BIOBEHAVIOURAL PREDICTORS OF TREATMENT OUTCOME IN ADDICTION

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By: Sabrina Kaur Syan, H.BSc., Ph.D.

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AUTHOR: Sabrina Kaur Syan, H.BSc., Ph.D. (McMaster University, Hamilton, Canada)
SUPERVISOR: Dr. James Ma1cKillop, Ph.D.

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ABSTRACT

Substance and alcohol use disorders are highly prevalent and confer a considerable burden of morbidity and mortality including medical, psychosocial, and economic consequences. Although evidence-based treatments to treat substance and alcohol use disorders are present, treatment retention and efficacy within these treatment modalities remains low. Further, individuals with substance and alcohol use disorders are clinically complex and often present with concurrent psychiatric disorders, which makes treatment delivery and response more challenging. Developing novel treatments and improving clinical outcomes in patients with substance and alcohol use disorders is predicated upon basic scientific advances in understanding the biological and behavioural determinants of treatment response. The purpose of this dissertation is to examine the biobehavioural predictors of treatment outcome in substance and alcohol use disorders through three distinct studies that each used pre-treatment variables to predict addictions treatment response. The first study used latent profile analysis to elucidate clinical profiles and independent variables associated with premature treatment termination from clinically complex sample of individuals with concurrent disorders at a large residential addiction treatment centre. The second study systematically synthesized and critically appraised empirical findings of delayed reward discounting, a transdiagnostic behavioural economic indicator of impulsivity, as a predictor of smoking cessation treatment outcome. Finally, the third study used baseline resting state functional connectivity (rsFC) to predict response to a brief intervention to reduce alcohol consumption at three-month follow-up in individuals with alcohol use disorder. The results of this dissertation extend the current literature and highlight the utility of pre-treatment clinical, behavioural, and neuroimaging data in predicting treatment response and elucidating pre-treatment patterns of rsFC that are associated with poor prognosis. The pre-treatment variables identified in this dissertation

can be used to identify high-risk patient populations that may benefit from additional care pathways, adjunctive treatment, or further resources to improve patient outcomes and prognosis.

LAY ABSTRACT

Approximately 1 in 5 Canadians will use alcohol or substances problematically within their lifetime. While there are well-researched treatments for problematic alcohol or substance use, individuals either have considerable difficulty completing treatment, or relapse following treatment. Investigating factors that can help individuals remain in treatment and maintain progress can be challenging since individuals with substance and alcohol use challenges are clinically complex patients who often present with additional mental health disorders. Understanding the pre-treatment factors that contribute to treatment outcome is critical to improving patient outcomes during and following addictions treatment. This dissertation examined the role of pre-treatment clinical patient profiles, impulsivity, and brain functional connectivity in predicting addictions treatment outcome. Clinically, these results will help identify patients at high risk of poor prognosis, who may benefit from additional resources during treatment to improve progress through treatment and treatment outcome.

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LIST OF ALL ABBREVIATIONS AND SYMBOLS

AAL	Automated Anatomical Labelling
ACC	Anterior cingulate cortex
AIC	Akaike Information Criterion
AMS	Addictions medicine service
AUC	Area under the curve
AUD	Alcohol Use Disorder
AUDIT	Alcohol Use Disorders Identification Test
BIC	Bayesian Information Criterion
BOLD	Blood oxygen-level dependent
C/D	Cigarettes per day
CBT	Cognitive Behavioural Therapy
CET	Cue Exposure Treatment
CM	Contingency management
CO	Carbon Monoxide
COVID	Coronavirus disease
CSF	Cerebrospinal fluid
CTRL	Control
DART	Diagnostic Assessment Research Tool for DSM-5
DDM	Delay Discounting Measure
DDQ	Delay Discounting Questionnaire
DMN	Default mode network
DRD	Delayed Reward Discounting
DrInC	Drinker Inventory of Consequences
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
dTMS	Deep repetitive transcranial magnetic stimulation
DUDIT	Drug Use Disorders Identification Test
EDT	Experiential Discounting Task
EFT	Episodic Future Thinking
EOT	End of Treatment
FC	Functional connectivity
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FPN	Frontoparietal Network
FTND	Fagerstrom Test For Nicotine Dependence
FWHM	Full width at half maximum
GAD-7	Generalized Anxiety Disorder-7
GE	General Electric
GM	Gray matter

GROMIT	Global Rating of Motivational Interviewing Therapists
Hz	Hertz
ICD	International Classification of Diagnosis
IFG	Inferior frontal gyrus
L	Left
LEC-5	Life Events Checklist for DSM-5
LMR	Lo-Mendell-Rubin
LPA	Latent profile analysis
M	Mean
MATCH	Matching Alcoholism Treatment to Client Heterogeneity
MCQ	Monetary Choice Questionnaire
MDD	Major Depressive Disorder
MET	Motivational enhancement therapy
mFTQ	Modified Fagerström Tolerance Questionnaire
Mg	Milligram
MI	Motivational interviewing
Mm	Millimetres
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
n	Sample size
NA	Not abstinent
NAc	Nucleus Accumbens
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NR	Not reported
NRT	Nicotine replacement therapy
OFC	Orbital Frontal Cortex
PCL-5	Posttraumatic Stress Disorders Checklist for DSM-5
PFC	Prefrontal Cortex
PHQ-9	Patient Health Questionnaire-9
PICOS	Population, Intervention, Comparison, Outcomes and Study
PP	Postpartum
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	Posttraumatic Stress Disorder
QUIPS	Quality in Prognosis Studies
R	Right
ROIs	Regions of Interest
rsFC	Resting state functional connectivity
SBA	Seed based analysis
SBIRT	Screening, Brief-Intervention and Treatment
SD	Standard deviation

SEM	Standard Error
SPM12	Statistical Parametric Mapping Software 12th Edition
SPSS	Statistical Package for the Social Sciences
SUD	Substance Use Disorder
TLFB	Alcohol Timeline Follow Back Interview
TMS	Transcranial magnetic stimulation
vACC	Ventral anterior cingulate cortex
WHO	World Health Organization
WM	White matter

DECLARATION OF ACADEMIC ACHIEVEMENT

Chapter 2: Data presented in this chapter was collected by staff at Homewood Research Institute (Guelph, ON) and managed under the direction of B. Rush, S. Sousa, and J. Costello. This study was conceptualized by S.K. Syan and J. MacKillop. Data analysis was conducted by S.K. Syan and M. Minhas. Writing of the manuscript was completed by S.K. Syan. Further, J. MacKillop, A. Oshri, A. Samokhalov, B. Rush, and M. Minhas contributed to the composition of the text. This study was partially supported by charitable donations to Homewood Research Institute and by the Peter Boris Chair in Addictions Research.

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CHAPTER 1

1. INTRODUCTION

1.1. Burden of Substance and Alcohol Use Disorders

Substance and alcohol use disorders are highly prevalent with approximately 21% of Canadians meeting criteria within their lifetime (Pearson et al., 2013). They are also estimated to have the highest burden among non-communicable diseases (Degenhardt et al., 2018) and were responsible for 99.2 million and 31.8 million disability adjusted life years (DALY's) globally in 2016 (Degenhardt et al., 2018). In 2017, alcohol and tobacco use specifically accounted for over 66,000 preventable deaths in Canada and 571,030 years of life were lost due to substance abuse (Harms Scientific Working Group, 2020). With regards to economic consequences, substance and alcohol use are anticipated to cost Canadian society 46 billion dollars per year (Harms Scientific Working Group, 2020).

1.2. Comorbid Substance Use and Mental Health Disorders

Substance and alcohol use disorders are highly comorbid with mental health disorders (Grant et al., 2015, 2015). Literature estimates that individuals with substance use disorders are three times more likely to experience a comorbid mental health disorder than those without a substance use disorder (Rush et al., 2008). For example, the National Epidemiological Survey on Alcohol and Related Conditions (NSEARC) found that individuals with a substance use disorder were 1.6 times more likely to experience posttraumatic stress disorder and 1.3 times more likely to experience a major depressive disorder or generalized anxiety disorder (Grant et al., 2015). Those with alcohol use disorder were 1.2 times more likely to meet criteria for posttraumatic stress disorder and 1.3 times more likely to meet criteria for a major depressive disorder or any anxiety disorder (Grant et al., 2015). Furthermore, high rates of concurrent disorders are also present within inpatient addiction treatment settings (Chen et al., 2011). A large study found that

approximately 60% of patients with substance dependence being treated within an inpatient facility also met criteria for one psychiatric comorbidity, with 30% meeting criteria for two psychiatric comorbidities (Chen et al., 2011). Notably, the most common diagnoses were major depressive disorder (25.8%) and posttraumatic stress disorder (14%) (Chen et al., 2011).

With regards to the burden of concurrent substance and mental health disorders, research suggests that individuals who meet criteria for both major depressive disorder and a substance use disorder experience worse patient outcomes including, but not limited to, greater suicide risk, poor treatment response, and high rates of relapse (Davis et al., 2008). Further, the presence of severe depressive symptomology at treatment entry has been found to predict early attrition from intensive outpatient substance use programs (Curran et al., 2002). Comorbid posttraumatic stress disorder and substance use disorder has also been associated with higher rates of suicide attempts, decreased treatment response, poorer psychosocial functioning, and worse treatment adherence (McCauley et al., 2012). Moreover, in individuals with alcohol use disorder, comorbid anxiety disorders are associated with an increased severity of alcohol withdrawal, higher relapse rates following treatment, and an increased lifetime severity of alcohol use disorder (Smith & Book, 2010). High rates of psychiatric comorbidities in individuals with substance and alcohol use disorders and worse prognosis in individuals with concurrent disorders, underscores that patients who present to addictions treatment are clinically complex and multifarious (Curran et al., 2002; Davis et al., 2008; McCauley et al., 2012). This research also highlights that concurrent disorders may have deleterious effects on substance and alcohol use treatment response and outcome (Curran et al., 2002; Davis et al., 2008; McCauley et al., 2012).

1.3. Treatment Retention and Outcomes

Despite high rates of substance and alcohol use disorders and the presence of evidence-based treatments, treatment uptake remains low (Alonso et al., 2004; Blanco et al., 2015; Tarp et al., 2022). A large epidemiological study found that only 13% of individuals with substance use disorders sought treatment following the first year of disorder onset (Blanco et al., 2015). Meanwhile, the percent of individuals that seek treatment for alcohol use disorder is also low, with only 10% of individuals that meet criteria for alcohol use disorder estimated to seek treatment (Alonso et al., 2004). These low rates of treatment seeking rates are largely caused by low problem awareness and may highlight the importance of Screening Brief Intervention, and Referral to Treatment (SBIRT) style public health interventions (Alonso et al., 2004; Hargraves et al., 2017). These interventions can help identify and target problematic substance related behaviours and employ brief interventions or refer to more intensive treatment resources (Hargraves et al., 2017).

Moreover, evidenced-based interventions for the treatment of substance and alcohol use disorders demonstrate limited efficacy and high attrition rates (Brorson et al., 2013; Stark, 1992). For example, less than 35% of individuals with nicotine use disorder achieved successful abstinence of smoking behaviours in the 12 months following formal smoking cessation treatment (Koçak et al., 2015). Retention through inpatient addictions treatment is also poor, with literature estimating that between 17-51% of individuals prematurely withdraw from inpatient addictions treatment (Brorson et al., 2013). Furthermore, 37-60% of individuals that complete inpatient treatment will likely relapse within the 3 months (Andersson et al., 2019; Gossop et al., 2002). Among individuals with alcohol use disorder, between 60-70% of individuals who receive treatment will relapse within three years (Chiappetta et al., 2014). As such, identifying factors that contribute to relapse and predict premature withdrawal from treatment have the potential to

substantially improve patient outcomes and improve treatment efficacy by identifying high-risk patient profiles and suggesting care pathways to reduce attrition.

1.4. Novel Approaches to Study Treatment Outcome

Improving addictions treatment retention and efficacy remains an important aspect of improving patient outcomes as successful treatment completion is critical for patient outcomes (Brorson et al., 2013; Stark, 1992). While studies have investigated the change in clinical, behavioural, and neuroimaging variables through treatment, research investigating the prognostic utility of this data at baseline is limited. However, novel prognostic indicators of successful addictions treatment are needed to improve the science of prognosis in addictions research due to high rates of attrition and relapse (Brorson et al., 2013; Stark, 1992). Moreover, clinical populations with substance and alcohol use disorders are complex and multifarious with common comorbidities and underlying symptomology, which further complicate symptoms associated with acute withdrawal (Wiktorowicz et al., 2019). As such, isolating prognostic indicators of treatment outcome can be challenging. Nonetheless, prediction of treatment response and outcome is a specific facet of prediction science and is a valuable tool to identity high-risk patient populations that may require more intensive treatment or adjunct resources to further support them through treatment (McMahon, 2014; Poldrack et al., 2020).

As stated above, while baseline clinical data may be a useful indicator of treatment prognosis, heterogeneity in clinical presentation and patient complexity make it challenging to determine which specific clinical variables or combinations of variables may be most useful in determining treatment outcome (Saunders et al., 2016). Statistical modelling and analytic techniques such as logistic regressions and latent profile analyses may be useful in determining specific predictors and clinical profiles associated with treatment response (Spurk et al., 2020).

Latent profile analysis is an analytic strategy that attempts to identify latent subpopulations (latent profiles) within a larger population based on responses to a set of continuous variables (Spurk et al., 2020). It is useful in identifying different profiles that exist within larger populations and may be valuable in determining subgroups and profiles within a larger heterogenous dataset, or clinical complex individuals, that may vary in their response to treatment (Spurk et al., 2020). Similarly, traditional statistical modelling such as binary logistic regressions may also be useful in determining individual factors across heterogenous patient populations that are useful prognostic indicators (King, 2008). Latent profile analysis has been used to determine patient profiles related to psychological treatment outcome in patients with depression and anxiety (Saunders et al., 2016), and in delineating subgroups of high-risk individuals that are at greatest likelihood to develop psychosis based on their clinical symptoms (Healey et al., 2018). A current gap in the addiction's literature is the use of statistical modeling such as latent profile analysis to identify groups of patient populations in addition to independent variables that are associated with treatment outcome and prognosis.

The complexity of clinical populations and considerable variations within and across diagnostic profiles in individuals that present with substance and alcohol use disorders make it challenging to rely on the prognostic utility of clinical indicators or diagnosis alone (Cuthbert, 2014). Therefore, identifying biobehavioural predictors of treatment response is important to improve treatment outcome. A Research Domain Criteria (RDoC) style approach favouring research on transdiagnostic behavioural constructs or neuroimaging techniques that investigate neurobiological mechanisms may be helpful in elucidating novel markers of treatment response in individuals with substance and alcohol use disorders (Cuthbert, 2014).

Behavioural constructs that span across clinical presentations may underlie mechanisms of disease causality and inform understanding of prognosis (Amlung et al., 2019). One example of a behavioural variable that has been studied in addictive disorders is delayed reward discounting, a behavioural economic indicator of impulsivity that reflects the precipitous decline of reward value with delay in time (MacKillop et al., 2011; Odum, 2011). An individual with high delay reward discounting values smaller immediate rewards relative to larger delayed rewards (MacKillop et al., 2011; Odum, 2011). Furthermore, the steepness with which the delayed reward declines in value is the index of impulsive decision making (MacKillop et al., 2011; Odum, 2011). Steeper delayed reward discounting has been associated with psychiatric disorders and with addiction and addictive behaviour (Amlung et al., 2019; MacKillop et al., 2011; Owens et al., 2019). Independent studies have also found that steeper delayed reward discounting upon intake is associated with poorer treatment outcomes in individuals with addictions (MacKillop & Kahler, 2009; Stanger et al., 2012) and that delayed reward discounting decreases through addictions treatment (García-Pérez et al., 2020; Landes et al., 2012). Although delayed reward discounting has been investigated as a predictor of treatment outcome in addictions treatment, the utility of delay reward discounting as a prognostic factor of smoking cessation treatment outcome is unclear as studies yield conflicting results (González-Roz et al., 2019; Krishnan-Sarin et al., 2007; Lopez et al., 2015; MacKillop & Kahler, 2009). Investigating delayed reward discounting may be exceptionally helpful context of addictions treatment as it may be useful in identifying those at highest risk of treatment drop out or poor treatment response upon intake.

Additionally, biological variables may also function as objective pre-treatment variables to inform treatment response that are more resilient and unbiased than self-reported clinical measures (Yip et al., 2020). Neuroimaging provides unique methods to investigate prognosis at a granular

neurobiological level and may be useful in elucidating novel treatment targets to inform neuromodulatory techniques (Ho et al., 2018; Luigjes et al., 2012; Pierce & Vassoler, 2013). Resting state functional connectivity (rsFC) is a neuroimaging technique that uses functional magnetic resonance imaging to investigate fluctuations in blood oxygen-level dependent (BOLD) signal to provide an indirect measure of neuronal activity in the absence of task-based engagement (Fox & Raichle, 2007; Raichle, 2015). This technique is useful in examining the pathophysiology associated with disease processes and biological basis of behaviour associated with addiction (Fox & Greicius, 2010; Fox & Raichle, 2007). Aberrant patterns of rsFC have been reported in individuals across a range of addictive disorders (Abdallah et al., 2021; Fedota & Stein, 2015; Zhai et al., 2021). A growing body of literature has focused on rsFC patterns associated with relapse and treatment response within several psychiatric disorders, such as major depressive disorder (Martens et al., 2021) and posttraumatic stress disorder (Zhou et al., 2012). However, the use of rsFC in predicting treatment response is more modest in the addiction's literature.

1.5. Current Dissertation

This current dissertation attempts to address the gaps in literature described above and examine clinical, behavioural, and biological factors that contribute to addictions treatment outcome and retention. This is achieved through the results of three original studies that were conducted across a range of addictive disorders, treatment formats, and analytic techniques. Importantly, this dissertation aims to understand prognostic factors associated with addictions treatment outcome from various vantage points ranging from delineating complex clinical presentation and comorbidity (aerial view) to behavioural constructs that underlie psychological mechanisms associated with addiction, to finally the most granular approach using rsFC. In each study within this dissertation, pre-treatment clinical, behavioural, or biological variables were used

to predict treatment outcome. The results of this dissertation highlight that pre-treatment variables can be used to predict treatment outcome and identify high-risk patients that may benefit for adjunctive treatment or more intensive treatment to improve patient outcomes.

The first study (Chapter 2) aims to investigate clinical factors associated with inpatient treatment outcome in individuals with complex clinical presentations (i.e., multiple comorbidities) and polysubstance use. It addresses the challenges associated with heterogeneity in clinical presentations through use of statistical modelling. This study uses two complementary analysis approaches – a binary logistic regression and latent profile analysis – to examine independent clinical predictors and profiles associated with premature discharge from an inpatient addictions program in individuals with polysubstance use. The results of this study identified several independent predictors upon intake that were associated with treatment outcome and identified four independent profiles associated with treatment outcome. These results suggest that addictions treatment services may benefit from identifying patients at high-risk of treatment termination upon entry to treatment and development of care pathways to provide additional support across high-risk symptom clusters.

The second study (Chapter 3) takes a more in-depth view at investigating prognostic factors associated with treatment outcome by examining impulsivity – a behavioural construct and psychological mechanism that underlies various clinical presentations. This study is a systematic review that investigates the use of delay reward discounting as a predictor of smoking cessation treatment outcome, delivered within an outpatient setting. Fourteen studies were systematically reviewed and assessed for methodological quality. The results of this study support that steeper delay reward discounting (greater impulsivity) is associated with significantly worse smoking cessation treatment outcome and that pre-treatment delay reward discounting may be a useful

treatment target or for identifying high-risk populations that may require additional resources through treatment. This study is particularly important in providing insight into improving smoking cessation treatment outcomes, which currently have a low efficacy of 22-45% (Ucar et al., 2014).

The third study (Chapter 4) approaches investigating prognostic factors at the most granular level of this dissertation and investigated patterns of rsFC associated with response to a brief-intervention aimed at reducing alcohol use at a three month follow up. All individuals in this study met criteria for alcohol use disorder and consumed above the National Institute for Alcohol Abuse and Alcoholism (NIAAA) recommended weekly drinking limits. Study participants were not explicitly treatment seeking in nature, reflecting the majority of individuals with alcohol use disorder, and received feedback on their drinking as part of a brief intervention to increase positive health behaviours. Additionally, seed-to-voxel analytic approach was used to investigate the rsFC of several key regions of the reward network, frontoparietal network, default mode network, and salience network. The results of this study found several pre-intervention patterns of rsFC within the reward network, frontoparietal network, and salience network that were associated with treatment response (as defined as a reduction in alcohol use) at three-month follow-up. They also have the potential to inform future research and novel treatment targets for deep brain stimulation or transcranial magnetic stimulation in individuals with alcohol use disorder.

When taken together, evidence-based treatments for substance and alcohol use disorder are limited in their ability to retain individuals in treatment and their efficacy among individuals that complete treatment (Brorson et al., 2013; Stark, 1992). Identifying pre-treatment prognostic indicators remains challenging due to heterogeneity within clinical presentation and comorbid psychopathology that accompanies substance and alcohol use disorders (Wiktorowicz et al., 2019).

This dissertation aims to address these gaps in the literature through the following aims: 1) investigating the use of statistical modeling to delineate heterogeneity clinical presentation and use clinical and demographic variables at intake to create profiles of premature treatment retention; 2) investigating use of transdiagnostic behavioural economic variables at intake as predictors of treatment outcome; and 3) the use of rsFC at intake to elucidate neurofunctional profiles of intervention response.

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CHAPTER 2

PREDICTORS OF PREMATURE TREATMENT TERMINATION IN A LARGE RESIDENTIAL ADDICTION MEDICINE PROGRAM

Sabrina K. Syan, PhD[a], Meenu Minhas, PhD[a], Assaf Oshri, PhD [b], Jean Costello, PhD [c], Sarah Sousa, MSc[c], Andriy V. Samokhalov, MD, PhD[c], Brian Rush, PhD [c], & James MacKillop, PhD [a,c]

[a]Peter Boris Centre for Addictions Research, McMaster University & St. Joseph's Healthcare Hamilton, Hamilton ON Canada
[b]Department of Human Development and Family Sciences, University of Georgia, Athens, GA, USA
[c]Homewood Research Institute, Guelph, ON, Canada

ABSTRACT

Background: While inpatient programs are a common setting for addiction treatment, patients' premature termination is a major concern. Predicting premature treatment termination has the potential to substantially improve patient outcomes by identifying high-risk profiles and suggesting care paths that might reduce dropout. The current study examined the predictors of premature termination from an inpatient addiction medicine service.

Methods: In 1,082 patients admitted to a large inpatient addiction medicine service, we used intake assessments of severity of alcohol use disorder, illicit drug use disorder, post-traumatic stress disorder (PTSD), anxiety disorders, and major depressive disorder to predict planned termination (n=922) or premature termination (n=160). We used two complementary analytic approaches—traditional binary logistic regression and data-driven latent profile analysis (LPA).

Results: Binary logistic regression revealed that alcohol use severity, illicit drug use severity, and PTSD severity significantly predicted termination status, although alcohol use severity notably exhibited an inverse relationship. The LPA revealed four distinct profiles, with one profile exhibiting a significantly higher rate of premature termination and another exhibiting a significantly lower rate of premature termination. The high-risk profile was characterized by high drug severity, high comorbid psychopathology (PTSD, depression, and anxiety symptoms), but low alcohol severity. The low-risk profile was characterized by high alcohol severity, but low drug use and low comorbid psychopathology.

Conclusions: These results provide converging evidence that illicit drug severity and psychiatric severity, and particularly PTSD, were associated with premature termination. Moreover, the LPA revealed distinct latent subgroups of patients with meaningfully higher and lower risk of premature termination, suggesting that addiction services should develop strategies for identifying high-risk

individuals or develop care paths for high-risk symptom clusters. Approaches that are trauma-informed or otherwise focus on the management of comorbid psychiatric conditions may be particularly appropriate for reducing patients' premature termination.

1. INTRODUCTION

The use of alcohol and other psychoactive substances is highly prevalent and is associated with considerable burden due to death, disability and injury (Grant et al., 2016; Rehm, Taylor, & Room, 2006). Moreover, prolonged and repeated use of any of these substances can lead to substance use disorders (SUDs) that require specialized treatment (McKellar, Kelly, Harris, & Moos, 2006). Alcohol and other substance use are estimated to have the highest burden of disease among noncommunicable diseases (Degenhardt et al., 2018; Rehm et al., 2006); they were responsible for approximately 99.2 million (alcohol) and 31.8 million (drug use) disability adjusted life years (DALYs) globally in 2016 (Degenhardt et al., 2018). Although evidence-based treatments exist for SUDs (Garner, 2009), a sizable proportion of patients is not successful, and understanding factors that predict treatment outcomes for patients is a high priority in clinical research (Hser, Longshore, & Anglin, 2007; Pinaire, Azé, Bringay, & Landais, 2017).

A large body of literature currently exists that focuses on treatment trajectories and predictors of relapse (Bradizza, Stasiewicz, & Paas, 2006; McKay, 1999). For example, research suggests patients who are younger and have a co-occurring mental disorder present an increased risk of relapse (Andersson, Wenaas, & Nordfjærn, 2019). Psychosocial stressors and vulnerability have also been linked to relapse in men with alcohol use disorder (Brown, Vik, Patterson, Grant, & Schuckit, 1995). Key predictors of relapse following inpatient SUD treatment include comorbid anxiety disorders (Schellekens, de Jong, Buitelaar, & Verkes, 2015), inpatient desire to drink (craving) (Gordon et al., 2006), and poor quality of life (Picci et al., 2014). In addition, poor self-efficacy, relationship status, and gender have all been found to influence drug and alcohol use following addiction treatment (Walton, Blow, Bingham, & Chermack, 2003). It is important to note that research has shown completion of SUD treatment to be significantly associated with

decreased rates of relapse and future readmission (Andersson et al., 2019). Similarly, research has identified simply the amount of time spent in treatment as a strong predictor of post-treatment patient outcomes (McLellan, Luborsky, Woody, O'brien, & Druley, 1983).

In addition to helping us to understand post-treatment relapse, research should examine successful treatment completion as a critical indicator of patient outcomes. Treatment completion can be a critical first step in the process of recovery (Brorson, Ajo Arnevik, Rand-Hendriksen, & Duckert, 2013; Stark, 1992). Studies estimate that approximately 17–57% of individuals drop out from inpatient addictions treatment, while more general estimates suggest that dropout rates may be as high as 50% within the first month of treatment (Brorson et al., 2013; Stark, 1992). The reason for this large range of outcomes may be due to the heterogeneity of inpatient treatment settings and the variability within treatment approaches, client motivation, and use of treatment modalities administered (e.g., psychotherapy, pharmacotherapy) (Brorson et al., 2013). High rates of attrition are problematic for several reasons; they prevent administration of a full dose of treatment and can instill and influence treatment-related biases (i.e., expectations of symptom improvement, expectations of healthcare providers) (Brorson et al., 2013; Stark, 1992).

As a result, an emerging body of literature has focused on factors that predict early drop-out from addictions treatment. For example, in a moderately sized sample (n=122), Lopez-Goni et al. (2012) examined clusters of characteristics associated with dropout from outpatient SUD treatment. Their results suggested that individuals who were unemployed and had higher alcohol consumption were more likely to prematurely withdraw from treatment. Interestingly, they also found that this group of patients had more dependent, phobic, and schizotypal personality features than other groups of patients (López-Goñi, Fernández-Montalvo, & Arteaga, 2012). Further, another study that examined outpatient treatment found higher retention (i.e., lower premature

drop out) in individuals who were male, Caucasian, and had a high employment composite scores (as measured by length of their longest full time job, minimum monthly income, and employment prospects at the time of the study) (McCaul, Svikis, & Moore, 2001). A larger study (n=3649) that aimed to identify predictors of attrition found that younger age, greater incidence of cognitive dysfunction, more drug use, and lower alcohol use increased the probability of premature treatment termination (McKellar et al., 2006). These results were echoed by a large systematic review that investigated risk factors for drop-out from addictions treatment. It highlighted lower education, younger age, cognitive deficits, low treatment alliance, and a comorbid personality disorder as the most consistently observed risk factors across the studies reviewed (Brorson et al., 2013). Importantly, research has also identified factors that contribute to social stability (marital status, employment, and fewer prior arrests) as significant predictors of patient retention beyond 60 days of treatment (Simpson & Joe, 1993). Research has also identified depressive symptoms upon admission to inpatient addictions programs as a significant risk factor for early attrition (Curran, Kirchner, Worley, Rookey, & Booth, 2002).

With respect to program-related factors, literature suggests that higher staff ratios, greater per capita expenditure, and smaller, decentralized clinics have lower rates of attrition (Stark, 1992). Research has also found rapid assessment upon admission and individual attention coupled with small groups to contribute to lower attrition rates (Stark, 1992). A study investigating premature termination of inpatient addictions treatment in the UK (n=187) found that patients with a weaker counselor-rated alliance dropped out of treatment significantly sooner than those with higher patient-counselor ratings (Meier, Donmall, McElduff, Barrowclough, & Heller, 2006).

The extant literature has a number of limitations. In their systematic review of risk factors for early drop-out from addictions treatment, Brorson et al. (2013) noted that 91% of the literature

was exclusively focused on demographic factors (i.e., age, sex, race). These factors are necessarily very coarse, not conducive to purposeful change, and likely to tell only a small fragment of a much larger story. Further, the majority of studies have relatively small sample sizes, meaning that they have relatively low statistical power. Possibly related to this, few studies have gone beyond traditional linear models in predicting premature termination. While traditional statistical methods are useful in identifying single predictors, they do not allow for the examination of symptom clusters or latent subgroups that are differentially related to program attrition.

The current study aimed to address a number of these limitations. Specifically, the study sought to identify correlates of premature termination from an inpatient addiction medicine service (AMS), using a large sample of more than a thousand patients. Beyond demographic characteristics, the study assessed common comorbid psychopathology (depression, anxiety, and posttraumatic stress disorder [PTSD]) and severity of SUD in predicting premature termination. We used two main analytical strategies—logistic regression and latent profile analysis (LPA)—to predict premature termination. These two strategies are complementary insofar as one is a traditional linear variable-centred approach (e.g., logistic regression) and the other is a person-centred approach that seeks to determine whether latent subgroups of patients are present (e.g., LPA). The former examines the linear relationships between predictors and outcomes, whereas the latter delineates unobserved configurations of correlations among key variables to ascertain underlying clusters of individuals, and then examines those clusters in relation to the outcome. As a heuristic, a variable-centred analysis can be thought of as a mean-level grouping strategy or "one-size-fits-all" approach, whereas a person-centred approach can be thought of as a pattern-based analyses or "which-configuration-fits-best" approach.

2. METHODS

2.1 Participants

Participants were 1,082 individuals admitted to a 105-bed inpatient addiction medicine service located in a larger mental health and addictions treatment centre in southwestern Ontario, Canada. The program offered group-based treatment that was 35 days in length to adults aged 19+ with alcohol and/or substance use disorders and specialized programming (56 days in length) for patients with concurrent PTSD. Overall, the AMS admits ~1,000 patients each year and uses an abstinence-based approach to recovery, which is informed by 12-step facilitation therapy. Treatment is provided by a multidisciplinary team comprising physicians with certifications in addictions medicine and registered addictions counselors. Programming is paid for through public (e.g., Ontario Health Insurance Program) or semiprivate/private insurance, and direct payment.

Among the sample, 922 patients (age = 44.12 (11.34) years old, 66% male) completed the program as planned and 160 patients (44.57 (11.25) years old, 61% male) discharged early from the program (i.e., premature discharge; discharged home unplanned or signed out against medical advice). Participant characteristics can be found in Table 1.

2.2. Procedures

Patients completed an intake assessment battery to obtain information regarding symptomatology associated with mood, anxiety, and substance use. Patients completed the paper-based assessment battery as part of the standard clinical practice within the first seven days of admission and served a primary goal of informing patient care. Assessments were self-report and participants completed them between October 19, 2015, and April 18, 2017. We later transcribed data for research purposes. We obtained discharge status via program administrative data, which indicated whether the patient was discharged as planned (i.e., standard completion) or unplanned

(i.e., premature termination). We requested both clinical and administrative data for analysis via an approved research protocol from the Regional Centre for Excellence in Ethics, Research Ethics Board in Guelph, Ontario, Canada.

2.3 Intake assessment measures

We assessed symptoms of major depressive disorder (MDD) using the Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams, 2001), which is a brief, self-report, nine-question measure. Each question is scored from 0 (not at all) to 3 (nearly every day), yielding a maximum score of 27, with the following clinical ranges: 5 = mild; 10 = moderate; 15 = moderately severe; 20 = severe depression. We assessed symptoms of anxiety disorders using the Generalized Anxiety Disorder-7 (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006), which is a brief, self-report, 7-item measure. Each item is rated from 0 (not at all) to 3 (nearly every day) and a composite score out of 21 is generated, with scores of 5, 10, and 15 reflecting mild, moderate, and severe anxiety, respectively. We assessed symptoms of PTSD using the Posttraumatic Stress Disorders Checklist for DSM-5 (PCL-5; Blevins, Weathers, Davis, Witte, & Domino, 2015), which is a brief, self-report, 20-item measure. All patients also completed the Life Events Checklist for DSM-5 (LEC-5; Weathers et al., 2013) to characterize traumatic exposures descriptively. Very high rates of traumatic exposure were present and only 5% reported no exposure to any events on the LEC-5. Consistent with this, the mean score on the PCL-5 (Table 1) exceeded the recommended cut-off of 33. We assessed self-report alcohol use disorder using the alcohol items from the Psychoactive Substance Use Module from the International Classification for Diagnosis (ICD)–10 Symptom Checklist for Mental Disorders (Janca, Ustun, van Drimmelen, Dittmann, & Isaac, 1994), with augmentation for non-ICD symptoms in the Diagnostic and Statistical Manual, 5th Edition (American Psychiatric Association, 2013). This measure consists of 11, yes/no

questions to determine the presence of symptomology that is consistent with alcohol use disorder. We assessed other psychoactive drug severity using the Drug Use Disorders Identification Test (DUDIT), which is an 11-item measure of drug use frequency and severity (Hildebrand, 2015).

2.4 Data analysis

We conducted prospective chart analysis of 1,143 individuals, of whom we identified 1,082 as having completed the assessment battery (95%) and included in the final sample. We used independent sample t-tests to compare continuous variables across patients in the premature discharge and planned completion groups. We compared categorical variables using the Pearson Chi-squared tests. We completed bivariate correlations among all measures to examine zero-order associations and test for potential multicollinearity. First, for the traditional linear analysis, we included demographic and clinical variables that demonstrated statistically significant differences between the two groups via bivariate analyses as covariates and clinical predictors (respectively) in a logistic regression model. We excluded statistically nonsignificant variables to create a final, more parsimonious, model. Second, we completed an LPA to investigate the association between demographic and clinical variables and program completion status, as well as to identify subgroups that may be differentially related to premature discharge. We used the following variables to classify patients: (1) depressive symptomatology; (2) anxious symptomatology; (3) trauma-related symptomatology; (4) severity of alcohol use; and (5) severity of drug use. We used an LPA over a latent class analysis because the variables of interest were continuous, rather than categorical. Furthermore, although cut-off scores are available for the measures, using dichotomized variables would artificially truncate variability and the associated conditions are dimensional in nature (e.g., Keyes, Krueger, Grant, & Hasin, 2011). We used the following indices to examine goodness of fit: Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample size

adjusted BIC, Lo-Mendell-Rubin test (LMR), and entropy. In this approach, a smaller AIC and BIC represent a parsimonious solution and thereby a better model fit. We used the LMR to compare whether a *k* profile solution results in a better fit compared to a model with k-1 profiles. Finally, entropy represents the model's overall classification quality with values closer to 1, suggesting less entropy and thus better model classification. We examined profile assignment probability of the optimal class solution to investigate precision of group classification. We completed data analyses using SPSS v.24, Mplus v.7.0, and R v. 3.4.4 Statistical Software.

3. RESULTS

3.1. Bivariate analyses

Among demographic variables assessed, we found age, marital status, employment prospects, and program upon discharge to be significantly different between groups (Table 1). We found no significant differences in sex between groups ($p>0.05$). We found significant differences between groups for all investigated clinical variables, including alcohol use severity, drug use severity, depressive symptomatology (PHQ-9), anxious symptomatology (GAD-7), and trauma-related symptomatology (PCL-5) ($p<0.001$). A bivariate correlation matrix (Figure 1) highlighted strong positive associations between the GAD-7 and PHQ-9 ($r=0.82$, $p<0.05$), and PCL-5 and both the PHQ-9 ($r=0.67$, $p<0.05$) and GAD-7 ($r=0.68$, $p<0.05$). Interestingly, alcohol use severity was negatively correlated with drug use severity ($r=-0.41$, $p<0.05$). Associations among other variables differentiating program completion status varied from negligible to moderate magnitude.

3.2 Logistic regression analysis

We entered clinical and demographic variables that differed significantly between groups (as demonstrated in the bivariate analyses) into a single logistical regression model. Alcohol use severity (ß= –0.069, p=0.004), drug use severity (ß= 0.011 p=0.062), trauma symptomatology (ß=

0.015, p<0.001), and employment prospects (ß= –0.875, p<0.001) all emerged as significant predictors of group termination status. These variables predicted 85.06% of group status correctly (Cox and Snell R^2= 0.059, Nagelkerke R^2=0.105) (Table 5).

3.3. Latent profile analysis

While we evaluated five latent profiles, we deemed a four-profile solution to be the optimal profile solution based on the following indicators: (1) superior AIC and BIC relative to two, three, and five profile solutions; (2) the highest entropy value of all five solutions; and (3) Lo-Mendell-Rubin tests demonstrating superior model fit compared to the two- and three-profile solution. In other words, the four-profile solution was superior to the two- and three-profile solutions on multiple measures, and better than the five-profile solution, as well as best overall in terms of entropy. Furthermore, four distinct and theoretically interpretable profiles emerged, further supporting the interpretation (Figure 2).

The average latent profile probabilities for most likely profile membership is shown in Table 3. Probabilities were approaching 1.0; therefore, we considered them to be very high. We characterized Profile 1 (27.7%) by comparably higher levels of alcohol use, the lowest levels of drug use, and the lowest levels of psychopathology (depressive, anxious, and trauma-related symptomatology) among profiles. As a result, we designated Profile 1 as High Alcohol/Low Psychiatric Severity and exhibited the highest program completion rate, encompassing 92.8% of individuals with planned discharge, and 7.2% premature termination. We characterized Profile 2 (27.6%) by the lowest levels of alcohol use, high levels of drug use, and highest levels of psychopathology. Consequently, we designated this profile as High Drug Use/High Psychiatric Severity. Individuals in this profile exhibited the highest rates of premature termination (23.1%), and lowest levels of planned discharge (76.9%) among profiles examined. We characterized

Profile 3 (28.6%) by the highest levels of alcohol use, lowest levels of drug use, and comparably high levels of psychopathology. Therefore, we designated this profile as High Alcohol/High Psychiatric Severity; accounting for 14% of patients who prematurely terminated treatment and 86% in the planned discharge group. Finally, Profile 4 (16.1%) demonstrated the lowest levels of alcohol use among all patients, comparably high levels of drug use, and low levels of psychopathology. We designated this class as High Drug Use/Low Psychiatric Severity. Approximately 15% of patients in this profile prematurely terminated treatment, whereas 85% had a planned discharge.

Finally, results of χ^2 tests revealed that the four distinct profiles had significant differences overall in terms of discharge rates (Table 4). Specifically, Profile 1 and Profile 2 were significantly different from the other profiles (Table 4), with a significantly lower rate of discharge for Profile 1 and a significantly higher rate of discharge for Profile 2.

4. DISCUSSION

The current study examined the predictors and profiles of premature (unplanned) discharge from an inpatient SUD treatment service, using two parallel analytic methods—a traditional binary logistic regression and data-driven latent profile analysis. A binary logistic regression highlighted that alcohol use severity, drug use severity, trauma symptomatology, and employment status all emerged as significant predictors of program completion status, predicting 85.06% of discharge/termination status. A parallel data-driven approach conducted to investigate further associations between demographic and clinical variables and program completion status found four distinct profiles of patients with differing levels of alcohol and drug use and psychopathology. Of these profiles, the best predictor of premature discharge was a profile of patients that endorsed high drug use, high psychopathology, and low alcohol use (High Drug Use/High Psychiatric

Severity)—this group encompassed 23.1% of individuals who met criteria for premature discharge. Alternatively, the profile of patients endorsed the highest planned discharge and lowest premature termination experienced high alcohol use, low drug use, and low psychopathology (High Alcohol Use/Low Psychiatric Severity). To our knowledge, there are no other studies that have used latent profile analysis to investigate the predictors of premature termination among patients seeking inpatient addictions treatment.

Our results highlighted four distinct subgroups characterized by differences in symptom severity of psychopathology and drug and alcohol use. The High Drug Use/High Psychiatric Severity profile was associated with the greatest premature termination of treatment. We hypothesize that this may occur for several reasons. First, the cognitive dysfunction and neurological consequences associated with more severe drug use may make treatment engagement more challenging and decrease patient motivation. Furthermore, patients with high levels of psychopathology may experience greater levels of negative emotionality (Hodgins, el-Guebaly, & Armstrong, 1995) and higher anxiety sensitivity (Lejuez et al., 2008), both of which have been identified as predictors of substance use relapse and may influence treatment completion. As a result, this profile may also warrant additional treatment resources that go beyond those that have historically been allocated for the treatment of AUD, specifically. Interestingly, individuals who endorsed high alcohol use and low drug use and psychopathology (High Alcohol Use/Low Psychiatric Severity) experienced the highest rate of planned termination (lowest premature termination). This suggests that individuals who solely endorsed high alcohol consumption and low consumption of other substances demonstrated the most favorable treatment outcome out of the four profiles of patients studied. Therefore, highlighting that AUD, without co-existing SUDs or other psychopathology, may be well suited toward this particular inpatient addiction treatment

program/model; or AUD may present as a less complex disorder for which to provide treatment, compared to the treatment of other SUDs. This is consistent with the literature, which suggests that individuals with co-occurring severe mental illness and SUD will have adversely affected treatment outcomes and treatment course due to the additional psychological burden that their mental illness poses (Drake, Mueser, & Brunette, 2007). In addition to this, the addictions program may not have adapted itself to support the increased complexity of clients over time. This highlights a need for ongoing program adaptation to meet the needs of clients with multiple and complex substance use challenges.

Studies using traditional statistical methods (i.e., binary logistic regression, general linear models) to investigate predictors of premature program discharge or treatment retention find similar results to those discussed in our study. Studies using binary logistic regressions have identified "labor problems" and unemployment as a predictor of treatment drop out; both of which can be conceptualized under the broader domain of psychosocial stability, which has been found to positively contribute to treatment completion (Laudet, 2012; Simpson & Joe, 1993). Individuals who are employed may be less likely to suffer from homelessness and have increased motivation to complete treatment (because of their motivation to remain employed) (Laudet, 2012). In the context of this study, employment and employment insurance may have enabled many individuals to have the cost of their treatment covered in this facility. Therefore, our results confirm an important link between employment status and treatment completion, which may also highlight the predictive value of factors that contribute to psychosocial stability.

Our results also highlighted the role of trauma, and drug and alcohol use severity as independent predictors of premature program discharge. Several studies have highlighted the role of substance use as a maladaptive coping strategy to reduce symptoms associated with trauma and

PTSD (Chilcoat & Breslau, 1998; Leeies, Pagura, Sareen, & Bolton, 2010; Rubin et al., 2014; Ullman, Relyea, Peter-Hagene, & Vasquez, 2013). Trauma has also been associated with an increased burden of disease that may warrant additional resources beyond those that drug and alcohol use treatment facilities offer (Rosenberg, 2011). Moreover, PTSD symptomatology may be related to other known predictors of treatment dropout, including cognitive dysfunction (Brandes et al., 2002; Vasterling, Constans, Brailey, & Sutker, 1998) and greater difficulty establishing trusting patient-counselor alliances (Dalenberg, 2004). High drug use and lower levels of alcohol use also emerged as independent predictors of treatment termination. Drug use severity has been associated with higher rates of psychopathology and increased neurological sequelae, both of which may pose challenges relate to treatment engagement (Enevoldson, 2004; Friedman, Utada, Glickman, & Morrissey, 1987). Further, withdrawal from illicit substances often results in significant psychological and physical symptoms, which can create further challenges for SUD treatment (Daughters et al., 2005).

4.1 Strengths and Limitations

The current study should be considered in the context of its strengths and limitations. Among its strengths are its large sample size; inclusion of predictors beyond demographic risk factors; and that it is the first study to use LPA to identify unobserved patient subgroups associated with premature discharge from an inpatient SUD treatment program. Specifically, using LPA allowed for the characterization of profiles of patients that appear to differentially complete or not complete treatment. Such patterns are useful for highlighting groups of patients who may be more vulnerable for premature discharge and may require additional resources and support to complete treatment. Further, to our knowledge, this is the largest study to date to examine premature discharge in this patient population. This large sample size allowed for the use of novel statistical

methods, such as the LPA, in addition to traditional statistical approaches, such as logistic regression. The parallel analytic strategies allowed us to elucidate different profiles of individuals that leave treatment early; binary logistic regression allowed for the identification of independent predictors that contribute to premature discharge/termination, thereby providing a complementary comprehensive analysis of factors and group-based characteristics/profiles that contribute to premature discharge or termination.

In the current study patients completed a relatively limited number of assessments; individuals completed one assessment within the first week of admission to the program. Further, this assessment consisted of self-reported measures that allowed clinicians to obtain data from patients quickly and efficiently, but they did not complete objective diagnostic interviews or specific behavioral tasks. This approach may be affected by a patient's experiential state or introspective ability during the first 7 days of treatment, which may be a particularly difficult period. Relatedly, the self-report measures cannot disambiguate overlap in symptoms, such as negative affectivity attributable to depressive symptoms versus PTSD symptoms or sleep disturbance resulting from withdrawal versus nightmares. Another factor that may have influenced the results of the self-reported assessments include social desirability, which we did not assess. Our assessment also did not account for the presence of notable personality features or the presence of personality disorders, which are highly prevalent in individuals with SUDs (Casadio et al., 2014; Rounsaville et al., 1998) and associated with treatment drop-out (López-Goñi et al., 2012; Samuel, Lapaglia, MacCarelli, Moore, & Ball, 2011). Also, the term *premature termination* encompasses substantial clinical heterogeneity, including both patients who may have chosen to leave against medical advice and patients who the program staff discharged for reasons such as violating the treatment's substance use policies (e.g., bringing drugs on the unit) or exhibiting aggressive or

disruptive behavior. Others no doubt leave treatment for very personal reasons, such as work or childcare responsibilities, or the program simply does not "fit" their perceived needs. Thus, heterogeneity within the definition of premature termination itself creates ambiguity and made the dependent variable necessarily imprecise. Finally, this study was conducted in a semiprivate hospital and thus may reflect a subset of the population that has the means to cover the cost of treatment or was able to have the cost of treatment covered through their employer or provincial healthcare funds.

A final limitation of our study is the generalizability of our findings to other clinical settings. In this case, the SUD treatment was built upon a 12-step facilitation approach—the traditional "Minnesota Model"—and has a principal focus on abstinence. This is similar to many other treatment settings, but by no means all. For example, a growing body of literature has highlighted the benefits of harm reduction approaches (Tatarsky, 2003) and transdiagnostic approaches for treatment of concurrent disorders (Vujanovic et al., 2017). Furthermore, as this model of treatment is variably suited toward different patients, the heterogeneity in discharge and treatment outcomes may reflect the efficacy of this type of treatment among different patient profiles. In other words, premature treatment termination is not a monolithic construct, but reflects the interaction of the treatment program and patient characteristics. Predictors of premature termination may differ for treatment programs with different orientations. Moreover, the fit between patient perspectives and program orientation is a critical feature worth examining as a predictor in future studies.

5. CONCLUSIONS

Our results indicate that high illicit drug severity and high comorbid psychopathology are associated with the least favorable treatment outcomes (highest rate of premature termination). As

such, our results highlight the need for SUD treatment programs to call on greater resources and implement greater management of comorbid psychopathology. Notably, two of the four profiles identified had high psychopathology, emphasizing the high rates of concurrent disorders in this population. This further underscores the need for resourcing treatment paths that focus on management of concurrent disorders and high levels of comorbidity. In this capacity, mindfulness-based relapse prevention may be useful to provide additional support and resources for individuals with concurrent disorders. Research shows that this therapeutic approach is efficacious in reducing addictive behaviors and symptoms of craving and may be a useful care path for individuals with concurrent disorders (Witkiewitz & Bowen, 2010; Witkiewitz, Bowen, Douglas, & Hsu, 2013; Witkiewitz, Marlatt, & Walker, 2005). Within comorbid psychopathology, trauma severity was significantly implicated, underscoring the need for a trauma-informed approach in addiction treatment. Employment status emerged as a strong predictor of premature treatment termination; this association is well-established in the literature on treatment completion and highlights the importance of addressing factors pertaining to psychosocial stability. In sum, our results implicate a number of significant predictors of premature termination that may inform treatment targets to optimize the likelihood of successful recovery.

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Table 1: Treatment success rate and participant characteristics across planned vs. prematurely discharged patients. Values reflect mean (standard deviation), mode, or percentage response, and contrasts reflect t-tests or χ^2 tests.

	All Patients (*N*=1082)	**Planned Termination (n=922)**	**Premature Termination (n=160)**	***p***
Age	44.12 (11.34)	44.57 (11.26)	41.52 (11.50)	0.001
Gender	65% male	66% male	61% male	0.29
Marital Status	33% Never Married	33% Never Married	42% Never Married	0.03
Education	56% University/College	57% University/College	50% University/College	0.09
Employment Prospects	67% Employed/Seeking	79% Employed/Seeking	57% Employed/Seeking	<0.001
Length of Stay		39.10 (8.77)	23.62 (13.67)	<0.001
Alcohol Use Severity (ICD-9)	6.85 (3.92)	7.04	5.75	<0.001
Drug Use Severity (DUDIT)	16.83 (16.78)	15.8	22.76	<0.001
Depression Severity (PHQ-9)	14.03 (7.41)	13.65	16.19	<0.001
Anxiety Severity (GAD-7)	11.38 (6.30)	11.03	13.36	<0.001
Trauma Severity (PCL-5)	36.26 (22.70)	34.85	44.39	<0.001

Notes: ICD-9: International Classification of Diseases, 9th Edition; DUDIT: Drug Use Disorders Identification Test; PHQ-9: Patient Health Questionnaire-9; GAD-7; Generalized Anxiety Disorder 7 Item Scale; PCL-5; Posttraumatic Stress Disorder Checklist (DSM-V).

Table 2: Model fit statistics across latent class solutions.

Number of Latent Profiles	1	2	3	4	5
AIC	15372.91	13686.31	13280.99	12529.32	12331.09
BIC	15422.78	13766.09	13390.70	12668.95	12500.64
BIC (Sample Size Adjusted)	15391.01	13715.27	13320.82	12580.01	12392.6
Entropy	N/A	0.87	0.82	0.92	0.89
Lo-Mendell-Rubin Value	N/A	1659.02	407.59	745.87	205.33
Lo-Mendell-Rubin P-Value	N/A	<.001	<.001	<.001	<.001

Table 3: Average latent profile posterior probabilities for most likely latent class membership N (Row) by latent class C (column).

	C=1	**C=2**	**C=3**	**C=4**
N=1	0.956	0	0.038	0.007
N=2	0	0.963	0.008	0.029
N=3	0.036	0.008	0.953	0.002
N=4	0.011	0.043	0.001	0.945

Table 4: Latent profile analysis class comparisions based on rates of premature termination.

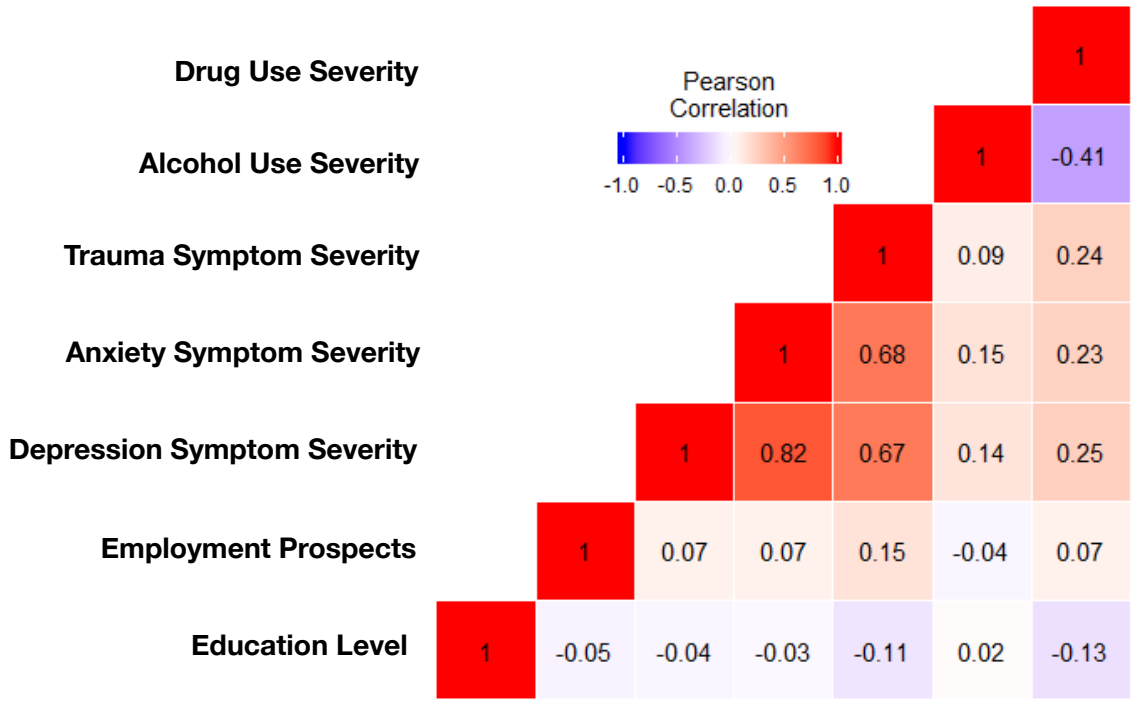
	χ^2	DF	*p*
Omnibus Test	31.124	3	<.001
Class 1 vs. 2	29.107	1	<.001
Class 1 vs. 3	6.683	1	0.01
Class 1 vs. 4	5.8	1	0.016
Class 2 vs. 3	7.701	1	0.006
Class 2 vs. 4	4.352	1	0.037
Class 3 vs. 4	0.082	1	0.775

Table 5: Clinical predictors of premature discharge using a binary logistic regression.

	B	SE	Odds Ratio	Wald χ^2	P-Value
Constant	-1.530	0.298	0.216	26.386	0.000
Employment Prospects	-0.875	0.186	0.417	22.135	0.000
Alcohol Severity (ICD-9)	-0.069	0.024	0.934	8.192	0.004
Illicit Drug Severity (DUDIT)	0.011	0.006	1.011	3.492	0.062
PTSD Severity (PCL-5)	0.015	0.004	1.015	12.809	0.000

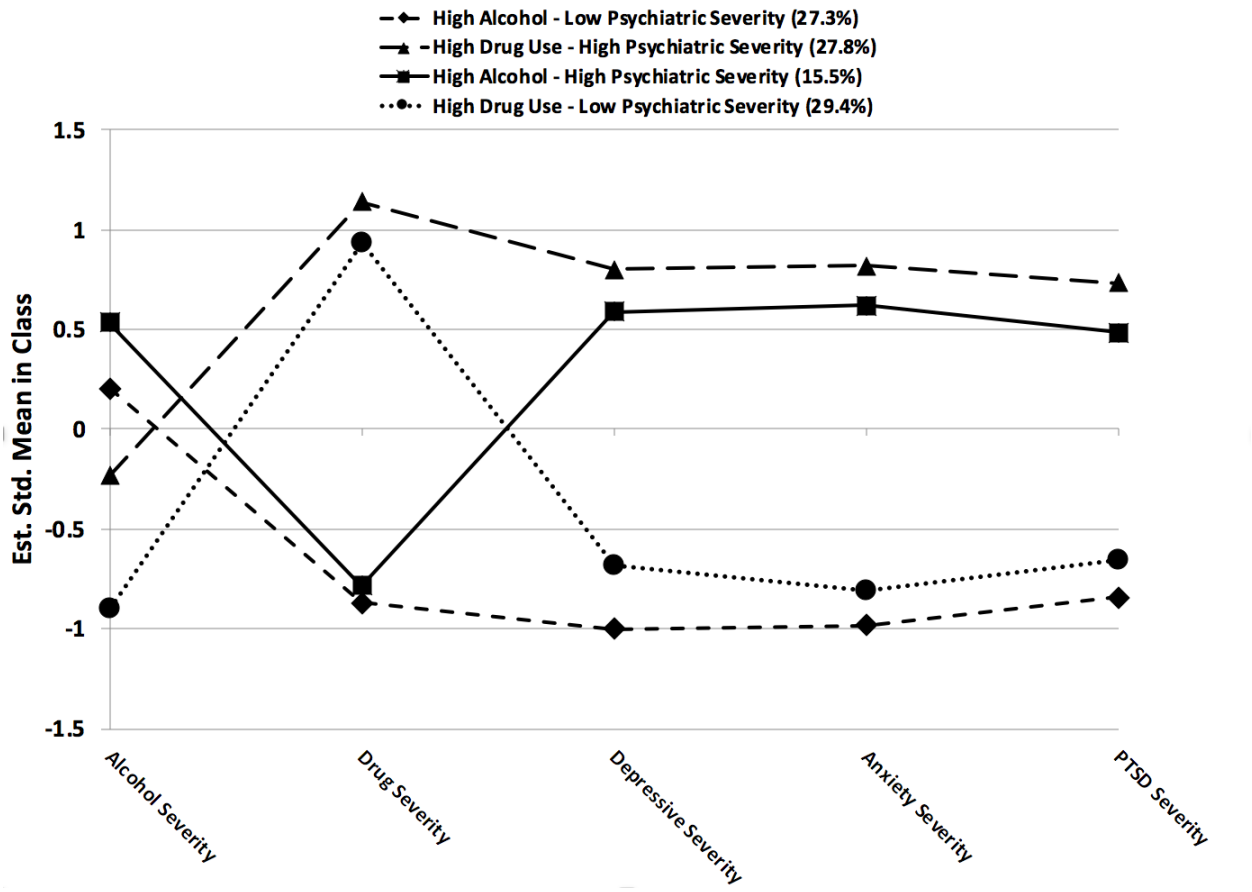
Notes: ICD-9: International Classification of Diseases, 9th Edition; DUDIT: Drug Use Disorders Identification Test; PCL-5; Posttraumatic Stress Disorder Checklist (DSM-V).

Figure 1: Heatmap of associations (zero order correlations) among the measures used. [*r*s >|.09], *p*<.05].



Notes: Drug Use Severity was measured by the Drug Use Disorders Identification Test; Alcohol Use Severity was measured by the: International Classification of Diseases, 9th Edition; Trauma Symptom Severity was assessed with the Posttraumatic Stress Disorder Checklist for DSM-5; Anxiety Symptom Severity was assessed with the Generalized Anxiety Disorder 7 Item Scale; Depression Symptom Severity was assessed with the Patient Health Questionnaire-9.

Figure 2: Estimated standardized means of latent class indicators for the four-class solution.



CHAPTER 3

DELAYED REWARD DISCOUNTING AS A PROGNOSTIC FACTOR FOR SMOKING CESSATION TREATMENT OUTCOME: A SYSTEMATIC REVIEW

Sabrina K. Syan, PhD[1]; Alba Gonzalez-Roz, PhD[2]; Michael Amlung, PhD[1,3],
Lawrence H. Sweet, Ph.D.[4], & James MacKillop, PhD[1]

1. Peter Boris Centre for Addictions Research, McMaster University & St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada
2. University of the Balearic Islands, Majorca, Spain
3. Cofrin Logan Center for Addiction Research and Treatment, University of Kansas, Lawrence, Kansas, USA
4. University of Georgia, Athens, GA, USA

ABSTRACT

Background: While large proportions of smokers attempt to quit, rates of relapse remain high and identification of valid prognostic markers is of high priority. Delayed reward discounting (DRD) is a behavioural economic index of impulsivity that has been associated with smoking cessation, albeit inconsistently. This systematic review sought to synthesize the empirical findings on DRD as a predictor of smoking cessation treatment outcome, to critically appraise the quality of the literature, and to propose directions for future research.

Methods: A total of 734 articles were identified, yielding $k = 14$ studies that met the eligibility criteria. The Quality in Prognosis Studies (QUIPS) tool was used to assess methodological quality of the included studies.

Results: Individual study methods were highly heterogeneous, including substantial variation in research design, DRD task, clinical subpopulation, and treatment format. The predominant finding was that steeper DRD (higher impulsivity) was associated with significantly worse smoking cessation outcomes (10/14 studies). Negative results tended to be in pregnant and adolescent subpopulations. The QUIPS results suggested low risk of bias across studies; 11/14 studies were rated as low risk of bias for 5/6 QUIPS domains.

Conclusions: This review revealed consistent low-bias evidence for impulsive DRD as a negative prognostic predictor smoking cessation treatment outcome in adults. However, methodological heterogeneity was high, precluding meta-analysis and formal tests of small study bias. The prospects of targeting impulsive DRD as a potentially modifiable risk factor or providing targeted treatment for smokers exhibiting high levels of discounting are discussed.

IMPLICATIONS

These findings indicate consistent evidence for DRD as a prognostic factor for smoking cessation outcome in adults. As such, DRD may be a useful as a novel treatment target or for identifying high-risk populations requiring more intensive treatment.

1. INTRODUCTION

Cigarette smoking has been identified as a leading cause of preventable death worldwide[1,2]. The World Health Organization estimates that over 1.3 billion individuals smoked in 2020, putting a significant portion of the world's population at increased risk of premature morbidity and mortality[3]. Estimates suggest that more than 55% of smokers will make at least one attempt to quit smoking annually[1], however, only 3-5% of individuals who make a quit attempt without formal treatment achieve long-term abstinence[4,5]. Indeed, following intensive formal treatment consisting of psychotherapeutic and pharmacological interventions, less than 35% of individuals achieve successful abstinence at 12 months[6,7].

Studying factors that contribute to relapse may help identify targets to aid in treatment and recovery, ultimately increasing the likelihood of long-term abstinence[8]. Novel prognostic factors can be found in constellations of behaviours etiologically associated with addiction (e.g., executive function, impulsivity)[8]. One of these is delayed reward discounting (DRD), a behavioural economic index of impulsive behaviour[9] that reflects how much a person values smaller immediate rewards relative to larger delayed rewards. The steepness with which the delayed reward loses value is the index of impulsive decision-making[10] and it has been investigated in a variety of addictive behaviours[10–12]. More recently, DRD has been hypothesized to be a transdiagnostic process in an array of other psychiatric disorders and health behaviours[12–14]. Specific to smoking behaviours, one previous review investigating the relationship between temporal discounting across the life course found that smokers with lower time-discount rates achieved higher quit rates, highlighting the clinical utility of DRD [15].

In addiction clinical settings, more precipitous DRD has been found to predict short-term relapse in polysubstance-dependent individuals attending inpatient detoxification programs[16],

treatment response among individuals receiving outpatient treatment for cocaine use disorder[17], and response during early treatment for individuals with methamphetamine use disorder[18]. Similarly, DRD was also predictive of shorter treatment retention and associated with higher odds of premature treatment termination[19]. Identification and further study of factors which predict clinical outcome following addictions treatment may aid in providing greater support and intervention to patients who require specialized attention to achieve and maintain abstinence or clinically meaningful reductions in tobacco use.

The literature examining DRD as a predictor of smoking cessation treatment outcomes has grown considerably over the past several years, albeit with inconsistent findings, both implicating DRD as a significant predictor in some cases and not in others. Studies that have been published focus on a wide array of treatments such as contingency management (CM), cognitive behavioural therapy (CBT), social and cognitive psychotherapeutic approaches and standard smoking cessation counseling[20,21]. Further, heterogeneity in published literature also arises from the use of adjunctive pharmacological therapy to support nicotine withdrawal, such as nicotine replacement therapy (NRT) and varenicline[6,23]. Amongst the studies currently published, another layer of heterogeneity is brought upon by the delivery of the therapy (i.e. internet based or in person)[24], the subpopulations studied (e.g., women during the perinatal period, adolescents, adults)[25,26], and the measure of DRD that is used to assess impulsive behaviour. Studies also range in their use of paper-based or computerized DRD tasks and differing time intervals that investigators assess post-treatment outcomes. Conducting a systematic review of the breadth of research findings across smoking cessation treatment studies is warranted to characterize the overall evidence on whether DRD is a successful prognostic factor. Therefore, this study aims to (i) systematically review and synthesize the current literature that investigates the predictive potential of DRD as a prognostic

factor of smoking cessation treatment outcomes; (ii) provide a critical appraisal of the methodological quality of the literature, particularly in terms of bias; and (iii) propose directions for future research.

2. METHODS

This review follows the PRISMA systematic review guidelines[27] and was registered with PROSPERO (**Registration Number: CRD42020199112**). The PRISMA checklist is provided in Supplementary Material.

2.1 Inclusion/Exclusion Criteria

Studies were included if they: (i) were original primary research published in a peer-reviewed journal; (ii) contained a sample of treatment-seeking individuals with tobacco use disorder or another definition of tobacco addiction; (iii) delivered a form of formal smoking cessation treatment (i.e., pharmacological, psychological or combined therapy) to reduce or eliminate smoking; (iv) administered a pre-treatment measure of DRD for money or cigarette rewards; and (v) included post-treatment follow-up period of at least 1 week. Lab-based experimental manipulations of smoking motivation were excluded for not representing clinical settings with treatment-seeking patients. Reviews, case reports and conference abstracts were also excluded.

2.2 Search Strategy

We identified relevant studies published in English from PubMed/MEDLINE, Embase, and PsycINFO with no publication date restriction. The search strategy was run in June 2020 and completed prior to submission to ensure all relevant articles were included. A manual search of citations of included studies was also completed to locate articles that were not captured by our initial search strategy. To maximize literature reviewed, relevant MeSH terms were used: smok*,

nicotine, tobacco, cigarette*, discounting, delay of gratification, impulsive choice, abstinence, relapse, cessation, retention, treatment, cessation, relapse. The specific combination of Boolean operators is shown in Table 1.

2.3 Data Screening and Collection

After removal of duplicate articles, two reviewers independently reviewed and selected papers based on titles and abstracts (S.K.S and A.GR). Data were then extracted into a predetermined data extraction form. Reviewers recorded the following information: (i) study characteristics (first author, year of publication, journal); (ii) demographic information (sample size, % male, mean age); (iii) treatment description; (iv) DRD characteristics (task type, discounting index and reward magnitude); (v) characteristics of smoking severity (e.g., Fagerström Test of Nicotine Dependence, FTND, cigarettes per day); (vi) follow up period; and (vii) DRD effects on smoking cessation treatment outcomes. In the case of discordance between the 2 reviewers, a third reviewer (J.M.) was consulted. A quantitative meta-analysis was not undertaken because of the highly heterogeneous literature.

2.4 Quality assessment of the reviewed studies

The Quality in Prognosis Studies tool (QUIPS)[28] was used to critically examine the quality of the studies included in the systematic review as it pertained to addressing the questions posed by this study (Table 1). Each study was given a quality rating of “low”, “moderate”, or “high” quality. The QUIPS tool was developed to assess the quality of a variety of study designs such as non-randomized controlled clinical studies, which were the most common study design included in this systematic review. Two reviewers (S.K.S and A.GR) independently assessed the studies against each of the following six domains: 1) study participation; 2) attrition; 3) prognostic factor measurement; 4) outcome measurement; 5) study confounds and; 6) statistical analysis and

reporting. Following prior recommendations, each of the domains were rated as high, moderate, or low risk of bias. In the case of discordance between the 2 reviewers, a third reviewer (J.M.) was consulted. Further information regarding this quality assessment tool can be found in Hayden et al..(2013)[28].

3. RESULTS

The PRISMA flow diagram of studies included and excluded at various points of the review process is in Figure 1. The initial search strategy identified 1244 possible studies. A total of 734 remained following title screening and removal of duplicate studies; these studies were retained for abstract screening. Abstracts of the remaining studies were screened, yielding 85 full-text papers, which were further screened for inclusion in the study. A final set of 14 studies met the inclusion/exclusion criteria.

3.1 Participant and Treatment Characteristics

The 14 studies comprised 3,978 patients in smoking cessation treatment. Eleven studies investigated smoking cessation in adult samples; two focused on women through the perinatal period (pregnancy and postpartum[26,29]); one focussed on heavy drinkers seeking smoking cessation[23], and the remaining three focussed on adolescents[30–32]. Qualitatively, of the 14 studies, eight studies reported uniformly statistically significant results (i.e., baseline DRD predicted smoking cessation treatment outcome), two reported both positive and negative results, and four reported negative results. For the purpose of further analysis, studies were grouped according to the treatment strategy used.

3.2 Smoking Cessation in Adults

The details of findings from studies on adults are in Supplementary Materials. A total of 9/14 studies examined DRD as a predictor in adults in the context of various treatment

modalities[7,21,24,33–37]. Most commonly, CBT for smoking cessation was used in 6/9 studies[7,21,23,33,35,36], contingency management (CM) was used in 3/9 [24,34,36], and pharmacotherapy in 5/9[21,23,33,35,36]. Most pharmacological studies (5/7) used a combination of CBT and pharmacological treatment for smoking cessation[21,23,33,35,36].

In terms of CBT, Sheffer et al. (2012) (n=97) investigated DRD using the Computerized Delay Discounting Task (DDT), following an intensive program of CBT for tobacco dependence[7]. In this study, participants were not provided any medication and completed 6 structured sessions of weekly CBT, which included content included psychoeducation on tobacco dependence, self-monitoring, problem solving, management of conflict, cigarette refusal training, enhancing social support and goal setting. A smoking quit date for all participants was set for the date of the third treatment session. Of the individuals that attended treatment, the abstinence rate was 10% one month following the quit date and 7% at 6 months following the quit date. With regard to DRD, discounting of an actual $100 and hypothetical $100 and $1000 were all predictive of abstinence.

Similarly, Sheffer et al. (2014) (*n*=90) further investigated the relationship between baseline DRD (a computerized task) and days to relapse among smokers following completion of a multicomponent, 6 session, weekly CBT program aimed at smoking cessation and 8 weeks of NRT[21]. Sixty-minute CBT sessions were comprised of strategies to improve self-monitoring, stress management, goal setting, enhancing of social supports, problem solving, and conflict management. Relapse prevention, stimulus control, and cigarette refusal training were also central features of the program. The third CBT session was the scheduled smoking quit date. Participants were followed by telephone once per week for 6 months following the third treatment session to assess days to relapse. Of the measures administered at baseline, DRD for $100 emerged as having

the strongest association with days to relapse, with smokers with higher rates of DRD maintaining fewer days of abstinence and relapsing more quickly.

A recent study by González-Roz (2019) (n=188) found similar prognostic effects of DRD after examining baseline DRD (Computerized DDT) before 6-weeks of CBT either administered with or without the use of contingency management (CM) or cue exposure treatment (CET) (i.e. CBT only, CBT + CM, CBT + CET) [36]. Approximately 57.9% of the sample relapsed within six months following treatment. Combining all three treatment conditions, more impulsive baseline DRD, younger age, high nicotine dependence, as measured by the FTND, and having over 5 previous quit attempts all emerged as significant predictors of smoking relapse at the six-month follow up period.

In terms of CM alone, Dallery at el. (2013) (*n*=77) investigated smoking cessation across an internet-based CM intervention to promote smoking cessation, in which incentives were independent of and contingent upon negative CO samples[24]. DRD was measured using a computerized task. Individuals were randomized to two conditions: (1) incentives contingent upon abstinence; (2) incentives provided irrespective of abstinence; and could earn a maximum of $530.00 in vouchers over the course of the study. An Internet-based platform allowed for participants to upload videos that contained participant providing a breath sample on the CO meter. Treatment was comprised of three phases, which included baseline, tapering, abstinence, and thinning; the final day of tapering (day 7) was assigned as the quit date. Treatment was comprised of brief supportive counselling in person during the tapering phase, by phone after the quit date and after week 4, and an additional in-person session was provided at the end of week 7. At the end of the 3-month follow-up period, 18% of participants in the contingent group were abstinent as compared to only 7.7% in the non-contingent group. Rates of abstinence further decreased at

the 6-month follow up where only 8% of the contingent group and 15.8% of the non-contingent group were abstinent. CO level was estimated to decrease by 1.02 ppm for each additional increase of 0.1 of area under the curve (AUC).

Halpern et al. (2016) conducted the largest CM study to date (n=2,471), investigating abstinence following reward-based financial incentives amounting to $800 or incentive-based programs that require refundable deposits to become eligible for rewards (consisting of a refundable $150 and $650 reward) using a randomized control trial[34]. DRD was assessed using the Monetary Choice Questionnaire (MCQ)[22]. Approximately 6% of individuals in the control group, 10.2% of individuals in the deposit-based group, and 15.7% of individuals in the reward-based incentive group achieved abstinence. DRD was predictive of smoking cessation outcomes following both the reward-based incentive programming (n=990) and the deposit-based incentive programing (n=1,024).

With regard to the combination of CBT and pharmacotherapy, MacKillop & Kahler (2009) (n=57) found that DRD, as assessed by the MCQ, predicted smoking cessation outcomes in heavy drinking smokers seeking smoking cessation[23]. Treatment was comprised of four individual counseling sessions administered over three weeks and eight weeks of NRT. Counseling sessions were comprised of motivational interviewing, problem solving in high-risk situations for smoking relapse, especially when drinking, and encouragement for social support. Overall DRD, as well as, large ($75-$85) and medium ($50-$60) magnitude discounting all emerged as significant predictors of days to smoking relapse, although small magnitude discounting constituted a statistical trend. More precipitous discounting of delayed rewards was associated with fewer days until smoking lapse. Baseline DRD was greater in individuals that had lapsed at both 2-week and 8-week follow-up sessions, however, no differences in baseline DRD were found at sixteen and

twenty-six week follow up sessions, suggesting that DRD may be more relevant to early-stage relapse.

Also using CBT with pharmacotherapy, Lopez-Torrecillas et al. (2014) (*n*=140) investigated DRD as a prognostic factor of smoking cessation treatment outcome in two studies [35]. In the first study, DRD, assessed using the MCQ, was used to predict smoking status following treatment consisting of psychoeducation and counselling to reduce smoking, varenicline to pharmacology aid in smoking reduction, and relapse prevention training. The predictive value of DRD was studied among other measures of impulsivity and was not a significant prognostic factor. The authors published another study (n=113) which further investigated whether differences in DRD were predictive of smoking cessation treatment outcome. They found that higher rates of DRD were associated with smoking relapse and continued cigarette use.

Finally, Coughlin et al. (2020) (n=161) investigated predictors of smoking cessation following 6-week, manualized CBT for tobacco dependence[33]. Individuals were split into two cohorts (training, n=90, and validation, n=71). The training was treated with the CBT program discussed above and the validation cohort was treated with CBT and NRT. Similar to other studies, the sessions were one hour in length and occurred weekly, with the quit date being the third session. Abstinence was confirmed following completion of the CBT program and 6 months following the end of treatment. This study was the first to apply a machine learning approach through the use of decision trees to identify DRD rate as the first split for identifying treatment responders vs. non-responders both at post-treatment and 6 months follow up. Baseline DRD (a computerized task) predicted outcome status with 69.53% accuracy (and 81.88% when additional measures were added) in the training cohort (only CBT), it predicted 76.4% which reduced to 63.3% when additional variables were added. These results suggest that those with lower rates of discounting

may respond better to group CBT for smoking cessation. Interestingly, authors provided a "cut point" of DRD at the first decision split, which was most predictive of smoking cessation outcome; this was identified as ln(k)=-7.1, which may provide an estimate for an initial cut-off point for determining treatment response, such that those with lower rates of discounting are likely to respond to group CBT for smoking cessation. This cut-point correctly predicted treatment status in 81% of patients at posttreatment and 80% of patients at 6-month follow up.

3.3 Pregnant and Postpartum Females

Pregnancy and the postpartum period also emerge as a unique opportunity to study smoking behaviours. Research suggests that the rate of smoking cessation among pregnant women is over 50%, however among women who quit smoking, between 47-50% of those women relapse within one year following childbirth [38,39]. Predictors of smoking cessation during pregnancy and the postpartum period have important implications on maternal and fetal health[40–42]. Studies on pregnant and post-partum females are summarized in Table 2. Only two studies were identified and yielded conflicting results[25,26]. Yoon et al. (2007) (n=48) found that DRD (a computerized task) was predictive of postpartum relapse to cigarette smoking among pregnant women who discontinued smoking during pregnancy[26]. Participants entered this study, a randomized clinical trial on relapse prevention, while they were approximately 10.5 weeks gestational age and were randomized to either an abstinence-contingent voucher-based condition or a non-contingent voucher-based condition (vouchers were provided independent of smoking status). Combining the treatments, 46% of women had relapsed by 24 weeks postpartum and baseline DRD predicted smoking status at 24 weeks post-partum. Interestingly, greater discounting was also associated with younger age, less education, and a positive history of depressive symptomology, suggesting multiple therapeutic targets to help women cope with a significant stressor such as childbirth. The

second study that investigated prognostic factors of smoking cessation within pregnant and newly postpartum women was conducted by Lopez et al. (2015) (n=236)[25]. All participants completed an incentive-based smoking cessation intervention on which vouchers were obtained contingent on smoking cessation and completed up to 8 counselling sessions at various times throughout their participation in the study (during treatment and post-partum visit). In this case, DRD, as measured by a computerized task, did not emerge as a significant predictor of smoking cessation in late pregnancy of 24 months postpartum.

3.4 Smoking Cessation in Adolescents

Adolescence is an important time for development of smoking behaviours; these behaviours often persist into adulthood, after which smoking has been reinforced for several years, making cessation difficult [30,31]. Adolescent studies are summarized in Table 2. Krishnan-Sarin et al. (2007) (n=30) investigated smoking cessation in a group of adolescents age 14-18 years old [30]. The program consisted of weekly CBT for smoking cessation and further reinforced positive behaviour changes using contingency based smoking abstinence; sixteen participants were abstinent at the end of treatment. DRD as measured using the computerized Experiential Discounting Task (EDT) was found to be predictive of smoking cessation treatment outcome; individuals that did not have a positive treatment outcome (were non-abstinent) discounted to a greater degree on the EDT at baseline than individuals that did achieve abstinence. The MCQ was also administered at baseline but was not found to be predictive of treatment outcome.

In a second study on adolescents, Harris et al. investigated smoking behaviours in adolescents following a four-week school-based smoking cessation treatment (n=81)[32]. They investigated smoking cessation in adolescent smokers (47% female sample) that completed a voluntary 10 session (50-minute) weekly smoking cessation program. The program focused on

providing social and cognitive training, which specifically aimed at improving participant's social skills, management of withdrawal and peer pressure, enhancing self-management strategies, and psychoeducation regarding relapse prevention. Baseline DRD was assessed using the Question-Based Delay Discounting Measure (DDQ). Of the individuals that completed treatment, 17 individuals reduced their smoking behaviours and reported smoking an average of 1.13 cigarettes post treatment (7.57 cigarettes pre-treatment), however, DRD was not predictive of treatment outcomes Interestingly, of the variables of impulsivity studied, only the Continuous Performance Test (CPT) was found to be predictive of treatment outcomes; smokers with better attention as characterized by fewer errors of omission were found to be more successful in reducing their smoking behaviour or quitting smoking. Interestingly, this was consistent with the aforementioned adolescent study in which individuals who did not achieve abstinence also had greater errors on the CPT.

Most recently, smoking cessation in adolescents was also studied by Harvanko et al. (2019) (n=189)[31]. In this case, the program followed a contingency management approach in which reductions in smoking cessation were rewarded with incentives. Baseline DRD was assessed using the DDQ. The treatment program was comprised of 5 phases: Baseline (7 days), Shaping (4 days), Abstinence (21 days), Thinning (5 Days), and Return to Baseline (5 Days). Greater DRD was associated with both poorer adherence to treatment and treatment outcomes (smaller reduction in CO levels). However, DRD was not predictive of change in CO levels during the Abstinence phase of the study, which was hypothesized to possibly be due to the influence of contingent rewards on smoking behaviour.

3.5 Quality assessment

The methodological risk of bias (quality) assessment of the included studies across each of the six QUIPS domains is presented in Table 3. Agreement on methodological quality scores between reviewers was 97.62%. Discrepancies concerned the rating of attrition in two studies and were resolved after discussion. Overall low risk of bias was detected, with 28.57% (4/14) of the studies showing a low risk of bias for each of the six QUIPS domains [34]. Risk of bias was highest for 'study attrition' (nine studies scoring moderate to high), 'study confounding' (three studies scoring high), and the 'study participation' (one study scoring moderate) domains. Overall, studies had a moderate quality score, and none of them were deemed to be weak. Importantly, all studies achieved a high-quality rating in the areas of "study participation", "prognostic factor measurement", "outcome measurement", and "statistical analysis reporting". The main component that decreased overall quality was the high drop-out rate of the interventions. More specifically, Coughlin et al.[33], Krishnan-Sarin et al.[30], and Lopez-Torrecillas et al.[35] had low quality scores in the areas of "study attrition" and "study confounding". In contrast, Lopez et al.[25] and Sheffer et al.[21] had lower ratings for "study attrition" only. Halpern et al.[34], Dallery et al.[24], and Gonzalez-Roz et al.[36] were found to have a moderate quality rating in "study attrition".

4. DISCUSSION

The goal of this systematic review was to examine the role of DRD as a prognostic factor of smoking cessation treatment outcome. A systematic search of the literature yielded 14 studies that investigated the predictive potential of DRD in determining smoking cessation treatment outcome. Of those 14 studies, approximately 70% (10 studies) found consistent or partial evidence that DRD was predictive of treatment outcome, while 30% (4 studies) did not find evidence of a prognostic relationship. Most notably, three of the four studies that did not find an association

between baseline delay discounting and smoking cessation treatment outcome were in special populations; two were conducted amongst adolescents and one studied women in the perinatal period. Thus, on balance, the review identifies relatively consistent evidence of a prognostic relationship specifically in adults. This is consistent with research in other addictive disorders (i.e. alcohol use disorder, gambling disorder) that also highlight the role of pre-treatment DRD in predicting post-treatment outcome[17,18,43,44]. In these studies, higher rates of DRD were also associated with poorer prognosis following treatment.

The substantially weaker evidence in adolescents may be attributable to differences in DRD, motivation to smoke and smoking behaviours as a function of age[45]. Adolescents are more likely to discount to a greater degree than adults; therefore, high levels of DRD in adolescents may be a function of age, rather than being stable and trait-like. Perhaps this instability (or malleability) leads to a reduction in the sensitivity of DRD as a prognostic factor, consistent with the results by Harris et al., and Krishnan-Sarin et al.[30,32].

Interestingly, in some studies, other behavioural markers of impulsivity, such as the CPT, demonstrated prognostic value where DRD did not. Participants in both the Krishnan-Sarin et al. (2007) study and Harris et al. (2014) that did not achieve abstinence had greater errors on the CPT[30,32]. Performance on the CPT is thought to be relatively stable through adolescence and decreases as a function of later age; usually characterized by deficits in selective response inhibition[46,47]. This supports the above assertion that perhaps markers of impulsivity that are prone to age-related variability may not be the most useful variables to use as predictive factors of treatment response. On the other hand, a prospective longitudinal cohort study investigating smoking and DRD from mid-adolescence to young adulthood found that DRD actually did not change significantly across time[48]. Moreover, baseline DRD had a significant positive effect on

smoking trend and DRD was higher in individuals that identified as early/fast smoking adopters and slow smoking adopters compared to non-smokers. This evidence undermines the interpretation that DRD may be too unstable to be informative during adolescence. Alternatively, although Krishnan-Sarin et al. (2007) did not find that DRD was associated with treatment outcome, cessation response was predicted by EDT[30]. This delay discounting task yields salient rewards in real-time and may be more salient to adolescents, as opposed to hypothetical amounts of money. On the other hand, these results may need to be interpreted with caution as the EDT has both elements of risk and delay, and thus may have captured risk-based decision making in this population. It also highlights the need for further research on delay discounting in adolescents to inform patterns of delay discounting and changes in behaviours through this period of prefrontal brain development [49].

Studies investigating DRD as a prognostic factor of smoking cessation treatment among pregnant women also reported conflicting results. Importantly, although the Lopez et al. (2015) study did not find an association between baseline DRD and treatment outcome, these results may have been influenced by participant characteristics known to influence DRD and therefore may reflect an effect of the population studies rather than null effects of DRD. For example, the relationship between DRD and education and socioeconomic status (SES) is well established; individuals of low SES are more likely to discount future rewards to a greater degree and this relationship is amplified in smokers vs. non-smokers[50–52]. As such it is important to note that only 55% of the participants in the Lopez et al., (2015) study reported that they were working for pay, as compared to 88% of the participants in the Yoon et al. (2007) study. Further, secondary support through supplemental or spousal income may be helpful in contributing to socioeconomic status especially during pregnancy and the postpartum period where income may be temporarily lost;

approximately 46% of the Yoon et al. (2007) study sample was married as compared to 16% of the Lopez et al. (2015) sample. Further 55% of the Yoon et al. (2007) sample had access to private insurance whereas only 23.7% of the Lopez et al. (2015) had access to private insurance, further suggesting that the participants in the Yoon et al. sample may be of a higher socioeconomic status. This may be important when interpreting the Lopez et al. results since lower socioeconomic status may make these participants more prone to discount at higher rates overall, thereby reducing the variability of discounting rates between those who abstain from smoking or relapse. Finally, pregnancy is a unique period for the implementation of positive health behaviours, although this period may increase extrinsic motivation to reduce smoking behaviours, it may not address that this extrinsic reinforcer (i.e., pregnancy) is temporary, which may decrease motivation to continue endorsing positive behaviours such as smoking cessation. Also, the postpartum period is associated with a substantial increase in stress, which may precipitate the return of smoking behaviours.

Of the studies that investigated the prognostic value of DRD in adult samples, combination approaches such as CM in conjunction with pharmacological or psychological intervention demonstrated the most robust treatment effects and found that DRD was predictive of treatment outcome. This may be in part, due to the nature of CM as a behavioural intervention that provides monetary incentives and the ability of DRD to capitalize on this and capture monetary reward sensitivity[20,25,31]. CM has also been suggested to influence the decision-making processes associated with DRD through preference for delayed rewards through demonstrating positive behaviour vs. immediate rewards (smoking)[20].

A further aim of the study was to examine risk of bias and the studies collectively exhibited limited bias on the QUIPS. Moreover, most studies described a moderate-high treatment adherence. Each of the treatments employed in the studies was evidence-based and aided in the

reduction of smoking behaviours and smoking cessation in some portion of individuals that adhered to treatment. Although it was highly heterogeneous, the methodological quality of the literature was generally high.

4.1 Strengths and Weaknesses

The current study should be considered in the context of its strengths and weaknesses. Among its strengths, it provides a synthesis of a growing body of literature regarding the efficacy of prognostic indicators of treatment response. This study focused on clinical samples, those with well-established tobacco dependence. In doing so, included studies that had high level of impulsive behaviours, as literature highlights that subclinical samples do not exhibit the same highly impulsive discounting seen in clinical samples [23]. As such, the results of this study are based on an aggregate of clinically significant impulsive behaviour. This study also highlights several opportunities for future research, such as the role of adjunctive interventions to modulate DRD to improve outcomes and further research integration of these adjuncts with combination therapies consisting of pharmacological and psychotherapeutic interventions.

In terms of weaknesses, the heterogeneity of the literature did not allow a meta-analysis to be conducted. Studies included used multiple different DRD paradigms which made it challenging to synthesize results and suggest potential DRD cut off scores that may reflect populations that require more attention or resources when quitting smoking. Considerable heterogeneity in treatment approaches administered, also made it challenging to synthesize results across different therapeutic programs and treatment modalities. For instance, even among studies that used CM or CBT, certain studies elected to combine these interventions with pharmacological intervention such as varenicline or NRT. In addition, a large portion of the studies investigated did not report patient characteristics that are likely to impact DRD behaviours such as education, income, and

psychiatric history. We encourage future research to report outcomes that can influence impulsivity and related variables and may act to confound results if appropriately integrated into analysis. Further, studies investigating smoking cessation in special populations such as adolescents and pregnant women may confer unique limitations pertaining to the generalizability of results. For instance, the two studies that investigated smoking cessation during pregnancy both acknowledged that pregnancy acted as profound extrinsic motivation to quit smoking during pregnancy and therefore could limit the generalizability of findings to individuals who are trying to quit smoking long term [25,26]. Importantly, many studies measured progress by strictly employing an abstinence-based approach. Although abstinence is an important goal in smoking cessation, it is a high bar and a growing body of literature suggests that harm reduction approaches may lead to a decrease in smoking cessation that may also be an important indicator of treatment success[53–56]. For example, an individual who reduces their smoking behaviours by half due to participation in treatment may incur significant health benefits as a result of this reduction, however according to an abstinence-based approach would still be viewed as a treatment failure[56]. Abstinence-based approaches place emphasis on fixed definitions of success and failure which contradict the idea that relapse and abstinence are dynamic processes [56]. For example, the average individual has 8-11 quit attempts prior to quitting smoking permanently and each successive quit attempt may act to reduce DRD and improve prognosis towards complete cessation of smoking behaviour [57]. Importantly, the use of vaping and e-cigarettes as harm reduction strategies may also be useful to aid smoking cessation efforts [58]. Research suggests that e-cigarettes with or without nicotine may be helpful in reducing cigarette smoking[59,60] and, despite being part of the contemporary smoking cessation landscape, were not incorporated into any of the studies identified.

4.2 Future Directions

Overall, this review highlights several areas of future study and clinical application. First, there is a need for future research to establish clear clinical DRD cut-offs to better inform treatment outcome. This may be a challenge given that researchers often use different DRD tasks, with different magnitudes and parameters, however, the use of widely-used DRD paradigms, such as the MCQ, may help accomplish this task. Only one study of the included studies used machine learning to identify a potential cut off that was associated with treatment outcome[33]. While the predictive value of DRD in smoking cessation is moderate in adults, determining a specific DRD cut-off that predicts treatment outcome is of critical clinical relevance, as it would inform the provision of resources to further engage individuals, improve treatment adherence, and maintain treatment gains.

Second, research investigating DRD suggests that it may be a modifiable risk factor and may be addressed using interventions such as Episodic Future Thinking (EFT) [61,62]. EFT is an evidence-based method used to decrease DRD that capitalizes on one's ability to imagine personal future events[61,62]. Studies investigating EFT in nicotine use disorder found that it reduced both DRD and smoking behaviours[61–63]. As such, adding EFT as an adjunct to smoking cessation treatment may be efficacious in further reducing smoking behaviours and impulsive behaviour associated with DRD. Therefore, by using EFT to modify and potentially reduce DRD either prior to the onset of formal CBT/NRT or during treatment, individuals may be able to improve smoking cessation outcomes. On the other hand, it is also plausible that rather than focussing on DRD per se, higher DRD may indicate greater clinical severity in general and, in turn, the need for more clinically intensive treatment, such as multiple modalities or extended treatment.

In sum, this systematic review suggests that DRD is a significant prognostic factor of smoking cessation treatment outcome in adults, although not necessarily in adolescent or perinatal

samples. Risk of bias and methodological rigor were generally high, although so was heterogeneity of methodologies, preventing meta-analysis and revealing a highly multifarious literature. Nonetheless, these findings suggest the need for future research to investigate adjunctive interventions that can be used to address impulsive DRD or to otherwise augment treatment for high-DRD smokers.

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Table 1. Search strategy

1. discounting
2. “delay of gratification”
3. “delay discounting”
4. “impulsive choice”
5. time discounting
6. time preference
7. delayed reward discounting
8. impulsivity
9. smok*
10. nicotine
11. tobacco
12. cigarette*
13. treatment
14. abstinence
15. cessation
16. relapse
17. “treatment outcome”
18. **DRD RELATED TERMS:** 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
19. **SMOKING RELATED TERMS**: 9 OR 10 OR 11 OR 12
20. **TREATMENT RELATED TERMS**: 13 OR 14 OR 15 OR 16 OR 17
21. **FINAL SEARCH**: 18 AND 19 AND 20

Table 2: Study Characteristics of Studies with Perinatal and Adolescent Samples

Author	N	Sex (% Male)	Age Mean (*SD*)	Treatment Description	DRD Index	Delay Amount	Smoking characteristics	Follow up	Effect Sizes/Results	Outcome
					Perinatal Period: Pregnancy and Postpartum					
Yoon et al. (2007)	48	0	25.9 (5.1)	CM (vouchers contingent on and not contingent on smoking abstinence)	Log*k*,	$1000	C/D: 9.6 (6.0)	24-weeks PP	Baseline DRD (Log*k*) predicted smoking status at the 24-week- postpartum assessment (OR: 1.82 per one-unit change in log *k*, 6.10, $p = .01$). As *k* increases the estimated probability of being classified as a smoker at 24 weeks post-partum also increases.	+
Lopez et al. (2015)	236	0%	24.6 (0.5)	CM and Counseling	Log*k*	$1000	Cig/Day: 9.0 (0.4)	24 weeks PP	DD was not predictive of treatment outcome.	-
					Adolescents					
Krishnan-Sarin et al. (2007)	30	46.6	A: 16.7 (0.24) NA: 16.4 (0.25)	CM + CBT	AUC, log*k*	$25 $55 $85	C/D: 14.35 (2.5) mFTQ: 2.88 (0.81)	1 month	EDT: Non-abstinent participants discounted more significantly on the EDT than abstinent ones ($F= 2.67$; $p<0.05$). DDM: No differences were observed between DDM in abstinent and non-abstinent individuals ($F=0.3$, $p=0.6$).	-
Harris et al. (2014)	81	58	16 (1.28)	Social cognitive smoking cessation program	NR	$10	C/D :7.57 (5.11) FTND: 1.35 (0.59)	8 days after EOT	DDQ was not predictive of treatment outcome. OR = 0.77, 95%CI (0.11-5.29), $t = -0.27$, $p = .78$	-
Harvanko et al., (2019)	189	Active: 51.1% Control: 49.5% Drop Out: 65.8%	Active:16.8 (1.5) Control: 16.8 (1.51) Drop Out: 17.3 (1.5)	Active Condition: CM (contingent on punctual submission of samples at specific CO levels) CM (contingent on CO submission samples not CO dependent)	AUC	$10	NA	3 and 6 months	DRD predicted a trend towards change in CO levels from baseline to abstinence and return to baseline phase ($F=15.61$; $p=0.07$)	+

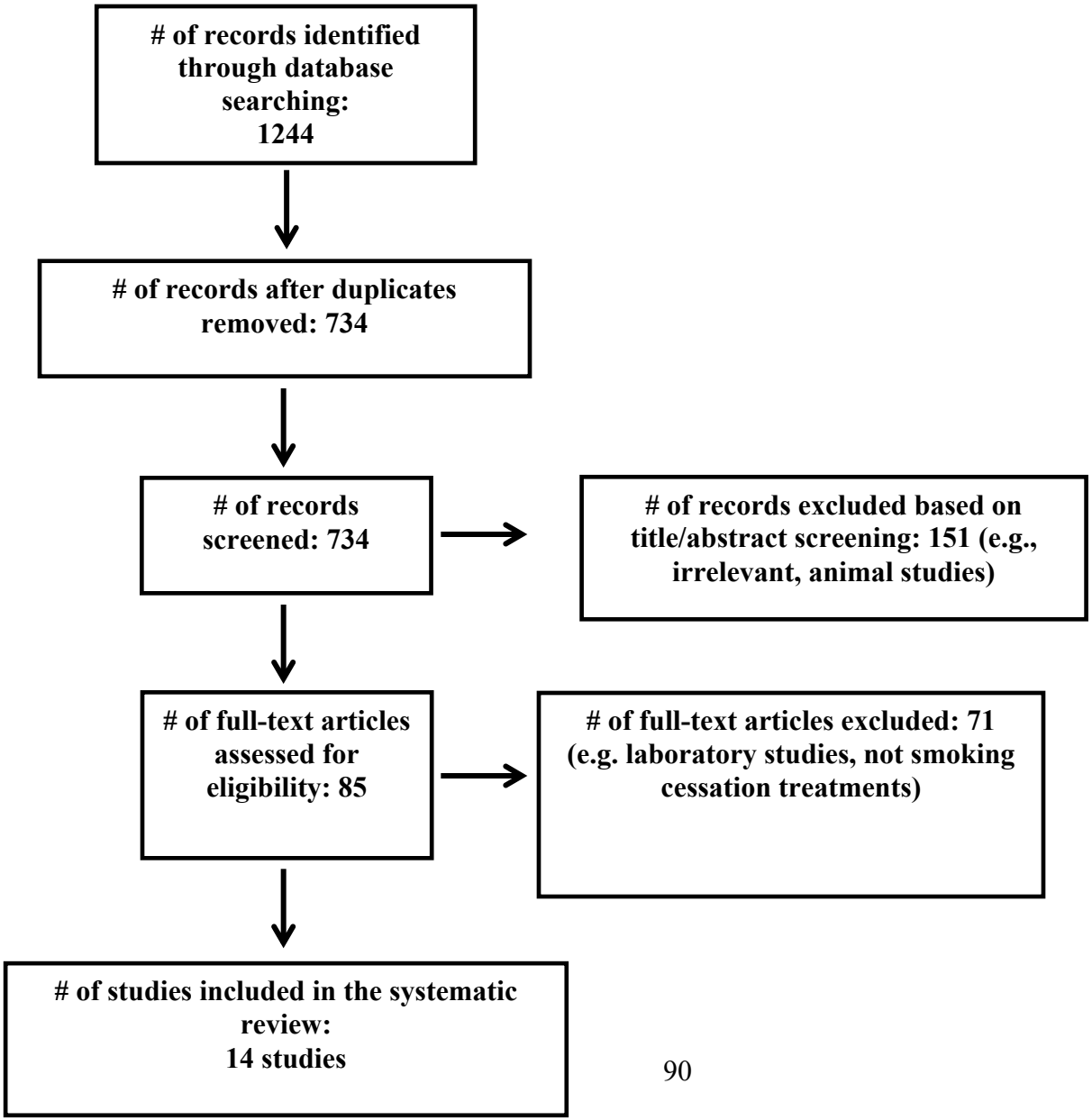
Note: CM + CBT = contingency management; CBT = cognitive-behavioural treatment; EDT = experiential delay discounting; DDM = delay discounting measure; AUC = area under the curve; C/D = cigarettes per day; mFTQ = modified Fagerström Tolerance Questionnaire; DDQ = delay discounting questionnaire; EOT = end of treatment; NA; not abstinent; +/- indicates both positive and negative results; PP: Postpartum; NR: Not Reported

Table 3: QUIPS Quality Assessment Results

Study	Study participation	Study attrition	Prognostic factor measurement	Study confounding	Outcome measurement	Statistical analysis and reporting
Coughlin (2020)	+++	+	+++	+	+++	+++
Dallery et al. (2020)	+++	++	+++	+++	+++	+++
Harris et al. (2014)	++	+++	+++	+++	+++	+++
Krishnan-Sarin (2007)	+++	+	+++	+	+++	+++
Lopez-Torrecillas et al. (2014)	+++	+	+++	+	+++	+++
Harvanko et al. (2019)	+++	+++	+++	+++	+++	+++
Halpern et al. (2016)	+++	++	+++	+++	+++	+++
López-Torrecillas (2014)	+++	+++	+++	+++	+++	+++
López et al. (2015)	+++	+	+++	+++	+++	+++
MacKillop et al. (2009)	+++	+++	+++	+++	+++	+++
Sheffer et al. (2012)	+++	++	+++	+++	+++	+++
Sheffer et al. (2014)	+++	+	+++	+++	+++	+++
Yoon et al. (2007)	+++	+++	+++	+++	+++	+++
Gonzalez-Roz et al. (2019)	+++	++	+++	+++	+++	+++

Note: +++: high quality; ++: moderate quality; +: low quality

Figure 1: Flow-chart on the literature search procedure



SUPPLEMENTARY MATERIALS

Table S1: Study Characteristics of Studies with Adult Samples

Author	N	Sex (% Male)	Age Mean (*SD*)	Treatment	DRD Index	Delay Amount	Smoking Characteristics(cig/day)	Follow up	Effect Sizes/Results	Outcome
Contingency Management and Cognitive Behavioural Therapy										
Sheffer et al. (2012)	97	41	48.16 (11.62)	mCBT w/ relapse prevention; 6 (1hour) sessions (once/week)	Log*k*	$100, $1000	FTND: 6.43(1.75)	1, 6 months	(1) DRD mean baseline log*k* of real $100 and hypothetical $100 and $1,000 gains (SD = 2.93), OR = .623, 95%?CI = .912, *p*=.021; (2) DRD $100 hypothetical gains (SD = 3.28), OR = .662, 95%?CI = 0,942, *p*=0.027; (3) DRD $1,000 hypothetical gains (SD = 3.42), OR = .684, 95%¿CI = .966, *p*= .035)	+
Sheffer et al. (2014)	90	53	47.5 (12.7)	CBT + 8 weeks of NRT	Log*k*	$1000 $100	C/D: 23.6 (11.80) FTND: 6.04 (1.91)	Days to relapse	DRD at $100 was strongly associated with days to relapse: DRD of $100 M(SD) = -4.93(2.9) 95%CI (1.066. 1.983) X^2(1df) = 5.58, *p* = .018 DRD of $1000 M(SD) = -5.81(2.52) 95%CI (0.961, 1.766) X^2(1df) = 2.91, *p*= .088 Association of DRD with days to relapse when combine with FTND, PSS and number of missed treatments: DRD mean of $100 and $1000 M(SD) = -5.38 (2.42) 95%CI (1.062, 2.099) X^2(1df) = 5.32, *p*= .021	+
Gonzalez-Roz et al. (2019)	188	35.6%	42.9 (12.9)	CBT CBT + CET CBT + CM	AUC	Small: $25-$35 Medium: $50-$60	FTND: 5.19 (2.09)	6 months	Greater DD rates (*OR*: 0.18; 95% CI [0.03, 0.93]) increased the likelihood of smoking relapse at six-month follow-up.	+

						Large: $75-$85				
Cognitive Behavioural Therapy and Pharmacology										
MacKillop et al. (2009)	57	61	41.4 (13.2)	Individual Counselling + NRT	Log*k*	Small: $25-$35 Medium: $50-$60 Large: $75-$85	C/D: 20.9 (10.7) FTND: 4.98 (2.65)	2, 8, 16, and 26 weeks	DRD was a predictor of days to first smoking lapse: Overall *k*: HR= 1.48, $p \leq 0.01$ Large magnitude. *k*: Hazard Ratio= 1.14, $p \leq 0.05$ Medium magnitude *k*: Hazard Ratio = 1.53, $p < 0.01$ Small Mag K: Hazard Ratio = 1.41 $p \leq 0.05$.	+
Lopez-Torecillas et al. (2014a)	113 DP: 24 AB: 69 RL: 20	39.8 DP: 33.3 AB: 42.0 RL: 40.0	DP: 48.4 (7.9) AB: 45.6 (8.8) RL: 48.7 (6.1)	CBT + varenicline	NR	Small: €25-€35 Medium: €50-€60 Large: €75-€85	C/D: DP: 21.0 (10.6) AB: 18.6 (9.0) RL: 22.0 (8.1) FTND; DP: 4.5 (2.0) AB: 4.4 (2.5) RL: 5.0 (2.7)	1 month	$F = 5.762$; Mce = 0.313; $p = 0.004$ Differences in DRD (SD) AB: 0.49 (0.24) RL: 0.54 (0.17) DP: 0.33 (0.25)	+/-
López-Torrecillas et al. (2014b)	140	85	47.36 (8.19)	Psychoeducation and counseling + varenicline	AUC	Small: €25-€35 Medium: €50-€60 Large: €75-€85	C/D: 19.85 (9.17) FTND: 4.65 (2.32)	3,6,12-months	3-months follow-up: Dropout: Wald = 0.63, 95%CI (0.05-3.53) $p = .429$ Relapse: Wald = 2.91, 95%CI (0.75-61.72) $p = .088$ 6-months follow-up: Dropout: Wald = 0.000, 95%CI (.09-10.94), $p = 1.00$ Relapse: Wald = 2.98, 95%CI (.76-71.61), $p = .084$ 12-months follow-up: Dropout: Wald = .06, 95%CI (.12-14.92), $p = .811$ Relapse: Wald = 3.01, 95%CI (.78-60.6), $p = .083$	-
Coughlin et al. (2020)	90	53.77%	46.55 (12.69)	CBT + NRT	Log*K*	$100	FTND: 5.99 (1.92)	Post treatment and 6 months	DD emerged as the single best predictor of group CBT treatment response with an average baseline discount rate of ln(*k*)=-7.1.	+

									Smoking status at post-treatment was correctly predicted 80% of the time and of 80% at follow-up	
Only Contingency Management										
Dallery et al. (2013)	CG: 39 NCG:38		CG: 39.3 (13.20);NCG: 40.1 (13.28)	Internet based CO monitoring + CM (7 Weeks). (vouchers delivered contingently, vs.? not)	AUC	$100	FTND: CG: 5.13 (1.90); NCG: 5.24 (2.54); C/D CG: 20.4 (8.74); NCG: 20.6 (9.65)	3, 6 months	CO level was estimated to decrease by 1.02 ppm for each additional increase of 0.1 of AUC (95% CI = −2.111, −0.713, p =.069).	+/-
Halpern et al. (2016)	990 1024	NA	NA	Reward based incentive arm Deposit based incentive arm	Log*k*	Small: $25-$35 Medium: $50-$60 Large: $75-$85	NA	6 months	Log*K* at baseline was an independent predictor of smoking cessation at 6 months (OR=0.88, p=0.008) in the reward-based incentive and in the deposit-based incentive (OR=0.89, p=0.038)	+

Note: CM + CBT = contingency management; CBT = cognitive-behavioral treatment; EDT = experiential delay discounting; DDM; DDM = delay discounting measure; AUC = area under the curve; C/D = cigarettes per day; mFTQ = modified Fagerström Tolerance Questionnaire; DDQ = delay discounting questionnaire; EOT = end of treatment; NA; not abstinent; +/- indicates both positive and negative results; PP: Postpartum; NR: Not Reported

Table S2: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Materials B. & p14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary Materials B. & p14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA – rationale for no meta-analysis on p6

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary Materials B. & p14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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CHAPTER 4

RESTING STATE FUNCTIONAL CONNECTIVITY PREDICTS BRIEF INTERVENTION RESPONSE IN ADULTS WITH ALCOHOL USE DISORDER: A PRELIMINARY STUDY

Sabrina K. Syan, PhD[1,2], Carly McIntyre-Wood, MSc[2], Emily Vandehei, BA(Hons)[2], Mae Linda Vidal, HBSc[2], Tegan Hargreaves, MSc[2], Emily MacKillop, PhD[3], Heidi Sarles-Whittesley[4,]Michael Amlung PhD[5,6], Lawrence Sweet PhD[4], James MacKillop PhD[2,3]

[1]Department of Psychology, Neuroscience and Behaviour, McMaster University, Hamilton, Canada
[2]Peter Boris Centre for Addictions Research, St. Joseph's Healthcare Hamilton, Hamilton, Canada
[3]Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Canada
[4]Department of Psychology, University of Georgia, Athens, GA, USA
[5]Cofrin Logan Center for Addiction Research and Treatment, University of Kansas, Lawrence, Kansas, USA
[6]Department of Applied Behavioral Science, University of Kansas, Lawrence, Kansas, USA

Short Title: RsFC predicts brief intervention response

ABSTRACT

Background: Brief interventions are efficacious in reducing alcohol use among individuals with alcohol use disorder (AUD), with wide variability in response. No previous studies have investigated the resting state functional connectivity (rsFC) of response to brief interventions in AUD. The present study utilized rsFC at baseline to predict response to a brief intervention at three-month follow-up.

Methods: Forty-six individuals with AUD (65.2% female), completed a resting state fMRI scan, immediately followed by a brief intervention aimed at reducing alcohol consumption. Reductions in alcohol consumption by at least one WHO drinking level at 3-month follow-up were classified as responders. RsFC was analyzed using seed-to-voxel analysis using seed regions from four networks: salience network, reward network, frontoparietal network, default mode network.

Results: At baseline, responders vs. non-responders demonstrated increased rsFC between (i) anterior cingulate cortex (ACC) and left postcentral gyrus, right supramarginal gyrus; (ii) right posterior parietal cortex and right ventral ACC; (iii) right interior frontal gyrus (IFG) *pars opercularis* and right cerebellum, right occipital fusiform gyrus; (iv) right primary motor cortex and left thalamus. Decreased rsFC in responders vs. non-responders was seen between the (i) right rostral prefrontal cortex and left IFG *pars triangularis*; (ii) right IFG *pars triangularis* and right cerebellum; (iii) right IFG *pars triangularis* and right frontal eye fields, right angular gyrus; (iv) right nucleus accumbens and right orbital frontal cortex and right insula.

Conclusions: RsFC in responders at baseline may reflect increased motivation to engage in behaviour change. Further research to understand underlying behavioral mechanisms is warranted.

Keywords: Alcohol Use Disorder, Resting State Functional Connectivity, fMRI, Relapse, Treatment Response

1. INTRODUCTION

Alcohol use disorder (AUD) confers significant psychosocial, medical, and economic burdens on society (Carvalho et al., 2019; Grant et al., 2016). For example, the World Health Organization estimates approximately 300 million individuals meet criteria for AUD worldwide and harmful alcohol use is responsible for 3 million deaths annually (World Health Organization, 2018). Despite this, treatment uptake in individuals with AUD is low (Tarp et al., 2022), with only 10% of individuals with AUD in high income countries receiving treatment, irrespective of having access to low-cost or free treatment services (Alonso et al., 2004). Lack of problem awareness is the most frequent reason for not seeking treatment and suggests that routine monitoring in healthcare settings using a Screening, Brief-Intervention and Treatment (SBIRT) approach may be useful in raising awareness, catalyzing self-directed change, and connecting individuals to more intensive treatments (Hargraves et al., 2017; Probst et al., 2015). Rates of relapse are also high in individuals that engage in treatment, with between 60-70% of individuals relapsing (Chiappetta et al., 2014). As such, research aimed at understanding the determinants of response to treatment plays a critical role in the development of novel strategies to improve clinical outcomes for individuals with AUD.

Resting state functional connectivity (rsFC) is a technique that uses blood oxygen-level dependent (BOLD) signal collected via functional magnetic resonance imaging (fMRI) to provide an indirect measure of neuronal activity during the absence of specific engagement in cognitive, emotional, or other tasks (Fox and Raichle, 2007). This technique may be particularly useful for examining functional brain organization and potential neuropathophysiology that may manifest behaviorally when these brain systems are engaged. This provides a versatile tool to gain insight into the biological basis of AUD and neural mechanisms accounting for a range of clinical

outcomes. A modest number of studies have investigated the rsFC in individuals that exhibit problematic alcohol use or meet criteria for AUD. An initial study found problematic alcohol use, as defined by binge drinking (5+ drinks for men, 4+ drinks for women in a single drinking episode) at least five times in the past month, exhibited lower network connectivity than healthy controls within the left executive control network, basal ganglia, and primary visual cortices (Weiland et al., 2014). A subsequent seed-based analysis (SBA) study found that greater lifetime alcohol consumption was associated with weaker rsFC between the left nucleus accumbens (NAc) and the bilateral dorsolateral prefrontal cortex, inferior frontal gyrus (IFG), left caudate nucleus, left putamen, and left insula (Veer et al., 2019)—regions linked to the central executive network and reward processing network. Related, a study by Fede et al. found that activity in the executive network, salience network, and default mode network (DMN) were associated with Alcohol Use Disorders Identification Test scores, in moderate-heavy drinkers (mean AUDIT score = 24.25) (Fede et al., 2019). Further, Song et al. found disrupted integrity of the DMN, as characterized by lower efficiency, between the posterior cingulate cortex and cerebellum in 15 participants with AUD relative to 15 controls (Song et al., 2020). Finally, Abdallah et al. (2021) found that individuals with AUD exhibited greater rsFC variability between the cerebellum and the frontoparietal executive and the ventral attention networks relative to controls, highlighting cerebro-cerebellar network alterations in individuals with AUD (Abdallah et al., 2021).

As described above, the majority of the rsFC literature in AUD has focused on differentiation between AUD and control participants or investigated rsFC in relation to AUD-associated psychopathology. A small number of studies have gone further, using rsFC to investigate clinical prognosis and rsFC changes through treatment. Srivastava et al., scanned a modest sample of individuals with AUD (n=18) pre and post 12 weeks of outpatient cognitive-

behavioural therapy for AUD. They found that reductions in rsFC between the anterior insula and the bed nucleus of the stria terminalis (BNST) from pre-post CBT was associated with reductions in the number of heavy drinking days of the previous 28 days (Srivastava et al., 2021). Muller et al. examined rsFC one month following alcohol abstinence in individuals with AUD who completed outpatient treatment (Muller and Meyerhoff, 2020). They found higher global across-community interaction (graph theory approach) in the ventromedial PFC in individuals that relapsed at 3-month follow up (n=22) compared to health controls (n=30), and found that these differences were absent once individuals relapsed (Muller and Meyerhoff, 2020). They also found significant global across-community interaction with the visual cortex at baseline in individuals who relapsed, whereas individuals that abstained demonstrated the opposite pattern (negative association) suggesting that this pattern of interaction may be an early indicator for treatment failure (Muller and Meyerhoff, 2020). In a recent study, the same authors found that individuals that relapsed following AUD outpatient treatment showed maladaptive community configuration (groupings of brain regions and networks) at baseline and that these patterns became more similar to the community organization seen in light/non-drinking controls once individuals with AUD relapsed (Muller and Meyerhoff, 2021). Interestingly, they found that successful recovery from AUD was associated with brain network organization that distinctly differed from both light/non-drinking controls and individuals with AUD who relapsed (Muller and Meyerhoff, 2021). Further, an additional study reported that increased network centrality of the anterior insula was associated with increased risk of relapse in individuals with AUD (n=35) vs. CTRLs (n=34) who had been sober for at least 2 weeks and treated for symptoms of alcohol withdrawal and with naltrexone (50mg, once daily) (Bordier et al., 2022). Finally, a proof-of-concept trial used deep repetitive transcranial magnetic stimulation (dTMS) to target the medial PFC and anterior cingulate cortices

(n=51; 15 sessions across 3 weeks and 5 sessions over 3 months of follow-up) in recently abstinent, treatment seeking individuals with AUD (Harel et al., 2022). They found that treatment reduced alcohol craving and percent heavy drinking days at 3-month follow-up and was associated with decreased rsFC between the dorsal anterior cingulate cortex (ACC) and caudate nucleus and decreased rsFC between the medial PFC and subgenual ACC (Harel et al., 2022).

Collectively, these findings suggest rsFC may be a valuable tool to predict treatment response in individuals with AUD and has potential to elucidate the neurobiological markers of relapse and treatment response. Notably, the individuals in the above studies were all explicitly treatment seeking (a small subset of the population with AUD) and completed a formalized treatment for AUD (which requires significant healthcare resources). As such, these results may not be generalizable to most individuals with AUD who may not have access to formalized treatment or may not recognize that they require treatment for AUD. To our knowledge, no study has used rsFC to predict a reduction in alcohol use following an SBIRT-style brief motivational interviewing (MI) intervention in individuals with AUD (Probst et al., 2015). The primary aim of the present study was to investigate the patterns of rsFC associated with response to an SBIRT-style brief intervention to reduce alcohol use in individuals with AUD. Individuals in this study were not actively seeking treatment and were recruited to participate in a study investigating rsFC in AUD. All individuals were provided with a brief intervention as they met diagnostic criteria for AUD as part of the study participation. RsFC was investigated across brain networks and regions associated with the pathophysiology of AUD, alcohol salience, reward, and resting state networks more broadly, based on the literature reviewed above. Specifically, we examined rsFC using seed-to-voxel analysis and selected seed points from the salience network, reward network, frontoparietal network (FPN), and default mode network.

These four a priori networks were examined based on their implications in comparative and prognostic studies, however specific hypotheses were not made due to paucity of literature, variable findings to date, and the exploratory nature of this preliminary study.

2. METHODS

2.1. Study Design

This study used a quasi-experimental within subject's design, comparing baseline rsFC in individuals that reduced their alcohol use following a brief MI style intervention (responders), to individuals that did not change their alcohol use (non-responders) at 3-month follow-up. Individuals that reduced their alcohol consumption by at least one WHO drinking level were classified as treatment responders; individuals that did not change or increased their alcohol consumption were classified as non-responders. These definitions were selected from current literature and have shown to be efficacious markers of treatment response in individuals with AUD (Witkiewitz et al., 2019). Reductions in WHO drinking levels in individuals with AUD have also been associated with an improvement of functioning (Witkiewitz et al., 2019). A description of WHO drinking levels is available in Supplementary Materials S1. These definitions of response, in addition to a categorical (responder vs. non responder) analytic approach were used to prioritize a clinically meaningful outcome associated with intervention response as compared to a continuous approach which may have highlighted subclinical changes in alcohol use and behaviour.

2.2. Participants

Participants were recruited through community advertisements in Hamilton ON, Canada. Inclusion criteria were: (i) diagnosis of moderate or severe AUD according to the DSM-5 (3+

symptoms); (ii) consumption above the NIAAA high-risk drinking guidelines (i.e., >14/7 drinks per week for men/women, respectively) in the 90 days preceding study enrolment; (iii) right handedness; (iv) fluent English speakers; (v) age between 21-55 years. Exclusion criteria included the following: (i) inability to provide informed consent; (ii) current DSM-5 substance use disorder diagnosis other than alcohol, tobacco, or cannabis; (iii) greater than weekly use of recreational drugs other than alcohol, tobacco, or cannabis; (iv) history of schizophrenia-spectrum/psychotic disorders or bipolar disorder; (v) MRI contraindications (e.g., metallic implants, claustrophobia, pregnancy); (vi) history of significant neurological disorders (i.e. traumatic brain injury or stroke); (vii) lower than ninth grade education (to ensure adequate literacy); (viii) currently receiving/seeking treatment or recently (within past 90 days) received treatment for alcohol or other substance related problems.

Fifty-six individuals between 21 and 55 years of age were enrolled. Four participants were excluded from the analysis as they were consistently in the WHO low-risk category (baseline and follow-up) and six participants were lost to follow up (89% retention). The final sample included 46 participants, of which 26 were classified as treatment responders and 20 as non-responders (see Table 1 for participant characteristics). This study was approved by the Hamilton Integrated Research Ethics Board (protocol #4551). All subjects provided written informed consent in accordance with the Declaration of Helsinki.

2.3. Procedures

Initial study eligibility was confirmed during a telephone assessment. Study participation consisted of two in-person visits at the baseline timepoint, typically held within 1 month of each other. All participants provided a breath sample using an Alco-Sensor Breathalyzer at the

beginning of each study visit to confirm sobriety. Due to COVID protocols, a subset of participants did not provide a breath sample. Instead, sobriety was assessed by the clinical and research staff using visual/auditory cues and by asking questions about their drinking over the previous 14 hours. During the initial in-person baseline visit, participant demographics and other assessments were obtained and an orientation to the scanning session was provided.

2.4. Brief Intervention

The second baseline visit consisted of a 1-hour MRI scan followed by the brief intervention which comprised one session of manualized structured feedback and MI, adapted from previous manuals in clinical trials (Halladay et al., 2018; MacKillop et al., 2015; "Project MATCH," 1993). The brief intervention manual used is provided in Supplementary Materials. More specifically, the intervention began with a conversation regarding the risks and benefits of alcohol use, followed by personalized feedback about the frequency of their alcohol use, the financial cost associated with their use, and consequences of alcohol use on their life. They were also provided with personalized feedback highlighting how their alcohol use compared to Canadian low-risk drinking guidelines (Butt, P., Beirness, D., Gliksman, L., Paradis, C., & Stockwell, T., 2011). This was followed by a conversation about physical and mental health risks associated with use, and a discussion about alcohol use in relation to participant values. Sessions followed a MI style, emphasizing the agency of the individual participant. Abstinence, moderation, harm reduction, or no short-term change were all acceptable outcomes. Goal setting regarding alcohol reduction and behaviour change plans were only created if the participant was receptive. Each session of motivational enhancement therapy (MET) was approximately 30-45 minutes. All MET sessions were conducted by a trained doctoral trainee in clinical psychology (SKS, EL, TP, MS) and were

supervised by a registered clinical psychologist (EM). Individuals were given voluntary uncompensated access to three additional follow-ups with their clinician to discuss changes. Treatment sessions were audio recorded and coded for therapist adherence to the clinical protocol. Participants completed a virtual visit using an encrypted version of Zoom for Healthcare Providers at 3 months.

A minority availed themselves of these additional visits: 11 (24%) completed follow-up 1, 5 (11%) completed follow-up 2, and 3 (6.5%) completed follow-up 3. Forty-five of forty-six sessions (one excluded due to missing data) were scored for adherence to the MET protocol during the first session; adherence was 92.46%, suggesting high adherence. The Global Rating of Motivational Interviewing Therapists (GROMIT) was used to rate the quality of the MI sessions (Moyers, 2004). The mean GROMIT score across sessions was high: session 1 – 90.90%; follow-up 1 – 91.85%; follow-up 2: 90.44%; follow-up 3: 94.44%.

2.5. Neuroimaging Assessment

Images were acquired using a GE whole-body, short-bore 3T scanner with eight parallel receiver channels (General Electric, Milwaukee, WI, USA). Whole-brain anatomical images were acquired using high-resolution T1-weighted images (3D BRAVO sequence, straight axial plane, repetition time [TR] = 8.2 ms, echo time [TE] = 3.2 ms, inversion time [TI] = 450 ms, 12° flip angle, 25.6 cm field of view [FoV], 256 x 256 matrix, 192 slices, slice thickness = 1 mm [1 mm isotropic voxels], bandwidth = 31.25 kHz [244 Hz/pixel], acceleration factor 2, scan time 4:43). Resting state gradient echo, echo planar fMRI images were acquired with the following acquisition parameters (TR = 2000 ms, TE = 30 ms, 90° flip angle, 22.4 cm FoV, 64 x 64 matrix, 40 3.5 mm-thick axial slices [3.5 mm isotropic voxels], bandwidth = 250 kHz [7812 Hz/pixel], acceleration

factor 2). All sequences were acquired within a single session. Once participants were positioned in the scanner, they were instructed to passively observe a fixation cross. The resting state fMRI run was 9 min in length and yielded 270 continuous volumes. Following the scanning session, participants were interviewed to ensure that they did not fall asleep during the scan.

2.6. Out-of-Scanner Assessments

Alcohol use was captured by the Alcohol Timeline Follow Back Interview (TLFB; (Sobell et al., 2001)) over the past 28 days and past 90 days (at 3 month follow up). Diagnosis of AUD was obtained by the Diagnostic Assessment Research Tool for DSM-5 (DART; (McCabe, R. E., Milosevic, I., Rowa, K., Shnaider, P., Pawluk, E. J., Antony, 2017)). Consequences of alcohol use were assessed using the Drinker Inventory of Consequences (DrInC; (Miller et al., 1995). Nicotine dependence and smoking behaviours were assessed using the Fagerstrom Test for Nicotine Dependence (FTND; (Heatherton et al., 1991)). Symptoms of anxiety were assessed using the Generalized Anxiety Disorder 7 Item Scale (GAD-7; (Johnson et al., 2019, p. 7)). Depressive symptomology was assessed using the Patient Health Questionnaire (PHQ-9; (Urtasun et al., 2019)). Symptoms of PTSD were assessed using the PCL-5 Posttraumatic Stress Disorder Checklist for DSM-5 (Blevins et al., 2015).

2.7 Data Analysis

Resting-state and anatomical MRI data were preprocessed using Statistical Parametric Mapping Software (SPM12) and CONN Functional Connectivity Toolbox Version 19c. Imaging data were obtained in DICOM file format and converted to NIFTI using SPM and then uploaded to CONN for further preprocessing. The default CONN preprocessing pipeline for volume-based analyses was optimized to preprocess both structural and functional scans. Briefly, structural scans were translated and centered to (0, 0, 0) coordinates and subsequently underwent direct

segmentation (gray matter [GM], white matter [WM], and cerebrospinal fluid [CSF]) and Montreal Neurological Institute (MNI) normalization. Functional scans were realigned and unwrapped (motion estimation and correction), and translated and centered to (0, 0, 0) coordinates. Images with motion greater than 0.9 mm in the translational plane and rotational plane and those with a global signal z-value over 5 were discarded. Finally, functional data were segmented (GM, WM, CSF), normalized to MNI space, and spatially smoothed to increase the signal-to-noise ratio and minimize individual variation in functional neuroanatomy with a 4.5-mm FWHM Gaussian filter. Seed-to-voxel analysis was completed using the CONN toolbox, which correlates mean BOLD signal in predefined "seed" regions with the BOLD signal from each voxel of the brain (seed-to-voxel), which is then averaged in predefined target regions (region of interest [ROI]-ROI) (Whitfield-Gabrieli and Nieto-Castanon, 2012). Subject-specific maps of CSF and WM were used as nuisance regressors during the denoising step of analysis. The aCompCor strategy was employed within CONN to control for the effects of physiological motion, residual head movement, and white matter and CSF noise. The BOLD signal time course was then extracted, and functional images were then temporally band-pass filtered (0.008–0.09 Hz). All images were manually inspected to ensure signal dropout artifacts were not present.

ROIs were taken from the default-atlas implemented in the CONN toolbox which is comprised of regions from the Harvard-Oxford and the Automated Anatomical Labelling (AAL) atlases. Seed-to-voxel analyses were performed to examine the functional coupling of regions of interest associated networks involved in the pathophysiology of AUD, reward, impulsivity, and addiction more broadly. As such, the rsFC of the DMN was investigated using the medial prefrontal cortex and posterior cingulate cortex as seed points. The rsFC of the FPN was investigated using the bilateral lateral prefrontal cortex and bilateral posterior parietal cortex. The

bilateral anterior insular cortex, anterior cingulate cortex, and bilateral rostral prefrontal cortex were used as seed points of the Salience Network. Finally, to further investigate rsFC associated with reward, impulsivity, and addiction more broadly, the bilateral NAc, bilateral inferior frontal gyrus - pars opercularis (IFG pars opercularis) and triangularis (IFG pars triangularis), bilateral caudate, and bilateral putamen were used as seed points. A seed-to-voxel analytic approach was used whereby the correlations between the mean BOLD time-series of the seed ROIs and the time-series of each voxel throughout the whole brain were computed for each subject. Following this, the correlation maps created were used for group-level analysis (treatment responders vs. non-responders) with two sample t-tests to investigate the difference in BOLD signal correlations between groups. To minimize the risk of type 1 error, the significance of group effects was thresholded using a voxel-level uncorrected $p<0.001$ and cluster-level false discovery rate (FDR) corrected $p<0.05$. All results were covaried for years of education. Analysis of out-of-scanner variables used SPSS 26.0 and R Version 3.4.4.

3. RESULTS

3.1. Preliminary Analyses

Treatment responder and non-responder groups did not differ by age ($p=0.429$), sex ($p=0.529$), years of education ($p=0.088$), or race ($p=0.638$). Groups also did not differ in smoking status ($p=0.455$) or the number of AUD symptoms endorsed at baseline ($p=0.938$). There were also no differences in baseline alcohol consumption between treatment responders and non-responders among men ($p=0.593$) or women ($p=0.733$). At 3-month follow-up, male treatment-responders consumed approximately 24 standard alcoholic beverages across the previous 28 days less than male non-responders ($p=0.006$) and female treatment responders consumed

approximately 18 standard alcoholic beverages less than non-responders (p=<0.001). Changes in drinks per week through study participation can be seen in Figure 1. There were no differences in depressive, anxious, and trauma symptomology between responders and non-responders (ps>0.05), Table 1. Participants in the responder group completed 1.61 sessions compared to the non-responder group, which completed 1.10 sessions (p=0.035). A greater number of responders attended follow-up sessions than non-responders. All responders and non-responders attended session 1 (compulsory brief intervention session). A total of 9 (34.6%) responders attended follow-up 1, 4 (15.4%) attended follow-up 2, and 3 (11.5%) attended follow-up 3, as compared to 2 (10%) non-responders who attended follow-up 1 and 1 (5%) that attended follow-up 2. No non-responders attended follow-up 3.

3.2. Salience Network

Intervention responders vs. non-responders exhibited increased rsFC between the ACC (seed) and the (i) left postcentral gyrus; and (ii) right supramarginal gyrus (Table 2; Figure 2A). Compared to non-responders, intervention responders exhibited decreased rsFC between the right rostral prefrontal cortex (seed) and IFG (Table 2; Figure 3A).

There were no differences in rsFC associated with the left rostral prefrontal cortex or the bilateral anterior insula between intervention responders and non-responders.

3.3. Reward Network

Intervention responders exhibited decreased rsFC between the right NAc (seed) and the (i) right orbital frontal cortex (OFC); and (ii) right anterior insula (Table 2; Figure 3D) compared to non-responders. There were no between group differences in rsFC associated with the bilateral caudate, bilateral putamen, and left NAc. Decreased rsFC was found in intervention responders vs. non-responders between the left IFG pars triangularis (seed) and the right cerebellum and the

right IFG pars triangularis (seed) and the (i) right frontal eye fields; and (ii) right angular gyrus (Table 2; Figure 3C).

Conversely, intervention responders demonstrated increased rsFC between the right IFG pars opercularis (seed) and the (i) right cerebellum; and (ii) right occipital fusiform gyrus (Table 2; Figure 2C). There were no between group differences in rsFC associated with the left IFG pars opercularis.

3.4. Frontoparietal Network

Intervention responders demonstrated increased rsFC between the right posterior parietal cortex (seed) and the ventral ACC as compared to non-responders (Table 2; Figure 2B). There were no differences in rsFC associated with the bilateral lateral prefrontal cortex or left posterior parietal cortex between treatment responders and non-responders.

3.5. Default Mode Network

There were no differences in rsFC associated with the medial prefrontal cortex and posterior cingulate cortex between intervention responders and non-responders.

4. DISCUSSION

The current study examined differences in baseline (pre-intervention) rsFC between individuals with AUD who responded to a brief intervention to increase positive health behaviours and reduce alcohol consumptions (responders) vs. those that did not change their alcohol consumption (non-responders) at 3-month follow-up. We found significant differences in baseline rsFC between responders and non-responders in regions associated with the FPN, salience network, and reward processing. Specifically, responders demonstrated increased rsFC between several brain regions associated with conflict monitoring, higher-order cognitive processes, and reward, compared to non-responders. Responders also demonstrated decreased rsFC between brain

regions associated with reward processing, interoceptive attention, impulsivity, and salience compared to non-responders. Our results suggest the patterns of rsFC seen in responders may reflect a favourable state of internal motivation or perhaps a less severe disruption of the brain from AUD. These patterns may allow participants to respond favourably to a brief-intervention to reduce alcohol consumption and engage in associated behaviour changes.

4.1.Salience Network

The salience network plays an integral role in attending to motivationally salient stimuli and recruiting appropriate brain regions and associated networks to promote changes in behaviour (Galandra et al., 2018; Seeley et al., 2007). Therefore, the salience network may play a unique role in facilitating engagement in the brief-intervention used and behaviour change (Feldstein Ewing et al., 2011). We found increased rsFC in responders compared to non-responders between the ACC and supramarginal gyrus (located within the posterior parietal cortex, FPN) and postcentral gyrus (primary somatosensory cortex). As discussed above, increased rsFC between the ACC and FPN may reflect a pattern of functional connectivity (FC) in responders that makes them more receptive to change elicited by the brief intervention. This is supported by a study that found that increased BOLD activation in the supramarginal gyrus was associated with self-generated vs. experimental-generated change talk (statements supporting behaviour change) in individuals who reported binge drinking (Feldstein Ewing et al., 2014). Collectively, results suggest these patterns of FC may be associated with an intrinsic motivation to change behaviour (Feldstein Ewing et al., 2014). Further, a review by Kropf et al. highlighted the role of the postcentral gyrus (primary somatosensory cortex) in emotion regulation and emphasized its value as a treatment target for mood and addiction related disorders (Kropf et al., 2018). Increased rsFC between regions of the

salience network and the primary somatosensory cortex in this population may reflect dynamic integration between the salience network and regions involved in emotional regulation.

Results also found that responders demonstrated decreased rsFC between the right rostral PFC, a region involved in prospective memory - the ability to carry out an intended action (Volle et al., 2011), and the left IGF (pars opercularis) a region associated with response inhibition and integral to reward processing (Swick et al., 2008). Task-based FC of the rostral PFC has been associated with treatment response in individuals with AUD (Charlet et al., 2014). A study examining FC associated with relapse risk in individuals with alcohol dependence found increased FC of the rostral PFC during high vs. low cognitive working memory load in the low relapse risk group (Charlet et al., 2014). Authors suggested that this pattern of FC may highlight engagement of executive control areas in individuals that respond to treatment (Charlet et al., 2014). When taken together, decreased rsFC between the rostral PFC and IFG during a resting state (low cognitive load) scan may reflect decreased engagement between regions associated with salience and cognition and impulsivity and reflect decreased top-down cognitive processing during rest and suggest a healthy functional adaptability in intervention responders.

4.2. Reward Processing Network

Structural and functional abnormalities in brain regions associated with reward processing and emotion regulation have been well documented in AUD. In this study, responders demonstrated decreased rsFC between several brain regions involved in reward processing including the IFG and NAc. The IFG plays a central role in mediating impulsivity (Hampshire et al., 2010; Swick et al., 2008). Literature highlights that the right IFG is also responsible for attentional control and cognitive appraisal (Hampshire et al., 2010; Tops et al., 2014), and the left IFG is primarily responsible for response inhibition (Swick et al., 2008), inhibiting irrelevant

information (Berman et al., 2011) and may play a role in rumination (Tops et al., 2014). Research has highlighted a well-established relationship between impulsivity and alcohol use, in which increased AUD severity is associated with decreased self-control. Claus et al., highlighted the association between impulsivity, AUD, and IFG connectivity and reported that individuals with more severe AUD demonstrated greater delayed reward discounting and greater activation within the IFG, insula, and orbitofrontal cortex (Claus et al., 2011). In addition, increased BOLD activation of the IFG was reported in a sample of individuals that reported recently binge drinking and was associated with sustain talk (speech that favours alcohol intake) (Feldstein Ewing et al., 2014). Further, higher-levels of within-session sustain talk were found to predict poorer alcohol use outcomes at 3 and 12-months following a brief MI intervention in college students (Apodaca et al., 2014). When taken together, decreased rsFC between the left IFG (pars triangularis) and the cerebellum – a region which has been implicated in emotional control and cognitive functioning (Brissenden et al., 2016; Gold and Toomey, 2018), suggests that at baseline, intervention responders had decreased rsFC between regions associated with impulsivity and emotional and cognitive processes at baseline in intervention responders. Interestingly, the opposite pattern of rsFC was seen between the right IFG (attentional control, cognitive appraisal, and inhibition) and the cerebellum and right occipital fusiform gyrus. Greater BOLD activation in the occipital fusiform gyrus was reported during both self vs. experimenter generated sustain and change talk in binge drinkers, highlighting a potential role of the occipital fusiform gyrus in self-generated motivation to reduce or sustain alcohol use (Feldstein Ewing et al., 2014). Further, decreased rsFC between the right IFG (pars triangularis) and right frontal eye fields (region associated with the dorsal attention network (Vossel et al., 2014)) and angular gyrus (default mode network (Seghier,

2012)) may reflect patterns of rsFC that are associated with greater openness to engage in treatment and reflect on challenges associated with current alcohol use.

Finally, the NAc has been widely studied across addictions and AUD research (Cservenka et al., 2014; Mitchell et al., 2012; Veer et al., 2019) and was also identified as a candidate for deep brain stimulation for the treatment of AUD (Ho et al., 2018). A recent study examined rsFC between the NAc and the OFC in recently abstinent patients with AUD (n=39) and found that alcohol craving was associated with increased rsFC between the NAc and OFC. Further, alcohol intake induces opioid release in both the NAc and the OFC; changes in opioid binding in the OFC were significantly correlated with problem alcohol use, suggesting that connectivity between the NAc and OFC plays an important role in contributing to excessive consumption of alcohol. Interestingly, in our sample, we found decreased rsFC between the right NAc and both the right OFC and right anterior insular cortex at baseline in intervention responders. In the context of reward processing and addiction, activation of the OFC is hypothesized to occur and aid decision making in the presence of insufficient information to determine an appropriate solution and through connections with the insular cortex and amygdala, may change behaviour by supressing previously rewarding responses – thus making it an attractive target for positive behaviour change and treatment in AUD (Adinoff, 2004; Elliott, 2000). Literature has also highlighted the role of the anterior insular cortex in reward circuitry and alcohol salience and valuation (Adinoff, 2004; Feldstein Ewing et al., 2011; MacKillop, 2016) and suggests that the insula provides interoceptive information to the NAc to shape reward processing (Cho et al., 2013). As such, this pattern of rsFC may reflect activation in subcortical and prefrontal brain regions that is associated with decreased alcohol salience and valuation, adaptive decision making, and leads to positive behaviour change.

4.3. Frontoparietal Network

Behaviour change requires executive control, therefore making the FPN a valuable candidate network to investigate in psychotherapeutic treatment response. The FPN is responsible for accomplishing goal-oriented and cognitively demanding tasks, sustaining attention, and additional aspects of cognitive functioning (Marek and Dosenbach, 2018). It achieves this through robust cortical and subcortical connections with various brain regions, allowing it to interact with networks responsible for self-referential processing, salience, and emotion regulation (Marek and Dosenbach, 2018). Although the rsFC of the FPN has not been studied with regards to treatment response in AUD, rsFC from 3 of 98 dorsolateral prefrontal cortex loci (n=43) were used to predict cocaine relapse with a combine accuracy of 87.5% in patients with cocaine use disorder following a psychosocial treatment intervention (Zhai et al., 2021). With regards to the wider mental health literature, a study examining the prognostic value of rsFC in determining treatment outcome following 6 weeks of escitalopram (10mg once daily) for treatment of MDD found that treatment responsivity was associate with increased rsFC between the right FPN and posterior DMN (50% reduction in HAMD scores) (Martens et al., 2021). Similarly, FC strength of the FPN and the subgenual ACC predicted treatment outcome following one session of electroconvulsive therapy in individuals with treatment resistant MDD (Leaver et al., 2018). Consistent with these findings, our results found increased rsFC between a hub of the FPN, the right posterior parietal cortex, and the vACC, a region involved in conflict monitoring (Kanske and Kotz, 2011) and affect regulation (Stevens, 2011). Importantly, literature also suggests that the vACC plays a role in computing self-efficacy and in social decision making (Lockwood and Wittmann, 2018). As such, rsFC between the PPC and vACC may reflect a heightened ability of intervention responders to engage higher-order thinking, social decision making, and conflict monitoring. This may reflect enhanced top-

down processing and increased ability to engage in goal-directed activity via increased recruitment of regions associated with conflict monitoring and emotion regulation. These patterns may have made individuals more receptive to change talk and information delivered through the MI-style intervention and increased the likelihood of behaviour change.

4.4. Strengths and Limitations

The current findings should be considered in the context of this study's strengths and limitations. A strength of the current study is the use of a manualized protocol to administer the brief intervention, which allowed for the treatment team to deliver a high-quality brief intervention and monitor treatment fidelity. The use of manualized treatment protocols also allows for this study to be replicated and for other groups to expand on this current research. Further, study clinicians also demonstrated high adherence to the protocol used and MI principles. Additionally, our study demonstrated high participant retention (89%) from baseline to the 3-month follow-up visit which allowed us to capture outcomes in the majority of individuals scanned at baseline. Moreover, neuroimaging analysis was completed using the CONN fMRI neuroimaging software, which uses the widely available Harvard-Oxford Cortical Atlas and allows for results of this study to be replicated and similar regions of interest to be investigated by other groups. Limitations of our study include that the sample size of this preliminary study was modest. While, our sample size was sufficient for detecting FDR-corrected differences between groups, this sample size may be underpowered to detect smaller effect sizes or correlate neuroimaging differences to clinical variables. Moreover, although the brief intervention employed was on average a single hour-long meeting and was more substantial than brief primary care-based interventions (i.e., 5 minutes of brief advice) it is still less than the standard of care for AUD (i.e., 12 sessions of CBT or inpatient treatment). Finally, the study enrolled non-treatment-seeking AUD+ individuals, who represent

most individuals with AUD. However, this study cannot speak to patterns of brain activity in individuals initiating a recovery attempt or following formalized treatment.

4.5. Conclusions

In summary, we employed a brief-intervention to reduce alcohol use in individuals that sought to participate within a neuroimaging study on AUD and examined whether baseline rsFC was associated with behavioural response (reduced alcohol consumption) to the intervention at a 3-month follow-up. Our results largely highlighted patterns of decreased rsFC between brain regions associated with reward processing, impulsivity, and alcohol valuation and salience in intervention and increased rsFC between brain regions responsible for higher order cognitive processes and emotional regulation in responders vs. non-responders. These patterns of rsFC may suggest increased top-down processing and decreased rsFC within reward systems in responders at baseline. These patterns of rsFC may be important in contributing to positive health behaviour changes and reductions in alcohol use in individuals with AUD.

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Zhai T, Salmeron BJ, Gu H, Adinoff B, Stein EA, Yang Y (2021) Functional connectivity of dorsolateral prefrontal cortex predicts cocaine relapse: implications for neuromodulation treatment. Brain Communications 3:fcab120.

Table 1: Participant demographics, alcohol use severity and psychopathology

Variable	All Participants	Responders (n=26)	Non-Responders (n=20)	*p*-value	d
Demographics and IQ					
Sex (% Female)	65.2	69.2	60	.529	-0.19
Years of Education (M [SD])	14.44 [2.90]	13.81 [3.03]	15.25 [2.57]	.088	0.51
Age (M [SD])	34.07 [10.70]	32.96 [10.93]	35.50 [10.51]	.429	0.24
Race (% European White)	84.8	80.8	90	.638	-0.14
% Monthly Smokers	41.3	46.2	35	.455	-0.22
Shipley Standard Score (M [SEM])	103.20 [14.13]	102.85 [2.90]	103.65 3.04]	.849	0.06
Psychiatric Symptoms					
PHQ-9 Score (M [SD])	10.33 [6.29]	10.00 [6.32]	10.75 [6.40]	.694	0.12
PCL-5 Score (M [SD])	22.63 [18.29]	24.69 [18.49]	19.95 [18.14]	.388	-0.26
GAD-7 Score (M [SD])	7.85 [5.62]	7.85 [6.03]	7.85 [5.19]	.998	1.0E-3
Drinking Variables					
AUD Sxs (M [SD])	6.57 [2.58]	6.54 [2.52]	6.60 [2.72]	.938	0.02
DRINC: Physical	0.31 [0.19]	0.32 [0.22]	0.29 [0.15]	.661	-0.13
DRINC: Interpersonal	0.15 [0.19]	0.17 [0.24]	0.13 [0.10]	.380	-0.24
DRINC: Intrapersonal	0.32 [0.23]	0.30 [0.26]	0.36 [0.19]	.391	0.25
DRINC: Impulse Control	0.14 [0.12]	0.17 [0.14]	0.12 [0.10]	.150	-0.42
DRINC: Social Responsibility	0.20 [0.17]	0.20 [0.19]	0.20 [0.14]	.976	-0.01

Note: PHQ-9: Patient Health Questionnaire; GAD-7: Generalized Anxiety Disorder 7-Item Scale; PCL-5: Posttraumatic Stress Disorder Checklist for DSM-V; SEM: Standard Error, M: Mean; MI Physical Consequences, Interpersonal Consequences, Impulse Control, and Social Responsibility Consequences are subscales of the Drinker Inventory of Consequences (DRInC) Questionnaire.

Table 2: Differences in resting state functional connectivity at baseline between treatment responders and non-responders, FDR-corrected $p<0.05$, (T min = 3.29).

Seed Regions	Associated Network (Seed)	Region	Coordinates (X,Y,Z)	Cluster size (K)	P-Value
RESPONDER > NON-RESPONDER					
Anterior Cingulate Cortex	Salience	Supramaringal Gyrus (R)	+40 -36 +38	158	0.0035
		Primary Sensory Cortex (L)	-36 -36 +32	110	0.0126
Posterior Parietal Cortex (R)	Frontoparietal	Ventral Anterior Cingulate Cortex	+02 +26 +04	83	0.049
Inferior Frontal Gyrus Pars Opercularis (R)	Reward	Cerebellum (R)	+30 -56 -22	173	0.0015
		Occipital Fusiform Gyrus (R)	+34 -76 -14	148	0.002
NON-RESPONDER > RESPONDER					
Rostral Prefrontal Cortex (R)	Salience	Inferior Frontal Gyrus Pars Opercularis (L)	-42 +22 +00	238	0.000146
Inferior Frontal Gyrus Pars Triangularis (R)	Reward	Angular Gyrus (R)	+46 -54 +32	499	<0.00001
		Frontal Eye Fields (R)	+38 +18 +44	145	0.0037
Inferior Frontal Gyrus Pars Triangularis (L)	Reward	Cerebellum	+30 -76 -40	135	0.0081
Nucleus Accumbens (R)	Reward	Orbital Frontal Cortex (R)	+06 +48 -18	100	0.022
		Insula (R)	+40 -04 -16	77	0.037

Figure 1: Change in drinks per week consumed through study participation.

Panel A highlights drinks per week in male participants, Panel B highlights drinks per week in female participants. Reduction in drinks per week from baseline to 3-month timepoints in responders was statistically significant $p<0.05$.

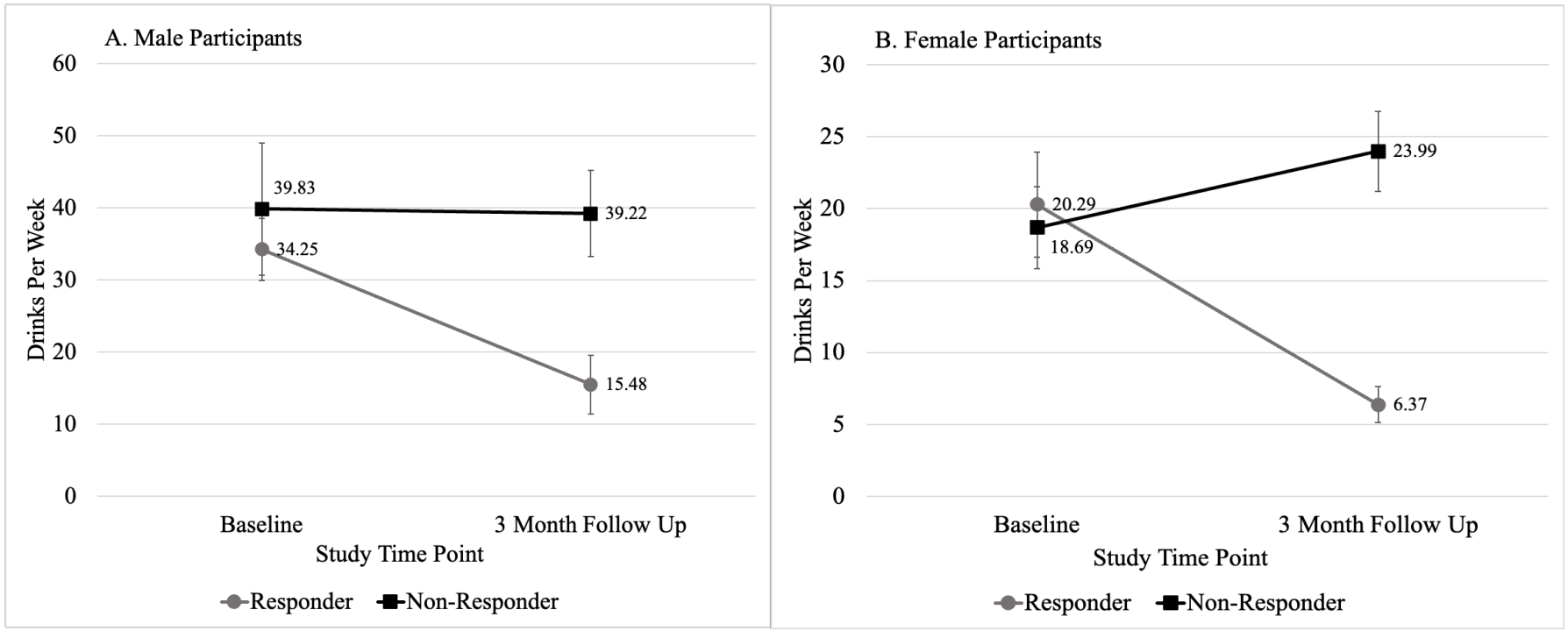


Figure 2: Increased RsFC between treatment responders and non-responders at baseline, FDR-corrected $p<0.05$, (T min = 3.29).

Clusters resulting from a seed to voxel analysis are shown above. All results are FDR-corrected ($p<0.05$). Red represents increased RsFC in responders vs. non-responders between seed regions and cluster. The following patterns of coupling are described with the seed underlined; only corresponding clusters are shown: A. Anterior Cingulate Cortex – Left Postcentral Gyrus ($p=0.0126$); Right Supramarginal Gyrus ($p=0.0035$); B. Right Posterior Parietal Cortex - Ventral Anterior Cingulate Cortex ($p=0.049$); C. Right Inferior Frontal Gyrus (Pars Opercularis – Right Cerebellum ($p=0.0015$); Right Occipital Fusiform Gyrus ($p=0.002$).

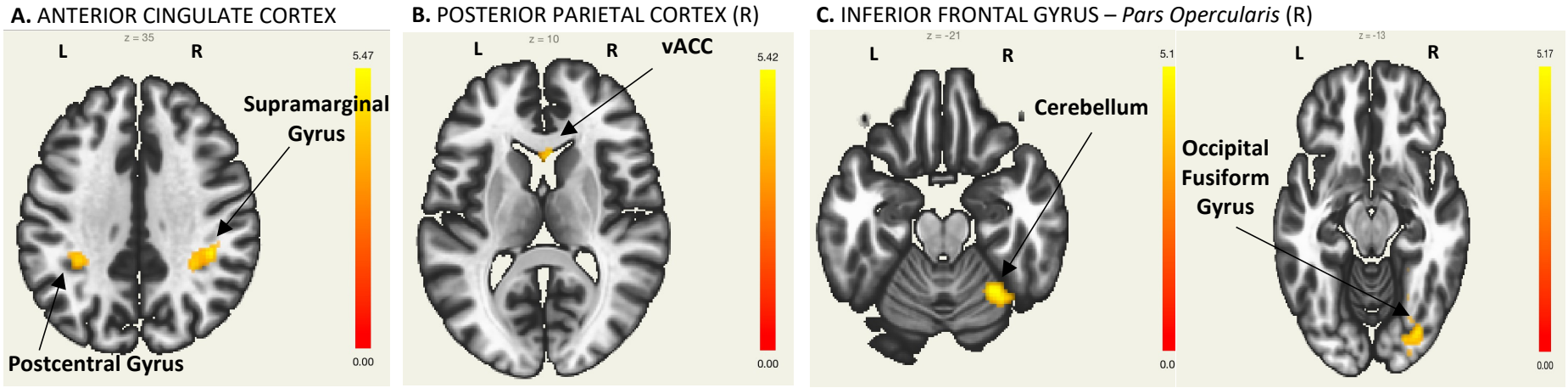
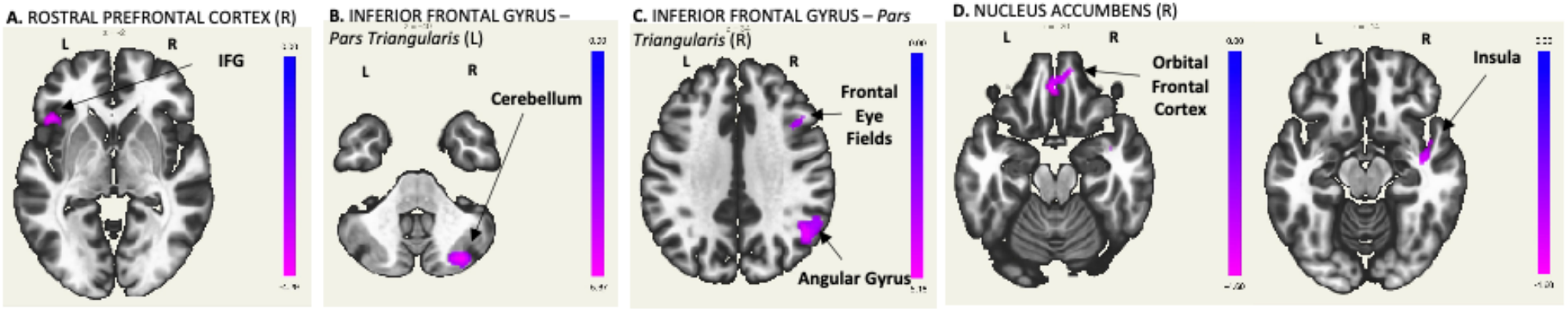


Figure 3: Decreased RsFC between treatment responders and non-responders at baseline, FDR-corrected p<0.05, (T min = 3.29).

Clusters resulting from a seed to voxel analysis are shown above. All results are FDR-corrected (p<0.05). Blue represents decreased RsFC in responders vs. non-responders between seed regions and cluster. The following patterns of coupling are described with the seed underlined; only corresponding clusters are shown: A. Right Rostral Prefrontal Cortex – Left Inferior Frontal Gyrus (Pars Opercularis) (p<0.001); B. Left Inferior Frontal Gyrus (Pars Triangularis) – Right Cerebellum (p=0.0081); C. Right Inferior Frontal Gyrus (Pars Triangularis) – Right Frontal Eye Fields (p=0.0037); Right Angular Gyrus (p<0.001); D. Right Nucleus Accumbens – Right Orbital Frontal Cortex (p=0.022); Right Insula (p=0.037)



SUPPLEMENTARY MATERIALS

Table S1: World Health Organization drinking risk levels

	Low Risk	**Medium Risk**	**High Risk**	**Very High Risk**
Standard Drinks/Day (Men)	0-2.9 drinks	3.0-4.3 drinks	4.4-7.1 drinks	7.2+ drinks
Standard Drinks/Day (Women)	0-1.4 drinks	1.5-2.8 drinks	2.9-4.3 drinks	4.4 drinks

Table S2: Changes in drinks per week through study participation

Variable	**Responders** (n=26)	**Non-Responders** (n=20)	***p*-value**	**d**
Baseline Drinks/Week Male (M [SD])	34.25 [12.18]	39.83 [25.87]	.593	0.28
Baseline Drinks/Week Female (M [SD])	20.29 [15.43]	18.69 [9.89]	.733	-0.12
3 Month Drinks/Week Male (M [SD])	15.48 [11.56]	39.22 [16.84]	.006	1.64
3 Month Drinks/Week Female (M [SD])	6.37 [5.24]	23.99 [9.67]	3.4E-5	2.41

S3: Manual for brief-interventions sessions

Overview

This is the clinical implementation manual for the research study "*Using Neuroeconomics to Understand Alcohol Overvaluation in Alcohol Use Disorder"* (NEURO ALC; Multiple Principal Investigators: James MacKillop, PhD & Lawrence Sweet, PhD), funded by the National Institute on Alcohol Abuse and Alcoholism (R01 AA025911). For study participants who have an alcohol use disorder (AUD), up to four therapy sessions with a mental health clinician are provided. These sessions are both to encourage reductions in alcohol use in the participants and to examine indicators collected in the study as predictors of changes in drinking behavior over time. The core approach is motivational interviewing, and the four-session regimen is broadly adapted from the Motivational Enhancement Therapy used in Project MATCH.

Participants in the study receive the first session as part of the magnetic resonance imaging (MRI) session in the study. They then have the option of up to three subsequent stand-alone meetings during the three weeks that follow (up to one per week). Transportation costs are provided for the stand-alone sessions, but additional study incentives are not provided.

DOMAIN	ASSESSMENTS
Descriptive Information	Demographics
Substance Use Frequency	Timeline Followback Interview
Drinking Motives	Drinking Motives Questionnaire (DMQ)
Drinking Consequences	Drinker Inventory of Consequences – Revised (DRINC)
Alcohol Use Disorder Symptoms	Alcohol Use Disorders Module, Diagnostic Assessment for Research and Treatment (DART) *Therapist Review Only*
Motivation to Change	Alcohol Motivation Rulers (Readiness, Importance, Confidence) *Collected in Session*

Session #1

Overview

1. Pre-Session Preparation
2. Introduction: confidentiality, brief intro to patient, assessment (~5mins)
3. Pros and Cons of substance use (~15mins)
4. Personalized feedback reports (~15mins)
    a. Feedback #1: Drinking motives
    b. Feedback #2: Risk relative to Canadian Low-risk Drinking Guidelines
    c. Feedback #3: Personal negative consequences from alcohol
    d. Feedback #4: Personal values card sort
5. Decisional Balance (~1-2mins)
6. Goal Setting (~5-10mins)
7. Change Plan (~10mins)
8. Recapitulation (~1-2mins)
9. Conclusion (~5mins)

Preparation

1) Feedback Report Production (~10minutes)
    a. Aggregate the participant's data and generate the feedback reports
    b. This information should be provided by a Research Assistant, however, instructions are provided in case of an oversight

2) Generate hypotheses about the participant.
    a. Review patterns of motives
    b. Note level of discrepancy from recommended drinking levels
    c. Note <u>three</u> highest domains of impairment
    d. Review number of symptoms, nature of symptoms (e.g., predominantly physiological [tolerance and withdrawal] vs. adverse psychosocial consequences), and severity designation (mild, moderate, severe)
    e. Generate candidate insights from the objective data to juxtapose with the subjective cons reported

INTRODUCTION

1. Introduce yourself and build rapport.

Example language: *How are you today? How was the brain scan? Would you like to use the bathroom or a bottle of water?*

2. Ask the participant what they know about this part of the visit.
3. Let the person know that, because this is a research study, we try to standardize everything we do so you'll be referring to the manual. The conversation will be audio-recorded for the same reason.
4. Inform the participant you are a learner, and you are being supervised by a registered psychologist, which is the other reason we are recording the session.
5. Establish confidentiality and its limits.

Suggested language:

"Before we start, I want you to know that everything we talk about today will be kept confidential, but there are some exceptions to that. I would need to break confidentiality under the following circumstances:

1) If you inform me that you post a threat to your own safety or the safety of another individual, I will have to inform the appropriate authorities.

2) If you inform me that a child under the age of 18 is at risk of sexual, emotional, or physical abuse then I would need to report that to child protective services

3) If you inform me that a registered healthcare provider in the provider of Ontario has acted in a way that is sexual inappropriate with you then I would need to report this to their college or governing body.

4) If you inform me that a senior citizen being cared for in a long-term care facility is at risk of harm, neglect, or being taken advantage of then I would need to report this to the Registrar of the Retirement Homes Regulatory Authority.

None of these topics will be a focus of our conversation today, but I want to make sure you are aware of these requirements. Apart from this, we will keep everything else 100% confidential to the extent of the law. Do you have any questions?"

6. Explicitly state that this part of the visit is for having an open conversation about alcohol use and providing them with some feedback. It will last about 45 minutes.

   Example language: *I am not here to tell you what to do. The goals are to have an open conversation about alcohol use and for me to give you some information. In particular, I will be providing you with some feedback from the assessments you completed during the first visit. What, if anything, you decide to do with that information is 100% up to you."*

7. Establish engagement (or lack thereof). Within an MI framework, behavior change is determined by the participant. Explicitly establishing their autonomy and agency from the start is important.

   Example language: *"How does that sound? What do you think?"*

Section 2: Pros and Cons OF ALCOHOL USE

The first substantive section is discussing the positives and negatives of alcohol use. Recognizing both aspects acknowledge the functional reasons people use substances and is intended to understand their motives and reduce defensiveness. It also allows the person to describe their substance use in their own words.

Example language: *"A little later I'm going to be giving you feedback based on the information we collected previously, but first I want to hear how you see your present situation. Tell me about your alcohol use."*

<table>
<tr><th>PROS</th><th>CONS</th></tr>
<tr><td rowspan="2">(1) "What do you like about drinking? What are the good things about alcohol?
Do <u>not</u> probe for additional positives.</td><td>(2) "What don't you like about alcohol?"
Probe for additional negatives: "Anything else?"</td></tr>
<tr><td>(3) "Which Con(s) would you identify as most important?"</td></tr>
</table>

When pros and cons have been fully elaborated, provide a summary back to the person and solicit their evaluation.

Example language: *"So, it sounds like you enjoy the social aspects of drinking and using it to relax, but you don't like that it sometimes gets out of hand, and you have had some run-ins with the law as a result. Plus, it leads to fights with your husband, and you don't like how much you spend on it. Is that right? Is there anything we missed?"*

PERSONALIZED FEEDBACK REPORTS

The next section involves systematically reviewing the information the participant provided. In each instance, the clinician will show the participant their data and solicit their feedback. As appropriate, the clinician will probe and explore each of the domains.

Example language: *"Next, I'm going to be providing you with feedback from the assessments you did at the initial session. Remember that what I am going to show you is based on your responses, but that doesn't mean it's 100% accurate. Our assessments are imperfect so let me know if you agree or disagree with what I present to you.*

Feedback #1: Drinking Motives

The first feedback is focused on the individual's self-reported motives for using alcohol. This is an objective way to capture the 'likes' and 'dislikes' that were solicited earlier.

The clinician presents the graph of motives, explains what the bars mean, and asks the participant whether this representation is accurate (see Appendix B for specific explanations).

This feedback is non-evaluative and is intended to enhance the participant-clinician relationship by giving the participant a further sense that the clinician understands where they are coming from. Furthermore, it demonstrates to the participant that the previous assessment can accurately measure their experience.

Draw attention to the two highest domains.

Example language: "*First, we assessed the most common reasons you use alcohol. Based on this, you most commonly use alcohol for social reasons and to cope with feeling bad."*

Draw parallels to the previous discussion of pros and cons, where possible. (e.g., "*The elevation here seems to reflect what you described before in terms of enjoying using with friends").*

Point out discrepancies also. (e.g., "*You didn't mention using alcohol to help when you're feeling down before. Do you think that's accurate?")*

If the participant doesn't see the overlap, don't feel the need to defend the measure. Simply note that it doesn't seem to have captured the participant's motives optimally.

Feedback #2: risk relative to the Canadian low risk drinking guidelines and costs of drinking

Review the person's alcohol use in the context of recommendations for same-sex Canadians.

Example language: "*Next, we're going to take a look at your drinking compared to recommended levels."*

Review the participant's data in terms of objective indicators of risk.

Example language: "*This figure focuses on your substance use compared to objective recommendations."*

First, show Canadian Low-Risk Drinking Guidelines handout. Second, show comparison figure.

Discuss the participant's drinking relative to Canadian Low-Risk Drinking Guidelines:

- Males = 15/week and no more than 3 on a given day
- Females = 10/week and no more than 2 on a given day

Example language: "*In other words, these data suggest you drink quite a bit more than most people and above low-risk recommendations."*

Add probes:

1) "*What are your thoughts about that?"*
2) *"Does that make sense to you?"*
3) *"Is that surprising?*"
4) "*You're really surprised about how high you seem to be."*

Financial Costs

Next, provide feedback on the amount of money the individual is spending and the number of calories that are associated with their drinking

Example language: "*Here's some more objective information about your drinking. You spent about $1300 on alcohol over the last year. What are your thoughts about that? …"*

The focus is on developing discrepancy and ambivalence.

Example language: *"Are you surprised to see it's that much?"*

If the person challenges our estimate, do not get defensive. It may indeed be inaccurate, even though it is based on arithmetic based on their estimates. If they are surprised, probe for what they think it might be.

Example language: "*How much do you think you spend in a typical week?"*

Explore alternative uses.

Example language: *"If you had that money today, what would you buy with it?"*
"Let's say you won a prize for $[1400], how would you spend the money?"

Avoid drawing too close a connection (e.g., *"Don't you wish you hadn't spent that money on alcohol so you could use it on something different"*) to avoid appearing judgmental.

Inquire about other financial costs (e.g., transportation, fines, legal costs, impulsive purchases).

Example language: *"Are there any other financial costs of drinking?"*

Start open ended but suggest examples if the individual does not volunteer additional costs (recognizing there may not be any).

If the financial costs do not elicit a significant response, move on.

Calories

Provide feedback on the calories associated with drinking.

Example language: "*Next, on drinking days, you consumed, on average,* [500] *additional calories per day. That actually adds up to approximately* [10] *kilograms over the last year. What are your thoughts about that?"*

If salient, probe further: "What might be different

Explore any other nutritional consequences (e.g., eating unhealthy food, eating excessively/binge eating).

Example language: *"Are there any other ways that drinking affected healthy eating?"*

If nutritional aspects are not salient, move on.

Feedback #3: Personal negative consequences

The participant now gets feedback on the areas where they are reporting negative consequences, from the DRINC.

Explain what each elevation means and solicit reactions from the individual. Note if elevations are congruent with earlier comments on dislikes. In addition, if not, note that these data reveal other potentially problematic areas that weren't identified before.

Highlight the three highest scores.

Example language: *"In this handout, we have information about the areas where you reported substance use having a negative impact on your life. There are elevations in three areas: academic/occupational, poor self-care, and blackout drinking. The first reflects drinking having a negative effect on your schoolwork. Does that make sense to you? [Yes] This is an objective representation of the point you made about school earlier. The next elevation reflects [ETC.]"*

If the individual is not reporting meaningful levels of negative consequences, this handout may be juxtaposed with the preceding and interpreted to suggest risk in the future.

Example language: *"Although you are not experiencing any negative consequences at the moment, you are at a high risk of experiencing them in the future. Among these domains, where do you see the biggest risk down the road?"*

Solicit the participant's impression of this feedback.

Example language: *"Does this seem right to you?" "What do you make of this? "What does this elevation make you think of? "Why do you think you scored highest here?"*

Avoid defensiveness if the participant disputes the validity of the figure or measure.

would this figure represent the consequences of drinking if it was accurate?"

Section 4: Values Card Sort

Introduce the activity.

Example language: *"Okay, I'm going to give you one more piece of feedback today. This involves a card sorting activity.*"

The values card sort is an activity to help the individual identify the things that are important in their life and juxtapose those core values with their alcohol use. The values card sort can be found here: http://casaa.unm.edu/inst/Personal%20Values%20Card%20Sort.pdf

(1) Place the first three anchor cards in front of the participant: **Not Important To Me, Important To Me, and Very Important To Me**. Give the instructions for the first section (sorting the value cards into the three piles). The cards can be distributed as the participant chooses. Clarify as necessary.

Example language: "*Next, we're going to do an exercise together to explore your personal values. Here are three title cards - Not Important To Me, Important To Me, and Very Important To Me - I'm going to give you a stack of value cards. Each card describes something that may represent a personal value for you. First, I would like you to look at each card and place each card under one of the title cards. I would like you to sort all 50 cards. Do you have any questions?"*

(2) Give the instructions for the second section. Ask the participant to select the ten most important values from the *Very Important to Me* category. If the person has fewer than 10, they should use that number.

(3) Ask the participant to prioritize the most important values by rank.

Example language: *"Next, I'd like you to focus on the top values you chose and sort them from your first most important value to your 10 most important values (or the pertinent number).*

(4) When participant indicates s/he is finished rank ordering, check to make sure you understand how the cards were sorted (ascending or descending)

Example language: [Point to the #1 spot] *"I just want to make sure I have this right--Is this your number one value"*

Write down the participant's 10 most important values.

(5) Use the values task to identify if alcohol conflicts with other personal values. Start broadly, with asking the individual how their drinking relates to their personal values in general. (As much as possible, avoid the opposite, identifying how drinking results in outcomes that are positively compatible with personal values.)

Start with broad questions.

Example language:

1) *"Where does drinking fall in the context of these values?"*
2) *"How does drinking fit in to your values?"*

If it does not emerge naturally, transition to adverse effects of drinking on values.

Example language:

1) "Does drinking have any negative consequences in the context of your personal values?"

2) "If you cut down your drinking or took a break, would there be any positive or negative effects on these values?

(6) There will not be time to discuss every value, so probe in the context of specific values that are relevant to earlier points in the discussion.

(7) If multiple or numerous values are adversely affected, inquire which values are the most negatively affected by drinking. Ask the participant to rank the areas to further elaborate and increase encoding in memory.

If values do not provide additional information or discrepancies with substance use, you can acknowledge this.

Example language: "*For some people, drinking can have an adverse impact on a person's consistency with their values. I hope you still found this to be a good exercise to explore our values as a person and to realize what you prioritize in life."*

Section 4: Decisional Balance

Summarize the discussion from the session up to that point, enumerating the major points. Make at least one review comment per handout.

Example language: "*We've talked about a lot so far. [Review of previous sections}.*

Ask the participant if your summary is accurate.

Set the stage for motivation questions. Example language: *"Do you mind if I ask you some direct questions possible changes?"*

"On a scale from zero to ten, how important do you think changing your drinking is?"
Example follow-up: *"What are the reasons that make it as high as X?"*
"Why is it X out of 10?" (Focus on why it is greater than 0, why it is less than 10.)

"On a scale from zero to ten, how confident are you that if you wanted to, you could change your drinking?"
Example follow-up: *"What gives you the confidence it as high as X?"*
"Why is it X out of 10?" (Focus on why it is greater than 0, why it is less than 10.)

"On a scale from zero to ten, how ready are you to change your drinking?"
Example follow-up: *"What are the reasons that make it as high as X?"*
"Why is it X out of 10?" (Focus on why it is greater than 0, why it is less than 10.)

Ask the individual if they want to change their drinking.

Example language:

1) *"What are your thoughts about what's next for you?"*
2) *"At this point, how do you feel about your alcohol use?"*
3) *"Is it time to make a change?"*

If the individual endorses positive behavior change, ask the participant what were the most salient things about the preceding discussion. Then, move on to clarifying a goal in Section 6.

If the person expresses no interest in behavior change, probe to clarify their perspective.

Example language: "*You feel pretty much the same way you did when you arrived.*"

Inquire if the participant ever plans to change their behavior. Many people consider drinking and drug use acceptable at certain times of their lives (e.g., during university) but ultimately plan to reduce their substance use.

Example language: "*You like drinking and don't plan on changing it for the foreseeable future, but is there ever a time you think you might want to change your use?"*)

Avoid sarcasm or incredulity. For some individuals, this will be the outcome. Be prepared and do not exhibit surprise or frustration, simply move forward.

Inform the person that the next stage in the session is to develop a plan for how a person would change their drinking if they wanted to. Ask them if they are comfortable proceeding. If no, skip the next section.

Example language: *"The next thing we're going to do is discuss how you would change your drinking if you did want to in the future. How's that sound?"*

Section 6: Goal Setting, trouble shooting, & Change plan

Goal Setting

In discussing goals, focus on defining changes in specific objective terms (e.g., quantity of use on using days, numbers of drinking days per week).

If the individual is ambiguous (*"I think it's time to cut down"*), guide them toward specificity (e.g., *"What's your definition of cutting down?" "How will you know if you've successfully cut down your drinking?"*).

Example language: *"Can we put that into more black and white definition. Do I have it right that you'd like to drink only on the weekends and when you do, not have more than three drinks and always make alternative driving arrangements?"*

The goal is determined by the participant and may or may not be abstinence. If it is not abstinence or if the individual asks the clinician's advice, note that the recommendations are to remain within the *Canadian Low-risk Drinking Guidelines*.

If the individual selects a goal that is still within a high-risk range, solicit permission to provide information about the recommended guidelines and ask their opinion of them. Try to avoid defensiveness by couching the guidelines in informational terms.

Example language: "*I'm not saying this is what you have to do, but I want to make sure you know what the recommended guidelines are. What's your impression of the guidelines?*"

The person may reconsider or may think they are too conservative or unrealistic. In either case, do not press further about the guidelines.

For an unmotivated participant, frame the discussion in the abstract. Hypothetically, if the person wanted to drink within the low-risk guidelines, how would they do so?

Restate the goal and elicit strategies to achieve the preceding goal/change from the individual. Example language: "*"So, you'd like to drink only on the weekends and when you do, not have more than three drinks and always make alternative driving arrangements. What are some of the things you could do to achieve that?*

Reinforce strategies with accurate reflections. Continue to probe until no further suggestions are made and provide ample silence to permit the individual to think hard (e.g., *"Anything else?"*)

As necessary, solicit permission to make recommendations

- Suggest alternative non-substance recreational activities or non-substance using peers
- Suggest within-episode strategies, such as setting personal limits or enlisting a friend's help
- Ask the individual what they think about the suggestions (e.g., "*Which of those might work for you?"*)

Identify and Troubleshoot High-Risk Situations

Identify risks for setbacks and reinforce strategies to address those strategies. Example language: *"Let's think about it a little differently. What are the things that you think might get in the way of your sticking to that goal?"*

Orient the person to salutary people and activities.

Try to identify 2 helpful people.

Example language: *"Who are the people who you think will be helpful in changing your drinking?"*

Give the person time to elaborate and probe for more people until 2 are identified or they clearly have no one further to add:

Example language: *"Who else might be helpful?"*

Try to identify high-risk people.

Example language: *"Are there any people who may undermine your decision to change your drinking/who you think you need to avoid?"*

Identify whether high-risk individuals can be temporarily avoided or whether there are non-drinking activities that can replace drinking together. Avoid dichotomous thinking about personal relationships (e.g., "*So I'm never going to visit my brother again?*").

A significant other who is a heavy drinker is a challenging clinical situation and cannot be fully addressed within this framework. Where relevant, focus on identifying shared non-drinking activities.

Other high-risk situations.

Identify other high-risk situations that do not involve other people.

Example language: *"Other than specific people, drinking often happens in specific places, situations, or emotional states, like feeling a lot of stress or very good or bad emotionally. They are the situations people most commonly report getting in the way of making a change. Can you think of what your high-risk situations will be? What's going to be the most challenging one for you?"*

Identify two high-risk situations. These can be places, days of the week/times of day, or emotional states (e.g., stress, anxiety). Use "What else might be a high-risk situation?" as a prompt as necessary.

Troubleshoot each situation.

The general recommendation is to avoid high-risk situations as much as possible, with the rationale that if the client is not in it, it can't lead to drinking.

Example language: *"In general, we recommend you do everything possible to avoid high-risk situations, at least in the short run. A high-risk situation can't lead to drinking if you're not in it and avoiding these situations will maximize the probability of a strong start."*

For each situation, directly ask the participant how they can avoid the situation or, if unavoidable, how they will cope with it.

Example language: *"Let's plan for how you will address your high-risk situations. For [situation 1, 2, 3+], what can you do to minimize the probability of drinking?"*

Address each situation identified one-by-one, not in aggregate. Identify strategies for each one, even if it is only applying a previously used strategy (e.g., avoid situation, delay exposure).

If a permanent solution elicits resistance (e.g., never seeing certain family/friends again, never going to certain parts of town, stress will not go away forever), respond with empathy and try to resolve the ambivalence by identifying realistic intermediate strategies. Use the metaphor of 'taking a vacation' from someone or something to avoid dichotomous thinking about behavior change.

Example language:

1) *"Even though spending time with X puts you at risk for drinking, you don't like the idea of giving up your friendship with X. What about avoiding this high-risk situation for a*

period of time to help you get started? Could that work? What would be an advantage of taking a break from X?"

2) *"Stress is definitely a challenging part of life, and you feel like you'll never be 100% stress free. But minimizing stress will reduce the likelihood it will lead to drinking. What about try to minimize stress as much as possible at first to help get you started. Could that work? What could you do to reduce stress as much as possible in the short run?"*

Support self-efficacy.

Directly ask the person why they think they could change (if they wanted to).

Example language:

1) *"Now we've identified some of the resources you have and developed some strategies for addressing the high-risk situations you're likely to face. Tell me a bit about what gives you confidence you'll be able to make these changes?"*
2) "*Can you think of things in the past that you've been able to achieve if you set your mind to it?*" --- "*Do you think you can apply that mindset and commitment to changing your drinking?*"

Change Plan

Bring the discussion together by filling out the change plan together (Appendix E). The participant should do the writing and put all the information in his/her words.

Section 7: Conclusion

Summarize the session in narrative terms. Enumerate the themes to facilitate encoding.
Example language: *"Okay, we're at the end of the session, let me make sure I have a good sense of things. We talked about five different aspects of drinking today…"*

Directly ask the participant if anything was missed.

Ask the participant what were the most salient things about the preceding discussion. Example language: *"What were the aspects of our discussion that stood out the most for you? Why was that? Were there any surprises today?"*

Inform them that the information is theirs to keep.
Example language: *"We covered a lot of ground, and we want to make sure you have this information."*
Review the folder of information the participant will receive:

- Motives feedback
- Drinking feedback
- Consequences feedback
- Values feedback
- Change plan
- Resources: (*Canadian Low-risk Drinking Guidelines, Rethinking Drinking,* Local substance use and mental health resources)

Inform them they have the option to meet with you up to three more times (once weekly for up to three weeks), if they would like. Clarify the limited window and missed appointment parameters. Ask of they would like to schedule future appointments. Note that these meetings will be at SJHH West 5th and that we will pay for parking or bus transportation, but there is no study incentive. Let them know the research staff member will do the scheduling.

SESSIONs #2, 3, & 4

Pre-session

Review information from Session 1, especially with regard to drinking patterns and most salient reasons for change.

Identify the putative stage of change the individual was in at the end of the last session. Although MI is distinct from the transtheoretical stages of change, this will nonetheless orient the focus of the session (e.g., continuing to build ambivalence and discrepancy vs. troubleshooting progress).

Overview

1. Breathalyzer
2. Drinking assessment (Timeline Followback)
3. Progress review
4. Amendments to the change plan
5. Summary

Session

Check-in.

Greet participant and welcome them back.

Initial Assessment

"As you know, the first thing we will do at the beginning of each session is verify sobriety, so let's do that now."

Breathalyze (Record on data sheet)

Timeline followback.

Example Language: *"Now I'm going to follow-up on drinking last session."*

Inquire how the days since the first session have gone. Orally review data from TLFB.

Vary MI techniques based on progress.

Successes (if notable reductions present).

Strongly reinforce each day of successful abstinence and success in general.

Example Language: *"You're off to a great start; you've really followed through on the goals from last time"*

Support self-efficacy. Investigate the reasons for success.

Example Language: *"What where the things that helped you not drink?"*

Address heavy drinking episodes (as relevant).

Do not be judgmental or critical about lapses. Express empathy.

Example language: *"Changing your drinking can be hard. You're trying to break habits that have been years in the making."*

Review drinking episodes and surrounding factors. Attempt to reverse-engineer where things went wrong (presuming they are presumed to have done so).

Identify contributing factors (as relevant)

Who and what were the people, places, and emotional states that contributed?

Example language: *"Tell me a bit more about what happened."*

Was it in a high-risk situation? Should it be added to the high-risk situations?

Future prevention.

Could it have been prevented? How?

Example language:

1) *"If you had a time machine and could go back to Tuesday night, what would you do differently?"*
2) *"Was there anything you could have done to avoid this happening?"*
3) *"It was completely impossible not to drink on Tuesday?"* (amplified reflection)

Evaluate the interim period in general and goals.

Based on outcome:

1) Further strengthen success by supporting self-efficacy

   -OR-

2) Empathically address disappointment/regret and attempt to mobilize motivation going forward.

Example language: *"So, what's the plan going forward?"*

Relatively low success may require developing discrepancies to foster greater ambivalence
Example language: *If you don't keep trying to stop drinking, what do you think will happen?*
Example language: *You said your original goals were A, B, and C; what will it take to make progress towards those goals?"*

Relatively high success may require greater emphasis on positive experiences to date, supporting self-efficacy, and trouble-shooting future challenges
Example language: *"You feel really proud of your success so far,"* [reflection of successful change]

"You've been able to turn your short-term goals into reality [reflection]*, what will it take to achieve the long-term goals?* [trouble-shooting]*"*

Review change plan in the context of the intervening period.

Session summary.

Review and reiterate positive change, change talk, and upcoming goals.

Example language: *"Today we followed up on our first conversation in a number of ways . . ."*

Confirm next appointment or, for Session 4, express appreciation for the participant's engagement in sessions and the study in general.

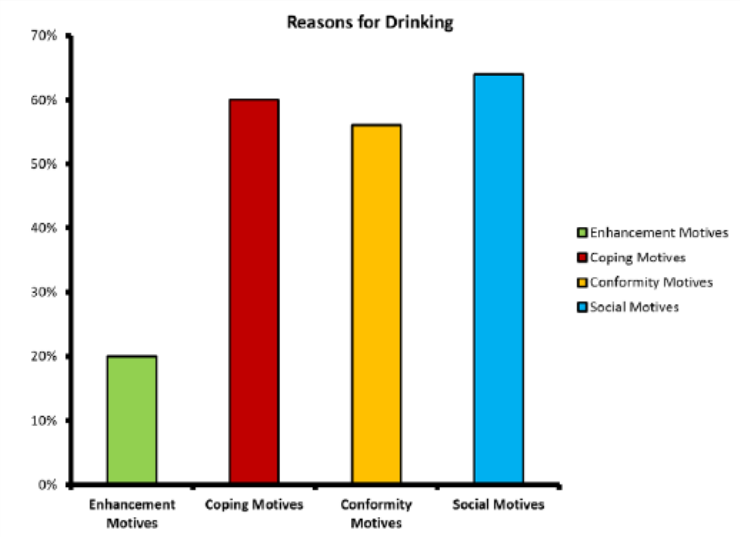
Appendices

Appendix A: Drinking Motives Feedback Summary Sheet

ALCOHOL AND YOU

Objective Feedback about the Motives, Patterns and Consequences of Your Alcohol Use

Your Reasons for Drinking



Enhancement motives refer to drinking to feel good.

Coping motives refer to drinking to help deal with stress or other aversive feelings or situations.

Conformity motives refer to drinking to be more similar to other people who are drinking.

Social motives refer to drinking to improve social experiences.

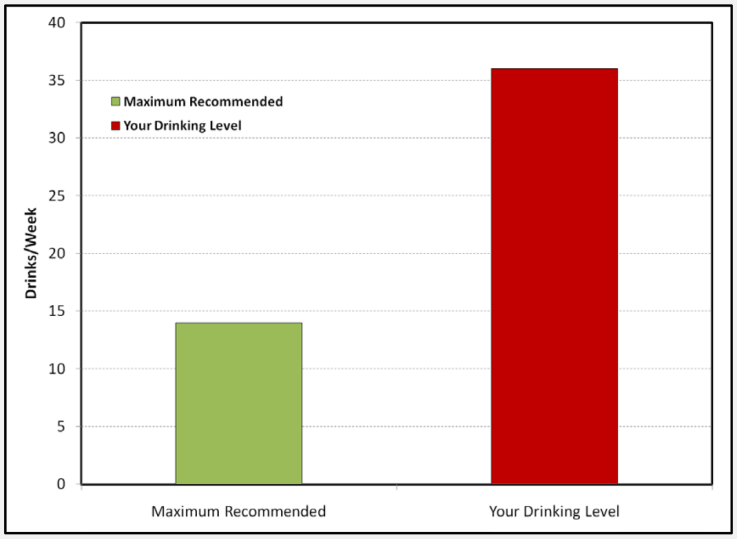
Appendix B: Timeline Followback Feedback Sheet

Your Drinking Level

Canadian Low-Risk Drinking Guidelines:

→ Less than 15 drinks per week for males

→No more than 3 drinks in a day for males



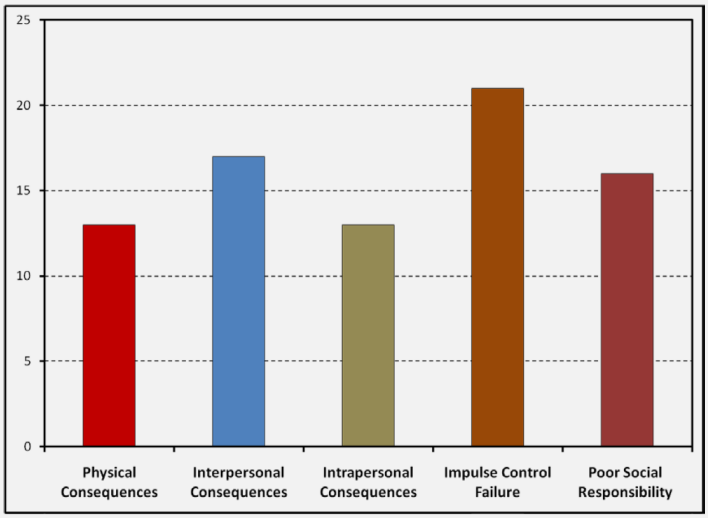
You drink above 3/day XX % of the time when you drink.

Estimated annual expenditures on alcohol: $XXX

Estimated additional calories/week from alcohol: XX (Kgs/Year)

Appendix C: DRINC Summary Sheet

Your Personal Negative Consequences



Physical Consequences = Hangover, Nausea, Sleep Problems, Physical Risks, Poor Nutrition, Sexual Dysfunction, Appearance

Interpersonal Consequences = Worried Friends & Family, Bad Parenting, Embarrassing Acts, Malicious Word Choice, Damaged Reputation & Social Life, Damaged/Lost Friendships and Romantic Relationships

Intrapersonal Consequences = Low Self-Esteem, Unhappiness, Guilt, Shame, Negative Personality, Deteriorating Sex Life, Dissatisfaction with Life, Harmed Personal Growth, Negative effect on Morals, Spiritual Damage

Impulse Control Failure = Drunk Driving, Risk Taking, Regret, Physical Fights, Increased Tobacco Use, Unhealthy Weight, DUI & Other Legal trouble, Accidents, Caused Injuries to Others, Destruction

Poor Social Responsibility = Work and/or School Absence, Unsatisfactory Work, Unreliable, Misbehavior, Money Troubles, Loss of Job or Removal from School

Appendix E: Change Plan Worksheet

CHANGE PLAN

1. My goals are:

a. _____

b. _____

c. _____

d. _____

2. The steps I plan to take to avoid drinking between now and the next session:

a. _____

b. _____

c. _____

d. _____

3. Some things that could interfere with my plan are:

a. _____

b. _____

c. _____

d. _____

4. I will avoid possible obstacles by:

a. _____

b. _____

c. _____

d. _____

5. The ways other people can help me are:

a. _____

b. _____

c. _____

d. _____

Appendix F: Mental health Resources Handout

Resources for Treatment and Other Information about Alcohol and Tobacco Use

This sheet provides information about programs, helplines, online materials, and other resources related to treatment and support for alcohol problems. If you have any questions about any of these resources, please ask the research staff. We would be happy to connect you with appropriate services. We also have free print copies of the brochures listed at the bottom of this sheet. If you would like a copy, please ask the research staff.

Addictions Services at St. Joseph's Healthcare Hamilton

Men's Withdrawal Services (Males)
Telephone 905 522-1155 ext. 35219

Womankind Addiction Service (Females)
Telephone: 905-521-9591 ext. 237

Other Hamilton and Ontario-wide Resources for Alcohol and Drug Services

- **Alcohol, Drug, and Gambling Services** (ADGS; Hamilton)- self referral (905) 546-3606 21 Hunter St. E. http://www.hamilton.ca/HealthandSocialServices/PublicHealth/AlcoholDrugsGambling/
- **Ontario Drug and Alcohol Registry of Treatment** - a toll-free, province-wide, treatment information and referral service 1-800-565-8603 http://www.dart.on.ca/
- **Ontario Drug and Alcohol Helpline -** The Drug and Alcohol Helpline (funded by the Government of Ontario) provides information about drug and alcohol addiction services in Ontario. Live, 24/7, confidential, and free. Call 1-800-565-8603 or visit http://www.drugandalcoholhelpline.ca

Brochures and Other Resource Guides Copies are available online, or you can ask the research staff for a free printed copy.	
Description	**Web Address**
Rethinking Drinking: Alcohol & Your Health A resource guide with tools to check your drinking patterns, notice signs of a drinking problem, and tools for making a change. Published by the US National Institutes of Health	http://rethinkingdrinking.niaaa.nih.gov/
Canada's Low-Risk Alcohol Drinking Guidelines Two-page brochure designed to help Canadians moderate their alcohol consumption and reduce alcohol-related harm	http://www.ccsa.ca/Eng/topics/alcohol/drinking-guidelines/

CHAPTER 5

5. DISCUSSION

The previous three chapters of this dissertation demonstrate the use of baseline clinical, behavioural, and neuroimaging data to predict addictions treatment outcome and highlight the ability of pre-treatment clinical data to inform clinical judgement and treatment outcome.

Chapter 2 used statistical modeling to delineate patterns associated with inpatient addictions treatment outcome within a clinically complex patient population with multiple comorbidities. This study found that low alcohol use severity, high illicit drug use severity, and high posttraumatic stress disorder symptom severity upon entering treatment significantly predicted premature termination from residential addictions treatment. Latent profile analysis revealed four distinct profiles of patients and identified groups of patients that were at "high-risk" and "low-risk" of premature treatment withdrawal. Patients at the highest risk of premature treatment termination demonstrated high drug use severity, high comorbid psychopathology (aggregate of PTSD, depressive, and anxious symptomology), and low alcohol use severity. While patients that exhibited the lowest risk of prematurely terminating treatment demonstrated high alcohol severity, low drug use severity, and low comorbid psychopathology. This study was the first study to examine predictors and profiles of premature treatment withdrawal from a large inpatient addiction setting and demonstrated the potential role of adjunctive care pathways for individuals at high-risk of premature treatment termination.

Chapter 3 systematically evaluated the existing literature to demonstrate that steeper pre-treatment delayed reward discounting was associated with significantly worse smoking cessation outcomes following formalized smoking cessation treatment. It highlighted that this association may be less likely in adolescent population and pregnant woman who may discontinue smoking during pregnancy and resume smoking during the postpartum period. This study was the first to

evaluate the existing smoking cessation literature and identify delayed reward discounting as a negative prognostic factor for smoking cessation outcome in adults. This highlights the role of pre-treatment delayed reward discounting as a novel treatment target for identifying high-risk populations requiring more intensive treatment.

Lastly, in Chapter 4, pre-treatment resting state functional connectivity (rsFC) of several regions of the brain within the reward network, frontoparietal network, and salience network were found to predict response to a brief intervention at three-month follow-up. When compared to individuals that did not change or increased their alcohol consumption (non-responders), individuals that responded to the intervention demonstrated increased rsFC between regions associated with the salience network and frontoparietal network and decreased rsFC between regions associated with reward processing such as the inferior frontal gyrus and nucleus accumbens. Overall, the results suggest that patterns of rsFC seen in responders may reflect a favourable state of internal motivation or perhaps a less severe disruption of the brain from AUD. This was the first study to investigate the association between pre-treatment rsFC and response to a brief intervention to reduce alcohol consumption in individuals with alcohol use disorder. The results of this study are especially important as they provide insight into brief intervention response and behaviour change within a population that was not explicitly seeking to change their behaviour and instead received feedback as part of a larger study on neuroimaging and alcohol use.

5.1. Implications and Future Directions

The implications of the studies included in this dissertation span across various aspects of addictions and behavioural neuroscience literature. Broadly, this body of work highlights the prognostic utility of pre-treatment clinical, behavioural, and neuroimaging data in determining treatment outcome and identifying those at highest risk of experiencing poor treatment outcomes

(i.e., treatment attrition, relapse). Given the high prevalence and burden of addictive disorders, coupled with low treatment completion and efficacy, it is imperative that novel strategies to better understand treatment outcome and prognostic indicators of treatment outcome are evaluated. In doing so, these indicators can allow for the identification of "high-risk" patients and populations, leading to development of adjunct strategies or treatment modifications based on their clinical, behavioural, or neurofunctional profiles. This key implication of this dissertation was echoed within each presented study.

The potential utility of identifying high-risk profiles in patients upon entry to treatment was highlighted in Chapter 2, in which latent profile analysis and binary logistic regressions were used to identify both independent predictors and high-risk profiles of individuals that presented to treatment. A critical finding from this chapter was the use of statistical modeling to demonstrate that high illicit substance severity and high comorbid psychopathology were associated with the highest rates of premature treatment termination. These results emphasize the need for greater treatment resources and management of comorbid psychopathology within the framework of inpatient addictions treatment. This was underscored by the finding that two of four profiles identified by the latent profile analysis had high psychopathology, which is consistent with research on the high rates of concurrent disorders in patients that present to residential addictions treatment. This further emphasizes the need for greater management of concurrent disorders within inpatient addictions treatment. Future research and clinical implications may focus on the development of intensive care pathways for high-risk individuals, which place greater emphasis on CBT for concurrent disorders or mindfulness-based relapse prevention – an evidence-based intervention to reduce symptoms of craving and addictive behaviour in patients with concurrent disorders (Ramadas et al., 2021). Notably, one profile was identified as "low-risk" and was

comprised of patients with high alcohol use severity and low illicit substance use severity. This profile demonstrated the most favourable treatment outcomes and provided valuable information about the treatment program itself, suggesting that this particular program may be well-suited towards treating patients with alcohol use disorder and limited psychological comorbidities. In this capacity, statistical modelling may be useful from a quality assurance perspective to determine whether a treatment program's goals are being met and whether patient populations are receiving adequate treatment.

Chapter 3 demonstrated two central findings related to the prognostic utility of delayed reward discounting. First, it highlighted that pre-treatment delayed reward discounting is an important indicator of smoking cessation treatment outcome and should be measured in individuals before engaging in treatment. Second, individuals with steep delayed reward discounting may benefit from more intensive or adjunctive treatment to help improve their outcomes. Research on delayed reward discounting suggests that it may be amenable to change through interventions such as episodic future thinking, an evidence-based method to reduce delayed reward discounting that relies on one's ability to imagine personal future events (Stein et al., 2018). Research by Stein et al., found that episodic future thinking reduced delayed reward discounting and cigarette smoking in a laboratory-based cigarette self-administration task (Stein et al., 2016). These results suggest that episodic future thinking may have implications for clinical treatment of substance use disorders (Stein et al., 2016). In the context of this literature, the results of this chapter suggest that individuals with high pre-treatment delayed reward discounting prior to smoking cessation treatment may benefit from an adjunct episodic future thinking intervention prior to engaging in treatment to decrease their pre-treatment delayed reward discounting and potentially improve treatment outcome. While further research is needed to determine whether episodic future thinking

interventions administered prior to formalized smoking cessation treatment would result in improved treatment outcomes in individuals with high pre-treatment delayed reward discounting, the results of this dissertation and current episodic future thinking literature provide support for this hypothesis. Chapter 3 also emphasized the need for future research to establish clear delayed reward discounting cut-offs to better inform treatment outcome and efficiently highlight individuals at highest risk of poor treatment outcome or attrition. However, this may be challenging given the heterogeneity in tasks used to determine delayed reward discounting.

To our knowledge, Chapter 4 is the first study to use rsFC to predict behaviour change (reduction in alcohol use) following a brief-intervention for alcohol use disorder. This chapter provides several important results and implications. First, a brief-intervention to decrease alcohol use is efficacious in a population that is not explicitly seeking treatment, as demonstrated by the reduction of alcohol use in individuals that responded to the intervention. This is important given that the majority of individuals with alcohol use disorder lack problem awareness (Blanco et al., 2015). Second, this study highlighted several patterns of brain activity at rest which may highlight an internal motivation to engage in positive behaviour change and reduce alcohol consumption. Responders demonstrated increased rsFC at baseline (pre-intervention) between regions of the brain associated with the conflict monitoring (anterior cingulate cortex, ventral anterior cingulate cortex), higher-order cognitive processes (posterior parietal cortex, supramarginal gyrus), and reward processing (inferior frontal gyrus), compared to non-responders. Individuals that responded to the brief intervention also demonstrated decreased rsFC between regions of the brain associated with reward processing (inferior frontal gyrus, nucleus accumbens), interoceptive attention (rostral prefrontal cortex), impulsivity (inferior frontal gyrus and orbital frontal cortex), and salience (insula), compared to non-responders. These results suggest the patterns of rsFC seen in responders

may also reflect an increase in processes related to working memory, conflict monitoring, and evaluation of risk and reward. Third, this preliminary research emphasizes the need for additional research into the role of these brain regions in behaviour change and general psychophysiology of alcohol use disorder. It also suggests that additional research may investigate the utility of these brain regions and functional patterns as useful targets for pre-treatment neuromodulatory techniques to "prepare the brain" for a favourable response to an intervention. Finally, these preliminary results suggest that pre-treatment rsFC may be a valuable tool to predict treatment response and should be evaluated on a larger scale (i.e., increased sample size, across multiple time points).

5.2. Limitations

This dissertation and included studies should be considered in the context of their limitations. Overall, the three studies included in this dissertation focused on predicting treatment outcome using baseline clinical, behavioural, or neuroimaging data across a diverse range of treatment options and addictive disorders. However, the assessment of psychopathology and clinical variables used to predict treatment outcome in Chapter 2 consisted of self-reported measures. While this provided clinicians with efficient access to data it may not be as objective as a clinical interview or behavioural tasks. Contrastingly, Chapter 3 utilized well-validated behavioural tasks to determine delayed reward discounting and Chapter 4 focused on the use of rsFC (a biological variable). It should be noted that within Chapter 4, the assessment of alcohol consumption was completed using the Timeline Followback Method, which while being a well-validated and reliable measure of alcohol use, relies on participant recollection of alcohol consumption. Further, while the studies above accounted for major mood and anxiety disorders (*Axis I*), they did not assess for the presence of personality disorders (*Axis II*), which are known to

be associated with substance and alcohol use disorders. The extent to which personality disorders may have been present within the clinical samples of the above studies is not known. Another notable challenge that should be considered when interpreting the results of this dissertation is study power. While Chapter 2 had statistical power to conduct all necessary analyses, the heterogeneity of smoking cessation treatment types in Chapter 3 made it challenging to have adequate statistical power to synthesize results, therefore limiting our ability to conduct a meta-analysis. Similarly, although FDR corrected results between responders and non-responders were demonstrated in Chapter 4, this clinical sample may have been underpowered to draw correlations between rsFC and clinical data.

Another limitation of two of the three included studies was the focus on abstinence versus harm reduction. Chapter 2 focused on treatment response within a residential addictions treatment facility which employed an abstinence-based approach, while Chapter 3 used a similar framework and defined treatment response using an abstinence approach (0 cigarettes consumed). As stated within the independent limitations of Chapter 3, although abstinence is an important goal of addictions treatment, it focuses on fixed definitions of treatment success and failure and does not appreciate recovery as a dynamic process. A growing body of literature suggests that harm reduction approaches may be an important indicator of treatment success and lead to a decrease in addictive behaviours outcome (Marlatt & Witkiewitz, 2002; Tatarsky, 2003; Witkiewitz, 2013). From this perspective, a reduction in the problematic behaviour would still be considered a treatment success or positive treatment outcome (Marlatt & Witkiewitz, 2002; Tatarsky, 2003; Witkiewitz, 2013). A harm reduction-based approach was modeled within Chapter 4, in which a reduction of alcohol use from one high-risk category to a lower category was considered a treatment response.

5.3. Strengths

There are several notable strengths of this dissertation overall. First, it provides a strong argument for the utility of a diverse range of prognostic indicators of treatment response (clinical, behavioural, and neuroimaging) which can be used to improve treatment outcome. It also demonstrates that heterogeneity within clinically complex populations that present with substance and alcohol use disorders can be delineated through (i) the use of statistical modeling; (ii) by investigating transdiagnostic markers of psychopathology/addiction such as impulsivity (delayed reward discounting); and (iii) biological variables such as rsFC. Further, the studies contained within this dissertation investigated prognosis across treatment options that ranged in their intensity from residential treatment (high-intensity), outpatient treatment (medium-intensity), and a brief intervention directed at positive behaviour change (low intensity). As such, the results of this dissertation are generalizable to a variety of clinical populations, addictive disorders, and treatment outcomes and demonstrate the opportunity to predict treatment response within these treatment options. Finally, this dissertation bridges clinical psychology and neuroscience research to obtain clinical outcomes and provide several opportunities for further research and advance the clinical and neuroscience literature in several ways. It also highlighted predictors associated with treatment outcome that can be gathered with relative ease and adopted in clinical contexts (i.e., use of clinical questionnaires to measure psychopathology, delayed reward discounting tasks to measure impulsivity). With regards to clinically oriented future directions, this dissertation highlighted the need for future research to establish clinical and behavioural cut offs associated with treatment response and outcome. It also suggests evidence-based clinical interventions for specific patient populations and pre-treatment variables (i.e., delayed reward discounting and episodic future thinking) that can be researched to improve treatment response. For example, more

intensive CBT for concurrent disorders or adjunctive treatment for individuals with high levels of comorbid psychopathology in addition to substance use (Chapter 2), the potential utility of episodic future thinking to reduce pre-treatment delayed reward discounting (Chapter 3), and the potential use of neuromodulatory techniques to modulate pre-treatment rsFC (Chapter 4).

5.4. Conclusions

Taken together, the studies in this dissertation illustrate the utility of pre-intervention clinical, behavioural, and neuroimaging variables in determining treatment response and behaviour change. This was completed using statistical modeling to delineate clinical profiles and independent predictors that were associated with attrition from inpatient addictions treatment. In addition, synthesis of the existing smoking cessation literature highlighted that steep pre-treatment delayed reward discounting was associated with poor smoking cessation treatment outcome. Furthermore, several patterns of rsFC at baseline were associated with response to a brief intervention to reduce alcohol use at 3 month follow up. These studies inform future research by providing clinical, behavioural, and rsFC targets to investigate treatment response on a larger scale. They also provide clinical hypotheses that can be used to improve addictions treatment and patient outcomes such as the adjunctive use of episodic future thinking interventions or mindfulness-based relapse interventions in high-risk patient populations. Importantly, regions implicated in intervention response within the final study may be used to inform future neuroimaging research and provide potential targets for neuromodulatory techniques. Finally, these studies advance the literature by showcasing that treatment response can be predicted using baseline patient data using a variety of methods, across a range of treatment intensities, and across addictive disorders. These results can be used to improve treatment adherence and response and overall patient outcomes.

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