Screen (SOGS): a new instrument for the identification of pathological gamblers. *Am J Psychiatry*, 144(9), 1184-1188.
- Liu, X., Powell, D. K., Wang, H., Gold, B. T., Corbly, C. R., & Joseph, J. E. (2007). Functional dissociation in frontal and striatal areas for processing of positive and negative reward information. *J Neurosci*, 27(17), 4587-4597.
- McClure, S. M., Daw, N. D., & Montague, P. R. (2003). A computational substrate for incentive salience. *Trends Neurosci*, 26(8), 423-428.
- McClure, S. M., York, M. K., & Montague, P. R. (2004). The neural substrates of reward processing in humans: the modern role of fMRI. *Neuroscientist*, 10(3), 260-268.
- McCormick, R. A. (1987). Pathological gambling: A parsimonious need state model. *Journal of Gambling Behavior*, 3, 257-263.
- McCormick, R. A., & Taber, J. I. (1988). Attributional style in pathological gamblers in treatment. *J Abnorm Psychol*, 97(3), 368-370.
- Montague, P. R., & Berns, G. S. (2002). Neural economics and the biological substrates of valuation. *Neuron*, 36(2), 265-284.
- Montague, P. R., Hyman, S. E., & Cohen, J. D. (2004). Computational roles for dopamine in behavioural control. *Nature*, 431(7010), 760-767.
- O'Brien, C. P., Potenza, M. N., & Cottler, L. B. (2010, Nov. 1 - 16). *Rethinking pathological gambling: Proposed changes for DSM-V*. Paper presented at the 11th Annual NCRG conference on gambling and addiction: Redefining diagnosis, treatment, research and responsible gaming for the 21st century, Las Vegas, Nevada.
- O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., & Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science*, 304(5669), 452-454.
- O'Doherty, J. P. (2004). Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Curr Opin Neurobiol*, 14(6), 769-776.
- O'Doherty, J. P., Deichmann, R., Critchley, H. D., & Dolan, R. J. (2002). Neural responses during anticipation of a primary taste reward. *Neuron*, 33(5), 815-826.
- Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends Cogn Sci*, 9(5), 242-249.
- Petry, N. M. (2005). *Pathological gambling: Etiology, comorbidity, and treatment*. Washington, DC: American Psychological Association Press.
- Petry, N. M. (2006). Should the scope of addictive behaviors be broadened to include pathological gambling? *Addiction*, 101 Suppl 1, 152-160.
- Petry, N. M. (2009). Disordered Gambling and Its Treatment. *Cognitive and Behavioral Practice*, 16(4), 457-467.
- Petry, N. M., Ammerman, Y., Bohl, J., Doersch, A., Gay, H., Kadden, R., et al. (2006). Cognitive-behavioral therapy for pathological gamblers. *J Consult Clin Psychol*, 74(3), 555-567.
- Potenza, M. N. (2006). Should addictive disorders include non-substance-related conditions? *Addiction*, 101(Suppl 1), 142-151.
- Potenza, M. N. (2008). Review. The neurobiology of pathological gambling and drug addiction: an overview and new findings. *Philos Trans R Soc Lond B Biol Sci*, 363(1507), 3181-3189.
- Potenza, M. N., & Taylor, J. R. (2009). Found in translation: Understanding impulsivity and related constructs through integrative preclinical and clinical research. *Biological Psychiatry*, 66(8), 714-716.
- Potenza, M. N., & Winters, K. C. (2003). The neurobiology of pathological gambling: translating research findings into clinical advances. *J Gambli Stud*, 19(1), 7-10.
- Rademacher, L., Krach, S., Kohls, G., Irmak, A., Grunder, G., & Spreckelmeyer, K. N. (2010). Dissociation of neural networks for anticipation and consumption of monetary and social rewards. *Neuroimage*, 49(4), 3276-3285.

- Ross, D., Collins, P., Dellis, A., Hofmeyr, A., Kincaid, H., Rousseau, J., et al. (2010). *Summary of basic data on the National Urban Prevalence Study on Gambling Behaviour*. The Research Division of the National Responsible Gambling Programme.
- Ross, D., Hofmeyr, A., Dellis, A., Rousseau, J., Schuhr, A., Sharp, C., et al. (2009, Nov. 14th - 18th). *Predictors of problem gambling in a developing country: The 2008 South African urban prevalence study*. Paper presented at the 10th Annual National Center for Responsible Gambling (NCRG) Conference on Gambling and Addiction, Las Vegas, Nevada.
- Ross, D., Sharp, C., Vuchinich, R., & Spurrett, D. (2008). *Midbrain mutiny: The piceoeconomics and neuroeconomics of disordered gambling*. Cambridge, Massachusetts: The MIT Press.
- Rutledge, R. B., Dean, M., Caplin, A., & Glimcher, P.W. (2010). Testing the reward prediction error hypothesis with an axiomatic model. *J Neurosci*, 30(40), 13525-13536.
- Schultz, W., Dayan, P., & Montague, P.R. (1997). A neural substrate of prediction and reward. *Science*, 275 (5306), 1593-1599.
- Schultz, W. (2004). Neural coding of basic reward terms of animal learning theory, game theory, microeconomics and behavioural ecology. *Curr Opin Neurobiol*, 14(2), 139-147.
- Schultz, W. (2010). Dopamine signals for reward value and risk: basic and recent data. *Behav Brain Funct*, 6, 24.
- Sharp, C., Hofmeyr, A., Dellis, A., Kincaid, H., Rousseau, J., Ainslie, G., et al. (2010, Nov., 14th - 18th). *The comorbidity of gambling problems, anxiety, depression and substance use in a representative urban sample of 3000 South Africans*. Paper presented at the 11th Annual National Center for Responsible Gambling (NCRG) Conference on Gambling and Addiction.
- Sharp, C., Steinberg, L., Yaroslavsky, I., Hofmeyr, A., Dellis, A., Ross, D., et al. (submitted, 2010). An item response theory analysis of the Problem Gambling Severity Index in a national representative sample. *Psychological Medicine*.
- Sharp, C.**, Steinberg, L., Yaroslavsky, I., Hofmeyr, A., Dellis, A., Kincaid, H., & Ross, D. (in press). An item response theory analysis of the Problem Gambling Severity Index. *Assessment*.
- Sinha, R., Lacadie, C., Skudlarski, P., Fulbright, R. K., Rounsaville, B. J., Kosten, T. R., et al. (2005). Neural activity associated with stress-induced cocaine craving: a functional magnetic resonance imaging study. *Psychopharmacology (Berl)*, 183(2), 171-180.
- Spreckelmeyer, K. N., Krach, S., Kohls, G., Rademacher, L., Irmak, A., Konrad, K., et al. (2009). Anticipation of monetary and social reward differently activates mesolimbic brain structures in men and women. *Soc Cogn Affect Neurosci*, 4(2), 158-165.
- Stewart, S. H., & Zack, M. (2008). Development and psychometric evaluation of a three-dimensional Gambling Motives Questionnaire. *Addiction*, 103(7), 1110-1117.
- Stewart, S. H., Zack, M., Collins, P., & Klein, R. M. (2008). Subtyping pathological gamblers on the basis of affective motivations for gambling: relations to gambling problems, drinking problems, and affective motivations for drinking. *Psychol Addict Behav*, 22(2), 257-268.
- Turner, N., & Littman-Sharp, N. (2006). *Inventory of Gambling Situations User's Guide*. Toronto: Centre for Addiction and Mental Health.
- van Holst, R. J., van den Brink, W., Veltman, D. J., & Goudriaan, A. E. (2010a). Brain imaging studies in pathological gambling. *Curr Psychiatry Rep*, 12(5), 418-425.
- van Holst, R. J., van den Brink, W., Veltman, D. J., & Goudriaan, A. E. (2010b). Why gamblers fail to win: a review of cognitive and neuroimaging findings in pathological gambling. *Neurosci Biobehav Rev*, 34(1), 87-107.
- Wareham, J. D., & Potenza, M. N. (2010). Pathological gambling and substance use disorders. *Am J Drug Alcohol Abuse*, 36(5), 242-247.
- Wells, A., & Davies, M. I. (1994). The Thought Control Questionnaire: a measure of individual differences in the control of unwanted thoughts. *Behav Res Ther*, 32(8), 871-878.
- Winters, K. C. (2010, Nov. 1 - 16, 2010). *DSM-V discussion groups: Research group*. Paper presented at the 11th Annual NCRG conference on gambling and addiction: Redefining diagnosis, treatment, research and responsible gaming for the 21st century, Las Vegas, Nevada.
- Young, M. M., & Wohl, M. J. (2009). The Gambling Craving Scale: Psychometric validation and behavioral outcomes. *Psychol Addict Behav*, 23(3), 512-522.
- Zuckerman, M., Eysenck, S. B. J., & Eysenck, H. J. (1978). Sensation seeking in Europe and America: Cross-cultural, age, and sex comparisons. *Journal of Consulting and Clinical Psychology*, 46(1), 139-149.



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