EFFECTS OF DOPAMINE ANTAGONISTS ON GAMBLING REINFORCEMENT
AND THE IMPACT OF PRIOR EXPOSURE IN PATHOLOGICAL GAMBLERS AND
CONTROLS

By

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A thesis submitted in conformity with the requirements for the degree of
Master of Science
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This study sought to determine the roles of D1 and D2 receptors in mediating gambling reinforcement in pathological gamblers and controls (n=24/group), and the influence of reward novelty on these effects. Subjects received D2 antagonist, haloperidol (3mg), or D1-D2 antagonist, fluphenazine (3mg) in a placebo-controlled, counterbalanced, two-session design. Incentive motivation and hedonic impact were assessed before and after a 15-min slot machine game. Haloperidol tended to increase pre-game motivation but reduce the priming effect of the slot machine, while fluphenazine increased positive mood ratings but reduced motivation to gamble. Haloperidol effects were stronger when it was received on the first session, while fluphenazine had stronger effects after prior drug-free exposure. Results suggest D1 signaling is central to reward expectancy and motivation to gamble, and that moderate stimulation increases positive affect while reducing motivation to gamble. D1 blockade may also enhance reinforcement of a familiar task by interfering with reward expectancy.
ACKNOWLEDGMENTS

I would like to sincerely thank my supervisor Dr. Martin Zack for his expertise and guidance. In addition to his invaluable patience and practical assistance, his vision and enthusiasm for this project has been very important both the present work and my future goals. I’m very grateful for the opportunity to learn from him for the past two years.

Thanks also to my advisor Dr. Krista Lanctôt for contributing important support, direction, and perspective to my work in addition to practical assistance.

I am very grateful to my colleagues Daniel Tatone, Tim Fang, and Alice Chen for their assistance with the project and helpful discussions. I’d also like to acknowledge Aditi Kalia for her previous work on this project.

I would also like to thank Dr. Daniela Lobo for her expertise and generosity with her time, without which this project would not have been completed. Thanks also to Dr. Dan DiGiacomo for his help in the recruitment process.

I would also like to acknowledge the valuable contributions of the CAMH pharmacy, Dr. Dale Wiebe and the staff at the CAMH Addiction Medicine Clinic, CAMH Clinical Laboratory, and Amanda King and the nurses in the Women’s Inpatient Program for their help with this study.
# TABLE OF CONTENTS

1. INTRODUCTION .................................................................................................................1
  1.1 Overview and Rationale .................................................................................................1
  1.2 Literature Review ...........................................................................................................2
    1.2.1 Pathological Gambling ...........................................................................................2
      1.2.1.1 Treatment .......................................................................................................3
      1.2.1.2 Etiology .........................................................................................................4
    1.2.2 Overview of the Dopamine System ..........................................................................5
      1.2.2.1 Dopamine Receptor Subtypes .........................................................................5
    1.2.3 Dopamine Dysfunction in PG ................................................................................6
      1.2.3.1 Sensitization ....................................................................................................7
    1.2.4 Dopamine in Reward and Addiction ........................................................................8
      1.2.4.1 Differential Effects of D1 and D2 Receptors ....................................................8
      1.2.4.2 Hedonic Impact, Inventive Salience, and Dopamine .........................................9
      1.2.4.3 Phasic and Tonic Signaling ............................................................................10
    1.2.5 D1 Activation in Reward .......................................................................................11
      1.2.5.1 D1 and D2 Receptors in Gambling Reinforcement and PG ............................13
    1.2.6 Learning, Conditioning and Novelty in Reward Response ....................................14
      1.2.6.1 Cue Conditioning ............................................................................................14
      1.2.6.2 Uncertainty and Reward Prediction Error ......................................................15
      1.2.6.3 Temporal Difference Reinforcement Learning ...............................................16
      1.2.6.4 Implications for PG .......................................................................................16
  1.3 Objectives .....................................................................................................................17
  1.4 Hypotheses ...................................................................................................................18

2. MATERIALS AND METHODS .............................................................................................20
  2.1 Study Design .................................................................................................................20
  2.2 Study Medications ........................................................................................................20
    2.2.1 Haloperidol ..........................................................................................................20
    2.2.2 Fluphenazine ........................................................................................................21
    2.2.3 Rationale for Drug Selection ..................................................................................21
    2.2.4 Diphenhydramine ...............................................................................................22
2.3 Participants ........................................................................................................................................22
  2.3.1 Study Payment ..........................................................................................................................23
  2.3.2 Participant Safety and Precautions .........................................................................................24
2.4 Apparatus ........................................................................................................................................24
2.5 Screening Instruments ..................................................................................................................25
2.6 Trait Scales ......................................................................................................................................27
2.7 Neuropsychological Tasks ............................................................................................................27
2.8 Experimental Indices .....................................................................................................................29
  2.8.1 Self-Report Questionnaires .....................................................................................................29
  2.8.2 Cognitive/Behavioural Tasks .................................................................................................31
2.9 Procedure .........................................................................................................................................33
  2.9.1 Recruitment and Screening ....................................................................................................33
  2.9.2 Group Assignment and Matching ............................................................................................35
  2.9.3 Test Day Procedure ..................................................................................................................35
2.10 Data Analysis ................................................................................................................................37
3. RESULTS ...........................................................................................................................................39
  3.1 Recruitment and Study Subjects .................................................................................................39
    3.1.1 Subject Characteristics ............................................................................................................40
  3.2 Experimental Outcomes ..............................................................................................................42
    3.2.1 Self-Report Scales ..................................................................................................................42
      3.2.1.1 Desire to Gamble ................................................................................................................42
      3.2.1.2 Confidence to Resist Gambling .........................................................................................46
      3.2.1.3 VAS – Pleasurable Effects of the Slot Machine ...............................................................50
    3.2.2 Specificity of Subjective Effects .............................................................................................54
      3.2.2.1 VAS – Desire to Drink Alcohol .........................................................................................54
    3.2.3 Subjective Drug-Like Rewarding and Aversive Effects: ARCI Subscales .......................57
      3.2.3.1 ARCI-MBG (Euphoria) ......................................................................................................57
      3.2.3.2 ARCI-AMPH (Psychomotor Stimulation) ..........................................................................61
      3.2.3.3 ARCI-LSD (Dysphoria) ....................................................................................................65
    3.2.4 Mood States: POMS Subscales ..............................................................................................69
      3.2.4.1 POMS – Vigor ...................................................................................................................69
      3.2.4.2 POMS – Depression/Dejection .........................................................................................72
3.2.4.3 POMS – Anger/Hostility ................................................................. 75
3.2.5 Betting Behaviour on the Slot Machine ........................................... 79
3.2.6 Slot Machine Winnings (Final Credit Tally) ....................................... 83
3.2.7 Cognitive Tasks .................................................................................. 85
  3.2.7.1 Rapid Reading Task ...................................................................... 85
  3.2.7.2 Stop-Signal Task .......................................................................... 89
3.2.8 Risk-Taking: Game of Dice Task ....................................................... 92
3.2.9 Physiological Measures ...................................................................... 95
  3.2.9.1 Systolic BP .................................................................................... 95
  3.2.9.2 Diastolic BP .................................................................................. 99
  3.2.9.3 Heart Rate .................................................................................... 101
3.2.10 Supplemental Results ....................................................................... 10
  3.2.10.1 Capsule Contents Evaluation ...................................................... 104
  3.2.10.2 Symptom Side Effects Checklist .................................................. 104

4. DISCUSSION .......................................................................................... 106
  4.1 Subjective Reinforcement ................................................................... 108
    4.1.1 VAS – Incentive Motivation ............................................................ 108
    4.1.2 Hedonic Impact: VAS – Pleasurable Effects of the Slot Machine .... 109
    4.1.3 Drug-Like Rewarding and Aversive Effects: ARCI Subscales ........ 109
    4.1.4 Mood States: POMS Subscales .................................................... 110
  4.2 Betting Behaviour ................................................................................ 110
  4.3 Cognitive/Behavioural Tasks ............................................................... 111
    4.3.1 Rapid Reading Task ...................................................................... 111
    4.3.2 Stop-Signal Task .......................................................................... 112
  4.4 Game of Dice Task .............................................................................. 112
  4.5 Physiological Effects ........................................................................... 113
  4.6 Hypothesis 1 ....................................................................................... 113
  4.7 Hypothesis 2 ....................................................................................... 114
  4.8 Hypothesis 3 ....................................................................................... 115
  4.9 General Discussion ............................................................................ 116
  4.10 Limitations ........................................................................................ 120
  4.11 Future Directions .............................................................................. 121
4.12 Conclusions ........................................................................................................122

REFERENCES ............................................................................................................124

APPENDICES ............................................................................................................134
LIST OF TABLES

Table 1  Inclusion criteria…………………………………………………………………………23
Table 2  Test session timeline……………………………………………………………………36
Table 3  Mean (SD) background characteristics of each subgroup…………………40
Table 4  Mean (SD) scores and measures of personality, gambling beliefs, drug/alcohol use in each subgroup …………………………………………………………….41
Table 5  Mean (SD) cognitive proficiency scores for each subgroup .................41
Table 6  Capsule contents evaluation response frequencies for haloperidol subgroups ………………………………………………………………………………………………104
Table 7  Capsule contents evaluation response frequencies for fluphenazine subgroups ………………………………………………………………………………………………104
# LIST OF FIGURES

1. Proposed inverted U relationship between D1 receptor activation and stimulant reinforcement ........................................................................................................11

2. Proposed inverted U relationship between D1 receptor activation and gambling reinforcement, and predicted effects of DA antagonists ..................................................14

3. Flow chart showing subject recruitment ..........................................................................................................................39

4. Mean VAS Desire to Gamble scores under drug and placebo for HCs ..................43

5. Mean VAS Desire to Gamble scores under drug and placebo for PGs .................44

6. Mean VAS Confidence to Resist Gambling scores under drug and placebo for HCs ....47

7. Mean VAS Confidence to Resist Gambling scores under drug and placebo for PGs ....48

8. Mean VAS scores for subjective pleasurable effects of the slot machine under drug and placebo for HCs ...................................................................................................... 51

9. Mean VAS scores for subjective pleasurable effects of the slot machine under drug and placebo for PGs ...................................................................................................... 52

10. Mean VAS Desire to Drink Alcohol scores under drug and placebo for HCs ............ 55

11. Mean VAS Desire to Drink Alcohol scores under drug and placebo for PGs ........... 56

12. Mean ARCI-MBG scores under drug and placebo for HCs ....................................... 58

13. Mean ARCI-MBG scores under drug and placebo for PGs ....................................... 59

14. Mean ARCI-AMPH scores under drug and placebo for HCs ....................................... 62

15. Mean ARCI-AMPH scores under drug and placebo for PGs ....................................... 63

16. Mean ARCI-LSD scores under drug and placebo for HCs ......................................... 66

17. Mean ARCI-LSD scores under drug and placebo for PGs ......................................... 67

18. Mean POMS-Vigor scores under drug and placebo for HCs ..................................... 70

19. Mean POMS-Vigor scores under drug and placebo for PGs ..................................... 71

20. Mean POMS-Depression/dejection scores under drug and placebo for HCs ............. 73

21. Mean POMS-Depression/dejection scores under drug and placebo for PGs ............ 74
22. Mean POMS-Anger/hostility scores under drug and placebo for HCs .......................... 76
23. Mean POMS-Anger/hostility scores under drug and placebo for PGs .......................... 77
24. Mean number of lines selected per spin on a slot machine game in HCs ..................... 80
25. Mean number of lines selected per spin on a slot machine game in PGs ..................... 80
26. Mean number of credits bet per line on a slot machine game in HCs ......................... 81
27. Mean number of credits bet per line on a slot machine game in PGs ......................... 81
28. Mean number of credits remaining after 15 minutes of play on a slot machine game in HCs ........................................................................................................................................ 84
29. Mean number of credits remaining after 15 minutes of play on a slot machine game in PGs ........................................................................................................................................ 84
30. Percent difference in Reading Time from Neutral for words in four categories for HCs under drug and placebo ........................................................................................................................................ 87
31. Percent difference in Reading Time from Neutral for words in four categories for PGs under drug and placebo ........................................................................................................................................ 88
32. Stop-signal reaction time (SSRT) scores (ms) for HCs under drug and placebo .......... 90
33. Stop-signal reaction time (SSRT) scores (ms) for PGs under drug and placebo .......... 90
34. Mean Game of Dice Task risk-taking scores for HCs ................................................. 93
35. Mean Game of Dice Task risk-taking scores for PGs ................................................. 94
36. Mean systolic blood pressure (mmHg) under drug and placebo for HCs ...................... 96
37. Mean systolic blood pressure (mmHg) under drug and placebo for PGs ...................... 97
38. Mean diastolic blood pressure (mmHg) under drug and placebo for HCs .................... 99
39. Mean diastolic blood pressure (mmHg) under drug and placebo for PGs .................... 100
40. Mean heart rate (beats per minute) under drug and placebo for HCs .......................... 102
41. Mean heart rate (beats per minute) under drug and placebo for PGs .......................... 103
### LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT</td>
<td>Serotonin</td>
</tr>
<tr>
<td>ADS</td>
<td>Alcohol Dependence Scale</td>
</tr>
<tr>
<td>ARCI</td>
<td>Addiction Research Clinical Inventory</td>
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<tr>
<td>ARCI-AMPH</td>
<td>ARCI Amphetamine subscale</td>
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<tr>
<td>ARCI-BG</td>
<td>ARCI Benzedrine Group subscale</td>
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<td>ARCI-LSD</td>
<td>ARCI Lysergic Acid Diethylamine subscale</td>
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<td>ARCI-MBG</td>
<td>ARCI Morphine/Benzedrine subscale</td>
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<tr>
<td>ARCI-PCAG</td>
<td>ARCI Pentobarbital/Chlorpromazine/Alcohol subscale</td>
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<tr>
<td>BAC</td>
<td>Blood alcohol concentration</td>
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<td>BDI</td>
<td>Beck Depression Inventory</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
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<td>CCE</td>
<td>Capsule contents evaluation</td>
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<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<tr>
<td>DA</td>
<td>Dopamine</td>
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<td>DAST</td>
<td>Drug Abuse Screening Test</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorder, fourth edition</td>
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<tr>
<td>EIS</td>
<td>Eysenck Impulsiveness Scale</td>
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<tr>
<td>EPI</td>
<td>Eysenck Personality Inventory</td>
</tr>
<tr>
<td>FTND</td>
<td>Fagerström Test for Nicotine Dependence</td>
</tr>
<tr>
<td>GBQ</td>
<td>Gambling Beliefs Questionnaire</td>
</tr>
<tr>
<td>GDT</td>
<td>Game of Dice Task</td>
</tr>
<tr>
<td>GPCR</td>
<td>G-protein coupled receptor</td>
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<tr>
<td>HC</td>
<td>Healthy Control</td>
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<tr>
<td>HR</td>
<td>Heart rate</td>
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<td>PFC</td>
<td>Prefrontal cortex</td>
</tr>
<tr>
<td>PG</td>
<td>Pathological Gambling</td>
</tr>
<tr>
<td>POMS</td>
<td>Profile of Moods State</td>
</tr>
<tr>
<td>RPE</td>
<td>Reward prediction error</td>
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<tr>
<td>RRT</td>
<td>Rapid Reading Task</td>
</tr>
<tr>
<td>RT</td>
<td>Reaction time</td>
</tr>
<tr>
<td>SCID</td>
<td>Structured Clinical Interview for the DSM-IV</td>
</tr>
<tr>
<td>SOGS</td>
<td>South Oaks Gambling Screen</td>
</tr>
<tr>
<td>SST</td>
<td>Stop Signal Task</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>VLT</td>
<td>Video Lottery Terminal</td>
</tr>
<tr>
<td>WAIS</td>
<td>Wechsler Adult Intelligence Scale</td>
</tr>
<tr>
<td>WCST</td>
<td>Wisconsin Card Sort Task</td>
</tr>
</tbody>
</table>
LIST OF APPENDICES

Appendix A: Binding profiles of haloperidol and fluphenazine..........................134
  Table A-i. Receptor binding of haloperidol and fluphenazine at D2 receptors ........135
  Table A-ii. Receptor binding of haloperidol and fluphenazine at D1 receptors ..........136
  Table A-iii. Receptor binding of haloperidol and fluphenazine at D2, D3, and D4 receptors ..........................................................137
  Table A-iv. Receptor binding of haloperidol and fluphenazine at serotonin receptors ..........................................................138
  Table A-v. Receptor binding of haloperidol and fluphenazine at muscarinic acetylcholine receptors ..........................................................139
  Table A-vi. Receptor binding of haloperidol and fluphenazine at histamine H1 receptors ..........................................................139
  Table A-vii. Receptor binding of haloperidol and fluphenazine at α1 adrenergic receptors ..........................................................139
  Table A-viii. Receptor binding of haloperidol and fluphenazine at α2 adrenergic receptors ..........................................................139

Appendix B: Recruitment ads for HC and PG subjects ........................................140
  Healthy Volunteers .............................................................................................................141
  Pathological Gamblers ...........................................................................................................142

Appendix C: Informed Consent Form .................................................................143
1. INTRODUCTION

1.1 Overview and Rationale

Pathological gambling (PG) affects 1-3% of the Canadian population (el-Guebaly et al. 2006). Though numerous trials have been conducted, no medication is currently approved for the treatment of this disorder. Previously classified as an impulse control disorder, PG has been re-assigned, in the just published fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), to the same category as substance dependence. This re-categorization reflects the important similarities between PG and substance use disorders, including a pivotal role for dopamine (DA) (Potenza 2008, Zack and Poulos 2009). Genetic, neuroimaging, and behavioural studies demonstrate the importance of DA in gambling behaviour and PG. The fundamental role of DA in this disorder is also underlined by mounting evidence for the ability of direct DA agonist medications to ‘induce’ PG in 7-10% of patients with Parkinson’s disease (Santangelo et al. 2013).

DA systems are complex and widespread, with receptors distributed throughout the brain. DA is important for cognition, motor control, and reward response, among other functions, and is released in response to both natural rewards and drugs of abuse. Different receptor subtypes are associated with different biochemical responses, and so separate populations of DA receptors are thought to mediate separate aspects of responses to rewarding stimuli, and ultimately, behaviour.

Variations in the availability and/or function of DA receptors may exist in individuals who develop PG, with important implications for response to gambling rewards. The specific functions of different DA receptors and their role in PG have not yet been identified. Although a variety of animal models have been developed to investigate the biochemical basis of gambling behaviour (e.g., risk taking, impulsivity), to date no well-defined and validated phenotype of the ‘pathological gambler’ has been developed for use in animals. Therefore, studies with human pathological gamblers are currently needed to investigate the biological basis of the syndrome itself as opposed to gambling behaviour per se. Information from this line of investigation could have direct benefits for the design of pharmacotherapy to treat PG.

The characterization of PG as a ‘behavioral addiction’ (Holden 2001, Potenza 2008) suggests that chronic exposure to gambling (like drugs of abuse; cf. Leshner 1997) mediates the brain changes that give rise to PG symptoms – that is, gambling activity itself, if encountered often enough, may be pathogenic. A hallmark feature of gambling is the ongoing
expectation of rewards whose delivery is never fully predicted. These are the ideal conditions for eliciting DA release (Fiorillo et al. 2003). DA is closely linked to reward learning, conditioning and motivation. Phasic DA has been said to encode a reward prediction error (RPE), whereby DA is released in response to stimuli that are novel, uncertain or better than expected. This suggests that familiarity with a specific gambling activity can directly affect the pattern of DA signaling induced by reward in the context of that activity. Accordingly, DA release during a simulated slot machine game has been found to change after just one prior session of playing it (Shao et al. 2013). The specific mechanisms that mediate this transition from novelty to familiarity remain to be determined. A better understanding of this dynamic aspect of gambling could further inform our understanding of maladaptive DA functioning in PG subjects.

**Study Aims**

The specific aims of this study are

(a) to begin to determine the role of signaling at DA D1 and D2 receptor in mediating the subjective pleasurable, motivational, cognitive/behavioural, and physiological responses to gambling activity (commercial slot machine game);

(b) to determine the impact of prior exposure to the game on these responses in PGs and healthy controls (HCs).

Isolating the contribution of different DA receptor responses to gambling reinforcement under novel and familiar conditions in these two groups may suggest what kinds of interventions may be effective in treating PG, and in mitigating the brain changes that may contribute to its development.

**1.2 Literature Review**

**1.2.1 Pathological Gambling**

PG is associated with adverse financial, social, and interpersonal consequences including increased criminality, impaired relationships and decreased quality of life (Bergh and Kuhlhorn 1994, Grant and Kim 2005, Thompson et al. 1997). In addition to lifestyle consequences, psychiatric comorbidities are very common in this population both preceding and following the development of PG. A recent meta-analysis found that substance use
disorders were present in 58% of PGs, mood disorders in 39%, and anxiety disorders in 37% (Lorains et al. 2011). Similarly, PG is present in higher rates in those with substance use disorders compared to the general population (Baldo et al. 2006, Hall et al. 2000). These comorbidities further complicate disease course and treatment strategies for PG.

Several distinct symptoms and behaviours characterize PG. ‘Chasing losses’, wherein gamblers compulsively persist in gambling despite depleted winnings in an effort to try to win back money they have lost; tolerance (betting with increased amounts of money to achieve the desired feeling); and withdrawal-like symptoms (feelings of restlessness or irritability when trying to stop gambling) are among the diagnostic criteria for PG (DSM 4th edition; APA 1994), and are preserved in the DSM-V syndrome (Gambling Disorder; APA 2013).

Individuals with PG also commonly exhibit a number of characteristic cognitive distortions, including impaired perception of wins and losses (Savoie and Ladoucer 1995) and illusions of control over gambling outcomes (Gilovich and Douglas 1986). As in substance use disorders, PG is associated with deficiencies in some aspects of cognitive function including increased compulsivity and decision-making impairments (Leeman and Potenza 2012). In personality, PGs are more likely to be impulsive (Vitaro et al. 1997) and thrill seeking (Blanco et al. 1996).

1.2.1.1 Treatment

Cognitive behavioural therapy and other psychotherapeutic techniques are commonly used to treat PG but long-term efficacy has not been clearly demonstrated (Cowlishaw et al. 2012). As noted earlier, no pharmacotherapy has been approved for this disorder. However, a variety of medications have been tested, including selective serotonin reuptake inhibitors (Hollander et al. 1998, Kim et al. 2002, Grant et al. 2003), glutamatergic agents (Olive et al. 2012), and opioid antagonists such as naltrexone (Kim et al. 2001), with mixed results for all drug classes. These trials are limited by very large placebo effects and variability in rates of response to the active medication. Thus, the overall clinical effectiveness of these agents and the patient features that predict a beneficial response are unclear. Nevertheless, the results of previous medication trials demonstrate the potential for pharmacological interventions to be beneficial for PG.
1.2.1.2 Etiology

Numerous neurotransmitter systems have been implicated in the etiology of PG based on genetic, biochemical, and pharmacological analyses. Most of the research has focused on DA, serotonin (5-HT), and norepinephrine (NE).

**Serotonin**

The 5-HT system is critically involved in the control of a variety of physiological and behavioural functions, including regulation of mood, learning and impulsivity. Biochemical analyses of patients with PG have demonstrated reduced activity of the major 5-HT metabolizing enzyme, monoamine oxidase (Blanco et al. 1996), lower levels of 5-HT and its precursor (5-hydroxytryptophan), and higher CSF levels of the major 5-HT metabolite 5-hydroxyindoleacetic acid (Nordin and Sjödin 2006). Decreased density of platelet serotonin reuptake transporter has also been demonstrated in PG subjects (Marazziti et al. 2008). A link exists between polymorphisms in the gene for the 5-HT$_{2A}$ receptor and PG (Wilson et al. 2013), and a PET study with $[^{11}\text{C}]$P943 found that symptom severity in PGs was positively correlated with availability of 5-HT$_{1B}$ receptors (Potenza et al. 2013). PG is therefore associated with dysfunction in 5-HT signaling and impairments in this system may contribute to the development of the disorder.

**Norepinephrine**

Norepinephrine is thought to mediate arousal, vigilance, and response to novel stimuli. In rats, the NE reuptake transporter inhibitor atomoxetine enhances impulse control (Robinson 2012) while the α2 adrenergic receptor antagonist atipamezole increases reactivity to novel situations (Haapalinna et al. 1999). Elevated urinary levels of NE and higher cerebrospinal fluid (CSF) levels of NE metabolites have been demonstrated in PG subjects, and these levels correlated positively with measures of impulsivity (Roy et al. 1988). Gambling increases heart rate and plasma norepinephrine levels more strongly in problem gamblers compared to HCs (Meyer et al. 2004). Differences in NE transmission may therefore play a role in impulsive or novelty-seeking aspects of PG.

**Dopamine**

DA has long been considered a key mediator of addictive and impulsive behaviours and
is central to stimulant dependence in particular (Callahan et al. 1991, Woolverton 1996). DA disruptions have been reliably demonstrated in PG as well. Several studies have linked alterations in expression of genes for DA D1 and D2 receptors with PG (Comings et al. 1996, Comings et al. 1997, Lobo et al. 2010). PG subjects have increased CSF concentration of DA metabolites and higher blood DA levels while gambling, suggesting elevated DA release (Bergh et al. 1997).

Notably, direct DA agonists such as pramipexole and ropinorole administered to treat Parkinson’s disease or Restless Leg Syndrome can induce PG and other compulsive behaviours in a subset of patients (Voon et al. 2011a, Potenza et al. 2013), further indicating a key role for DA in these behaviours. DA signaling in reward and its relevance to PG is reviewed in detail below.

1.2.2 Overview of the Dopamine System

Drugs of abuse including stimulants, alcohol, and opiates, as well as natural rewards such as food and water all stimulate DA release. These signals have a well-established role in the subjective and motivational effects of rewarding stimuli (reviewed in Schultz et al. 1997).

DA transmission proceeds along several anatomically distinct but functionally interconnected pathways. The mesolimbic pathway is central to reward processing, consisting of DA neurons with cell bodies in the ventrotegmental area (VTA) that project to the nucleus accumbens (NAc) in the ventral striatum. The mesocortical pathway, projecting from the VTA to the prefrontal cortex (PFC) and mesostriatal pathway, from the VTA to the dorsal striatum, are increasingly recognized for their role in reward processing (Tzschentke et al. 2000, Wise 2009). Nigrostriatal DA transmission, from the SN to the striatum, while traditionally associated with motor control, has also been demonstrated to modulate these processes (Wise 2009).

1.2.2.1 Dopamine Receptor Subtypes

There are two major classes of DA receptors. D1-like receptors, including D1 and D5 subtypes, are excitatory G-protein-coupled receptors (GPCRs). Agonist binding at these receptors activates adenylyl cyclase, increasing cyclic AMP (cAMP) levels and a variety of downstream signaling cascades. D1 receptors are found throughout the striatum and the PFC and are involved in reward response and movement control (Beaulieu and Gainetdinov 2011),
as well as many aspects of cognition, including working memory, set-shifting, and attention (Fletcher et al. 2005, Castner and Williams 2007). D1 receptors are located mainly in extra-synaptic sites (Caillé et al. 1996) and have lower affinity for endogenous DA relative to other subtypes, so they respond primarily to phasic/stimulus-induced bursts of large amounts of DA (Dreyer et al. 2010). D5 receptors are expressed in several brain regions including the PFC, striatum, substantia nigra, and the hippocampus. These receptors are thought to contribute to learning and memory (Beaulieu and Gainetdinov 2011), particularly in the hippocampus where D1 receptors are less prevalent (Missale et al. 1998).

D2-like receptors, including D2, D3, and D4 subtypes, are inhibitory GPCRs, so agonist binding reduces activity of adenylyl cyclase and decreases cAMP levels. D2 receptors are located throughout the brain but are found in highest concentrations in the striatum, nucleus accumbens, and olfactory tubercle (Beaulieu and Gainetdinov 2011). D2 receptors have higher affinity for DA relative to D1 receptors, responding primarily to tonic/basal low levels of DA (Schultz et al. 1997), and are expressed both pre- and post-synaptically. A subset of D2 receptors function as inhibitory autoreceptors on DAergic neurons to reduce neurotransmitter release after stimulation. Decreased availability of D2 autoreceptors in the VTA has been linked with increased trait impulsivity and increased DA release following a challenge dose of d-amphetamine (Buckholtz et al. 2010). Signaling through D2 receptors in the hippocampus also influences cognitive function through interaction with D1 receptors in the PFC (Takahashi et al. 2012) and potentiates response to fearful stimuli in the amygdala (Bissiere et al. 2003).

D3 and D4 receptor subtypes also reduce adenylyl cyclase activity and cAMP levels. D3 receptors are expressed in the greatest density in the nucleus accumbens (Sokoloff et al. 2006) and contribute to presynaptic regulation of DA release. D3 receptor activation appears to moderately inhibit locomotion and can modulate reward-seeking behaviour and cue response in animals (Beaulieu and Gainetdinov 2011, Sokoloff et al. 2006). D4 receptors are similarly involved in modulating DA release and response to drugs of abuse, and have been linked to schizophrenia and ADHD in genetic studies (Rondou et al. 2010).

1.2.3 Dopamine Dysfunction in PG

In a functional magnetic resonance imaging (fMRI) study, PG subjects demonstrated reduced activation in the ventral striatum in response to monetary reward compared to controls and degree of activation was negatively correlated with symptom severity (Reuter et al. 2005).
Reduced striatal activation in response to reward is a hallmark of substance addiction, despite the fact that striatal DA release is associated with subjective pleasurable effects of stimulants (Volkow et al. 1997, Volkow et al. 2002). Indeed, DA release in the ventral striatum as measured by \[^{11}\text{C}\]-raclopride PET imaging correlated positively with subjective feeling of “high” while playing a high-reward gambling task (Joutsa et al. 2012). Interestingly, the Joutsa et al. study found a positive correlation between PG severity and striatal DA release during the slot machine – but only in response to large rewards. This suggests that the negative correlation between PG severity and ventral striatal activation in the Reuter et al. study may reflect tolerance to normative or low levels of monetary reward in PG, while the Joutsa et al. data may reflect preferential activation by large rewards in subjects with greater chronic exposure to gambling. Collectively, these results demonstrate the key role for striatal DA in mediating gambling-related reward in both normal and pathological states and point to possible parallels between gambling and stimulant drug effects.

1.2.3.1 Sensitization

Stimulant sensitization is a process by which exposure to chronic low doses of stimulant drugs induces certain well-defined behavioural and neural changes (Wolf et al. 2004). In animals, sensitization manifests as increased stereotypy and locomotor activation in response to a challenge dose of a DA agonist following prior exposure to drugs of abuse. This effect is most robust and consistent in response to a stimulant such as amphetamine. Chronic intermittent low-dose amphetamine is associated with elevated levels of DA in synaptic clefts, likely due to adaptive changes resulting in increased DA release (Paulson and Robinson 1995, Robinson and Becker 1986). Sensitization has been demonstrated in healthy humans after as few as three modest doses of amphetamine (@ 0.3 mg/kg), with effects persisting for up to one year (Boileau et al. 2006). Behavioural sensitization to stimulants is dependent in part on changes in function of D2 receptors (Ujike et al. 1990, Liu et al. 2009). Low D2 expression is also associated with increased behavioural sensitization in rats, indicating this receptor may be involved in susceptibility to, as well as development of, these changes (Tournier et al. 2013).

The long lasting behavioural and neurochemical changes associated with chronic amphetamine use, together with the existence of similar DA disruptions in both substance abuse disorders and PG, suggest that sensitization may be relevant to PG. These commonalities were recently demonstrated in a \[^{11}\text{C}\]-PHNO PET study examining DA release in response to
oral amphetamine in stimulant-naïve PG and healthy control subjects (Payer et al. 2012). Amphetamine-induced DA release (0.4 mg/kg) was significantly greater in PG than HC subjects in the midbrain and dorsal striatum. This finding is consistent with micro-dialysis studies of rodents chronically exposed to modest doses of amphetamine (Robinson et al. 1988) and suggests that common pathways may be engaged by amphetamine and gambling. These results provide empirical, although indirect, support for the relevance of stimulant-like sensitization-effects on DA transmission in the brains of individuals with PG, which in turn suggests that receptor anomalies seen in amphetamine-sensitized rodents may also exist in PG. However, recent PET studies using \([^{11}C]\)-raclopride have found similar D2/D3 receptor expression in PGs as in HCs (Boileau et al. 2013, Clark et al. 2012), suggesting that D2 receptor expression may not be the primary mechanism underlying changes in DA transmission in PGs and other receptors may be involved.

1.2.4 Dopamine in Reward and Addiction

1.2.4.1 Differential Effects of D1 and D2 Receptors

Functional changes in D1 and D2 receptors in the striatum and elsewhere are likely critical to the development of substance dependence. In animals, long-term stimulant use is associated with decreased binding at both D1 and D2 receptors (Nikolaus et al. 2007). In rats previously exposed to cocaine, D1 receptors are thought to primarily mediate rewarding effects of the drug while D2 receptors control craving or motivation (Self et al. 1996). Reward, in this context, refers to the attribution of incentive salience to a stimulus or context and is indexed by the tendency for an animal to return to a context in which it previously received a drug (e.g., the side of a Skinner box where cocaine was received, as opposed to the side of the box in which placebo was received). D1 receptor antagonists reliably disrupt such “conditioned place preference” for cocaine (Baker et al. 1998, Cervo and Samanin 1995). In contrast, the D1 antagonist SCH23390 increases voluntary self-administration of cocaine (achieved by pressing a lever) in rats, which is thought to indicate compensation for a decrease in the per-unit reward value of cocaine with antagonist present (Quinlan et al. 2004). D2 antagonists elicit compensatory self-administration of high doses of cocaine only (Caine et al. 2002), suggesting D1 is necessary for cocaine reward and reinforcement, whereas D2 facilitates acquisition of cocaine reward without mediating its discriminative effects (i.e., subjective effects of the drug).
In humans, acute blockade of D1-like receptors with ecopipam (10-100mg) in cocaine addicts decreased self-reported pleasurable effects and craving ratings in response to intravenous cocaine (30-mg) (Romach et al. 1999), suggesting a role for D1 in both the subjective rewarding and incentive motivational aspects of the drug response. In contrast, a $^{[11]}$C-raclopride PET study of healthy men found that low D2 receptor availability predicted increased subjective rewarding effects of the cocaine-like stimulant and indirect DA agonist methylphenidate (Volkow et al. 1999). This inverse relationship was not seen in cocaine addicts, however, who exhibited lower D2 levels overall than control subjects but reported greater craving (for cocaine) rather than more enjoyment (subjective reward) from a dose of methylphenidate (Volkow et al. 1997). Collectively, these data indicate important roles for D1 and D2 DA receptors in the subjective rewarding and incentive motivational (craving) effects of stimulants, which vary as a function of chronic exposure to these drugs. To the extent that PG mirrors stimulant addiction, dysfunction, adaptive responses, and pharmacological modulation at D1 or D2 receptors may therefore have contrasting effects on response to gambling reward in PG vs. control subjects.

1.2.4.2 Hedonic Impact, Incentive Salience, and Dopamine

It has been theorized that hedonic impact (‘Liking’) and incentive salience (‘Wanting’) of rewarding stimuli are not just separable dimensions of reinforcement, but that DA is critically responsible for only the latter effects (Berridge 2004, 2007). Evidence for this comes from the fact that DAergic manipulations that affect craving do not reliably induce corresponding changes in actual liking of a reinforcer. For example, in animals lesions of mesolimbic DA transmission reduce motivation for rewards (Berridge 2004) but maintain liking as assessed by analysis of facial expressions and movements (Peciña 1997). Similarly, in a subset of Parkinson’s disease patients who compulsively abuse their selective DA agonist medications, DA transmission as measured by $^{[11]}$C-raclopride is correlated with ratings of wanting but not liking (Evans et al. 2006). Therefore DA may be primarily involved in mediating incentive salience but may not be necessary for or central to the experience of pleasure. Behavioural or subjective measures (as outlined above, including self-administration in animals and self-report in humans) commonly used to assess hedonic impact may in fact be mainly affected by changes in motivation and craving in response to DAergic manipulations (Berridge 2004). With gambling, however, the distinction between liking and wanting is
further complicated by the abstract nature of the reward – for example, the ‘rush’ of betting money in a game is presumably a source of pleasurable effects but is itself closely tied to desire or motivation for a given reward and the anticipation/expectation of its delivery. The extent to which these concepts are separable or differentially modulated by DA in PG is not clear, although the neuroimaging data linking gambling ‘high’ with DA release suggest a role for DA in this subjectively pleasurable state (Joutsa et al 2012).

1.2.4.3 Phasic and Tonic Signaling

Phasic and tonic DA signals also likely have different functions in reward, reinforcement, and learning, potentially related to their different receptor activation profiles as outlined above. Phasic DA is thought to encode the primary reward signal that occurs when a stimulus that is better/more pleasant than expected is delivered (Grace 2000). The phasic DA spike is also thought to assign incentive salience to the stimulus that led to its occurrence. As a result, the next time that stimulus is encountered, phasic DA release occurs immediately following delivery of the cue for reward (e.g., the sight or smell of palatable food) rather than after reward delivery itself (i.e., the consumption of the palatable food). This shift in the timing of the phasic DA spike is referred to as Temporal Difference Learning (TDL) (see Redish 2004, reviewed below in section 1.2.6.3), and is considered a fundamental process by which organisms adapt to their environment. In line with this formulation, the amplitude of cue-induced DA release has been found to predict reward-seeking behaviour in rats (Wassum et al. 2012), suggesting it plays a key role in reward learning and incentive motivation. In healthy humans, an acute dose of the D2/D3 agonist pramipexole (0.5 mg) impairs reward learning on a probabilistic reward task (Pizzagalli et al. 2008), an effect attributed to reduced reward-induced phasic DA release under continuous activation of (inhibitory) autoreceptors.

With respect to tonic DA, mice with low basal DA levels exhibit normal reward learning but reduced ability of that learning to guide behaviour, suggesting tonic DA may help to enable animals to respond to reward signals transmitted through phasic activation (Beeler et al. 2010). In general, it is likely that phasic DA bursts are the major substrate of reward signals, whereas tonic DA may modulate the expression or extent of these learned responses through autoreceptor activation.
1.2.5 D1 Activation in Reward

A series of studies by de Wit et al. examined the effects of D2 receptor antagonists with different affinities for D1 receptors on stimulant reward in humans. Healthy subjects were administered pimozide, a selective D2 antagonist (Brauer and de Wit 1996), haloperidol, a preferential D2 antagonist with some D1 affinity (Wachtel et al. 2002), or fluphenazine, a mixed D1-D2 antagonist (Brauer and de Wit 1995), followed by d-amphetamine or methamphetamine. Effects on the Addiction Research Centre Inventory (ARCI) Morphine/Benzedrine (MBG) subscale, a measure of drug-induced euphoria, were dependent on dose and receptor affinity. Pimozide enhanced MBG scores after 10mg amphetamine in a dose-dependent fashion, with 1mg pimozide inducing stronger effects compared to 2mg, but all doses reduced the euphoric effects of 20mg amphetamine. At these doses, D2 antagonism with pimozide is expected to enhance post-synaptic D1 stimulation by blocking pre-synaptic D2 autoreceptors (Shi et al 1997, Pucak and Grace 1994). These results are consistent with a hypothetical model in which the pleasurable effects of stimulants are mediated by D1 receptor activation and an optimum range of D1 stimulation exists for these effects. In other words, the ability of D1 activation to produce hedonic effects follows an inverted U relationship, wherein rewarding effects increase as D1 receptor activation increases until the optimum level is reached, after which additional D1 activation causes less pleasurable or aversive effects (Figure 1).

![Proposed inverted U relationship between D1 receptor activation and stimulant reinforcement](adapted_from_seamans_and_yang_2004.png)
Therefore, a low dose d-amphetamine (10 mg) combined with low dose (1 mg) pimozide may have induced ‘optimal’ levels of D1 stimulation whereas moderate dose amphetamine (20-mg) and high (or low) dose (1-mg, 2-mg) pimozide may have induced supra-optimal D1 stimulation, with associated increases and decreases in subjective euphoria (MBG) respectively. This relationship also implies reinforcing effects of stimulants are in part dependent on baseline D1 activation: the same increase in activation induced by a given intervention may have different effects depending on whether an individual’s baseline D1 activation is near-optimal or sub-optimal, for example.

This interpretation is supported by an experiment with fluphenazine (Brauer and de Wit 1995), a DA antagonist, which would cause D2 blockade similar to that induced by pimozide (with associated increases in DA release) but also partially block D1 receptors. Results revealed that fluphenazine (3mg) enhanced euphoric effects of 20mg amphetamine in a manner similar to 1 mg pimozide and 10 mg d-amphetamine. Thus, combined blockade of D2 and partial blockade of D1 plus a moderate dose of amphetamine led to comparable effects (enhancement of euphoria) as selective blockade of D2 and low dose amphetamine. This suggests that through somewhat different mechanisms the two combinations each optimized D1 receptor stimulation.

In contrast to pimozide or fluphenazine, 3mg haloperidol had no differential effect on euphoric ratings of 20mg methamphetamine compared to placebo pre-treatment. This treatment combination would have resulted in substantial DA release by the agonist, together with robust blockade of D2 receptor-mediated inhibitory feedback but only modest blockade of D1. The lack of enhancement in MBG scores may be similar to 1-mg pimozide plus 20 mg d-amphetamine: both combinations would have been expected to induce slightly supra-optimal levels of D1 stimulation. The equivalent effect to placebo plus 20-mg d-amphetamine or methamphetamine may reflect slightly sub-optimal D1 stimulation in the latter conditions (i.e., no antagonist) with comparable subjective euphoria, in keeping with the idea of an inverted U relation between D1 activation and reward. The emergence of this pattern is interesting given that an inverted U relationship has previously been described between cortical D1 activation and cognitive function, particularly working memory performance (Seamans and Yang 2004).
1.2.5.1 D1 and D2 receptors in Gambling Reinforcement and PG

The experiments by de Wit and colleagues suggest that, in healthy humans, stimulant reinforcement is modulated by inhibitory D2 autoreceptors controlling the rate of DA release acting on post-synaptic D1 receptors. If the role of DA in stimulant and gambling reinforcement is similar, manipulation of D2 receptor availability may have similar effects to those observed by de Wit. Accordingly, Zack and Poulos (2007) demonstrated that the D2 antagonist haloperidol, at a dose of 3-mg, selectively enhanced desire to gamble and subjective rewarding effects in PG subjects, but not HC subjects, after playing a commercial slot machine. The equivalent effect of 3-mg haloperidol and placebo pre-treatment in HCs is consistent with de Wit et al.’s findings regarding haloperidol pre-treatment with methamphetamine where no change in subjective rewarding effects was observed. The group differences between healthy subjects and those with PG suggest that differences in baseline DA function may exist between these groups. Recent evidence for similar D2 availability in PGs (Boileau et al. 2013, Clark et al. 2012) suggests these differences may exist, instead, at the level of D1 receptor function.

Together these data are consistent with a model in which reduced baseline D1 activation in PG subjects accounts for their enhanced response to pre-synaptic autoreceptor blockade with haloperidol. Increased DA release in PG subjects enhanced reinforcement, potentially by optimizing D1 stimulation, whereas no difference was seen in controls with haloperidol present, potentially because D1 stimulation was slightly sub-optimal at baseline and slightly supra-optimal with antagonist present in these subjects, with no net change in reward under drug vs. placebo (Figure 2). Concurrent D1/D2 blockade during a slot machine game would test the hypothesis that downstream D1 stimulation is the locus of haloperidol’s facilitative effects on gambling reinforcement in PGs observed by Zack and Poulos (2007).
1.2.6 Learning, Conditioning and Novelty in Reward Response

DA release is strongest in response to novel tasks and environments (Feenstra et al. 1995). Coupled with the fact that DA is strongly implicated in reward learning responses, this suggests the DAergic response to rewarding stimuli may differ in important ways when a reward is received for the first time compared to later exposure. This section reviews the shifts in DA signaling with repeated exposure to a given reward.

1.2.6.1 Cue Conditioning

With repeated exposure to rewarding stimuli, DA neurons exhibit conditioned responses, such that neutral stimuli paired to reward receipt develop the ability to evoke DA release themselves on future exposure (Robinson and Becker 1986). This has been
demonstrated both with pharmacological agents that act by physically releasing DA, and with other reinforcers such as food (Owesson-White et al. 2009, Schultz 2010). In stimulant-dependent humans, fMRI studies have demonstrated that activation of the NAc in response to drug cues is stronger than that observed after exposure to stimulant drugs themselves (Risinger et al. 2005). This cue-induced DA release is correlated with subjective reports of craving in frequent cocaine users (Wong et al. 2006). Conditioned responding also develops rapidly with gambling, such that DA signaling in the ventral striatum shifts from post-reward delivery on the first encounter with a simulated slot machine to post-cue delivery – i.e., while the reels are spinning – on the second encounter with the game in healthy individuals (Shao et al. 2013). The rapid transition to conditioned reinforcing effects of a slot machine may help to explain cue reactivity in PG subjects who report increased enjoyment of the sensory aspects of a video lottery terminal (VLT)-style slot machine compared to healthy controls (Loba et al. 2001).

1.2.6.2 Uncertainty and Reward Prediction Error

Phasic DA neuron activation to conditioned cues for reward varies depending on reward probability, with the strongest response (between the onset of the cue and reward delivery) seen with a reward probability of 50% - the circumstance when information about the likelihood of reward delivery imparted by the cue is minimized (Fiorillo et al. 2003). This suggests reward uncertainty, rather than just reward itself, may have reinforcing properties in the context of gambling. This may help to explain the enjoyment of and motivation to gamble despite sometimes substantial losses. Reward probability (win >0 credits) was previously found to be 45.8% over the course of thousands of spins on a commercial slot machine (Zack and Poulos 2007), very close to the maximal uncertainty (50% variable reward), which evokes maximum post-cue DA release. Based on this example, it would appear that the conditioned reward schedule on slot machines is optimized to exploit the rewarding impacts of uncertainty.

Cue conditioning and increased DA release with uncertain reward underlie the theory that DA encodes a reward prediction error (RPE). In non-human primates DA neuron activation was high when animals were in the process of learning to associate cues with probable rewards and lower later in trials once rewards had become predictable (Hollerman and Schultz 1998; Waelti et al. 2001). In humans, activation of SN neurons increased for unexpected reward compared to unexpected losses, with no difference between wins and losses when these outcomes were expected (Zaghloul et al. 2009). These results are corroborated by
fMRI studies demonstrating that activation in the striatum, mPFC, and other regions corresponds closely with RPE models (Rutledge et al. 2010). Thus, phasic DA firing may encode the difference between expected and received reward, facilitating reward learning by conferring stronger value to rewards not yet associated with known cues. In line with this possibility, Pessiglione et al. (2006) found that treatment with the DA precursor L-DOPA enhanced striatal response to reward in HCs, and this increase in RPE-like signals was correlated with improved performance in an instrumental learning task. This demonstrates that RPE signals play a causal role in the acquisition of reinforced responses in healthy humans.

1.2.6.3 Temporal Difference Reinforcement Learning

One model for addictive behaviour is centered on temporal-difference reinforcement learning (TDRL), which describes the process by which the DA signal encoding RPE is diminished over time as a natural reward becomes predictable. Phasic DA signaling tracks this difference between reward expectation and receipt, decreasing as predictions of future reward improve. However, this system of graduated responses is disrupted by drugs of abuse, which increase DA release unconditionally through their pharmacological action. As a result, the reward signal evoked by the drug does not diminish as it is becomes better predicted by cues. Instead it persists indefinitely, leading to perpetual increases in cue-drug associative learning – a positive feedback cycle (Redish 2004). This model has direct implications for gambling, in which conditioned stimuli (e.g., spinning reels) also precede reward delivery (monetary payoff), but reward prediction remains imperfect: by definition reward delivery in gambling is uncertain, so monetary payoffs always evoke an RPE. Thus, wins are able to induce DA release indefinitely during gambling because they are unpredictable, and cues continue to evoke cue-payoff associative learning (as they do for all reinforcing stimuli), with the result that gambling behaviour is perpetually reinforced in a manner that closely mimics the reinforcing effects of drugs of abuse.

1.2.6.4 Implications for PG

Given the critical role of D1 and D2 receptors in reward learning, the novelty/familiarity of a gambling activity could well influence the effects of DA antagonists that act at these receptors. More specifically, these agents could disrupt reward learning to a greater extent when administered on first rather than second exposure to a slot machine game. On day
1, the drugs would exert their effects primarily following reward delivery, whereas on day 2, the drugs would exert their effects after cue delivery (based on a TDRL shift in phasic DA response) as well as after reward delivery (which remains uncertain).

The idea that novelty will interact with the effects of DA ligands on conditioned reward learning is supported by a study by Mehta et al. (2001) in which healthy individuals who received the D2 agonist bromocriptine (1.25mg) demonstrated reduced performance on a reversal-learning task when, through counterbalancing, they received the drug on the first vs. the second session of a cross-over design. The authors proposed this could be related to excessive DA receptor activation in subjects who received the drug on day 1 due to augmentation of the drug effect by DA release induced by the novelty of the task. A similar effect may occur when the conditioned rewarding stimulus is a slot machine game.

The overlapping role of DA in reward learning/conditioning and incentive motivation strongly suggests that the effect of DA receptor blockade on reward response to a given stimulus could be critically different during the first exposure to that stimulus compared to effects on later sessions. This may be especially important for activities like gambling that are heavily dependent on secondary cues (e.g., monetary credits, bells and lights) for reinforcement rather than a pharmacologically-induced neurochemical reward signal. A better understanding of the respective contributions of the novelty of the game and the roles of D1 and D2 receptor signaling in its rewarding and incentive motivational properties could inform strategies to deter both the initial development and the consolidation of maladaptive reward-related responding in PG.

1.3 Objectives

The primary goal of this study is to investigate the roles of DA modulations on subjective, behavioural, cognitive, and physiological responses to gambling in PGs and healthy controls in order to reveal potential neurobiological differences between these two groups. Our specific objectives are as follows:

1) To isolate the specific roles of D1-like and D2-like receptors (hereafter referred to as D1 and D2, respectively) in mediating gambling reinforcement.

2) To examine how dopaminergic manipulations interact with reward novelty to affect reinforcement.
3) To differentiate the effects of these manipulations on measures of hedonic impact (liking) vs. incentive salience (cue reactivity, wanting) of gambling rewards.

4) To identify differences between PG and HC subjects in D1 and D2 receptor function in these processes.

These aims will be achieved by examining the effects of haloperidol, a preferential D2 antagonist, and fluphenazine, a mixed D1/D2 antagonist, on responses to a 15-minute slot machine game in PGs and HCs, who receive their assigned antagonist before initial exposure to the game vs. subjects from these groups who, through counterbalancing, receive their antagonist after a previous session of play (under placebo). The haloperidol arm will seek to replicate previous results from our lab (Zack and Poulos 2007), while the addition of a fluphenazine arm will permit us to test the role of D1 activation in responses on the various outcome measures, and indirectly to determine the role of D1 in mediating the (predicted) increase in gambling reinforcement by haloperidol. Comparison of the effects of drug sequence (drug received on the first session vs. drug received on second session) will reveal the importance of novelty to the observed effects.

1.4 Hypotheses

Based on the previous study of haloperidol in PG subjects and HCs, it is expected that PG subjects may have deficits in baseline D1 signaling. Therefore, the following predictions can be made:

1) By increasing transmission at post-synaptic D1 receptors, autoreceptor blockade with a low-dose of the D2 antagonist haloperidol will increase reinforcement of a gambling task (slot machine game) in PG but not HC subjects.

2) By partially reducing D1 activation enhanced by autoreceptor blockade, a low-dose of the mixed D1/D2 antagonist fluphenazine will optimize the D1 signal and increase gambling reinforcement in HCs but not in PGs.

3) Given the augmented DAergic response to novel rewards, the effects of the antagonists will be stronger when the drug is received on day 1 compared to day 2.

Based on the presumed role of DA in wanting vs. liking of addictive rewards, these manipulations were expected to be more evident on measures of incentive salience as opposed
to hedonic impact in both groups. Wanting/Incentive Salience will be operationally defined by scores on Visual Analog Scales (VAS) assessing motivation to gamble (Desire to Gamble and Confidence to Resist Gambling), betting behaviour on the slot machine, and performance on an automatic assessment of reward cue salience, the Rapid Reading Task (RRT). Liking/Hedonic Impact will be operationally defined by scores on VAS self-reports of enjoyment of a slot machine game and scores on ARCI MBG and amphetamine-like (AMPH) subscales assessing drug-like pleasurable and activating effects.
2. MATERIALS AND METHODS

2.1 Study Design

This study used a 2 Group (HC / PG) x 2 Drug (haloperidol / fluphenazine) x 2 Sequence (drug first / placebo first) x 2 Session (drug / placebo) repeated measures between-within subjects design. Each of 48 participants was assigned to either haloperidol or fluphenazine and received the DA antagonist or visually identical non-active placebo on 2 test sessions in a counterbalanced, double blind sequence with a one-week washout period between sessions. Test sessions assessed the effects of the antagonist on pleasurable and motivational aspects of a standard session of play on a Video Lottery Terminal (VLT)-style slot machine.

The study took place at the Centre for Addiction and Mental Health (CAMH) and participation consisted of a telephone screening, an in-person interview screening including the Structured Clinical Interview for DSM-IV, a physician’s exam and four test sessions. The last two test sessions assessed the effects of 20-mg d-amphetamine (Dexedrine) prior to playing the slot machine as part of a separate, related set of experiments. All data presented here were gathered prior to amphetamine administration, from telephone and interview screening and test sessions 1 and 2. Thirty-two participants were tested by two prior experimenters using the same standardized protocol, with the remaining 16 added to the sample between April 2012 and May 2013.

2.2 Study Medications

2.2.1 Haloperidol

Haloperidol is a typical antipsychotic and preferential D2 receptor antagonist. Haloperidol has a $K_i$ value of 0.6 for D2 receptors, indicating high affinity, as well as moderate affinity for D1 receptors ($K_i$=17). It also shows moderate affinity for $\alpha_1$ adrenergic receptors and low affinity for $\alpha_2$, histamine, and muscarinic acetylcholine receptors (Appendix 1). After oral administration, haloperidol has a bioavailability of $60 \pm 18\%$, volume of distribution of $18 \pm 7 \text{ L/kg}$, half-life of $18 \pm 5 \text{ hours}$ (Froemming et al. 1989), and reaches peak plasma concentration after a mean 2.75 hours (Wachtel et al. 2002). Haloperidol is metabolized mainly by CYP3A4 and is an inhibitor of this enzyme (Kudo and Ishikazi 1999). At peak blood levels, a 3-mg dose would be expected to occupy $\sim65\%$ of D2 receptors (Nordstrom et al. 1992). In addition to D1 and D2 receptors, haloperidol has high affinity for D3 receptors ($K_i = 0.2$),
moderate affinity for D4 receptors \( (K_i = 22) \), and low affinity for D5 receptors \( (K_i = 169) \) (Burstein et al. 2005, Cravchick and Gejman 1999).

Systemic administration of DA antagonists increases the rate of firing of DAergic neurons in the substantia nigra in animals. This process is mediated by activation of somatodendritic D2 autoreceptors (Pucak and Grace 1994). At low doses, haloperidol is expected to block these autoreceptors and result in increased synaptic DA release upon stimulation.

2.2.2 Fluphenazine

Fluphenazine is a typical antipsychotic with high affinity for D1 and D2 receptors \( (K_i = 0.85 \) and 0.4, respectively) and low affinity for adrenergic and cholinergic receptors (Appendix 1). Fluphenazine has a bioavailability of 2.7\%, volume of distribution of 11 ± 10 L/kg, half-life of 14.4 ± 7.8 hours, reaches peak plasma concentration after 2 hours with oral administration, and is metabolized primarily by CYP3A4 (Jann et al. 1985, Brauer et al. 1995). Occupancy of D2 receptors by fluphenazine is unknown, but its similar affinity for D2 as haloperidol suggests comparable D2 occupancy at peak blood levels for an identical dose (i.e., 3 mg). Similar to haloperidol, fluphenazine also has moderate affinity for D3 and D4 receptors \( (K_i = 1.4 \) and 7.1, respectively) and low affinity for D5 receptors \( (K_i = 54) \) (Burstein et al. 2005, D’Aoust and Tiberi 2010).

2.2.3 Rationale for Drug Selection

Haloperidol was used to determine the role of D2 receptors in response to gambling and reward novelty. Despite moderate affinity for D1 receptors, haloperidol is the most selective D2 antagonist available for human use in Canada. Furthermore, using haloperidol permitted direct comparison of present findings with the results from a previous study in which 3-mg haloperidol increased hedonic and incentive motivational aspects of gambling in PGs (Zack and Poulos 2009).

To identify the role of D1 receptors in these reward responses, a selective D1 antagonist would be ideal. However, in Canada no such drug is approved for use in humans. Comparing responses under haloperidol to those under fluphenazine, which has similar D2 affinity but stronger D1 affinity, will permit inferences about the role of post-synaptic D1 activation in the
responses seen under haloperidol. Comparing HCs and PGs under both drug treatments will provide information about the relative function of each receptor subtype in each group.

Both haloperidol and fluphenazine have some affinity for other DA receptors, notably D3 and D4. Although the effects of haloperidol on its own cannot unambiguously reveal the roles of the different DA receptors in gambling reinforcement, the comparative pattern of effects of haloperidol vs. fluphenazine can speak to the role of D1 given their similar binding profiles for non-D1 DA receptors (as well as other non-DA receptors).

2.2.4 Diphenhydramine

Diphenhydramine is a first-generation antihistamine with anti-muscarinic properties that is commonly used to treat extrapyramidal side effects associated with first-generation antipsychotics (Dayalu and Chou 2008). At the end of each test session, participants were provided with 50-mg diphenhydramine HCl (Benadryl®) and instructed to take it only if they felt symptoms emerge after leaving the laboratory, to counteract delayed dystonia or akathisia induced by haloperidol or fluphenazine.

2.3 Participants

This study included 48 participants, 24 HCs and 24 PGs between 19 and 65 years of age. To minimize the impact of co-morbidities, eligible participants were restricted to individuals who were generally healthy with no DSM-IV Axis I diagnosis besides PG and nicotine dependence. Inclusion criteria are summarized in Table 1.

Participants with prior exposure to stimulants (amphetamine, cocaine, or methylphenidate), regular recreational drug use, or heavy alcohol use were excluded, to better isolate effects of gambling per se on the reward systems being studied. Participants were also screened for and excluded on the basis of current or past manic or depressive episodes (excepting one past depressive episode >1 year prior), current or prior anxiety disorders, alcohol abuse <1 year prior, current or past alcohol dependence, and presence of psychotic symptoms. Participants who were pregnant, trying to become pregnant, or breastfeeding were excluded to prevent exposure of a fetus to the study medications. Due to the potential for both slot machine play and study medication to increase desire to gamble, PG participants who were abstinent or desired to abstain from gambling were excluded.
Table 1. Inclusion criteria.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Healthy Controls</th>
<th>Pathological gamblers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>19 – 65</td>
<td></td>
</tr>
<tr>
<td>SOGS</td>
<td>≥ 5</td>
<td>0</td>
</tr>
<tr>
<td>DSM-IV PG questionnaire</td>
<td>≥ 5</td>
<td>0</td>
</tr>
<tr>
<td>Gambling behaviour</td>
<td>Played slot machine &gt; 5x</td>
<td>Not abstinent or trying to abstain from gambling</td>
</tr>
<tr>
<td>BDI</td>
<td>&lt; 10</td>
<td></td>
</tr>
<tr>
<td>ADS</td>
<td>&lt; 13</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>&lt; 35</td>
<td></td>
</tr>
<tr>
<td>WAIS-vocabulary</td>
<td>&gt; 18</td>
<td></td>
</tr>
<tr>
<td>Alcoholic drinks / week</td>
<td>≤ 20 (men) ; ≤ 15 (women)</td>
<td></td>
</tr>
<tr>
<td>Cigarettes / day</td>
<td>≤ 20</td>
<td></td>
</tr>
<tr>
<td>Caffeinated beverages / day</td>
<td>≤ 8</td>
<td></td>
</tr>
<tr>
<td>Recreational drug use</td>
<td>No prior use of psychostimulants</td>
<td>&lt; 2 prior uses of MDMA or hallucinogens</td>
</tr>
<tr>
<td></td>
<td>Prior use of &lt; 1 marijuana cigarette / month</td>
<td></td>
</tr>
</tbody>
</table>

SOGS, South Oaks Gambling Screen; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4e.; PG, pathological gambling; BDI, Beck Depression Inventory; ADS, Alcohol Dependence Scale; BMI, body mass index; WAIS, Wechsler Adult Intelligence Scale. Details of screening instruments are provided below.

2.3.1 Study Payment

Upon completion of all six sessions (including the two amphetamine sessions), participants received a cheque for $1000 mailed to them 2-3 weeks after their final session, representing a $920 ‘participation fee’ plus a standard $80 ‘gambling bonus’ in lieu of winnings from the slot machine. The total time commitment for the study was approximately 42 hours including interview screening (3 hours), physician’s exam (1 hour), 4 test sessions (8 hours each) and travel time (1 hour for each of six sessions), giving an hourly pay rate of $23.80. The rate of pay was chosen based on prior experience with similar studies, which indicated a minimum payment of $500 per 2 test sessions was necessary for efficient recruitment of PG participants. A prior similar study from this lab paid $800 for 2 test sessions (Zack and Poulos 2007).
2.3.2 Participant Safety and Precautions

This study was approved by the CAMH Research Ethics Board. All participants were screened thoroughly to ensure they were physically healthy and without contraindications for any of the study medications (including d-amphetamine). Prior to discharge at the end of each test session, a registered nurse or physician examined each participant to ensure they were not experiencing any adverse effects and that their vital signs had returned to normal levels. Participants received 50-mg diphenhydramine to use as needed, as well as a wallet card (in the event of emergency), containing the name, dose, and administration time of the medication (or placebo) and the contact number for the study’s qualified physician. Participants were sent home in a pre-paid taxi and agreed to avoid physically strenuous activity and operating heavy machinery for the rest of the day following testing. Participants were also instructed to abstain from caffeine and other medications for 24 hours and from alcohol for 72 hours to avoid potential interactions with study medications.

Recruitment ads specifically stated the study was not intended to treat gambling problems (see Appendix 2). However, at the end of the study, following debriefing, PG participants were provided with information about CAMH’s Problem Gambling Service to facilitate treatment if desired.

2.4 Apparatus

Breathalyzer

The absence of blood alcohol was confirmed using a calibrated J4X Alert Breathalyzer or DriveSafe Breathalyzer (Alcohol Countermeasure Systems Inc., Mississauga, Ontario) at the beginning of each test day.

Blood Pressure/Heart Rate Monitors

Regular blood pressure and heart rate measurements were taken with HEM-601 (OMRON, Vernon Hill, IL) wrist cuff instruments.

Slot Machine

The gambling intervention on each test session was performed on a VLT slot machine, ‘Cash Crop’ (WMS Gaming, Detroit MI), played in a mock-bar environment. This machine has recently been used in Ontario casinos. Details of play are outlined below (section 2.8.2).
2.5 Screening Instruments

**South Oaks Gambling Screen (SOGS) (Lesieur and Blume, 1987)**

The SOGS is a validated, widely used measure to identify PG status. The scale consists of 16 items, 11 of which are scored, with a maximum score of 20. Participants who scored 0 were eligible as HCs and those who scored ≥5 were eligible as PGs. The questionnaire was administered during the telephone screening and repeated in the interview screening. For PG participants, the study psychiatrist administered the SOGS in an oral interview to confirm PG status and severity and ensure full comprehension. HC participants completed it as a self-report measure in the interview session questionnaire package.

**DSM-IV based problem gambling questionnaire (Beaudoin and Cox 1999)**

The DSM-IV PG questionnaire is based on the formal diagnostic criteria for PG as outlined in the DSM-IV and consists of 10 items scored based on the time period in which symptoms occurred (0 [never] → 3 [within the last month]). HC participants scored 0, while PG participants received a total score of ≥5 and endorsed at least five separate symptoms. As with the SOGS, this scale was administered during the telephone screening and repeated during the interview screening by self-report or through interview with the study psychiatrist as a secondary measure of PG status and severity.

**Beck Depression Inventory-short form (BDI) (Beck and Beck 1972)**

The BDI is a 13-item scale developed for use in primary care settings which assesses a variety of depressive symptoms and in the present study provided a quantitative index of subclinical depressed mood. Each item is scored from 0-3 depending on symptom severity. The BDI was administered during the telephone screening and in the questionnaire package on the interview screening, and participants who scored <10 were eligible for the study.

**Alcohol Dependence Scale (ADS) (Skinner and Allen 1982)**

The ADS is a 25-item scale used to identify evidence of alcohol abuse or dependence within the previous year. This scale was administered during the telephone screening and in the questionnaire package on the interview screening. Participants with an ADS score <13 (bottom quartile for the scale) were considered for inclusion.
**Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al. 1991)**

This 6-item scale, administered to smokers during the interview screening, characterized the participant’s level of nicotine dependence from 1 (very low) → 10 (high). PG and HC groups and drug subgroups were matched on FTND score.

**Timeline Follow-back (Sobell and Sobell 1992)**

**Alcohol:** A 90-day Timeline Follow-Back was used to estimate typical alcohol use in each participant. Participants recorded the number of alcoholic drinks taken each day for 90 days prior, working from present day backward. This was administered during the interview screening to confirm alcohol use levels reported during the phone screening and the psychiatric interview (see below). Participants who consumed > 20 (men) or > 15 (women) alcoholic drinks per week on average were excluded.

**Nicotine:** A 7-day nicotine Timeline Follow-Back was given to smokers during the interview screening to confirm smoking status and level of use. To minimize potential withdrawal effects during the 4-hr non-smoking assessment phase of each test session, participants who smoked > 20 cigarettes/day on average were excluded.

**Drug Abuse Screening Test (DAST) (Skinner 1982)**

The DAST consists of 20 yes-or-no questions used to determine extent of recreational drug use. It was administered on the interview screening to verify lack of regular drug use. Participants with DAST scores ≤ 4 were eligible for inclusion.

**Structured Clinical Interview for the DSM-IV (SCID) (First et al. 1995)**

The SCID is a semi-structured interview designed to assess psychiatric patients and non-patient research participants across a variety of Axis I diagnoses based on DSM-IV diagnostic criteria. The interviewer asks a series of yes-or-no screening questions and goes into further detail about any items endorsed. The discussion is open-ended and ambiguous responses are clarified with pre-determined follow-up questions if necessary in order to get a comprehensive assessment of the participant’s current and past psychiatric profile.

This study included modules covering mood episodes (covering current and past depressive and manic episodes), anxiety disorders, alcohol use, substance use, and psychotic symptoms. The experimenter administered the SCID during the interview screening.
Participants were excluded if they met criteria for current or past depressive or manic episodes (a single prior depressive episode >1 year prior was permissible), anxiety disorders, alcohol abuse or dependence (alcohol abuse >1 year prior was permissible), or psychotic symptoms.

2.6 Trait Scales

Several self-report questionnaires were administered during the interview screening to characterize the personality of participants in each subgroup.

Eysenck Personality Inventory (EPI; Eysenck and Eysenck, 1963)

The EPI is a self-report questionnaire of 57 yes-or-no questions surveying domains of Extraversion (range 0-24), Neuroticism (range 0-24), and Lie Scale (range 0-9). The Lie Scale assesses tendency to choose socially acceptable responses over truthful ones, and thus is an index of likelihood that a participant would modify their self-report answers to comply with perceived experimental demand.

Eysenck Impulsiveness Scale (EIS; Eysenck et al. 1985)

The EIS is a self-report questionnaire consisting of 54 yes-or-no questions covering domains of Impulsivity (range 0-16), Venturesomeness (range 0-16), and Empathy (range 0-19).

Gamblers’ Belief Questionnaire (Steenbergh et al. 2002)

The GBQ is a 21-item self-report measure of cognitive distortions in gamblers across two related domains, Luck/Perseverence (Factor 1) and Illusion of Control (Factor 2). Each item (e.g., “Gambling is more than just luck”) is rated on a 7-point scale: 1 (Strongly Agree) → 4 (Neutral) → 7 (Strongly Disagree). Thus, lower scores indicate greater cognitive distortions.

2.7 Neuropsychological Tasks

Selected tasks from the Weschler Adult Intelligence Scale (WAIS-R) (Wechsler 1981) were administered during the interview visit to screen participants and assess basic cognitive function.
WAIS Digit Span

The Wechsler Digit Span task assesses attention, short term rote memory (Forward Subscale) and working memory (Backward Subscale). For the Forward subscale, participants listened to the experimenter read aloud a series of numbers, then repeated the digits back in the same order. Fourteen total series of increasing length were read (2 series each of 3 - 9 digits) with each response scored 0 or 1. Participants then completed the Backward subscale, in which 14 new series of digits were read and participants repeated each series back in the reverse order (e.g., 2-9 becomes 9-2), with 2 series each of 2 - 8 digits administered in order of increasing length. The maximum possible score on each subscale is 14 for a combined maximum score of 28.

WAIS Digit Symbol-Coding

The Wechsler Digit Symbol-coding task assesses visual working memory and motor coordination. Participants are asked to match digits (0-9) to symbols, penciling each symbol into a box below its corresponding number. Participants completed as many of these as possible in a one-minute span with the symbol legend visible during the task. The maximum possible score was 92.

WAIS Vocabulary Task – split half

The Wechsler Vocabulary task was used to confirm English proficiency in order to ensure full comprehension of reading-based self-report and cognitive/behavioural tasks. Participants were asked to orally define 15 English language words of increasing difficulty (e.g. “winter”, “sentence”, “ponder”) in their own words. Each definition was scored 0-2 by the experimenter, for a maximum total score of 30. Participants with scores <18 were excluded from the study.

Wisconsin Card Sort Task (WCST) (Heaton 2003)

The WCST was administered once, by computer, during the interview screening as a measure of learning and cognitive flexibility. Participants were asked to match a series of different cards to one of four standard cards on-screen. Cards could be matched on one of 3 domains (colour, number, or type of symbol) with 4 choices in each domain (e.g., red, yellow, blue, green). They were not told the rules for matching but the computer provided feedback
(CORRECT or INCORRECT) for each trial. After participants had matched cards correctly based on a given domain, the domain for matching would change without notice and participants would have to learn the new rule based on the computer feedback. The task had no set number of trials and continued until correct responses were chosen for 6 new rules. The number of trials required for the participant to learn the correct matching rule after each change was used to assess cognitive flexibility in response to visual cues. Previous studies have found impairments in WCST performance in PG participants compared to HCs (Goudriaan et al. 2006, Rugle and Melamed 1993).

2.8 Experimental Indices

2.8.1 Self-Report Questionnaires

Self-report questionnaires were administered at 5 time points in each test session to assess mood and response to gambling under each drug condition as the session progressed.

Visual Analog Scales (VAS) (Fischman and Foltin 1991)

These scales provided self-report measures of subjective pleasurable and motivational responses to gambling. Motivation for alcohol was also assessed to determine if drug effects were selective for gambling rather than other types of addictive reinforcement. Additional scales assessed energy, engagement, and alertness. Scales generally ranged from 0 (Not at all) to 10 (Extremely) with 0.5-point gradations.

Gambling: Gambling items on all questionnaires (packages A-E, Table 2) were: (1) Right now I desire or feel like gambling; and (2) Right now I am confident I could resist gambling (if there was a casino across the street).

Alcohol: Alcohol items on all questionnaires were (1) Right now I would like to drink some alcohol; and (2) Right now I am confident I can resist drinking alcohol (if there was a bar across the street).

Slot Machine Effects: After slot machine play, VAS scales assessed subjective pleasurable effects of the game: Enjoyment, (A) I enjoyed playing the slot machine; Excitement, (B) I found playing the VLT slot machine exciting; Engagement/Involvement, (C) While playing the VLT slot machine game, I found myself engaged or involved (i.e., ‘I got into it’); and High, (D) While playing the VLT slot machine, I felt a ‘buzz’ or a ‘high’.
Profile of Mood States (POMS), short form (Shacham 1983)

The POMS was used to track changes in mood over the course of each test session. Participants rated their experience of 37 mood adjectives from 0 (Not at all) \( \rightarrow \) 4 (Extremely). The POMS quantifies mood across six domains: Tension-Anxiety (0-24), Depression-Dejection (0-32), Anger-Hostility (0-28), Fatigue-Inertia (0-24), Vigor-Activity (0-20), and Confusion-Bewilderment (0-20).

Addiction Research Centre Inventory (ARCI) (Haertzen 1965)

The ARCI assessed drug-like effects of slot machine play. It consists of 49 true-or-false questions covering 6 drug effect domains: (1) Amphetamine (AMPH), measuring amphetamine-specific effects (range 0-9; sample statement, “My thoughts come more easily than usual”), (2) Morphine/Benzedrine Group (MBG) for euphoria (range 0-16; e.g. “I would be happy all the time if I felt as I do now”), (3) Lysergic Acid Diethylamine (LSD) for dysphoria (range 0-14; e.g. “I feel anxious and upset”), (4) Benzedrine Group (BG) for stimulant effects (range 0-13; e.g. “My movements seem faster than usual”), and (5) Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) for sedation (range 0-15; e.g. “I have a feeling of just dragging along”). In PGs, the ARCI has been used to measure drug-like euphoric effects of gambling wins, with increases seen on measures of psychostimulant effects in particular (Hickey et al. 1986).

Symptom Side Effect Checklist (Zawertailo et al. 1994)

At the end of each test session, participants completed a Side Effects Checklist to determine the presence and severity of 24 potential medication side effects, from 0 (Absent) \( \rightarrow \) 5 (Needs intervention).

Capsule Contents Evaluation (CCE)

At the end of the second test session, participants completed a CCE form indicating which capsule(s) they believed contained active drug on test sessions 1 and 2.
2.8.2 Cognitive/Behavioural Tasks

Slot machine

At peak drug level on each test session, participants played a VLT-style slot machine game for up to 15 minutes or until 400 pre-loaded cash credits (equivalent to $100) ran out. To encourage naturalistic betting behaviour participants were informed they would receive a cash bonus proportional to the number of credits remaining at the end of the slot machine session. To enhance external validity, the slot machine was located in a mock bar environment separate from other testing rooms and play was unsupervised.

As with all slot machines, the object was to get as many of the same symbol on a line as possible. For each spin, players selected the number of horizontal and diagonal lines to bet on (1-9) and the number of credits to bet on each line (1-5) for a total bet size of 1-45 credits. Selection of more lines per spin increased odds of winning. Boxes onscreen displayed a running tally of total credits as well as number of credits won on the previous spin. Wins (credits > 0 received) were accompanied by visual and auditory cues (flashing lights and bells/dings proportional to the number of credits won), while losses garnered no feedback. Bet size and credits won on each spin were recorded electronically. Participants were not aware during the test sessions that their betting was recorded but were advised of this during debriefing.

Rapid Reading Task (RRT) (Zack and Poulos 2004)

The RRT was administered after slot machine play on each test session and provided an objective measure of implicit priming effects of the slot machine on gambling-related semantic memory networks to complement self-reports. Participants were asked to read aloud words appearing one at a time on a computer screen as quickly as possible. Before each word a warning signal (‘&&&&&&’) appeared for 350ms to focus the participant’s attention. Response time was measured with millisecond precision using a microphone attached to the computer and outfitted with MicroExperimental Laboratory (MEL, v. 2.01; Psychology Software Tools, Pittsburgh, PA) software. The experimenter coded response accuracy (correct, incorrect, or discard, e.g., cough tripped microphone) on every trial using a serial response box (Psychology Software Tools, Pittsburgh, PA). Each word remained onscreen until the response was received then disappeared, and the experimenter manually cued the next word to appear.
The task consisted of 20 practice trials followed by 150 test trials. Words were drawn from one of 5 categories: Gambling-Related (e.g. casino, bet), Alcohol-Related (e.g. bourbon, drink), Positive Affect (e.g. joy, hopeful), Negative Affect (e.g. sad, hopeless), and Neutral (e.g. window, lattice). Thirty words were presented from each category in random order. Words appeared with asterisks between each letter (e.g. c*a*s*i*n*o*) to enhance priming effects (Stanovich and West 1983).

Faster reading speed for Gambling words compared to Neutral words is believed to reflect increased incentive salience of gambling stimuli – for example, in PGs, a dose of amphetamine increases subjective motivation to gamble and reduces reading speed of words related to gambling, but not that of neutral words (Zack and Poulos 2004). The difference in reading speed for Gambling-related words relative to Neutral words operationally defined incentive salience after slot machine play under each drug condition.

**Stop-Signal Task (Logan et al. 1997)**

The SST was administered during the interview screening and after the RRT on each test session to assess inhibitory control at baseline and after gambling under drug or placebo treatment. Participants were instructed to press a key (“z” or “/” with their left or right index fingers, respectively) in response to visual stimuli (a / b [interview, test session 1] or c / d [test session 2]) but to inhibit their response when an auditory tone sounded on a random 25% of trials. Participants completed two sets of practice trials each time they did the task to stabilize day-to-day psychomotor fluency.

Other things being equal, the longer the delay between the onset of the visual Go stimulus and the onset of the Stop signal tone, the greater the likelihood of committing the key press. By manipulating the length of this interval it is possible to determine the delay that permits 50% successful inhibition for a given participant. The difference between this interval and the average response time to the visual stimuli (Stop Signal Response Time [SSRT]) provided a unitary index of inhibitory efficiency. Response time and response errors to Go and Stop signals were recorded. The principal outcome measure was SSRT, with higher values indicating poorer inhibitory control. SSRT is elevated in PGs vs. controls (Brevers et al. 2012) and predicts relapse in treated PG patients (Goudriaan et al. 2008), suggesting it may be functionally related to motivation for gambling.
**Game of Dice Task (GDT) (Brand et al. 2005)**

The GDT was administered during the interview screening and after the slot machine and all other tasks on each test session to assess risk-taking behaviour. Participants bet on the outcome of a virtual die throw, choosing a single number (1-6) or combinations of two, three, or four possible outcomes. When the thrown number was the selected number or among those in a selected combination, the player won and had a designated amount of money added to their total, otherwise he or she lost and had the same amount deducted. Bet size was $1000 for a single number, $500 for a combination of two numbers, $200 for a combination of three numbers, and $100 for a combination of four numbers. Play lasted for 18 throws and participants continued gambling into negative balances when necessary.

Risk-taking was measured by the number of possible outcomes selected on each throw, from a single number (odds of correctly matching the outcome on that throw = 1 in 6; highest risk) to four numbers (odds of correctly matching the outcome on that throw = 4 in 6; lowest risk). Mean number of outcomes selected per throw was calculated for three blocks of 6 trials during early (1-6), middle (7-12), and late (13-18) stages of the game. Blocking of individual trial scores enabled assessment of changes in risk-taking as the task progressed while controlling non-systematic inter-trial variability (cf. Brand et al 2005).

**2.9 Procedure**

**2.9.1 Recruitment and Screening**

**Telephone Screening**

Participants were recruited from the community using online and print classified ads on Craigslist.com, Kijiji.ca, and in the Job Classifieds paper (Appendix 2, Recruitment Advertisements). Potential participants phoned the study line and were given a brief overview of study requirements and procedure. If interested, they continued to a 20-minute telephone questionnaire to assess eligibility, including questions covering basic demographics, health background, and past substance use, as well as SOGS, DSM PG questionnaire, BDI, ADS, and EIS. If participants were eligible based on these measures, an interview screening session was scheduled at CAMH.
**Interview Screening**

After passing the telephone screening, potential participants proceeded to an in-person interview with study personnel. First, written informed consent was obtained (Appendix 3, Informed Consent Form), followed by measurements of breath alcohol (0% required), heart rate, blood pressure, weight and height. Female participants were also given a urine pregnancy test. Study personnel then conducted the SCID to determine psychiatric profile and history. Potential PG participants also underwent a subsequent interview to verify PG status with a study psychiatrist with experience in PG treatment and research. This included administering the SOGS and DSM-IV PG questionnaire as well as a detailed history of the individual’s gambling habits. This screening component helped to identify individuals falsely reporting PG symptoms to gain entry to the study simply to earn the sizeable payment.

Eligible participants then completed written screening questionnaires including SOGS and DSM-IV PG criteria (for HCs), BDI and ADS to confirm telephone questionnaire responses, as well as FTND, DAST, Alcohol and Nicotine Timeline Follow-backs and trait questionnaires (EIS, EPI, GBQ). The WAIS Vocabulary, Digit Symbol-Coding, and Digit Span tasks were administered next, followed by the SST, GDT, and WCST computer tasks.

Lastly, participants were escorted to the CAMH Clinical Laboratory. Blood samples were drawn from their arm by a registered nurse for bloodwork, and urine samples were obtained to confirm the absence of recent recreational drug use. A technician performed an electrocardiogram (ECG) to confirm the absence of any heart arrhythmias. Lab test results were sent to the study’s Qualified Investigator (supervising physician) to assess medical eligibility of each participant. If potential health problems were identified at this point, the qualified investigator contacted the participant to inform him or her and advised follow-up with a family doctor or walk-in clinic.

**Physician’s Exam**

Approximately one week after interview screening, eligible participants underwent a standard physical examination by a doctor and registered nurse at the CAMH Addiction Medicine Clinic to confirm health status and medical suitability for the study. Participants considered eligible at this point proceeded to the test phase of the study.
2.9.2 Group Assignment and Matching

Participants were assigned to either haloperidol or fluphenazine in matched pairs. As far as possible, PG and HC groups, as well as antagonist subgroups, were matched on PG severity (SOGS, where relevant), gender, age, alcohol use (ADS), depressive symptoms (BDI), nicotine dependence (FTND), and impulsiveness (EIS).

After the physician’s exam, pharmacy personnel randomized each enrolled participant to a drug sequence: sequence 1, drug on session 1 followed by placebo on session 2; or sequence 2, placebo on session 1 followed by drug on session 2. The experimenter and participants were blind to drug sequence.

2.9.3 Test Day Procedure

Eligible participants attended two test sessions with a one-week washout period between sessions. The procedure for these sessions is summarized in Table 2. Participants arrived at the testing facility at 8:30am. On arrival, the experimenter measured heart rate and blood pressure and administered the breathalyzer to confirm the absence of alcohol in his or her bloodstream. Participants were then given a standard breakfast and completed the first questionnaire package, consisting of VAS for gambling and alcohol, POMS, and ARCI. Pregnancy tests were administered to female participants at this time, and smokers were permitted one cigarette, and none thereafter until the test phase was over (4-5 hrs later).

The medication was administered in the form of 3 capsules containing 1-mg per capsule of haloperidol/fluphenazine, or visually identical placebos. Participants then waited for drug absorption (2 hours for fluphenazine, 2 hours 45 minutes for haloperidol) with blood pressure and heart rate measurements taken every 30 minutes. Participants completed a second questionnaire package 15 minutes prior to expected peak plasma drug level. When this time was reached, participants played the slot machine for 15 minutes as described above, and then completed the third questionnaire package in the mock-bar environment.

Participants then proceeded to cognitive computer-based tasks: the RRT, followed by a fourth questionnaire package, then the SST and GDT followed by a final questionnaire package including Symptom Side Effect checklist. The Capsule Contents Evaluation form was administered at the end of the second test session. Heart rate and blood pressure were measured after the slot machine and each computer task.
Participants were given lunch and, after a detoxification period, examined by a study physician or registered nurse to ensure blood pressure and heart rate had returned to baseline and no adverse effects were present. At discharge, participants were given one capsule containing 50-mg diphenhydramine to use in the event of delayed side effects, and the wallet card with medication information, and then sent home in a pre-paid taxi.

Table 2. Test Session Timeline

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>• Breathalyzer and baseline HR/BP measurements</td>
</tr>
<tr>
<td></td>
<td>• Breakfast</td>
</tr>
<tr>
<td></td>
<td>• Package A administered (VAS – Desire to Gamble/Drink Alcohol; POMS; ARCI)</td>
</tr>
<tr>
<td></td>
<td>• HR/BP measured pre-capsule 1</td>
</tr>
<tr>
<td>30 min</td>
<td>• Capsule 1 administered</td>
</tr>
<tr>
<td></td>
<td>• <em>HR/BP measured every 30 minutes post-capsule</em></td>
</tr>
<tr>
<td>2 hr 15 min (FLU)</td>
<td>• Package B administered (VAS – Desire to Gamble/Drink Alcohol; POMS; ARCI)</td>
</tr>
<tr>
<td>2 hr 45 min (HAL)</td>
<td></td>
</tr>
<tr>
<td>2 hr 30 min (FLU)</td>
<td>• Capsule 2 (amphetamine dummy capsules) administered</td>
</tr>
<tr>
<td>3 hr 15 min (HAL)</td>
<td>• Slot machine game in mock bar (15 mins)</td>
</tr>
<tr>
<td>2 hr 45 min (FLU)</td>
<td>• HR/BP measured (in mock bar)</td>
</tr>
<tr>
<td>3 hr 30 min (HAL)</td>
<td>• Package C administered (VAS – Desire to Gamble/Drink Alcohol, VAS-Enjoyment/Excitement/Engagement/High from slot machine game; POMS; ARCI)</td>
</tr>
<tr>
<td>3 hr (FLU)</td>
<td>• RRT</td>
</tr>
<tr>
<td>3 hr 45 min (HAL)</td>
<td></td>
</tr>
<tr>
<td>3 hr 15 min (FLU)</td>
<td>• HR/BP measured</td>
</tr>
<tr>
<td>4 hr (HAL)</td>
<td>• Package D administered (VAS – Desire to Gamble/Drink Alcohol; POMS; ARCI)</td>
</tr>
<tr>
<td>3 hr 30 min (FLU)</td>
<td></td>
</tr>
<tr>
<td>4 hr 15 min (HAL)</td>
<td></td>
</tr>
<tr>
<td>3 hr 45 min (FLU)</td>
<td>• HR/BP measured</td>
</tr>
<tr>
<td>4 hr 30 min (HAL)</td>
<td>• GDT</td>
</tr>
<tr>
<td>4 hr (FLU)</td>
<td>• HR/BP measured</td>
</tr>
<tr>
<td>4 hr 45 min (HAL)</td>
<td>• Package E administered (VAS – Desire to Gamble/Drink Alcohol; POMS; ARCI; Symptom Side Effect Checklist)</td>
</tr>
<tr>
<td></td>
<td>• CCE administered (session 2)</td>
</tr>
<tr>
<td>4 hr 15 min (FLU)</td>
<td>• Lunch</td>
</tr>
<tr>
<td>5 hr (HAL)</td>
<td></td>
</tr>
</tbody>
</table>
**2.10 Data Analysis**

Data analysis was completed using SPSS (v. 15, Chicago IL). Each outcome measure was examined using analysis of variance (ANOVA) or analysis of covariance (ANCOVA) as outlined below. Data were analyzed separately for each drug sequence subgroup in order to identify patterns associated with prior exposure to the slot machine game. Because of this, a Drug Sequence x Session interaction represented a significant drug effect (as well as a possible difference in the magnitude of this drug effect as a function of drug sequence).

This study represents a preliminary analysis of an experiment for which the projected final sample size is 80 participants. As a result, power to detect hypothesized effects is considerably reduced. Therefore, effects with p values between 0.05 and 0.10 will be identified in the present analyses, as these could well achieve significance once the full sample is completed.

**Participant Characteristics.** Baseline characteristics, screening scale scores, and WCST scores were analyzed using *t* tests to identify differences between groups.

**Subjective Effects.** Self-report measures taken at multiple time points in each session, including VAS-gambling and alcohol, POMS and ARCI subscales, were each analyzed using 2 (Group: HC, PG) x 2 (Drug Group: haloperidol, fluphenazine) x 2 (Sequence: drug first / placebo first) x 2 (Session) x 4 (Time point: peak drug level, post-slot machine, post cognitive tasks, post-risk taking task) repeated measures ANCOVA. These analyses controlled for baseline scores on the respective scales to account for individual differences and for final credits remaining on the slot machine, as winning or losing outcomes may influence enjoyment and reinforcement of slot machine play.

Subjective pleasurable effects of the slot machine were assessed at a single time point in each test session and so were analyzed using 2 (Group) x 2 (Drug Group) x 2 (Sequence) x 2 (Session) x 4 (Subscale: Enjoyment, Excitement, Involvement/ Engagement, and ‘Buzz/High’) repeated measures ANCOVA controlling for final slot machine credits.

**Betting Behaviour.** Mean bet per line (credits; 1-5), mean number of lines per spin (1-9), and mean total bet size per spin (credits; 1-45) were each analyzed using 2 (Group) x 2 (Drug Group) x 2 (Sequence) x 2 (Session) repeated measures ANOVA.
**Physiological Measures.** HR, systolic BP, and diastolic BP were analyzed using 2 (Group) x 2 (Drug Group) x 2 (Sequence) x 2 (Session) x 4 (Time point: peak drug level, post-slot machine, post-cognitive tasks, post-risk task) repeated measures ANCOVA controlling for baseline scores and final credits on the slot machine.

**Computer Tasks.** Percent difference in reading speed (ms) relative to Neutral words on the RRT was analyzed using 2 (Group) x 2 (Drug Group) x 2 (Sequence) x 2 (Session) x 4 (Word Category: Gambling, Alcohol, Positive Affect, Negative Affect) repeated measures ANOVA. For the SST, SSRT was analyzed in a 2 (Group) x 2 (Drug Group) x 2 (Sequence) x 2 (Session) repeated measures ANOVA. GDT analysis consisted of 2 (Group) x 2 (Antagonist) x 2 (Sequence) x 2 (Session) x 3 (Trial Block: 1-5, 7-12, 13-18) repeated measures ANOVA.

Study hypotheses (see section 1.4) are that (1) haloperidol will enhance gambling reinforcement in PGs but not HCs, and (2) fluphenazine will enhance gambling reinforcement in HCs but not PGs, respectively. Therefore, each study drug (i.e., Drug Group effect) should have different effects (Treatment effect, = Sequence x Session interaction as discussed above), in HC and PG groups (Group effect) on increases in measures of reinforcement post-slot machine (Time effect). As a result, a significant highest-order interaction (typically, Group x Drug Group x Sequence x Session x Time) was expected for most outcome measures.

**Simple Effects.** Significant and marginal (0.05 < p < 0.10) interactions were decomposed using within-subjects t tests to identify simple effects of Time and drug treatment in each Group, Drug Group, and Sequence condition. These tests were computed using mean square error term for the effect in question from omnibus ANOVA or ANCOVA analyses for each outcome measure, incorporating variance from all time points (Winer 1971). To assess hypothesis (3), that drug effects would be stronger relative to placebo on day 1 than on day 2 (due to novelty of the slot machine and corresponding effects on DA), secondary between-subjects simple effects t tests were computed to identify significant differences between drug and placebo treatment on each test session separately – that is, comparing mean scores from a given subgroup who received drug on the first test session to scores from participants who received placebo on the first test session, and similarly for session 2. These tests were performed when a significant effect of Session emerged on the ANOVA/ANCOVA to verify the treatment effect and assess whether session (i.e., novelty) influenced magnitude or direction of these effects.
3. RESULTS

3.1 Recruitment and Study Subjects

Between March 2012 and May 2013, 670 phone calls were received at the study line (376 responding to the PG ad, 294 responding to the Healthy Volunteers ad). From these, 52 potential participants (38 PG, 14 HC) were eligible based on the telephone screening. Thirty-eight potential participants completed these screening visits (27 PG, 11 HC) and 16 were enrolled in the study (8 PG, 8 HC). From these groups, four PGs and four HCs were each assigned to haloperidol and to fluphenazine. Thus, including previously collected data, total N is 48, and overall n in each of the four subgroups (PG-haloperidol, PG-fluphenazine, HC-haloperidol, HC-fluphenazine) is 12. Half (n=6) were randomly assigned to each drug sequence (Figure 3).

Figure 3. Flow chart showing subject recruitment.
3.1.1 Subject characteristics

Background characteristics and trait scores for each subgroup are shown in Table 3. In a 2 (Group) x 2 (Drug group) MANOVA, significant univariate group effects emerged on SOGS and DSM-IV PG scores, as well as EIS-impulsiveness scores ($p$s < 0.05), with higher scores in PGs. PGs also had higher scores on the BDI though all scores were well below clinical thresholds for depression. No differences existed between antagonist subgroups.

**Table 3.** Mean (SD) background characteristics of each subgroup.

<table>
<thead>
<tr>
<th></th>
<th>PG</th>
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<th>HC</th>
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<tbody>
<tr>
<td></td>
<td>HAL FLU</td>
<td></td>
<td>HAL FLU</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>12 12</td>
<td>12 12</td>
<td>12 12</td>
<td>12 12</td>
</tr>
<tr>
<td>Age [mean (SD)]</td>
<td>33.9 (7.8)</td>
<td>32.3 (10.1)</td>
<td>36.5 (12.8)</td>
<td>37.3 (14.4)</td>
</tr>
<tr>
<td>Gender (n male : n female)</td>
<td>9 : 3</td>
<td>8 : 4</td>
<td>8 : 4</td>
<td>7 : 5</td>
</tr>
<tr>
<td>Smokers (n) : non-smokers (n)</td>
<td>1 : 11</td>
<td>1 : 11</td>
<td>1 : 11</td>
<td>0 : 12</td>
</tr>
<tr>
<td>SOGS [mean (SD)] *</td>
<td>10.5 (5.1)</td>
<td>10.6 (5.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>DSM-IV PG [mean (SD)] *</td>
<td>13.5 (5.6)</td>
<td>15.3 (5.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>BDI [mean (SD)] *</td>
<td>2.2 (2.6)</td>
<td>2.9 (3.5)</td>
<td>0.25 (0.45)</td>
<td>0.58 (1.0)</td>
</tr>
<tr>
<td>ADS [mean (SD)]</td>
<td>0.83 (1.2)</td>
<td>1.4 (2.4)</td>
<td>0.83 (1.5)</td>
<td>0.33 (0.78)</td>
</tr>
</tbody>
</table>

* = main effect of Group, $p$<0.05. SOGS = South Oaks Gambling Screen; DSM-IV PG = DSM-IV Pathological Gambling Questionnaire; BDI = Beck Depression Inventory; ADS = Alcohol Dependence Scale.

Table 4 presents scores on personality and Gambling Belief scales as well as measures of drug abuse (DAST) and alcohol use (mean drinks/week from 90-day Timeline Followback). In a 2 x 2 MANOVA of these scales, univariate main effects of group were observed on EPI and EIS impulsiveness subscales and GBQ – Luck/Perseverance and Illusion of Control domains, reflecting more extreme scores in PGs relative to HCs (lower scores on GBQ denote more severe cognitive distortions). PGs also had significantly greater scores on the EPI – Extraversion subscale.
Table 4. Mean (SD) scores and measures of personality, gambling beliefs, drug/alcohol use in each subgroup.

<table>
<thead>
<tr>
<th></th>
<th>PGs</th>
<th></th>
<th>HCs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HAL</td>
<td>FLU</td>
<td>HAL</td>
<td>FLU</td>
</tr>
<tr>
<td>EPI – Impulsiveness *</td>
<td>4.0 (2.0)</td>
<td>4.1 (1.2)</td>
<td>2.5 (1.4)</td>
<td>2.7 (1.4)</td>
</tr>
<tr>
<td>EPI – Extraversion *</td>
<td>13.5 (4.2)</td>
<td>13.8 (3.0)</td>
<td>9.8 (4.0)</td>
<td>11.6 (3.6)</td>
</tr>
<tr>
<td>EPI – Neuroticism</td>
<td>5.8 (3.2)</td>
<td>5.9 (5.0)</td>
<td>4.4 (2.9)</td>
<td>3.1 (3.6)</td>
</tr>
<tr>
<td>EPI - Lie</td>
<td>3.3 (1.5)</td>
<td>3.8 (2.2)</td>
<td>4.3 (2.0)</td>
<td>4.5 (1.8)</td>
</tr>
<tr>
<td>Mean drinks/week (past 90 days)</td>
<td>2.2 (2.4)</td>
<td>2.2 (2.9)</td>
<td>1.1 (1.1)</td>
<td>0.91 (0.91)</td>
</tr>
<tr>
<td>DAST</td>
<td>0.25 (0.62)</td>
<td>0.14 (0.49)</td>
<td>0.58 (0.67)</td>
<td>0.42 (0.79)</td>
</tr>
<tr>
<td>EIS – Impulsiveness *</td>
<td>7.9 (5.1)</td>
<td>7.6 (4.9)</td>
<td>3.0 (3.0)</td>
<td>2.6 (3.1)</td>
</tr>
<tr>
<td>EIS – Venturesomeness</td>
<td>11.5 (4.8)</td>
<td>12.8 (8.7)</td>
<td>13.4 (7.3)</td>
<td>12.1 (8.3)</td>
</tr>
<tr>
<td>EIS – Empathy</td>
<td>8.1 (6.7)</td>
<td>7.1 (6.3)</td>
<td>8.3 (6.6)</td>
<td>7.8 (6.2)</td>
</tr>
<tr>
<td>GBQ – Luck/ Perseverance *</td>
<td>49.9 (18.6)</td>
<td>46.5 (16.0)</td>
<td>85.1 (5.4)</td>
<td>82.6 (9.2)</td>
</tr>
<tr>
<td>GBQ – Illusion of control *</td>
<td>22.8 (8.2)</td>
<td>23.1 (8.3)</td>
<td>46.5 (7.9)</td>
<td>45.0 (7.7)</td>
</tr>
</tbody>
</table>

* = main effect of group, p<0.05

EPI = Eysenck Personality Inventory; EIS = Eysenck Impulsiveness Scale; DAST = Drug Abuse Screening Test; GBQ = Gambling Beliefs Questionnaire (lower scores denote greater cognitive distortions).

Table 5 presents the mean (SD) scores for cognitive proficiency tasks in each subgroup. A 2 x 2 MANOVA found no significant group or drug group effects, indicating roughly similar basic cognitive function in each subgroup.

Table 5. Mean (SD) cognitive proficiency scores for each subgroup.

<table>
<thead>
<tr>
<th></th>
<th>PGs</th>
<th></th>
<th>HCs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HAL</td>
<td>FLU</td>
<td>HAL</td>
<td>FLU</td>
</tr>
<tr>
<td>WAIS-Vocabulary</td>
<td>28.3 (2.4)</td>
<td>27.5 (2.5)</td>
<td>29.3 (1.4)</td>
<td>28.7 (2.1)</td>
</tr>
<tr>
<td>WAIS – digit span</td>
<td>24.4 (12.7)</td>
<td>19.3 (10.4)</td>
<td>18.1 (3.9)</td>
<td>19.9 (6.8)</td>
</tr>
<tr>
<td>WAIS – digit symbol coding</td>
<td>43.9 (20.1)</td>
<td>40.7 (2.5)</td>
<td>43.5 (9.2)</td>
<td>36.5 (7.1)</td>
</tr>
<tr>
<td>WCST</td>
<td>80.3 (11.2)</td>
<td>90.2 (21.7)</td>
<td>81.1 (14.9)</td>
<td>82.8 (13.8)</td>
</tr>
</tbody>
</table>

WAIS = Wechsler Adult Intelligence Scale. Vocabulary: maximum score = 30; Digit Span: number of correctly repeated sequences; Digit Symbol: number of correctly coded items in 60 seconds; WCST = Wisconsin Card Sort Task: number of completed trials.
3.2.1 Experimental Outcomes: Self-Report Scales

3.2.1.1 Desire to Gamble

In a 2 x 2 x 2 x 2 x 4 ANCOVA controlling for baseline Desire to Gamble scores and winnings on the slot machine, significant main effects of Group \( [F(1,37)=12.2, p=0.001] \) and Time \( [F(3,37)=7.16, p<0.001] \) emerged, reflecting higher motivation to gamble in PGs than HCs and higher scores post-game, as expected. A significant Session \( [F(1,37)=4.30, p=0.045] \) effect reflected a tendency towards higher overall Desire scores on session 1 than session 2, particularly pre-game.

Figures 4 and 5 present Desire to Gamble scores across four time points (peak drug level/pre-game, post-game, post-cognitive tasks, and post-risk task) in HCs and PGs respectively, for haloperidol (panels a and b) and fluphenazine (panels c and d) subgroups. Results are presented separately for subjects in sequence 1 (panels a and c), who received the drug on day 1, and sequence 2 (panels b and d), who received the drug on day 2. Error bars represent standard error of the mean (SEM) for scores at each day and time point in each subgroup. Simple effects tests were performed within-subjects between sessions 1 and 2 for each subgroup, with ‘*’ indicating \( p<0.05 \). Because \( t \) tests were computed using mean square error values from the ANCOVA and thus accounted for variance across all 48 subjects (Winer 1971), while error bars were derived from 6-subject subgroups (i.e., greater within-cell variance), statistically significant simple effects emerged in some cases despite overlapping error bars.

A significant Time x Group interaction \( [F(3,37)=5.57, p=0.001] \) likely reflects elevation in Desire to Gamble post-game that persists through the last time points in PGs but not HCs, while a marginal Session x Time x Drug Group \( [F(3,37)=2.19, p=0.093] \) effect reflects higher scores post-game in session 1 for haloperidol.

A marginal Session x Drug Group x Group \( [F(1,37)=3.25, p=0.080] \) interaction also emerged. In HCs, both haloperidol and fluphenazine tended to increase motivation to gamble post-game (figure 4a-d). As noted in the Methods section, to determine if these were true drug effects or mainly driven by the Session effect, between-groups \( t \) tests were performed comparing scores under drug on session 1 to those under placebo on session 1, and similarly for session 2. This strategy enabled assessment of the effects of each drug while controlling for number of exposures to the game. In these comparisons, drug effects were only significant on session 1 \( (ps < 0.02) \) but not session 2 \( (ps > 0.15) \). In PGs, haloperidol had minimal apparent
effect (figure 5a-b), while fluphenazine consistently lowered Desire to Gamble (figure 5c-d). Between-subjects, this effect was consistent across time points on session 2 ($ps < 0.01$) and significant pre-game and post-risk task on session 1 ($ps <0.001$), but not post-game or post-cognitive tasks on session 1 ($ps > 0.18$).

![Figure 4(a-d). Mean VAS Desire to Gamble scores under drug and placebo for HCs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1 (drug on day 1, placebo on day 2); panel b: haloperidol, sequence 2 (placebo on day 1, drug on day 2); panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = $p<0.05$.](image-url)
Figure 5(a-d). Mean VAS Desire to Gamble scores under drug and placebo for PGs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1; panel b: haloperidol, sequence 2; panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.

In summary, in HCs the within-subjects’ simple effects depicted in the individual panels indicate that haloperidol significantly increased Desire to Gamble before and after the game when the drug was received on session 1, and the between-subjects’ simple effects suggest that the post-game elevation was not due solely to differential exposure to the game.
Thus, haloperidol interacted with novelty to enhance post-game Desire to Gamble in HCs when the task was novel, but not when it was familiar. Fluphenazine had no significant effects whatsoever on Desire to Gamble in HCs.

In PGs, within-subjects simple effects indicated elevations in Desire to Gamble under haloperidol vs. placebo at pre-game/peak blood drug levels and after the risk-task, and between-subjects’ simple effects revealed that, when effects of novelty were controlled, only the elevation in pre-game Desire under the drug persisted. In contrast, within-subjects’ simple effects revealed consistent reductions in Desire to Gamble under fluphenazine vs. placebo at all time points, and between-subjects’ simple effects revealed that pre-game and post-risk task differences persisted, whereas post-game and post-cognitive task reductions under drug were due partly to elevated ratings under placebo on day 1 – i.e., when the game was novel. Because pre-capsule scores for each session are controlled, lower scores at all time points under fluphenazine are not attributable to variations in baseline Desire. Thus, in PGs, haloperidol increases pre-game Desire to Gamble when the situation is novel whereas fluphenazine decreases Desire to Gamble at this time point and immediately following a risk-taking task, regardless of novelty.

(Note: A Treatment [Drug, Placebo] x Drug Sequence interaction would be indicated graphically by a larger difference between drug and placebo in the separate panels for sequence 1 vs. sequence 2; or by a difference in the direction [increase vs. decrease] of the scores under drug vs. placebo for sequence 1 vs. sequence 2 in combination with significant between-subjects’ effects for drug vs. placebo at each level of Session [i.e., differences not due solely to degree of exposure to the game]).
3.2.1.2 Confidence to Resist Gambling

Figures 6 and 7 display changes in Confidence to Resist Gambling over time in HCs and PGs respectively. In a $2 \times 2 \times 2 \times 2 \times 4$ ANCOVA, significant main effects of Group [$F(1,37)=4.72$, $p=0.036$] and Session [$F(1,37)=8.52$, $p=0.006$] were observed, reflecting lower Confidence to Resist Gambling in PGs compared to HCs and on session 1 compared to session 2 across groups, in line with results for Desire to Gamble. Significant Time x Group x Drug Sequence [$F(3,37)=3.04$, $p=0.032$] and Time x Group x Drug Group [$F(3,37)=3.11$, $p=0.029$] interactions were also observed, though absence of an interaction with Session indicates these effects reflect random differences between assigned groups, rather than drug-related effects.

A marginal Session x Time x Drug Group x Drug Sequence [$F(3,37)=2.53$, $p=0.061$] interaction reflects drug effects, mainly evident in PGs. Haloperidol appeared to reduce Confidence to Resist Gambling in HCs pre-game in sequence 1 only (figure 6a). Otherwise in HCs, Confidence was slightly lower post-game on the first test session in all cases (figure 6a-d).

PGs showed a session effect of reduced Confidence pre-game on the first test session (figure 7c-d). In this group, haloperidol consistently reduced scores pre-game but increased them post-game (figure 7a-b), while fluphenazine increased Confidence post-game in sequence 2 only (figure 7d). Only day 2 comparisons were significant between subjects ($ps < 0.001$).
Figure 6(a-d). Mean VAS Confidence to Resist Gambling scores under drug and placebo for HCs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1 (drug on day 1, placebo on day 2); panel b: haloperidol, sequence 2 (placebo on day 1, drug on day 2); panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.
Figure 7(a-d). Mean VAS Confidence to Resist Gambling scores under drug and placebo for PGs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1; panel b: haloperidol, sequence 2; panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.

In HCs, the within-subjects’ simple effects suggest that Confidence to Resist Gambling was reduced by haloperidol prior to the game but only when it was novel. In all other cases, Confidence to Resist Gambling was lower post-game on the first session compared to the second with no apparent Treatment effects.
In PGs, within-subjects’ simple effects indicated reduced Confidence to Resist Gambling under haloperidol vs. placebo at pre-game/peak blood drug levels and elevated scores post-game. Between-subjects’ comparisons confirmed that these effects persisted in all cases except the pre-game reduction in sequence 1, where the drug effect may have been masked by the general tendency for lower Confidence on session 1. Thus, haloperidol appears to reduce Confidence pre-game but increase it post-game in these PG subjects. For fluphenazine, within-subjects’ comparisons again showed that pre-game Confidence was generally lower on session 1 regardless of treatment. However, between-subjects’ comparisons suggest that fluphenazine increased scores relative to placebo at post-game and post-cognitive task time points, as well as post-risk task on session 1. Therefore, fluphenazine moderately increased Confidence to Resist Gambling at various intervals after, but not before, the game.

Taken together, the findings for Desire and Confidence in HCs suggest that motivation to gamble was strongly influenced by test session pre- and post-game, with stronger motivation on the first test session. Haloperidol appeared to augment this session-based effect. Fluphenazine had little effect on gambling motivation in HCs. In PGs, haloperidol slightly elevated motivation to gamble pre-game but appeared to reduce the motivational effects of slot machine play (priming), particularly on session 1. Fluphenazine reliably decreased motivation to gamble in PGs, with more consistent effects across time points on session 2.
3.2.1.3 VAS – Pleasurable Effects of the Slot Machine

Figures 8 and 9 show mean VAS ratings on 4 measures of pleasurable effects of the slot machine game – Enjoyment, Excitement, Engagement/Involvement, and High – in HCs and PGs respectively.

In a 2 x 2 x 2 x 2 x 4 (Measure) MANCOVA controlling for credits remaining on the slot machine, a multivariate main effect of Session [F(4,39)=9.04, p<0.001] and a Drug Group x Group x Drug Sequence interaction emerged [F(4,39)=3.93, p=0.009]. A marginal Session x Drug Group x Drug Sequence interaction emerged for Excitement [F(1,39)=4.84, p=0.066] and significant Session x Group x Drug Sequence interaction emerged for High [F(1,39)=5.584, p=0.047].

In HCs given haloperidol, High increased post-game in sequence 1 only in both within-subjects’ and between-subjects’ comparisons (ps < 0.05, figure 8a). For fluphenazine in HCs, Enjoyment and Excitement were reduced under drug in sequence 1 but increased under drug in sequence 2. In contrast, ratings of High were consistently higher under drug treatment regardless of sequence (figure 8b). In PGs, ratings of Engagement were significantly lower under haloperidol treatment in both sequences; but between subjects’ tests found that this effect was only significant on session 1 (t(39)=5.61, p<0.001). All other measures appeared to be reduced under haloperidol in sequence 2 only (figure 9a). In PGs given fluphenazine, scores were consistent across sessions (figure 9b) with no difference in response under drug vs. placebo.
Figure 8(a-b). Mean VAS scores for subjective pleasurable effects of the slot machine under drug and placebo for HCs. Each bar represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol panel b: fluphenazine. * = p<0.05 for within-subjects comparison of scores on day 1 compared to day 2.
Figure 9(a-b). Mean VAS scores for subjective pleasurable effects of the slot machine under drug and placebo for PGs. Each bar represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol panel b: fluphenazine. * = p<0.05 for within-subjects comparison of scores on day 1 compared to day 2.

For HCs, the within-subjects’ increase in game-induced High under haloperidol in sequence 1 only suggested haloperidol increased the High induced by the slot machine when it was novel but not when it was familiar; and between-subjects’ tests confirmed this was a Drug
Treatment x Sequence interaction not driven by novelty alone. Within-subjects’ comparisons for fluphenazine indicate decreased Enjoyment and Excitement when given in sequence 1 and increased scores on these indices when given in sequence 2 (i.e., the familiarity of the game rather than the drug appeared to enhance these subjective measures).

In PGs, within-subjects’ simple effects demonstrated reduced Engagement under haloperidol in both sequences, which persisted in between-subjects’ analyses on session 1. All other effects declined in sequence 2 only. Thus, haloperidol appeared to reduce perceived Engagement in the game in PGs and subjective rewarding effects decline when the game was familiar. Fluphenazine did not alter the subjective rewarding effects of the game in PGs.

In sum, in HCs fluphenazine but not haloperidol primarily enhanced the perceived High from the slot machine, and in PGs haloperidol but not fluphenazine primarily reduced perceived engagement in the game.
3.2.2 Specificity of Subjective Effects

3.2.2.1 VAS – Desire to Drink Alcohol

Figures 10 and 11 show mean ratings of desire to drink alcohol. In a 2 x 2 x 2 x 2 x 4 ANCOVA, a significant main effect of Time \([F(3,38)=2.98, p=0.035]\) emerged due to an increase in desire for alcohol post-game in some cases. A significant Time x Group x Drug Group x Drug Sequence interaction \([F(3,38)=3.17, p=0.027]\) reflected random group differences rather than treatment or session effects given the absence of a main effect or interaction with Session. In HCs, desire for alcohol increased post-game under haloperidol in sequence 1 but not sequence 2 (figure 10a-b) and fluphenazine had little apparent effect (figure 10c-d). In PGs, desire for alcohol tended to be slightly higher on session 2 (figure 11a-d). PGs’ slightly enhanced desire for alcohol under fluphenazine directly contrasts with their decreased desire to gamble under this drug.

In summary, changes in desire for alcohol from session 1 to session 2 were modest and inconsistent across all subgroups, indicating that observed motivational effects of study interventions for gambling did not solely reflect a change in generic motivation for an addictive reinforcer.
Figure 10(a-d). Mean VAS Desire to Drink Alcohol scores under drug and placebo for HCs. Each curve represents means for \(n=6\), with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1 (drug on day 1, placebo on day 2); panel b: haloperidol, sequence 2 (placebo on day 1, drug on day 2); panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.
Figure 11(a-d). Mean VAS Desire to Drink Alcohol scores under drug and placebo for PGs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1; panel b: haloperidol, sequence 2; panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2.
3.2.3 Subjective Drug-Like Rewarding and Aversive Effects: ARCI Subscales

3.2.3.1 ARCI-MBG (Euphoria)

Figures 12 and 13 show mean ARCI-MBG scores in each subgroup across time points in HCs and PGs, respectively. In a 2 x 2 x 2 x 2 x 4 ANCOVA controlling for baseline scores and credits remaining on the slot machine, significant Session x Drug Group x Group x Drug Sequence [F(1,38)=5.51, p=0.024] and Session x Time x Drug Group x Drug Sequence [F(3,38)=13.05, p=0.007] interactions emerged. In HCs, haloperidol increased MBG scores at peak drug level pre-game (figure 12a-b) in within-subjects’ comparisons and between-subjects’ on session 1 (ps < 0.001). Under fluphenazine in HCs, MBG scores were slightly reduced pre-game and post-cognitive tasks and slightly elevated post-game in sequence 1 (figure 12c-d); between-subjects’ comparisons were significant on session 1 pre-game (t(38)=2.14, p=0.038) and post-risk task (t(38)=2.14, p=0.039).

In PGs, haloperidol decreased MBG scores at post-game only when administered in sequence 2 (figure 13b). Between-group comparisons were significant for day 1 (t(38)=5.63, p<0.001), suggesting haloperidol reduced the post-game increase in MBG that occurred when the game was novel. Fluphenazine reliably increased within-subjects’ MBG ratings across all time points in PGs (figure 13c-d), although between subjects’ tests found higher MBG scores under fluphenazine vs. placebo on session 2 only (ps < 0.001).
Figure 12(a-d). Mean ARCI-MBG scores under drug and placebo for HCs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1 (drug on day 1, placebo on day 2); panel b: haloperidol, sequence 2 (placebo on day 1, drug on day 2); panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.
Figure 13(a-d). Mean ARCI-MBG scores under drug and placebo for PGs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1; panel b: haloperidol, sequence 2; panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.

In summary, in HCs, within-subjects’ comparisons found drug-like euphoria scores were slightly elevated under haloperidol, with stronger effects during the first test session. When novelty effects were controlled in between-subjects’ comparisons, the treatment effect only emerged consistently pre-game. Under fluphenazine, euphoria scores were reduced at pre-
game and post-risk task vs. placebo, and this effect was more pronounced on the first session. Fluphenazine did not alter post-game euphoria ratings.

In PGs, haloperidol appeared to increase euphoria ratings pre-game in sequence 1, but the absence of a significant between-subjects’ difference suggested this was driven in part by a general tendency toward higher scores on session 1. Conversely, the pattern of simple effects indicated that haloperidol led to a decline in post-game euphoria ratings only when the game was novel. Fluphenazine consistently enhanced euphoria scores across time points and this effect was significant compared to placebo when the game was familiar on session 2, whereas novelty effects partly obscured the drug effect on session 1.
3.2.3.2 ARCI-AMPH (Psychomotor Stimulation)

Figures 14 and 15 show mean ARCI-AMPH scores for HCs and PGs, respectively. A significant main effect of Time [F(3,38)=4.50, p=0.005] reflects higher scores at the first two time points (peak drug effect and immediately post-game).

A Session x Time x Drug Group x Drug Sequence interaction was significant [F(3,38)=4.72, p=0.004]. In HCs, haloperidol tended to increase AMPH scores at peak blood level (figure 14a-b), with significant between-subjects’ effects on session 1 (t(38)=7.5, p<0.001). Fluphenazine consistently increased AMPH scores post-game (figure 14c-d), though between-subjects’ comparisons found that these effects were only significant on session 2 (ps < 0.02). In PGs, AMPH scores were consistently higher on session 1 pre-game and post-game under haloperidol and placebo (figures 15a-b), reflecting a strong influence of novelty. However, as with MBG scores, between-subjects’ comparisons found a significant decrease under haloperidol vs. placebo on session 1 (t(38)=7.54, p<0.001). Similarly, fluphenazine consistently increased AMPH scores post-game in PGs (figure 15c-d) and between subjects’ tests were only significant on session 2 (ps < 0.01).
Figure 14(a-d). Mean ARCI-AMPH scores under drug and placebo for HCs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1 (drug on day 1, placebo on day 2); panel b: haloperidol, sequence 2 (placebo on day 1, drug on day 2); panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.
Figure 15(a-d). Mean ARCI-AMPH scores under drug and placebo for PGs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1; panel b: haloperidol, sequence 2; panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.

Thus, in HCs, haloperidol increased psychomotor stimulation at pre-game on session 1 only, suggesting the drug interacted with the novelty of the situation. Fluphenazine increased post-game scores on session 2 only, suggesting that the drug effect interacted with the familiarity of the situation.
In PGs, the pattern of simple effects indicated that haloperidol reversed the increase in stimulant-like effects of the game, but only when it was novel. Fluphenazine increased psychomotor stimulation at pre-game, post-game, and post-cognitive tasks but only when the game was familiar, suggesting that novelty-related stimulation partially obscured the enhancing effect of the drug on session 1.
3.2.3.3 ARCI-LSD (Dysphoria)

Figures 16 and 17 present mean scores on the ARCI-LSD score, measuring drug-like dysphoria. PGs displayed higher LSD scores than HCs (significant main effect of Group, F(1,38)=4.34, p=0.044). A marginal Session x Group interaction [F(1,38)=3.74, p=0.061] reflected a tendency for higher LSD scores on session 2 in HCs, particularly in the groups assigned to haloperidol (figure 16a-b), whereas this trend was not evident in PGs (figure 17).

In HCs the strong Session effect drove LSD scores in haloperidol groups (figure 16a-b), while scores were similar on each session in fluphenazine groups (figure 16c-d), indicating that neither drug changed dysphoric effects appreciably in these subjects. In PGs, scores were lower within subjects under haloperidol in sequence 2 only (figure 17b). In between-subjects’ comparisons haloperidol reduced scores on session 1 and session 2 at most time points (ps < 0.046), suggesting drug effects in sequence 1 may have been masked by the tendency for higher dysphoria on day 1 (under placebo). Fluphenazine consistently reduced ratings of dysphoria post-cognitive tasks (figure 17c-d; between-subjects ps < 0.001).
Figure 16(a-d). Mean ARCI-LSD scores under drug and placebo for HCs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1 (drug on day 1, placebo on day 2); panel b: haloperidol, sequence 2 (placebo on day 1, drug on day 2); panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.
Figure 17(a-d). Mean ARCI-LSD scores under drug and placebo for PGs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1; panel b: haloperidol, sequence 2; panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.

In sum, neither antagonist reliably affected dysphoria ratings in HCs, whereas both antagonists led to modest reductions in dysphoria in PGs.
Taken together, the results for the ARCI scales in HCs suggest that both drugs moderately increase subjective pleasurable effects, which were stronger when combined with a novel situation on test session 1. At these doses, neither drug was subjectively unpleasant in HCs.

In PGs, haloperidol reduced both subjective pleasurable and aversive states when the situation was novel on session 1. In contrast, fluphenazine consistently increased stimulant-like pleasurable effects across time points, and these effects were more evident compared to placebo in the absence of novelty on session 2. The drug also decreased dysphoria at time points after the game.
3.2.4 Mood States: POMS subscales

3.2.4.1 POMS – Vigor

POMS – Vigor scores were analyzed in a 2 x 2 x 2 x 2 x 4 ANCOVA controlling for credits remaining on the slot machine and baseline scores on the subscale. Results are presented in figure 18 for HCs and figure 19 for PGs.

A marginal main effect of Session \([F(1,38)=3.08, p=0.087]\) and marginal Session x Time x Drug Group x Drug Sequence interaction \([F(1,38)=2.51, p=0.063]\) emerged. In HCs, haloperidol consistently increased ratings of Vigor in HCs pre-game (figure 18a-b), and effects were marginal \((ps < 0.09)\) in between-subjects’ comparisons. POMS-Vigor scores were similar across sessions in HCs given fluphenazine.

In PGs, haloperidol decreased ratings of Vigor post-game (figure 19a-b), and this effect was consistent on both test sessions in between-subjects’ comparisons \((ps < 0.003)\). Fluphenazine increased Vigor ratings post-game in sequence 1 (figure 19c) and between subjects’ comparisons confirmed this effect relative to placebo on session 1 \((t(38)=2.52, p=0.02)\), but not on session 2.
Figure 18(a-d). Mean POMS-Vigor scores under drug and placebo for HCs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1 (drug on day 1, placebo on day 2); panel b: haloperidol, sequence 2 (placebo on day 1, drug on day 2); panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.
In HCs, haloperidol increased Vigor scores before the game and novelty did not account for these effects. Fluphenazine did not reliably affect Vigor in these subjects.

In PGs, opposing within-subjects’ effects of haloperidol vs. placebo at pre-game for different sequences along with the absence of between-subjects’ effects suggest that novelty rather than the drug (or placebo) enhanced Vigor. At post-game, haloperidol reduced Vigor ratings in both within- and between-subjects’ comparisons, indicating a consistent drug effect. For fluphenazine, the pattern of simple effects suggests that the drug interacted with exposure to the game to augment Vigor during the post-game phase when the game was novel.
3.2.4.2 POMS – Depression/Dejection

POMS-Depression/Dejection scores are shown in figures 20 (HCs) and 21 (PGs). In subjects assigned to haloperidol, a marginal Session x Group x Drug Group x Drug Sequence interaction [F(1,38)=2.89, p=0.097] reflected higher scores on session 1 regardless of treatment in HCs (figure 20a-b) and for haloperidol in PGs (figure 21a-b). Depression/Dejection scores were constant and low regardless of treatment in HCs assigned to fluphenazine. In PGs, fluphenazine increased Depression/Dejection scores compared to placebo at pre-game and post-cognitive tasks (figure 21c-d) within-subjects and between-subjects on both test days (ps < 0.02).
Figure 20(a-d). Mean POMS-Depression/dejection scores under drug and placebo for HCs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1 (drug on day 1, placebo on day 2); panel b: haloperidol, sequence 2 (placebo on day 1, drug on day 2); panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.
In HCs, haloperidol increased Depression/Dejection ratings following the game when it was novel, and fluphenazine had no effects.

In PGs, haloperidol increased Depression/Dejection scores before the game when the situation was novel. Fluphenazine reliably increased Depression/Dejection at pre-game and post-cognitive tasks for both sequences on both sessions.
3.2.4.3 POMS – Anger/Hostility

POMS-Anger/Hostility scores are presented in figures 22 and 23. A marginal Session x Time x Group x Drug Sequence interaction [F(3,38)=2.19, p=0.093] emerged. Scores were slightly higher on session 1 regardless of drug treatment in HCs (figure 22a-d) and pre-game in PGs (figure 23a-d). In HCs, scores increased post-game under haloperidol for those who received drug on session 1, whereas fluphenazine did not affect Anger ratings. In PGs, haloperidol had little effect (figure 23a-b) and fluphenazine decreased Anger scores post-game (figure 23c-d).
Figure 22(a-d). Mean POMS-Anger/hostility scores under drug and placebo for HCs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1 (drug on day 1, placebo on day 2); panel b: haloperidol, sequence 2 (placebo on day 1, drug on day 2); panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.
Figure 23(a-d). Mean POMS-Anger/hostility scores under drug and placebo for PGs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1; panel b: haloperidol, sequence 2; panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.

In HCs, Anger/Hostility ratings only emerged in one subgroup of subjects who displayed a modest post-game increase, which was augmented by haloperidol. Fluphenazine negated the very modest Anger scores exhibited under placebo in those who received drug on day 2.

In PGs, haloperidol increased Anger/Hostility at pre-game in those who received it when the game was novel. In those who received haloperidol when the game was familiar on...
session 2, the drug modestly but significantly increased post-game Anger. In contrast, fluphenazine generally reduced Anger scores relative placebo, except at pre-game for those who received drug on session 1, as was the case for haloperidol.

Taken together, the results from the POMS subscales revealed that haloperidol increased Vigor, Depression/Dejection and Anger/Hostility ratings in HCs who received the drug when the game was novel, and fluphenazine had no reliable effect on any of these measures. In PGs, haloperidol decreased post-game Vigor but did not reliably affect Depression/Dejection or Anger/Hostility ratings. Fluphenazine increased Vigor post-game when the task was novel, and tended to increase Depression/Dejection scores but decrease Anger/Hostility.
3.2.5 Betting Behaviour on the Slot Machine

A 2 x 2 x 2 x 2 MANOVA of mean number of lines bet per spin (figures 24-25) and mean number of credits bet per line (figures 26-27) demonstrated a significant multivariate effect of Session [F(2,37)=3.802, p=0.032] driven by a tendency for lower bets on session 2 than session 1.

On **mean number of lines per spin**, a marginal Session x Drug Sequence interaction [F(1,38)=7.05, p=0.090] reflected a tendency to select more lines under drug vs. placebo in HCs given haloperidol (figure 24a), though between-subjects’ tests were only significant on day 2 (t(38)=2.22, p=0.03). No drug effect was evident for HCs under fluphenazine (figure 24b). PGs selected more lines under haloperidol or fluphenazine (figure 25) vs. placebo, though again between subjects’ tests were only significant on day 2 (\(p_s < 0.049\)).

On the measure of **mean credits bet per line**, a marginal main effect of Drug Group [F(1,38)=3.45, p=0.071] reflected slightly higher bets in the fluphenazine group regardless of sequence or drug treatment. In HCs, the session effect predominated in within-subjects’ comparisons (figure 26a-b).

In PGs, credits bet per line were consistently higher under haloperidol vs. placebo (figure 27a). Between subjects’ tests found that credits/line were only marginally higher under haloperidol vs. placebo on session 1 (t(38)=1.72, p=0.09). Credits were consistently higher within-subjects on session 1 than session 2 for PGs under fluphenazine, though between-subjects’ tests found that mean credits were higher for subjects receiving fluphenazine vs. placebo on day 2 (t(38)=2.16, p=0.04).
In HCs, the pattern of simple effects suggested that haloperidol only increased lines selected when the game was familiar and fluphenazine had no reliable effects. In PGs, the
pattern of simple effects revealed that, compared to placebo, both haloperidol and fluphenazine increased lines selected when the game was familiar but not when it was novel.

Figure 26(a-b). Mean number of credits bet per line on a slot machine game in HCs. Each bar represents means for n=6, with mean under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol; panel b: fluphenazine. * = p<0.05.

Figure 27(a-b). Mean number of credits bet per line on a slot machine game in PGs. Each bar represents means for n=6, with mean under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol; panel b: fluphenazine. *=p<0.05.
In HCs the pattern of simple effects suggested that credits/line were higher on day 1 regardless of treatment and apparent differences under drug vs. placebo were entirely attributable to this novelty effect. In PGs, the pattern of simple effects indicated that haloperidol reliably increased credits bet per line whereas fluphenazine had no reliable effect.

Taken together, the slot machine data for HCs show that haloperidol increased number of lines selected per spin but did not affect credits per line. This pattern is consistent with a tendency to increase opportunities to win under the drug, by distributing risk across lines. Fluphenazine did not affect either measure in these subjects. In PGs, haloperidol consistently increased both measures of betting behaviour, though between-subjects’ comparisons confirmed an increase in lines on session 2 only and an increase in credits on session 1 only. Thus, haloperidol encouraged distribution of risk when the game was familiar but increased risk magnitude when the game was novel. Fluphenazine increased both measures on session 2 relative to placebo, indicating an increase in distribution and magnitude of risk.
3.2.6 Slot Machine Winnings (Final Credit Tally)

A 2 x 2 x 2 x 2 ANOVA assessed winnings from the slot machine (credits remaining at the end of 15 minutes of play) on each test session in HCs and PGs (figures 28 and 29). A marginal Session x Group x Drug Sequence interaction emerged [F(1,40)=3.48, p=0.069], but no significant effects on the ANOVA or in t-tests were observed. Differences in winnings are due to random factors and not attributable to study interventions or group differences. Despite the absence of statistically significant differences in winnings between groups or conditions, this measure may have affected subjective scores. Hence, the rationale for including it as a covariate in the other analyses.
Figure 28(a-b). Mean number of credits remaining after 15 minutes of play on a slot machine game in HCs. Each bar represents means for n=6, with mean under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol; panel b: fluphenazine.

Figure 29(a-b). Mean number of credits remaining after 15 minutes of play on a slot machine game in PGs. Each bar represents means for n=6, with mean under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol; panel b: fluphenazine.
3.2.7 Cognitive Tasks

Analyses of cognitive and risk tasks (RRT, SST, and GDT) were performed using ANOVAs. To determine if slot machine winnings mediated any of the observed effects, ANCOVAs including credits remaining on the slot machine were performed as follow-up. In no case did significant discrepancies emerge between the two sets of analyses, suggesting winnings on the slot machine had minimal impact on performance in these tasks.

3.2.7.1 Rapid Reading Task

Repetition priming (faster response time to previously encountered stimuli) is a reliable effect on verbal naming tasks (Neely 1991). To mitigate the impact of this general process, data were analyzed by examining the percent difference in reading time (RT) relative to neutral words for each clinically relevant category (gambling-related, alcohol-related, positive, and negative) on session 1 and session 2. Greater difference scores indicate faster RT relative to neutral words, and thus greater relative availability in memory (i.e., salience).

Figures 30 and 31 present the data for HCs and PGs respectively for drug sequence and each word category, on session 1 and 2. Solid bars indicate drug treatment and patterned bars indicate placebo treatment. Because the transformation of scores to % difference from neutral RT effectively equated the two drug sequences on exposure to the game, between-subjects’ comparisons provided a direct test of the effects of drug treatment. In these figures, asterisks thus denote significance (p<0.05) in simple effects comparisons for drug vs. placebo at each level of session (rather than within-subjects’ across sessions).

In a 2 x 2 x 2 x 2 x 4 (Word Type) ANOVA, a main effect of Session emerged [F(1,39)=31.23, p<0.001] due to higher % difference scores on session 1 compared to session 2. This reflects the floor effect on response latency (one cannot speed up beyond some minimum RT), whereby % difference from neutral diminished as RT approached asymptotic levels.

A significant Session x Word Type x Group x Drug Sequence [F(3,39)=3.37, p=0.021] interaction also emerged. In HCs, haloperidol consistently increased % RT difference for gambling, positive, and negative words on session 1 (figure 30a). Fluphenazine significantly decreased % RT difference for positive and negative words on session 2 (figure 30b), with no effect on RT to gambling-related words.
In PGs, haloperidol increased RT difference for negative words only on session 1, and decreased RT difference for both gambling and alcohol-related words on session 2. Fluphenazine decreased RT difference for gambling- and alcohol-related words on session 1 only (figure 31).

These results and trends in figures 30 and 31 indicate that haloperidol increased the salience of clinically relevant stimuli when they were novel but decreased the salience of these stimuli when they were familiar, and this pattern was evident in both groups. In contrast, fluphenazine appeared to consistently decreased the salience of clinically relevant stimuli, aside from negative affective words, when they were novel as well as when they were familiar in both groups.
Figure 30(a-b). Percent difference in Reading Time from Neutral for words in four categories for HCs under drug and placebo. Each bar represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, panel b: fluphenazine; solid bars: drug treatment, patterned bars: placebo treatment. Word categories: 1=Gambling-related, 2=Alcohol-related, 3=Positive, 4=Negative. * denotes p<0.05 for comparisons between RT difference from session 1 to session 2 within each word category. Error bars represent standard error of the mean.
Figure 31(a-b). Percent difference in Reading Time from Neutral for words in four categories for PGs under drug and placebo. Each bar represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, b: fluphenazine; solid bars: drug treatment, patterned bars: placebo treatment. Word categories: 1=Gambling-related, 2=Alcohol-related, 3=Positive, 4=Negative. * denotes p<0.05 for comparisons between RT difference from session 1 to session 2 within each word category. Error bars represent standard error of the mean.
3.2.7.2 Stop-Signal Task

In a 2 x 2 x 2 ANOVA of SSRT, a significant Session x Drug Group interaction [F(1,39)=5.89, p=0.02] emerged. Figures 32 and 33 demonstrate that this is due to the fact that in both HCs and PGs, subjects in the haloperidol groups tended to have higher scores (poorer motor inhibition) on the second session compared to the first (figures 32a and 33a), while those in the fluphenazine groups showed the opposite trend – better motor inhibition on the second session compared to the first (figures 32b and 33b).

Given the strong sequence effects in all groups, between-subjects’ comparisons were computed for all scores on session 1 (drug vs. placebo) and session 2 (drug vs. placebo). For HCs, a marginal increase in SSRT emerged under haloperidol in session 1 comparisons (t(37)=2.00, p<0.10) and a significant decrease emerged under haloperidol in session 2 comparisons (t(37)=2.23, p<0.05). Similar patterns emerged for HCs given fluphenazine and PGs given either drug, though the only change that reached significance was the increased SSRT scores under fluphenazine on session 1 for HCs (t(37)=2.61, p<0.05).
Figure 32(a-b). Stop-signal reaction time (SSRT) scores (ms) for HCs under drug and placebo. Each bar represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, panel b: fluphenazine. *p<0.05.

Figure 33(a-b). Stop-signal reaction time (SSRT) scores (ms) for PGs under drug and placebo. Each bar represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, panel b: fluphenazine. *p<0.05.
The reliability of the pattern of scores across HC and PG groups is noteworthy and supports *a bona fide* effect of treatment on inhibitory control. Between-subjects’ comparisons looking at scores under drug in the two sequences suggest that haloperidol negated the benefit of practice, whereas fluphenazine appeared to modestly enhance the practice effect in both groups.

Collectively, the results from the cognitive tasks suggest that novelty consistently interacted with the effects of haloperidol on cue salience and stimulus-response learning but did not reliably do so for fluphenazine.
3.2.8 Risk-Taking: Game of Dice Task

Level of risk-taking during GDT play was analyzed by examining the number of possible responses selected for each roll, from 1 (high risk) to 4 (low risk), such that lower scores indicate a propensity for riskier behaviour. Mean number of choices selected was determined for each Block (trials 1-6, 7-12; 13-18), and these scores were analyzed in a 2 x 2 x 2 x 2 x 3 (Block) ANOVA.

A significant main effect of Block \([F(2,38)=17.79, p<0.001]\) reflected overall decreasing scores (that is, riskier choices) as the game progressed. A marginal Session x Block x Drug Group x Group \([F(2,38)=3.08, p=0.052]\) reflected a tendency for PGs to make riskier choices as play progressed in subjects assigned to haloperidol (figure 35a) but less risky choices as play progressed in subjects assigned to fluphenazine (figure 35b), particularly on the first session. Level of risk was consistent across blocks in HCs in most cases.

A significant Session x Block x Drug Group x Drug Sequence \([F(2,38)=3.14, p=0.049]\) interaction indicated a treatment effect. In HCs, little change was seen across sessions in subjects assigned to haloperidol (figure 34a). In contrast, fluphenazine tended to increase scores, encouraging less risky choices (figure 34b). In PGs, scores were higher under haloperidol vs. placebo (figure 35a) and lower under fluphenazine vs. placebo, particularly early in trials (figure 35b). No significant effects emerged on between-subjects’ comparisons \( (ps > 0.56)\), though the consistent patterns of drug effects regardless of treatment sequence suggests true drug effects rather than effects of novelty vs. familiarity.

In sum, haloperidol had little effect in HCs but tended to encourage safer bets in PGs. Conversely, fluphenazine encouraged safer choices in HCs but encouraged consistently riskier choices in PGs. The increase in risk-taking in PGs is noteworthy as it contrasts with the consistent decrease in self-reported desire to gamble in these subjects (see VAS Desire to Gamble, section 3.2.1.1).
Figure 34(a-b). Mean Game of Dice Task risk-taking scores for HCs. Each bar represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol; panel b: fluphenazine. *=p<0.05. Solid bars = drug treatment, patterned bars = placebo treatment.
Figure 35(a-b). Mean Game of Dice Task risk-taking scores for PGs. Each bar represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol; panel b: fluphenazine. *p<0.05. Solid bars = drug treatment, patterned bars = placebo treatment.
3.2.9 Physiological Measures

3.2.9.1 Systolic BP

A 2 x 2 x 2 x 2 x 4 ANCOVA controlling for baseline systolic BP and credits remaining on the slot machine revealed a marginal interaction among all factors [F(3,38)=2.22, p=0.09] for systolic BP. Results are presented in figure 36 for HCs and figure 37 for PGs.

In HCs, haloperidol tended to increase systolic BP pre-game but decrease it at later time points (figure 36a-b), while fluphenazine had no consistent effect (figure 36c-d). Systolic BP was consistently higher post-game on session 1 in HCs. In PGs, haloperidol consistently decreased systolic BP (figure 37a-b), at post-game and post-cognitive tasks in between-subjects’ comparisons (p<0.02). Fluphenazine increased systolic BP post-cognitive tasks but decreased it post-risk task (figure 37c-d). Between-subjects’ comparisons were significant post-cognitive task on session 1 only and post-risk task on both sessions (p<0.001). Unexpectedly, the game itself did not reliably increase systolic BP in either group, with the highest readings occurring post-cognitive tasks in most cases.
Figure 36(a-d). Mean systolic blood pressure (mmHg) under drug and placebo for HCs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1 (drug on day 1, placebo on day 2); panel b: haloperidol, sequence 2 (placebo on day 1, drug on day 2); panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.
Figure 37(a-d). Mean systolic blood pressure (mmHg) under drug and placebo for PGs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1; panel b: haloperidol, sequence 2; panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.

In HCs, generally opposing drug effects for the two treatment sequences derived from an increase in systolic BP when the situation was novel. Haloperidol increased pre-game and decreased post-risk task systolic BP scores but otherwise no consistent drug effects emerged.
In PGs, haloperidol reduced systolic BP post-game and post-cognitive tasks when the drug was received on session 2. The pattern of simple effects suggested that the drug effect was masked on session 1 by elevated BP following game and tasks when they were novel. In these subjects, fluphenazine reliably increased BP post-cognitive tasks, suggesting that the drug may have interacted with the demand for skilled performance.
3.2.9.2 Diastolic BP

Results for diastolic BP are shown in figure 38 for HCs and figure 39 for PGs. A marginal effect of Time [F(3,38)=2.24, p=0.087] emerged from a tendency for diastolic BP to increase at later time points. A Session x Drug Sequence interaction [F(1,38)=7.07, p=0.011] reflects treatment effects, with both drugs tending to decrease diastolic BP in HCs (figure 38) and PGs (figure 39).

![Graphs showing diastolic pressure changes](image)

Figure 38(a-d). Mean diastolic blood pressure (mmHg) under drug and placebo for HCs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1 (drug on day 1, placebo on day 2); panel b: haloperidol, sequence 2 (placebo on day 1, drug on day 2); panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.
Figure 39(a-d). Mean diastolic blood pressure (mmHg) under drug and placebo for PGs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1; panel b: haloperidol, sequence 2; panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.
3.2.9.3 Heart Rate

HR measurements are presented for HCs and PGs in figures 40 and 41 respectively. A marginal Drug Sequence x Drug Group interaction [F(1,38)=3.17, p=0.083] emerged, likely driven by PGs, for whom heart rates on both sessions were higher in the sequence 1 subgroup for haloperidol (figure 41a) and higher in the sequence 2 subgroup for fluphenazine (figure 41d). The only consistent drug effects were an increase in HR pre-game and a decrease post-risk task under fluphenazine in PGs (figure 41c-d).
Figure 40(a-d). Mean heart rate (beats per minute) under drug and placebo for HCs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1 (drug on day 1, placebo on day 2); panel b: haloperidol, sequence 2 (placebo on day 1, drug on day 2); panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.
Figure 41(a-d). Mean heart rate (beats per minute) under drug and placebo for PGs. Each curve represents means for n=6, with scores under drug and placebo in each panel assessed in the same subjects. Panel a: haloperidol, sequence 1; panel b: haloperidol, sequence 2; panel c: fluphenazine, sequence 1; panel d: fluphenazine, sequence 2. * = p<0.05.

Collectively the physiological data for HCs show that haloperidol increased all indices at peak blood levels but decreased these measures over time within each session, whereas fluphenazine had little effect. In PGs, haloperidol moderately reduced all three measures, and notably reduced systolic and diastolic BP post-game reliably. Fluphenazine interacted with the events in the session, increasing systolic BP post-cognitive tasks, and HR pre-game, but consistently decreasing diastolic BP immediately after the game and the risk task.
3.2.10 Supplemental Results

3.2.10.1 Capsule Contents Evaluation

Results of capsule contents evaluation are presented in Tables 6 and 7. A 2 (Drug Sequence) x 4 (Choice: no active drug; first capsule active; second capsule active; both capsules active) chi-square test was used to evaluate ability to detect effects of each drug on each test session. Note that the second capsule was always a placebo in these sessions; on later sessions, amphetamine was administered at that time. No significant change was observed in frequency of responses in HC or PG subgroups on either drug or test session (ps > 0.135) or across all participants receiving haloperidol (session 1, $\chi^2=2.8$, p=0.43; session 2, $\chi^2=2.8$, p=0.42) or fluphenazine (session 1, $\chi^2=6.9$, p=0.075; session 2, $\chi^2=3.2$, p=0.37).

Table 6. Capsule contents evaluation response frequencies for haloperidol subgroups.

<table>
<thead>
<tr>
<th>Actual Drug Sequence</th>
<th>Reported Capsule Content</th>
<th>No active drug</th>
<th>Capsule 1</th>
<th>Capsule 2</th>
<th>Both capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Session 1 (active drug)</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>Session 2 (placebo)</td>
<td>6</td>
<td>0</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Session 1 (placebo)</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Session 2 (active drug)</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 7. Capsule contents evaluation response frequencies for fluphenazine subgroups.

<table>
<thead>
<tr>
<th>Actual Drug Sequence</th>
<th>Reported Capsule Content</th>
<th>No active drug</th>
<th>Capsule 1</th>
<th>Capsule 2</th>
<th>Both capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Session 1 (active drug)</td>
<td>3</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Session 2 (placebo)</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Session 1 (placebo)</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Session 2 (active drug)</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

3.2.10.2 Symptom Side Effects Checklist

A 2 (Group) x 2 (Drug Group) x 2 (Drug Sequence) x 2 (Session) ANOVA was used to assess results from the symptom side effect checklist. A significant main effect of drug sequence was present [$F(1,38)=36.87$, p=0.007] indicating differences between the two drug sequence groups (i.e., a cohort effect) in terms of perceived side effects. Absence of any
significant interactions with session ($ps > 0.137$) indicates this is not related to drug treatment and a mean (SD) overall score of 0.1 (0.4) out of 5 shows that each of the study drugs was well tolerated.
4. DISCUSSION

The aim of this project was to begin to describe the roles of D1-like and D2-like DA receptors in mediating pleasurable and motivational effects of a slot machine game in PGs and HCs, and to explore the impact of prior experience with the game on these effects. DA plays a central role in both normal rewarding behaviour and addictive disorders, including gambling. A previous study found that DA D2 receptor blockade with 3-mg haloperidol enhanced reinforcing effects of a slot machine game in PGs but not HCs, suggesting important differences may exist in DA systems in PGs that influence their experience of, and motivation for, gambling (Zack and Poulos 2007). At low doses, haloperidol preferentially binds to pre-synaptic D2 autoreceptors. By removing feedback inhibition, blockade of these receptors could increase DA release during gambling. Based on previous experiments on stimulant reinforcement (Brauer and de Wit 1995, Brauer and de Wit 1996, Wachtel et al. 2002), it was proposed that haloperidol exerted its effects by increasing signaling at post-synaptic D1 receptors, and that an optimum level of stimulation existed for these receptors such that both under- and over-activation would reduce reinforcing effects of a given reward. Enhanced reinforcing effects of gambling under haloperidol therefore suggested that the drug optimized D1 signaling during gambling in PGs (Zack and Poulos 2007), which in turn implied a deficit in baseline D1 function in these individuals.

Differences in gambling-induced DA release due to the novelty of the game could also influence D1 signaling under drug-free conditions. Moreover, such novelty effects could interact with drug-induced D2 auto-receptor blockade, and this effect could increase or decrease gambling reinforcement depending on whether the net effect was optimal or supra-optimal D1 stimulation. A recent study found that patterns of DA release during gambling differ depending on prior exposure to a simulated slot machine, with DA release occurring in response to the delivery of gambling rewards (i.e., monetary payoffs) when the game was played for the first time, but occurring after the initiation of the trial (i.e., in response to gambling cues) when the game had been played on one previous occasion (Shao et al. 2013). This result suggested that the observed effects of a D2 antagonist may differ in subjects randomized to receive the drug on test session 1 vs. session 2, due to differences in the specific events in the game that evoked DA release on each session. This effect would not be apparent when scores were aggregated across subjects who, due to counterbalancing, received the drug
on session 1 vs. session 2 (cf. Zack and Poulos 2007). Therefore, this was an important question for follow-up investigation in the present study.

In light of these unresolved questions, the present study sought to determine the role of D1 signaling and novelty of the game in the effects of D2 auto-receptor blockade on gambling reinforcement in PG and HC subjects. The study employed a repeated-measures, between-within subjects’ design, assessing subjects on a variety of subjective, cognitive, behavioural, and physiological outcome measures at various time points before and after playing the slot machine. Subjects were assessed on two test sessions, once under placebo and once under a DA antagonist, with a one-week wash-out period between sessions. HC and PG subjects were matched on key background variables and assigned to receive either the preferential D2 antagonist, haloperidol (3-mg) or the mixed D1/D2 antagonist, fluphenazine (3-mg), with treatment sequence (drug on session 1 and placebo on session 2; or vice versa) randomized across subjects in each drug group.

It was predicted that (1) haloperidol would increase reinforcement from the slot machine game in PG but not HC subjects; (2) by partially blocking D1 receptors, fluphenazine would optimize gambling-induced D1 stimulation during D2 auto-receptor blockade in subjects with normal baseline D1 function, thereby enhancing gambling reinforcement in HCs but not PGs; and (3) by enhancing DA release due to reward delivery, effects of both antagonists on gambling reinforcement would be stronger when the drug was received on the first test session compared to the second.

As this was a preliminary analysis of 60% of the full projected sample (48 participants of a final N=80), the discussion will address marginally significant results (p ≤ .10) that can be expected to persist and achieve significance (based on their magnitude and consistency) as the sample approaches its target size.

The primary effect of haloperidol and fluphenazine at this dose was presumed to be blockade of pre-synaptic D2 autoreceptors (Pucak and Grace 1994), reducing feedback inhibition at DAergic neurons and leading to increased transmission through post-synaptic D1 receptors (Shi et al. 1997), concurrent with partial blockade of post-synaptic D1 receptors in the case of fluphenazine. At clinical doses, both drugs also bind post-synaptic D2 receptors as well as other DA receptors, notably D3 and D4. Therefore, observed results cannot be unambiguously attributed to removal of feedback inhibition and modulation of other receptors may also contribute to the observed effects. However, the drugs have similar binding profiles
at all DA receptors aside from D1, for which fluphenazine has much stronger affinity than haloperidol. Therefore, any differences between haloperidol and fluphenazine are likely attributable to D1. Blockade of post-synaptic D2 and D3 receptors also may contribute to observed effects that are similar between both haloperidol and fluphenazine.

4.1 Subjective Reinforcement

4.1.1 VAS – Incentive Motivation

As expected, VAS Desire to Gamble scores were higher in PGs compared to HCs. A priming effect of the slot machine was also apparent, with higher scores post-game vs. pre-game in both HC and PGs. In HC, haloperidol increased priming effects of the slot machine game when it was novel but not when it was familiar; and fluphenazine had no significant effects. In PGs, haloperidol increased Desire to Gamble at pre-game only. As predicted, fluphenazine consistently decreased Desire to Gamble in PGs at all time points, with more pronounced effects when the game was familiar.

Confidence to Resist Gambling was generally lower on session 1 vs. session 2 in HC. Haloperidol reduced Confidence before the game when it was novel but not when it was familiar, and no other drug effects emerged, in line with the findings for Desire. In PG, haloperidol consistently reduced Confidence relative to placebo at peak drug level but increased Confidence post-game, in partial support of the hypothesis. In line with the findings for Desire and the hypotheses, fluphenazine increased Confidence in PG with most pronounced effects at post-game. Thus, haloperidol augmented gambling motivation during anticipation of the game but appeared to reduce post-game priming effects, whereas fluphenazine reduced both anticipatory and primed motivation to gamble, and the effects of both drugs were more pronounced in PG than HC subjects.

VAS ratings of Desire for Alcohol increased post-game in most cases, potentially reflecting an association between gambling and alcohol use, or a priming effect of the mock-bar environment in which the slot machine is played. No consistent effects of drug treatment or experimental session emerged, suggesting that drug effects on reinforcement and reward motivation were largely specific to gambling in these PG and HC subjects.
4.1.2 Hedonic Impact: VAS – Pleasurable Effects of the Slot Machine

In HCs haloperidol increased subjective feeling of ‘High’ following the slot machine only when it was novel. Fluphenazine had no apparent effect. In PGs, haloperidol consistently reduced perceived Involvement/Engagement in the slot machine, whereas fluphenazine had no apparent impact on pleasurable effects of the slot machine. These effects are not consistent with the hypotheses.

4.1.3 Drug-Like Rewarding and Aversive Effects: ARCI Subscales

The ARCI-MBG scale is a measure of subjective drug-like euphoric effects. In HCs, haloperidol increased scores at peak drug level and fluphenazine reduced scores. Neither drug had a consistent impact on euphoria at post-game. In PGs, haloperidol appeared to reduce the euphoric effects of the slot machine when it was novel, whereas fluphenazine consistently increased euphoria before and after the game, with more pronounced effects on the second test session.

The ARCI-AMPH subscale measures amphetamine-specific effects, including psychomotor activation as well as positive subjective arousal. In HCs, haloperidol increased AMPH scores at peak drug level in anticipation of the game when it was novel, while fluphenazine increased AMPH scores after the game when it was familiar. In PGs, the pattern of results for AMPH was consistent with that seen for MBG, suggesting that euphoria and positive arousal reflect a common process in PG subjects.

The ARCI-LSD subscale assessed drug-like dysphoric effects. In HCs, these scores were generally higher during the second test session compared to the first and neither drug was associated with subjective unpleasant effects. In PGs, both drugs modestly reduced dysphoria. Therefore, neither of the drugs nor the slot machine was associated with unpleasant effects, suggesting that, at modest doses, these typical neuroleptics are well-tolerated and effects on reinforcement do not seem to be attributable to aversive subjective effects of the drugs.

Collectively, the ARCI results were not consistent with the hypotheses. The pattern of drug effects on MBG and AMPH subscales tended to be opposite to the pattern of drug effects on Desire / Confidence ratings. Therefore, D2 and D1 manipulations appear to have countervailing effects on incentive motivation vs. subjective drug-like states. In HCs, preferential blockade of D2 autoreceptors with haloperidol enhanced euphoria and positive arousal during anticipation of the game when it was novel, but not when it was familiar, nor at
any point after the game. The generally opposite pattern of effects for fluphenazine in these subjects suggests that haloperidol’s effects were mediated by increased stimulation of D1 and that a novel situation, rather than exposure to winning or gambling cues, was the primary rewarding stimulus. In PGs, the pattern of effects suggests that preferential blockade of D2 autoreceptors selectively reduced euphoria and arousal associated with reward delivery, whereas concurrent blockade of D1 enhanced the euphoric and positively arousing aspects of the situation (relative to placebo), perhaps by reducing its perceived familiarity.

4.1.4 Mood States: POMS Subscales

The POMS questionnaire assessed changes in mood during the test sessions across several domains. The Vigor subscale assessed the impact of the drugs and the game on subjective energy or activation. In HCs, haloperidol increased Vigor ratings pre-game, consistent with its stimulant-like effects on the ARCI-AMPH subscale. Fluphenazine had no consistent effects. In PGs, haloperidol consistently reduced the activating effects of the game on both sessions. Fluphenazine increased post-game scores on the first session.

The POMS Depression/Dejection and Anger/Hostility subscales assessed negative mood changes under the study interventions. Scores on these scales were relatively low, consistent with ARCI-LSD scores to indicate drug and study components were not perceived as unpleasant. Rates of Depression/Dejection and Anger/Hostility were higher under haloperidol on the first session only in HCs; fluphenazine did not affect these scores. In PGs, haloperidol had minimal effect on these indices, while fluphenazine tended to increase Depression/Dejection but reduce Anger/Hostility. Collectively, the POMS data suggest that preferential blockade of D2 autoreceptors increases both positive and negative affective responses to a novel situation in HCs, and that activation of D1 receptors may mediate these effects. In PGs, preferential blockade of D2 autoreceptors obscured the activating effects of the game, whereas concurrent blockade of D1 appeared to enhance both the positive and negative affective response to the game.

4.2 Betting Behaviour

The intensity of betting, in terms of both the number of lines selected per spin and number of credits bet per line, was generally higher on the first test session compared to the
second, potentially reflecting that reinforcing effects of the slot machine on gambling behavior were stronger when the game was novel.

In HCs, haloperidol increased number of lines selected per spin but not credits bet per line, suggesting that D2 auto-receptor blockade encouraged strategic betting in this subgroup, risking more credits per spin overall but increasing opportunities to win. Fluphenazine had no effect on these measures, suggesting that activation of D1 may have mediated the effects of haloperidol in these subjects. In PGs, haloperidol increased number of lines bet on session 2 and number of credits bet per line in session 1, suggesting that D2 autoreceptor blockade encouraged distribution of risk when the game was familiar (i.e., when DA release was associated with cue exposure rather than reward delivery) but encouraged risky betting when the game was novel (i.e., when DA release was associated with reward delivery). Fluphenazine led to similar effects as haloperidol on session 2, suggesting that D2 rather than D1 mediated the effects of familiarity (i.e., decreased DA release) on risky betting behavior in these subjects.

4.3 Cognitive/Behavioural Tasks

4.3.1 Rapid Reading Task

The RRT assessed salience of gambling and other motivationally relevant concepts following slot machine play, providing an objective measure of automatic semantic priming to complement self-report (conscious, voluntary) measures. As expected, percent difference in RT to gambling-related words under placebo was higher in PGs than HCs. This relationship was not seen consistently for any other word category, reflecting higher salience for gambling concepts specifically in PGs, across subgroups and conditions, and supporting the validity of the paradigm.

In both groups, haloperidol tended to increase the salience of all motivationally relevant stimuli when the game and RRT were novel but tended to reduce their salience when the prime (game) and target (words) stimuli were familiar. In contrast, fluphenazine tended to reduce reward salience consistently in both drug sequences, and the pattern was similar in both PGs and HCs. Haloperidol’s effects suggest that D2 auto-receptor blockade preferentially increases the attention-eliciting effects of motivationally relevant stimuli when they are novel, but encourages extinction when they are familiar. Fluphenazine’s effects suggest that stimulation
of D1 receptors mediates reactivity to motivationally relevant stimuli when they confer new information as well as when they are redundant.

### 4.3.2 Stop-Signal Task

Stop Signal Reaction Time (SSRT) was used to measure psychomotor inhibitory efficiency. A clear interaction between drug treatment and sequence of administration emerged on this measure, with performance improved under haloperidol on the first session but worsened under the drug on the second session. This represents a reversal of the general trend for improved performance with practice as sessions progressed. SSRT scores were consistently higher (poorer inhibition) on the first test session in fluphenazine groups, whereas the drug tended to augment the benefits of practice on the second test session. These patterns were highly consistent between PGs and HCs. The effects for haloperidol suggest that involuntary response to novel eliciting (go) stimuli is mitigated by D2 auto-receptor blockade, and effects for fluphenazine suggest that D1 receptor stimulation helps to regulate involuntary response to novelty but may hinder the ability to disregard familiar distracting stimuli. The consistency of these effects across PG and HC groups suggests that when signals are motivationally neutral, D2 and D1 receptor-related processes are not affected by gambling-related pathology.

### 4.4 Game of Dice Task

The GDT assessed risky decision making in a simulated gambling task. On this task, haloperidol had no apparent effect in HCs, while fluphenazine encouraged safer choices. In PGs, subjects made less risky choices under haloperidol and riskier ones under fluphenazine. No prominent sequence effects emerged on this measure, suggesting that risk-based decision-making, unlike betting behaviour on an actual slot machine, is not strongly affected by novelty of the task. More importantly, the different effects of the drugs in the two groups suggest that when stimuli are motivationally relevant and gambling-related (unlike the SST), activation of D1 may help to regulate risky decision making in PGs. By implication, D1 deficits (intensified by fluphenazine) in PGs may contribute to their risky behavior outside the laboratory.

### 4.5 Physiological Effects
Unexpectedly, BP and HR did not increase following slot machine play in these subjects. These measures tended to be highest following cognitive tasks, which may reflect the stressful nature of these reaction time-dependent tasks.

In HCs, haloperidol tended to increase physiological activation pre-game but decrease it as the session progressed. Fluphenazine had no consistent effects on these measures. In PGs, haloperidol tended to reduce BP and HR across time points. Fluphenazine had complex effects, increasing HR pre-game, and increasing systolic BP post-cognitive tasks, but consistently decreasing diastolic BP following the slot machine game and the risk task. Thus, combined D1/D2 blockade reduces the physiologically activating effects of gambling and simulated gambling tasks in PG subjects only. This is notable in light of the reduction in post-game Vigor scores under fluphenazine discussed above and suggests that stimulation of D1 receptors mediates both the subjective and physiological activating effects of these tasks. The results for haloperidol suggest that drug-induced stimulation of D1 during D2 auto-receptor blockade may obscure the additional stimulation that would otherwise be conferred by gambling activity. That is, haloperidol may mask game-induced arousal via D1, while fluphenazine may block this effect in PG subjects.

4.6 Hypothesis 1

Subjective Effects The first hypothesis (see p. 18) was that haloperidol would enhance the reinforcing effects of a slot machine game in PGs but not in HCs. This hypothesis was not consistently supported. In PGs, haloperidol increased subjective motivation to gamble pre-game but appeared to reduce this motivation post-game as measured by Confidence to Resist Gambling, while in HCs haloperidol modestly increased Desire to Gamble post-game. Similarly, on VAS measures of subjective rewarding effects of the slot machine, haloperidol reduced Involvement/Engagement in the game in PGs but increased High in HCs. On the ARCI, haloperidol reduced the pleasurable and stimulant-like effects of the slot machine in PGs when it was novel, while in HCs the drug enhanced these effects primarily before the game. On the POMS Vigor scale, haloperidol again reduced scores post-game in PGs and increased scores pre-game in HCs. Haloperidol did not reliably affect Anger/Hostility or Depression/Dejection scores in PGs, but increased scores on both measures after the game in HCs when it was novel. The pattern of effects suggests that haloperidol optimized D1 signaling due to novelty in HCs but may have induced supra-optimal stimulation from the game. In PGs
haloperidol appeared to obscure the positive effects of novelty as well as the subjective reinforcing effects of the game. The decrease in Involvement/Engagement in PGs suggests that the processes normally recruited by the game (e.g., D1 stimulation) may have become redundant in the presence of haloperidol.

**Behavioral-Physiological Effects** On the slot machine, haloperidol encouraged larger bets in PGs and larger but risk-distributed betting in HCs. Haloperidol had consistent effects on cognitive tasks in the two groups, with bidirectional sequence-dependent effects on salience of reward cues in the RRT and on motor inhibition in the SST. On the GDT, haloperidol encouraged safer choices in PGs only. Finally, haloperidol seemed to reduce diastolic BP following the slot machine game and the risk task in PGs with no effects in HCs.

Overall, increased DA release during D2 autoreceptor blockade moderately increased motivation to gamble at peak drug levels but appeared to reduce subjective reinforcing effects of the game itself, as well as the physiological activation of the slot machine and risk tasks. These effects were unexpected given the prior study of haloperidol in PG in which the drug reliably increased both hedonic and motivational effects of a slot machine game in a similar design (Zack and Poulos 2007). Participants in the previous study were slightly older (mean age 38.9 years compared to 33.1 years in the present study) and had slightly higher scores on the BDI and slightly lower scores on the DSM-IV PG questionnaire. While modest, these differences may have contributed to differences in DA system function and drug response. Despite these subjective effects, haloperidol did increase behavioural reinforcing effects of gambling as measured by bet size on the slot machine with more pronounced effects in PGs than HCs. In the present sample, preferential blockade of D2 autoreceptors would increase basal DA release under haloperidol, and this may have led to increased pre-game Desire but also made it difficult to detect the additional increase in DA release caused by the game (relative to placebo). Blockade of post-synaptic D2 receptors or other DA receptor subtypes may also have contributed to these effects.

**4.7 Hypothesis 2**

**Subjective Effects** Hypothesis 2 predicted that, by preventing excessive activation of post-synaptic D1 receptors, fluphenazine would increase reinforcing effects of a slot machine in HCs but not in PGs due to proposed deficits in D1 function in the latter group. This prediction was not consistently supported. On VAS measures of motivation to gamble,
fluphenazine had no apparent effect in HCs and reliably reduced Desire to Gamble in PGs. The latter effect is consistent with our hypotheses. The drug had no apparent effect on VAS measures of subjective pleasurable effects of the game in HCs or PGs. The absence of effects in PGs is not inconsistent with our hypotheses. On the ARCI, fluphenazine increased stimulant-like effects of the slot machine in HCs, whereas in PGs the drug increased both euphoria and positive arousal before and after the game. On the POMS, fluphenazine had no apparent effect in HCs, whereas in PGs it increased Vigor and Depression/Dejection scores and decreased Anger/Hostility scores. The pattern of effects for PGs is complex and suggests that D1 blockade amplified both the positive and negative affective response to the game. Reasons for these inter-study discrepancies are not readily apparent, and the pattern of effects may become more congruent once the full sample of 80 has been tested.

**Behavioural-Physiological Effects** There were no changes in betting behaviour under fluphenazine in HCs, while in PGs the drug tended to encourage higher bets. On cognitive tasks, fluphenazine consistently decreased salience of gambling words (as well as positive and negative words) in HCs and PGs. On the GDT, fluphenazine encouraged less risky choices in HCs and riskier choices in PGs. Increased betting and risk taking under fluphenazine in PGs combined with decreased salience of motivationally relevant cues suggests that signals for reward may have been less influential (i.e., less reinforcing) than rewards themselves under the drug.

Overall, decreased D1 activation with fluphenazine did not reliably optimize gambling reinforcement in HCs as predicted and differentially affected pleasurable vs. motivational aspects of gambling in PGs. Although not entirely in accord with the hypothesis, the results nevertheless clearly indicate a role for D1 signaling in the reinforcing effects of gambling in PGs. The general lack of effects of fluphenazine in HCs indirectly supports the possibility of differences in PG vs. HC subjects with respect to baseline D1 sensitivity, the functional role of D1 in gambling reinforcement, or both.

### 4.8 Hypothesis 3

The third hypothesis was that antagonist effects would be stronger when drugs were administered on the first vs. the second test session, given the greater DA release in response to novel rewards. This prediction was largely supported by the data. Reinforcing effects of the slot machine tended to be stronger on the first test session compared to the second under
placebo as expected, though more complex interactions between drug and order effects emerged across outcome measures.

Several notable effects of drug sequence emerged. The effects of novelty were more pronounced under both drugs in HCs vs. PGs. This is consistent with the fact that the relative increase in exposure to a slot machine from session 1 to session 2 was much greater in HCs with limited exposure to slot machines than in PGs with extensive exposure to these games.

In HCs, haloperidol increased High from the game only when it was novel, while fluphenazine appeared to have bidirectional effects, tending to decrease pleasurable effects of the game when it was novel but to increase these ratings when the game was familiar. Haloperidol also increased ratings of positive mood states (MBG and AMPH scores) more consistently when the game was novel in HCs. In PGs, neither drug appreciably affected pleasurable effects of the game but mainly affected general mood state, not explicitly attributable to the game: haloperidol decreased MBG and AMPH scores following the game when it was novel, whereas fluphenazine increased Vigor following the game when it was novel. Clear sequence effects also emerged in both groups under haloperidol on the RRT and the SST, with salience and psychomotor inhibition both increasing under drug when the tasks and game were novel and but tending to decrease under drug after prior exposure to these stimuli. Collectively, these data indicate that novelty-enhanced DA release generally had iso-directional effects with haloperidol on gambling reinforcement in HCs, whereas effects of novelty on gambling reinforcement appeared to be antagonized by haloperidol in PGs.

4.9 General Discussion

Overall, results of haloperidol and fluphenazine administration on HCs and PGs in these experiments were consistent with some of the predicted effects of D1 and D2 blockade on gambling reinforcement. Increased motivation to gamble pre-game under haloperidol is consistent with results from a similar prior study (Zack and Poulos 2007) as well as with evidence from studies in stimulant dependence. In individuals who abuse cocaine, increased DA transmission in the dorsal striatum is associated with craving in response to drug cues (Volkow et al. 2006). However, though effects were moderate, haloperidol appeared to reduce reinforcement from slot machine play itself, as indicated by increased post-game confidence to resist gambling in PGs, reduced engagement in the game, and reduced post-game Vigor scores. This was unexpected based on the prior study, but suggests that in these subjects, increased DA
release during gambling (when feedback inhibition was removed by haloperidol) reduced the reinforcing and priming effects of slot machine play. This may reflect a satiation effect of D1 stimulation in the presence of D2 autoreceptor blockade.

In rats exposed to stimulant drugs such as cocaine, preferential D1 stimulation reduces drug-induced cocaine-seeking behaviour, and satiation of incentive motivation with continuous D1 receptor occupancy has been proposed to account for this effect (Self 1996). While the present study did not assess direct D1 stimulation, increased DA release via D2 blockade with haloperidol may have had similar effects by increasing tonic DA levels and blunting the relative impact of reward-induced ‘phasic’ (burst) signaling. Alternately, DA release during slot machine play may have been excessive under haloperidol in these subjects (as noted above), leading to subjective feelings of disengagement and reduced pleasure. Notably, bet size increased consistently under haloperidol in PGs, indicating that elevated DA release during gambling reliably increased behavioural reinforcement on the gambling task despite reductions in subjective reinforcing effects.

In contrast to the effects of haloperidol, combined D1/D2 blockade with fluphenazine consistently enhanced positive affective responses in PGs. These findings suggest that positive affect is enhanced by moderate as opposed to strong D1 activation in these subjects. However, the absence of effects on VAS measures of slot machine reward itself suggests D1 signaling may not be primarily involved in mediating hedonic impact of the game in PGs. Instead, these effects may be secondary to D1’s role in craving. This is consistent with the distinction proposed by Berridge (2004) that striatal DA mediates motivation but not hedonic effects of rewarding stimuli. In the present data, reduction in motivation to gamble in PGs may itself have been related to increased positive affect as measured by elevated ratings of drug-like euphoric effects across time points. In animals, it has been suggested that cravings were associated with a negative affective state (Carelli and West 2013); the present results may represent the converse situation, such that fluphenazine, by decreasing D1 receptor activation, reduced craving in PGs and “corrected” their affective state. At the same time, ratings of Depression/Dejection increased under fluphenazine, despite concurrent increases in ARCI-MBG scores, suggesting that POMS depression scores may be related to a general lack of motivation in addition to a specific decrease in desire to gamble. Together, these results suggest a role for D1 receptor activation in reward expectancy, such that blockade reduces the anticipation of gambling reward (lower Desire to Gamble) but also the anticipation of reward
in general (higher POMS Depression), and a state of complacency (higher ARCI-MBG) may contribute to this motivational change.

These preliminary analyses are consistent with some aspects of the proposed inverted U relationship between D1 activation and reinforcement (section 1.2.5), in which an optimum range exists for D1 activation, beyond which effects are aversive or less reinforcing. In PGs, comparisons between haloperidol and fluphenazine effects suggest optimal D1 activation may reduce compulsive motivation to gamble in PGs, concurrently increasing pleasurable effects as seen under fluphenazine, while supra-optimal stimulation may increase this motivation in the absence of the reward itself, as seen pre-game under haloperidol. Drug effects appeared to more strongly influence incentive motivation in PGs but tended to more strongly influence hedonic impact of gambling in HCs, suggesting that the role of D1 in mediating normal vs. pathological reinforcement processes may differ. This is consistent with the progressive shift from positive to negative reinforcing effects of addictive substances (or activities) with increasing chronic exposure to these reinforcers (Koob and Le Moal 2005).

The pattern of sequence effects under haloperidol is consistent with its presumed effects to increase DA release in a stimulation-dependent manner through removal of inhibitory autoreceptor feedback. Since greater DA release is stimulated by novel rewards (Feenstra et al. 2000), excessive DA release post-game may have satiated the reinforcing properties of a gambling task on first exposure to it, as indicated by reductions in pleasurable effects post-game under haloperidol in PGs; this increase was not seen on the second session, in which DA response is expected to be relatively smaller. In contrast, fluphenazine’s effects to increase reinforcement were often more pronounced on the second test session. This suggests that drug effects may have interacted with changes in DA signaling in the process of cue conditioning as outlined by Shao et al. (2013), wherein DA release shifts from reward-induced to cue-induced after a single gambling episode. When administered on the first test session, fluphenazine may have blunted the DA response to the novel reward by preventing normal reinforcing activation of D1 receptors in response to reward delivery, leading to reduced subjective pleasurable effects. However, since phasic signaling through D1 receptors is thought to mediate the reward prediction error (Schultz 2001), fluphenazine administration when the game was familiar may have blocked cue-induced D1 signaling and indirectly enhanced the contrast effect – i.e., reward prediction error - in response to reward delivery (monetary payoff). That is, playing the game under fluphenazine on session 2 may have been functionally
equivalent to playing it for the first time drug-free. In PGs, fluphenazine increased positive drug-like effects and decreased motivation to gamble more consistently on the second test session and encouraged higher bets only on session 2. This suggests that fluphenazine may have reduced compulsion to gamble and increased pleasurable effects by interfering with cue-based DA signaling.

In summary, drug effects on subjective reinforcement were strongly influenced by order of administration, though these interactions were often more complex than originally predicted. The ability of haloperidol to blunt pleasurable effects post-game on the first session only is consistent with an aversive effect of supra-optimal D1 activation when novelty was combined with the removal of feedback inhibition. Enhanced subjective reinforcement under fluphenazine but not haloperidol on session 2 is consistent with preferential interference with cue effects and restoration of the RPE by partial D1 blockade when the game was familiar.

Results from cognitive tasks provide further information about the roles of D1 and D2 receptors in gambling response. These results tended to be consistent between PGs and HCs (RRT and SST) and between drug sequence subgroups (GDT). On the RRT, the pattern of drug effects suggests a central role for the D1 signaling on an objective measure of reward salience. In particular, the consistent effect of fluphenazine to reduce RT difference to motivationally relevant words suggests that D1 activation is crucial to the facilitatory processing of these reward signals. Conversely, haloperidol effects were sequence-dependent, enhancing the priming effect of the slot machine game when it was novel but reducing this effect when it was familiar. This suggests a role for enhanced D1 signalling primarily in the reactivity to reward signals that impart new information but not to signals that are redundant.

As with the RRT, haloperidol effects on the SST were highly dependent on sequence of administration. Haloperidol reduced post-game SSRT, indicating better psychomotor inhibition, when the game was novel but impaired psychomotor inhibition when the game was familiar, negating the usual benefits of practice on the task. This is consistent with the idea that increased D1 activation during autoreceptor blockade impedes processing of signals that are familiar (low intensity phasic DA response) such that information that could be beneficial (i.e., practice effects) as well as information that is genuinely redundant are both obscured.

Fluphenazine had more modest effects on performance, but appeared to lead to lower SSRT scores on the second test session, potentially enhancing the effect of practice on the SST. Decreased stimulation of D1 receptors in response to familiar cues may have reduced the
ability of visual stimuli to elicit an overt go response (approach), indirectly improving inhibitory performance by facilitating inaction rather than action.

GDT results suggest that the role of D1 in mediating risky decision-making does differ between HCs and PGs. D2 blockade with haloperidol tended to encourage safer choices on the GDT in PGs only, while under fluphenazine HCs made safer selections and PGs more risky ones. Haloperidol’s effects in PGs are broadly consistent with the finding that direct D2/D3 receptor agonists increase risk-taking on similar tasks in Parkinson’s disease patients with impulse control disorders (Voon et al. 2011b) given that D2 antagonism appeared to have the opposite effect (i.e., decreased risk-taking).

Opposing effects of haloperidol and fluphenazine in PGs further suggest these changes are mediated by downstream D1 receptor activation. Differential effects of fluphenazine in PGs and HCs suggest differences in the way D1 signaling affects risk-taking in the two groups. This could reflect reduced D1 availability in PGs, such that fluphenazine leads to suboptimal D1 stimulation in these subjects but not in HCs, for whom D1 stimulation may be naturally higher. In line with this, Takahashi et al. (2010) found in a PET study that low D1 receptor availability was associated with a tendency to overestimate low probabilities and underestimate high probabilities. Such an effect would promote selection of risky response options on the GDT in PG subjects, and would be compounded by a drug that further reduced D1 receptor availability. Patterns of drug responses on the GDT did not conform to those seen with subjective motivation or actual betting behaviour, emphasizing that risk-based decision making (simulated dice game) is not identical to slot machine gambling and is differentially mediated by DA. Whether this reflected differences between the games in opportunity to win money, sensory features (bells, lights) or the probabilistic vs. completely uncertain nature of the outcomes in the GDT vs. slot machine, respectively, is a matter for future investigation.

Altogether, these results support a role for optimized (i.e., moderate) D1 stimulation in increasing subjective pleasurable affect states, and for elevated D1 signaling in reward expectancy and cognitive processing of highly salient reward signals.

4.10 Limitations

This preliminary analysis is limited by a small sample size in each subgroup. Because of this, individual genetic differences in pharmacokinetics or pharmacodynamics of study drugs may have influenced the observed responses, potentially affecting functional drug doses
(blood levels) or baseline receptor availability. Primary analyses were performed within-subjects to minimize these effects. The final projected sample size of 80 subjects will clarify the importance of emerging trends described here.

Subjects in this study had moderate PG severity on average (mean SOGS score of 10.5 and 10.6 for haloperidol and fluphenazine subgroups respectively). This may have limited the ability to detect differences between the Drug Groups due to deficits in D1 functions, and conclusions may not apply to more severe PG cases. Similarly, potential participants were excluded on the basis of psychiatric comorbidities and substance abuse in order to attribute between-group differences to PG per se. Because of this, PG subjects in this study may not be representative of the broader population of PGs in whom these problems are common.

The primary outcome measures in these analyses were self-report measures, which may be influenced by differences in subjective interpretation. A complementary cognitive index, the RRT, is included to partially address this limitation, however data from this measure rely even more on a full sample size to interpret with confidence.

Because no selective D1 antagonist is available for human use in Canada, effects of D1 blockade alone could not be determined. The role of this receptor was inferred from comparisons between responses under haloperidol and fluphenazine, but the effect of D1 receptor blockade on the present indices in the absence of concurrent D2 blockade remains unknown.

DA transmission and receptor function were not measured directly in this study (e.g., with PET or neuroendocrine challenge), so definitive conclusions about the function of these systems in gambling reinforcement cannot be provided nor can inferences about neuroanatomical location of the drug effects be confirmed. Both medications bind DA receptors throughout the brain, and while effects on striatal DA transmission are likely an important factor, changes in receptor function in other brain regions such as the nucleus accumbens, PFC, and hippocampus also presumably contribute to the observed results.

4.11 Future Directions

Expanding the sample size will help to clarify differences in DA receptor function between PGs and HCs as well as explore the impact of factors such as age, gender, and ethnic background, which may strongly influence DA systems and responses. Exploring genotypes for these receptors will also help inform understanding of variation in responses to gambling
and the drug effects. Some evidence suggests that certain polymorphisms in DRD1 and DRD2 genes are associated with PG (Comings et al. 1996, Comings et al. 1997). However, in general there is little evidence of substantial functional polymorphism in genes for DA receptors. Therefore, although a positive result would be informative, a negative result is possible and would be difficult to interpret.

Future studies examining DA release and receptor availability directly using PET analyses in PGs and controls would complement the present study by helping to determine the function of specific DA pathways in gambling reinforcement. D1 receptor occupation can be assessed using the ligand $[^{11}\text{C}]-\text{SCH-23390}$, while a recent PET study using $[^{11}\text{C}]-\text{raclopride}$ found no evidence of significant differences in D2 receptor availability in PGs relative to HCs (Boileau et al. 2013). Neuroendocrine challenges can also be used to assess dopamine receptor sensitivity (Hollander et al. 1990). Assessing prolactin and growth hormone responses to the non-selective DA agonist apomorphine and the D2-like agonist bromocriptine can be used as a measure of responsiveness of these receptors. If PGs had low D2 receptor function, reduced growth hormone/prolactin response to both drugs would be expected, while reduced response to apomorphine only would indicate low D1 function.

Nevertheless, the present results underline the importance of experimental context when examining DA release and reinforcement in gambling on multiple occasions. Finally, studies examining gambling reinforcement under the influence of direct DA receptor agonists would help to clarify the role of increased D1 activation on the effects outlined here. A better understanding of the way these systems function in normal and pathological reward, and how they are affected by pharmacological manipulations, will be beneficial for refining treatment strategies for PG.

4.12 Conclusions

This study provides several distinct findings with regard to the role of DA receptors in behavioural reward. Results generally support the notion that D1 modulation is crucial for the subjective rewarding, incentive motivational and cognitive aspects of addictive behaviour. The pattern of effects supports an interaction between cue conditioning and subjective rewarding effects, with DA D1 manipulations differentially modulating the two processes. These analyses suggest several preliminary conclusions: (1) Elevated DA release may increase reward expectancy and concomitant compulsive motivation to gamble in PGs through post-synaptic
D1 receptor stimulation. (2) Optimal D1 stimulation in PGs may be associated with a reduction in reward expectancy and compulsive motivation to gamble and a concurrent increase in positive affect, suggesting a distinction between pleasure (subjective “Liking”), motivation (subjective “Wanting”), and incentive salience (involuntary cue reactivity). (3) Reward novelty had a strong impact on gambling reinforcement in these subjects, and this may be related to reduced RPE in response to monetary payoffs after prior exposure to the game, particularly in HCs. (4) Elevated D1 stimulation may improve reward learning and psychomotor inhibition in a manner depending on context and conditioning, while the role of D1 as a mediator of risk assessment may differ in individuals prone to PG. These results help to advance the understanding of the role of DA in reinforcement and cue conditioning and the interaction between the two, and may be beneficial to the development of treatment strategies to reduce undue conditioned reward seeking in people with PG.
REFERENCES


Robinson, E.S.J. (2012). Blockade of noradrenaline re-uptake sites improves accuracy and impulse control in rats performing a five-choice serial reaction time tasks. Psychopharmacology (Berl.) 219, 303–312.


APPENDIX A:
Binding Profiles of Haloperidol and Fluphenazine
Table A-i. Receptor binding of haloperidol and fluphenazine at D2 receptors.

<table>
<thead>
<tr>
<th>Ligands</th>
<th>D2 Response</th>
<th>IC$_{50}$</th>
<th>$K_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromperidol</td>
<td>-54 ± 6</td>
<td>2.1 ± 0.6</td>
<td>1.0 ± 0.6</td>
</tr>
<tr>
<td>Spiperone</td>
<td>-49 ± 1</td>
<td>0.3 ± 0.1</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>Fluspirilene</td>
<td>-48 ± 6</td>
<td>0.2 ± 0.1</td>
<td>0.2 ± 0.0</td>
</tr>
<tr>
<td>Pimozide</td>
<td>-45 ± 14</td>
<td>0.5 ± 0.1</td>
<td>2.4 ± 1.3</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>-43 ± 16</td>
<td>0.2 ± 0.0</td>
<td>1.1 ± 0.4</td>
</tr>
<tr>
<td><strong>Haloperidol</strong></td>
<td>-43 ± 15</td>
<td>0.8 ± 0.2</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td>Trifluperidol</td>
<td>-42 ± 12</td>
<td>0.2 ± 0.2</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>Cisflupenthixol</td>
<td>-41 ± 7</td>
<td>0.2 ± 0.1</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>-41 ± 4</td>
<td>11 ± 9</td>
<td>8.6 ± 1.9</td>
</tr>
<tr>
<td>Chlorproethazine</td>
<td>-40 ± 14</td>
<td>10 ± 5</td>
<td>11 ± 5</td>
</tr>
<tr>
<td>Butaclamol</td>
<td>-40 ± 2</td>
<td>0.3 ± 0.3</td>
<td>0.4 ± 0.4</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>-40 ± 3</td>
<td>38 ± 6</td>
<td>3.6 ± 1.5</td>
</tr>
<tr>
<td><strong>Fluphenazine</strong></td>
<td>-39 ± 6</td>
<td>0.2 ± 0.1</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>Sertindole</td>
<td>-39 ± 4</td>
<td>2.7 ± 1.1</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>Ocaperidone</td>
<td>-38 ± 11</td>
<td>0.1 ± 0.0</td>
<td>0.4 ± 0.3</td>
</tr>
<tr>
<td>Risperidone</td>
<td>-37 ± 3</td>
<td>0.3 ± 0.3</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td>Remoxipride</td>
<td>-37 ± 3</td>
<td>16 ± 6</td>
<td>105 ± 38</td>
</tr>
<tr>
<td>Tiapride</td>
<td>-35 ± 10</td>
<td>31 ± 13</td>
<td>226 ± 223</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>-34 ± 12</td>
<td>3.0 ± 1.1</td>
<td>5.7 ± 1.5</td>
</tr>
<tr>
<td>Raclopride</td>
<td>-34 ± 9</td>
<td>0.5 ± 0.3</td>
<td>2.4 ± 0.8</td>
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<tr>
<td>Melperone</td>
<td>-34 ± 7</td>
<td>1.0 ± 0.6</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>Tefludazine</td>
<td>-33 ± 2</td>
<td>0.3 ± 0.2</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>Transflupenthixol</td>
<td>-32 ± 6</td>
<td>17 ± 6</td>
<td>21 ± 6</td>
</tr>
<tr>
<td>Clozapine</td>
<td>-31 ± 10</td>
<td>71 ± 21</td>
<td>72 ± 20</td>
</tr>
<tr>
<td>Molindone</td>
<td>-30 ± 8</td>
<td>3.8 ± 1.5</td>
<td>20 ± 7</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>-29 ± 14</td>
<td>1.7 ± 1.1</td>
<td>8.1 ± 2.1</td>
</tr>
<tr>
<td>Sulforidazine</td>
<td>-29 ± 13</td>
<td>0.2 ± 0.0</td>
<td>0.3 ± 0.2</td>
</tr>
<tr>
<td>9-OH-risperidone</td>
<td>-29 ± 13</td>
<td>1.0 ± 0.2</td>
<td>0.4 ± 0.4</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>-27 ± 15</td>
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<td>0.03 ± 0.01</td>
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<tr>
<td>Sulthiopride</td>
<td>-24 ± 6</td>
<td>4.5 ± 0.7</td>
<td>1.6 ± 1.0</td>
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<td>Melperone</td>
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<td>N.D.</td>
<td>3.6 ± 0.5</td>
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<td>Octoclohepin</td>
<td>-24 ± 6</td>
<td>0.2 ± 0.1</td>
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<tr>
<td>Promazine</td>
<td>-18 ± 13</td>
<td>N.D.</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>-14 ± 10</td>
<td>N.D.</td>
<td>16 ± 12</td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>-14 ± 9</td>
<td>N.D.</td>
<td>4.3 ± 1.4</td>
</tr>
<tr>
<td>N-Desmethylolanzapine</td>
<td>-14 ± 7</td>
<td>N.D.</td>
<td>32 ± 29</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>-13 ± 12</td>
<td>N.D.</td>
<td>106 ± 43</td>
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<td>Thoridazine</td>
<td>-12 ± 15</td>
<td>N.D.</td>
<td>21 ± 16</td>
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<tr>
<td>L-745,870</td>
<td>N.D.</td>
<td>N.D.</td>
<td>343 ± 297</td>
</tr>
<tr>
<td>Aripiprazole</td>
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<td>N.D.</td>
<td>4.4 ± 0.9</td>
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<tr>
<td>N-Desmethylclozapine</td>
<td>129 ± 21</td>
<td>N.D.</td>
<td>89 ± 26</td>
</tr>
</tbody>
</table>

N.D., not done; N.R., no response.

Table A-ii. Receptor binding of haloperidol and fluphenazine at D1 receptors.

Table 6. *Inhibition of* $^3$H-SCH 23390 *binding to rat striatal membranes in vitro*

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC 50 nM</th>
<th>Ki nM</th>
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</thead>
<tbody>
<tr>
<td><strong>Thioxanthenes</strong></td>
<td></td>
<td></td>
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<tr>
<td>Cis(Z)-chlorprothixene</td>
<td>3.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Trans(E)-chlorprothixene</td>
<td>270</td>
<td>130</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>1.4</td>
<td>0.66</td>
</tr>
<tr>
<td>Trans(E)-clopenthixol</td>
<td>110</td>
<td>52</td>
</tr>
<tr>
<td>Cis(Z)-flupentixol</td>
<td>2.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Trans(E)-flupentixol</td>
<td>130</td>
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<tr>
<td>Cis(Z)-piflutixol</td>
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<td>Teflutixol</td>
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<td>Cis-thiothixene</td>
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<td><strong>Phenothiazines</strong></td>
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<td>Thioridazine</td>
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<td>Trifluoperazine</td>
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<td>3.7</td>
</tr>
<tr>
<td><strong>Butyrophenones + analogues</strong></td>
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<tr>
<td>Bromperidol</td>
<td>25</td>
<td>12</td>
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<tr>
<td>Domperidone</td>
<td>3,900</td>
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<td>Droperidol</td>
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<td>410</td>
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<td>Halopemide</td>
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<td>Haloperidol</td>
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<td>Firenperone</td>
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<td>Setoperone</td>
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<td>Spiperone</td>
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<td>100</td>
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<td><strong>Diphenylbutylpiperidines</strong></td>
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<td>Pimozide</td>
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<td>250</td>
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<tr>
<td>Clopimozide</td>
<td>670</td>
<td>320</td>
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Table A-iii. Receptor binding of haloperidol and fluphenazine at D2, D3, and D4 receptors.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>D2 Response</th>
<th>IC₅₀</th>
<th>Kᵣ</th>
<th>D3 Response</th>
<th>IC₅₀</th>
<th>Kᵣ</th>
<th>D4 Response</th>
<th>Kᵣ</th>
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<tr>
<td>Bromoperidol</td>
<td>-54 ± 6</td>
<td>2.1</td>
<td>0.6</td>
<td>-57 ± 18</td>
<td>2.3</td>
<td>0.7</td>
<td>8 ± 8</td>
<td>48 ± 41</td>
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<tr>
<td>Sipiperone</td>
<td>-49 ± 6</td>
<td>0.3</td>
<td>0.01</td>
<td>-46 ± 6</td>
<td>0.2</td>
<td>0.1</td>
<td>8 ± 3</td>
<td>3.7 ± 1.7</td>
</tr>
<tr>
<td>Fluspiridene</td>
<td>-46 ± 8</td>
<td>0.2</td>
<td>0.12</td>
<td>-55 ± 14</td>
<td>4.3</td>
<td>0.4</td>
<td>8 ± 3</td>
<td>8.8 ± 4.7</td>
</tr>
<tr>
<td>Pimozide</td>
<td>-44 ± 14</td>
<td>0.5</td>
<td>0.13</td>
<td>-40 ± 11</td>
<td>0.2</td>
<td>0.2</td>
<td>8 ± 3</td>
<td>8.8 ± 4.7</td>
</tr>
<tr>
<td>Pimozide</td>
<td>-43 ± 16</td>
<td>0.2</td>
<td>0.06</td>
<td>-50 ± 13</td>
<td>2.4</td>
<td>0.4</td>
<td>8 ± 3</td>
<td>8.8 ± 4.7</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>-43 ± 15</td>
<td>0.8</td>
<td>0.17</td>
<td>-53 ± 12</td>
<td>3.6</td>
<td>0.6</td>
<td>11 ± 2</td>
<td>22 ± 11</td>
</tr>
<tr>
<td>Trifluoperidol</td>
<td>-42 ± 12</td>
<td>0.2</td>
<td>0.1</td>
<td>-46 ± 12</td>
<td>3.5</td>
<td>0.2</td>
<td>13 ± 3</td>
<td>326 ± 91</td>
</tr>
<tr>
<td>Clozapine</td>
<td>-41 ± 7</td>
<td>0.2</td>
<td>0.1</td>
<td>-48 ± 14</td>
<td>2.9</td>
<td>0.3</td>
<td>17 ± 10</td>
<td>131 ± 82</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>-41 ± 4</td>
<td>11</td>
<td>0.9</td>
<td>-45 ± 13</td>
<td>8.2</td>
<td>0.4</td>
<td>16 ± 8</td>
<td>54</td>
</tr>
<tr>
<td>Chlorprothixene</td>
<td>-40 ± 14</td>
<td>10</td>
<td>0.5</td>
<td>-37 ± 23</td>
<td>18</td>
<td>0.9</td>
<td>30 ± 9</td>
<td>29 ± 11</td>
</tr>
<tr>
<td>Butaclamol</td>
<td>-40 ± 2</td>
<td>0.3</td>
<td>0.1</td>
<td>-41 ± 22</td>
<td>1.6</td>
<td>0.4</td>
<td>21 ± 5</td>
<td>162 ± 77</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>-40 ± 3</td>
<td>36</td>
<td>0.6</td>
<td>-32 ± 5</td>
<td>31</td>
<td>0.7</td>
<td>8 ± 3</td>
<td>40 ± 35</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>-38 ± 6</td>
<td>0.2</td>
<td>0.1</td>
<td>-49 ± 15</td>
<td>2.1</td>
<td>0.2</td>
<td>22 ± 2</td>
<td>7.1 ± 17</td>
</tr>
</tbody>
</table>

Table A-iv. Receptor binding of haloperidol and fluphenazine at serotonin receptors.

Table 2 Antipsychotic Medication Serotonin Receptor $K_i$ Values

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinically effective dose (mg)</th>
<th>$K_i$ Values (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S-HT$_{1A}$</td>
<td>S-HT$_{1B}$</td>
</tr>
<tr>
<td>Antipiprazole</td>
<td>5-30</td>
<td>5.6</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>300-900</td>
<td>3115</td>
</tr>
<tr>
<td>Chlorprothixene</td>
<td>50-100</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>300-900</td>
<td>105</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>2-15</td>
<td>145</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2-15</td>
<td>1202</td>
</tr>
<tr>
<td>Loxapine</td>
<td>25-100</td>
<td>2456</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>100-400</td>
<td></td>
</tr>
<tr>
<td>Molindone</td>
<td>20-100</td>
<td>3797</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10-20</td>
<td>2063</td>
</tr>
<tr>
<td>Perhexazine</td>
<td>8-64</td>
<td>421</td>
</tr>
<tr>
<td>Pimozide</td>
<td>2-10</td>
<td>650</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>250-800</td>
<td>431</td>
</tr>
<tr>
<td>Remoxipride</td>
<td>200-400</td>
<td>6225</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2-8</td>
<td>527</td>
</tr>
<tr>
<td>Sertraline</td>
<td>12-24</td>
<td>280</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>200-800</td>
<td>108</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>5-30</td>
<td>410</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>80-160</td>
<td>76</td>
</tr>
</tbody>
</table>

Neil M Richaard$^{1,2}$, Jeffrey A Welge$^{3,3}$, Aaron D Logue$^{1,2}$, Paul E Keck Jr$^{1,2}$, Stephen M Strakowski$^1$ and Robert K McNamara$^2$

Dopamine and Serotonin Receptor Binding and Antipsychotic Efficacy

Neuropsychopharmacology (2007) 32, 1715-1726; dx.doi.org/10.1038/npp.2010.306; published online 24 January 2007
Table A-v. Receptor binding of haloperidol and fluphenazine at muscarinic acetylcholine receptors.

<table>
<thead>
<tr>
<th>Neuroleptics</th>
<th>K_D (nM)</th>
<th>Hill coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>12 ± 4</td>
<td>0.95 ± 0.06</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>18 ± 1</td>
<td>1.0</td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>69 ± 2</td>
<td>1.1</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>70 ± 6</td>
<td>1.05 ± 0.01</td>
</tr>
<tr>
<td>Promazine</td>
<td>150 ± 30</td>
<td>1.0</td>
</tr>
<tr>
<td>Losapine</td>
<td>450 ± 80</td>
<td>1.0</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>540 ± 120</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>660 ± 40</td>
<td>1.1</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>3,500 ± 30</td>
<td>1.0</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>1,900 ± 500</td>
<td>1.32 ± 0.08</td>
</tr>
<tr>
<td>Siperonone</td>
<td>2,700 ± 800</td>
<td>1.01 ± 0.09</td>
</tr>
<tr>
<td>cis-Thiothixene</td>
<td>2,900 ± 100</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>d-Butaclamol</td>
<td>12,000 ± 3,000</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>24,000 ± 9,000</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>Molindone</td>
<td>390,000 ± 90,000</td>
<td>1.3 ± 0.1</td>
</tr>
</tbody>
</table>

Antimuscarinics
- QNB: 0.04 ± 0.005, 1.02 ± 0.04
- Atropine: 2.4 ± 0.6, 1.1 ± 0.1

Table A-vi. Receptor binding of haloperidol and fluphenazine at histamine H1 receptors.

<table>
<thead>
<tr>
<th>Neuroleptics</th>
<th>K_D (nM)</th>
<th>Hill coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesoridazine</td>
<td>1.8 ± 0.1</td>
<td>0.66 ± 0.09</td>
</tr>
<tr>
<td>Promazine</td>
<td>2.0 ± 0.1</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>Clozapine</td>
<td>2.8 ± 0.1</td>
<td>1.03 ± 0.04</td>
</tr>
<tr>
<td>Losapine</td>
<td>4.9 ± 0.8</td>
<td>0.71 ± 0.03</td>
</tr>
<tr>
<td>cis-Thiothixene</td>
<td>6 ± 2</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>8 ± 1</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>9 ± 3</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>16 ± 3</td>
<td>0.97 ± 0.06</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>19.0 ± 0.2</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>21 ± 4</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>62 ± 7</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>Siperonone</td>
<td>390 ± 70</td>
<td>1.00 ± 0.07</td>
</tr>
<tr>
<td>Spiropine</td>
<td>480 ± 70</td>
<td>1.08 ± 0.05</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1,900 ± 300</td>
<td>0.77 ± 0.05</td>
</tr>
<tr>
<td>Molindone</td>
<td>124,000 ± 12,000</td>
<td>0.53 ± 0.07</td>
</tr>
</tbody>
</table>

Antihistamines
- d-Chlorpheniramine: 15 ± 2, 0.85 ± 0.06

Table A-vii. Receptor binding of haloperidol and fluphenazine at α1 adrenergic receptors.

<table>
<thead>
<tr>
<th>Neuroleptics</th>
<th>K_D (nM)</th>
<th>Hill coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siperonone</td>
<td>1.2 ± 0.2</td>
<td>0.82 ± 0.03</td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>2.0 ± 0.5</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>2.6 ± 0.3</td>
<td>0.97 ± 0.08</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>5 ± 1</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>Promazine</td>
<td>6 ± 2</td>
<td>0.82 ± 0.04</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>6.1 ± 0.8</td>
<td>0.83 ± 0.07</td>
</tr>
<tr>
<td>Clozapine</td>
<td>9 ± 3</td>
<td>0.90 ± 0.05</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>9 ± 2</td>
<td>1.02 ± 0.06</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>10 ± 2</td>
<td>1.10 ± 0.04</td>
</tr>
<tr>
<td>Promazine</td>
<td>24 ± 7</td>
<td>1.10 ± 0.05</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>24 ± 3</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>Losapine</td>
<td>28 ± 6</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>d-Butaclamol</td>
<td>56 ± 8</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>Molindone</td>
<td>2,500 ± 600</td>
<td>0.71 ± 0.07</td>
</tr>
</tbody>
</table>

Antihypertensives
- Prazosin: 0.09 ± 0.01, 0.98 ± 0.02
- Phenolamine: 15 ± 4, 0.82 ± 0.03

Table A-viii. Receptor binding of haloperidol and fluphenazine at α2 adrenergic receptors.

<table>
<thead>
<tr>
<th>Neuroleptics</th>
<th>K_D (nM)</th>
<th>Hill coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siperonone</td>
<td>160 ± 20</td>
<td>0.98 ± 0.02</td>
</tr>
<tr>
<td>cis-Thiothixene</td>
<td>200 ± 20</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>d-Butaclamol</td>
<td>310 ± 40</td>
<td>0.96 ± 0.06</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>510 ± 20</td>
<td>1.10 ± 0.08</td>
</tr>
<tr>
<td>Molindone</td>
<td>640 ± 100</td>
<td>0.91 ± 0.05</td>
</tr>
<tr>
<td>Siperonone</td>
<td>660 ± 20</td>
<td>0.89 ± 0.04</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>750 ± 50</td>
<td>1.33 ± 0.02</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>900 ± 100</td>
<td>1.23 ± 0.06</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>900 ± 100</td>
<td>1.00 ± 0.02</td>
</tr>
<tr>
<td>Promazine</td>
<td>1,600 ± 100</td>
<td>0.70 ± 0.03</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>1,550 ± 200</td>
<td>0.86 ± 0.04</td>
</tr>
</tbody>
</table>

Antidrenergic
- Yohimbine: 1.6 ± 0.2, 1.04 ± 0.08
- Ravucloline: 2.7 ± 0.2, 0.96 ± 0.03

---


APPENDIX B:
Recruitment Ads for HC and PG Subjects
Healthy Volunteers
You may be eligible for a medication research study.

If you are:
19-65 years of age
Drug- and Medication-Free
Available for Weekly Day-long Sessions (M – F)

Call Study Line: (416) 535-8501, ext. 36574

NOTE: This is not a treatment study.

• FINANCIAL COMPENSATION IS PROVIDED
• All Information Provided Will Remain Confidential To The Extent Allowed By Law.

CAMH provides treatment options for mental illness and addictions. For more information about programs and services at CAMH, visit www.camh.net or call (416) 535-8501, or 1-800-463-6273
Do you gamble?

You may be eligible for a medication research study.

If you are:

19-65 years of age

Drug- and Medication-Free

Available for Weekly Day-long Sessions (M – F)

Call Study Line: (416) 535-8501, ext. 36574

NOTE: This is not a treatment study.

• FINANCIAL COMPENSATION IS PROVIDED

• All Information Provided Will Remain Confidential To The Extent Allowed By Law.

CAMH provides treatment options for mental illness and addictions. For more information about programs and services at CAMH, visit www.camh.net or call (416) 535-8501, or 1-800-463-6273
APPENDIX C:
Informed Consent Form
Study Information Sheet

Mental and behavioral effects of central nervous system medications in frequent and occasional gamblers

Principal Investigator: Martin Zack, PhD
Co-Investigators: James Kennedy, MD, PhD
               Daniela Lobo, MD, PhD
               Daniel DiGiacomo, MD
Study Site: Centre for Addiction & Mental Health,
            33 Russell Street & 250 College Street, Toronto Ontario

Confidentiality and Continuing Review

As part of continuing review of the research, your study records may be assessed on behalf of the Research Ethics Board and 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.

Purpose:

This study is intended to test the effects of the central nervous system (CNS) medications, Haloperidol, Fluphenazine and Dexedrine on mental processes and feelings in individuals who gamble frequently and in a comparison group of people who gamble rarely or occasionally. The study is not intended to treat any aspect of your gambling. If you are eligible, based on the conditions outlined below (see Study Requirements), you will be one of 80 participants in the study.

Study Procedure

1. Participation involves coming to the 33 Russell Street of the Centre for Addiction and Mental Health (CAMH) 6 separate times: A pre-experimental interview, a physician’s examination, and 4 test sessions, scheduled at 1-week intervals. You will receive transit tokens to cover round-trip fare to CAMH for the interview and physician’s exam, as well as the cost of travel to CAMH on all test sessions. You will be sent home by pre-paid taxi at the end of all test sessions.

2. Pre-experimental Interview. This session will involves answering some questions and filling out some questionnaires about your gambling experiences, alcohol and drug use, and personality characteristics. You will meet with a doctor who will ask you questions about any mental or emotional concerns you may have. In addition, you will be asked to provide a urine sample and a registered nurse will take a blood sample from your arm (3-4 finger-sized vials). The blood sample may cause minor discomfort and temporary bruising on your arm. The urine and blood samples will be used to make sure you have not recently used any mood-altering drugs and will also ensure that you have no health condition that would make it risky to receive the study medications. During this session you will also undergo an electrocardiogram (EKG), administered by a trained technician. The EKG is a harmless test that examines your heart’s activity over the course of several minutes. This session will take 2 - 2.5 hours.
3. **Physician’s Exam.** If the information from your interview shows that you meet the initial requirements for participation, you will be asked to undergo a physical examination by a doctor at CAMH. The purpose of the exam is to make sure you have no physical condition that would make it risky for you to receive any of the study medications. The exam will take \( \frac{3}{4} \) - 1 hour.

4. **Test Sessions.** If your physician's exam shows that you are fit to receive the study medications, you will be asked to attend 4 test sessions scheduled at 1-week intervals. Each test session will be identical in terms of the things you will be asked to do. You will have an opportunity to ask questions throughout the study. You are free to not answer any question or to not perform any task or withdraw from the study without penalty. Payment for partial participation is pro-rated as outlined below.

**Details of Test Sessions:**

a) You will abstain from alcohol and all mood-altering drugs for 12 hours prior to the start of each test session and for 72 hours after the completion of each test session. This is extremely important to prevent potentially dangerous interactions between the study medications and other drugs.

b) You will also abstain from caffeinated beverages and eat no food on the morning of each test session. You will receive a standard breakfast (with coffee if you wish) at the laboratory when you arrive.

c) You will report to the laboratory at 8:15 am on each test session. At that time, you will take a breathalyzer test to ensure there is no alcohol in your bloodstream. You will then receive your breakfast. You will take your first pill after you finish breakfast. You will take a second pill between 2-3 hrs after you receive your first.

d) On your test sessions, you may receive 3-mg Haloperidol, 3-mg Fluphenazine, 20-mg Dexedrine, or a placebo (an inactive pill). Neither the experimenter nor you will know which pills you will receive. The pharmacist who provides the pills and the principal investigator on the study will determine which pills you receive. This will be done before the study begins and will be based on a participant number so that all participants will have an equal chance of receiving the different pills on their test sessions.

e) After receiving your pills you will fill out some questionnaires; these questionnaires will be re-administered several times during the session. You will then read magazines or the newspaper for about 2 hours while the first pill is being absorbed before receiving your second pill.

f) At specified intervals throughout the session, the experimenter will assess your heart rate and blood pressure using a small device that slips over your wrist. The device will produce a feeling of mild pressure while it takes the reading but is not painful. Each reading takes about a minute.

g) Next you will play a VLT-style slot machine game, of the kind currently in use in Ontario. You will be provided with cash credits (tokens) for the machine and allowed to play for a standard period of time (10-20 minutes; to be confirmed on test day) or until your tokens run out, whichever comes first. To make the game more interesting, a monetary bonus will be provided based on the amount of your winnings in the game. The bonus will be paid upon completion of the study when you receive your standard payment for participation.

h) Following the VLT-game you will do a short (5-minute) reaction time task on a computer and fill out some more questionnaires dealing with your impressions of the game and how you feel generally (thoughts and feelings).

i) You will then perform two additional tasks on the computer, this time focusing on decision-making (20-min).

j) Between 1:30 and 2 you will receive lunch after which you can relax and read or watch videos until 5 p.m.
k) On the remaining test sessions, you will do the exact same things as you did on the first. In addition, at the end of the final test session, you will be given information about how you did in the various aspects of the study as well as more information about what the study was about.

l) You will be paid by cheque (participation fee plus any bonus payment you may have earned) which you can pick up 2 to 4 weeks after the study is over or have mailed to you.

**Study Requirements:**

1. To be eligible for this study you must have no mental or physical illness apart from problems related to gambling.

2. You must be free of all mood-altering drugs or medication.

3. You must not operate a motor vehicle or heavy equipment for 8 hours after completion of EACH test session.

4. You must not take any drugs or alcohol for 12 hours before and 72 hours after each test session.

5. You must follow the experimenter’s instructions during the interview and test sessions. This will include adhering to schedules and arriving at the laboratory on time.

6. Just as you are free to drop out of the study for any reason at any time (for partial payment), the experimenter is free to stop your participation before the study is over if you do not follow any of the study requirements. In this case, you would receive the payment earned for your participation up to that point.

7. The schedule of payment is as follows:

<table>
<thead>
<tr>
<th>Component</th>
<th>Payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Test Interview</td>
<td>$40</td>
</tr>
<tr>
<td>Physician’s Exam</td>
<td>$30</td>
</tr>
<tr>
<td>Test Session 1</td>
<td>$200</td>
</tr>
<tr>
<td>Test Session 2</td>
<td>$200</td>
</tr>
<tr>
<td>Test Session 3</td>
<td>$200</td>
</tr>
<tr>
<td>Test Session 4</td>
<td>$250</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$920</strong></td>
</tr>
</tbody>
</table>

8. You will receive a copy of this Study Information Sheet and Agreement to Participate (below).

**Risks:**

**Haloperidol**

Haloperidol has been in use for many years. Many experimental participants in other laboratories have taken the dose being tested in this study (3 mg) without negative effects. Some people may experience temporary muscle stiffness, slowing of movement, difficulty with balance or co-ordination. Both sedation and agitation (feeling 'uptight') have been reported. Although extremely rare, it is possible that this medication could cause difficulty swallowing. Measures have been taken to deal with this possibility should it occur (see below).

**Fluphenazine**

Fluphenazine is a medication in the same drug class as Haloperidol. As such, its side effect profile and the precautions surrounding its use are the same as those described for Haloperidol above.

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Dexedrine®

Dexedrine® is a stimulant medication currently in clinical use in Canada for the management of attention deficit hyperactivity disorder (ADHD) and sleep-disorder (narcolepsy). Side-effects of this drug include palpitations, mildly elevated blood pressure, restlessness, headache and dizziness. In some cases, anxiety, euphoria or agitation may occur. All of these effects are transient and wear off after about three hours. Some may find it hard to fall asleep in the evening following Dexedrine®. Because Dexedrine® can stimulate the heart and the blood vessels there is the rare possibility that the drug could over-stimulate your heart and cause a stroke or even death. All study subjects undergo a comprehensive medical exam before testing, which will evaluate risk for such a rare effect. In addition, it has not been confirmed that the low dose of Dexedrine® that you will receive could cause these serious side effects.

The unintended effects of the drugs to be used in this study are uncommon at the doses being tested. Also, the likelihood that they will occur goes down with time as the drug wears off. In addition, we have taken several steps to minimize negative effects:

a) First, we require that you stay under observation at the laboratory until 5 p.m. on test days.

b) Second, prior to leaving the lab at this time, you will be examined by a health care practitioner at our Clinic. She or he will make sure you are feeling all right before you go home that day. If you are experiencing any side effects at that time, the doctor can treat them and you can stay at the Clinic until you are feeling well enough to leave.

c) Third, you will be sent home from the laboratory by pre-paid taxi after all test sessions. Do not drive to the laboratory on test days; use the tokens we provide for you and take public transit.

d) Fourth, you will receive a wallet card stating that you may have received the various study medications as part of a research study and providing the phone number of the study physician who will be on-call after you leave the lab. You should keep the card with you at all times and contact the physician immediately if you experience any side effects.

e) Finally, when you leave the lab after test sessions you will receive a sealed capsule containing 50-mg Benadryl. This safe, non-prescription allergy medication is effective in countering the side effects of the study medications and will provide rapid relief if such symptoms do occur. The Benadryl is strictly a back-up measure. Take it ONLY if you are experiencing side effects. If you do take the Benadryl, you should not drive or operate heavy machinery for 8 hours, because it will likely make you sleepy. Regardless of whether or not you take the Benadryl, you should NOT DRIVE or OPERATE HEAVY MACHINERY on test days. If, after taking the Benadryl, you continue to experience any side effects, apart from drowsiness, contact the study physician at the phone number on your wallet card. He will tell you what to do from there.

f) Difficulty Swallowing: If you experience this rare side effect you should immediately take the anti-side effect medication (Benadryl). If this symptom persists or worsens after several minutes, proceed to the nearest hospital emergency room and present your wallet card to the medical staff to inform them that you may have received Haloperidol or Fluphenazine. You are also advised to contact the study physician at the number provided on the wallet card AFTER you go to the emergency room.

Benefits:

You should expect no benefit to your gambling from participating in this study. However, you will receive information about your performance on the various tasks at the end of the study that may be interesting to you. Although the research will not directly help your gambling now, the results may help in developing new and better treatments for gambling problems that may assist you or others with gambling difficulties, in the future.
Payment, Conditions, and Confidentiality:

If you complete the study you will receive $920. In addition, you will be required to play a slot machine for a short time (10-20 minutes) during each test session (see below). We will provide you with cash credits to play the VLT and you will receive a cash bonus proportional to your winnings from each test session at the end of the study. The bonus, if you win, will be in addition to your standard $920 payment for participation.

You can drop out of the study at any time and receive payment for the parts of the study you have completed (as outlined above). All information you provide will remain confidential to the extent allowed by law. Your name will not appear on any of the test materials (e.g., questionnaires, rating scales) or in any of the data from the computer task. You will be assigned a participant number which will be used to code all of your data. Names and identifying information will be stored in locked cabinets. Similarly, any reports of the study findings will be made so that you and all study participants remain anonymous.

As part of the Research Services Quality Assurance role, studies may be audited by the Manager of Quality Assurance. Your research records and CAMH records may be reviewed during which confidentiality will be maintained as per CAMH policies and to the extent permitted by law.

Questions
We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully - as long as you feel is necessary - before you make a decision.

Contact
If you have any further questions, please feel free to contact Dr. Martin Zack at 416-535-8501-ext. 6052 regarding the procedures involved in the study.

If you have any questions about your rights as a participant in this study, you may contact Dr. Padraig Darby, Chair, Research Ethics Board, Centre for Addiction and Mental Health, at 416 535 8501 ext. 6876.

Genetics Screen

As part of the blood sample you provide on the Interview session (first visit to CAMH) we will be collecting information about genes that may be related to how people respond to the medications tested in this study. Dr. Kennedy’s laboratory at CAMH looks for genetic variants that are related to preference for gambling and other personality variables. This could help to identify people at risk for gambling problems before they develop.

The genetic sample will be stored in a locked refrigerated cabinet and identified only by a code number. Your name will be stored in a separate area in a password protected computer file, but not on any computer network. Your clinical information will be stored in a locked file cabinet. Stated another way, there will be no direct connection between your blood sample and your name. The stored DNA material will be kept until our research is finished, which may take many years, although the samples will not be kept more than 25 years. The DNA can be used to test any gene that may be relevant to gambling or problem gambling. Other laboratories may be involved in analyzing the genetic material, and if so this will be confidential, and your name will not be given out. Results from this study may be presented at meetings and may be published. Your identity will not be disclosed at these presentations or in any publications.

Your decision to allow your blood to be assessed for genes is COMPLETELY UNRELATED to your decision to participate in the rest of the study. However, because it is so important to have a complete data set we try very hard to obtain genetic information from all research participants.

Please indicate your willingness to allow your blood to be assessed for genes related to gambling (as outlined above):

[ ] I do wish to have my blood used for genetic analysis.

[ ] I do NOT wish to have my blood used for genetic analysis.

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Mental and behavioral effects of central nervous system medications in frequent and occasional gamblers

• The investigator or a member of the investigator’s staff has discussed with me the risks of participation in this study.

• I have read all of the information in the Study Information Sheet, and I have had time to think about the information, and all of my questions have been answered to my satisfaction.

• I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the investigator or other staff members as requested.

• I am under no pressure to participate in the study, and I understand that I may withdraw from the study at any time. I also understand that my participation in the study may be terminated by the study investigator if necessary.

• By signing this consent form, I am not giving up my legal rights or releasing the investigators or sponsors from their legal and professional obligations.

• I have received a copy of the Information Sheet and will receive a copy of this signed consent form.

Print Participant’s Name ___________________________ Date __________

Participant’s Signature ___________________________

Signature of Individual Obtaining Consent ___________________________ Date __________

Signature of Investigator __________________________________________
(If investigator did not obtained the consent)

Date __________

Research at CAMH is ongoing and it is often helpful to investigators to contact individuals who have participated in previous studies, who have expressed interest in participating in future research.

Please indicate your interest in being contacted for future studies:

I do □ OR do NOT □ wish to be contacted for future studies at CAMH.

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