SEEKING SENSATIONS THROUGH SPORT: AN INTERDISCIPLINARY INVESTIGATION OF PERSONALITY AND GENETICS ASSOCIATED WITH HIGH-RISK SPORT

by

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Abstract

Sensation seeking involves a desire to seek out thrilling experiences and a willingness to take risks in exchange for rewards. Sensation seekers are drawn to risky activities and high-risk sports represent potentially positive outlets for such individuals. Sensation seeking is moderately heritable and variants in genes involved in dopaminergic transmission have been associated with sensation-seeking phenotypes, although no studies have investigated personality and genetic variants in high-risk sport practitioners. This interdisciplinary dissertation explores personality (general sensation seeking and contextual sensation seeking in sport) and genetic variables (polymorphisms in monoamine pathway genes) in proficient high-risk sport practitioners. In the first series of projects two independent cohorts ($n = 220$, $n = 668$) of skiers/snowboarders (risky, yet popular sports) completed questionnaires and provided DNA samples. Data derived from questionnaires were used to evaluate the reliability and predictive validity of a new sensation-seeking tool for downhill sports that was developed as part of this study. The questionnaire showed strong psychometric properties and significantly predicted injury ($\beta = .358$, p < .001) in skiers and was used to define phenotypes in subsequent genetic studies. Using designs that employed independent replications, the newly defined phenotype was significantly associated ($p < .001$) with a functional variant (-521C/T) in the dopamine-4-receptor gene (*DRD4*), and an association between general sensation seeking and a variant (rs167771, intronic G/A) in the dopamine-3-receptor gene (*DRD3*) was also observed in the ski cohorts ($p = .004$). Personality and genetic variables were then compared using a *quasi* case-control design between practitioners of very high-risk (e.g., paragliding, ski-mountaineering, $n = 141$) and low-risk sports (e.g., running, $n = 132$). The high-risk group scored higher than low-risk athletes on sensation seeking ($p < .05$), but not impulsivity, a trait commonly associated with deviant risk-

taking and there were marginal associations between sport group and genetic variants in the stathmin ($p = .004$) and brain-derived neurotrophic factor ($p = .03$) genes, but the associations did not survive correction for multiple testing. The finding that risk-taking through sport may be, in part, predicted by genetic background provides a novel insight into the potential antecedents of performance.

Preface

Almost all of the work described in this dissertation was conducted during my doctoral studies with collaborations from the co-authors listed below. A portion of the work described in Chapter 3 was conducted during my master's thesis with guidance from Dr. Mark Beauchamp (acknowledged in the published version) and a version of the work has been published (Thomson, Morton, Carlson, & Rupert, 2012, shown below). I conducted all of the testing and wrote the manuscript. I consulted with the co-authors on research methods and analyses, and all authors contributed by assisting with editing.

C.J. Thomson, K.L. Morton, S.R. Carlson, J.L. Rupert. (2012*).* The contextual sensation seeking questionnaire for skiing and snowboarding (CSSQ-S): Development of a sport specific scale. *International Journal of Sport Psychology, 43*(6): 503-521.

Chapter 4 is based on work conducted in part during my master's thesis (74 genotypes from the pilot sample ($n = 117$) used at stage 1 of the analyses), the result was then replicated during my doctoral studies in an independent study ($n = 386$). A version of the work has been published (Thomson, Hanna, Carlson, & Rupert, 2013, shown below). I conducted all of the recruitment, testing, analyses, and wrote the manuscript. I consulted with the co-authors on research methods, and C. Hanna assisted with the genetic analysis. All co-authors helped edit the manuscript.

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Chapter 5: A version of the work has been published (Thomson, Carlson, & Rupert, 2013, shown below). I conducted all of the recruitment and analyses, and a majority of the sample preparation. A. Rajala assisted with DNA isolation and an external facility (Genome Quebec) performed the genetic analysis. I wrote the manuscript and the co-authors assisted with editing the manuscript.

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List of Abbreviations

5-HT: serotonin (5-hydroxytryptophan)

A: adenine

ADHD: attention deficit hyperactivity disorder

AGFI: adjusted goodness-of-fit index

ANKK1: ankyrin-repeat and kinase-domain-containing-1

ANOVA: analysis of variance

ANCOVA: analysis of variance (with covariates)

ASD: autism spectrum disorder

ASRS: Adult Self Report Symptom checklist

BART: balloon analogue risk task

BAS: behavioural activation system

BASE jump: building, antenna, span, earth (the sport involves parachuting off any of these)

BDNF: brain-derived neurotrophic factor

BIS: behavioural inhibition system

bp: nucleotide base pair

BS: boredom susceptibility (subscale of the SSS)

C: cytosine

cAMP: cyclic adenosine monophosphate

CAST: cannabis abuse screening test

CD: conduct disorder

CFA: confirmatory factor analysis

CFI: comparative fit index

COMT: catechol-*O*-methyltransferase

CSSQ: Contextual Sensation Seeking Questionnaire

DA: dopamine

DAT1: dopamine transporter

DBH: dopamine-*beta*-hydroxylase

df: degrees of freedom

Dis: disinhibition (subscale of the SSS)

DNA: deoxyribonucleic acid

DRD1, DRD2, DRD3, DRD4: dopamine receptors types 1, 2, 3, or 4

DV: dependent variable

EFA: exploratory factor analysis

ES: experience seeking (subscale of the SSS)

fMRI: functional magnetic resonance imaging

g: gram

G: guanine

GABA: gamma-amino butyric acid

GWAS: genome-wide association study

H: heterozygosity

HA: harm avoidance

HTR1A, HTR2A: serotonin receptors types 1A or 2A

HWE: Hardy Weinberg Equilibrium

Imp: impulsivity

L: litre

M: mean or molar

MAF: minor allele frequency

MAO: monoamine oxidase

n: nano unit or sample size

NEO-FFI: NEO Five-Factor Personality Inventory

NS: novelty seeking

PAGE: polyacrylamide gel electrophoresis

PCR: polymerase chain reaction

PET: positron emission tomography

r: correlation coefficient

RFLP: restriction fragment length polymorphism

RMSEA: root mean square error of approximation

RST: Reinforcement Sensitivity Theory

s: seconds

SD: standard deviation

SLC6A3: dopamine transporter

SLC6A4: serotonin transporter

SNP: single nucleotide polymorphism

SPSRQ: Sensitivity to Punishment/Sensitivity to Reward Questionnaire

SS: sensation seeking

SSS: Sensation Seeking Scales

STMN1: stathmin

T: thymine

Taq: *thermos aquaticus* polymerase

TAS: thrill and adventure seeking (subscale of the SSS)

TH: tyrosine hydroxylase

TCI: Temperament and Character Inventory

U: unit

UBC: University of British Columbia

UTR: untranslated region

V: volt

VNTR: variable number of tandem repeats

ZKPQ: Zuckerman-Kuhlman Personality Questionnaire

List of Symbols

α: alpha, used for Cronbach alpha reliability statistic or threshold for significance

ß: beta, regression coefficient

χ: *Chi* statistic

Δ: delta, representing a change

λ: eigenvalue

μ: micro unit

Glossary

-521C/T: a single nucleotide polymorphism (C to T transition 521 bases upstream from the start codon) in the *DRD4* promoter region

Allele: one version of a genetic variant at a particular polymorphic locus (e.g. 'C' or 'T' at a 'C/T' polymorphism).

Approach-related traits: a constellation of personality traits that involve strong motivation towards reward. Personality traits that have been grouped under this broader term include: extraversion, novelty seeking, sensation seeking, reward sensitivity, behavioural activation, and, in some cases, impulsivity.

Avoidance-related traits: personality traits that involve sensitivity to punishment. Personality traits that have been grouped under this broader term include: anxiety, neuroticism, behavioural inhibition, and punishment sensitivity.

Autoreceptor: a ligand receptor located on the pre-synaptic membrane.

Behavioural measures: in psychology, behavioural measures involve assessing behavioural responses using laboratory tasks/paradigms or through observation. These differ from trait measures, which often rely on self-report questionnaires.

Disinhibition: a term used in psychology to describe a lack of restraint, this may involve a disregard of social conventions and/or impulsivity. A number of traits are grouped under the broader term of disinhibition, including impulsivity, sensation seeking, and aggression.

Disinhibited behaviours: these can range from violence, promiscuity, gambling, substance use, binge drinking, and other socially deviant acts.

Dopamine: a neurotransmitter in the brain that has both excitatory and inhibitory functions related to motor control, motivation and reward pathways.

Externalizing disorders: a cluster of syndromes generally involving behaviours directed outward (towards others, as opposed to inward, towards self). Disorders grouped under this broad term include: attention deficit hyperactivity disorder, conduct disorder, operational defiant disorder, substance abuse, alcoholism, etc.

Factor: items that describe different components of the same larger dimension (e.g. a personality trait) comprise a factor. A factor is a single dimension that is independent, but is composed of highly related items.

Factor Analysis: a statistical method used to group items (e.g. in a questionnaire) according to their relatedness.

Joint-analysis: a two-stage method of analysis in which *p*-values from the stages are combined. Firstly, the analysis is carried out in a "discovery" sample, followed by the same analysis in an independent "replication" sample.

Gene: a protein-encoding segment of DNA. Genes are located on chromosomes.

Genotype: the combination of alleles at a particular locus (e.g. CC, CT or TT at a 'C/T' polymorphism).

Haplotype: a block of alleles located on the same chromosomal region that are inherited together.

Heterozygosity: a measure of the amount of genetic variability at a locus.

HPLC: high performance liquid chromatography, a purification method.

Knockout: a mutant organism (e.g., mouse) in which the function of a gene has been eliminated.

Knockdown: a mutant organism (e.g., mouse) in which the function of a gene has been downregulated.

Linkage disequilibrium: when alleles at two or more loci are sorting in a non-random fashion. Combinations of alleles at multiple loci on the same chromosome are present in a greater frequency than would be expected due to chance (if the alleles had been randomly assorting during meiosis).

Maximum likelihood rotation: a rotation of eigenvalues by 90 degrees, used in factor analysis.

NEO-FFI: NEO Five-Factor model measures five basic dimensions of personality traits including neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness.

Neurotransmitter: a brain chemical that transmits signals between neurons.

PCR: polymerase chain reaction, a method that allows amplification of a specific DNA segment via varied cycled temperatures.

Personality: the consistent pattern of behaviours that is characteristic of an individual. Personality is often organized in conceptual taxonomic structures.

Phenotype: an observable characteristic of an individual that is influenced by genetic and environmental factors.

Polymorphism: a common variation in DNA in which alternate sequences occur in

populations.

Promoter: a segment of DNA that lies before the start codon of a gene that commonly acts as a regulator of gene expression.

RFLP: restriction fragment length polymorphism, a method used to identify polymorphisms using an enzyme that either recognizes a specific allele and cuts at the specific site in the sequence, or does not recognize the allele resulting in an un-cut strand.

SNP: single nucleotide polymorphism, a variation in the gene sequence that occurs at a single locus (one nucleotide base).

Trait: a behavioural characteristic of a person that is stable over time.

Varimax rotation: a type of rotation in space that maximizes the variance captured by the items in a factor, used in factor analysis.

SSS-IV, V: Sensation Seeking Scales forms IV and V measures four subscales of sensation seeking: thrill and adventure seeking, experience seeking, boredom susceptibility and disinhibition.

Tag SNP: a SNP that is representative of other SNPs in the region due to the presence of high linkage disequilibrium.

TCI: Temperament and Character Inventory, which was developed by Cloninger to measure four temperaments traits: novelty seeking, harm avoidance, reward dependence and persistence.

ZKPQ: Zuckerman-Kuhlman Personality Questionnaire measures five traits: impulsive sensation seeking, aggression-hostility, neurotism-anxiety, sociability and activity.

VNTR: variable number of tandem repeats occurs when a segment of the gene sequence is repeated a variable number of times.

Acknowledgements

I feel that it is important to acknowledge how the idea for this thesis came about. After making a research plan to study exercise-induced asthma during the fall term of my MSc, my supervisor, Dr. Jim Rupert asked me: "why do you and your friends spend *all* of your free time skiing/climbing? Do you think there is something genetic that drives this urge?" I subsequently spent the winter break diving into the research, because in my opinion this was the coolest thing I could imagine for a thesis project. Thank you, Jim, for inspiring me to delve deeper into this question, and for understanding that my love for recreation made this project the best fit for my graduate research. Jim has been an incredibly supportive supervisor, always willing to provide thoughtful insight and advice. I am especially thankful for Jim's willingness to join me in entering the world of personality genetics, a field that was new to both of us. I have great respect for Jim's never-ending curiosity about a vast range of topics, his expansive knowledge, and his ability to maintain balance despite the demands of academic life.

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I dedicate this work to my husband, Chris,

his passion for adventure, and

joie de vivre!

Chapter 1: Introduction

1.1   Overview

Personality is a combination of qualities or traits that can influence many aspects of our lives, including choice of friends, partners, career, and even what we do in our spare time. This dissertation focuses on personality traits related to approach motivation, namely sensation seeking, and how traits influence choice of sport and patterns of behaviours within certain sports. It is generally accepted that personality traits are influenced by complex interactions and relationships between genetics and the environment, and genetic association studies are one common method to investigate the relationships between genotype and phenotype. Sport provides a domain in which context-specific tools can be used alongside general trait measures to quantify phenotypes for genetic association.

There exists a substantial body of literature that has explored associations between approach-related traits and genetic variants in both healthy and clinical populations; and similarly, the evidence linking sensation seeking and sport participation is overwhelming, but prior to carrying out the current research program, no studies had used self-reported patterns of athletic behaviours and participation to define a prosocial phenotype for approach-related traits. This dissertation explores psychological and genetic characteristics of athletes who participate in high-risk sports. The first series of projects involve developing and testing a tool to measure patterns of sensation seeking in multiple samples of skiers and snowboarders. The second project involves investigating associations between genetic variants and the newly developed domain-specific phenotype (along with established trait measures) in skiers and snowboarders. Finally, personality and genetic variants are investigated in independent samples of high- and low-risk sport participants.

1.2   Why study sport?

To an uninformed bystander, soloing (climbing without protection) a rock face may seem as, if not more, reckless than taking drugs or gambling. Often times, what the onlooker does not realize is that the climber is highly practiced in his/her sport, has likely climbed the route dozens of time (with protection), memorizing each move, and has full confidence in his/her abilities to complete the task unharmed. Regardless, there is still an inherent risk to climbing a high wall without protection. So why take the risk? Many athletes claim that the risk is not the goal, instead, they seek an inner peace or connectedness to the natural world (Brymer & Oades, 2009), although risk-taking, escape from boredom, and seeking challenge and excitement are other common themes that emerge from the qualitative research data (Hallin & Mykletun, 2006; J.H. Kerr & Mackenzie, 2012). There is an extensive body of literature in which researchers have examined characteristics of elite practitioners of high-risk sports in an attempt to understand the motivation for participation, the personalities most likely to pursue such sports, along with the perceived risks and benefits of the activities. Fewer studies have explored the underlying physiological mechanisms driving motivation, and few-to-none have explored the potential of a genetic underpinning.

High-risk sports carry a potential for severe injury or death as an inherent part of the activity (Willig, 2008). They are commonly referred to as "adventure" or "extreme" sports. The latter term was picked up by marketing companies to promote competitions like the X-games or energy drinks (e.g., Xtreme), and many high-risk sport participants do not identify with this term (personal communications). In this dissertation the terms "high-risk sports" or "adventure sports", will be used rather than "extreme sports".

High-risks recreation is not new, people have been practicing parachuting, paragliding, alpine skiing, and surfing (and many other sports involving risk) for over a century, but participation rates saw drastic increases over the last 30 years (reviewed in Celsi, Rose, & Leigh, 1993). In the United States participation levels in these types of sports increased 244% from 1978 to 2000 (Puchan, 2004). With the rise in high-risk sport participation, industry has capitalized on the market and there has been an increase in media devoted to the sports (including magazines, films, and TV series, e.g., Fear Factor), further increasing the popularity of these once fringe sports (Creyer, Creyer, Ross Jr, & Evers, 2003). With the surge in participation rates there has also been a corresponding surge in injuries and deaths (Creyer et al., 2003; Le Breton, 2000) and these have been documented by reviews on adventure sports (e.g., Celsi et al., 1993). The repertoire of high-risk sports has increased over the years as well, with the evolution of skydiving (with roots in the military) to BASE-jumping (jumping off a building, antenna, span, or the earth (i.e., a cliff) in 1978 (Hallin & Mykletun, 2006), and sports that are just gaining momentum now include high-lining (walking across a slack line of nylon webbing spanning a high gap) and speed flying (skiing with a kite). An extensive list of high-risk sports, including descriptions of each, is included in Appendix A.

Understanding the motivations that drive people to participate in high-risk sports may help injury prevention research, but may also be useful for treatment and prevention of other deviant risk-practices. There are similarities in personality profiles of high-risk athletes and deviant risk takers (e.g., Franques et al., 2003), but there are also interesting differences between these risk-inclined populations (e.g., Goma-I-Freixanet, 1995; Goma-i-Freixanet, 2001). Prosocial and antisocial risk takers often report high levels of personality traits associated with seeking rewards, but athletes may differ from deviant risk-takers on traits involved in planning

and premeditation (discussed in detail below). Research into personality, emotional regulation, neurophysiology, and genetics are all avenues for understanding motivation for high-risk recreation.

1.3   Sensation seeking

While motivation to participate in high-risk sport may vary between individuals, high sensation seeking is a common trait among these athletes (Goma-i-Freixanet, Martha, & Muro, 2012). Sensation seeking, involves,

"… the seeking of varied, novel, complex, and intense sensations and experiences, and the willingness to take physical, social, legal, and financial risks for the sake of such experience" (p. 27, Zuckerman, 1994).

The willingness to take risks is not the goal *per se*, but an important correlate of the trait (Zuckerman, 1994). Sensation seekers often underestimate the risk associated with an experience, or place such a high value on the reward that they are willing to accept the risk, but it is important to note that few prosocial sensation seekers seek the risk itself (Zuckerman, 1994). Not surprisingly, sensation seeking has been associated with a variety of high-risk social activities including unprotected, casual sex (Kalichman, Cain, Zweben, & Swain, 2003; Zuckerman & Kuhlman, 2000), illicit drug use (M.T. Bardo et al., 2007), gambling (Rosenbloom, 2003; Verdejo-Garcia, Lawrence, & Clark, 2008) and crime, as well as with high-risk sport participation (reviewed in Goma-i-Freixanet et al., 2012; for review of all domains, see: Roberti, 2004).

Marvin Zuckerman coined the term "sensation seeking" in the 1970s, following a series of sensory deprivation experiments, in which he noticed shared characteristics among study volunteers. Most of the volunteers were "free-spirited", young men who dressed in an alternative fashion (long hair, ripped jeans) and were drawn to the study by rumours of euphoric

side-effects. Zuckerman would later classify these study volunteers as "high sensation seekers" (Zuckerman, 1979). Soon thereafter, C. Robert Cloninger defined a similar trait, "novelty seeking" (NS) as a dimension in his tri-dimensional personality questionnaire (TPQ) (Cloninger, 1987). Novelty seeking is defined as "… a tendency toward intense exhilaration or excitement in response to novel stimuli or cues for potential rewards or potential relief of punishment" (p. 574, Cloninger, 1987). The two traits, novelty and sensation seeking, are often used interchangeably in behavioural genetics and psychology literature today.

1.3.1   Sensation seeking and other personality models: Approach traits

Novelty and sensation seeking are moderately correlated ($r = 0.4$ to 0.7) (McCourt, Gurrera, & Cutter, 1993; M. R. Munafo, Yalcin, Willis-Owen, & Flint, 2008; Zuckerman & Cloninger, 1996) and are members of a larger group of "approach-related traits'" which also include extraversion, sociability, and impulsivity (M. R. Munafo et al., 2008; Zuckerman, 2005a). Motivational tendencies can broadly be grouped as "approach" and "avoidance" orientations, and approach traits involve an increased sensitivity to positive stimuli (or removal of negative stimuli) (Elliot & Thrash, 2002). The Reinforcement Sensitivity Theory (RST) (Gray & McNaugton, 2000) is a contemporary theory of personality that influenced Zuckerman's neurobiological model of sensation seeking (Zuckerman, 2007a), also pertaining to sensitivity to stimuli. A brief description of RST is provided below in order to provide context for discussing sensation seeking as an approach trait. For full review of RST as it relates to personality, please refer to Corr (2004).

The RST proposes that individual differences exist in sensitivity to unconditioned and conditioned signals of reward and punishment (Gray & McNaugton, 2000). Under the RST,

there are systems governing behavioural activation (BAS) and inhibition (BIS): the former is thought to respond in a goal-directed manner to appetitive stimuli and to the removal of aversive stimuli (i.e., positive and negative reinforcement), while the latter is involved in resolving goal conflicts that can arise between BAS activation and activation of a third system, the Fight-Flight-Freeze System (FFFS) which is activated upon presentation of aversive stimuli and cues predicting positive or negative punishment (Corr, 2004). BIS influences how an individual values a reward over the risk of punishment, e.g., the pleasure of speeding down a mountain versus the risk of losing control by going too fast. Self-report measures that putatively relate to the RST, including Carver and White's (1994) BIS/BAS scale, and the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) by Torrubia, Avila, Moto and Caseras (2001), have been used in a few high-risk-sport studies, but are less commonly employed compared to the sensation-seeking measures (e.g., Goma-i-Freixanet et al., 2012).

Other self-report measures may relate to the RST, as Elliot and Thrash (2002) proposed that several personality traits could be grouped into the broad temperaments of approach and avoidance orientation. Using factor analytic processes they found measures of extraversion, positive affect, and behavioural activation loaded together as approach traits, sharing a sensitivity to positive stimuli (i.e., reward); while measures of neuroticism, negative emotionality, and behavioural inhibition loaded together as avoidance, sharing a sensitivity to negative stimuli (i.e. punishment) (Elliot & Thrash, 2002). Approach-traits tend to reflect heightened reward sensitivity and strong BAS, whereas avoidance-traits are influenced jointly by activation of the BIS and FFFS and reflect punishment sensitivity (Corr, 2004). The trait most commonly associated with strong BAS is impulsivity (discussed in section 1.3.2), but sensation seeking also putatively relates to strong BAS (Corr, 2004; Zuckerman, 1994). An overview of sensation

seeking as it relates to reward sensitivity, behavioural activation, and approach is provided in order to understand neuro- and psychophysiological paradigms and to understand how meta-analytic studies of personality genetics have grouped multiple traits under the broader term "approach".

1.3.2   **Impulsivity**

Impulsivity is a multidimensional trait that involves acting without forethought (Evenden, 1999). Depending on the instrument, impulsivity sometimes appears as a subfactor within instruments that measure either novelty seeking and sensation seeking (Cloninger, 1987; Zuckerman, Kuhlman, Joireman, Teta, & Kraft, 1993), or *vice versa,* i.e., measures of impulsivity include sensation seeking as a subfactor. Zuckerman's latest personality instrument (1993) places sensation seeking within the broader trait "impulsive-sensation seeking", where sensation seeking represents the tendency to approach novel stimuli, and impulsivity governs the decision-making style of whether or not to approach, and although they represent distinct facets, they load together onto a single factor (Zuckerman, 1994, 2005b; Zuckerman et al., 1993). Various measures of impulsivity correlate both with Zuckerman's combined impulsive sensation seeking scale and with each component (impulsivity and sensation seeking) separately (see Appendix B for results from an unpublished study); however, many studies demonstrate that they are dissociable traits (Cross, Copping, & Campbell, 2011; Flory et al., 2006; Magid, MacLean, & Colder, 2007). Impulsivity is not considered a unitary construct (Evenden, 1999), and commonly at least three dimensions of impulsivity have emerged from factor analysis of data derived from various impulsivity questionnaires, these include: reward sensitivity (and approach motivation), punishment sensitivity (and avoidance), and higher order cognitive impulsivity

(sometimes called rash impulsivity) (Cross et al., 2011; I. H. A. Franken & Muris, 2006; Miller, Joseph, & Tudway, 2004; Quilty & Oakman, 2004; L. D. Smillie, Jackson, & Dalgleish, 2006).

A person can be impulsive without being high in sensation seeking, and *vice versa*. For example, a sensation-seeking skier might be inclined to jump off a small cliff, but whether or not the skier scopes out the landing ahead of time may depend on his/her trait impulsivity. Participation in many high-risk sport activities requires planning and expertise and is more likely related to the approach motivation aspects of impulsivity. Not surprisingly, participation in high-risk sports is more commonly associated with sensation seeking (Goma-i-Freixanet et al., 2012), whereas associations with impulsivity independent from sensation seeking are rare (i.e., no associations found with high risk sport participation (Goma-I-Freixanet, 1991, 1995; Goma-i-Freixanet, 2001; Jack, Jack, & Ronan, 1998; J. H. Kerr & Svebak, 1989). A variety of non-athletic risk-taking behaviours are associated with high scores on the combined impulsive sensation seeking scale (Zuckerman & Kuhlman, 2000), but sensation seeking and impulsivity are also independently associated with high-risk behaviours, many of which are discussed below in section 1.4. The following sections focus mainly on correlates of sensation seeking, the trait most commonly associated with sport participation, with less focus on impulsivity as an independent factor.

1.3.3   **Laboratory correlates of sensation seeking**

There are laboratory paradigms that measure behavioural inhibition and impulsivity (Cross et al., 2011; Verdejo-Garcia et al., 2008), and there exist laboratory tasks that measure risk taking, but there are fewer tasks designed specifically to measure sensation seeking. There are, however, tasks that are moderately *correlated* with sensation seeking. Two such risk-taking

tasks include the Balloon Analogue Risk Task (BART) and a balance beam activity. The BART involves pushing buttons on a computer to inflate a balloon and monetary gains are incurred with each pump, at the risk of the balloon exploding due to over-inflation (maximum balloon circumference randomly altered per trial) (Lejuez et al., 2002). Risk taking as assessed using the BART was moderately correlated with sensation seeking scores (Lejuez et al., 2002). Performance on the BART has also been related to impulsive sensation seeking, in that low scorers were more risk averse when there was a greater potential for loss, whereas high scorers did not adjust their behaviour despite increased risk for loss (Bornovalova et al., 2009). Another risk-taking activity for children designed by Morongiello and colleagues (2006) involves crossing a balance beam set to variable heights and they found that the degree of risk taking was correlated with sensation seeking. Brocke and colleagues (1999) attempted to move beyond behavioural correlates of sensation seeking by testing three paradigms: continuous performance task, delayed reaction time task, and the augmenting-reducing paradigm in an attempt to validate behavioural paradigms that would reliably predict (or act as *indicators* of) sensation seeking. The chosen tasks had been used in attention deficit hyperactivity disorder (ADHD) research and the authors suggested that ADHD is an extreme manifestation of sensation seeking. They observed significant correlations between the tasks and sensation seeking, but only the delayed reaction time task was able to predict a small portion of variance in sensation seeking (Brocke et al., 1999). None of the above-mentioned tasks were designed specifically for *sensation seeking*, and although risk-taking and attentional tasks correlate with self-report measures of sensation seeking, they are only capturing a facet of the complex trait.

Other behavioural correlates of the sensation-seeking trait involve measuring orienting responses to novel stimuli (either visual or auditory). Zuckerman (1994, 2005b, 2007a) reviews

studies finding that high sensation seekers have stronger orienting responses, measured by skin

conductance and heart rate deceleration, to novel, non-aversive, intense stimuli than low

sensation seekers. Researchers can vary the novelty or intensity of a stimulus in order to elicit

orienting responses, startle responses, or defensive responses. Orienting responses are typical of

low to moderate intensity stimuli, whereas high intensity stimuli may result in a defensive

response, or a startle response if the stimulus is unexpected. High and low sensation seekers

differ in their response to the same intensity stimulus, and a moderate tone can elicit an orienting

reflex in high scorers and a defensive reflex in low scorers (Zuckerman, 1994). High sensation

seekers also show a positive correlation between cortical arousal responses as measured by

visual and auditory evoked potentials and stimulus intensity, whereas the converse is seen in low

sensation seekers. These patterns of responses, which are referred to as either "augmenting" or

"reducing", have been observed in animal models (including cats and rats). Augmenter cats

(those showing increasing evoked potentials in response to intense stimuli) displayed more

exploratory behaviours (analogous to sensation seeking in humans), while reducer cats showed

more withdrawal (reviewed by Siegel, 1997). Differences between high- and low-sensation

seekers are observed not only in cortical responses, but hormonal responses too. Both animal

and human experiments have shown that when exposed to aversive stimuli or stressors, high

sensation seekers show a blunted cortisol response (Zuckerman, 1994, 2007a).

Another task that has been shown to differentiate high- and low-sensation seekers

involves measuring acoustic startle reflex after presentation of images differing in their affective

valence. The International Affective Picture System is a set of normative emotional stimuli often

used to measure arousal (P. J. Lang, Bradley, & Cuthbert, 1997); and images are grouped by

affective valence: positive, neutral, or threatening. Startle responses in low sensation seekers

were increased after the presentation of threatening images compared to neutral images, but no differences were observed in high sensation seekers (Lissek & Powers, 2003). The data from this study suggest that high sensation seekers have weaker avoidance systems, which is further supported by studies described below.

More recently, imaging studies have shed light on regions of the brain that are activated during laboratory tasks that measure phenotypes related to sensation seeking (i.e., risk-taking, arousal). Joseph and colleagues (2009) used functional magnetic resonance imaging (fMRI) to show that brain regions are differentially activated in high- and low-sensation seekers in response to intense visual stimuli from the International Affective Picture System, and the results supported the framework for strong approach and weak avoidance systems in the high scorers. Similarly, Kruschwitz and colleagues (2012) observed differences in magnitude and location of neural activation (recorded using fMRI) between approach and avoidance related responses in a Risky Gains Task[1] in high and low sensation seekers. High sensation seekers show greater activation to reward compared to low sensation seekers, and low scorers showed greater activation to punishment compared to high scoring individuals (Kruschwitz et al., 2012). Taken together, these findings provide support for strongly activated approach systems and weak avoidance systems in high sensation seekers.

1.3.4   **Sensation-seeking instruments**

There are a number of laboratory tasks that measure impulsivity, and we have seen that there are tasks that correlate with sensation seeking, but many researchers measure sensation

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[1] Numbers are displayed on a screen and participants can choose to either accept the choice or to wait for a higher value number (at the risk of being presented a negative number). The numbers each represent a monetary reward (e.g., 20 = $0.20), but some numbers represent negative values. Participants can select the lowest (safe) value, or can wait for higher values at the risk of a negative (punishment) value.

seeking using self-report questionnaires. These include the Sensation Seeking Scale (SSS) versions IV or V (Zuckerman, 2006); the Brief Sensation Seeking Scale (BSS) (Hoyle, Stephenson, Palmgreen, Lorch, & Donohew, 2002); the Arnett Inventory of Sensation Seeking (AISS) (Arnett 1994); and questionnaires that contain sensation seeking as a factor within a broader questionnaire: the UPPS (Whiteside & Lynam, 2001) and the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ, Appendix C) (Zuckerman et al., 1993). There is considerable overlap of items between the BSS, UPPS and ZKPQ, however the SSS, BSS, and UPPS all contain items with specific references to sports (e.g., water skiing, parachute jumping, skiing, and bungee jumping), while the ZKPQ Impulsive Sensation Seeking scale (ImpSS) makes no such references (Zuckerman, 2007a). The BSS, UPPS and ZKPQ also use modern language compared to the SSS. For example, the SSS uses the words/phrases "hippie", "surf-board riding", "far out friends", and is not reflective of some social norms of today (e.g., SSS item: "I stay away from anyone I suspect of being "gay" or "lesbian"). Taking these into consideration, the ZKPQ is better suited for sport populations containing a large proportion of young adults, and because it lacks potentially confounding items relating to sport.

Zuckerman's SSS contains four subscales, thrill and adventure seeking (TAS), experience seeking (ES), boredom susceptibility (BS), and disinhibition (Dis). Items from each subscale relate to different expressions of sensation seeking; for example TAS reflects a desire for exciting physical activities, ES reflects a desire for exciting cultural experiences, BS is an aversion to monotony, and Dis reflects seeking excitement through social expressions (Zuckerman, 2005b). The ZKPQ ImpSS scale emerged from factor analysis of the SSS items, and therefore contains elements from each of the four expressions (Zuckerman et al., 1993). See

Table 1-1 for correlations between subscales of novelty- and sensation-seeking measures, and

Table 1-2 provides a summary of novelty and sensation-seeking instruments and subscales.

Table 1-1

Correlations between novelty and sensation-seeking instruments

Instrument-Subscale	Correlation with ZKPQ ImpSS
SSS-total	.66[a]
SSS-TAS	.43[a]
SSS-Dis	.43[a]
SSS-BS	.37[a]
SSS-ES	.43[a]
TCI-NS-total	.68[b]

Note. Data obtained from the following sources: [a](Zuckerman, 2007a); [b](Zuckerman & Cloninger, 1996).

Table 1-2

Summary of commonly employed measures of novelty and sensation seeking

	Instrument		
	Zuckerman SSS	Zuckerman-Kuhlman (ZKPQ)	Cloninger TCI
Brief description	Trait measure of total sensation seeking, divided into four subscales.	Personality measure, five dimensions (traits).	Personality measure, three dimensions (temperaments), further subdivided into subscales.
Approach measure	Total sensation seeking (SSS_Tot)	Impulsive sensation seeking (ImpSS)	Novelty seeking (NS)
	Boredom susceptibility (BS)	Impulsivity (Imp)	Exploratory excitability *vs.* stoic rigidity (NS1)
	Disinhibition (Dis)	Sensation seeking (SS)	Impulsiveness *vs.* reflection (NS2)
	Experience seeking (ES)		Extravagance *vs.* reserve (NS3)
	Thrill and adventure seeking (TAS)		Disorderliness *vs.* regimentation (NS4)
Other traits		Sociability (Soc)	Harm avoidance (HA)
		Aggression-hostility(Agg-Hos)	Reward dependence (RD)
		Neuroticism-anxiety (Neu-Anx)	
		Activity (Act)	

Note. SSS = Sensation Seeking Scale, ZKPQ = Zuckerman-Kuhlman Personality Questionnaire, TCI = Temperament and Character Inventory.

The ZKPQ measures five personality traits, but its ImpSS (the instrument used for this dissertation) has been used in isolation. The ImpSS contains a total of 19 items, but may also be divided into its two factors: impulsivity (Imp, eight items) and sensation seeking (SS, 11 items), (Appendix D). The impulsivity factor measures lack of planning and forethought; while the sensation-seeking factor measures the desire to seek out new and thrilling experiences and the willingness to take risks (Zuckerman et al., 1993). The two-component scale allows for the consideration of impulsivity and sensation seeking as dissociable traits (e.g., Cross et al., 2011). The full ZKPQ has shown high re-test reliability (.82 to .87, retest interval of 2 months), and internal consistencies for the ImpSS subscale were .77 and .81 for males and females respectively (Zuckerman & Kuhlman, 2000), and .83 for ImpSS in an unpublished sample

(Thomson, 2008). The ImpSS scale used independently has also shown acceptable internal

consistency (.84 and .87 in two samples, McDaniel & Mahan, 2008; .77 in one sample, Robbins

& Bryan, 2004). Although the SSS remains the most commonly employed tool for assessing

sensation seeking, there is support for the ImpSS as a valid, reliable alternative (McDaniel &

Mahan, 2008). The ImpSS demonstrates concurrent validity with the SSS (McDaniel & Mahan,

2008), and based on a meta-analysis the reliability estimates of the SSS subscales are less than

.70 (except for the TAS which is .75) (Deditius-Island & Caruso, 2002), which is generally lower

than reliability estimates for the ImpSS (McDaniel & Mahan, 2008; Zuckerman, 2007a).

Finally, the ImpSS is brief enough to administer in the field.

While a majority of psychology and sociological studies continue to measure sensation

seeking using the SSS (and ImpSS), it appears that a majority of studies in the fields of

neuroscience and behaviour genetics measure approach using Cloninger's Temperament and

Character Inventory (TCI; Cloninger, 1987) novelty seeking subscale (perhaps because of

language used to describe the traits in rat and mouse models). The disparity between the fields

with respect to phenotype definition is further exemplified in the sport literature, where, to my

knowledge, there exist only a handful of studies that have investigated approach in athletes using

a tool to measure *novelty* seeking, since most sport studies measure *sensation* seeking.[2] I have

chosen to measure sensation seeking to be consistent with the sport psychology literature and the

suitability of the sensation-seeking content for a sport population. Although the research

described in this thesis focuses on impulsive sensation seeking, when reviewing the neuroscience

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[2] A "web of science" search of the terms "sport" + "novelty seeking" resulted in *two* articles; whereas a search for
the terms "sport" + "sensation seeking" resulted in 157 articles. When searching the terms "genes" + "novelty
seeking" as opposed to "genes" + "sensation seeking", the novelty seeking search resulted in seven times (total >
700) more articles, and of this fraction of studies that mention sensation seeking, many actually measured novelty
seeking as the phenotype of interest.

and genetics literature, literature from both novelty seeking and sensation seeking measures are reviewed and the overall results are discussed as they relate to "sensation seeking" from herein.

1.3.5   Demographic trends in sensation seeking

Sensation seeking varies between the sexes and with age. Sensation seeking is positively associated with "masculine" interests and characteristics and negatively associated with "feminine" interests and characteristics in North American culture (Daitzman & Zuckerman, 1980; Kish, 1971), and has been related to lower levels of felt gender compatibility among women (Saxvik & Joireman, 2005). In line with these findings, men consistently score higher on all sensation-seeking subscales except experience seeking (Zuckerman, 2007a). The largest differences between men and women are on the thrill and adventure seeking and disinhibition subscales from the SSS (Zuckerman, 2007a). Men also score higher on ImpSS than women (Thomson, 2008; Zuckerman & Kuhlman, 2000), though the differences in ImpSS scores between the sexes are less pronounced than sensation seeking measured using the SSS (Cross et al., 2011).

Sensation seeking is lower in children, and scores generally peak in adolescence, and decline thereafter (Zuckerman, 1979, 2007a), although longitudinal research on sensation seeking in children is lacking. Significant age-related decline in all subscales except boredom susceptibility have been reported (Zuckerman, 2007a). Even after removing "age-dependent" items, such as those that require a certain level of physical fitness (e.g., skiing, mountaineering), the same post-adolescence inverse relationship between sensation seeking and age was observed (Roth, Hammelstein, & Braehler, 2007). Despite this overall decline, individuals maintain a relatively stable rank within a cohort as they age, in that high sensation seekers in adolescence

remain at the higher end of their cohort into adulthood (M.T. Bardo et al., 2007). Sensation-seeking scores also purportedly vary between self-reported "ethnicities"[3]. Individuals reporting African American descent score lower on SSS subscales, with the exception of disinhibition compared to individuals of European descent (Zuckerman, 1994), and Western cultures score higher than Asian cultures, although these cultural differences have not been consistently reported across all sensation-seeking subscales (M.T. Bardo et al., 2007).

Other demographic variables (e.g., marital status, education, religion) have also been associated with sensation-seeking scores. Divorced males scored significantly higher than single and married males and there was a similar trend in females, although the finding was not significant (Zuckerman & Neeb, 1980). Sensation seeking appears to play a role in mate selection, in that high sensation seekers tend to marry individuals similarly high in the trait (Bratko & Butkovic, 2003; Zuckerman, 2007a), and sensation seeking is an exception to the usually small-to-zero spousal correlations for most personality traits (e.g., Donnellan, Conger, & Bryant, 2004).

1.4   Lifestyle correlates of sensation seeking

1.4.1   Deviant high-risk behaviours

Sensation seeking and many related disinhibited traits have been associated with a number of high-risk behaviours. Mind-altering drugs, gambling, risky sex, and crime are common outlets for satisfying exploratory urges (reviewed in M.T. Bardo et al., 2007; Zuckerman, 2007a). Numerous studies have shown that individuals who partake in these deviant

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[3] Depending on the self-report choices, the term "race" is sometimes used instead of "ethnicity". For example, the term Hispanic does not refer to a race, but is an ethnic group, but researchers that assess ancestry based on categories like "white" or "black" are referring to race. There are inconsistencies in the literature, but most researchers use the term ethnicity as it applies to a population sharing common ancestry.

activities report higher levels of sensation seeking, and the trait is considered a reliable predictor

of drug use and abuse (M.T. Bardo et al., 2007). One study found that sensation seeking was a

stronger predictor of drug-use amongst adolescents than socio-economic status, self-esteem, and

mental health (W. Pedersen, Clausen, & Lavik, 1989). Similarly, sensation seeking predicted

tendencies for both occasional and frequent risk-taking across multiple contexts (including

substance use, driving, sexual relations), whereas demographic variables (i.e., age) were only

associated with frequent risk-taking (Desrichard & Denarie, 2005).

Disinhibited traits, including sensation seeking have also been correlated with alcohol use

(Sher, Grekin, & Williams, 2005). A meta-analysis found low to moderate effect sizes for

associations between sensation seeking and alcohol use, but the size of the effect decreased in

studies that included demographic covariates (e.g., age, sex, socio-economic status) (Hittner &

Swickert, 2006). Another study found that the relationship between sensation seeking and

alcohol use disappeared with the inclusion of additional variables, such as high scores on an

inventory designed to measure antisocial features (Whiteside & Lynam, 2003). While other

personality and demographic variables are likely to contribute to the aetiology of alcohol use and

substance use disorders, sensation seeking is considered an important indicator of liability to

develop patterns of disordered use (Kelly et al., 2006; Stacy & Newcomb, 1999).

Disinhibition[4], in particular, is the sensation-seeking facet (from the SSS) most strongly

associated with alcohol use (Hittner & Swickert, 2006); however, the subscale includes a number

of items that contain potentially confounding references to substance and alcohol use. Carlson

and colleagues (2010) included only the thrill-and-adventure-seeking and boredom-susceptibility

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[4] Note: the term "disinhibition" does not refer to the lack of inhibitions a person might experience while under the influence of alcohol, but refers to the personality dimension within the SSS, which is reflective of seeking excitement through social situations.

subscales from the SSS (to avoid subscales containing references to substance-related behaviours) in a model to predict binge drinking, and found that both SSS subscales were significant predictors.

Other common outlets for sensation seeking include gambling, risky sexual behaviours, and criminal activities. Higher sensation-seeking scores have been reported in studies of pathological gambling (Potenza et al., 2003), but the findings are not ubiquitous, and some studies report no differences in sensation-seeking scores between pathological and non-pathological gamblers or between scores on gambling questionnaires in non-clinical populations (reviewed by Hammelstein, 2004; Zuckerman & Kuhlman, 2000). The findings for high sensation seeking among individuals who take sexual risks are more consistent (Hoyle, Fejfar, & Miller, 2000; Zuckerman, 2007a). One-night-stands, sexual acts under the influence of alcohol and drugs, unprotected sex, and promiscuity have been related to sensation seeking and impulsive sensation seeking (Donohew et al., 2000; Zuckerman & Kuhlman, 2000). Finally, a range of unlawful activities have been linked to sensation seeking. These include speeding, drinking and driving, vandalism, and theft (Horvath & Zuckerman, 1993; reviewed in Zuckerman, 2007b). Sensation seeking is moderately correlated with general deviance (e.g., attitudes towards law abidance, sexual events, illicit substance use) in adolescence and young adulthood, but a longitudinal study following youth from grades 10-12 until their early 20s found that the trait was not predictive of general deviance over time. Instead, it was found that sensation seeking predicted specific deviance related to substance use, and use of substances then predicted general deviance (Newcomb & McGee, 1991). Similarly, high sensation seeking is seen in schizophrenic patients, but more commonly when individuals have a comorbid substance use disorder or alcoholism (e.g., Dervaux et al., 2010; Zhornitsky et al., 2012). While sensation

seeking is most commonly associated with substance use disorder and alcoholism, the trait has

been associated with characteristics common to other externalizing disorders, including conduct

disorder (reviewed in J. S. Kotler & McMahon, 2005) and ADHD (Faraone et al., 1999).

1.4.2   Sensation seeking and sport

Sensation seeking has been associated with disinhibited behaviours described above, but

also to non-deviant, prosocial outlets like travel and entrepreneurship (Lepp & Gibson, 2008;

Nicolaou, Shane, Cherkas, & Spector, 2008). High-risk sports are another prosocial outlet for

sensation seeking. High-risk sports were once fringe activities, but are now gaining mainstream

popularity with increased media exposure and accessibility. Sports are considered "high-risk"

when there is a high chance of severe injury or death if something goes wrong during the activity

(i.e., falling, equipment failure, weather change, etc.) (Willig, 2008; Zuckerman, 2007b), yet

people are drawn to such sports, even with full disclosure of the inherent dangers they present.

Table 1-3 shows estimated fatality rates for select sports. Examples of high-risk sports include

paragliding, skydiving, scuba diving, downhill mountain biking, mountaineering, big mountain

skiing and snowboarding, surfing, high-lining, and more high-risk sports are invented each year

(for an expansive list, please see Appendix A).

Table 1-3

Estimated fatality rates for a selection of sports

Sport	Fatality rate	Year of census	Reference
BASE	1/2317 jumps	1995-2005	1
Skydiving	1/18333 jumps	1979-1983	2
Mountaineering	1/1 000	1983	3
>7000 m peaks	1/5 expeditions	1986	4
Hang gliding	1/1250 flights	1983	3
Scuba diving	1/100 000 dives	1983	3
Skiing	1/150000[a] skier days	1996-2006	5
Professional Football	1/200000	1983	3

Note. [a]permanent injury or death (Alberta & British Columbia). 1) (Soreide, Ellingsen, & Knutson, 2007); 2) (Ellitsgaard, 1987); 3) (Celsi et al., 1993); 4) (Pollard & Clarke, 1988); 5) (McBeth, Ball, Mulloy, & Kirkpatrick, 2009).

Athletes who participate in high-risk sports might share a number of qualities, e.g., a passion for the outdoors (Brymer & Oades, 2009), nonchalance towards heights (or an attempt to conquer a fear (J.H. Kerr & Mackenzie, 2012)), and perhaps a need for thrill and excitement. Numerous studies have shown that high-risk sport practitioners report higher levels of sensation seeking than low-risk sport practitioners (Diehm & Armatas, 2004; I. H. Franken, Zijlstra, & Muris, 2006; Franques et al., 2003; Gelernter et al., 1997; Kelly et al., 2006; Michel, Cazenave, Delpouve, Purper-Ouakil, & LeScanff, 2009; Zuckerman & Kuhlman, 2000). A selection of studies is shown in Table 1-4, for a recent review see Goma-i-Freixanet et al., (2012). To my knowledge there are no studies reporting contrary findings. Studies that have looked at other measures related to disinhibition, such as behavioural activation measured using the BIS/BAS scale (C. S. Carver & White, 1994), and reward sensitivity measured using the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) (Torrubia et al., 2001) similarly find higher "fun seeking" in skydivers compared to rowers (I. H. Franken et al., 2006). Likewise, mountaineers and other high-risk sportsmen scored higher on measures relating to

reward sensitivity (e.g., sensitivity to reward, and thrill and adventure seeking) (Castanier, Le Scanff, & Woodman, 2010a, 2010b; Goma-I-Freixanet, 1991).

Many of the high-risk sport studies that exist have looked at sports that carry a very high degree of risk that are practiced by a select group of individuals. For example, Michel and colleagues (2009) studied BASE jumping which is practiced by only a few thousand people world wide and for which many clubs require that jumpers have skydived over 250 times before admission (e.g., Hallin & Mykletun, 2006) Franques et al. (2003) studied paragliders, a sport that requires a license to fly solo, and practiced by less than 1% of people reporting participation in adventure recreation (Ewert & Hollenhorst, 1997). Other sports that carry some physical risk, and are therefore considered high-risk, but are commonly practiced by the general public have been less thoroughly explored. In particular, skiing and snowboarding are popular, mainstream sports that are considered high-risk activities (Malkin & Rabinowitz, 1998) with a risk for injury of approximately 2 to 4 per 1000 participant days and that accounts for 28% of all injuries related to ice and snow sports (Warda & Yanchar, 2012). Another common trend in high-risk sport literature is that many studies include largely male (or male-only) samples (as shown below in Table 1-4) since there are more males that participate in many of the very high-risk sports (Jensen & Guthrie, 2006). Choosing commonly practiced downhill sports, such as skiing and snowboarding, allows for the recruitment of large samples with almost an equal representation of females.

Table 1-4

Studies comparing sensation seeking between high- and low-risk athletes or controls

High-risk (*n*)	Controls and low-risk (*n*)	Tool	Findings	Ref.
Downhill skiing (219), M + F	Matched reference (299), M + F	SSS	Skiers scored higher on TAS	1
Bungee jumping (80), M + F(29)	General public, M + F(45)	SSS V (Fr)	Bungee jumpers scored higher on TAS	2
"Extreme risk takers" (20) rock climbing, skiing, stunt flying, kayaking, males	High risk-takers (20) (safer version of same sports), males Low-risk athletes (20), males	SSS V	TAS higher in both risk groups (high and extreme) compared to controls. No differences between risk groups	3
Hand-gliding, mountaineering, skydiving, auto racing (93), M + F(10)	Swimming, marathon runners, aerobics, golf (73), M + F(37)	SSS V	SS higher in high-risk group	4
Parachuting (experts) (21), males	Parachuting (novice) (14), males	SSS V (Nor)	Both groups scored higher on SSS than controls, experts scored higher than novices on ES	5
Risky sports (52), females	Controls (58), females	SSS V (Sp)	Risk group scored higher on TAS, ES, and Dis	6
Paragliding (34), M + F	Matched reference group (34), M + F	SSS IV (Fr)	Paragliders scored higher on BS, TAS, and Dis	7
Surfing (41), M + F(11)	Golfing (44), M + F(15)	SSS V	Surfers scored higher on TAS and ES	8
Recreational (53) and professional (37) risk sports athletes, females	Low-risk athletes (90), females	SSS (Fr)	Recreational athletes scored higher on SSS (and TAS and ES) than both controls and pros, and pros scored higher than controls	9
Rock climbers (118), M + F(28)	No control group, measured risky behaviours	ImpSS	Risky behaviours were not associated with sensation seeking, impulsivity, or ImpSS	10
BASE jumpers (11), males	Controls (11), males	SSS IV (Fr)	BASE jumpers scored higher on SSS total and TAS	11
Skiers, M + F (683)	No controls group, inquired about risky behaviours	SSS V (D)	SS score was associated with risky behaviours	12
Parachuting, wakeboarding, snowboarding, scuba, alpinism, paragliding (217), males	Non-athletic controls (54), males	SSS IV (P)	Risk group scored higher on all SSS subscales	13

Note. [1](Bouter, Knipschild, Feij, & Volovics, 1988); [2](Michel, Carton, & Jouvent, 1997); [3](Slanger & Rudestam, 1997); [4](Jack et al., 1998); [5](Breivik, Roth, & Jorgensen, 1998); [6](Goma-i-Freixanet, 2001); [7](Franques et al., 2003); [8](Diehm & Armatas, 2004); [9](Cazenave, Le Scanff, & Woodman, 2007); [10](D.J. Llewellyn & Sanchez, 2008); [11](Michel et al., 2009); [12](Ruedl et al., 2010); [13](Guszkowska & Boldak, 2010). M = male, F = female, Fr = French, Nor = Norwegian, Sp = Spanish, D = German, P = Polish.

It is important to note that although the risk sports mentioned above and in Appendix A carry a risk, most participants report that risk is not the goal of the activity (Brymer, 2010). High-risk athletes often describe themselves as self-aware, disciplined, controlled, and their sport offers them a state of relaxation and emotional clarity (Brymer, 2010). Athletes interviewed in Brymer's (2010) study were not carelessly taking risks within these sports, and most of the above-listed activities require great skill and planning. While sensation seeking is the trait most commonly associated with participation in high-risk sports (reviewed in Goma-i-Freixanet et al., 2012), many participants report high self-efficacy (D.J. Llewellyn, Sanchez, Asghar, & Jones, 2008; Slanger & Rudestam, 1997) and low anxiety (Goma-I-Freixanet, 1991). Another trait that has been associated with prolonged participation in high-risk sport is alexithymia; studies have found that high-risk athletes have a difficulty in identifying and expressing emotions (Cazenave et al., 2007; Woodman, Hardy, Barlow, & Le Scanff, 2010; Woodman, Huggins, Le Scanff, & Cazenave, 2009), which perhaps explains why sport offers "emotional clarity" (described in Brymer, 2010) for some.

While multiple traits likely work together to motivate high-risk sport participation, high sensation seeking and/or strong reward sensitivity are the most consistently reported. In order to explore whether genetic influences motivate sport participation, we must first understand the neurobiological pathways that underlie these approach traits.

1.5   Neurobiology of sensation seeking

Researchers categorize individuals as high or low sensation seekers based on scores on questionnaires, and variations in the functioning of our neurotransmitter systems putatively contribute to these individual differences. Cloninger (1987) hypothesized that three

neurotransmitters underlie broad temperaments and he created the Tri-dimensional Personality Questionnaire (TPQ, now modified and expanded to the Temperament and Character Inventory, TCI) under this premise. According to Cloninger (1987), dopamine, serotonin and norepinephrine underlie novelty seeking, harm avoidance, and reward dependence, respectively. Similarly, Zuckerman proposed that sensation seeking, which involves behavioural mechanisms of strong approach, weak avoidance, and weak arousal, is associated with strong dopamine reactivities, weak serotoninergic, and weak norepinephrine reactivities, respectively (Zuckerman, 2007a). Zuckerman (2007a) notes that with regards to reactivities of neurotransmitter systems, it is the sensitivity of the receptors in response to stimuli and not the levels of circulating neurotransmitters that is important. These three neurotransmitter systems interact, and similarly, behavioural mechanisms involving approach and avoidance interact (see Figure 1-1 for a simplified version of Zuckerman's psychobiological model; Zuckerman, 1994). Zuckerman's model is in line with the RST (section 1.3.1), which proposes that brain structures underlying BAS (approach) involve mesolimbic dopaminergic pathways, whereas the structures underlying BIS (avoidance) involve serotonergic pathways arising from the septo-hippocamppal system (C. S. Carver, 2004; Gray & McNaugton, 2000; Zuckerman, 2005a).
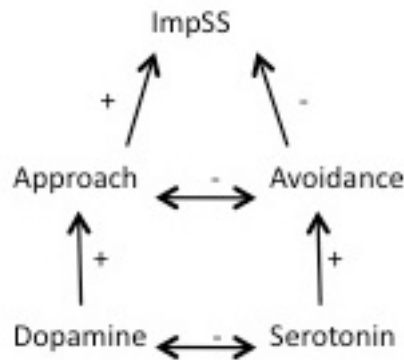
Figure 1-1. Simplified version of Zuckerman's psychobiological for impulsive sensation seeking (ImpSS). Model shows behavioural mechanisms (approach and inhibition) that underlie ImpSS, their interactions, and how the neurotransmitters interact to influence the mechanisms. + represents an excitatory pathway and – represents an inhibitory pathway (Adapted from Figure 14.2; Zuckerman, 1994).

Prior to his psychobiological model of ImpSS, Zuckerman proposed a model for sensation seeking that was based on optimal levels of catecholamine system activity (CSA) (Zuckerman, 2007a). The CSA model suggested that under basal arousal conditions, high sensation seekers have low levels of dopamine and norepinephrine activity and are therefore are under-aroused at rest with a susceptibility to boredom. In basal conditions low sensation seekers maintain optimal levels of catecholamine activity but additional stimulation may produce adverse effects, whereas an identical level of stimulation in high sensation seekers might be optimal (Zuckerman, 2007a). Many researchers still refer to optimal arousal and/or catecholamine system activity models when disseminating biological and genetic findings relating to sensation seeking and anhedonia[5] (I. H. Franken et al., 2006). The arousal model is also called the "inverted U-shape" (e.g., Cross et al., 2011), in which an increase in the hedonic

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[5] Anhedonia refers to the inability to experience pleasure (or hedonic feelings).

valence of an activity ("pleasant" *vs.* "unpleasant") is associated with increasing

arousal/stimulation up until a maximum point, after which increased arousal becomes aversive

and reduces the enjoyment of the activity. Individuals differ in their starting point along the

arousal axis (see Figure 1-2).
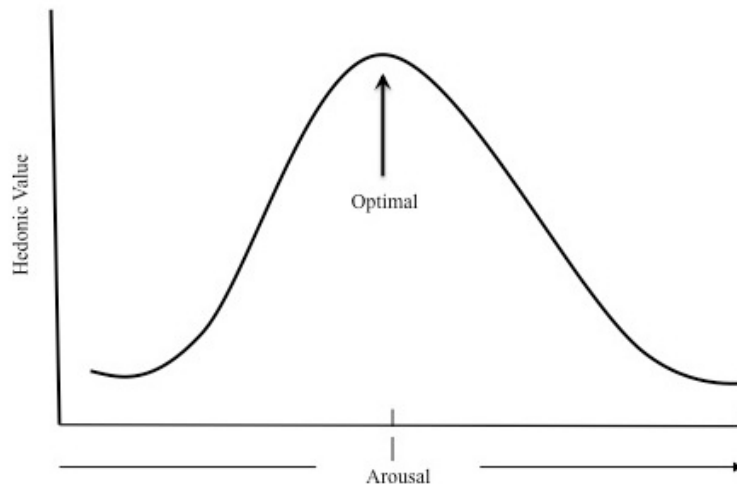
Figure 1-2. Inverted U-shape model of arousal.

As arousal increases, enjoyment of an activity will increase up until a maximum point at which any increase in

arousal may induce anxiety and/or be viewed as unpleasant. Individuals purportedly differ in their optimal levels of

arousal.

While a complex network of neurotransmitters appear to underlie mechanisms for

approach and avoidance, a prominent role for dopamine in sensation seeking is widely supported

by neuro-imaging studies, animal models, and genetics (Ebstein, 2006; Ebstein & Israel, 2009;

reviewed in Hariri, 2009). All drugs of abuse increase extracellular levels of dopamine,

particularly in the mesocorticolimbic system (Koob, Sanna, & Bloom, 1998), and natural

rewards like sex and food stimulate the release of extracellular dopamine (Hernandez & Hoebel,

1988).

Dopamine has been most widely cited for its involvement in "reward processes", but it is much more complex in reality and participates in a wide range of cognitive and sensorimotor functions (Salamone, Correa, Farrar, & Mingote, 2007; Salamone, Correa, Mingote, & Weber, 2005). Dopamine blockade has been shown to impair response habits in mice (reviewed in Wise, 2004), supporting a role in learning. Agonists for dopamine are sometimes used to treat ADHD, suggesting a role for dopamine in sustained attention (Avale et al., 2004). Animal models provide additional support for dopamine's role in memory encoding and learning; for example: in mice, dopaminergic neurons are activated when an unexpected reward is presented (Pecina, Cagniard, Berridge, Aldridge, & Zhuang, 2003) and in rats, exposure to novel environments elicit increases in dopamine release (Rebec, Christensen, Guerra, & Bardo, 1997). It is important to note that the reward-related dopamine release is not associated with an increase in the "liking" of the reward, but rather an increase in the "wanting" of the reward (Pecina et al., 2003); a finding that supports a model in which dopamine is important for modulating functions related to motivation towards goal-directed behaviours, but not the consummatory reward enjoyment itself (Wise, 2004).

1.5.1   **Dopamine synthesis and transport**

Dopamine is produced in the cell bodies in dopaminergic neurons and then stored in vesicles at the axonal termini until signalled for release into the synapse. Once released, dopamine either binds to G-protein coupled dopaminergic receptors on the post-synaptic cell, or to autoreceptors on the pre-synaptic neuron (Zuckerman, 2005a). Dopaminergic neurons fire tonically releasing a small amount of dopamine into the synaptic cleft, or phasically (when activated by excitatory stimuli) due to a burst of firing resulting in a spike-dependent release of a

large amount of dopamine into the cleft (Grace, 2000). Reward-related mechanisms have been

linked to the phasic release of dopamine, but dopaminergic tone can influence the phasic release

via negative feedback (i.e., autoreceptors on pre-synpatic neuron are inhibitory) (Grace, 2000).

Currently, there are five known types of dopamine receptors, and the genes that encode

them are named *DRD1*[6] to *DRD5*. The D2-like receptors (which include D2, D3 and D4) behave

both as standard post-synaptic receptors projecting a signal to neighbouring neurons, and as

autoreceptors (D2 and D3) sending negative feedback signals to decrease dopamine release. In

general, D2-like receptors are considered inhibitory, decreasing the downstream release of cyclic

AMP (cAMP); whereas D1-like receptors (D1 and D5) are considered excitatory, increasing

cAMP. D1-like receptors exclusively act post-synaptically on target cells, whereas D2-like

receptors are expressed both post- and pre-synaptically (autoreceptors) (reviewed by Beaulieu,

2010). Once released, the dopamine transporter (DAT1) recycles dopamine back into the pre-

synaptic cell (Hong, Cheng, Shu, Yang, & Tsai, 2003); therefore the combined effects of the

transporters and receptors regulate the amount of dopamine in the synapse (see Figure 1-3).

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[6] By convention, human gene names are capitalised and italicized e.g., *DRD1* (a gene) encodes the D1-receptor (a protein).
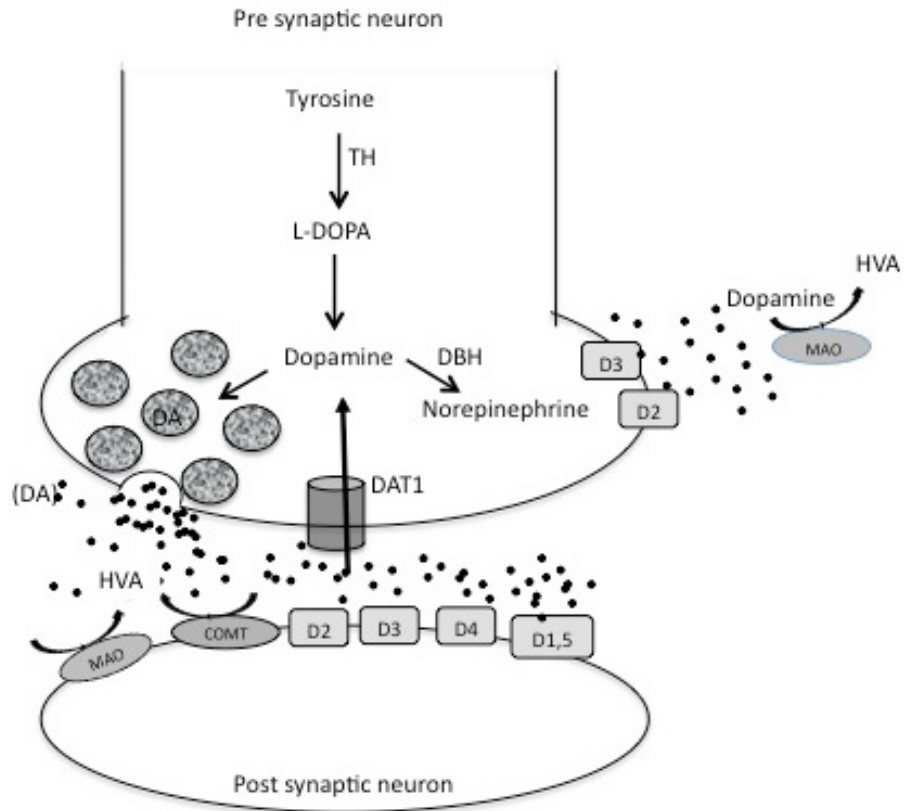
Figure 1-3. Dopaminergic neuron.

Tyrosine is converted to TH (tyrosine hydroxylase), which is converted to L-DOPA (dihydroxphenylalanine) and finally to dopamine (DA). Upon arrival of an action potential, dopamine is released from the pre-synaptic cell, and may bind to five receptor types: D1-like excitatory (D1,D5) or D2-like inhibitory (D2,D3,D4). Alternatively, dopamine may be metabolized by MAO (monoamine oxidase) or COMT (catechol-o-methyltransferase) into HVA (homovillac acid), or recycled back into the neuron by DAT1 (dopamine tansporter). D2 and D3 act as both pre and post-synaptic receptors. Dopamine may also be converted to norepinephrine, by DBH (dopamine-β-hydroxylase). (adapted from Nernoda, Szekely, & Sasvari-Szekely, 2011; adapted from Tavernarakis website "Sensory transduction and integration," n.d.).

1.5.2 **Dopamine and sensation seeking**

Dopamine participates in a wide range of functions, but there is support for its specific involvement in novelty or sensation seeking. Dopamine agonists used in the treatment of Parkinson's disease increased reward processing and novelty seeking in young patients (Bodi et al., 2009). Marginal positive correlations have been observed between novelty seeking and dopamine receptor (D2/D3) availability (H. Y. Huang et al., 2010). These results are in accordance with another study that found high novelty seeking scores were associated with lower midbrain D2-like receptor availability (Zald et al., 2008). A decrease in autoreceptor density purportedly contributes to vulnerability for disinhibited behaviours. This vulnerability hypothesis has been supported by multiple studies including positron emission tomography (PET), which showed that trait impulsivity is positively correlated with amphetamine-induced dopaminergic release and negatively correlated with D2/D3 autoreceptor availability. In other words, reduced autoreceptor availability results in less inhibition of dopaminergic firing and release, thus resulting in increased neuronal firing and dopaminergic release in response to novel/rewarding stimuli (Buckholtz et al., 2010). Low D2 receptor availability has also been observed in susceptibility to alcoholism based on the finding that non-alcoholic members of families with alcoholic subjects had higher D2 receptor densities in caudate and ventral striatum (Volkow et al., 2006). Imaging techniques further support a role for dopamine in sensation seeking, specifically, finding positive correlations between activation in dopaminergic brain regions (e.g., nucleus accumbens) and thrill and adventure seeking (from SSS) and exploratory excitability (NS subscale) (Abler, Walter, Erk, Kammerer, & Spitzer, 2006).

Data from knockout models in mice also support involvement of dopamine receptors and transporters in behavioural approach. For example, mice lacking D2 autoreceptors show

increases in dopamine release upon stimulation, are hyperactive, hypersensitive to the effects of cocaine, and showed enhanced motivation towards food reward (Bello et al., 2011). Similarly, *Drd4*[7]- and *Drd3*-knockout mice are hyperactive, hypersensitive to ethanol and amphetamines, and display exploratory behaviours (Accili et al., 1996; Rubinstein et al., 1997). A link between D4 and ADHD was demonstrated by knocking out the *Drd4* in mice that had been lesioned with 6-hydroxydopamine (a compound shown to alter central dopaminergic pathways) to exhibit hyperactive (or ADHD-like) symptoms. Mice lacking *Drd4* did not exhibit the hyperactive behaviours typical of the lesioned model, suggesting the involvement of D4 in hyperactivity and behavioural inhibition (Avale et al., 2004). Dopamine neurotransmission is affected not only by receptors but also by the dopamine transporter. *Dat1* knockout mice exhibited behaviours analogous to symptoms of ADHD compared to wild-types (Giros, Jaber, Jones, Wightman, & Caron, 1996). While the involvement of dopamine in ADHD does not directly relate to sensation seeking, people high in this trait display impulsive, excitable, and exploratory tendencies, some of which are features of ADHD (Faraone et al., 1999; Zuckerman, 2007a). In summary, manipulating dopaminergic systems in the brains of mice and humans have resulted in altered reward-seeking and exploratory behaviours. These findings provide support for dopamine as a candidate pathway for sensation-seeking behaviours.

1.6   Sensation-seeking genetics: A review of "candidate genes"

Sensation seeking is moderately heritable, with approximately 60% of trait variation due to genetic factors (Hur & Bouchard, 1997; Koopmans, Boomsma, Heath, & van Doornen, 1995; Stoel, De Geus, & Boomsma, 2006). Many genetic association studies attempt to identify the

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[7] By convention, mouse genes are italicized with the first letter capitalised.

genetic variants that underlie the novelty-seeking and sensation-seeking traits, and genes that encode proteins involved in each stage of dopamine and dopamine-related pathways (including synthesis, transport and metabolism) are potential candidates for such studies. Serotonin is a neurotransmitter most commonly cited for its involvement in anxiety-related disorders and avoidance-related traits (reviewed in Hariri, 2009; M. R. Munafo et al., 2003), but has also been implicated in impulsivity (C.S. Carver & Miller, 2006). Weak avoidance and strong approach are the motivational tendencies that are thought to underlie sensation seeking (see sections 1.3.3 and 1.5); therefore, serotonin, which has been implicated in avoidance-related traits, may be another potential candidate system for sensation seeking.

1.6.1   **Dopaminergic pathway genes**

As discussed earlier, imaging, pharmaceutical manipulations in humans and animals, and animal knockout models strongly support a role for the dopamine receptors' involvement in approach-related processes, and therefore dopamine receptors genes are potential candidates for novelty- and sensation-seeking genetic studies. Polymorphisms within dopamine receptors have been investigated for associations with approach traits (e.g., sensation seeking, novelty seeking, extraversion), externalizing behavioural disorders (e.g., ADHD, conduct disorder (CD), operational defiant disorder (ODD)), and substance use (e.g., alcohol, amphetamine, nicotine) (see Appendix E for a list of polymorphisms and phenotypes). The D2-like receptors are more commonly studied than D1-like receptors, in particular, the DRD2 and DRD4 genes are the most frequently studied candidates for approach traits and/or disinhibited behaviours (M. R. Munafo et al., 2003).

1.6.1.1 The DRD4 gene

DRD4 is located on chromosome 11, at 11p15.5. The promoter region of the *DRD4* is highly polymorphic (Okuyama et al., 2000) and multiple variants of the gene have been associated with novelty seeking, extraversion, schizophrenia, and externalizing disorders (Lai et al., 2010; Mitsuyasu et al., 2001; reviewed by M. R. Munafo et al., 2003; reviewed by M. R. Munafo et al., 2008). The D4 receptor is found in the entorhinal and prefrontal cortex, the dorsomedial thalamus, and parts of the limbic system including the lateral septal nucleus, the hypothalamus, and the hippocampus (Primus et al., 1997), all of which are regions of the brain thought to be involved in emotional regulation, attention, and motivation (Kreek, Nielsen, Butelman, & LaForge, 2005).

Two hallmark studies in 1996 reporting associations between alleles of a 48-bp variable number tandem repeat (VNTR) polymorphism in exon III and novelty seeking (Benjamin et al., 1996; Ebstein et al., 1996) spurred a flurry of studies into the genetic underpinnings of personality traits in healthy populations (reviewed by Oak, Oldenhof, & Van Tol, 2000; Paterson, Sunohara, & Kennedy, 1999). Both studies found that individuals carrying at least one copy of the 7-repeat (7R) allele reported higher novelty seeking scores than those carrying the more common 4-repeat allele. Although the two most common alleles in Caucasian populations are the 4- and 7-repeat, allelic versions between 2 and 11 repeats have been reported, and the frequencies vary greatly between populations (Ding et al., 2002). High novelty seeking in carriers of the long (7R) allele have since been inconsistently replicated (reviewed by M. R. Munafo et al., 2008; Oak et al., 2000; Paterson et al., 1999), though less ambiguous associations with externalizing disorders and the 7R allele have been observed (e.g., ADHD; Gizer, Ficks, & Waldman, 2009). Other variants in *DRD4* have similarly been explored in association with

approach-related traits and externalizing disorders, notably a single nucleotide in the promoter region, -521 C/T (db SNP rs1800955) and a 120-bp tandem duplication (db SNP rs4646984) (Nernoda et al., 2011). Purported functional differences between alleles at all three of these loci have been reported and will be discussed in detail in the chapters that follow (and shown in Table 2-1).

1.6.1.2   The DRD2 gene

DRD2 is located on a different arm of chromosome 11, at 11q23.1. The *Taq*IA polymorphism (dbSNP rs1800497), also located near *DRD2*, has been associated with reward-seeking behaviours (including substance use, binge eating, gambling, and sensation seeking) (Blum, Sheridan, et al., 1996) and extraversion (L.D. Smillie, Cooper, Proitsi, Powell, & Pickering, 2010). Although the findings are not ubiquitous, a meta-analysis found a significant association with alcoholism (M. R. Munafo, Matheson, & Flint, 2007). The *TaqI*A (resulting in a thymine to cytosine transition, referred to as A1 and A2 alleles, respectively) is located near the termination codon of the DRD2 gene, but the polymorphism was later mapped to lie within a downstream neighbouring gene called ankyrin-repeat and kinase-domain-containing-1 gene (*ANKKI),* and it is still sometimes referred to as a *DRD2* variant (Ponce et al., 2009). The A1 allele exhibits reduced expression and brain autopsies revealed that individuals carrying this allele have 30% fewer D2 receptors than those carrying the A2 allele (Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991). PET scans on healthy participants provide additional support for reduced striatal density of D2 receptors in the presence of the A1 allele (Jonsson et al., 1999).

Blum and colleagues (1996) proposed the "reward deficiency theory" as the mechanism underlying reward/stimulus-seeking behaviours associated with *DRD2*. Specifically, individuals

with fewer D2 receptors would exhibit lower dopaminergic activity in the reward areas of the brain. In theory, A1 carriers would experience less reward in response to a stimulus than A2 carries, leading the A1 carriers to seek more stimuli (i.e., stimulus seeking) (Blum, Sheridan, et al., 1996). A handful of other functional SNPs within the *DRD2* have been identified. Intronic SNPs, A/C rs2283265 and G/T rs1076560 (also known as *Taq*1B), were associated with decreased expression and increased striatal activity and poor performance during attentional tasks (Y. Zhang et al., 2007) and both intronic SNPs have been implicated in amphetamine abuse (Moyer et al., 2011).

1.6.1.3   Other dopamine receptors

D3 and D1-like receptors (D1, D5) are less commonly studied in association with approach traits and disnhibited behaviours. *DRD3* maps to chromosome 3q13.31. The most commonly studied variant in *DRD3* is a functional polymorphism in exon I, Ser9Gly (312 C/T, dbSNP rs6280) which has been investigated in association with a wide range of phenotypes, from migraine-risk to personality, addiction, schizophrenia, and ADHD (migraine: Garcia-Martin et al., 2010; ADHD: Gizer et al., 2009; smoking: Novak et al., 2010; schizophrenia: F. Zhang et al., 2011). A meta-analysis found that the association between the Ser9Gly polymorphism and schizophrenia was not significant (Jonsson, Kaiser, Brockmoller, Nimgaonkar, & Crocq, 2004), and although the SNP has been associated with sensation seeking and novelty seeking (Duaux et al., 1998; Staner et al., 1998), there are several personality studies reporting non-significant findings (Jonsson et al., 2003; Schosser et al., 2010). More recently a handful of studies have found associations between an intronic *DRD3* SNP (dbSNP rs1677771) and various psychiatric phenotypes related to autism spectrum disorder (de Krom et al., 2009;

Staal, de Krom, & de Jonge, 2012). Variants in *DRD3* and relevant phenotypes will be discussed in Chapter 5.

D1 receptors are the primary target for dopamine in the pre-frontal cortex and have been shown to be involved in working memory and attention based on mouse models (Rinaldi, Mandillo, Oliverio, & Mele, 2007). *DRD1* maps to chromosome 5q35.2 and is intronless. Two SNPs, the *Dde*I RFLP[8] (-48 A/G; dbSNP rs4532) and 1403 T/C (dbSNP rs686), in the *DRD1* have been associated with schizophrenia (Zhu et al., 2011), alcoholism (Batel et al., 2008), nicotine dependence (H. Y. Huang et al., 2010), and addictive behaviours (Comings et al., 1997; Liu, Chen, Leu, Wu, & Lin, 2006). Though there are fewer studies that have explored *DRD1* variants in association with personality traits, alleles at the *Dde*I RFLP have been associated with sensation seeking in alcoholic males (Limosin, Loze, Rouillon, Ades, & Gorwood, 2003).

1.6.1.4   The dopamine transporter

The dopamine transporter gene (*DAT1*), sometimes referred to as solute carrier family 6 (*SLC6A3*), has also been investigated as a candidate gene in studies of approach-related traits and ADHD. Stimulant medication widely prescribed to treat ADHD directly inhibits the action of the dopamine transporter, and is effective in reducing ADHD symptoms, suggesting a role for *DAT1* in the aetiology of ADHD (reviewed by Turic, Swanson, & Sonuga-Barke, 2010). Of greater relevance to my research, the *DAT1* has also been linked to risk-taking (Mata, Hau, Papassotiropoulos, & Hertwig, 2012) as measured using the Balloon Analogue Risk Task (see section 1.3.3). *DAT1* is located on chromosome 5p15, and codes for the protein responsible for recycling dopamine back to the pre-synaptic neuron (see Figure 1-3). The most commonly

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[8] RFLP stands for restriction fragment length polymorphism. Polymorphisms are sometimes named after the restriction enzymes used in genotyping.

studied variant in *DAT1* is a 40-bp VNTR (3 to 13 repeats) in the 3' untranslated region (UTR)

of the gene; however, the results are not consistent (Nernoda et al., 2011). Both the 9-repeat and

the 10-repeat alleles at the VNTR have been associated with drug and alcohol use, ADHD,

schizoid-avoidant behaviours, and other personality traits (Blum et al., 1997; Comings et al.,

1996; Ujike et al., 2003), but there have been numerous null findings (Hong et al., 2003; Hou &

Li, 2009; Jorm et al., 2000; D. W. Li, Sham, Owen, & He, 2006). Functional studies have shown

reduced expression of *DAT1* in carriers of the 9-repeat allele (*versus* the more common 10-

repeat) (VanNess, Owens, & Kilts, 2005). While most studies have focused on the *DAT1* UTR

VNTR, there are a few notable SNPs that have been associated with approach-related traits and

externalizing disorders, including rs6347 and rs27072 (Feng et al., 2003; Ouellet-Morin et al.,

2008).

1.6.1.5 Dopamine metabolism

Dopamine is either recycled into the pre-synaptic cell by the dopamine transporter, or is

hydrolyzed or metabolized by various enzymes (catechol-0-methyltransferase, monoamine-

oxidase, or dopamine-β-hydroxylase; Figure 1-3). Changes in these enzyme levels can affect the

amount of dopamine in the cell, and therefore enzymes in the dopamine pathway are candidates

for personality and behavioural studies. Dopamine-β-hydroxylase (encoded by *DBH*) is an

enzyme that hydrolyses dopamine to norepinephrine (Kamata et al., 2009). *Dbh* knockout mice

and patients with a rare null *DBH* allele have higher levels of dopamine and its metabolite, 3,4-

Dihydroxyphenylacetic acid (DOPAC) (reviewed in Kamata et al., 2009). High sensation

seeking has been related to low levels of dopamine-β-hydroxylase (reviewed in Zuckerman,

1994). A functional SNP in the *DBH* promoter region, -970 C/T (formerly called -1021 C/T,

dbSNP rs1611115) that results in a cytosine to thymidine substitution, may explain some of the variation that exists in dopamine-β-hydroxylase activity. Carrying the T allele results in reduced expression, and therefore a lower level of the enzyme and reduced dopamine-β-hydroxylase activity (Zabetian et al., 2001). The -970 C/T SNP has been associated with harm avoidance in healthy females (Kamata et al., 2009) a trait that has been negatively correlated with sensation seeking (McCourt et al., 1993). This SNP has also been associated with alcohol dependence and withdrawal (reviewed in Koehnke, 2008). A non-synonymous SNP located in exon 11 of *DBH*, 1654[9] C/T (Arg549Cys, dbSNP rs6271) and an intronic SNP, intron 5 *Taq*I (dbSNP rs2519152) also appear to influence dopamine-β-hydroxylase enzyme activity (Tang et al., 2006; Zabetian et al., 2001). The two aforementioned SNPs (rs6271, rs161115) in combination with intronic SNP rs1611122 significantly contributed to the linkage signal observed in a study of schizophrenics (Cubells et al., 2011). *DBH* has also been studied in association with other externalizing disorders such as ADHD. Strong correlations between enzyme activity and rs161115 and rs2519152 were observed in both ADHD cases and matched controls, and there was over – transmission of the rs2519152 G allele to ADHD probands (Bhaduri, Sarkar, Sinha, Chattopadhyay, & Mukhopadhyay, 2010).

Catechol-*O*-methyltransferase (encoded by the gene *COMT*) is an enzyme that metabolizes dopamine in the synaptic cleft (Reuter & Hennig, 2005). *COMT* genetic association studies have focused on a functional variation in the gene, where a G to A (at base 472) transition causes a valine to methionine substitution at amino acid 158 (Val158Met, dbSNP rs4680). The Met158 allele has been linked to lower catechol-*O*-methyltransferase enzyme activity than the Val158 allele, and is often called 'COMT L' (low activity) (Lotta et al., 1995).

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[9] 1654 C/T is sometimes called 1603 C/T (Arg503Cys).

Similarly, in *post-mortem* brain tissue, the Val158 variant has been shown to exhibit approximately 38% higher activity than the Met158 variant (Chen et al., 2004). In theory, a higher activity allele would result in decreased synaptic dopamine levels, and because catechol-*O*-methyltransferase is highly expressed in the pre-frontal cortex, this may contribute to impaired cortical function (Chen et al., 2004). The *COMT* Val158Met polymorphism has been extensively studied in association with neuropsychiatric disorders and traits in healthy populations and there have been many conflicting findings (Lachman, 2008). The *COMT* Val158 allele has been associated with lower responses to reward measured by either surveys or fMRI techniques (Ettinger et al., 2008; Wichers et al., 2008). These results support the "reward deficiency" hypothesis for dopamine (discussed briefly in section 1.6.1.2), suggesting that Val158 homozygotes (who presumably have lower synaptic dopamine) might require additional stimulation to attain reward from everyday pleasures (Lachman, 2008). Differences in fear processing measured using the startle reflex have also been observed, and Val158 carriers showed a decreased startle reflex compared to Met158 homozygotes (Montag et al., 2008), and similarly Val158 carriers had lower sensitivity (measured by event-related potentials) to aversive stimuli than Met158 carriers (Herrmann et al., 2009). The high-activity Val158 allele has also been associated with sensation seeking and reward dependence in females (U. E. Lang, Bajbouj, Sander, & Gallinat, 2007; Tsai, Hong, Yu, & Chen, 2004) and extraversion in males and females (Reuter & Hennig, 2005). Conflicting findings associating the Met158 allele with approach-related traits and disinhibited behaviours have also been reported (e.g., risky sex: Bousman et al., 2010; novelty seeking in methamphetamine users: Hosak, Libiger, Cizek, Beranek, & Cermakova, 2006; cocaine abuse: Lohoff et al., 2008); therefore there is no clear consensus on which allele confers a susceptibility to reward seeking (Lachman, 2008; Nernoda et al., 2011).

Bilder (2004) reconciles the reported inconsistencies by considering both tonic and phasic release of dopamine (one allele affecting each type of dopaminergic release); however, distinguishing which allele is associated with a given phenotype is difficult because true replication studies employing identical phenotype characterization are rare. Two other *COMT* SNPs, a synonymous coding SNP (C/T rs4633) and promoter SNP (A/G rs6269) have also been studied in association with approach-related phenotypes (e.g., Choudhry et al., 2012; Halleland, Lundervold, Halmoy, Haavik, & Johansson, 2009; Roe et al., 2009), and a four-SNP-haplotype including the three above-mentioned SNPs along with synonymous coding SNP (C/G; rs4818) together alter the secondary mRNA structure and affect protein expression (Nackley et al., 2006).

Monoamine-oxidase types A and B (encoded by the genes *MAO-A* and *MAO-B*) are also enzymes that catabolize endogenous monoamines (including neurotransmitters), but monoamine-oxidase B has been the focus of many personality associations since its preferred substrate is dopamine (Oreland, 2004). The enzyme is found in blood platelets, and low levels of platelet monoamine-oxidase B have been correlated with high sensation seeking (reviewed in Zuckerman, 1994). Production of this enzyme increases with age, and is increased in females compared to males (N. L. Pedersen, Oreland, Reynolds, & McClearn, 1993; Zuckerman, 2005b). Theoretically, dopamine levels would decrease with age and be lower in females - a similar trend to that seen in sensation-seeking scores, making *MAO-B* a potential candidate for sensation-seeking genetics research (Zuckerman & Kuhlman, 2000). *Mao-B* knockouts (mice) display reduced habituation to novel environments (based on locomotor activity) (M. Lee, Chen, Shih, & Hiroi, 2004), and therefore lower levels of monoamine-oxidase (and theoretically higher levels of dopamine) may influence novelty/sensation seeking (M.T. Bardo et al., 2007). Monoamine-oxidase activity has a high heritability ($h^2 = 0.76$) (N. L. Pedersen et al., 1993) and has been

linked to variations in the MAO-B gene, located on the X chromosome (Garpenstrand, Ekblom, Forslund, Rylander, & Oreland, 2000). The intron 13 A/G SNP (rs1799836) is the most commonly studied variant, and has been studied in association with MAO enzyme levels, but the results are mixed (Garpenstrand et al., 2000; Pivac et al., 2006).

1.6.2   Serotonergic pathway genes

The neurotransmitters do not act in isolation, and Cloninger's (1987) model is somewhat oversimplified in that novelty seeking may not be influenced by dopamine alone. The serotonin (also called 5-hydroxytryptamine (5-HT)) and dopamine systems interact, exerting regulatory control over each other (Malmberg, Wargelius, Lichtenstein, Oreland, & Larsson, 2008; Zuckerman, 2005a). As previously described in section 1.5, dopamine is involved in mediating "approach" behaviours and serotonin, in mediating "avoidance". Rats with low levels of serotonin are more impulsive and have reduced harm avoidance (Winstanley, Dailey, Theobald, & Robbins, 2004). Other animal (monkey) studies support a role for serotonin in impulsive behaviours and risk-taking (Fairbanks, Melega, Jorgensen, Kaplan, & McGuire, 2001; Long, Kuhn, & Platt, 2009), though most personality genetic studies that investigate serotonergic genes focus on internalizing disorders (e.g., anxiety and depression) (reviewed in Hariri, 2009).

1.6.2.1   Serotonin transporter

The serotonin transporter gene (*SLC6A4*, located at 17q.11) is involved in regulating the magnitude and duration of serotonin action in serotonergic neurons (Lesch et al., 1996), and it is the most extensively studied gene in the field of personality research (M. R. Munafo et al., 2003; M.R. Munafo et al., 2009). A repeat polymorphism in the regulatory region of *SLC6A4*, the 5-

HTTLPR, has been associated with a range of conditions and traits (see Appendix E), but it is most commonly linked to avoidance traits (M. R. Munafo et al., 2003; M.R. Munafo et al., 2009). Lesch and colleagues' (1996) study demonstrated functional differences in the transcriptional efficiency, the "S" (short, 14 repeats) allele showing reduced activity and acting in a dominant-recessive fashion (replicated by Bradley, Dodelzon, Sandhu, & Philibert, 2005). This study also linked the 5-HTTLPR S allele to harm avoidance, neuroticism, and anxiety measured using three different personality scales (Lesch et al., 1996). More recently, however, a meta-analysis indicated that the 5-HTTLPR polymorphism was not associated with harm avoidance, and while there was support for an association with one measure of neuroticism (from Costa & McCrae's 1997 five-factor model of personality), there was no association with neuroticism defined by a different instrument (Eysenck's Personality Questionnaire) (M.R. Munafo et al., 2009). Some externalizing disorders and approach-related traits (especially impulsivity) have been studied in association with the 5-HTTLPR variant (Aluja, Garcia, Blanch, De Lorenzo, & Fibla, 2009). A few studies included sensation seeking, and one found that the S allele was associated with items from the ZKPQ sociability subscale and there was a trend for higher ZKPQ ImpSS in a sample of borderline personality disorder patients (Pascual et al., 2007), though others report no association (Patkar et al., 2002).

1.6.2.2   Serotonin receptors

Similar to dopamine receptors, the serotonin receptors are G-protein coupled receptors (with the exception of subtype 3) that have either inhibitory or excitatory effects via the second messenger, cAMP, and as many as 14 receptor subtypes have been identified (Nichols & Nichols, 2008). Several variants in 5-HT receptor 2A located on chromosome 13 (*HTR2A*) have

been studied in association with approach-phenotypes, including -1438 A/G (dbSNP rs6311), -783 A/G (dbSNP rs6312), 1354 C/T (His452Tyr: dbSNP rs6314) and 102 T/C (Ser34Ser: dbSNP rs6313), though the findings have been inconsistent (reviewed by Gizer et al., 2009; Nomura et al., 2006). A functional SNP in the gene that encodes 5-HT receptor subtype 1A (*HTR1A*), the -1019 C/T (dbSNP rs6295) has been associated with internalizing psychiatric disorders (Lemonde et al., 2003), but also with impulsivity (Benko et al., 2010). While serotonergic and dopaminergic systems interact (see Figure 1-1), and serotonin has been implicated in impulsivity and aggression, there is less support for an independent role in sensation seeking. Studies that have found significant associations with approach-related traits have mostly looked at interactions between genes encoding serotonin and dopamine receptors and transporters (see section 1.6.4).

1.6.3   **Other potential candidate genes for sensation seeking**

Neural plasticity is the capacity of the brain to remodel networks in response to environmental changes, and neuronal growth-associated proteins regulate these changes. One particular protein, stathmin, plays a role in neural plasticity (Ehlis et al., 2011). Stathmin (encoded by the gene *STMN1*) is of potential interest in the study of high-risk sports and sensation seeking because knockout mice were shown to be "fearless" (Shumyatsky et al., 2005). Although Zuckerman suggests that sensation seeking is not related to fearfulness, fear accompanies many high-risk sport activities (e.g., skydiving), and a person experiencing more pleasure and less fear and anxiety, may be more likely to repeat the activity (Zuckerman, 2007c). Many risk sports involve heights (i.e., mountain and gravity sports), an innate fear in humans, and individuals with reduced anxiety associated with such innate fears might be more likely to

participate in such activities. Fearlessness in mice was measured by a task involving a raised

platform to test for fear of heights, and mice lacking the gene encoding stathmin spent more time

on the raised platform (Shumyatsky et al., 2005). A role for stathmin in fear processes in human

was supported by a study finding associations between a tag[10] SNP (dbSNP rs182455) and startle

responses and cortisol release following a stressor (Brocke et al., 2010). The same SNP was

associated with errors on the Stroop test (a measure of behavioural inhibition) (Ehlis et al.,

2011).

Another protein implicated in neuronal plasticity is the brain-derived neurotrophic factor

(encoded by *BDNF* located on chromosome 11). Brain-derived neurotrophic factor is involved

in memory and learning (reviewed by Tyler, Alonso, Bramham, & Pozzo-Miller, 2002). In mice,

Bdnf knockouts showed abnormal *Drd3* expression, suggesting an involvement for brain-derived

neurotrophic factor in controlling *DRD3* expression (Guillin et al., 2003). A non-synonymous

variant at codon 66 in *BDNF* (Val66Met, dbSNP rs6265) has been studied in association with

anxiety disorders and neuroticism. A meta-analysis found that individuals carrying at least one

Met66 allele report lower neuroticism scores (Frustaci, Pozzi, Gianfagna, Manzoli, & Boccia,

2008). *BDNF* has also been proposed as a candidate for sensation seeking (Kang, Song,

Namkoong, & Kim, 2010), and a genome-wide association study found an association between

Val66Met and the approach-related trait extraversion (Terracciano, Sanna, et al., 2010). This

was replicated in a study finding that *BDNF* Met66 homozygotes scored lower than Val66

carriers on extraversion (Terracciano, Tanaka, et al., 2010).

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[10] Tag SNPs are SNPs that are chosen to be representative of a block of DNA because the surrounding
polymorphisms pass from one generation to the next with little "re-shuffling" between generations.

1.6.4   **Interactions between candidate genes**

Sensation seeking is a complex trait likely influenced by many genes, with each polymorphism explaining only a small proportion of phenotypic variance (Ebstein, 2006; Nernoda et al., 2011). As discussed in section 1.5, Zuckerman's psychobiological model of sensation seeking suggests that there are interactions between dopamine and serotonin systems. Similarly, data from candidate gene association studies support intergenic interactions; for example, interactions between three major "candidate polymorphisms" (*DRD4* VNTR, *SLC6A4* 5-HTTLPR, *COMT* Val158Met) and novelty seeking have been reported (Benjamin et al., 2000; Strobel, Lesch, Jatzke, Paetzold, & Brocke, 2003). In the Benjamin et al. (2000) study, novelty seeking and harm avoidance were negatively correlated and there were interactions between the genes associated with each trait. Furthermore, one study on financial risk-taking and another study measuring harm avoidance both found similar interactions between the *DRD4* VNTR and the *SLC6A4* 5-HTTLPR (Kuhnen & Chiao, 2009; Szekely et al., 2004).

Intergenic interactions have also been observed between other genes encoding proteins within the dopamine pathway, including enzymes, transporters, and neurotrophic factors. Yacubian and colleagues (2007) observed an interaction between polymorphisms in genes encoding proteins involved in dopamine re-uptake (*DAT1*) or catabolism (*COMT)* and striatal activity (measured using fMRI) during a guessing task. The study provided support for *COMT*'s involvement in regulating basal (or tonic) secretions of dopamine, and *DAT1*'s involvement in regulating phasic dopamine secretions (released in response to drugs, novelty, reward) (Bilder et al., 2004); suggesting that both genes are involved in inter-individual variations in sensitivity to reward. *COMT* has also been explored in association with *BDNF* and *DRD4*. An interaction between coding SNPs in *BDNF* and *COMT* was significantly associated with the boredom

susceptibility subscale of the SSS (Kang et al., 2010), and Li and colleagues (2004) found an interaction between polymorphisms in *DRD4* (120-bp duplication) and *COMT* (Val158Met) in methamphetamine users. Finally, the two most commonly studied candidate genes for ADHD are *DRD4* and *DAT1*, and a recent meta-analysis reported an interaction between the *DRD4* 120-bp duplication and two downstream variants in *DAT1* (3' UTR VNTR and intron 8 VNTR) (Sanchez-Mora et al., 2011). Significant gene-gene interactions illustrate the complexity of the genetic background and suggest a role for non-additive or epistatic contributions to approach phenotypes (Ebstein, 2006; Ebstein & Israel, 2009). While the presence of these complex molecular interactions might explain some inconsistencies plaguing single gene association studies, few interactions have been convincingly replicated and many studies lack *a priori* functional hypotheses linking the polygenic loci.

1.7 Genetics of risk-inclined behaviours

There have been numerous genetic studies on other risk-inclined populations including substance users, alcoholics, and gamblers (reviewed in Dick, Prescott, & McGue, 2009; Goodman, 2008; and in section 1.6), but to my knowledge there has only been one genetic association study on personality traits in high-risk sport populations (Cam et al., 2010). The physiological mechanisms that underlie the motivation to participate in antisocial pastimes may be similar to those that attract people to high-risk sports (Zuckerman, 1983), but high-risk sports participants may represent true "arousal seekers" (Fjell et al., 2007), potentially unconfounded by other variables like impulsivity. Cam and colleagues (2010) compared genotype frequencies at three loci (*DRD4* VNTR, *DAT1* VNTR, and *HTR2A* 102 T/C) between university students who reported participation in high-risk ($n = 60$) and low-risk ($n = 133$) sports, and they also

compared personality scores obtained from the Five Factor Personality Inventory between genotype groups. There were no significant differences in genotype frequencies between the sport groups and although they observed small differences between *HTR2A* genotype groups on sub-dimensions of neuroticism and "openness to experience" the association would not have survived correction for multiple tests. Other than the Cam et al. (2010) study, researchers have yet to examine polymorphisms in populations actively involved in seeking out, and experiencing physical risks in sports, and no studies have characterized a phenotype by quantifying patterns of sport-specific behaviours.

Chapter 2: Research overview

Chapter 1 defined the importance of sensation seeking within the context of high-risk behaviours, from prosocial sports to antisocial activities including drug and alcohol use. Individuals who partake in high-risk activities generally score higher on sensation seeking than their low-risk counterparts, and these findings are especially consistent among high-risk athletes. Sensation seeking was placed in a broader theoretical framework, grouping it with other traits like novelty seeking, reward seeking, extraversion, and behavioural activation – all sharing a sensitivity towards reinforcing stimuli. Neurotransmitters have been implicated in reward and punishment sensitivity, and the main neurotransmitter implicated in motivation towards reward is dopamine, while serotonin is commonly implicated in punishment sensitivity. Animal models and imaging studies provide support for these purported roles of dopamine and serotonin in motivational tendencies and personality traits. Genetic association studies on a range of personality traits and psychiatric phenotypes were reviewed, as were findings that support genes encoding proteins within the dopaminergic and serotonergic pathways as potential candidate genes for sensation seeking.

Since the 1990s, behavioural geneticists have tested associations between personality traits and variants in numerous candidate genes; some associations have been replicated, while numerous others have failed. Inconsistent reports may stem from weak phenotype measures, improper screening of controls, small sample sizes, failure to correct for multiple tests, and failure to consider interactions (Attia et al., 2009; Ebstein & Israel, 2009; Lusher, Chandler, & Ball, 2001). With these potential faults in mind, when designing and executing the studies described in this thesis, attempts were made to recruit relatively large, homogeneous samples of athletes, multiple variants were tested and stringent corrections were applied, and when the

sample was large enough joint-analysis (two-stage) designs were used to replicate significant findings.

Studying sensation seeking in athletic samples allowed phenotypes to be measured in a novel way: one based on patterns of sports behaviours, using questionnaires with strong psychometric properties in order to characterize "approach-related" phenotypes. Sports provide a context where patterns of sensation-seeking behaviours can be quantified through self-report, and unlike other disinhibted expressions of sensation seeking, sensation seeking in sport may be potentially unconfounded with impulsivity. Psychiatric studies have similarly recruited groups exhibiting common disinhibited behaviours (e.g., gambling problems, alcohol misuse) and have quantified patterns of behaviours specific to that population (e.g., quantity-frequency indices). One advantage of investigating genetic associations in cohorts that have distinctive, shared characteristics is that there exist domain-specific tools to measure phenotypes (e.g., Dick et al., 2009) and in some cases, studies have found genetic associations with domain-specific measures but not when comparing genotypes across groups defined by broad diagnostic criteria or personality traits (e.g., J. E. McGeary, Esposito-Smythers, Spirito, & Monti, 2007). Sensation seeking, rather than novelty seeking, was the phenotype selected as being a more appropriate construct for assessing personality in a sports population. Although sensation seeking is moderate-to-highly correlated with novelty seeking, tools that measure sensation seeking are more reflective of the intense and complex sensations (Zuckerman, 2005b) sought after by high-risk athletes.

Exploring the biological (using genetics) and psychological (using personality questionnaires) characteristics among risk-inclined athletic populations may shed some light on the factors that underlie a predisposition towards risk-taking, leading to more personality-tailored

prevention programs for other deviant forms of risk-taking. If genetic variants commonly associated with addiction phenotypes are also overrepresented in a cohort of high-risk athletes, then the high-risk sport could potentially act as an outlet for an innate predisposition to risky behaviours. In a document published by the United Nations (United UNODCCP, 2002) sport in general has been cited as a strategy for drug prevention, but little research has focused on high-risk sports, which may be better suited to the personalities (and potentially innate needs) of risk-seeking individuals.

This dissertation includes multiple studies involving comprehensive investigation of personality traits and candidate genes in high-risk sport populations. The first series investigate associations in cohorts of skiers and snowboarders as practitioners of potentially hazardous, yet popular sports where patterns of both low and high sensation seeking are commonplace. Most alpine ski resorts offer a variety of runs that, combined with the option of going "out-of-bounds", span the gamut from relatively safe to very hazardous; therefore, a range of sensation-seeking behaviour should be present in the skiing and snowboarding community. These projects were followed up with an exploratory study on high- and low-risk sport participants, carefully selected for ability and sport practices. Exploratory analyses of personality and genetic variables are carried out as a quasi case-control study. Variants from candidate genes were chosen based on purported functional differences between alleles (a summary of functional candidates is shown in Table 2-1, and based on previous associations with approach-related traits; see Appendix E).

Table 2-1

A summary of reportedly "functional" variants based on the literature

Gene	Polymorphism	rs ID	Function	References
BDNF	Vall66Met	rs6265	Impaired memory and hippocampal function	(Egan et al., 2003)
COMT	Val158Met	rs4680	Differences in enzyme activity	(Chen et al., 2004; Lotta et al., 1995)
DAT1	3' UTR VNTR	n/a	Differences in expression	(VanNess et al., 2005)
	3' UTR	rs27072	mRNA expression and translation	(Pinsonneault et al., 2011)
DBH	-1021 C/T (aka -970 C/T)	rs1611115	Differences in plasma enzyme activity	(Zabetian et al., 2001)
	Arg549(535)Cys	rs6271	Plasma enzyme activity	(Zabetian et al., 2001)
	Intron 5 *Taq*I	rs2519152	Plasma enzyme activity	(Tang et al., 2006)
DRD1	3' UTR A/G	rs686	Differences in expression	(W. H. Huang & Li, 2009; W. H. Huang, Payne, Ma, & Li, 2008)
DRD2	Taq1A	rs1800497	Differences in expression	(Noble et al., 1991)
	Intron 6	rs1076560	Differences in expression	(Y. Zhang et al., 2007)
DRD2	957 C/T	rs6277	Differences in expression	(Duan et al., 2003)
DRD4	-521 C/T	rs1800955	Transcriptional activity (mixed results)	(Kereszturi et al., 2006; Okuyama et al., 2000)
	120-bp duplication	rs4646984	Transcriptional efficiency	(D'Souza et al., 2004)
	Exon III VNTR	n/a	Antagonist binding profiles	(Asghari et al., 1994; Van Tol et al., 1992)
DRD3	Ser9Gly	rs6280	Agonist binding affinity	(Lundstrom & Turpin, 1996)
HTR1A	1019 C/T	rs6295	Differences in autoreceptor expression	(Lemonde et al., 2003)
HTR2A	-1438 G/A	rs6311	Differences in expression (mixed results)	(Myers, Airey, Manier, Shelton, & Sanders-Bush, 2007; Smith et al., 2012)
HTR2A	His452Tyr	rs6314	Altered cell signalling	(Hazelwood & Sanders-Bush, 2004)
MAO-A	Arg297Arg	rs6323	Enzyme activity	(Jansson et al., 2005)
MAO-B	Intron 13 A/G	rs1799836	MAO enzyme levels (mixed results)	(Garpenstrand et al., 2000; Pivac et al., 2006)
SLC6A4	5HTTLPR	n/a	Transcriptional efficiency	(Bradley et al., 2005; Lesch et al., 1996).
SLC6A4	C/T	rs25532	Differences in expression	(Wendland et al., 2008)
TH	-824 C/T	rs10770141	Differences in promoter activity	(Rao et al., 2008)

Note. *BDNF* = brain-derived neurotrophic factor, *COMT* = catechol-O-methytransferase, *DAT1* = dopamine transporter, *DBH* = dopamine-beta-hydroxylase, *DRD2, DRD3, DRD4* = dopamine receptors, *HTR1A*, *HTR2A* = serotonin receptors, *MAO*-A, *MAO*-B = monoamine oxidase, *SLC6A4* = serotonin transporter, *TH* = tyrosine hydroxylase, UTR = untranslated region, VNTR = variable number of tandem repeats.

2.1 Objectives

The work described in this dissertation can be broadly divided into three projects; all of which were carried out with a common goal in mind: to gain a better understanding of the psychological and genetic characteristics associated with participation in high-risk sports.

1) Project 1: Evaluate the psychometric properties of the newly developed contextual sensation-seeking questionnaire (CSSQ-S) in multiple samples of skiers and snowboarders.

2) Project 2:

   a. Replicate findings from unpublished research (Thomson, 2008; association in *DRD4* -521 C/T and sensation seeking in skiers/snowboarders).

   b. Analyze whether associations exist between sensation-seeking measures and other single nucleotide polymorphisms in dopaminergic and serotonergic pathways. These include genes involved in dopamine/serotonin transport, synaptic transmission and metabolism (see Appendix E and Table 2-1).

   c. Analyze whether associations exist between sensation-seeking measures and polymorphisms (both single nucleotide and repeat variants) in the *DRD4* promoter region.

3) Project 3:

   a. Analyze whether polymorphisms involved in dopaminergic and serotonergic neurotransmission (chosen based on Project 2 results, functional support, and previous associations) are over-represented in high-risk sport participants when compared to a low-risk sport group.

b. Confirm that risk-inclined sport populations exhibit higher levels of sensation seeking (as measured from questionnaires) compared to low-risk athletes.

2.2 Hypotheses

2.2.1 General hypotheses

Twin studies have shown that approximately 60% of variability in the sensation-seeking trait is due to genetic influences (Stoel et al., 2006). Dopamine has consistently been implicated in novelty and reward-seeking in mice and humans; therefore, it is generally accepted that dopamine is likely to be involved in other approach traits, including sensation seeking. The moderate heritability of sensation seeking combined with a proposed neural pathway lead me to hypothesize that variations within genes in the dopamine pathway will be associated with sensation-seeking scores. Sensation seeking is a complex trait and therefore a polygenic mode-of-inheritance is likely, and any associations found are likely to be small.

2.2.2 Specific hypotheses

Hypotheses for each project are shown below and are presented as null hypotheses (H_0) and alternative hypotheses (H_A).

Project 1

H_0: There will be no relationship between patterns of context-specific ski behaviours (measured using the CSSQ-S) and approach-related traits.

H_A: Contextual sensation-seeking scores will correlate moderately with established sensation-seeking scales in all samples.

Project 2

i) H_0: Contextual sensation-seeking scores will not vary between *DRD4* -521 C/T

genotypes in a sample of skiers.

H_A: *DRD4* -521 C/T will be associated with domain-specific sensation-seeking scores in

a sample of skiers and snowboarders (replicating unpublished results; Thomson, 2008).

Specifically, the CC genotype will be associated with high levels of sensation seeking.

ii) H_0: No SNPs within candidate genes investigated will be associated with sensation

seeking.

H_A: SNPs within genes involved in dopamine transport, synaptic transmission, and/or

metabolism will emerge as candidates for sensation seeking (see Appendix E).

Project 3

i) H_0: No SNPs within candidate genes will be associated with high-risk sport participation.

H_A: Alleles that have previously been associated with sensation seeking will be

overrepresented in the risk-inclined athletic group compared to the low-risk sport group.

ii) H_0: There will be no significant differences in personality traits between athletes grouped

by their participation in high- or low-risk sports.

H_A: Athletes who participate in high-risk sports will score higher on measures of

sensation seeking than low-risk sport participants.

2.3   Methodology overview

There are three projects described in this thesis, each including multiple participant cohorts. They are briefly described below and then discussed in detail in the following chapters.

The first project consists of studies to support the use of the contextual sensation-seeking questionnaire for skiing and snowboarding (CSSQ-S, Appendix F) that was developed as a reliable measure of sport-specific sensation seeking (development and validation of this tool is described in Chapter 3). Questionnaire development involved a series of studies to support item, content, and external validity of the CSSQ-S (and a generalized version of the questionnaire, the CSSQ, was later designed to be used for multiple downhill sports). The data described in Chapters 3 and 4 incorporate data gathered during my MSc research (Thomson, 2008) with data gathered during my tenure as a PhD student. The same samples recruited for Project 1 were used in the genetic analyses of Project 2 (described below), with the exception of a small sample recruited solely to obtain reliability data for the CSSQ-S.

The second project involves analyzing variants in candidate genes for sensation seeking in two populations of skiers and snowboarders ("MSc" sample and new "Festival" sample, described below). The data are presented in Chapters 4, 5, and 6 and all analyses involve comparing quantitative measures of personality (dependent variables = sensation-seeking measures) between genotype groups (independent variables).

The third project involves comparing frequencies of variants in candidate genes between high- and low-risk sport participants and psychological measures between groups (described in Chapter 8; employing a quasi case-control design). A separate analysis of variants that were associated with skiing and snowboarding phenotypes in Chapter 4 were analyzed in a subset of

athletes who reported participation in a downhill sport from the high- and low-risk sport cohorts (described in Chapter 7).

All of the participants in the projects described in this thesis were athletes who were moderately proficient at their sport (based on self-report). Inclusion criteria for age varied depending on the project (details are provided in respective chapters). For example, age in skiers was initially limited from older-youth to middle-age adults (17 to 49 years)[11], but the upper age was relaxed to 60 years for high- and low-risk sport participants because older adults are a significant demographic participating certain sports (e.g., mountaineering) (British Mountaineering Council, 2003). Although the same samples were used for genetic and psychology analyses, the sample sizes differ due to varying exclusion criteria (e.g., ethnic exclusions were felt to be necessary for the genetic analyses, but not for psychological analyses; exclusions for sport ability affect CSSQ-S data, but not personality traits) and/or missing data (e.g., incomplete questionnaires or failure to genotype). Specific rationale or explanations of exclusions for analyses are discussed in the corresponding chapters.

A brief overview of each sample is provided below. Further details about recruitment and variables measured, along with descriptive statistics are included in respective chapters.

2.4   Overview of participants and recruitment

All participants provided written, informed consent, and the studies were all reviewed and approved by the UBC Clinical and/or Behavioural Research Ethics Boards. Both the UBC Clinical Research Ethics Board and the University of Bordeaux Sagalen approved the studies

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[11] Initially, age was limited to 40 years (see consent form, Appendix H), but due to the significant number of >40 year olds (over 10% of the sample) reporting sufficient skiing ability and frequency the age criteria was relaxed.

involving high- and low-risk participants recruited from France and Canada. Ethics certificate

numbers are detailed in the Preface.
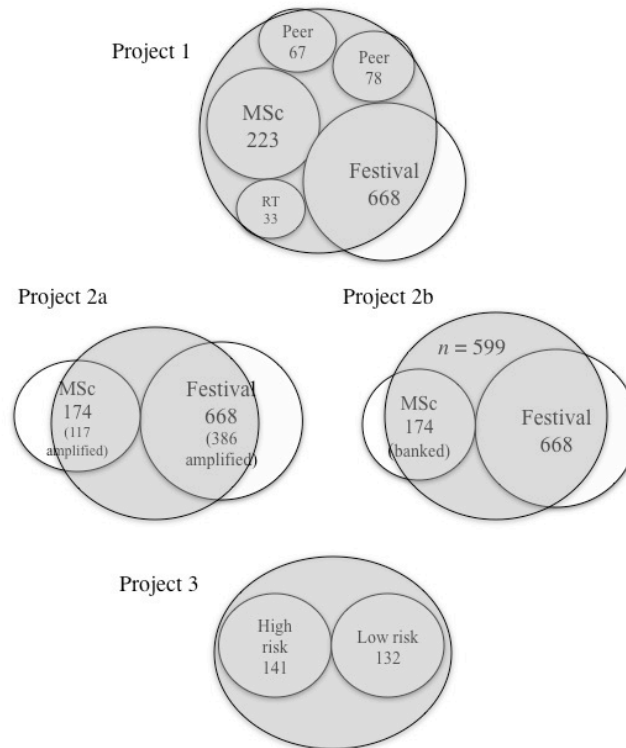
Figure 2-1. Sample Overview.

Numbers represent sample sizes. Project 1 includes the entire MSc sample, a portion ($n = 530$) of the Festival

sample (after exclusions), two peer samples, and a re-test reliability sample (RT). Project 2a includes portions of the

MSc and Festival samples successfully genotyped at the -521 C/T locus ($n = 117$ and 386, respectively). Project 2b

includes a portion of the MSc sample ($n = 174$) that consented to DNA banking and a portion of the Festival ($n =$

536) sample meeting exclusion criteria, of these a total of 599 amplified successfully. Project 3 includes athletes

participating in either high- or low-risk sports.

2.4.1 **Sample 1 (Pilot sample)**

The first sample included 223 skiers and snowboarders predominantly from Western

Canada, mostly recruited for my MSc thesis project. Due to low DNA yields and genotyping

difficulties, only 74 genotypes for the *DRD4* -521 C/T polymorphism (rs1800955) were

confirmed at the time of my MSc thesis defense (Thomson, 2008). Many participants were

willing to provide an additional sample of DNA and a large portion (~80%) of skiers and

snowboarders (Caucasian males = 86, females = 88, n = 174 out of 223) consented to DNA

banking, granting permission to analyze the DNA for other potential sensation-seeking candidate

genes (discussed in Chapter 5). Additional samples collected for my MSc studies were

genotyped for the -521C/T SNP, ultimately resulting in a total of 117 genotypes. These DNAs

comprise the "Pilot sample" for Chapter 4, entitled, "The -521 C/T variant in the dopamine-4-

receptor gene (*DRD4*) is associated with skiing and snowboarding behaviour".

The exploratory factor analysis stage of the CSSQ-S validation (Chapter 3) included

psychological data from Sample 1 (n = 198; analyses which were completed during my MSc

thesis; Thomson, 2008). The sample sizes for any analyses carried out post-MSc research are

slightly larger because after finalizing the MSc sample there was continued interest from

research subjects. By the time the injury data were formally analyzed (Chapter 3: to support

external aspect of validity for the CSSQ-S), the sample had increased to n = 220. None of the

injury data were included in my MSc thesis.

2.4.2 **Sample 2 (Festival sample)**

A total of 668 skiers and snowboarders (ages 17 to 49 years of age) visiting the Telus

World Ski and Snowboard Festival in Whistler, BC in April 2010 participated in the study. Table

2-2 provides detailed demographic information on the full sample. Chapters 3, 4, 5, and 6

include participants from the Festival sample, but sample sizes vary depending on exclusion

criteria (i.e., exclusions of 69 to 138 subjects). For example, no missingness was tolerated in the

data set that was used for questionnaire validation, and subjects had to meet the post-screening

ability requirement (see section 2.4.6) and after exclusions the questionnaire validation study

(Chapter 3) included 530 athletes from the Festival sample (Table 2-3). Because both

personality and CSSQ-S scores were included in the genetic analyses, personality scores could

be included (even if the participant did not meet the sport ability requirement for the CSSQ-S),

hence the genetic studies include as many as 599 Festival sample participants (Table 2-3). Data

from the Festival sample were used in the confirmatory factor analysis stage of questionnaire

validation (Chapter 3, $n = 530$), stage 2 of -521 C/T study (Chapter 4, $n = 386$), in the multi-SNP

study (Chapter 5 $n = 599$), and in the *DRD4* promoter study (Chapter 6, $n = 444$).

Table 2-2

Festival sample participant characteristics (pre-exclusions)

	Pre-exclusions ($n = 668$)	Exclusion details[a]
Age (years)	Mean = 27.42, *SD* = 7.34	$n = 10$, < 16 or > 49 yrs
Sex	58% male, 42% female	
Ethnicity	91% Caucasian descent, 9% other	$n = 55$ reporting non-Caucasian or mixed ethnicities
Education	69% post-secondary education	
Marital Status	20% married or common-law	
Dependents	9% reported having dependents	
Ability	24% intermediate, 28% advanced, 44% expert	$n = 24$ reported less than intermediate ability

Note. [a]there was overlap between exclusions, i.e., participant ID-839: a 14 year old reporting African descent. *SD* =

standard deviation.

2.4.3   **Peer samples**

Peers who had frequently skied/snowboarded with the participants completed a peer-CSSQ (Appendix G) for samples 1 (Pilot, $n = 67$) and 2 (Festival, $n = 78$). The numbers are substantially lower than the full samples because the participant had to be with a peer at the time of recruitment. A mail-back option was not offered, as this method could compromise the anonymity of the peer's responses leading to a greater chance of bias.

2.4.4   **Reliability sample**

Skiers and snowboarders ($n = 33$) recruited through UBC psychology pool and online postings participated in a reliability analysis of the CSSQ-S (described in Chapter 3 and in Table 2-3). Participants completed questionnaires only (no DNA analyses), and the data were not combined with any other samples for psychological analyses.

Table 2-3

Participant characteristics (post-exclusions) for Projects 1 and 2

Variable	Questionnaire validation (Chapter 3)		Genetic associations (Chapters 4, 5, 6)		
	Factor analysis ($n = 530$)	Reliability ($n = 33$)	Chapter 4 ($n = 386$)	Chapter 5 ($n = 599$)	Chapter 6 ($n = 444$)
Age (years)	26.70 (6.02)	26.4 (4.75)	26.3 (5.9)	27.12 (6.45)	26.92 (6.27)
Sex	41% female	33% female	42% female	43% female	42% female
Ethnicity	1% non-European	9% non-European	100% European	100% European	100% European
Education	29% high school, 71% post-secondary	100% post-secondary	30% high school, 67% post-secondary, 3% missing	28% high school, 72% post-secondary	28% high school, 72% post-secondary
Marital Status	19% married or common-law	36% married or common-law	17% married or common-law	22% married or common-law	22% married or common-law
Dependents	8% reported having dependents	3% reported having dependents	8% reported having dependents	9% reported having dependents	8% reported having dependents
Ability	24% intermediate, 32% advanced, 44% expert	3% intermediate, 42% advanced, 55% expert	23% intermediate, 32% advanced, 45% expert	24% intermediate, 31% advanced, 42% expert, 3% beginner/novice[a]	22% intermediate, 32% advanced, 42% expert, 4% beginner/novice[a]
Sport	60% skiers, 40% snowboarders	75% skiers, 25% snowboarders	54% skiers, 40% snowboarder, 6% both	56% skiers, 38% snowboarders, 5% both,	55% skiers, 39% snowboarders, 5% both

Note. All samples except the reliability sample are dependent (drawn from the sample larger Festival sample). Values for age represent mean (*SD*).

[a] CSSQ scores from individuals reporting less than intermediate ability were excluded from analyses.

2.4.5 High-risk/low-risk samples

Athletes participating in high-risk sports were largely recruited in France ($n = 141$), while low-risk athletes were recruited both from France and Canada ($n = 132$, Table 2-4). Genetic and psychological data from these samples are analyzed in Chapter 7 and 8. The high- and low-risk sport samples differ on more variables (i.e., sex, location of recruitment) than the selection variable (i.e., sport participation), so a number of additional screening analyses and exclusions were carried out in order to analyze these samples using a quasi case-control design (described in Chapter 8).

Table 2-4

Participant characteristics (pre-exclusions) for Project 3

Variable	High-risk sport group ($n = 141$)	Low-risk sport group ($n = 132$)
Age (years)	29.2 (9.2)	25.8 (9.8)
Sex	19% female	48% female
Ethnicity	96% European	83% European
Education	21% high-school, 79% post-secondary	30% high school, 70% post-secondary
Marital Status	40% married or common-law	25% married or common-law
Dependents	16% reported having dependents	8% reported having dependents
Ability	8% intermediate, 19% advanced, 71% expert	34% intermediate, 36 advanced, 19% expert

Note. Values for age represent mean (*SD*). Exclusions varied depending on the type of analysis, participants meeting sport and age criteria are shown in this table.

2.4.6 Participant exclusions

The exclusions for age and ability have been chosen to avoid confounding results. Levels of sensation seeking decrease after the age of 40 years (Zuckerman, 1979, p. 125), possibly due to an increase in levels of an enzyme that breaks down dopamine, monoamine oxidase type B (Zuckerman, 1979, p. 376). Although the genetic make-up of an individual does not change with age, lower levels of dopamine may have an effect on sensation-seeking, thus confounding studies

measuring quantitative traits if too broad an age range is included. In an attempt to be as inclusive as possible, minors (ages 17 and 18 yrs) were included in the Festival sample (Appendix H, consent form). A number of the festival competitors (and athletic festival goers) were underage and the study had ethical approval to treat these athletes as emancipated adults. Skiing/snowboarding ability was limited to intermediate or higher levels to ensure that all participants have the ability and experience to display so-called "sensation seeking" ski-behaviours in the field.

Participants from all ethnic background were included in the psychology-based analyses, but to minimize bio-geographical diversity, only participants self-reporting European descent were included in genetic analyses (for example see demographics, Table 2-2). Individuals reporting non-Caucasian ancestries were excluded in an attempt to control for population stratification (the presence of systematic differences in allele frequencies between experimental subgroups (e.g., case: control) that may be due to differential ancestry in the two groups (Attia 2009, B).

2.5   Procedures

Participants were recruited through a variety of methods including posters, email, online forums, word-of-mouth, and approached in person. Participants did not receive any financial compensation, but the Telus Festival offered a unique incentive, and details are provided below.

The 2010 Telus World Ski and Snowboard Festival provided an ideal recruitment ground for the study. The festival included competitions for elite riders along with 10 days of free concerts, attracting a large number of ski/snowboard enthusiasts. The festival organizers provided a tent in the concert plaza for recruitment of spectators (who were largely recreational

skiers and snowboarders visiting Whistler Blackcomb Resort for the festival), and a table in the athlete's registration building for recruitment of competitive athletes. In collaboration with a local ski company (Crown Skis Ltd.), we offered all kiosk visitors a chance to win a new pair of skis (no participation in the research necessary) and a voucher for a hot beverage at a local café. Riders filled out two questionnaires (CSSQ-S and ZKPQ ImpSS, Appendix D and F), provided demographic data, and two buccal samples by brushing the inner cheek with a cytobrush (Fisher Scientific, Canada). A peer of the subject (when present at the time of recruitment) was invited to fill out a third party questionnaire (optional component, a consensual validity check, shown in Appendix G). The entire process took between 10 and 15 minutes. During the pre-screening, all participants indicated that they were at least intermediate ability and were between the ages of 17 and 49 years.

2.6   Methods

Participants from each project described above (section 2-4) completed evolving versions of the same instruments. For example, the Pilot sample completed the very first template of the CSSQ-S, which was a 13-item questionnaire (described in Chapter 3). Participants recruited after my MSc defense and at the Telus Festival completed a 10-item version of the questionnaire since the factor structure of the 13-item CSSQ-S had been analyzed, and three items were removed because they appeared to represent a separate construct (loaded onto an independent factor). The instrument used to measure personality traits also varied between studies. After testing the correlations between the CSSQ-S and the ZKPQ subscales (to provide evidence for discriminant validity; Chapter 3) only the ImpSS subscale (Appendix D) was included in all other studies. See Appendix I for correlations between CSSQ and ZKPQ subscales. This

subscale was the most pertinent to the objectives (to investigate associations with sensation seeking) and the exclusion of the other four subscales greatly reduced the time commitment for the participants. The measures will be explicitly presented in the methods sections in the following chapters.

All samples, with the exception of a sample recruited for a reliability study within the questionnaire development chapter (Chapter 3), completed a questionnaire portion *and* provided a buccal cell sample for genetic analysis.

2.6.1   **Buccal DNA preparation**

After testing various methods of collection (saliva, blood, buccal) and isolation (Invitrogen PureLink genomic DNA extraction kit, Oragene-DNA kit) we concluded that our laboratory's standard alcohol-based isolation/purification technique produced the highest yields of DNA at the lowest cost, without significant impact on purity (estimated based on wavelength ratios 260/280) (see Appendix J; Mulot et al., 2005).

In an attempt to standardize the buccal swabbing technique, all participants that provided buccal cell samples were given visual, verbal, and written instructions (see Appendix K), and all subjects provided two samples. After brushing, the cytobrushes were stored in paper envelopes at room temperature, allowing them to air dry and then were frozen at -20°C for longer-term storage.

Buccal cell DNA was isolated from cytobrushes using a standard purification technique described by Saftlas et al. (2004) (Appendix L). The brushes were incubated at 55°C overnight (at least 8 hrs) in 700 μl lysis buffer (for recipes, see Appendix M) containing proteinease K (0.11 mg/ml) to breakdown cellular proteins and remove the cells from the cytobrush. After

incubation, the tubes were centrifuged for 2 minutes at 15 900 g at 4 °C. The brushes were discarded, and RNAse (0.03 mg/ml) was added to the supernatant which was then incubated for 60 minutes at 55°C to denature RNA. Subsequently, 320 μl of 5M potassium acetate precipitation buffer (KOAc) was added and the tubes were stored on ice for at least 20 minutes and then centrifuged (15 900 g) for 5 minutes. The supernatants were transferred to new tubes and the pellets of precipitate discarded. The DNA was then precipitated out of the remaining solution by the addition of glycogen (0.025 mg/ml) and 510 μl isopropanol followed by incubation on ice for 20 minutes. The tubes were centrifuged (15 900 g) for 10 minutes and the supernatants were discarded leaving DNA pellets, which were then rinsed with 70% ethanol (200 μl) followed by a 1-minute centrifuge to remove remaining salts. The ethanol was carefully discarded from each tube and the DNA pellets were air dried and re-suspended in 50 μl TE buffer (10 mM Tris/Cl, 1 mM EDTA pH 8.0) and stored at -20°C for future use. The protocol was modified slightly to include an extra alcohol rinse step, and lower elution volume (50 μl) to ensure the samples would meet the minimum purity and concentrations required by the genotyping facilities (laboratory protocol and recipes for reagents in are shown in Appendices K and L).

Copy-number variant polymorphisms were genotyped in the Rupert or Robinson laboratories (details in Chapters 6 and 7), and all SNPs (except -521 C/T, described in Chapter 4) were genotyped by Genome Quebec at McGill University using the Sequenom iPlex® platform. Genome Quebec requires 30 μl of DNA at a concentration of 20 ng/μl. Samples were quantified and diluted accordingly (Nanodrop 2000c, Thermo Fisher Scientific Inc.). Genome Quebec analyzed a total of eight plates in the study described in Chapter 5, and three plates in the study

described in Chapter 8. All 96-well plates contained two wells reserved for negative controls, and two reserved for positive controls. A sample plate layout is shown in Appendix N.

Genotyping of three copy number variants was attempted in the Rupert laboratory using polymerase chain reaction (PCR) and gel electrophoresis, but after numerous attempts failed optimization. These include the *SLC6A4* 5HTTLPR (the polymorphism most commonly associated with internalizing disorders, but that has also been associated with impulsivity and reward seeking); the *DAT1* 3' UTR 40-bp VNTR (commonly associated with externalizing disorders, especially ADHD, and approach-related traits); the *DRD4* 48-bp VNTR (one of the most studied variants for approach-related traits). Details about phenotypes that have been studied in association with these variants are found in Appendix E. Details about primers and attempted protocols are shown in Appendix O. As the *DRD4* VNTR was the most studied candidate for approach-traits, specifically, this variant was attempted again using a more sensitive genotyping technique in the Robinson laboratory with sizing of alleles using a capillary system (ABI Prism 310 Genetic analyzer) and genotyping was successful (details in Chapter 7).

Chapter 3: The Contextual Sensation Seeking Questionnaire for skiing and snowboarding: Development of a sport specific scale[12]

3.1 Summary

The Contextual Sensation Seeking Questionnaire (CSSQ-S) was developed to measure patterns of sensation-seeking behaviours in skiing and snowboarding. Three studies were conducted supporting several aspects of its validity. First, a focus group ($n = 4$) generated items representative of sensation seeking in skiing and the factor structure was explored in a sample of skiers ($n_1 = 220$). Second, the factor structure was confirmed using data from an independent cohort ($n_2 = 530$). Finally, evidence is provided for criterion-relevance and applied utility of CSSQ-S scores by demonstrating positive relationships between scores and self-reported injury. CSSQ-S scores explained greater variance ($n_1 = 217$, $\beta = .358$, $p < .001$) in injury prevalence than an established assessment tool (Zuckerman's Impulsive-Sensation Seeking scale). In summary, the CSSQ-S represents a psychometrically promising measure of contextual sensation seeking and may be used to explore factors associated with risk-taking in skiing and snowboarding.

3.2 Introduction

Sensation seeking is measured using a variety of trait-related questionnaires including the Sensation Seeking Scale (SSS; Zuckerman, 1994), the UPPS (Urgency, Premeditation, Perseverance, and Sensation Seeking) Impulsive Behaviour Scale (Whiteside & Lynam, 2001)

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[12] The data in this chapter was published as, "The Contextual Sensation Seeking Questionnaire for skiing and snowboarding: Development of a sport specific scale" in the International Journal of Sport Psychology, 2012.

and the impulsive-sensation seeking scale (ImpSS) of the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ; Zuckerman et al., 1993), all designed to measure sensation seeking across a range of life categories (e.g., social, career, physical, etc.). A significant limitation of these instruments for use in the study of narrow behavioural tendencies such as high-risk snow sport is that they measure sensation seeking in general as opposed to sensation seeking in specific activities. In addition, the items are typically worded in a hypothetical form (e.g., "I *would* like to…") rather than reflecting actual sensation-seeking behaviours or experiences (e.g., "I like to…"). From a construct validity perspective (cf. Messick, 1995), such instances may result in a lack of concordance between what a person claims that he/she would like to do, and his or her *actual* behaviours.

A lack of concordance between desires and actual behaviours make it difficult to characterize sensation seeking in studies that measure correlations between sensation seeking and other psychological factors (e.g., risk perception, self efficacy, disinhibition), or in studies that explore biological underpinnings for sensation-seeking behaviour using methods such as neuroimaging or genetic analysis. In a sport population, a context-specific measure of sensation seeking may help to identify psychological processes that are associated specifically with risky sport behaviour. For example, previous studies have examined psychological constructs such as self-efficacy (Bandura, 1997) and sensation seeking in a variety of high-risk sports and found that only self-efficacy was significantly associated with the level of risk-taking behaviour in the sport (D.J. Llewellyn et al., 2008; Slanger & Rudestam, 1997). However, it is important to note that differences in risk-taking behaviours were only observed when a *domain-specific* measure of self-efficacy was utilized. Specifically, no differences in risk-taking behaviour were observed when *general* self-efficacy was assessed (Slanger & Rudestam, 1997). Similarly, the lack of

association between risk-taking in sports and sensation seeking may be explained by the use of generalized measures of sensation seeking (e.g., ZKPQ ImpSS and SSS). Narrower traits (or facets) can predict variance in specific behaviours not accounted for by more general traits (e.g., Paunonen & Ashton, 2001) like sensation seeking. Arguably, a brief self-report instrument designed to assess sensation-seeking behavioural tendencies specific to a sport may provide stronger predictive utility in terms of an individuals' propensity to engage in risky behaviours within that context. Such a tool may be useful to provide a more focused characterization of participants when exploring motivations for participation or to help inform injury prevention in downhill sports by identifying risk-seeking athletes.

Three studies were conducted in order to develop a sport-specific questionnaire that measures patterns of sensation-seeking behaviours in skiers and snowboarders (called "The Contextual Sensation Seeking Questionnaire for Skiing and Snowboarding" (CSSQ-S)), and evidence for several aspects of construct validity are provided in this chapter (cf. Messick, 1989, 1995). Construct validity "comprises the evidence and rationales supporting the trustworthiness of score interpretation in terms of explanatory concepts that account for both test performance and score relationships with other variables'' (Messick, 1995, p. 743). The studies presented in this chapter involve (a) developing items and establishing evidence for the content aspect of construct validity (e.g., the content relevance and representativeness of items; study 1), (b) establishing evidence for the structural aspect of construct validity (i.e., factorial validity) using exploratory (study 1) and confirmatory factor analytic procedures (study 2), and, (c) providing evidence for the external aspect of construct validity (evidence based on relations to other variables, i.e., criterion relevance and applied utility) through an examination of the relationships between sensation-seeking measures (CSSQ-S and ZKPQ ImpSS, studies 1 and 2) and peer

evaluations (studies 1 and 2), as well as through an evaluation of relative associations of scores

on measures of sensation seeking (CSSQ-S and ImpSS) and injury prevalence (study 3).

3.3   Study 1: Item generation and preliminary evidence for validity

The purpose of study 1 was to develop a battery of items that reflect the sensation-

seeking construct in skiing and snowboarding, then to investigate the factor structure using

exploratory factor analysis (EFA), and finally to provide preliminary evidence for external

aspects of construct validity.

3.3.1   Participants and procedures

Item generation. The research literature on sensation seeking, risk-taking, and sensation

seeking in sports was reviewed in order to generate a detailed conceptualization of the specific

content and range of sensation seeking, such as what specific behaviours sensation seeking

encompasses. This initial review highlighted several "key words" (e.g., "new", "thrilling", and

"risks") associated with sensation seeking that were believed to be representative and relevant to

context-specific sensation seeking for skiing and snowboarding. A group of proficient skiers and

snowboarders were then recruited in order to develop the initial battery of items. Consulting

members of a target population is an important step to test the comprehensiveness and relevance

of items for a given construct (Vogt, King, & King, 2004). The group included two male and

two female advanced and expert skiers and snowboarders, average age 27.5 ($SD = 1.29$) years.

Two of the athletes (one expert skier, one expert snowboarder) had lived in a mountain town (in

Alberta, Canada) for at least two ski seasons, while the other two participants (one advanced

snowboarder, one expert skier) rode regularly but were "weekend riders" from British Columbia,

Canada. The group was provided with Zuckerman's definition of sensation seeking (Zuckerman, 1979) and several key words (i.e., thrilling) that the initial literature review had shown to be important aspects of sensation seeking in general. They subsequently generated a list of "sensation-seeking" behaviours specific to skiing and snowboarding, creating an item pool of approximately 20 items. The initial list was qualitatively reviewed, grouping items under "novelty", "speed/thrill", "risk/impulsive", and removed unrelated and/or redundant items (e.g., two items focused on "jumping", both capturing aspects of thrill and risk, but were too similar to include both). The initial ski/snowboard-specific scale used for exploratory factor analysis contained 13 items (Table 3-1).

Table 3-1

Factor loadings from the EFA (n = 198) and CFA (n = 530) for the CSSQ-S

N^O	CSSQ Items	Factor loadings	
		EFA	CFA
1	I like to ski/ride fast.	.65	.81
2	I like to ski/ride down runs that I have never been down before.	.64	.80
3	I like to start a run even if I cannot see what lies ahead (*i.e.,* big cornice).	.55	.74
4	I like to ski/ride out of bounds.	.74	.76
5	I like to attempt jumps even if I'm not sure of the quality of the landing area.	.53	.70
6	I like to push my boundaries when I ski/ride.	.73	.80
7	If I lose control, I don't try to immediately slow down, I just go with it.	.54	.66
8	If the only way down is a straight line through a narrow pass, I go for it without hesitation even if I know I will have to go fast.	.64	.78
9	I am always trying to find new and exciting ways down a run.	.73	.85
10	A 15-foot high drop off a cliff isn't too high a jump for me.	.68	.82
11	I slow down on busy runs.	.70†	-
12	I don't slow down on busy runs, instead I just dodge people.	.99†	-
13	If I see a "danger of avalanche" sign, I will usually try to find another safer route.	<.40	-

Note. The 13-item CSSQ-S was used in the EFA and the 10-item CSSQ-S was used in the CFA. Items 11, 12, and 13 were removed from the instrument for the CFA. EFA = exploratory factor analysis, CFA = confirmatory factor analysis.

†Item loaded onto a second factor.

Factor analysis and external aspects of construct validity. An independent sample of skiers and snowboarders (which is referred to from herein as "sample 1") was recruited to explore the factor structure and included 110 males and 110 females[13], mean age = 27.1 (*SD* = 4.8) years, 63% of whom were skiers (the remainder were snowboarders). Further sample characteristics are shown in Table 3-2. Participants were recruited in ski resorts in British Columbia and Alberta, Canada, through posters, online advertisements, and selection in the cafeteria areas. Skiers and snowboarders in sample 1, and the samples described below, were excluded from the analysis for not falling within the age range (17 to 49 years) or skiing/snowboarding ability range (at least intermediate level). Further exclusions for each study are detailed below. The sample age was limited to 49 years and at least intermediate in skill to ensure that all participants had the physical ability to carry out the behaviours described in the CSSQ-S, furthermore sensation seeking is thought to decrease after the age of 40 (Zuckerman, 1979, p. 125). Despite the limited inclusion criteria, it was still anticipated that ski-behaviours might be, to some extent, age and ability influenced; therefore, correlations between the CSSQ-S and demographic variables were measured. All participants provided informed consent and subsequently completed a questionnaire package (described below).

In psychological research, the "common method bias" can be problematic because the dependent variable is often measured from one source (e.g., self-report), which may be sensitive to the effects of impression management (Podsakoff, MacKenzie, Lee, & Podsakoff, 2003). With this in mind, a subset of individuals (peers who had frequently skied with the participant and were present at the time of sampling) was invited to fill out a peer-rating version of the

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[13] Subjects (*n* = 198) recruited during my MSc. thesis project comprised the majority of this sample. The additional 22 participants responded to the online advertisements and were included only in study 3 (investigating the applied utility of the CSSQ).

CSSQ-S in addition to their personal CSSQ-S (i.e., this subset acted both as a participant and an informant). A peer rating supplemented 67 subjects in sample 1.

Table 3-2

Participant statistics for each sample

	Sample 1 Exploratory Sample (*n* = 198)	Injury data (*n* = 217)[a]	Sample 2 Confirmatory Sample (*n* = 530)	Reliability (*n* = 33)
Age (years)	27.1 (4.8)	26.68 (4.49)	26.70 (6.02)	26.4 (4.75)
Sex	50% female	50% female	41% female	33% female
Ethnicity	8% non-European (6% Asian, 2% other)	7% non-European (5% Asian, 2% other)	1% non-European	9% non-European (3% Asian, 6% other)
Education	25% high school, 58% post-secondary, 17% post-graduate	27% high school, 55% post-secondary, 18% post-graduate	29% high school, 71% post-secondary	100% post-secondary
Sport	64% skiers	63% skiers	60% skiers	75% skiers
Ability	23% intermediate, 36% advanced, 40% expert	24% intermediate, 37% advanced, 39% expert	24% intermediate, 32% advanced, 44% expert	3% intermediate, 42% advanced, 55% expert
Days skied/year	27.0 (16.3) days/year	25.2 (15.5) days/year	30.9 (15.4) days/year	36.1 (11.4) days/year

Note. [a]the first two columns (exploratory and injury) are not independent samples. The numbers shown for variables "age" and "days" are in the following format: mean (standard deviation).

3.3.2   Measures

Demographic and sport information. Participants completed a brief demographic questionnaire that included age, sex, education, and ethnicity and questions about their sport participation that included ability and average number of days skied per year (Table 3-2). Ability was rated using a self-report scale: "beginner", "novice", "intermediate", "advanced", or "expert" (with a note defining "expert" as "any terrain, any condition") (Appendix F).

The Contextual Sensation Seeking Questionnaire for Skiing and Snowboarding (CSSQ-S). The preliminary measure of sensation seeking for skiing and snowboarding used in

the exploratory factor analysis had 13 items (see Table 3-1) scored using a 5-point Likert scale anchored by 1 (strongly disagree) to 5 (strongly agree). In addition to the self-rating of sensation seeking, the CSSQ-S was also used to obtain a peer rating of each participant's perceived sensation-seeking behaviour. For the peer-CSSQ-S, items were rated using the same 5-point scale, with the only difference being that the pronoun was amended to reflect the third-person perspective (i.e., "he/she" rather than "I").

Zuckerman-Kuhlman Personality Questionnaire (ZKPQ). To examine global sensation seeking, participants completed the full ZKPQ (Appendix C). The ZKPQ is a 99-item true or false inventory that assesses five dimensions of personality that include impulsive-sensation-seeking (ImpSS), aggression/hostility, sociability, neuroticism/anxiety, and activity (Zuckerman et al., 1993). The full ZKPQ includes an infrequency scale, which contains items that might be socially desirable, but are unlikely to be true for anyone (e.g., a high infrequency score would be suspect). Sample 1 completed the entire ZKPQ both to determine the correlation between the CSSQ-S and the ImpSS subscale, and to establish discriminant validity by comparing the correlations between CSSQ-S and the four remaining ZKPQ subscales (i.e., the correlation between data derived from sensation-seeking measures (CSSQ-S and ImpSS) should be greater than each correlation between the CSSQ-S and other ZKPQ subscales (e.g., D. T. Campbell & Fiske, 1959)). The ZKPQ subscales demonstrated acceptable internal consistencies in sample 1, Cronbach alphas ranging from .71 to .99 (shown in Appendix P, comparable with "norms" from Zuckerman et al., 1993).

3.3.3   Results

Exploratory factor analysis (EFA). EFA was used to examine the factor structure of
the data derived from the CSSQ-S. A total of 198 participants from sample 1 completed the
initial 13-item instrument (five subjects were excluded for not meeting age or ability inclusion
and 17 subjects had incomplete data for EFA). Generalized least squares estimation and varimax
rotation procedures were used to determine the amount of variance accounted for by the
factor(s). Using the parallel analysis method (PA) for factor retention (Hayton, Allen, &
Scarpello, 2004), two factors had eigenvalues greater than what would be expected in a series of
randomly generated parallel samples (Table 3-3). The ten items that loaded onto Factor 1,
labelled "contextual sensation seeking", accounted for the majority of the variance (Table 3-1).
Two items loaded onto a second factor, and one item did not load sufficiently onto either factor
(factor loading < .40; Table 3-1). These three items were deleted from the instrument. A second
EFA was conducted on the 10 items retained from the initial EFA. This demonstrated that the
items were best represented by a single factor ($\lambda = 4.94$), namely "contextual sensation seeking",
that represented 49.94 % of the variance. The factor loadings for the 10-item CSSQ-S ranged
from .54 to .79. The data derived from the 10-item instrument, herein referred to as the
"Contextual Sensation Seeking Questionnaire for Skiing and Snowboarding (CSSQ-S)" (see
Table 3-1; Appendix F), had a Cronbach alpha of .88, indicating a high internal consistency
(Clark & Watson, 1995).

Table 3-3

Results from parallel analyses showing average and 95th percentile eigenvalues for 50 randomly

generated samples

Factor	Actual λ $(N_1, n = 198)$	Average λ $(N_{50}, n = 198)$	SD	95th percentile
1	5.50	1.44	0.071	1.46
2	1.40	1.33	0.051	1.34
3	0.98	1.24	0.031	1.25
4	0.85	1.17	0.029	1.18
5	0.79	1.10	0.028	1.11
6	0.64	1.04	0.033	1.05
7	0.57	0.98	0.033	0.99
8	0.57	0.93	0.027	0.93
9	0.47	0.87	0.023	0.88
10	0.40	0.82	0.027	0.83

Note. λ = eigenvalues, N_1 = results from single study sample, N_{50} = results from 50 randomly generated samples. *SD* = standard deviation for mean eigenvalues.

External aspects of construct validity. The extent to which the CSSQ-S covaries with demographic variables was analyzed and data derived from the CSSQ-S were not correlated with age, education, or ethnicity ($p > .05$), but were significantly correlated with ability ($r(198) = .65$, $p < .001$). The data derived from the CSSQ-S and the ZKPQ ImpSS were compared using Pearson's correlation coefficient to establish evidence of criterion validity. A moderate correlation ($r = .35$ to $.60$) would show that the new measure is related to an established inventory, while not being redundant. Sample 1 data were normally distributed with no multivariate outliers. Pearson's correlation coefficient revealed a significant association between the data from global (ZKPQ ImpSS, $M = 11.85$, $SD = 4.12$) and context-specific sensation-seeking (CSSQ-S, $M = 33.61$, $SD = 7.16$) measures ($r(192) = .49$, $p < .001$). The correlation falls within the moderate effect size range and the size of the correlations indicated that the measures of sensation seeking are related, but share no more than 25% of their variance.

Sample 1 completed the entire ZKPQ (five subscales), therefore correlations between the data from the CSSQ-S and from the other ZKPQ subscales were compared to establish discriminant validity (e.g., D. T. Campbell & Fiske, 1959). The correlations were then compared using Steiger's (1980) t-test for dependent correlations. Scores from the aggression-hostility (Agg-Hos; $M = 6.77$, $SD = 3.20$) and activity ($M = 10.04$, $SD = 3.54$) subscales were correlated with CSSQ-S scores (r (192) = .23 and r (193) = .19, respectively, $p < .01$), and scores from the neuroticism-anxiety (Neur-Anx; $M = 6.04$, $SD = 4.11$) subscale were negatively correlated with CSSQ-S scores (r (193)= -.25, $p < .001$). There was no significant correlation between scores from the CSSQ-S and sociability subscale ($M = 9.13$, $SD = 3.53$). The correlation between scores from the CSSQ-S and the ImpSS subscale, however, was significantly greater than each of the correlations between scores from CSSQ-S and Agg-Hos, CSSQ-S and activity, and CSSQ-S and reverse-scored Neur-Anx ($t_{Agg-Hos} = 3.37$, $p = .001$; $t_{Activity} = 3.87$, $p = .0001$; $t_{Neur-Anx} = 2.92$, $p = .004$). Finally, the CSSQ-S was compared to the peer-CSSQ-S version described above. The correlation between the total scores from the self-report and the peer-report was .81 ($p < .01$).

3.4 Study 2: Structural aspects of construct validity and reliability

The purpose of the second study was to confirm the factor structure of the 10-item CSSQ-S through confirmatory factor analysis and to measure the reliability of the questionnaire over a two-week interval. Additionally, for the samples in which the relevant data were collected, the analyses conducted in study 1 were repeated to provide further evidence for validity (i.e., with a new independent sample).

3.4.1 **Participants and procedures**

Confirmatory factor analysis (CFA). A sample of skiers and snowboarders was recruited at alpine recreation sites (herein referred to as "sample 2") and included 313 males, 217 females, mean age = 26.7 (*SD* 6.0) years. Over 93% of the participants from all samples were Caucasian (self reporting European descent), and the majority (60%) of the participants from sample 2 were skiers (see Table 3-2 for additional details). Athletes were recruited through a display kiosk in Whistler Blackcomb ski resort during the Telus World Ski and Snowboard Festival.[14] A peer-rating process (as described in study 1) supplemented data from 78 participants in sample 2 (when participants arrived at the kiosk accompanied by peers a peer-CSSQ-S was included in the questionnaire package). No participants received monetary compensation.

Reliability. The third sample (herein referred to as "sample 3") was recruited through the UBC Psychology department subject pool (20 males, 13 females, mean age = 26.4 (*SD* 4.75) years (see Table 3-2 for additional details), and participants received a credit for their participation. The initial sample included 45 participants, but only 37 of them completed the survey at time 2 and of these four were excluded: three did not meet the skiing/snowboarding ability requirement and one was missing questionnaire data. A majority (75%) of the final sample participants were skiers. The size of sample 3, though small, is adequate (>80% power) based on the large effects (e.g., *r* = .8) that are common in short-interval reliability studies (e.g., Zuckerman & Kuhlman, 2000).

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[14] Telus Festival Sample (subset of the total, n = 668 described in Chapter 2). All participants with missing CSSQ data or not meeting ability requirement were excluded, leaving 530 participants. Details regarding recruitment are found in Chapter 2.

3.4.2 Measures

Sensation-seeking measures. To examine global and contextual sensation seeking participants in samples 2 and 3 completed the 19-item ZKPQ ImpSS subscale and the 10-item CSSQ-S. The other four subscales from the ZKPQ were omitted because although small-to-moderate correlations with other subscales were found in study 1, the ImpSS is the most frequently studied in association with risk behaviours and was significantly more correlated with the CSSQ-S when compared to the other ZKPQ subscales. Both sensation-seeking measures demonstrated acceptable internal consistency (ImpSS: sample 2: α = .79; sample 3 α = .68; CSSQ-S: sample 2 α = .85; sample 3 α = .87).

3.4.3 Results

CFA. The factor structure of CSSQ-S data from the larger sample of skiers and snowboarders (n = 530, sample 2) was assessed using LISREL 8.8. Specifically, the Weighted Least Squares estimation (WLS) method was employed (due to the ordinal nature of the data) which utilizes the polychoric correlation matrix (Flora & Curran, 2004). Multiple fit indices were considered to determine the quality of model-data fit. Comparative Fit Index (CFI) and Adjusted Goodness-of-Fit Index (AGFI) close to .95 and Root Mean Square Error of Approximation (RMSEA) close to .06 (but less than .08) are indicative of an acceptable fit (Hu & Bentler, 1999). Further, factor loadings greater than .63 provide support for a "very good" model-data fit for EFA studies, and may be considered as a rough guideline for CFA studies (DiStefano & Hess, 2005).

The correlation matrix was first screened for bivariate normality; no assumptions were violated. A unidimensional model was tested based on the structure found in the EFA. The

initial fit statistic was significant ($\chi^2(35) = 140.43$, p < .001), but χ^2 is sensitive to large sample sizes (Hair, Black, Babin, & Anderson, 2009), and therefore other fit statistics were considered. The results from the single factor model provided evidence for an acceptable fit; CFI = .93, AGFI = .97, RMSEA = .075. Factor loadings ranged from .66 to .85 (see Table 3-1), further supporting a unidimensional model. A path diagram is shown in Appendix Q.

Reliability analysis. Reliability was assessed through a re-test study (sample 3), comparing the inter-item correlations between responses at times 1 and 2 (two-weeks apart). The re-test reliability between scores at times 1 and 2 for the CSSQ-S and ImpSS were $r(31) =$ .94, *p* < .01 and $r(30) =$.70, *p* <.01, respectively. Means for the CSSQ and ImpSS were similar to the previous two projects, $M = 37.50$, $SD = 6.70$ and $M = 10.18$, $SD = 3.08$, respectively (at time 1).

External aspects of construct validity. Similar to study 1, analyses were carried out for both the correlation between data derived from the two sensation-seeking measures (ImpSS and CSSQ-S), and when available, the correlation between participant and peer CSSQ-S data. Data sets were normally distributed (skewness and kurtosis statistics < |1|) with no multivariate outliers. The correlation between the data from global (ZKPQ ImpSS, $M = 12.73$, $SD = 3.72$) and context-specific SS (CSSQ-S, $M = 36.77$, $SD = 6.97$) measures in sample 2 and 3 were significant ($r(530) = .37$, *p* < .01; $r(32) = .45$, *p* < .01) as was the correlation in sample 2 between the total scores from the self-report and the peer-report ($r(78) = .84$, *p* < .01). The inter-item correlations between peer and self-report were all significant at *p* < .01 ranging from .45 to .82.

3.5   Study 3: Sensation seeking and injury prevalence

Risk-taking is a facet of the sensation-seeking construct (Zuckerman, 1979, 1994), and

the CSSQ-S is designed to assess both *risky* and *sensation-seeking* behaviours in skiing and

snowboarding. Theoretically, sensation seekers differ in their optimal level of arousal and each

individual has a "target level" of risk he/she deems acceptable when balanced by expected

benefits (reviewed in Zuckerman, 2007a). For example, an individual might decide that his/her

behaviour (e.g., skiing at high speeds) carries an acceptable risk depending on the perceived

benefit of an activity (e.g., a rush of excitement). In line with these theories, an individual higher

in sensation seeking might risk more to obtain his/her optimal level of arousal. Risk involves the

possibility of a negative outcome, and in risky sports, injury is the most probable negative

outcome. Risk-taking behaviours have been associated with injuries and trauma in high-risk

sports and motor vehicle riders (including all-terrain vehicles and motorcycles) (Foley, Draus,

Santos, & Franklin, 2009); and because risk-taking is a facet of sensation seeking, it was

expected that the frequency of injuries would be higher in sensation seekers. Numerous

epidemiological studies on factors affecting injury in skiers and snowboarders exist, but most

have focused on environmental (e.g., visibility, snow conditions) and demographic variables

(e.g., age and sex) (Girardi, Braggion, Sacco, De Giorgi, & Corra, 2010). The few studies that

examined participant characteristics beyond demographics explored the frequency of ski

injuries/accidents and used the SSS, and abbreviated versions, to assess sensation seeking (e.g.,

Bouter et al., 1988; Cherpitel, Meyers, & Perrine, 1998)*,* and interestingly, found associations

between *low* levels of sensation seeking and injury. Context specific measures of sensation-

seeking behaviours in sport may be able to explain additional variance in risk-taking behaviour

more so than general sensation-seeking measures. Other studies that have investigated injury in

skiing and snowboarding have employed dichotomous measures of risk-taking, for example by simply asking participants whether they considered themselves "risky" or "cautious" (Ruedl, Abart, Ledochowski, Burtscher, & Kopp, 2012; Ruedl et al., 2010), or have created risk-taking and sensation seeking ski-measures, without providing evidence of validity for the instruments (Cooper, 2009). It was anticipated that scores derived from a multi-item scale (such as the CSSQ-S) specifically developed for skiing and snowboarding would be a better predictor of sensation-seeking-related outcomes than a single-item measure. In order to establish evidence for the external aspect of construct validity (i.e., the applied utility of the CSSQ-S), the relationship between self-reported injury counts and scores on the CSSQ-S and the ImpSS were assessed. It was hypothesized that sport-specific sensation seeking (CSSQ-S) would be associated with a higher injury rate over the course of multiple seasons. Furthermore, it was hypothesized that the CSSQ-S would explain more variance in injury rate than the more general ImpSS scale.

3.5.1 **Participants and procedures**

Male and female skiers and snowboarders from sample 1 who had reported the number of ski-related injuries sustained over the past three seasons were included in the analysis ($n = 217$, 50% female; see Table 3-2 for further details). In order to establish the incremental validity of data derived from the CSSQ-S relative to data from the more general ImpSS, a hierarchical regression was conducted with injury rate as the criterion.

3.5.2 Measures

Sensation-seeking measures. The 10-item CSSQ-S and the 19-item ZKPQ ImpSS described above (and in Appendices D and E).

Ski related injuries. Injury prevalence was measured by two self-report items: (a) number of ski-related injuries sustained during the past season (choice format: 0, 1, 2, >3); and (b) number of ski-related injuries sustained over the last three seasons (open-ended format). Self-report data are comparable to data obtained by other means (e.g., emergency room reports) when interested in frequency (and not the nature and severity) of an injury (Gabbe, Finch, Bennell, & Wajswelner, 2003; Valuri, Stevenson, Finch, Hamer, & Elliott, 2005). Participants were instructed to include only injuries that impaired their sport ability for at least one day (a commonly used definition in injury epidemiology; Goldberg, Moroz, Smith, & Ganley, 2007; Nicholl, Coleman, & Williams, 1995).

3.5.3 Results

Data derived from the CSSQ-S and ImpSS were normally distributed (CSSQ, $M = 34.28$, $SD = 7.41$; ImpSS, $M = 11.67$. $SD = 4.07$), whereas the injury rate over one season ($Mdn = 0$, $IQR = 1$) and three seasons ($Mdn = 1$, $IQR = 2$) were positively skewed. To normalize the injury counts square-root transformations were applied. Correlations between injury rate and sensation-seeking measures are shown in Table 3-4. A 3-step hierarchical regression was carried out for each: injury rate over one season and injury rate over three seasons as the criterion. Both criterion variables yielded similar final models (Table 3-5). Step 1 included age and sex and accounted for a significant amount of variance in injury over three seasons ($p < .001$), but not over one season ($p > .05$). On Step 2, ImpSS was added and this increased the variance in

injuries accounted for across three seasons ($p < .05$), but not over a single season. On Step 3, the

CSSQ-S was added and this accounted for a significant increase in injury variance over the

ImpSS for both criterion variables (one season, $p < .01$; three seasons, $p < .001$). In the final

models, the CSSQ-S was significantly related to injuries (single season: standardized $\beta = .271$, p

$< .01$ and three seasons: standardized $\beta = .358$, $p < .001$). The partial relationships between

injury rate and sex, age, and ImpSS were all non-significant ($p > .05$, Table 3-5).

Table 3-4

Intercorrelations for sensation seeking score and injury rate

	Intercorrelations			
Variable	CSSQ-S	ImpSS	Injuries, 1 season	Injuries, 3 season
CSSQ-S	-	.43**	.19**	.30**
ImpSS		-	.10	.15*
Injuries, 1 season			-	.36**
Injuries, 3 seasons				-

Note. $n = 217$. Correlations with injury data were measured using Kendall's *tau* and the correlation between CSSQ-S and ImpSS was measured using Pearson's *r*. CSSQ-S = contextual sensation seeking questionnaire for skiing and snowboarding, ImpSS = impulsive-sensation seeking.

p < .01. ***p* < .001.

Table 3-5

Hierarchical multiple regression analyses predicting injury rate from sensation seeking

	Injury rates							
	Injury count over a single season[†]				Injury count over three seasons[†]			
Predictor	ΔR^2	df	F	β	ΔR^2	df	F	β
Step 1	.016	2, 214	1.73		.050	2, 214	5.57**	
Sex				-.091				-.199**
Age				-.102				-.134
Step 2	.026	1, 213	2.29		.022	1, 213	5.09*	
Sex				-.071				-.169*
Age				-.095				-.124
ImpSS				.104				.152*
Step 3	.074	1, 212	10.96**		.083	1, 212	20.91***	
Sex				.044				-.019
Age				-.091				-.119
ImpSS				.010				.027
CSSQ-S				.271**				.358***

Note. .$n = 217$. [†]A square root transformation of injury count over one and three seasons was applied. CSSQ-S = contextual sensation seeking questionnaire for skiing and snowboarding, ImpSS = impulsive-sensation seeking.

p < .05, **p* < .01, ***p* < .001.

3.6   Discussion

Sensation seeking has been measured in a number of specialized populations (e.g., alcoholics, athletes, gamblers), but the questionnaires used were not specific to the populations being assessed, nor do they reflect actual behaviours that an individual engages in (i.e., they are hypothetical in nature). The purpose of the present study was to develop a self-report sensation-seeking questionnaire that is specific to a sport (skiing and snowboarding). An analysis of the psychometric properties of the CSSQ-S was carried out in three samples of skiers and snowboarders, and the data provides evidence for several aspects of construct validity (cf. Messick, 1995).

Discussions with the focus group provided support for the content validity (cf. Haynes, Richard, & Kubany, 1995) of the instrument since all of the items in the initial domain-specific sensation-seeking measure were deemed relevant and representative of what might be considered *sensation-seeking* behaviours in skiing and snowboarding. The CSSQ-S displays strong psychometric properties, with a unidimensional model providing the best fit for the data. The final CSSQ-S is a 10-item, unidimensional scale, which is brief enough to administer to a sport population in the field and appears to measure a person's tendency to seek out new, thrilling, or physically stimulating experiences while engaged in downhill snow sports, regardless of potential hazards. Although CSSQ-S scores are related to scores from the other ZKPQ subscales, the relationship between CSSQ-S and ImpSS scores was significantly stronger than the respective relationships to scores from the other subscales, thus demonstrating discriminant validity. It was not surprising that correlations between the CSSQ-S and other ZKPQ subscales were present, given that scores from the aggression-hostility subscale have been positively correlated with risk-taking behaviours, and high sensation seekers often have lower levels of anxiety (Zuckerman & Kuhlman, 2000). The moderate correlation between scores from the CSSQ-S and the ImpSS subscale of the ZKPQ provides support that the CSSQ-S is related to Zuckerman's definition of sensation seeking, yet is not a redundant instrument. Fjell and colleagues (2007) found physiological differences (e.g., cortical habituation) between individuals that have high global sensation seeking (as measured by the ZKPQ) that do not participate in extreme sports compared to those who also score high on the ZKPQ, but engaged in extreme sports; they suggest that the extreme sport practitioners might be the true arousal seekers. Furthermore, Slanger & Rudestam (1997) suggested that those who engage in risky snow sports may be too closely clustered together in the high end of the SSS scale dimensions, and that this

global sensation seeking scale may lack the resolution to discriminate among individuals scoring in the very high end of the continuum, e.g., extremely high-risk sports (such as extreme skiing which involves cliff jumping into unknown terrain), and the moderately high-risk versions of the same sport (skiing in controlled terrain). The CSSQ-S represents a facet of Zuckerman's sensation-seeking trait more closely related to risk-taking behaviours in downhill sports, and the use of both scales may improve the characterization of respondents. Another context-specific sensation-seeking measure created by Kalichman and colleagues (1994) to supplement general sensation-seeking scales relates more specifically to sexual sensation seeking, and has been used in numerous studies that investigate HIV and risky sexual behaviours. Narrow trait instruments can have a predictive advantage over broad traits instruments (Paunonen & Ashton, 2001).

Many self-report questionnaires inquire about behaviours that people would like to do, but these may not be aligned with what the individuals actually do. Although the studies presented in this chapter did not measure actual behaviours by field observation, the CSSQ-S was designed to inquire about actual, rather than hypothetical behaviours. Studies have shown that hypothetical behaviours are often exaggerated compared to actual behaviours (e.g., Alpizar, Carlsson, & Johansson-Stenman, 2008). The CSSQ-S, which measures sport-specific, recent patterns of behavioural tendencies, explained significantly more of the variance in injury rates than the ImpSS subscale, a broader, hypothetical trait-measure. Similarly, a study that explored the relationship between optimism and risk perception in a sport population found that there was no relationship between risk perception measured within a specific context and optimism as a general personality trait (even though links between these two traits have been established in occupational and health psychology literatures (e.g., Fontaine, 1994)). The authors suggested

that domain- and population-specific psychometric measures are more appropriate for measuring risk-taking in high-risk sports (Martha, Sanchez, & Goma-i-Freixanet, 2009).

While domain- or context-specific instruments might explain more variance in a given criterion, there are limitations to narrow psychometric instruments. For example, a limitation of a context-specific questionnaire like the CSSQ-S that inquires about actual behaviours is that it is to some extent age- and ability-influenced. The sample was restricted to include young- to middle-aged adults based on Zuckerman's observation that sensation seeking declines after 40 years of age, and although age did not significantly correlate with CSSQ-S score in this study, there might be a decline in sensation seeking that occurs at an earlier age when measured in a sport context. A majority of CSSQ-S items describe behaviours that involve taking physical risks and may be influenced by a person's physical fitness, which generally declines with age (Sallis, 2000). A minimum ability level was also imposed for study inclusion, but there was still a significant positive correlation between proficiency and CSSQ-S scores. Whether a skier is more likely to improve if he/she is high in sensation seeking and willing to take risks, or whether mastery of the sport makes a skier more likely to exhibit risky or sensation-seeking behaviours is not known, but links between ability and risk-taking have also been observed in other high-risk sports (D.J. Llewellyn et al., 2008). Future longitudinal studies might be useful to examine the association between ability levels and sensation seeking and also consider whether other variables such as physical fitness and/or previous injuries might be associated with sensation seeking in skiing and snowboarding.

Establishing validity is an ongoing process, not limited to one or two studies. With this in mind, future research may include an extension of the CSSQ-S for use in other high-risk sports studies, such as those investigating injury in mountain biking or river kayaking. Both are

"downhill sports" that share terrain characteristics with skiing and snowboarding (e.g., varying chute-width and slope-grade affecting the thrill and risk of the activity) and items might be generalized to examine the applicability of the CSSQ to such other sports. While the CSSQ may be transferable to downhill sports, its generalizability to other sports is limited due to its narrow scope. "Gravity sports" for example, which include sky-diving, BASE jumping, and speed-flying, would require entirely different items to operationalize sensation-seeking facets that pertain to novelty, thrill, and risk within the sport-context.

As the popularity of downhill and adventure sports continue to increase (Hudson, 2004), recreation sites create interesting natural settings for observing sensation-seeking behaviours in the field. Furthermore, high-risk sports athletes consistently report higher sensation seeking than controls, and may ultimately represent a homogeneous group in which to study extreme manifestations of the sensation-seeking trait. The development of the CSSQ-S, a focused trait instrument that measures patterns of sensation seeking in skiing and snowboarding, may be useful in future research to investigate relationships between sport experience, ability, risk-taking, injury, and a variety of psychological constructs. The CSSQ-S is used in the next chapters to explore associations between sensation seeking and dopaminergic genetic variants.

Chapter 4: The -521 C/T polymorphism in the dopamine-4-receptor gene (*DRD4*) is associated with skiing and snowboarding behaviour[15]

4.1   Summary

A single nucleotide polymorphism, -521 C/T (rs1800955) in the promoter region of the dopamine-4-receptor gene (*DRD4*), is associated with approach-related traits including novelty seeking and extraversion, in some, but not all studies. Using a joint-analysis approach, sensation seeking was measured in two cohorts of experienced male and female skiers and snowboarders (n = 503) using a sports-specific tool, the Contextual Sensation Seeking Questionnaire for Skiing and Snowboarding (CSSQ-S, Chapter 3), and a more general trait measure, the Zuckerman Kuhlman Personality Questionnaire (ZKPQ) impulsive sensation seeking subscale. A significant association between the *DRD4* -521CC genotype and sports-specific sensation seeking as measured using the CSSQ-S was detected and replicated ($p < .001$). These data suggest that the *DRD4* -521 C/T polymorphism contributes to a "sensation-seeking phenotype" in skiers and snowboarders, but the variant was not associated with impulsive sensation seeking ($p = .9$).

4.2   Introduction

Dopamine has been implicated in behavioural activation, instrumental learning (involving both positive and aversive motivations), appetitive approach, and emotional processing (Lauzon & Laviolette, 2010; Salamone et al., 2007; Wise, 2004), and is thought to contribute to the neurobiological basis for impulsive sensation seeking (Zuckerman, 2005b). The intensity of the

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feeling of pleasure immediately before and during a risky situation (e.g., the "high" that a skydiver might feel during a jump (I. H. Franken et al., 2006)) is thought to be related to dopamine levels (Di Chiara et al., 2004), levels that may be affected by the density and/or function of dopamine receptors (Blum et al., 2009). More details about the purported role of dopamine in sensation seeking are reviewed in Chapter 1. The D4 receptor is encoded by the gene, *DRD4*, and is located on chromosome 11 (11p15.5). There are numerous polymorphisms of the 3.4 KB *DRD4* in human populations (Okuyama et al., 2000); including the commonly studied 48 base-pair variable number tandem repeat (VNTR) in exon III and -521 C/T (a cytosine (C) to thymine (T) transition at base -521 in the upstream promoter region). The -521C allele is associated with a 40% increase in *DRD4* transcription in cultured cells (Okuyama et al., 2000), a phenotype, which if expressed *in vivo*, could have an impact on neuromodulation (Cordell & Clayton, 2005) and the emotional processing of stimuli (Lauzon & Laviolette, 2010). A number of studies have investigated the impact of *DRD4* variants (reviewed in Chapter 1, and Table 4-1 below) on approach-related traits. The results of these studies have been inconsistent (see reviews: Kluger, Siegfried, & Ebstein, 2002; Schinka, Letsch, & Crawford, 2002), although two meta-analyses found the -521 C/T to be a more promising candidate *DRD4* polymorphism for approach-related trait studies than the VNTR (M. R. Munafo et al., 2008; Schinka et al., 2002).

Table 4-1

Genetic association studies on -521 C/T and approach traits or externalizing disorders

Cohort	N	Measure	Findings	Reference
Young male (Japanese)	86	TCI	CC highest NS scores, TT lowest, *p* < .001 (no mechanisms proposed)	(Okuyama et al., 2000)
Extreme scorers (high and low) (European, Finland)	200	TCI	*n.s.*	(Ekelund, Suhonen, Jarvelin, Peltonen, & Lichtermann, 2001)
Schizophrenics and controls (Japanese)	173	TCI	*n.s.*	(Mitsuyasu et al., 2001)
Students (European, Hungary)	99	TCI	CC higher NS than CT and TT, especially in women, p = .008 (no mechanisms proposed)	(Ronai et al., 2001)
Healthy subjects (African-American)	71	NEO-FFI	CC highest scores on extraversion compared to CT + TT (no mechanisms proposed)	(Bookman, Taylor, Adams-Campbell, & Kittles, 2002)
Healthy subjects (European, Swedish)	381	TCI	*n.s.*	(Jonsson et al., 2002)
Community sample, including 95 children and their parents (European Hungary)	95	N/A	There was a significant interaction between -521C/T and the exon III VNTR associated with disorganized attachment	(Lakatos et al., 2002)
Healthy subjects (European, German)	276	TCI	*n.s.*	(Strobel et al., 2002)
Clinically depressed patients (European, New Zealand)	156	TCI and SCID	TT associated with avoidant and obsessive symptoms. No association between -521C/T and TCI NS (no mechanisms proposed)	(Joyce et al., 2003)
Adolescent females (Korean)	101	TCI	No association for -521 C/T, but a significant interaction between -521C/T and exon III VNTR and NS (no mechanisms proposed)	(H. J. Lee et al., 2003)
Schizophrenic patients (210) and healthy controls (206) (Han Chinese)	416	N/A	No association for -521C/T between groups, but significant difference in a haplotype containing -521C/T between groups (no mechanisms proposed)	(Xing et al., 2003)
Healthy subjects (European, German)	104	NEO-FFI	*n.s.*	(Eichhammer et al., 2005)
Healthy subjects (Russian)	220	EPI	A joint contribution of -521 C/T and -809 A/G to levels of extraversion (no mechanisms proposed)	(Golimbet, Gritsenko, Alfimova, & Ebstein, 2005)
6 year old boys and girls (European, Hungary)	57	ERP[a]	Analyzed -521C/T only as haplotype with exon III VNTR: T-7 haplotype associated with "resistance to distraction"	(Birkas et al., 2006)
Healthy subjects (Russian)	130	TCI, EPI	-521 C allele associated with extraversion and NS in women homozygous for the COMT Met allele (no mechanisms proposed)	(Golimbet, Alfimova, Gritsenko, & Ebstein, 2007)
Schizophrenic patients (216) and healthy controls (243) (Japanese)	459	N/A	-521C allele frequency was marginally higher in females with schizophrenia (no mechanisms proposed)	(Mitsuyasu et al., 2007)

Cohort	N	Measure	Findings	Reference
Extreme scorers (117 high and 192 low) (European, English)	309	EPI	*n.s.*	(M. R. Munafo et al., 2008)
Heroin dependent (84) and controls (168) (Chinese males)		N/A	T allele frequency higher in heroin-dependent group	(Ho, Tang, Cheung, & Stadlin, 2008)
Heroin users + healthy controls (Chinese)	600	n/a	-521 T allele frequency higher in heroin users (no mechanisms proposed)	(Lai et al., 2010)
Community sample (99) (European, USA) Clinical sample (136) (European, Hungary)	two-stage	N/A	TT overrepresented in patients with borderline and antisocial symptoms in US sample, but finding not replicated (no mechanisms proposed)	(Nemoda et al., 2010)

Note. *n.s.* = not significant, NS = novelty seeking, TCI = Temperament and Character Inventory (Cloninger), EPI = Eyesenck Personality Inventory, NEO-FFI =

NEO Five-Factor model (Costa & McCrae), ERP = novelty elicited event-related potentials, SCID = structured clinical interview for DSM-III-R (Diagnostic and

Statistical Manual of Mental Disorders). Most of the studies reporting significant findings do not propose a physiological mechanism and the few studies that do

propose a mechanism looked at the -521 C/T in combination with other variants or report findings in the opposite direction to the Munafo et al. (2008) and

Schinka et al., (2002) meta-analyses.

Previous associations have been reported between alleles at -521 C/T and novelty seeking, extraversion, and drug use (Lai et al., 2010; M. R. Munafo et al., 2008) (Table 4-1); however, at the time when data collection for the current chapter was underway, researchers had yet to examine the alleles in populations actively involved in seeking out and experiencing physical risks in sports. To address this gap, moderately- to highly-skilled skiers and snowboarders were recruited at mountain resorts in Western Canada to study whether there were associations between sensation seeking in snow sports and the *DRD4* -521C/T. These sports were chosen because 1) there is a wide range of established risk levels inherent in the sports (i.e., runs of varying degrees of danger), 2) there is a large pool of potential subjects, heterogeneous in their tolerance for risk (from the "cautious" to the "high risk-taker"), and 3) because tools that quantify patterns of sensation-seeking behaviours in a sport context can be used alongside more general trait instruments for genetic studies. Athletes' global sensation-seeking behaviour was assessed using the Zuckerman Kuhlman Personality Questionnaire (ZKPQ) impulsive sensation seeking subscale (ImpSS), while their context-specific (skiing/snowboarding) sensation-seeking behaviour was evaluated using the Contextual Sensation Seeking Questionnaire for Skiing and Snowboarding (CSSQ-S) which was developed and tested for this study (see Chapter 3).

4.3 Methods

4.3.1 Participants

Skiers and snowboarders between 17 and 49 years of age (joint-sample: $n = 503$: 287 males, 216 females; mean age = 26.8 years ($SD = 6.0$)) of intermediate ability or better

participated in this two-stage study. A pilot sample[16] ($n = 117$) was recruited from Whistler and Vancouver, British Columbia, and Lake Louise and Banff, Alberta. A second sample[17] ($n =$ 386) was recruited at the 2010 Telus World Ski and Snowboard Festival in Whistler, British Columbia. Skiing and snowboarding ability was self-assessed by participants and was based on ability to ski/ride runs classified as a "blue square" (the standard North American notation for "mid-level") or harder. For details about Festival recruitment, see Chapter 2. To minimize confounding effects of differing biogeographical backgrounds on allele frequencies, only participants self-reporting as "White/European descent" were included in the genetic analysis. A majority of participants (67%) had completed a post-secondary degree or diploma, 30% were in their final two years, or had completed secondary school (details Table 4-2).

Table 4-2

Participant characteristics

Demographic Variable	Pilot, $n = 117$	Festival, $n = 386$
Age (Mean (*SD*))	27.1 (4.5) years	26.3 (5.9) years
Sex	50% male, 50% female	58% male, 42% female
Ability	28% intermediate, 36% advanced, 37% expert	23% intermediate, 32% advanced, 45% expert
Sport	65% skier, 35% snowboarder	54% skiers, 40% snowboarder, 6% both
Education	27% high school, 60% post-secondary, 3% missing	30% high school, 67% post-secondary, 3% missing

Note. *SD* = standard deviation. There were no significant differences in any of the demographic variables between samples ($p > .13$).

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[16] Pilot sample is from MSc sample.
[17] A portion of the "Festival sample" that was successfully genotyped.

4.3.2 Measures

Impulsive sensation seeking. Global sensation seeking was assessed using the impulsive sensation seeking scale (ImpSS) from the ZKPQ (Zuckerman et al., 1993). In this study, scores derived from the ImpSS demonstrated acceptable internal consistency (Cronbach alpha = .82). The Pilot sample completed the full ZKPQ, which contains five subscales plus an infrequency scale, which was included to support data screening. The second sample (Festival sample); however, only completed the ImpSS subscale (with an infrequency scale) due to its hypothesized relationship with skiing and snowboarding behaviour (Chapter 3).

Contextual Sensation Seeking Scale for Skiing (CSSQ-S). Sensation seeking in the specific context of skiing and snowboarding was assessed using the 10-item CSSQ-S (questionnaire development is described in Chapter 3). In this study, CSSQ-S scores were significantly correlated with ImpSS scores, $r(480) = .46$, $p < .01$, and scores derived from the CSSQ-S demonstrated high internal consistency (Cronbach alpha = .86).

4.3.3 Genotyping

Buccal cell DNA was isolated from cytobrushes (Fisher Scientific, Ottawa, ON, Canada) using a standard alcohol purification technique (Saftlas et al., 2004) (Appendix L) and genotyped for the -521C/T polymorphism (dbSNP rs1800955). For the Pilot sample, DNA was genotyped initially using polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP) analysis; however, the assay was difficult to optimize and subsequently a more rapid pyrosequencing strategy was employed. The majority of the genotypes were ascertained using pyrosequencing.

RFLP-based genotyping. Primers used were *DRD4*-F: 5'-GAT CAA CTG TGC AAC GGG TG-3' and *DRD4*-R: 5'-GAG AAA CCG ACA AGG ATG GAG-3' (NAPS IDT, Vancouver, BC, Canada). The PCR cycled in a MJ Mini Cycler (Bio-Rad Laboratories, Hercules, CA, USA) as follows: 95°C for 5 minutes, followed by 39 cycles of 95°C for 45s, 60°C for 45s, and 72°C for 2 minutes. The 25 μL reactions contained 20 mM Tris-HCl pH 8.4, 50 mM KCl, 1.8 mM MgCl2, 0.2 mM dNTP, 0.6 μM of each primer, 10% BSA, 1.0 U *Taq* polymerase (Invitrogen Corporation, Carlsbad, CA, USA), and 10-20 ng DNA template. PCR products were digested using *Fsp*I (recognition sequence: 5' TGC▲GCA 3') restriction endonuclease (New England Biolabs, Beverly, MA, USA) at 37°C overnight, and genotypes were visualized using 8% polyacrylamide gel electrophoresis stained with Sybr Safe gel stain (Life Technologies, Burlington, ON, Canada) (see Figure 4-1 for a sample gel photograph).
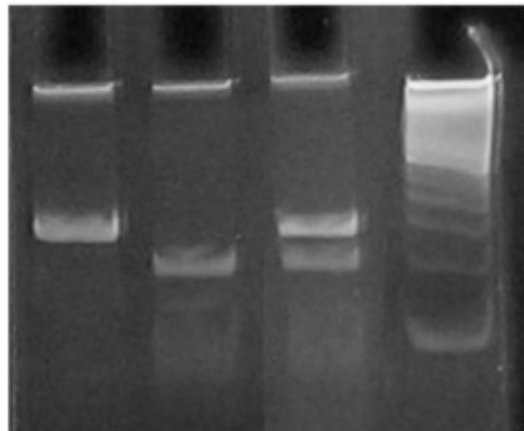
Figure 4-1. Sample gel electrophoresis photograph.

Genotypes from left to right: -521 CC, -521 TT, -521 CT, 100-bp marker. Samples were run for approximately 45 minutes at 125 volts.

Pyrosequencing-based genotyping. Primers were designed using the Biotage AB PSQ Assay Design Software (Version 1.0.6, USA; DNA sequence shown in Appendix R): forward

primer: 5'-TAG GCG TCG GCG GTT GAG-3'; reverse primer: 5'-GAC TCG CCT CGA CCT

CGT G-3'; and sequencing primer, 5' TCG GGG GCA GGG GGA 3' (the reverse primer was

biotinylated and HPLC purified, NAPS IDT, Vancouver, BC, Canada). DNA was PCR

amplified in 15 μL reactions containing 20 mM Tris-HCl pH 8.4, 50 mM KCl, 1.5 mM MgCl2,

0.2 mM dNTP, 0.4 μM of each primer, 1.0 U native *Taq* polymerase (Invitrogen), and 1.0 μL

DNA (approximately 20 ng/μL). Cycling conditions were: 95°C for 5 minutes, followed by 45

cycles 95°C for 20s, 60°C for 20s, and 72°C for 20s, followed by a 5 minute final extension at

72°C. Single-stranded biotinylated PCR products were prepared as per manufacturers

recommendations for sequencing using the Pyrosequencing Vacuum Prep Tool (Biotage AB,

Uppsala, Sweden). The following sequence was analyzed by the PyroQ SNP software (Biotage)

to determine sample genotypes: 5'GCGGGCGNGGAGGGYG 3' (see Figure 4-2 for a sample

PyroQ result; see Appendix R for additional result.
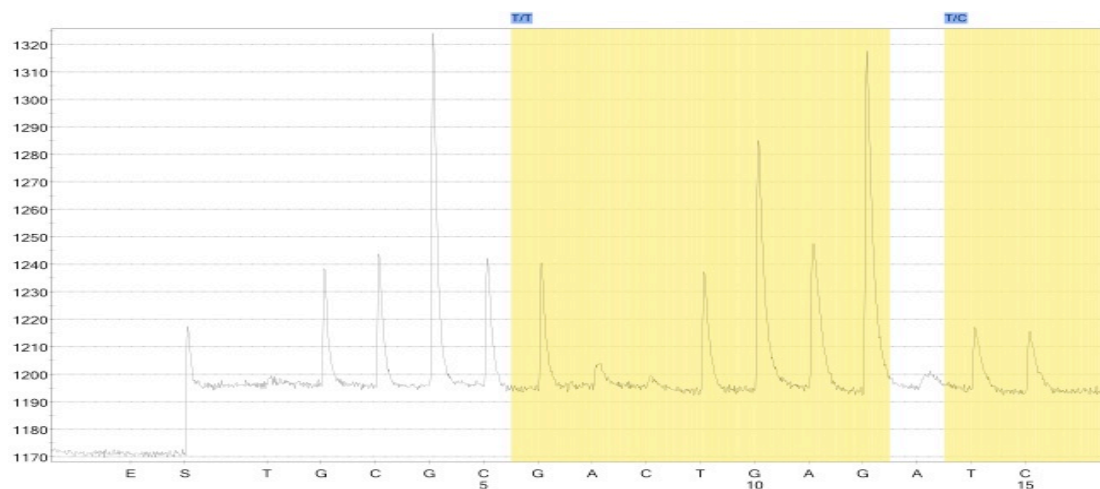
Figure 4-2. Sample PyroQ result.

Far right portion of the image shows a peak at "T" and "C", indicative of a -521 CT genotype.

4.3.4   **Statistical analyses**

CSSQ-S and ImpSS data were screened for normality, missing data, and univariate outliers. An analysis of co-variance (ANCOVA) was used for each dependent variable (ImpSS and CSSQ-S) to compare sensation-seeking scores between genotype groups (CC vs. CT *vs.* TT) in stage 1 (Pilot sample). As previous studies have shown a significant difference between sensation-seeking scores in males and females (males generally scoring higher (e.g., Zuckerman & Kuhlman, 2000)), sex was included as a covariate when there were significant differences in scores. Ability was included as a covariate for the CSSQ-S analysis since the sport-specific tool and ability were linearly correlated in Chapter 3. Dummy variables were used for sex (male = 0, female = 1) and ability (0 = beginner, 1 = novice, 2 = intermediate, 3 = advanced, 4 = expert); when ability was < 2 the CSSQ-S score was rejected. The CC genotype has been associated with approach behaviour (Bookman et al., 2002; Ronai et al., 2001); therefore, higher sensation-seeking scores were expected in the -521 CC genotype group.

The same statistical methods described in stage 1 were employed in stage 2 (the replication sample, n = 386), comparing the ImpSS and CSSQ-S scores across genotypes (CC *vs.* CT *vs.* TT) using a one-way ANCOVA. Fisher's method for combining independent probabilities (Fisher, 1932) was used to combine *p*-values from the pilot and replication samples (similar to joint-analysis design suggested by Skol, Scott, Abecasis, & Boehnke, 2006). Details about Fisher's method are shown in Appendix S. Joint-analysis is a form of internal replication that results in an increased power (compared to independent replication) to detect associations (Skol et al., 2006). Finally, the association was analyzed in the combined sample (pilot + replication, n = 503). In both stages, continuous variables (ImpSS and CSSQ-S scores) were analyzed by genotype, and therefore a control group is not needed. Similar single-cohort

research designs are common to behavioural genetic studies (Bookman et al., 2002; Okuyama et al., 2000; Ronai et al., 2001).

4.4 Results

4.4.1 Stage 1

Genotype frequencies of the 117 participants from stage 1 (.33 CC, .41 CT, .26 TT) were in Hardy-Weinberg Equilibrium (HWE), $\chi^2 = 3.57$, $p > .05$. The allele frequencies in the participants were 54% -521C and 46% -521T. To confirm that the genotyping results would be consistent regardless of the genotyping technology used, a random sample of DNAs that had been genotyped using RFLP was genotyped again using pyrosequencing. There was 100% agreement between the results obtained by the two methods. The ImpSS and CSSQ-S data were normally distributed and satisfied univariate assumptions. Two subjects were excluded either due to not meeting ability for CSSQ-S, or high infrequency scores on ZKPQ. ANCOVAs revealed that the -521 C/T polymorphism had a significant effect on both sensation-seeking measures: ImpSS ($F(2, 115) = 3.63$, $p = .03$), and CSSQ-S adjusted for sex and ability ($F(2,116) = 8.73$, $p < .001$, Table 4-3). CSSQ-S scores were linearly correlated with ability in the Pilot sample, $r(116) = .66$, $p < .001$) and males scored significantly higher than females on the CSSQ-S ($p < .001$), but there were no significant differences on ImpSS scores between the sexes ($p = .20$, see Table 4-4). There were no significant correlations between age and sensation-seeking measures ($p > .4$).

Table 4-3

Stage 1: A summary of sensation-seeking scores by genotype

| Genotype | ImpSS | | | | CSSQ-S | | | |
	N	Mean	SD	Range	n	Mean	SD	Range
CC	38	12.97	3.84	2-19	38	36.35	6.60	21-46
CT	49	10.65	4.43	2-19	48	33.10	7.64	18-45
TT	29	11.45	3.41	4-18	30	33.67	6.22	23-45
	$p =$	**.03**				**$p < .001$**		

Note. p values for univariate ANOVA are shown in bold. Sex and ability were included as covariates for CSSQ-S. Genotype group totals vary due to questionnaire exclusions (total $n = 117$). $SD =$ standard deviation.

4.4.2 Stage 2

Genotype data. In the replication sample (stage 2), genotypes at the -521 C/T SNP were established for 376 subjects; however, four subjects were excluded from subsequent association analyses due to missing data. Further subject exclusions specific to each questionnaire are described below. The genotype frequencies (.21 CC, .48 CT, .30 TT) showed no significant deviation from those predicted if the population was in Hardy-Weinberg equilibrium ($\chi^2 = 0.13$, $p > .05$) and the frequencies did not differ between stage 1 and 2 ($\chi^2 = 5.71$, $p > .05$). Genotypes did not differ on any other demographic variables (e.g., sex, age, education, marital status, $p > .5$).

Questionnaire data. The questionnaire data were normally distributed and variances for both personality and ski data sets were homogeneous (Levene's statistic, $p > .05$). Fifteen CSSQ-S scores were removed from stage 2 analysis for not meeting eligibility requirements (intermediate ski/snowboard ability), and three ZKPQ ImpSS scores were rejected due to high infrequency (social desirability scale) scores as per ZKPQ criteria (Zuckerman et al., 1993). The mean ImpSS score ($M = 12.45$, $SD = 3.84$, n = 487) for skiers and snowboarders (total sample,

males and females combined) was significantly greater than "norms" described elsewhere (M= 10.18, SD = 4.10, N = 2969 (Zuckerman et al., 1993); $t(3454) = 11.42$, $p < .0001$). Males scored significantly higher than females on both the ImpSS ($p < .05$) and the CSSQ-S scale ($p < .001$, Table 4-4). CSSQ-S scores were linearly correlated with ability in both the replication sample ($r(362) = .57$, $p < .001$) and the combined sample ($r(478) = .59$, $p < .001$). The relationships between sensation-seeking scores (ImpSS and CSSQ-S) and other demographic variables (e.g., marital status, age, education) were either not significant ($p > .05$) or only modestly correlated with small effect sizes ($r < .2$) and were not suitable for inclusion as covariates (Cohen, 1992).

Table 4-4

Differences in sensation-seeking scores between males and females

Measure	Sex	Pilot Sample			Replication Sample		
		n	Mean	SD	n	Mean	SD
ImpSS	Male	59	12.08	3.30	219	13.14	3.27
	Female	57	11.12	4.76	156	12.09	4.25
	t, p		1.27[a],	.20		2.59[a],	.010
CSSQ	Male	59	37.92	5.42	219	39.58	5.92
	Female	57	30.59	6.61	148	32.02	7.11
	t, p		6.51[a],	<.001		11.05[a],	<.001

Note. [a]Equality of variances between males and females was violated, therefore an alternate test that does not assume equal variances was employed. SD = standard deviation.

Gene associations. Stage 1 resulted in significant associations with both sensation-seeking measures (ImpSS and CSSQ-S); therefore both variables were analyzed in stage 2. In the replication sample, analysis of variance revealed a significant relationship between genotype at the -521 C/T polymorphism and ski/snowboarding behaviours (CSSQ-S scores). The -521 C/T polymorphism was significantly associated with sensation seeking in skiing when tested using an additive model with sex and ability as covariates ($n = 359$, $F(2, 354) = 3.85$, $p < .05$, η_p^2

= .021, Table 4-5). The joint-*p*-value, obtained using Fisher's method for combining

probabilities between the pilot and replication samples was also significant, $p < .0001$. Finally,

an ANCOVA on the combined sample revealed a significant association between -521 C/T and

CSSQ-S score ($n = 475$, $F(2, 470) = 7.93$, $p < .001$, $\eta_p^2 = .033$, Table 4-5). Pair-wise

comparisons (using least significant difference, LSD) between genotype groups revealed that

individuals with the CC genotype scored higher than CT individuals (LSD $= 2.37\pm 0.61$, $p <$

.001) and TT individuals (LSD $= 2.09 \pm 0.68$, $p = .002$). No significant differences between

genotype groups and ImpSS scores were observed in the replication sample ($n = 372$, $F(2, 368) =$

0.08, $p = .92$; adjusted for sex only). The relationship between genotype and CSSQ-S remained

significant when a correction for testing two variables (Bonferroni, $p = \alpha/2$ (Attia et al., 2009))

was applied.

Table 4-5

Stage 2: A summary of contextual sensation seeking (CSSQ-S) scores by genotype

	Replication Sample			Combined Sample		
Genotype	*n*	Mean	*SD*	*n*	Mean	*SD*
CC	77	37.84	7.62	116	37.33	7.28
CT	173	36.13[a]	6.89	222	35.51[b]	7.16
TT	107	36.64[a]	7.76	137	35.99[b]	7.53
		p < .05			**p < .001**	

Note. *p*-values for univariate analysis are shown in bold. Sex and ability were included as covariates. Means from

respective samples that have no superscript in common are significantly different from each other (LSD $p < .01$).

SD = standard deviation.

4.5   Discussion

There was a significant association between the *DRD4* -521 C/T polymorphism and

patterns of skiing/snowboarding behaviours as assessed using the CSSQ-S. There was an

association in a small sample of skiers and snowboarders, which was replicated in a larger independent sample recruited at a later date. The combined sample of skiers and snowboarders had higher ImpSS scores compared to other populations, which supports previous findings that high-sensation seekers are often involved in high-risk activities (reviewed in Goma-i-Freixanet et al., 2012); however, the ImpSS scores were not associated with the -521 C/T genotype in the replication sample.

This study presented in this chapter is the first to investigate the genetics of sensation seeking in a high-risk sport population using a tool specific to the population, and to my knowledge it is also the first to examine the relationship between the -521C/T *DRD4* polymorphism and *sensation seeking* (previous studies have investigated other approach traits such as novelty seeking and extraversion). One other sports study investigated genetic variants (*DRD4* VNTR, *DAT1* VNTR, and *HTR2A* 102T/C) and "Big Five" personality traits in high- and low- risk sport participants, but found no differences between groups (Cam et al., 2010). There was no association using the ZKPQ measure of impulsive sensation seeking in the current chapter, but the result of higher ski/snowboard-specific sensation seeking scores (CSSQ-S) in individuals with -521 CC genotypes is consistent with other studies on novelty seeking (Golimbet et al., 2005; Okuyama et al., 2000; Ronai et al., 2001). Studies that have investigated associations between the -521 C/T polymorphism and approach-related traits have found female-specific associations (Bookman et al., 2002; Ronai et al., 2001), while others have observed the association in all-male cohorts (Okuyama et al., 2000). Sex was included as a covariate since sensation-seeking scores differ significantly between males and females, and there was a significant relationship between -521 C/T polymorphism and patterns of ski behaviours (*p* < .001) that survived correction for multiple tests.

Results from previous studies of *DRD4* polymorphisms and novelty seeking have been inconsistent (M. R. Munafo et al., 2008), which may be due to broad phenotyping by general, trait measures. To address this, sensation seeking was measured using two scales: a global, trait-scale and a context-specific sensation-seeking scale. Many trait questionnaires inquire about responses to hypothetical situations, but these may not be aligned with what the individuals actually do. Although ski behaviours were not observed in the field, the CSSQ-S was designed to inquire about actual, rather than hypothetical behaviours (Chapter 3). This focused phenotyping impacted the sample size (e.g*.,* exclusion of less proficient skiers/snowboarders), but the cost of losing power due to smaller sample sizes can be offset by the gain of generating fewer false-positives or -negatives (Kreek et al., 2005). A note of caution, when interpreting data obtained from highly specific cohorts such as this skiing/snowboarding cohort: while there are benefits to sampling from a homogeneous population (e.g., reducing extraneous variability) there is a possibility of sampling bias and the results have limited generalizability. It should also be noted that no psychiatric screening was carried out, and that future studies would benefit from including additional screening.

A role for *DRD4* in approach-related behaviours has been supported in neurophysiology and genetic studies, but the effect sizes of complex phenotypes (e.g., personality traits) are usually small (Ebstein, 2006). While there was a significant association between genotype at -521 and patterns of skiing behaviour in the study described in this chapter, the locus accounted for only approximately 3% of the variance[18] in contextual sensation seeking ski scores in males and females. Sensation seeking has moderate heritability, with over 50% of the trait-variance

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[18] Based on ANCOVA partial *eta* (η_p^2), a measure of effect size.

due to genetics (Stoel et al., 2006), and is likely a polygenic trait with the inter-individual variance influenced by genotypes at multiple loci (Golimbet et al., 2007).

The -521 C/T polymorphism is in a known regulatory region of the DRD4 gene and has established phenotypic consequences (Okuyama et al., 2000); however, there may be other functional variants elsewhere in the gene (or in other genes involved in dopamine pathways) that could also affect sensation seeking. Other genes that have been previously investigated in association with approach-related traits include those encoding enzymes that metabolize, transport, or regulate dopamine (e.g., monoamine-oxidase B (*MAO-B*), catechol-*O*-methyl transferase (*COMT*), dopamine-β-hydroxylase (*DBH*), dopamine transporter (*SLC6A3*), and other dopamine receptor genes (e.g., dopamine receptors *(DRD1*, *DRD2*) (Ebstein & Israel, 2009; M. R. Munafo et al., 2003; Roe et al., 2009; Varga et al., 2012). As well as the serotonin receptor gene (*HTR2A*) and the gene encoding stathmin (*STMN1)*, which regulates microtubule formation, both have been associated with harm avoidance and fear-related behaviours (Brocke et al., 2010; Ebstein & Israel, 2009), making all of these genes potential candidates in sensation seeking in sport. Data from analyses including variants from the above-mentioned genes are presented in the following chapters.

In summary, genotyping revealed a significant association between alleles at a functional polymorphism in the DRD4 gene and sensation seeking in a sports context in male and female skiers and snowboarders. This observation raises the intriguing possibility that the predilection to risk-taking behaviour in sports is influenced by genetics.

Chapter 5: Association of a common D3 dopamine receptor gene variant is associated with sensation seeking in skiers and snowboarders[19]

5.1 Summary

The "sensation seeking" trait has been associated with risky behaviours including high-risk sport participation. Genes involved in dopaminergic neurotransmission have been investigated in studies of approach traits; however, not in sporting contexts. Using a joint-analysis the relationships between monoamine-neurotransmitter gene variants and impulsive and sport-specific sensation seeking were investigated in skiers and snowboarders from Western Canada ($n = 599$). Twenty-six SNPs in eight genes involved in dopaminergic and serotonergic transmission (*DRD1, DRD2, DRD3, DAT1, COMT, MAO-B, DBH, HTR2A*) were genotyped. An initial screen identified a few variants that were associated with sensation seeking, one of which, a G/A transition (rs167771) in the D3-receptor gene *(DRD3)*, remained significant in the combined sample and after correction for multiple testing ($p = .004$, $\eta_p^2 = .02$). *DRD3* variants have been associated with approach traits; however, the results presented in this chapter are the first to suggest a role for rs167771 in sensation seeking.

5.2 Introduction

Many genes have been explored in association with novelty and sensation seeking, and there are likely a number of genes contributing to this polygenic trait (Ebstein, 2006). Increased reward-seeking behaviour (an animal phenotype similar to sensation seeking) in

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[19] The data in this chapter was published as: "Association of a common D3 dopamine receptor gene variant is associated with sensation seeking in skiers and snowboarders" in the Journal of Research in Personality, 2013.

hyperdopaminergic mice (Pecina et al., 2003), and correlations between serotonin levels and impulsive behaviour in humans (C.S. Carver & Miller, 2006) suggest that genes in the dopaminergic and/or serotonergic pathways could contribute to this trait. Variants within candidate genes that encode proteins involved in dopaminergic and serotonergic neurotransmission are extensively reviewed in Chapter 1.

There have been only a handful of studies that have investigated genetic associations with the *sensation-seeking* trait (specifically). Most genetic studies have characterized approach phenotypes using the TCI novelty seeking subscale; however, Derringer et al. (2010) similarly employed a candidate gene association study design to test for associations with sensation seeking (measured using the SSS) by investigating 273 SNPs in eight candidate genes in a sample of alcoholics. They reported significant associations with 12 SNPs; however, a commentary on the study noted that the authors failed to correct for the number of SNPs tested and the findings were not significant after correction (Powell & Zietsch, 2011).

To investigate the possibility that variants in genes that are involved in dopaminergic and serotonergic neurotransmission affect sensation seeking, a two-stage joint-analysis (Skol et al., 2006) candidate-gene association study was carried out in a cohort of proficient skiers and snowboarders. Polymorphic loci at which both alleles were moderately common (heterozygosity > .2) were chosen in genes that encode proteins involved in transport (dopamine transporter: *DAT1 (SLC6A3))*, function (dopamine and serotonin receptors: *DRD1, DRD2, DRD3, HTR2A*), and metabolic inactivation (catechol-*O*-methyltransferase, (*COMT*), monoamine oxidase B (*MAO-B*), and dopamine-β-hydroxylase (*DBH*)). Initially (stage 1), 26 single nucleotide polymorphisms (SNPs) in the aforementioned genes (see Table 5-1) were assessed for associations with sensation-seeking phenotypes in a sub-sample of participants randomly chosen

from the full sample. SNPs significantly ($p < .05$) associated with any of the sensation-seeking phenotypes in this stage were subsequently tested in the remainder of the sample (stage 2). The results from both stages were combined and corrected for multiple testing.

Each athlete's global sensation seeking was measured using the (ZKPQ; Zuckerman et al., 1993) impulsive sensation seeking (ImpSS) scale, which can be analyzed as a single subscale or as two constructs: impulsivity and sensation seeking (Zuckerman et al., 1993). Athlete's sport-specific sensation seeking was measured using the Contextual Sensation Seeking Questionnaire for Skiing and Snowboarding (CSSQ-S), a tool that inquires about patterns of actual behaviours that relate to sensation seeking in sport (see Chapter 3 for details about CSSQ-S development).

Many high-risk sport participants actively seek out risks and have higher than average sensation-seeking scores (Goma-i-Freixanet et al., 2012). Numerous studies have explored genetic associations with approach-related behaviours and traits in deviant risk-taking populations (e.g., substance users, alcoholics, gamblers) or in populations exhibiting externalizing disorders (Gorwood et al., 2001; Ting Li et al., 2011; Lobo et al., 2010; Nemoda et al., 2010); however, practitioners of high-risk sports may represent a population that seeks stimulation though less deviant, more health-benefiting outlets.

Table 5-1

List of single nucleotide polymorphisms chosen for analysis

Gene (abbreviated and full name)		Physiological function	SNP
COMT	Catechol-*O*-methyl transferase	Metabolizes DA	rs737865[a], rs4633, rs4680, rs165599[b]
DAT1 or *SLC6A3*	Dopamine transporter	Reuptake of DA from the synapse	rs6347, rs27072, rs463379, rs2937639, rs2975226[b]
DBH	Dopamine *B*-hydroxylase	Converts DA to norepinephrine	rs1611115
DRD1	Dopamine receptor D1	Involved in dopaminergic neurotransmission	rs686, rs4532, rs251937, rs4867798
DRD2	Dopamine receptor D2	Involved in dopaminergic neurotransmission	rs6277, rs1076560, rs1079597, rs1800497, rs1800498, rs2283265, rs2734831, rs4245147, rs7131056, rs17601612
DRD3	Dopamine receptor D3	Involved in dopaminergic neurotransmission	rs6280, rs167771
MAO-B	Monoamine oxidase B	Metabolizes DA	rs1799836
HTR2A	Serotonin receptor	Involved in serotonergic neurotransmission	rs6311

Note. Heterozygosity of all SNPs > .2 (ALFRED database). DA = dopamine, 5HT = serotonin.

[a]lower call rate (marker performance 88%).

[b]Two SNPs failed optimization and were not genotyped.

5.3   Methods

5.3.1   Participants

Skiers and snowboarders were recruited at the 2010 Telus World Ski and Snowboard Festival in Whistler, British Columbia, Canada (details in Chapter 2). Participants completed a set of brief questionnaires and provided a buccal (cheek) cell swab for DNA preparation. A majority of the initial sample (89% of $n = 668$) self-reported as "White/European descent"; therefore, to avoid the potential confounding effect of inter-population variation in allele frequencies all non-Caucasian participants were excluded from analyses. After exclusions, the genotyped sample included 599 skiers and snowboarders, ages 17 to 49 years (341 male, $M =$

26.91 years, $SD = 6.81$; 258 female, $M = 27.41$ years, $SD = 5.93$)[20], and all were at least intermediate in skiing or snowboarding ability.

5.3.2 Measures

ZKPQ Impulsive Sensation Seeking (ImpSS). Participants completed the 19-item subscale scored true/false (Appendix D) (Zuckerman et al., 1993). In the current study, the Cronbach alphas for the combined sample ($n = 599$) were .80, .73, and .68 for ImpSS, Imp, and SS, respectively.

Contextual Sensation Seeking Questionnaire for Skiing and Snowboarding (CSSQ-S). Participants completed the 10-item CSSQ-S, scored on a five-point Likert scale (Appendix F). In this study the internal consistency of the CSSQ-S was .87.

Participants provided demographic information including age, sex, ethnicity, marital status, education, and occupation; and sport information including sport (skiing, snowboarding, telemarking), ability (same as previous chapters), and number of days skied per year. Participants' CSSQ-S score was included only if they reported at least intermediate ability.

5.3.3 Genetic analysis

Buccal cell DNA was isolated from cytobrushes using alcohol purification technique described in Chapter 2 (Saftlas et al., 2004), and samples were diluted to 20 ng DNA/μL. A total of 26 SNPs from eight genes were successfully genotyped using the Sequenom iPLEX®

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[20] Subset of Telus Festival Sample (n = 668 described in Chapter 2), after exclusions for ethnicity and age. Exclusion for ability were only applied to CSSQ-S analyses.

technique (San Diego, California, USA) at the McGill University and Genome Québec

Innovation Centre, Montréal, Quebec, Canada. The mean marker-call rate was 99 ± 0.021%

(sample plate layout shown in Appendix N; marker list and project report from Genome Quebec

shown in Appendix T).

5.3.4 **Statistical analysis**

To increase the power to detect associations, a two-stage joint-analysis model was used

(similar to that described by Skol and colleagues (2006)). In stage 1, approximately 50% of the

sample (n = 291, "discovery sample") was selected at random using the PAWS-SPSS (version

18.0) random case selector and screened for the 26 polymorphisms, with significance was set at

α = .05 (i.e., no correction for multiple testing). In stage 2, SNPs that met this inclusion

threshold were analyzed in the remainder of the sample, herein referred to as the "replication

sample" (n =308), and then in the combined sample (n = 599). A joint-p-value from the two

independent samples was calculated (using Fisher's combined probability test; Fisher, 1932) and

a correction for multiple testing was applied using the Bonferonni method (α = .05/x, where x is

the number of independent tests performed (e.g., Lunetta, 2008)). Details about Fisher's method

are shown in Appendix S.

An analysis of co-variance (ANCOVA) was used to compare sensation-seeking measures

(ImpSS and CSSQ-S, quasi-dependent variables) between genotypes for each SNP (between-

subject factors). In both stages of analysis, additive models of inheritance (three genotype

groups, i.e., three factor levels) were tested. Sex was considered a covariate as significant gender

differences were expected based on previous ImpSS (e.g., Zuckerman & Kuhlman, 2000) and

CSSQ-S data (Chapter 3). Skiing or snowboarding ability was considered as a covariate only for CSSQ-S analyses since ability significantly correlated with CSSQ-S score in a Chapter 3.

5.4   Results

Genotype frequencies for all of the SNPs tested in stage 1 were in Hardy-Weinberg Equilibrium (HWE, $p > .05$). Scores derived from CSSQ-S and ImpSS were normally distributed. As indicated in Table 5-2, the selected discovery sample for stage 1 analyses ($n = 291$) did not differ from the replication sample ($n = 308$) in terms of education, sport, and sensation seeking (i.e., the phenotypes of the study) variables; however, there were differences in the ability and sex compositions of the samples (Table 5-2; there were approximately 10% more females and more intermediate level participants in the replication sample).

In both stages, males scored higher than the females on impulsive sensation seeking (discovery: $t(289) = 2.12$, $p < .05$; replication: $t(276) = 2.51$, $p < .05$) and on the contextual sensation seeking in skiing and snowboarding assessment (discovery: $t(282) = 9.30$, $p < .001$; replication: $t(290) = 9.81$, $p < .001$); therefore, supporting the use of sex as a covariate. CSSQ-S score was significantly correlated with ability (discovery: $r(279) = .58$, $p < .0001$, replication: $r(289) = .62$, $p < .0001$) providing support for including ability as a covariate when analyzing CSSQ-S scores.

Table 5-2

Descriptive statistics and results comparing the samples at stages 1 and 2

Variables	Descriptive statistics				Stage 1 *vs.* 2	
	Discovery sample Stage 1 ($n_D = 291$)		Replication sample Stage 2 ($n_R = 308$)		*Statistic*	*p*
Grouped						
Sex	180 males, 111 females		162 males, 146 females		$\chi^2 = 5.24$	.02*
Education	64% post secondary or higher		65% post secondary or higher		$\chi^2 = 3.18$	.20
Sport	60% skiers, 35% snowboarders, 5% other		52% skiers, 40% snowboarders, 8% other		$\chi^2 = 2.96$	.23
Ability	19% intermediate, 30% advanced, 47% expert, 4% other		27% intermediate, 31% advanced, 35% expert, 7% other		$\chi^2 = 8.81$	.01*
Continuous						
Age	$M = 26.88$	$SD = 6.61$	$M = 27.35$	$SD = 6.61$	$t = 0.90$	.37
CSSQ-S[†]	$M = 36.89$	$SD = 7.05$	$M = 35.83$	$SD = 7.65$	$t = -1.73$	.09
ImpSS	$M = 12.73$	$SD = 3.85$	$M = 12.42$	$SD = 3.88$	$t = -0.58$	.55
Imp	$M = 3.83$	$SD = 2.29$	$M = 3.71$	$SD = 2.23$	$t = 0.64$	.53
SS	$M = 8.93$	$SD = 2.12$	$M = 8.70$	$SD = 2.25$	$t = 1.25$	.21

Note. Chi-square tests were used for grouped variables and *t*-tests for the continuous variables (age, CSSQ-S, and ImpSS). M = mean, SD = standard deviation.

[†]Total participants included in CSSQ-S means differ from sample total ($n_D = 284$ and $n_R = 293$) because skiing/snowboarding ability was less than intermediate or missing.

p < .05.

Genotype frequencies for three of the 26 polymorphisms were associated with a sensation-seeking phenotype in stage 1 ANCOVA (at $p < .05$; see Table 5-3) and therefore included in the stage 2 analysis of the replication sample. Data for all SNPs are shown in Appendix U. In stage 2, one SNP: rs167771 in *DRD3* was marginally associated with the sensation-seeking (SS) construct from the ZKPQ ($p = .055$, Table 5-3). The joint *p*-value, obtained by combining the *p*-values for the association between sensation seeking and rs167771 in the discovery and replication analyses, was significant ($p = .012$) and remained significant after correcting for multiple testing (at $\alpha = .017$). The association between sensation seeking and rs167771 was also present in the combined sample ($p = .004$, $\eta_p^2 = .02$). Pair-wise comparisons

(using the Least Significant Difference, LSD) between genotype groups in the combined sample

revealed that individuals with the rs167771 GG genotype scored lower than AG individuals

(LSD = -1.05, p = .049) or AA individuals (LSD = -1.46, p = .005), and AG individuals scored

lower than AA individuals (LSD = 0.39, p = .047), and this trend was present in the independent

samples (Table 5-4). In other words, the number of A alleles carried was positively correlated

with sensation seeking. The other two SNPs tested in stage 2 were not associated with either

sensation-seeking measures (p > .2) and the joint p-values were above the corrected level of

significance (Table 5-3). Genotype frequencies for the SNPs (including rs167771) that advanced

to stage 2 remained consistent with HWE.

Table 5-3

ANCOVA results from stage 1 and 2

	Gene	Marker	dbSNP	DV	Discovery sample				Replication sample				Combined sample		Joint Analysis
					N	MAF	F	p_D	n	MAF	F	p_R	F	p_C	p_{Joint} [a]
1	*DRD2*	C>G	rs17601612	ImpSS	290	.39	3.37	.036	308	.42	0.57	.564	1.35	.260	.100
				Imp			4.22	.016			0.06	.938	2.41	.090	.078
2	*DRD2*[†]	*Taq1A*	rs1800497	ImpSS	290	.23	3.73	.025	308	.21	0.08	.923	2.22	.110	.110
3	*DRD3*	A>G	rs167771	ImpSS	291	.17	3.98	.047	308	.16	1.43	.243	5.14	.006	.063
				Imp			3.47	.024			0.13	.877	2.56	.078	.102
				SS			3.55	.030			2.93	**.055**	5.54	**.004**	**.012***

Note. Only $p < .05$ are shown. Sex was included as a covariate. MAF = minor allele frequency, DV = dependent variable.

[†]rs1800497 is located in *ANKK1* (downstream from *DRD2*), but is often considered a "*DRD2*" polymorphism.

[a]p_{Joint} Independent *p*-values from the discovery and replication samples were combined using Fisher's method (Fisher, 1932).

*significant at α = .017.

Table 5-4

Descriptive statistics for ImpSS scale and subscales grouped by DRD3 rs167771

Sample	Genotype		Dependent variable		
		n	ImpSS	Imp	*SS*
Discovery (*n* = 291)	AA	203	13.07 (3.75)	4.01 (2.29)	9.05 (1.98)
	AG	77	12.38 (3.85)	3.56 (2.25)	8.81 (2.23)
	GG	11	9.73 (4.56)	2.36 (1.86)	7.36 (3.26)
Replication (*n* = 308)	AA	216	12.68 (3.81)	3.76 (2.25)	8.91 (2.17)
	AG	85	11.86 (4.05)	3.60 (2.23)	8.26 (2.35)
	GG	7	11.29 (3.90)	3.57 (1.99)	7.71 (2.50)
Combined (*n* = 599)	AA	419	12.87 (3.78)	3.89 (2.27)	8.98 (2.08)
	AG	162	12.10 (3.95)	3.58 (2.23)	8.52 (2.31)
	GG	18	10.33 (4.27)	2.83 (1.95)	7.50 (2.92)

Note. Values represent mean (*SD*).

5.5 Discussion

There was a significant association between one SNP, an intronic A to G transition (rs167771) in the DRD3 gene and sensation seeking: homozygotes for the G allele scored lower on sensation seeking than individuals homozygous for the A allele, with heterozygotes showing an intermediate level. No associations were found between the SNPs in any of the other genes investigated (*DRD1, DRD2, DAT1, COMT, MAO-B, DBH, 5HT2A*), or between the most commonly studied *DRD3* rs6280 (Ser9Gly) variant, which previously has been associated with sensation seeking and novelty seeking (Duaux et al., 1998; Staner et al., 1998).

DRD3 is expressed in limbic regions of the brain (e.g., hippocampus, nucleus accumbens, ventral striatum) suggesting that the receptor is involved in emotion and cognition (Bouthenet et al., 1991). A role for the gene in novelty seeking may be hypothesized based on the observation that *Drd3* knock-out mice display hyperactivity in a test for exploratory behaviour (Accili et al., 1996). The DRD3 gene has been investigated as a candidate gene for a number of phenotypes

including alcoholism (Gorwood et al., 2001), drug dependence (Duaux et al., 1998), and attention deficit hyperactivity disorder (ADHD) (Muglia, Jain, & Kennedy, 2002), all of which have been associated with impulsivity and sensation seeking (commentary from Kaplan, B. within Depue & Collins, 1999; Roberti, 2004; Verdejo-Garcia et al., 2008).

Recently associations were reported between the G allele in *DRD3* rs167771 and autism spectrum disorder (ASD) (de Krom et al., 2009) and extrapyramidal symptoms in psychiatric patients (Gasso et al., 2009). Another ASD study reported a conflicting finding: an association between the rs167771 G allele and a decreased risk for "insistence on sameness", a domain within the Revised Autism Diagnostic interview (Staal et al., 2012). Although no direct comparisons between ASD studies and these findings can be made, the relationship between ASD and sensation-seeking phenotypes may be relevant to this study as the sensation-seeking trait is associated with a desire for novelty, while the insistence on sameness domain includes the items: "difficulties with minor changes in personal routine and environment" and "resistance to trivial changes in environment" (Szatmari et al., 2006). High sensation seekers crave stimulation, respond better to novelty in the environment, and have less preference for routine than low sensation seekers (Zuckerman & Kuhlman, 2000) (e.g., ZKPQ SS item, "I would like the kind of life where one is on the move and travelling a lot, with lots of change and excitement"). The current finding that lower scores on sensation seeking were associated with the G allele is consistent with that of de Krom et al. (2009) who reported that the same allele (G at rs167771) was associated with stereotyped (or repetitive) behaviour in ASD.

Another important candidate gene in personality research is the *DRD4*, a highly polymorphic gene that has been associated with novelty seeking, extraversion, ADHD, schizophrenia, and drug use (Bookman et al., 2002; Ebstein et al., 1996; Kereszturi et al., 2007;

Okuyama, Ishiguro, Toru, & Arinami, 1999). Alleles at several loci in the *DRD4* promoter were investigated during the current series of research projects and results are presented in Chapter 6.[21]

While the results presented in the current chapter for *DRD3* and *DAT1* are consistent with earlier published results (Jonsson et al., 2003; Jorm et al., 2000), they differ from those reported for other approach and/or externalizing behaviour studies; for example: sensation seeking with *COMT* Val158Met (U. E. Lang et al., 2007), *DRD2 Taq1A* with impulsivity and alcohol use (Esposito-Smythers, Spirito, Rizzo, McGeary, & Knopik, 2009), rs463379 (*DAT1*) with ADHD (Friedel et al., 2007), and rs686 (*DRD1)* with drug use (Liu et al., 2006). The discordances between the current results and those listed above may be due to a number of factors, including the polygenic inheritance of complex phenotypes, heterogeneous phenotyping methods, and differences in sample demographics (e.g., ethnicity and sex) (M. R. Munafo et al., 2003). Comparing studies is difficult due to varying allele frequencies between populations and inconsistency in whether the sexes are combined for analysis.

There was a significant association between sensation seeking and rs167771 with sex as a covariate and the relationship between sex and sensation seeking was significant. In many cultures, sensation seeking has been associated with "masculine" characteristics and negatively associated with "feminine" characteristics (Daitzman & Zuckerman, 1980; Kish, 1971), and studies investigating associations between sensation seeking and dopaminergic genes (*COMT*) have found female-specific associations (Kang et al., 2010; U. E. Lang et al., 2007). The current findings and those mentioned above emphasize the importance of considering the influence of sex when analyzing a trait that differs consistently in magnitude between males and females.

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[21] Had these results been included in the analyses in the current chapter, the additional four SNPs would not have impacted the significant results, as none of them reach significance in stage 1.

Although the total sample (n = 599) was sufficient to achieve modest power (~ .80) based on small effect sizes (η^2 = .01 to .02) typical of SNP associations, the sample was split in order to carry out an internal replication in an attempt to reduce chance findings. As a result, there was reduced power in the split samples, but taking the joint p-value into account improves the overall power of the study compared to discovery and replication samples considered independently (Skol et al., 2006). To compensate for the risk of false findings (both positive and negative (Christley, 2010)) corrections for multiple testing were applied in the second stage.

In summary, 26 SNPS in eight dopaminergic and serotonergic genes were tested for associations with general and sport-specific sensation-seeking behaviour using a two-stage, joint-analysis design. After replication and correction for multiple testing, there was a significant association between sensation seeking and the *DRD3* rs167771 polymorphism in skiers and snowboarders. Other *DRD3* variants have been associated with externalizing phenotypes related to sensation seeking, but the results presented in this chapter are the first to suggest a role for the *DRD3* rs167771 in sensation seeking. While the present findings are intriguing, they are preliminary and the association should be investigated in other sports, cultures, and populations.

Chapter 6: No association between promoter variants of the dopamine-4 receptor gene and sensation seeking in skiers and snowboarders.

6.1 Summary

Twin studies have shown that impulsivity and sensation seeking are heritable traits, and candidate genes encoding components involved in dopaminergic transmission have been targets for association studies. The gene that is most commonly implicated in approach-related phenotypes is the dopamine-4-receptor gene (*DRD4*). The promoter of the *DRD4* contains a number of polymorphisms that have not been explored in association with sensation seeking. Five such common polymorphisms (-1106T/C, -906T/C, -809A/G, -291C/T, 120-bp duplication) were analyzed in a cohort of skiers and snowboarders: practitioners of commonly practiced but potentially hazardous sports. Impulsive sensation seeking and domain-specific (skiing) sensation seeking were compared between genotype groups in 599 skiers/snowboarders. No association was seen between genotype(s) and general or domain-specific sensation seeking.

6.2 Introduction

The promoter region of the dopamine-4-receptor gene (*DRD4*) is highly polymorphic (Okuyama et al., 2000) and multiple variants within the gene have been associated with novelty seeking, schizophrenia, and externalizing disorders (Golimbet et al., 2005; Lai et al., 2010; Mitsuyasu et al., 2001; M. R. Munafo et al., 2008; Rogers et al., 2004). A number of polymorphisms exist in a span of approximately 1000 bases upstream of *DRD4*, which despite their proximity, appear to independently segregate in Japanese and Caucasian populations (Mitsuyasu et al., 2007; Nakajima et al., 2007; Szantai et al., 2005). Among these are 19 SNPs

and four variable length polymorphisms (two repeat variants and two insertion/deletion) in the promoter region of the *DRD4* (Mitsuyasu et al., 2007 and shown in Table 6-1); however 13 of them are rare with minor allele frequencies (MAF) ≤ .05, and would not be very informative for studying continuous personality traits (Balding, 2006). *DRD4* is highly expressed in the frontal cortex and limbic regions of the brain and the receptor encoded by this gene is thought to be involved in attention, motivation, and emotional processing, all of which play a role in decision-making and risk-taking (Kreek et al., 2005).

Decision-making is central to the personality trait "impulsivity", which often involves acting without forethought (Evenden, 1999). The ZKPQ clusters impulsivity with a correlated trait, "sensation seeking", which involves a desire for novelty and seeking stimulation through intense experiences and taking risks for the sake of these experiences (Zuckerman et al., 1993). Impulsivity and sensation seeking have been associated with disinhibited behaviours including gambling (Alessi & Petry, 2003), binge drinking (Carlson et al., 2010), and drug use (Verdejo-Garcia et al., 2008), but also to non-deviant, prosocial outlets like travel and entrepreneurship (Lepp & Gibson, 2008; Nicolaou et al., 2008) (reviewed in Chapter 1).

Sports are another common prosocial outlet for sensation seekers, and numerous studies have putatively linked high-risk sports with sensation seeking (reviewed in Goma-i-Freixanet et al., 2012); however, the relationship with impulsivity is less clear (D. J. Llewellyn, 2008). Sports like skiing and snowboarding are considered high-risk due to the relatively high chance of severe injury (Goma-i-Freixanet et al., 2012). To my knowledge other than the studies presented in this dissertation, there has only been one genetic association study on personality traits in high-risk sport populations (Cam et al., 2010); whereas, there have been numerous genetic studies (including several which investigate *DRD4*) on other risk-inclined populations (reviewed

in Dick et al., 2009; Goodman, 2008). The physiological mechanisms that underlie the motivation to participate in antisocial pastimes may be similar to those that attract people to high-risk sports (Zuckerman, 1983).

To test the hypothesis that variants in *DRD4* influenced general sensation seeking and domain-specific sensation seeking, a cross sectional, single cohort design was employed to test for association(s) between *DRD4* genotypes in proficient skiers and snowboarders and their scores from: 1) the ZKPQ trait measures for impulsive sensation seeking (ImpSS) and 2) the Contextual Sensation Seeking Scale for Skiing and Snowboarding (CSSQ-S). Sensation seeking measures were compared between genotype groups at multiple loci in the 5'-upstream region of *DRD4*. Inclusion of polymorphisms was limited to informative, common SNPs (MAF > .05 in Caucasian populations) that could be analyzed using a multiplex genotyping technique (leaving a total of six SNPs, see Table 6-1), and an additional promising candidate, the 120-bp tandem duplication that required genotyping by standard PCR. Of the remaining six common promoter SNPs, the -521C/T (dbSNP rs180955) had already been previously studied in a portion[22] of this sample (see results in Chapter 4) and this SNP along with the nearby -616 G/C (dbSNP rs747302) failed to amplify at the genotyping facility. Excluding failed attempts, the following variants were analyzed: -1106 T/C, -906 T/C, -809 G/A, -291 C/T (see Table 6-1 for dbSNP ID), a few of which have been studied in association with disinhibited behaviours and traits (Mitsuyasu et al., 2001; Nemoda et al., 2010; Okuyama et al., 2000). As well, a 120-bp tandem duplication (starting at position -1.24 KB) that reportedly reduces transcriptional efficiency

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[22] The -521C/T failed amplification at the Genome Quebec genotyping facility using a Sequenom approach and failed to amplify in a large portion of the Festival sample when genotyping was attempted locally by RFLP and pyrosequencing. The -521C/T results were treated as a separate study, because the aim was to replicate findings from my MSc., and the manuscript (Chapter 4) was written long before carrying out the analyses presented in the current chapter.

(D'Souza et al., 2004) was included in the study. There has been no functional support for the

other deletion/repeats; therefore these were not genotyped. Other than the commonly studied -

521C/T, -616G/C, and 120-bp duplication, only two studies investigating *DRD4* promoter SNPs

in association with approach traits have been published, both of which analyzed the -906T/C

variant (Derringer et al., 2010; Heck et al., 2009).

6.3   Methods

6.3.1   **Participants**

Skiers and snowboarders visiting the 2010 Telus World Ski and Snowboard Festival in

Whistler, British Columbia, Canada completed two questionnaires and provided a buccal (cheek)

cell swab for DNA preparation (methods described in Chapter 2). Unrelated participants were

between 17 and 49 yrs of age (n = 599[23], M = 27.12 years, SD = 6.45) and were pre-screened for

ability, reporting at least intermediate ability, defined as capable of skiing/snowboarding a "blue

square run" comfortably. The majority of the participants were either skiers (56%) or

snowboarders (38%) while the remaining practiced both sports (5%) or were telemarkers (1%).

To minimize confounding effects due to differing biogeographical background, only Caucasian

participant (self-reported as of "European descent") were included in the genetic analysis

(participant demographics are shown in Table 6-2).

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[23] See also Chapter 5.

Table 6-1

A summary of DRD4 promoter polymorphisms

Marker	dbSNP	Reference	MAF	Population	Functional support
120-bp repeat	rs4646984	(Seaman, Fisher, Chang, & Kidd, 1999)	.20	European	Affects transcriptional efficiency (D'Souza et al., 2004)
-1217 G/del	rs12720364	(Okuyama et al., 2000)	.17	Japanese	-
-1123 C/T	-	(Okuyama et al., 2000)	<.01	Japanese	-
-1106 T/C	rs936460	NCBI dbSNP (Wang et al., 2004)	.26	European	-
-1102 G/A	-	(Mitsuyasu et al., 2007)	<.01	Japanese	-
-930 C/G/T	-	(Mitsuyasu et al., 2007)	<.03	Japanese	-
-906 T/C	rs3758653	NCBI dbSNP (Wang et al., 2004)	.20	European	-
-809 G/A	rs936461	(Mitsuyasu, Ozawa, Takeda, & Fukumaki, 1999)	.45	European	-
-768 G/A	rs4987058	(Mitsuyasu et al., 1999)	<.01	European	-
-713 C/T	rs11246224	(Mitsuyasu et al., 2007)	<.03	Japanese	-
-616 G/C	rs747302	(Mitsuyasu et al., 1999)	.44	European	Possible AP-2 binding site gain (Barr et al., 2001)
-615 A/G	rs936462	NCBI dbSNP	.05	European	-
-603 del/T	rs747303	(Mitsuyasu et al., 1999)	.46	Japanese	-
-600 G/C	rs10902180	(Mitsuyasu et al., 1999)	<.05	Japanese	-
-598 G/T	-	(Mitsuyasu et al., 2007)	<.01	Japanese	-
-597 $(G)_{2-5}$	rs3842250	(Mitsuyasu et al., 2007)	-	Japanese	-
-521 C/T	rs1800955	(Mitsuyasu et al., 1999)	.40	European	Affects transcriptional efficiency (Okuyama et al., 2000)
-376 C/T	rs916455	(Mitsuyasu et al., 1999)	.03	European	-
-364 A/G	rs916456	NCBI dbSNP	<.01	Japanese	-
-291 C/T	rs916457	(Mitsuyasu et al., 1999)	.07	European	-
-234 C/A	-	(Mitsuyasu et al., 2007)	<.01	Japanese	-
-128 G/T	-	(Mitsuyasu et al., 1999)	.03	Japanese	-
-11 C/T	-	(Cichon et al., 1995)	<.01	European	-

Note. MAF = minor allele frequency. (-) refers to missing information, e.g., no rs# available, or a lack of studies

investigating potential functional effects.

6.3.2   Measures

Impulsive Sensation Seeking (ImpSS). Participants completed the 19 item ImpSS, scored true/false (Appendix D) (Zuckerman et al., 1993). Data derived from the ImpSS subscales in this study demonstrated acceptable internal reliability (ImpSS α =.80). If there are significant differences between genotypes and ImpSS, the subscale may be divided into its components (SS and Imp) to investigate whether the association is driven by differences in impulsivity or sensation seeking.

Contextual Sensation Seeking Scale for Skiing (CSSQ-S). Participants completed the 10-item CSSQ-S, anchored on a Likert scale by 1 (strongly disagree) and 5 (strongly agree) (described in Chapter 3 and Appendix F). Data derived from the instrument in the current sample demonstrated high internal consistency (α = .87).

6.3.3   Genotyping

Buccal cell DNA was isolated from cytobrushes (Fisher Scientific, Ottawa, ON, Canada) using an alcohol purification technique (Saftlas et al., 2004) (described in Chapter 2; Appendix L) and diluted to 20 ng DNA/μl. Four polymorphisms (*DRD4* -1106 T/C, -906 T/C, -809 A/G, -291 C/T) were genotyped using the Sequenom iPLEX® technique (San Diego, California, USA) at McGill University and Génome Québec Innovation Centre, Montréal, Quebec, Canada.

The 120-base pair duplication was amplified using primers and PCR reagents described by Seaman et al. (1999) and using the "touchdown" thermal profile described in McCracken et al. (2000). Primers are shown in Appendix O. The PCR cycled in a MJ Mini Cycler (Bio-Rad Laboratories, Hercules, CA, USA) as follows: 95°C for 15 minutes, followed by 10 cycles of 95°C for 30s, 66°C for 30s, and 72°C for 90s, and then 25 cycles of 95°C for 30s, 55°C for 30s,

and 72°C for 90s, finishing with 72°C for 10 minutes. The 25 μL reactions contained 20 mM

Tris-HCl pH 8.4, 50 mM KCl, 1.5 mM MgCl$_2$, 0.2 mM dNTP, 0.2 μM of each primer, 5%

DMSO, 0.5 U *Taq* polymerase (Invitrogen Corporation, Carlsbad, CA, USA), and 10-20 ng

DNA template. PCR products were sized by electrophoresis using an 8% PAGE gel stained

using SYBR Safe DNA gel stain (Invitrogen, California), visualized using BIORAD Gel Doc^{TM}

EZ System and then identified as containing "short" (S; 429 bp) versus "long" fragments (L; 549

bp). Sample gel photographs shown in Appendix V.

6.3.4   **Statistical analyses**

An analysis of variance (ANOVA) was used to analyze main effects of individual

variants (120 bp duplication (LL + LS *vs*. SS), -1106 C/T (TT *vs*. CT *vs*. CC), -906 T/C (TT *vs*.

TC *vs*. CC), -809 G/A (GG *vs*. GA *vs*. AA), -291 C/T (CC *vs*. CT *vs*. TT)) between

polymorphisms and each of the dependent variables (Imp, SS, CSSQ-S). An additive model of

inheritance was applied for all SNPs because no support for an alternative model has been

proposed. The 120-bp tandem duplication was analyzed using both additive and grouped models

based on previous support for grouping carriers of the L allele (Rogers, 2004). The threshold for

significance was set at an alpha of .01 to account for the five variants tested (using a Bonferroni

correction (Attia et al., 2009)), though no correction for testing multiple dependent variables was

applied because they are not independent.

The effects of potential covariates were investigated before carrying out the analyses.

Sensation seeking putatively varies with age and between the sexes (Zuckerman et al., 1993);

therefore, the relationship between age and sensation seeking was measured using Pearson's

correlation, and the effects of sex across sensation-seeking variables were analyzed using an independent sample *t*-test.

6.4   Results

The distributions of the five variants were consistent with Hardy-Weinberg Equilibrium ($p > .05$). The mean marker call rate for SNPs analyzed using the Sequenom iPlex® was $98 \pm 0.33\%$. Genotype frequencies are shown in Table 6-3. Scores derived from the ZKPQ ImpSS and CSSQ-S scales were normally distributed, with no univariate outliers. Sex was entered in the initial analysis as a covariate, because there were significant differences between the sexes in both ski and global sensation seeking (CSSQ-S: $t(576) = 13.70$, $p < .001$; ZKPQ ImpSS: $t(494)$[24] $= 3.20$, $p = .001$). Age was related to both CSSQ-S and ImpSS (CSSQ-S $r(575) = -.24$, $p < .001$; ImpSS $r(597) = -.09$, $p = .04$), but the relationship between ImpSS and age was too weak to be included as a covariate. Finally, ability was significantly correlated with CSSQ-S, $r(570) = .60$, $p < .001$ and was included as a covariate for CSSQ-S analyses only.

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[24] Levene's test of equal variances was violated; therefore a test that does not assume equal variances was used.

Table 6-2

Descriptive statistics for demographic and personality variables

Variable	Descriptive statistics	
Sex	341 males, 258 females	
Education	65% post-secondary or higher	
Ability	24% intermediate, 31% advanced, 41% expert, 4% other	
CSSQ-S[†]	$M = 36.34$	$SD = 7.36$
ImpSS	$M = 12.59$	$SD = 3.87$
Imp	$M = 3.78$	$SD = 2.26$
SS	$M = 8.82$	$SD = 2.18$

Note. M = mean, *SD* = standard deviation. [†]Total participants included in CSSQ-S means differ from sample total (*n* = 578) because skiing/snowboarding ability was less than intermediate or missing.

The initial sample was 599 participants; however, not all were genotyped successfully (the 120-bp duplication was especially problematic) and the final sample sizes for the genetic analysis ranged from *n* = 445 to 578. Univariate analyses comparing ImpSS (with sex as a covariate) between genotypes at each loci revealed no significant associations, the results for the Imp and SS scales when analyzed separately were also not significant (see Appendix W). Similarly, there were no significant associations between domain-specific sensation seeking (with ability, age, and sex as covariates) and any of the polymorphisms tested (see Table 6-3).

Table 6-3

Descriptive statistics and ANOVA results for DRD4 promoter polymorphisms

Marker	dbSNP	Genotype	n	CSSQ-S		n	ImpSS	
				M	*SD*		*M*	*SD*
120-bp repeat	-	LL	296	36.72	7.54	300	12.78	3.84
		LS	126	36.35	7.00	131	12.53	4.00
		SS	14	40.14	4.72	14	13.07	3.65
		LS + SS	140	36.73	6.89	145	12.58	3.96
		F_A, F_G		1.13,	0.37		0.06,	0.11
		$p_A p_G$		.27,	.54		.94,	.75
-1106 T/C	rs936460	TT	272	36.32	7.50	281	12.75	3.72
		TC	244	36.07	7.45	256	12.61	4.06
		CC	61	37.56	6.43	62	11.81	3.73
		F_G		$0.71^†$			1.47	
		P_G		.49			.23	
-906 T/C	rs3758653	TT	393	36.30	7.46	409	12.58	3.94
		TC	163	36.06	7.42	169	12.58	3.63
		CC	21	39.38	4.41	21	12.81	4.63
		F		0.85			0.01	
		P		.43			.99	
-809 G/A	rs936461	GG	225	36.12	7.82	235	12.70	3.90
		GA	274	36.40	7.13	285	12.46	3.79
		AA	74	36.99	6.97	75	12.68	4.18
		F		0.60			0.18	
		P		.55			.84	
-291 C/T	rs916457	CC	507	36.10	7.45	528	12.52	3.91
		CT	51	37.67	6.61	62	13.00	3.63
		TT	5	39.91	6.06	5	13.40	2.51
		F		2.88			0.48	
		P		.06			.62	

Note. *F*-statistics and *p*-values for both additive and grouped models are shown for the 120-bp duplication, all other SNPs were analyzed using additive genetic models. Sex was included as a covariate for ImpSS, and sex, ability, and age were included as covariates for CSSQ-S analyses. F_A = additive model, F_G = grouped model, *M* = mean, *SD* = standard deviation. †Homogeneity of variances was violated; therefore, grouped model was tested.

6.5   Discussion

The goal of this study was to investigate the individual effects between five *DRD4* promoter polymorphisms and two measures of sensation seeking in skiers and snowboarders. There were no significant associations between either the CSSQ-S (the domain-specific sensation-seeking measure) or the ZKPQ ImpSS and any of the *DRD4* promoter variants studied.

The *DRD4* has been implicated in numerous association studies on approach-related personality traits and externalizing disorders (Gizer et al., 2009; M. R. Munafo et al., 2008). The 120-bp tandem duplication is of interest because it contains binding sequences for transcription factors (Seaman et al., 1999) and the long (240-bp) allele has, in some studies, reduced transcriptional activity compared to the short allele (D'Souza et al., 2004). Lower transcription could lead to lower *DRD4* expression, resulting in fewer D4 receptors and ultimately affecting levels of dopamine in the synapse (D'Souza et al., 2004). The long version of the tandem duplication has been associated with attention deficit hyperactivity disorder (ADHD) and schizophrenia, conditions that are sometimes characterized by impulsivity (Lai et al., 2010; McCracken et al., 2000). Associations between the long allele (possibly encoding fewer D4 receptors) are viewed as being congruent with one aetiology of ADHD, namely the "dopamine-deficit theory" (Swanson et al., 2007); however, there are inconsistencies in the data, as some studies have reported associations between the short allele and ADHD and/or high impulsivity scores (Kereszturi et al., 2007; Rogers et al., 2004). Additionally, two recent meta-analyses reported no associations with the 120-bp tandem duplication (Gizer et al., 2009; Sanchez-Mora et al., 2011) and ADHD. In the current study, there were no significant differences in self-reported impulsive sensation seeking (nor for impulsivity and sensation seeking measured separately) between the 120-bp duplication alleles.

There are few studies that include the four other promoter SNPs analyzed in the current study (-291 C/T, -809 G/A, -906 T/C, and -1106 T/C), and there are no reports in the literature demonstrating differential functionality for the alleles at these loci. The four SNPs have been investigated in association with schizophrenia in two Japanese populations (Mitsuyasu et al., 2007; Nakajima et al., 2007), in Caucasian family-based association tests for ADHD (Lasky-Su et al., 2007; Oades et al., 2008) (one of which only looked at two of the four SNPs, -906 C/T and -291 C/T), and in association with novelty and sensation seeking (both only looking at the -906 C/T) (Derringer et al., 2010; Heck et al., 2009), but none of the studies reported significant associations between *DRD4* promoter alleles and any of the phenotypes. Similarly, there were no significant main effects for any of the promoter SNPs analyzed in this study. Nakajima et al. (2007) examined interactions between *DRD4* promoter variants, and reported that a combination of four polymorphisms (-809 G/A, -291 C/T, -616 G/C, and 12-bp repeat) conferred a susceptibility to schizophrenia and they found a trend for overrepresentation of a haplotype that included -906 C and -1106 C in the cases. Oades and colleagues (2008) reported a trend for over-transmission of the -906 C allele in ADHD cases exhibiting behavioural impulsivity, but it was not significant after correction. Overall, there are no consistent results linking any of these polymorphisms to approach-related traits or externalizing disorders.

The study described in the current chapter had sufficient power to test for multiple variants, but the sample size was too small to adequately observe the effects of the rare genotypes. Oddly, the CSSQ-S scores for each "rare" genotype group tended to be higher and it would be interesting to see whether these trends held in larger samples. The goal of the study presented in this chapter was to assay all of the polymorphisms in the promoter region with high heterozygosity, but two (-521 C/T rs1800955 and 616 C/G rs747302) failed optimization both at

the genotyping facility and in the Rupert laboratory. Additionally, two deletion polymorphisms, -603 del/T and -1217 G/del (described by Mitsuyasu et al., 2007) were not included in the analysis because the multiplex genotyping technique used in this study was limited to transition and transversion polymorphisms. As the alleles at -603 del/T and -1217 G/del are in moderate-to-strong linkage disequilibrium with alleles at -1106 C/T (Mitsuyasu et al., 2007), which was assayed, an association would likely have been detected if the -603 del/T or -1217 G/del genotype contributed to the phenotype. While this sample is sufficient for assessing effects of highly heterogenic polymorphisms, it would be worthwhile to investigate the effects between *all* common polymorphisms in the 1.2 KB region of the *DRD4* promoter; however, a much larger sample would be necessary to obtain sufficient power to observe rare genotypes.

A homogeneous cohort of experienced athletes participated in this study, in whom both general and domain-specific sensation seeking could be measured. The sample was limited to include only experienced skiers and snowboarders (turning away beginners) to ensure that respondents had sufficient ability to carry out the sport behaviours described in the CSSQ-S. While there are benefits to sampling from a homogeneous population (e.g., reducing extraneous variability), the results have limited generalizability.

In summary, five common polymorphisms in the *DRD4* promoter were tested for associations with sensation seeking in a sample of skiers and snowboarders. There were no significant associations between genotypes at these loci and sensation-seeking measures. These findings are for the most part in line with previous studies, which reported no associations between approach-related traits and other *DRD4* promoter variants (excluding the -521 C/T).

Chapter 7: Interaction between allelic variants in the dopamine-4-receptor gene is associated with patterns of downhill sport behaviour

7.1 Summary

The objective of this chapter was to investigate main effects or interactions of two variants (-521C/T and the 48-bp VNTR) in the *DRD4* in association with global and domain-specific sensation seeking. Global (ZKPQ ImpSS) and domain-specific sensation seeking (CSSQ) was measured in downhill-sport participants ($n = 155$, after exclusions; independent from Chapter 4 sample) and scores were compared between genotypes at two variants in *DRD4*: a 48-bp repeated segment encoding a region in the third cytoplasmic loop and a polymorphism in the promoter region (-521 C/T). There was a significant interaction between the two variants and sport-specific sensation seeking using both an additive ($p = .001$) and a dominant model ($p = .001$) for -521 C/T, but there were no significant associations with the global trait measure ($p > .7$). These results support previous studies that found associations between patterns of ski-behaviour and the -521 C/T variant, and between novelty seeking and alleles at both loci.

7.2 Introduction

High-risk downhill sports like skiing and mountain biking are popular and, despite evidence for elevated rates of severe injury (Dodwell et al., 2010), have seen increases in participation rates (Puchan, 2004). Studies have shown that high-risk sports attract individuals who exhibit "thrill-seeking" tendencies and the personality trait sensation seeking has commonly been associated with high-risk sport participation (Goma-i-Freixanet et al., 2012), as well as with more "deviant" activities such as gambling, drinking, and drug use (M.T. Bardo et al., 2007;

Carlson et al., 2010). While environmental factors likely influence participation in mountain sports and/or other high-risk activities, twin-studies have shown sensation seeking to be moderately heritable (Stoel et al., 2006), suggesting that genotype may underlie some of the motivation for participation in such activities.

Sensation seeking falls under the broader class of approach traits (e.g., extraversion and novelty seeking), which reflect a sensitivity to reward and strong behavioural activation systems (C. S. Carver & White, 1994). Most studies of approach traits have investigated variants in dopaminergic genes due to the purported role of dopamine in behavioural activation and instrumental learning (Lauzon & Laviolette, 2010; Salamone et al., 2007). The dopamine-4-receptor gene (*DRD4*) is of particular interest in studies of approach traits as, unlike the four other common dopamine receptor sub-types, *DRD4* expression is highly concentrated in areas of the brain thought to be involved in emotional regulation, attention, and motivation (i.e., pre-frontal cortex, amygdala, and other regions of the limbic system) (Lauzon & Laviolette, 2010).

DRD4 is a highly polymorphic gene, and two commonly studied variants are a single nucleotide polymorphism (SNP) -521 C/T (a cytosine to thymine transition at base -521 in the upstream promoter region; dbSNP rs1800955) and a 48 base-pair variable number tandem repeat (VNTR) in exon III. The 48-bp VNTR alleles vary between 2 and 11 repeats (often grouped by the presence or absence of the "long" (6 or more repeats) and differences between *DRD4* alleles in their ability to inhibit cyclic AMP following dopamine stimulation have been observed (Asghari et al., 1995). Although the exon III VNTR is more commonly studied, a meta-analysis reported a larger effect size for the association between -521 C/T and "approach traits" (M. R. Munafo et al., 2008). The SNP could have an impact on function, since the -521 C allele is associated with a 40% increase in *DRD4* transcription in cultured cells (Okuyama et al., 2000).

Numerous studies have reported individual associations between either the -521 C or the "long" VNTR and sensation/novelty seeking, impulsivity, and externalizing disorders; however, few have considered intragenic effects (in which the phenotype is influenced by a combination of alleles at both loci).

The purpose of this study was to extend on the findings from Chapter 4 and to investigate interactions or main effects of alleles at the -521 C/T and the 48-bp VNTR in association with global (ZKPQ ImpSS) and domain-specific (CSSQ) sensation seeking in an independent sample of athletes. The CC genotype has been previously associated with sensation seeking in skiing (Chapter 4) and the VNTR long allele is more commonly associated with approach (M. R. Munafo et al., 2008); therefore, individuals carrying the CC genotype were expected to score higher on sensation-seeking measures but that the effect may vary depending on the VNTR genotype.

7.3 Methods

7.3.1 Participants

Individuals between 17 and 59 years of age (n =191: 139 male, 52 female; mean age = 27.25 years (SD = 8.71)) from the high- and low-risk sport cohorts (described in Chapter 2) who reported participation in a downhill sport (e.g., skiing, snowboarding, or mountain biking) at an intermediate or better ability participated in the study. Participants were recruited from Vancouver, British Columbia and Bordeaux and Chamonix, France. To minimize confounding effects of differing biogeographical backgrounds on allele frequencies, only participants self-reporting being of "European descent" (minimum third generation European) were included in

the genetic analysis. After providing informed consent, participants completed questionnaires (49% in French, 51% in English) and provided a buccal (cheek) cell sample for DNA analysis.

7.3.2   **Measures**

Demographic information. Athletes completed a brief demographic assessment that included questions about age, ethnicity, ancestry, language proficiency, and education. In addition, they provided information on sport, frequency, and ability (scored 0 = beginner, 1 = novice, 2 = intermediate, 3 = advanced or expert). Participants scoring ability < 2 were excluded from the analysis. Ability was converted to a dichotomous variable (intermediate *vs.* advanced/expert), because an ordinal variable with three levels led to a non-fitting model. As a proxy for psychiatric screening, participants completed a self-report section on history of prescribed medication (including type, reason for, and duration of use) that included a list of anxiolytics, anti-depressants, and neuroleptics (using common English and French names, Appendix X). Participants reporting current or past use of a medication for treatment of a psychiatric illness were excluded from the analysis.

CSSQ. Sensation seeking in the context of downhill sports was assessed using the Contextual Sensation Seeking Scale (CSSQ, Appendix Y), a generalized version of the ski-specific CSSQ-S described in Chapter 3 that was adapted to be compatible for skiing *and* biking[25]. The CSSQ comprises 10 items, anchored on a Likert scale by 1 (strongly disagree) and 5 (strongly agree). Exemplar items include "I like to ski/ride fast" and "I like to push my

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[25] The CSSQ adaptation involved minor word additions, such as adding "drops" where formerly the CSSQ-S included on the word "jump". E.g., CSSQ item 5: "I like to attempt jumps/drops even if I'm not sure of the quality of the landing area".

boundaries when I play my sport." Using back-translation from English to French, and back to English until the translation agreed, a French version of the CSSQ was created (Appendix Z). Scores derived from the CSSQ demonstrated high internal consistency (Cronbach alpha French = .85, English = .90).

ZKPQ ImpSS. Global sensation seeking was assessed using English (Zuckerman et al., 1993) and French (Rossier, Verardi, Massoudi, & Aluja, 2008) versions of the Zuckerman Kuhlman Impulsive Sensation Seeking scale (ZKPQ ImpSS). The scores derived from the ImpSS scales demonstrated acceptable internal reliabilities (Cronbach alphas: French = .71, English = .87).

7.3.3 Genotyping

Buccal cells were obtained from inside of the participant's cheek with a cytobrush (Fisher Scientific, Ottawa, Canada). DNA was isolated from the recovered cells using an alcohol purification technique (Saftlas et al., 2004) (described in Chapter 2) and genotyped for the -521 C/T[26] polymorphism at the McGill University Genome Québec Innovation Centre, Montréal, Canada using the Sequenom (San Diego, U.S.A.) iPLEX® technique (marker-call rate = 97.4%); and the exon III 48-bp VNTR was genotyped in the Robinson laboratory at Children's and Women's Hospital in Vancouver as described below.

The VNTR was genotyped using a protocol created by Smolen et al. (2002). Primers used were D4-VNTR-F: 5'-AGG ACC CTC ATG GCC TTG-3' (with a 5' HEX fluorescent label) and D4-VNTR-R: 5'-GCG ACT ACG TGG TCT ACT CG-3' (NAPS IDT, Vancouver,

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[26] The -521 C/T SNP failed amplification at the genotyping facility when the Festival samples were sent (Chapter 5), but for unknown reasons successfully amplified for the high- and low-risk samples.

BC, Canada). DNA was amplified in a MJ Mini Cycler (Bio-Rad Laboratories, Hercules, CA,

USA) using touchdown cycling as follows: 95°C for 10 minutes, followed by 2 cycles of 94°C

for 30s, 65°C for 30s, and 72°C for 60s. After 2 cycles the annealing temperature would drop

2°C and the cycle would repeat twice, and this continued until the annealing temperature reached

57°C. This was followed by 30 cycles of 94°C for 30s, 55°C for 30s, and 72°C for 60s, finishing

with 30 minutes held at 72°C. The 25 μL reactions contained 20 mM Tris-HCl pH 8.4, 50 mM

KCl, 2.0 mM MgCl2, 200 μM of each dNTP (+ 7-deaza-2-deoxy GTP; Roche Applied Science,

Indianapolis, IN, USA), 245 μM of each primer, 10% DMSO, 1.0 U Taq polymerase (Invitrogen

Corporation, Carlsbad, CA, USA), and 10-20 ng DNA template. PCR products (2 μL) were

mixed with 20 μL of Hi-Di formamide and 0.5 μL of Genescan 2500 Rox and then were

visualized on an ABI Prism 3100 Genetic Analyzer (Life Technologies, Carlsbad, USA).

Amplicons varied in length between 379-bp (2-repeats) and 667-bp (8-repeats). Approximately

40 additional genotypes were identified using gel electrophoresis. PCR products were

electrophoresed on an 8% PAGE gel stained using SYBR Safe DNA gel stain (Invitrogen,

California), visualized using BIORAD Gel Doc^{TM} EZ System and then identified as containing 2

to 8 repeats. Each gel was run with a reference sample already genotyped using the ABI Prism.

Sample gel photographs shown in Appendix AA.

7.3.4   **Statistical analysis**

Sensation seeking scores (CSSQ and ImpSS) between genotype groups were compared

using a mixed model with two fixed effects corresponding to the two variants (VNTR and -521

C/T) as categorical factors with ability, sex, and age as covariates. Random effects were

estimated for the model intercept with participants nested within their recruitment location

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(France or Canada) in order to account for non-independence of sampling. Both a 2 x 3 and a 2 x 2 design were tested, each employing two factor levels for the 48-bp VNTR and three and two factor levels for the -521 C/T SNP, respectively. The 48-bp VNTR factor levels include alleles grouped by length: the S (short) allele (2 to 5 repeats) is more common than the L (long) allele (6 to 11 repeats, commonly referred to as 7R allele and second most common to the 4R allele) and as different binding profiles between the SS and SL genotypes have been reported (Asghari et al., 1994) genotype groups were collapsed based on the presence of the long allele (SS *vs.* SL + LL). The -521 C/T alleles are both common (i.e., minor allele > 40%) in European populations (Rajeevan, Soundararajan, Kidd, Pakstis, & Kidd, 2012), therefore both an additive (three factor levels: CC *vs.* CT *vs.* TT) and a grouped model in which homozygotes for the minor allele were grouped with heterozygotes (two factor levels: CC + CT *vs.* TT) were tested based on a previous *DRD4* studies (Bellgrove et al., 2005; H. J. Lee et al., 2003; Nemoda et al., 2010). As CSSQ scores differ between males and females and are significantly correlated with ability and age (e.g., Chapter 6); relationships between these potential covariates and the CSSQ and ImpSS were tested.

7.4   Results

After excluding participants for non-European ancestry (8), use of medications related to a psychiatric illness (9) or for failure to genotype at both loci (19), 155 participants remained in the analysis (47 recruited from Canada, 108 from France). Scores derived from the CSSQ were significantly correlated with age ($r(155) = -.20$, $p < .05$), and there were significant differences between the sexes ($t(153) = 5.15$, $p < .001$) and abilities ($t(153) = 6.3$, $p < .001$), but no differences in sex, ability, or age were present across factor (genotype) levels ($p > .3$; shown in

Table 7-1); therefore, these variables were included as covariates. No significant trends were observed between the ZKPQ ImpSS measures and demographic variables ($p > .3$).

The distributions of genotypes at each locus did not differ by country (VNTR: $\chi^2(2)= 1.5$, $p = .5$; -521 C/T: $\chi^2(2)= 3.5$, $p = .2$) and satisfied Hardy-Weinberg Equilibrium when assessed independently (all $p > .3$) and in combination ($p > .6$), suggesting that the alleles were segregating independently (genotype frequencies are shown in Table 7-2). The longest allele observed for the VNTR was 8 repeats.

Table 7-1

Comparison of demographic variables between factor levels

Genotype	Sex, *n*		Ability, *n*		Age, *M (SD)*
	Male	Female	Int	Adv + Exp	
VNTR					
SS	65	24	26	63	27.20 (7.95)
SL	43	15	12	46	27.04 (8.59)
LL	7	1	2	6	26.43 (9.18)
SL + LL	50	16	14	52	
Statistical test	$\chi^2(1) = 0.15$		$\chi^2(1) = 1.27$		$F(2, 118) = 0.03$
p-value	.70		.26		.97
-521 C/T					
CC	22	8	9	21	28.65 (8.56)
CT	57	17	18	56	26.54 (8.46)
TT	36	15	13	38	27.10 (7.50)
Statistical test	$\chi^2(2) = 0.67$		$\chi^2(2) = 0.36$		$F(2, 152) = 0.55$
p-value	.72		.84		.58

Note. *Chi* square tests were used to compare counts between groups and analysis of variance was used to compare age between groups. Due to small cell sizes for LL genotype, 2 x 2 contingency tables were used comparing counts for SS and SL + LL for sex and ability. *n* = counts per genotype group, *M* = mean, *SD* = standard deviation, Int = intermediate, Adv = advanced, Exp = expert, VNTR = variable number of tandem repeats, S = short allele, L = long allele.

Table 7-2

Tests of Hardy-Weinberg Equilibrium (HWE) and genotype frequencies for each subsample

Genotype	France ($n = 108$)	Canada ($n = 47$)	Combined ($n = 155$)
VNTR			
SS	60	29	89
SL	41	17	58
LL	7	1	8
HWE	$\chi^2(2) = 0, p = 1.0$	$\chi^2(2) = 0.69, p = .41$	$\chi^2(2) = 0.13, p = .71$
521 C/T			
CC	17	13	30
CT	52	22	74
TT	39	12	51
HWE	$\chi^2(2) = 0, p = .96$	$\chi^2(2) = 0.19, p = .66$	$\chi^2(2) = 0.12, p = .73$

Note. VNTR = variable number of tandem repeats, S = short allele, L = long allele.

A mixed model analysis of CSSQ scores and genotypes at -521 C/T and exon III VNTR, when adjusted for age, sex, and ability, revealed a significant interaction between the genotype groups using either an additive model for -521 C/T ($F(2, 153) = 6.98, p = .001$) or a dominant model ($F(2, 152) = 10.52$ $p = .001$). Both results remain significant after correcting for testing two variants and an interaction for two dependent variables, tested using two models of inheritance (e.g., corrected alpha = $\alpha/12 = .004$). Least significant difference comparisons of simple effects based on model-estimated marginal means revealed that in the grouped -521 C/T model, individuals carrying at least one long VNTR allele had higher CSSQ scores if they also carried a -521 C allele (CT or CC) ($p = .004$) compared to those homozygous for the -521 T allele (shown in Figure 7-1 using marginal mean scores). Under the additive model, CSSQ scores for individuals carrying the CC genotype did not vary across levels of the VNTR (SS or SL + LL), but -521 C/T heterozygotes scored higher on CSSQ if they carried a long VNTR allele ($p = .035$) and conversely, TT homozygotes scored significantly lower if they carried a long VNTR allele ($p = .003$), Figure 7-2. No significant main effects or interactions between the loci

and ImpSS were observed (additive model: VNTR: ImpSS $F = 0.17$, $p = .68$; -521 C/T: ImpSS $F = 0.32$, $p = .72$; interaction: ImpSS $F = 0.09$, $p = .92$).
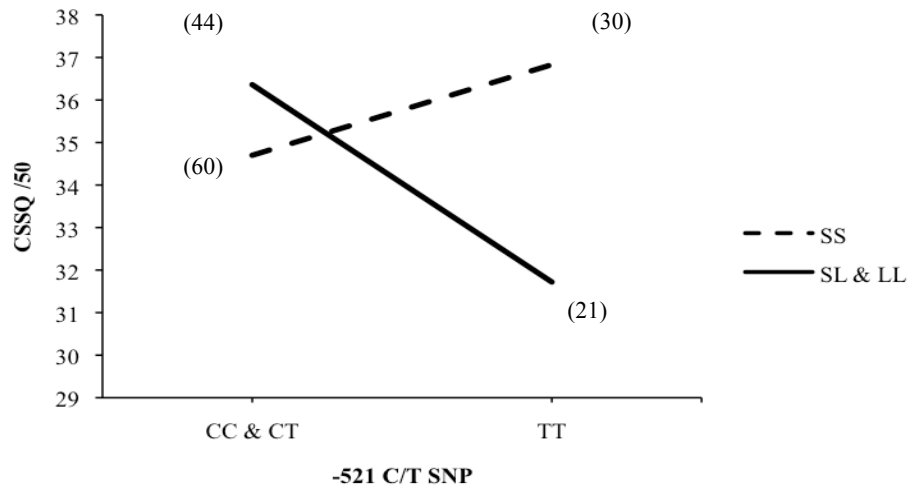
Figure 7-1. CSSQ scores grouped by genotypes for the 48-bp VNTR (SS *vs.* SL & LL) and the -521 C/T (CC & CT *vs.* TT).

Cell sizes for each group are shown (*n*). CSSQ = contextual questionnaire for sensation seeking, VNTR = variable number of tandem repeats, SNP = single nucleotide polymorphism, S = short allele, L = long allele.
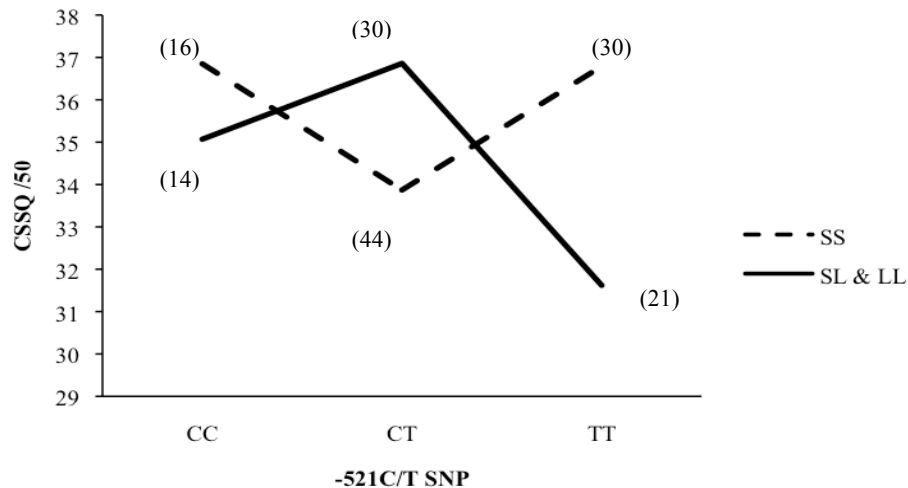
Figure 7-2. CSSQ scores grouped by genotypes for the 48-bp VNTR (SS *vs.* LL & LS) and the -521 C/T (CC *vs.* CT *vs.* TT).

Cell sizes for each group are shown (*n*). CSSQ, contextual questionnaire for sensation seeking; VNTR, variable number of tandem repeats; SNP, single nucleotide polymorphism; S, short allele; L, long allele.

CSSQ scores for -521 C/T genotype groups are shown below in Table 7-3 to show that the results are in the same directions as the findings from Chapter 4. There was a trend for individuals with the C allele scoring the higher on contextual sensation seeking. Scores for the 48-bp VNTR genotype groups are also shown, to see if the trend is in keeping with the literature (carriers of the L-allele scoring higher on approach); however, since a significant interaction between the factors was present, the main effects are not reported.

Table 7-3

CSSQ scores by genotype for the -521 C/T and 48-bp VNTR polymorphisms

Variant	Genotype	*n*	CSSQ, *M (SD)*
-521 C/T			
	CC	30	35.60 (6.30)
	CT	74	35.83 (8.50)
	TT	51	34.89 (7.28)
VNTR			
	LL	8	37.74 (7.71)
	LS	58	35.72 (7.93)
	SS	89	35.13 (7.58)

Note. CSSQ = contextual sensation seeking questionnaire, *M* = mean, *SD* = standard deviation, VNTR = variable number of tandem repeats, S = short allele, L = long allele.

7.5   Discussion

A significant interaction between two *DRD4* variants was associated with contextual sensation seeking; athletes carrying both "risk" alleles (-521 C and long VNTR) reported higher scores on the CSSQ (sport-specific questionnaire). Contrary to previous findings (Okuyama et al., 2000; Roussos, Giakoumaki, & Bitsios, 2009); however, there were no main effects on sensation-seeking scores for either variant, although trends for high contextual sensation seeking scores in carriers of the risk alleles were observed.

Inconsistent results have been reported for both *DRD4* variants in personality studies on healthy populations (M. R. Munafo et al., 2008). Though alleles at multiple loci in the *DRD4* have hypothesized functions (Asghari et al., 1995; Okuyama et al., 2000), few studies have investigated interactions between variants in the gene. Consistent with a study finding an interaction between the *DRD4* VNTR and -521 C/T was associated with novelty seeking; data presented in this chapter reveal that the combination of a long VNTR allele and a -521 C allele was associated with higher scores on approach (H. J. Lee et al., 2003). An interaction between alleles at the VNTR and -521 C/T was also observed in association with infant's attachment

disorganization (Lakatos et al., 2002), a phenotype that has been associated with childhood behavioural problems (Fearon, Bakermans-Kranenburg, van Ijzendoorn, Lapsley, & Roisman, 2010), and synergistic genetic interactions between other *DRD4* variants and externalizing disorders have been observed (Nakajima et al., 2007). A study that examined a -521 C/T-VNTR "genotype combination"[27] revealed that children carrying a long VNTR and a -521 T allele showed decreased event-related potential indicative of brain activity associated with reflexive attention shifting and orienting reflexes (Birkas et al., 2006), both of which are behavioural correlates of sensation seeking (Zuckerman, 2007a). Though not directly comparable, carriers of both a long VNTR and -521 T allele reported the lowest sensation-seeking scores in the current chapter.

Independently, both the -521 C and the VNTR long alleles have been associated with novelty seeking (Ebstein et al., 1996; Okuyama et al., 2000; Ronai et al., 2001), extraversion (Bookman et al., 2002; Golimbet et al., 2007), impulsivity (Congdon, Lesch, & Canli, 2008), financial risk taking (Dreber et al., 2009; Dreber et al., 2011), and sexual risk taking (Garcia et al., 2010); and while there are numerous null findings (Ekelund et al., 2001; Jonsson et al., 2002; M. R. Munafo et al., 2008), few studies report associations with the opposite alleles (e.g., the -521 T and VNTR short associated with risk-taking or approach). More recently, the *DRD4* 7R was associated with risk taking (Roussos et al., 2009) and slower response times (Szekely et al., 2011) in laboratory tasks, and while the latter study investigated other SNPs (including the -521 C/T), they did not explore interactions between variants. Interestingly, the current study reveals high CSSQ scores in carriers with one of each "risk" allele.

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[27] Birkas et al (2006) refer to the 7R-T genotype combination as a "haplotype"; however, the term haplotype implies the presence of linkage disequilibrium and studies on other European (Canadian) populations report no linkage between the -521 C/T and exon III VNTR loci (Barr et al., 2001).

The current study revealed an allelic interaction in association with domain-specific sensation seeking (CSSQ), but not with the ZKPQ ImpSS. Similarly, in the independent study described in Chapter 4, the -521 CC genotype was associated with high CSSQ scores in skiing and snowboarding, but there was no association with the broader trait measure. The sample used in the current study was smaller than the full sample used in Chapter 4 ($n = 503$); but was comparable to the Chapter 4 pilot sample ($n = 117$). The lack of significant findings in the current study could be due to low statistical power, or perhaps -521 C homozygotes in the Pilot sample in Chapter 4 were enriched with the VNTR long allele, but this is purely speculative. The loci are not in linkage disequilibrium (Barr et al., 2001) and the alleles should therefore segregate independently and combinations of alleles will vary from sample to sample. Perhaps many null findings associated with *DRD4* variants are because researchers failed to consider genotypes at both loci, and the combination of genotypes at the -521 C/T and exon III VNTR may be important.

As the popularity of downhill and adventure sports continue to increase, recreation sites create interesting natural settings for observing sensation-seeking behaviours in the field which may be used to measure correlates between self-report measures (i.e., the CSSQ) and physiological (e.g., cortisol, dopaminergic transmission, etc.) or genetic variables. An analysis of two variants in the *DRD4* revealed an interaction between the exon III VNTR and the -521 C/T was associated with patterns of sensation-seeking behaviours in downhill sports. Both variants have previously been associated with approach traits, and though there were no main effects for either variant, the results are in the same direction as previous findings. A few limitations should be noted: all of the participants reported being of European descent and; therefore, the results may not generalize to other populations, and larger samples are preferable

for genetic association studies. The *DRD4* is a highly polymorphic gene that contains a number of putatively functional variants. Future studies should consider both main and interaction effects of *DRD4* genotypes on the expression of phenotypes. Such studies will require large samples in order to obtain a sufficient number of individuals who are homozygous for both minor alleles.

Chapter 8: Exploratory analysis of personality and genetic variables in high- and low-risk sport participants

8.1 Summary

Athletes participating in high-risk sports consistently report higher scores on sensation-seeking measures than low-risk athletes or non-athletic controls, and may be an interesting group in which to study genetic variants commonly associated with sensation seeking. Personality traits (impulsivity and sensation seeking) and genetic variants (29 polymorphisms in 14 candidate genes) were compared between proficient athletes participating in high-risk sports ($n = 141$) and low-risk sports ($n = 132$). Sport cohorts differed on a number of demographic variables; therefore, whenever possible, matched subsamples were used to compare personality traits and were used for follow-up genetic analyses. Athletes participating in high-risk sports score higher than low-risk sport athletes on sensation seeking ($p < .05$), but not impulsivity. There were marginal associations between sport group and variants in two genes: stathmin ($p = .004$) and brain-derived neurotrophic factor ($p = .03$), trends that were also present when subsets of the sport cohorts were compared ($p < .05$), but the associations did not survive correction for multiple testing. This chapter also provides descriptive data on disinhibited behaviours (e.g., smoking, alcohol, substance use) in the two cohorts, and compares personality traits between athletes engaged only in prosocial sensation seeking (through sport) and other athletes engaged in both deviant (drug use) and prosocial outlets for sensation seeking.

8.2 Introduction

Participation rates in high-risk sports have been increasing over the last 30 years (Celsi et al., 1993). Certain sports, like skiing long ago attained mainstream popularity, but what were

once "fringe" sports, like snowboarding, rock climbing, kayaking, surfing, and mountain biking are becoming more common. The Outdoor Foundation (USA) (2010) studied participation rates for a multitude of outdoor activities in over 400,000 people and provided an estimate for growth within sports based on the percentage of first-time participants. In 2009, of the Americans reporting rock climbing, the percentage of first-time climbers was 43%. Similarly high growth was seen for a few other high-risk activities including whitewater kayaking (26.5%) and adventure racing (24%). It seems there has been a shift in leisure sport participation, and perhaps people are realizing that these high-risk sports satisfy a need for novelty that many people share.

High-risk sport participants often report a need for stimulation, as measured by sensation-seeking scales, and they consistently score higher than non-risky athletes or controls (Goma-i-Freixanet et al., 2012). Numerous studies have compared personality traits between participants from high- and low-risk sports, but only one study has compared genetic variations between these two groups. Cam and colleagues (2010) grouped athletes recruited from a Turkish university by participation in high- or low-risk sports and compared the frequencies of three variants commonly studied in association with approach-related traits: the *DRD4* VNTR, *HTR2A* 102 C/T, and the 3' UTR VNTR in *DAT1*. They did not observe any differences in allele frequencies between the sports groups, but when they examined continuous personality traits in the combined sample, there were trends between *HTR2A* genotype and a number of "Big Five" dimensions. The study has several weaknesses: they do not provide details about the ability or frequency of participation in high-risk sports, nor do they provide any details about the demographic characteristics of the two sport groups (e.g., age, sex, ethnicity, etc.). Furthermore, it is unclear whether members of the "risk" group were *regular*, *proficient* participants in high-risk leisure activities or whether or not other differences existed between the two groups that

may have contributed to the null findings in the between-groups comparison. Athletes who participate in high-risk sports are rarely studied, whereas there are numerous studies that compare genotype frequencies between high- and low-risk groups defined by substance use disorder, alcoholism, externalizing disorders, and also extreme scorers on novelty- and sensation-seeking subscales (Ekelund et al., 2001; M. R. Munafo et al., 2008; Nernoda et al., 2011).

There are number of genes that are candidates for association with participation in high-risk sports. Athletes engaged in high-risk sport not only report high levels of sensation seeking, but they report low levels of avoidance and neuroticism (Castanier et al., 2010b; I. H. Franken et al., 2006; Goma-I-Freixanet, 1991; Schaal et al., 2011; Tok, 2011) and may experience less fear associated with common triggers (e.g., heights) (Zuckerman, 2007c). Genes involved in dopaminergic neurotransmission are of particular interest due to dopamine's purported role in reward seeking and approach motivation (Depue & Collins, 1999; Pecina et al., 2003; Zuckerman, 2005a). Genes involved in serotonergic neurotransmission are also potential candidates because serotonergic genes have been associated with harm avoidance, and weak "avoidance" systems in combination with strong "approach" systems are thought to underlie the sensation-seeking trait (Zuckerman, 2007a). In addition, serotonin genes have been implicated in risk taking behaviour in animals (Fairbanks et al., 2001; Long et al., 2009). Dopamine and serotonin systems are thought to interact (Depue & Collins, 1999) supporting the inclusion of genes from both systems in an investigation of risk-taking through sport. A number of researchers suggest that high-risk sport participation is an expression of sensation seeking that is similar to taking drugs, drinking, or engaging in risky sex (M. T. Bardo, Donohew, & Harrington, 1996; Celsi et al., 1993; I. H. Franken et al., 2006), and therefore genetic variants associated with these behavioural expressions might also be associated with high-risk sport.

To investigate the possibility that variants in genes that are involved in dopaminergic and serotonergic neurotransmission might be associated with high-risk sport participation, variants in candidate genes were compared between cohorts of proficient high- and low-risk sport participants. Biallelic polymorphic loci at which both alleles were moderately common (heterozygosity > .2) were chosen in genes that encode proteins involved in transport (dopamine and serotonin transporters: *DAT1, SLC6A4)*, function (dopamine and serotonin receptors: *DRD1, DRD2, DRD3, HTR1A, HTR2A*), metabolic inactivation (catechol-*O*-methyltransferase, (*COMT*), monoamine oxidase A (*MAO-A*), dopamine-*β*-hydroxylase (*DBH*)) or precursors (tyrosine hydroxylase (*TH*)). Some of the same variants were tested for associations with sensation seeking in a cohort of skiers (see Chapter 5), but the choice of SNPs for the study described in the current chapter was based on the following criteria: 1) variants for which significant associations with global or contextual sensation seeking were found in Chapter 5 (i.e., rs167771), 2) any variants that have consistently been associated with approach-related traits and behaviours in the literature, 3) loci at which alleles have shown functional differences in the literature (i.e. affect structure or function of molecules encoded by the genes), and 4) additional candidate genes (that are not a part of dopamine and serotonin pathways) chosen based on genetic associations with fear-related phenotypes (stathmin, STMN1; Brocke et al., 2010; Shumyatsky et al., 2005) and sensation seeking (brain-derived neurotrophic factors, BDNF; Kang et al., 2010). Details about individual candidate genes are found in Chapter 1, and reasons for choosing SNPs are outlined in Table 8-1. The data presented in this chapter only include SNPs that were genotyped at Genome Québec (a genotyping facility based at McGill University). Two additional polymorphisms were analyzed in the high- and low-risk samples; however, analyses of one variant (the *DRD4* exon III VNTR) are included in a separate chapter (Chapter 7) because

analyses were carried out only in high- and low-risk athletes that had completed the CSSQ (downhill sport questionnaire). The *DRD4* VNTR and -521 C/T (rs1800955) were analyzed separately using a continuous trait design due to observed relationships between patterns of ski behaviour and -521 C/T in Chapter 4. Another copy number variant, the *DRD4* 120-bp tandem duplication (described and analyzed in skiers in Chapter 6), was successfully genotyped in only a portion of the high- and low-risk sport cohorts and analyses are shown in Appendix BB.

In addition to comparing genetic variants, sensation seeking, impulsivity, and disinhibited behaviours were compared between sport groups. There is strong support for a link between substance use and sensation seeking (M.T. Bardo et al., 2007); therefore, it was important to consider the chance that participants in high-risk sports, who presumably score high on sensation-seeking measures (Goma-i-Freixanet et al., 2012), may also be more likely to experiment with drugs. A number of the candidate genes chosen for this study have previously been implicated in substance use disorders; therefore, to avoid confounding results it was important to exclude problematic substance users. The presence of ADHD symptoms may be another potentially confounding variable. ADHD has been suggested to be an extreme manifestation of sensation seeking (Brocke et al., 1999), and ADHD, like sensation seeking, is putatively related to dopaminergic neurotransmission (Swanson et al., 2007; Turic et al., 2010). A symptom checklist was included to screen for possible ADHD cases since a number of the genes proposed as candidates for sensation seeking in the current chapter have been implicated in ADHD (Gizer et al., 2009).

Table 8-1

List of SNPS chosen for analysis

	Gene	Full Name	Protein Function	Marker	Ch. 5[†]	Functional support	Reason to include SNP
1	*BDNF*	Brain-derived neurotrophic factor	Nerve growth factor involved in neural plasticity	rs6265	-	missense SNP	GWAS with approach traits
2	*COMT*	Catechol-*O*-methyl transferase	Metabolizes DA	rs4633	Yes, ns	(Hirata et al., 2008)	Functional
3	*COMT*			rs4680	Yes, ns	(Chen et al., 2004; Lotta et al., 1995)	Functional
4	*COMT*			rs4818[a]	-		Association with approach
5	*COMT*			rs6269	-	-	Association with approach
6	*DAT1*	Dopamine transporter	Reuptake of DA from the synapse	rs2652511	-	-	Association with approach
7	*DAT1*			rs27072[a]	Yes, ns	(Pinsonneault et al., 2011)	Functional
8	*DAT1*			rs2975226[a]	Failed	-	Association with approach
9	*DAT1*			rs6347	Yes, ns	(Pinsonneault et al., 2011)	Functional
10	*DBH*	Dopamine-β-hydroxylase	Converts DA to norepinephrine	rs1611122	-	(Cubells et al., 2011)	Contributed to linkage signal in externalizing disorders
11	*DBH*			rs161115	Yes, ns	(Zabetian et al., 2001)	Functional
12	*DBH*			rs6271	-	(Zabetian et al., 2001)	Functional
13	*DRD1*	Dopamine receptor D1	Involved in dopaminergic neurotransmission	rs265981	-	-	Association with approach
14	*DRD1*		Metabolizes DA, NE, 5HT	rs4532	Yes, ns	(Ota et al., 2012)	Association with approach, pharmaco-genetic marker for antipsychotic drugs
15	*DRD1*			rs686	Yes, ns	(W. H. Huang & Li, 2009; W. H. Huang et al., 2008)	Functional
16	*DRD2*	Dopamine receptor D2	Involved in dopaminergic neurotransmission	rs1076560	Yes, ns	(Y. Zhang et al., 2007)	Functional
17	*DRD2*			rs1800497	Yes, ns	(Noble et al., 1991) (Jonsson et al., 1999)	Functional
18	*DRD2*			rs2283265	Yes, ns	(Y. Zhang et al., 2007)	Functional
19	*DRD2*			rs6277	Yes, ns	(Duan et al., 2003)	Functional

	Gene	Full Name	Protein Function	Marker	Ch. 5[†]	Functional support	Reason to include SNP
20	*DRD3*	Dopamine receptor D3	Involved in dopaminergic neurotransmission	rs167771	Yes, p < .01	-	Significant association in Chapter 5
21	*DRD3*			rs6280	Yes, ns	(Lundstrom & Turpin, 1996)	Functional
22	*DRD4*	Dopamine receptor D4	Involved in dopaminergic neurotransmission	rs11246226	-	-	DRD4 is top candidate for approach
23	*DRD4*			rs3758653	Yes, ns	-	DRD4 is top candidate for approach
24	*DRD4*			rs762502[a]	failed	-	DRD4 is top candidate for approach
25	*DRD4*			rs916457	Yes, ns	-	DRD4 is top candidate for approach
26	*DRD4*			rs936460	Yes, ns	-	DRD4 is top candidate for approach
27	*DRD4*			rs936461	Yes	-	DRD4 is top candidate for approach
28	*HTR1A*	Serotonin receptor 1A	Involved in serotonergic neurotransmission	rs6295	-	(Lemonde et al., 2003)	Functional
29	*HTR2A*	Serotonin receptor 2A	Involved in serotonergic neurotransmission	rs6311	Yes, ns	(Smith et al., 2012)	Functional
30	*HTR2A*			rs6312	-	(Myers et al., 2007)	Functional
31	*HTR2A*			rs6314	-	(Hazelwood & Sanders-Bush, 2004)	Functional
32	*MAOA*	Monoamine oxidase A	Metabolizes DA, NE, 5HT	rs6323	-	(Jansson et al., 2005)	Functional
33	*SLC6A4*	Serotonin transporter	Reuptake of 5HT from the synapse	rs25532	-	(Wendland et al., 2008)	Functional
34	*STMN1*	Stathmin	Regulates microtubule formation (involved in neural plasticity)	rs182455	-	-	Association with startle and cortisol response
35	*STMN1*			rs213641	-	-	Association with startle and cortisol response
36	*TH*	Tyrosin hydroxylase	Catalyzes step in dopamine synthesis	rs10770141	-	(Rao et al., 2008)	Functional, association with NS (Sadaihiro et al., 2010)

Note. Heterozygosity of all SNPs > .2 (ALFRED: www.alfred.med.yale.edu). SNPs that have been consistently associated with approach-related traits or that

have purported functional differences between alleles were included in the current study. Additional details about functional properties associated with alleles at

each loci are shown in Table 2-1. DA = dopamine, 5HT = serotonin, NE = norepinephrine, ns = not significant, GWAS = genome-wide association study.

[†]Some of the SNPs were investigated in association with sensation seeking in skiers in Chapter 5.

[a]Four SNPs failed optimization and were not genotyped.

8.3   Methods

8.3.1   Participants

A total of 146 high-risk athletes (mean age = 29.1 years, *SD* = 9.1; 81% male) and 141 low-risk athletes (mean age = 25.8 years, *SD* = 9.8; 55% male) participated in the study. After exclusions for missing data and sport group overlap (detailed below), the final sample included 141 high-risk athletes (age 29.2 years, *SD* = 9.2; 81% male), and 132 low-risk athletes (age 25.8 years, *SD* = 9.8; 52% male). All athletes were unrelated to each other. Further exclusions are detailed below. Demographic variables are shown in Table 8-2, and types of sports are shown in Table 8-3.

8.3.2   Procedures

The majority of the recruitment took place in France, specifically in Bordeaux, Chamonix, and Pau. Athletes were recruited using a variety of media, including Twitter, Facebook, online forums (e.g., www.basejump.org, www.chamonixdailydump.org), and through team managers (e.g., Red Bull Team), and posters displayed at the sites around Chamonix (e.g., Town Hall, Guides Bureau, Mountain Guide School, etc.). Participants were approached at locations frequented by high-risk sport enthusiasts (e.g., base of gondola to the Aiguille du Midi (a famous mountaineering and glacier traverse route in Chamonix), bus stops, the Chamonix Guides Bureau, adventure tour kiosks). While this one-to-one method was successful, it was difficult to obtain sufficient numbers for a genetic association study; therefore, additional recruitment occurred at festivals including the North Face Ski Challenge, Chamonix, France and the Openride Festival, Chamonix, France. Another "mass" recruitment occurred at an airfield in Pau, France where a number of BASE jumpers, skydivers, and wing-suit fliers participated in the

study. Low-risk athletes were recruited at the University of Bordeaux and through sports clubs in the city (a few were recruited in Chamonix). Due to the insufficient number of low-risk athletes recruited in France, recruitment continued after my return to Canada. A number of low-risk athletes were recruited through UBC sports teams (track & field, golf, cross country, and triathlon).

Once participants provided informed consent they completed a series of questionnaires (detailed below section 8.1.3). Both French and English versions of the instructions and the questionnaires were prepared so that athletes could complete the questionnaire in the language in which they were most proficient. The questionnaires took approximately 20 minutes to complete and the same instructions for completing the questionnaire package were used in France and in Canada. The participants could choose one of three media in which to complete the questionnaire (online, ipad, paper, detailed below).

Surveys were available on www.surveymonkey.com through a secure account. If the participant did not have time to complete the survey at the time of recruitment, after providing informed consent and a DNA sample (if interested in the DNA component) he/she had the option to provide an email address. The survey link was promptly sent to the participants with instructions and an ID code in order to complete the survey online from home. A second paperless option involved a survey software program iFormBuilder mobile platform (Herndon, Virginia, USA) on an iPad (Apple, California, USA) for the purpose of providing an environmentally friendly option to data collection. The questionnaires and consent forms used in both the online and ipad formats were identical in content to the third option: the paper version. Both digital surveys had "skip logic", meaning that if the participant answered "no" to a question such as: "do you participate in any of the following high-risk sports?" the survey would

automatically skip to the following question. Participants always had the option to return to the previous question, in order to make the paper and paperless options as similar as possible.

8.3.3   Measures

The questionnaire component for the study described in the current chapter was significantly more detailed than that in the projects on skiers and snowboarders described in Chapters 3 to 6. Additional screenings measures were included (e.g., psychiatric screening, ADHD screen, problematic substance use screen) to ensure that there was not an erroneous association with an underlying condition, because the study design involved comparing genetic and psychological variables between two sport groups (rather than comparing continuous variables between genotype groups).

8.3.3.1   Demographic variables

Participants provided information about age, sex, marital status, dependents, occupation, home country, education, ethnicity, grandparents' ethnicity, first language, fluency and number of years speaking language used for survey (see Appendix CC). Participants reporting non-European ancestry (3rd generation) were excluded from genetic analyses, but were not excluded from personality analyses.

8.3.3.2   Psychotropic medication

As a proxy for psychiatric screening (in lieu of a structure interview), participants were asked to report use of medications. A list of common names for anxiolytics, antidepressants, and neuroleptics was included in the questionnaire, and participants answered questions about history

and duration of use (Appendix X). Any participants reporting history or current use of psychotropic medication were excluded from all analyses.

8.3.3.3   Substance use inventories

Smoking. Participants provided information about tobacco smoking status, years smoking, and cigarettes per day. Smoking history was followed by a modified (four-item) version of the Fagerström Nicotine Dependence (Appendix CC) (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) or the French version (Test de Fagerstrom; OMS, 1998).

Alcohol use. Participant's alcohol use was measured using a modified version of the CAGE questionnaire (named after acronym: "**C**ut down on drinking, **A**nnoyances with criticisms about drinking, **G**uilt about drinking, and using alcohol as an **E**ye opener") (Ewing, 1984), a brief 4-item questionnaire used to assess at-risk drinking behaviours. In addition, participants provided information about weekly frequency of alcohol consumption. A French version of the CAGE (called the DETA in French) is available (Reynaud et al., 1997) and had been used by the psychology laboratory in Bordeaux (Santé et Qualité de vie, EA4319). The French version does not use expressions, such as "eye opener" or "cut down" and since it was expected that some participants would be non-native English or French speakers, the CAGE was modified slightly to include clear language (without expressions). For example, item 1: "have you ever felt that you need to decrease your consumption of alcoholic beverages", instead of "…cut down on your drinking" (Appendix CC).

Illicit substances. From a list of illicit substances, participants selected any substances that he/she had tried (a modified list from the Adolescent Drug Involvement Scale (Moberg &

Hahn, 1991); see Appendix CC). The list was followed with questions about frequency of use and social pattern of consumption. If the participant had only tried a substance, but no longer reported use, he/she then skipped the rest of the questions pertaining to use of that particular substance. Participants reporting current use completed a modified version of the Cannabis Abuse Screening Test (CAST) in order to characterize their drug-use patterns (available in French and English; Legleye, Karila L, Beck F, & M:, 2008). The CAST is a 6-item questionnaire with dichotomous answers (yes/no) (Appendix CC). The word "cannabis" was replaced with the more general "drugs", and will be referred to as the "modified-CAST". Participants reporting problematic substance use (as defined by a modified-CAST score > 2) were excluded from all personality and genetic analyses, with the exception of a comparison of drug use between high- and low-risk sport groups.

8.3.3.4   Sport inventories

Participants selected sports in which they *currently* participate from a list of high- and low-risk sports. In order to exclude individuals who had only tried the sport once[28], they were asked to list sports in which they participate "regularly" (more than twice per year[29]), followed by details about his/her most proficient sport (including ability and frequency). French translations for common names of sports were verified with local sport experts in Chamonix. The high-risk sport participants did not complete a low-risk sport inventory because there were no exclusions of high-risk sport participants for participating in low-risk sports as well (e.g., mountaineers might train during their off season by running). On the other hand, low-risk sport

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[28]Bungee jumping, paragliding, and skydiving are sports that many people try only once in a lifetime, but one attempt at a sport would not be sufficient for inclusion in the high-risk sport group.
[29] The term "regularly" is used liberally here, because some sports may only be practiced twice a year (e.g., if a person considers a mountaineering trip a single bout of practice).

participants completed both inventories because an athlete approached because of their participation in a low-risk sport (i.e., golf team) may also practice BASE jumping, which would exclude them from the low risk group. All athletes were pre-screened for their participation in high- or low-risk sports in order to ensure they completed the correct questionnaire. Sports in the high-risk inventory were chosen based on web searches of "high-risk" and "extreme" sports, sports featured at mountain film festivals, and personal communication with athletes. There are no comprehensive lists of high-risk sports in the literature. The list included the choice "other" to avoid missing new or obscure sports (Appendix DD).

In addition to the sport inventory, athletes reporting at least intermediate ability in mountain biking, skiing, or snowboarding completed a generalized version of the 10-item CSSQ (described in Chapter 3, see also Appendix Y), a context-specific sensation seeking measure. A French version of the CSSQ was created using back-translation from English to French and back to English until the translation agreed. Scores derived from the CSSQ demonstrated high internal consistency (Cronbach alpha French = .85, English = .90). Athletes reporting less than intermediate ability in the downhill sport of their choice were excluded from CSSQ analyses.

8.3.3.5   Adult Self-Report Symptom Checklist 1.1 (ASRS-V1.1)

Athletes completed a brief 6-item scale to measure symptoms of attention deficit hyperactivity disorder (ADHD; Appendix EE). The scale is available in English (Kessler et al., 2005) and French (Caci, Bayle, & Bouchez, 2008). The ASRS-V1.1 has been shown to be sensitive (Hines, King, & Curry, 2012), and has moderate internal consistencies (Kessler et al., 2005). An ASRS-V1.1 score > 3 suggests the participant has symptoms consistent with adult ADHD, but a formal diagnosis would require an in-depth clinical interview (Kessler et al., 2005).

Participants were not excluded from psychological analyses on the basis of high ADHD scores; however, individuals with ASRS-V1.1 > 3 were excluded from the genetic analysis due to the extensive overlap between candidate genes associated with sensation seeking and those that have been implicated in ADHD. Scores derived from the ASRS-V1.1 in the current study demonstrated modest internal consistency (Cronbach alpha French = .67, English = .67).

8.3.3.6 ZKPQ ImpSS

Participants completed the English or French 19-item version of the ImpSS, scored using true/false format (Appendix D) (French version validated by Rossier et al., 2008; Zuckerman et al., 1993). Scores derived from the ImpSS demonstrated acceptable internal consistency (Cronbach alpha French = .75, English = .86), and internal consistencies for the subfactors were modest (Cronbach alpha Imp (8 items): French = .65, English = .80; SS (11 items): French = .73, English = .79).

8.3.4 Genetic analysis

DNA collection and preparation. Participants provided two cheek swabs (instructions shown in Appendix K, a French translation of the instructions was available). Buccal cell DNA was isolated using the same alcohol-based purification technique described in Appendix L. The concentrations of all samples were measured using a Nanodrop ND-100 Spectrophotometer (Thermo Fisher Scientific Inc, Waltham, MA) and were diluted to approximately 20 ng/μl as per requirements outlined by the genotyping facility (Genome Quebec). Sample plate layout is shown in Appendix N.

Genotyping. The McGill University Genome Québec Innovation Centre (Montréal, Quebec, Canada) carried out the genotyping using the Sequenom iPLEX® technique (San Diego, California, USA). A total of 32 SNPs[30] in 14 genes were successfully amplified (Table 8-1). Amplification failed for four SNPs. The mean marker call rate was 99.16% ($SD = 0.012\%$). For additional information about markers and for the Genome Quebec project report see Appendix FF.

8.3.5   Analyses

In order to carry out case-control analyses, the control group must be as similar as possible to the case group for all variables except the grouping variable (reviewed by Attia et al., 2009). Attempts were made to 1) recruit equal representation of males and females in both groups, 2) to balance the age of the groups, and 3) to recruit the participants from similar geographic regions; however, the high-risk sport participants encountered during recruitment were largely male and over 30 years of age. Additionally, a majority of high-risk athletes were recruited in Chamonix, France, a place where high-risk recreation enthusiasts from around the world congregate,[31] and the majority of people who practice low-risk sports regularly in Chamonix do so as training for their high-risk sports. As such, low-risk athletes were not recruited in Chamonix, and instead attempts were made to recruit low-risk athletes while in Bordeaux, France, but the success rate was low, so most were recruited at a later date in Vancouver, Canada. As recruitment at two sites could have contributed to potentially

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[30] Genome Quebec genotyped 33 SNPs, but the -521C/T (rs1800955) was analyzed separately in a subset of the participants to test for associations with the CSSQ using a single cohort design (described in Chapter 7).
[31] A large number of the athletes recruited in Chamonix were not from France, they came from all over the world: e.g., USA, Canada, Australia, United Kingdom, Norway, etc.

confounding sample heterogeneity, the extent of the demographic differences between high- and low-risk groups were assessed and adjustments to the analyses are described below.

Personality and disinhibited behaviours. Demographic variables were compared between sports groups using Student's *t*-tests for continuous variables, and *Chi* square tests for categorical variables. Demographic characteristics are summarized for high- and low-risk sport groups in Table 8-2. Personality measures were compared between subsets of the high- and low-risk groups grouped by sex and location of recruitment (e.g., males recruited in France participating in high-risk were compared to males recruited in France participating in low-risk sports). Specifically, ANOVAs were used to compare the mean scores from the following measures between subsets of the sports groups: impulsive sensation seeking (and each subfactor: impulsivity, sensation seeking), and CSSQ (for those who reported participation in downhill sports). Consumption patterns for drugs, alcohol, and smoking were also compared between sport groups using *t*-tests of scores from the modified-CAST, modified CAGE/DETA, and modified Fagerström, respectively. Finally, impulsivity and sensation seeking in high-risk male athletes reporting problematic drug use (modified-CAST > 2, from France only) were compared to other high-risk male athletes reporting no problematic use. It was expected that the individuals excluded from all other analyses based on their drug use would score higher on impulsivity than the athletes from the high-risk sport group reporting no problematic drug use.

Genetic analyses. Genotype frequencies for all SNPs were tested to see if each satisfied Hardy-Weinberg Equilibrium. To provide support for comparing participants recruited in Europe with those recruited in Canada, additional analyses comparing genotype frequencies between recruitment locations were carried out in the low-risk sport participants. In order to investigate whether alleles in candidate genes involved in approach-related phenotypes were

overrepresented in athletes participating in high-risk sports, allele frequencies at each of the 32 SNPs were compared between high- and low-risk sport participants using *Chi* square analyses. When there were differences between allele frequencies (at an un-corrected alpha level of .05) in the un-matched sport samples, the analysis was re-tested in a subset matched for recruitment location. A Bonferroni correction for testing multiple SNPs was applied (Attia et al., 2009).

8.4   Results

8.4.1   Participant exclusions

There are a number of exclusion criteria, which vary depending on the analysis. The following athletes were excluded from *all* analyses: nine low-risk sport participants who also regularly participated in high-risk sports, two low-risk and five high-risk sport participants with missing data, and 14 low-risk and two high-risk sport participants reporting a history of medication-use related to psychiatric illness. Athletes reporting problematic[32] substance use based on a modified-CAST score > 2 were excluded from personality and genetic analyses that involved comparisons between sports groups ($n = 1$ from low-risk group, $n = 25$ from high-risk group); however, separate analyses were performed to investigate characteristics of the high-risk sport participants who reported problematic substance use ($n = 25$).

After exclusions, there were 114 high-risk athletes and 117 low-risk remaining for the between-sport group personality analyses. Participant characteristics for these cohorts are shown in Table 8-2. For the genetic analysis, and additional three (leaving $n = 111$) high-risk and 17 (leaving $n = 100$) low-risk sport participants were excluded for reporting non-Caucasian ancestry among grandparents. Due to the overlap between candidate genes implicated in sensation

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[32] A CAST score > 2 suggests that the individual is exhibiting disordered or problematic use (Legleye et al., 2008).

seeking and those implicated in ADHD, participants with ASRS-V1.1 scores > 3 were excluded

from the genetic analyses to avoid potentially confounding effects. There were 30 high-risk

athletes and 28 low-risk athletes reporting ASRS > 3, leaving 81 and 71 in the high- and low-risk

groups, respectively. Table 8-2 shows participant characteristics pre- and post-exclusions for

both personality and genetics analyses. Participation rates for sports chosen by high- and low-

risk athletes are shown in Table 8-3.

Table 8-2

Participant's characteristics pre- and post-exclusions

Demographic variable	Pre-exclusions		Post exclusions (Personality)		Post exclusions (Genetics)		Between-sport group
	High (141)	Low (132)	High (114)	Low (117)	High (81)	Low (71)	
Sex M/F (%)	81/19	52/48	79/21	53/47	78/22	48/52	<.01
Age, *M (SD)*	29.2(9.2)	25.8(9.8)	30.3(9.7)	25.1(9.2)	31.4(10.3)	26.7(10.8)	<.01
Marital status (%)							
Single	55	71	54	72	52	67	ns
Common-law	24	15	25	16	22	17	
Married	16	10	18	9	22	11	
Other	5	4	3	2	4	3	
Dependents (%)	16	8	19	8	25	11	
Education (%)							
High school	21	30	21	32	22	31	ns
Post-secondary	60	53	59	52	54	49	
Graduate	19	17	20	17	24	20	
Language for questionnaire (%)							
English	30	78	31	76	30	72	<.01
French	70	22	69	24	70	28	
Years spoken (%)							
<10 years	7	0	7	0	6	0	<.01
10-15 years	3	2	2	3	1	1	
16-20 years	11	28	10	30	11	30	
>20 years	79	70	82	68	82	69	
First language (%)							
English	19	73	18	72	16	71	<.01
French	65	21	65	22	68	27	
Other	16	6	17	6	16	1	

Demographic variable	Pre-exclusions		Post exclusions (Personality)		Post exclusions (Genetics)		Between-sport group
	High (141)	Low (132)	High (114)	Low (117)	High (81)	Low (71)	
Country of recruitment (%)							
Canada	8	77	9	75	7	70	<.01
France	92	23	91	25	92	30	
European ancestry (%)							
Northern	19	20	21	20	23	21	ns
Southern	7	2	6	1	7	1	
Eastern	8	15	10	13	12	11	
Western	63	61	60	65	53	65	
Other (SE, SW, EW)	3	2	4	2	5	2	
Ethnicity (%)							
European	96	83	96	86	100	100	ns
First Nations	0	2	0	1			
Asian (Japan)	0	3	0	1			
Asian (China)	0	4	0	3			
South America	2	0	2	0			
Other	2	8	2	9			
Ability of most proficient sport							
Beginner	1	1	1[a]	0	1	0	<.01
Novice	1	10	2[a]	7	2	9	
Intermediate	8	34	7	37	8	34	
Advanced	19	36	18	36	17	40	
Expert	71	19	70	20	72	17	
Days per year at sport, M (SD)	136.8 (113)	134.9 (100)	142 (118)	136(103)	129(108)	128 (102)	ns

Note. Sample sizes for each group are shown in the header row (*n*). *p*-values for between-sport group comparisons were obtained using *t*-tests for continuous variables and *Chi* square tests for categorical variables; ns = not significant.

[a]the three participants reporting "beginner" and "novice" ability were all skydivers who jumped an average of 60 times per year.

Table 8-3

Participation counts per high- and low-risk sports

High-risk sports	n	Most proficient[a] (n)	Low-risk sports	n	Most proficient[a] (n)
Adventure Racing	12	0	Athletics	47	11
BASE jumping	13	5	Badminton	10	2
BMX	11	0	Biathlon	1	0
Bungee jumping	8	0	Cross country skiing	24	4
Car racing	6	0	Curling	5	2
Cliff jumping	14	0	Cycling	64	5
Climbing (rock)	73	9	Dance/ballet	13	4
Dirt biking	15	0	Dragon boating	5	0
Freeride skiing[b]	79	44	Equestrian	2	1
Freeride snowboarding[b]	33	12	Figure skating	2	0
Freestyle skiing	4	4	Fishing	13	0
Ice Climbing	33	0	Golf	30	2
Kite surfing	13	3	Gym workouts	53	7
Luge	4	0	Gymnastics	6	1
Mountaineering (alpinism)	38	5	Iron Man	17	0
Mountain biking	57	2	Rollerblade	5	0
Paragliding	34	5	Rowing	19	5
Parkours (free running)	7	2	Running	83	30
Rappelling	47	0	Speed skating	13	0
Sailing	26	4	Swimming	64	16
Skateboarding	18	1	Tennis	26	5
Ski cross	9	0	Triathlon	34	16
Skydiving	46	20	Weight lifting	32	1
Snowboard cross	10	0	Yoga	48	4
Speed riding	17	3	Other		16
Speed skiing	8	0			
Steep skiing ("pente raide")	17	4			
Street luge	4	0			
Surfing	41	8			
Whitewater kayaking	13	0			
Windsurfing	1	2			
Wing-suit flying	11	4			
Other		2			

Note. Many athletes reported participation in multiple risk sports. "Other" high-risk sports included dry tooling (a subtype of mountaineering), ocean kayaking, scuba diving, wakeboarding, "Other" low-risk sports included race walking and team sports. For an explanation about each high-risk sport see Appendix A.

[a]Athletes were asked to choose their most proficient sports, and the numbers shown represent counts per sport.

[b]Freeride skiing and snowboarding involves substantially more risk than resort skiing/snowboarding and typically involves skiing "out of bounds".

8.4.2   **Results for personality analyses**

There were significant differences between the high- and low-risk sport groups in their sex representation, age, and recruitment country (see Table 8-2). To investigate whether differences in psychological variables exist between high- and low-risk sport groups, small subsamples matched for sex and recruitment location were compared (i.e., high- *vs.* low-risk males recruited in France). The matched group in each case was limited by the size of the smaller sample. If consistent trends or differences are seen in these small ($n < 15$ per group) samples, then the effect size of the difference between high- and low-risk sport personality traits is likely to be substantial.

Matched comparisons. A total of 15 low-risk male athletes were recruited in France, and there were a total of 82 high-risk male athletes. Confidence intervals (95%) for personality measures were calculated using a bootstrapping method in SPSS (version 21.0). The bootstrap method generates 1000 random samples from the original distribution and carries out the between-groups analysis on each of these randomly generated samples. Males from France who participated in high-risk sports scored higher on the ZKPQ sensation seeking subscale than those who participated in low-risk sports ($p = .001$, Table 8-4). There was a similar trend for the CSSQ measure, but the difference was not significant.

There were fewer women in the full sample and there were 14 females reporting participation in low risk sports and 23 females reporting participation in high-risk sports, all recruited in France. The results for ANOVAs using bootstrapping are shown in Table 8-4. There were trends for higher sensation-seeking scores in the high-risk group of females; however, the difference between groups was not significant. There were significant differences in CSSQ score between sport groups ($p = .007$).

Finally, high- and low-risk athletes recruited in Canada were compared. The samples sizes in Canada were limited by the small number of high-risk athletes ($n = 10$, 2 female) and were too small to analyze the sexes separately so only males were compared. There were a total of 46 low-risk males recruited in Canada. There were no significant differences between groups, although there was a trend for slightly higher sensation seeking in high-risk athletes. There were too few ($n < 5$) participants reporting proficiency in a downhill sport; therefore, the CSSQ was not included in the analysis. Results are shown in Table 8-4. In all three of the above-mentioned matched analyses, there were no differences in impulsivity between sport groups ($p > .42$).

Table 8-4

Bootstrap analysis of personality measures between high- and low-risk participants grouped by sex and location of recruitment

Sex	Recruitment location	Sport group	DV	n	Sample M	SD	Bootstrap 95% CI Lower	Upper	ANOVA F	p
Male	France									
		High-risk	ImpSS	82	10.80	3.56	10.08	11.62	4.97	**.03**
		Low-risk		15	8.47	4.61	6.21	10.87		
		High-risk	Imp	82	2.73	2.08	2.27	3.20	0.00	1.00
		Low-risk		15	2.73	2.22	1.69	4.00		
		High-risk	SS	82	8.07	2.27	7.58	8.55	12.11	**.001**
		Low-risk		15	5.73	3.01	4.25	7.27		
		High-risk	CSSQ	67	37.14	8.05	35.22[a]	39.07[a]	0.84	.36
		Low-risk		6	34.00	7.80	27.00[a]	40.20[a]		
Female	France									
		High-risk	ImpSS	23	12.35	2.77	11.32	13.45	3.17	.08
		Low-risk		14	10.21	4.54	7.77	12.50		
		High-risk	Imp	23	4.00	1.95	3.21	4.76	0.67	.42
		Low-risk		14	3.43	2.21	2.23	4.56		
		High-risk	SS	23	8.35	2.04	7.50	9.17	3.55	.07
		Low-risk		14	6.79	3.02	5.07	8.31		
		High-risk	CSSQ	21	32.96	5.95	30.39	35.52	8.44	**.007**
		Low-risk		8	25.63	6.44	20.50	29.36		
Male	Canada									
		High-risk	ImpSS	8	10.13	4.70	6.50	13.30	0.14	.71
		Low-risk		46	9.52	4.15	8.36	10.67		
		High-risk	Imp	8	2.13	2.23	3.00	13.00	0.17	.69
		Low-risk		46	2.46	2.12	1.88	3.07		
		High-risk	SS	8	8.00	2.93	5.78	10.00	0.77	.39
		Low-risk		46	7.07	2.76	6.23	7.86		

Note. Bootstrap results are based on 1000 unless otherwise specified. Significant results are shown in bold. DV = dependent variable, CI = confidence interval (lower and upper values), ImpSS = impulsive sensation seeking, Imp = impulsivity, SS = sensation seeking, CSSQ = contextual sensation seeking questionnaire. [a]Bootstrap based on 999 samples.

8.4.3   **Sex differences**

Personality measures between males and females within each sport category were compared. Participant exclusions were almost the same as the exclusions used in personality analyses listed above; however, a greater number of males reported positive ADHD-like symptoms. To minimize confounding effects all participants with an ASRS-V1.1 score > 3

were excluded for this analysis. Using data from participants recruited in France, a two-way

analysis of variance was carried out with sex (male *vs.* female) and sport group (high- *vs.* low-

risk) as the between-subjects factors and personality measure as the dependent variable

(impulsivity and sensation seeking). Limited by the smaller number of females in the high-risk

sport group, a random subset of 17 males from the high-risk sport group were selected for

comparison using SPSS random case selector. There were no significant interactions between

sex and sport group (Imp: $p = .7$; SS: $p = .5$) and there were no significant main effects of sex for

either personality variable measured (Imp*: $p = .16$*; SS: $p = .25$). There was a significant main

effect of sport group on sensation seeking ($F(1,53) = 10.2$, $p = .002$). Descriptive statistics are

shown in Table 8-5.

Table 8-5

Descriptive statistics for personality measures in males and females participating in high- and

low-risk sports (recruited in France)

DV	Sport group	Sex	*N*	M	*SD*
Imp	High-risk	M[a]	16	2.81	1.68
		F	17	3.35	1.77
	Low-risk	M	12	2.42	2.11
		F	12	3.33	2.22
SS	High-risk	M[a]	16	8.06	1.98
		F	17	8.41	2.00
	Low-risk	M	12	5.42	3.29
		F	12	6.67	3.08

Note. M = male, F = female, DV = dependent variable, *M* = mean, *SD* = standard deviation, *t* = student *t*-test

statistic. [a]randomly selected subset of full sample.

8.4.4 Results from genetic analyses

8.4.4.1 Preliminary tests of genotype distributions between recruitment sites

The number of athletes reporting Northern, Western, Eastern, and Southern European descent was not significantly different between high- and low-risk samples (2 x 3 contingency table, $\chi^2(2) = 0.68$, $p = .72$)[33]. Before carrying out the genetic analyses between sports groups, allele frequencies between recruitment countries were compared to test for differences in genotype distributions, possibly indicative of biogeographical stratification. The genotype frequencies at each SNP were compared between low-risk athletes recruited in France ($n = 24$) and Canada ($n = 81$) using *Chi*-square or Fisher's exact test. The genotype distributions for 30 of the 32 SNPs tested did not differ significantly between recruitment countries among the low-risk athletes sampled. The two following SNPs differed in genotype frequencies between recruitment countries: rs6271 $p = .00005$, rs6314 $p = .0004$, allele frequencies are shown in Appendix GG. Limited by the smaller sample of low-risk athletes recruited in France, the Canadian samples were compared to data from other European samples. There were no data available from European samples (still living in Europe) for either the rs6271 or rs6314, but the Canadian genotype distributions did not differ from HapMap European data (rs6271: $\chi^2 (1) = 1.09$, $p = .33$; rs6314, $\chi^2 (1) = 0.99$, $p = .33$)[34] (HapMap, 2013). There did not appear to be systematic differences in genotype distributions between participants recruited in France and those recruited in Canada; therefore, exploratory genetic analyses between high- and low-risk groups were performed.

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[33] Separate 2 x 2 tests were carried out to include "Southern European" counts which were too small to include in a 2x4 analysis, $p > .2$.

[34] For both rs6271 and rs6314, two cells in the 2x3 contingency table had counts less than 5 (due to the minor genotype), so the minor genotype was excluded and 2 x 2 (counts of major genotype and heterozygotes) were compared.

8.4.4.2   Genetic analyses of high- and low-risk athletes

Hardy-Weinberg Equilibrium (HWE) was tested in high- and low-risk groups separately.

The two following SNPs violated HWE assumptions ($p < .05$) and were excluded from the

analysis: *DAT1* rs6347 in the low-risk sport group, and *HTR1A* rs6312 in the high-risk sport

group (Table 8-6). There were fewer heterozygotes than expected for randomly mating

populations at both loci. A heterozygote deficiency can occur due to non-random mating or

genotyping error; however, if the HWE tests had been corrected for multiple testing, neither

violation would be significant. Allele frequencies were compared between high- and low-risk

athletic samples for the 30 SNPs that satisfied HWE, and differences were observed in three

SNPs, although two of them were in *STMN1* and were presumably linked (not independent, see

genotype frequencies in Table 8-6). Considering only independent SNPs, differences between

sports groups in allele frequencies were observed for *STMN1* rs182455 ($p = .004$) and *BDNF*

rs6265 ($p = .03$). Results are shown in Table 8-6. The sport groups differed by sex and

recruitment country; therefore, follow up analyses were carried out in the two SNPs (rs182455

and rs6265) to see if trends were observed in the smaller subsets (genotype and allele frequencies

are shown in Appendix HH). Firstly, males and females were analyzed separately and the

difference in *STMN1* rs182455 allele frequencies was present in the males ($n_{High} = 60$, $n_{Low} = 32$,

$\chi^2 = 7.05$, $p = .008$), but not in the females ($n_{High} = 17$, $n_{Low} = 31$, $\chi^2 = 0.26$, $p = .61$). Secondly,

recruitment country was considered and allele frequencies at *STMN1* rs182455 were compared

between high- and low-risk males recruited in France. The allele frequencies were as follows:

high-risk sport group: $n = 55$, .44T and .56C and low-risk sport group: $n = 11$, .09T and .90C.

The allele frequencies differed between sport groups ($\chi^2 = 4.65$, $p = .03$), but the subset is too

small to make any conclusions. The same procedures were followed for the *BDNF* rs6265 (i.e.,

analysis grouped by sex, followed by analysis by recruitment location). The difference in *BDNF* rs6265 allele frequencies was present in females ($\chi^2 = 7.35$, $p = .007$), but not in males ($\chi^2 = 0.22$, $p = .64$). When allele frequencies between sports groups for females recruited in France were compared, the difference was still significant, despite very small sample sizes ($n_{High} = 17$, $n_{Low} = 6$, $\chi^2 = 4.44$, $p = .04$; Appendix HH). Separate analyses for athletes recruited in Canada were not performed (limited by the small number of high-risk athletes, $n < 5$).

Four groups of SNPs that have been explored previously as haplotypes appeared to be in linkage disequilibrium in the current samples based on near identical genotype frequencies. The *COMT* rs4633 and rs4680 have previously been shown to be in linkage disequilibrium in North American-European populations (D' = .97; Choudhry et al., 2012; D = .19; Hirata et al., 2008), and in the current samples the genotypes at each loci were 100% matched in both high- and low-risk athletic samples. The *STMN1* rs182455 and rs213641 have also been shown to be in linkage disequilibrium in a German-European sample (D' = 1.0; Brocke et al., 2010), and similarly the current samples were nearly completely matched for genotypes at these loci. Strong linkage between rs2283265 and rs1076560 in *DRD2* has previously been observed (Moyer et al., 2011), and the genotype distributions in the current samples were very similar with a single mismatch in the high-risk sample. Finally, strong linkage between three SNPs in *DRD1* (rs686, rs265981, and rs4532) was found previously in a Han Chinese population (Zhu et al., 2011) and linkage in Caucasians has also been reported (Batel et al., 2008). In the current samples the genotype distributions at rs686 and rs4532 were completely matched, and there were two mismatches between rs265981 and rs686. Although haplotype analysis was not carried out in this study, near-identical genotype distributions between pairs of SNPs is likely not due to chance. A total of 30 SNPs were investigated; however, three pairs and one trio are likely dependent (linked), so

a correction factor of 1/25 was applied to alpha (.05) setting significance threshold at .002 (using

a Bonferroni correction). The differences in allele frequencies between high- and low-risk sport

groups observed at loci in *STMN1* and *BDNF* were not significant after considering the

correction for multiple testing.

Table 8-6

Comparison of allele frequencies between high- and low-risk athletic groups

Gene	SNP		Genotype Counts (n)		HWE High		HWE Low		Allele Frequencies (%) High		Allele Frequencies (%) Low		Between groups	
			High	Low	χ^2	p	χ^2	p	Maj	Min	Maj	Min	χ^2	p
BDNF	rs6265	GG	52	30	0.16	.69	1.75	.19	.82	.18	.71	.29	4.48	**.03***
		GA	24	30										
		AA	2	3										
COMT	rs4633[a]	CC	19	18	0.19	.66	1.03	.31	.52	.48	.51	.49	0.21	.65
		CT	37	27										
		TT	22	17										
COMT	rs4680[a]	GG	19	18	0.19	.66	1.29	.26	.52	.48	.50	.50	0.10	.75
		GA	37	27										
		AA	22	18										
COMT	rs6269	AA	31	20	0.01	.92	0.70	.40	.63	.37	.54	.46	2.26	.13
		AG	36	28										
		GG	11	15										
DAT1	rs2652511	CC	28	27	3.39	.07	0.03	.86	.57	.43	.65	.35	2.03	.15
		CT	29	28										
		TT	18	8										
DAT1	rs6347	AA	40	40	0.91	.34	8.08	**<.01**	*Test not performed*					
		AG	34	15										
		GG	4	8										
DBH	rs1611122	CC	23	22	1.27	.26	0.54	.46	.51	.49	.57	.43	0.96	.33
		CG	34	28										
		GG	21	13										
DBH	rs161115	TT	32	22	0.08	.77	0.23	.63	.37	.63	.40	.60	0.27	.60
		TA	35	26										
		AA	11	10										

Gene	SNP		Counts (n) High	Counts (n) Low	HWE High χ²	HWE High p	HWE Low χ²	HWE Low p	Allele Freq High Maj	Allele Freq High Min	Allele Freq Low Maj	Allele Freq Low Min	Between groups χ²	Between groups p
DBH	rs6271	CC	63	53	0.05	.83	0.68	.41	.90	.10	.91	.09	0.19	.66
		CT	14	9										
		TT	1	1										
DRD1	rs265981[b]	GG	24	30	0.41	.52	2.23	.14	.57	.43	.66	.34	2.28	.13
		GA	41	23										
		AA	13	10										
DRD1	rs4532[b]	TT	23	29	0.53	.47	2.03	.15	.56	.44	.65	.35	2.24	.13
		CT	41	23										
		CC	13	10										
DRD1	rs686[b]	AA	24	29	0.41	.52	3.14	.08	.57	.43	.65	.35	1.61	.20
		AG	41	22										
		GG	13	11										
DRD2	rs1076560[c]	CC	57	42	0.27	.61	0.34	.56	.86	.14	.81	.19	1.25	.26
		CA	20	18										
		AA	1	3										
DRD2	rs2283265[c]	GG	58	42	0.16	.69	0.34	.56	.87	.13	.81	.19	1.62	.20
		GT	19	18										
		TT	1	3										
DRD2	rs1800497	CC	51	35	1.35	.24	0.19	.66	.82	.18	.76	.24	1.64	.20
		CT	26	24										
		TT	1	3										
DRD2	rs6277	TT	25	18	0.71	.40	0.03	.86	.54	.46	.54	.46	0.01	.93
		CT	35	32										
		CC	18	13										
DRD3	rs167771	AA	49	39	1.89	.17	3.49	.06	.81	.19	.81	.19	0.00	.97
		AG	28	24										
		GG	1	0										
DRD3	rs6280	TT	30	23	2.48	.12	1.41	.23	.66	.34	.64	.36	0.08	.78
		CT	41	33										
		CC	6	6										
DRD4	rs11246226	AA	21	19	0.82	.37	0.00	.96	.51	.49	.45	.55	0.81	.37
		CA	35	31										
		CC	22	13										
DRD4	rs3758653	TT	55	44	0.00	1.00	3.18	.07	.84	.16	.82	.18	0.15	.70
		TC	21	14										
		CC	2	4										
DRD4	rs916457	CC	72	57	4.96	.03	0.16	.69	.96	.04	.95	.05	0.01	.91
		CT	5	6										
		TT	1	0										
DRD4	rs936460	TT	40	33	1.07	.30	0.01	.93	.70	.30	.72	.28	0.19	.67
		TC	29	25										
		CC	9	5										
DRD4	rs936461	GG	33	33	0.72	.40	3.05	.08	.67	.33	.69	.31	0.18	.67
		GA	38	21										
		AA	7	9										

Gene	SNP	Genotype	Counts (n) High	Counts (n) Low	HWE High χ²	HWE High p	HWE Low χ²	HWE Low p	Allele Freq High Maj	Allele Freq High Min	Allele Freq Low Maj	Allele Freq Low Min	Between groups χ²	Between groups p
HTR1A	rs6295	GG	24	17	0.15	.70	0.02	.89	.54	.46	.64	.56	0.03	.87
		GC	37	32										
		CC	17	14										
HTR2A	rs6311	CC	24	24	0.48	.49	0.03	.86	.58	.42	.56	.57	2.11	.15
		CT	40	28										
		TT	12	9										
HTR2A	rs6312	AA	66	58	4.58	**.03**	0.11	.74	*Test not performed*					
		AG	9	5										
		GG	2	0										
HTR2A	rs6314	CC	67	51	0.45	.50	0.20	.65	.93	.07	.90	.10	0.95	.33
		CT	11	11										
		TT	0	1										
MAO (F)	rs6323	TT	8	17	0.06	.81	0.00	.95	.68	.32	.74	.26	0.47	.50
		TG	7	12										
		GG	2	2										
MAO (M)	rs632	TT	44	21					.72	.28	.66	.33	0.99	.32
		TG	0	0										
		GG	17	11										
SLC6A4	rs25532	CC	57	46	1.55	.21	1.05	**.31**	.88	.12	.88	.12	0	1.0
		CT	19	14										
		TT	0	0										
STMN1	rs182455[d]	CC	24	35	0.07	.79	0.82	.37	.56	.44	.73	.27	8.20	**.004***
		CT	39	22										
		TT	14	6										
STMN1	rs213641[d]	TT	23	32	0.04	.83	0.38	.54	.55	.45	.71	.29	7.53	**.006***
		TG	39	23										
		GG	15	6										
TH	rs10770141	GG	30	23	0.90	.72	0.90	.34	.64	.36	.63	.37	0.05	.82
		GA	36	33										
		AA	9	7										

Note. Between-sports-group analysis was not performed in SNPs that violated Hardy-Weinberg Equilibrium (HWE,

$p < .05$). MAO is on the X-chromosome so analyses were carried out in males and females separately. HWE =

Hardy-Weinberg Equilibrium, Maj = major allele, Min = minor allele, M = males, F = females.

[a, b, c, d]Complete linkage disequilibrium is assumed based on identical genotype frequencies.

*$p < .05$.

8.4.5   **Results for consumption patterns**

8.4.5.1   Substance use

Participants scoring > 2 on the modified-CAST were not excluded from the following analyses (but were excluded in all analyses described above). Of the athletes reporting having tried drugs, 67% of high-risk sport athletes reported current drug-use compared to 37% of low-risk sport athletes reporting current use ($\chi^2 = 8.27$, $p = .004$). Males from the high-risk sport group that reported problematic substance use (modified-CAST score >2) scored significantly higher than other high-risk sport males on all measures of personality, including impulsivity, sensation seeking, and CSSQ ($p < .05$; Table 8-7). The analysis between high-risk athletes grouped by modified-CAST score revealed that the two groups differed significantly in age; therefore, the analysis was repeated on a sample restricted to include participants within the same age ranges for each group (ages 18-39 years), and the high-risk sport males reporting problematic substance use scored significantly higher than other males from the high-risk sport group on impulsivity and sensation seeking ($p < .01$; Table 8-7).

Table 8-7

Comparison of personality variables between males from the high-risk sport group reporting

problematic substance use and all other males from the high-risk sport group (all recruited in

France)

	Full groups				Age restricted (18-39 years)		
	Problematic	Non-problematic	Between groups		Non-problematic	Between groups	
DV	CAST ≥ 3 (*n* = 14)	CAST < 3 (*n* = 65)	*t*	*p*	CAST < 3 (*n* = 51)	*T*	*p*
Age	25.29 (5.21)	31.64 (10.08)	3.40	**.002**	27.39 (6.16)	1.17	.25
ImpSS	13.71 (2.76)	9.86 (3.34)	-4.02	**<.001**	10.10 (3.33)	-3.72	**<.001**
Imp	3.93 (2.37)	2.15 (1.82)	-3.13	**.002**	2.24 (1.86)	-2.84	**.006**
SS	9.79 (1.19)	7.71 (2.26)	-4.91	**<.001**	7.86 (2.22)	-3.10	**.003**
CSSQ (*n* = 55, 13)	42.35 (5.01)	36.97 (8.28)	-2.24	**.03**	38.74 (7.36)	-1.65	.10

Note. Values shown represent mean (standard deviation). Significant *p*-values are shown in bold. A smaller

proportion of athletes completed the CSSQ. DV = dependent variable, ImpSS = impulsive sensation seeking, Imp =

impulsivity, SS = sensation seeking, CSSQ = contextual sensation seeking questionnaire.

8.4.5.2 Smoking

There were eight smokers in the low-risk sport group (only two of these reported being

regular smokers), whereas there were 11 current smokers and 13 occasional smokers in the high-

risk sport group. There were too few regular smokers in the low-risk sport group to compare

modified Fagerström scores, but all scores in the low-risk sport sample were ≤ 1. There were

three athletes in the high-risk group that had Fagerström scores = 3. Based on the scores in both

samples, athletes reporting smoking show little-to-no nicotine dependence.

8.4.5.3 Alcohol

Similar proportions in each sport group admitted to having tried alcohol, 86% in high-risk

group and 92% in low-risk group. There were no significant differences in alcohol score (as

measured using the DETA/modified-CAGE) between either high- and low-risk sport groups recruited in France ($p = .29$) or Canada ($p = .50$).

8.5   Discussion

Personality traits, risk-taking behaviours (e.g., substance use), and variants in candidate genes were compared between proficient athletes participating in high- and low-risk sports. There were a number of interesting differences between athletic groups; athletes reporting participation in high-risk sports scored higher on sensation seeking, reported more drug use, and there was a non-significant trend for differences between sport groups in genotype frequencies at two loci: a SNP in *STMN1* and Val66Met in *BDNF*.

8.5.1   **Personality trait differences between and within sport group**

The low-risk athletic sample included a greater representation of females, was younger, and mostly recruited in Canada, whereas the high-risk sample had more males, was older and was mostly recruited in France. In order to reduce the potentially confounding effects of extraneous variables, subsets of the full samples (matched for sex and recruitment location) were used for comparisons. Both males and females participating in high-risk sports scored higher on sensation seeking than athletes from the low-risk sport group. The trends for high scores on each sensation-seeking measure were consistent for both sexes (and recruitment countries), although not all of the differences were significant. The reason why significant results in sensation seeking were not seen in all comparisons is likely due to the limited power afforded by the small sample sizes ($n = 8, 14, 15$). While numerous studies comparing personality traits between high- and low-risk sport participants similarly report that athletes who take up high-risk sports score higher on sensation seeking and related measures (Goma-i-Freixanet et al., 2012), there are fewer

studies that have explored impulsivity among risky recreation participants (e.g., Castanier et al., 2010b; I. H. Franken et al., 2006; Goma-I-Freixanet, 1991, 1995; Goma-i-Freixanet, 2001).

Contrary to findings in most non-athletic risk-taking domains that report high sensation seeking *and* impulsivity among risk-takers, there were no significant differences in impulsivity between high- and low-risk sports groups in any of the matched subsamples. This was not entirely surprising given that the few sports studies that have included measures of impulsivity similarly found no associations (Goma-I-Freixanet, 1991, 1995; Goma-i-Freixanet, 2001; Jack et al., 1998; J. H. Kerr & Svebak, 1989). In fact, there have been two studies that have found an inverse relationship between high-risk sport participation and impulsivity: Cazenave and colleagues (2007) found that amateur risk-sport practitioners scored higher on impulsivity than professional athletes (e.g., mountain guides) and Llewellyn & Sanchez (2008) reported risk-taking in rock climbing was inversely related to impulsivity. Both findings make sense from a self-preservation stand-point, as one wrong move in solo climbing (climbing without a rope) can result in death, and impulsive decisions made by a mountain guide could lead to catastrophe. These null or inverse findings between risk-taking and impulsivity in sport are contrary to findings from populations involved in other (non-athletic) forms of risk-taking (Krueger, Markon, Patrick, Benning, & Kramer, 2007; Verdejo-Garcia et al., 2008). The consequences of impulsive or rash decisions in a sport setting can result in severe injury which may deter a person from practicing the sport long enough to become proficient. As the athletes in the high-risk sport group in this study were proficient, the group may have self-selected out the highly impulsive individuals. High-risk sports may serve as an important example of an exception to the co-occurrence of common disinhibited traits.

Although no significant differences in impulsivity were observed across sports groups, there were significant differences in impulsivity when score on the substance use questionnaire was considered as a grouping factor. Male athletes from the high-risk sport group who reported problematic substance use were compared to those reporting no problematic use. Interestingly, the two groups differed significantly on *both* impulsivity and sensation seeking. Studies on substance use have consistently found that problematic users score higher on impulsivity than healthy controls (reviewed by Verdejo-Garcia et al., 2008; Zhornitsky et al., 2012); therefore, the high impulsivity observed in the athletes reporting problematic use are in line with these findings. Franques and colleagues (2003) compared sensation-seeking score (using the SSS) between non-athletic opioid-dependent subjects and drug-free athletes practicing high-risk sports and the athletes scored higher on the thrill and adventure seeking scale than the non-athletic opioid users, but the groups did not differ on the other SSS subscales (Franques et al., 2003). To my knowledge there have been no studies that have investigated substance use among high-risk athletes, but athletes who practice high-risk sports *and* report problematic substance use may represent a subset of very high risk-takers; whereas high-risk athletes reporting no problematic substance use may represent a group of non-impulsive, "thrill seekers".

8.5.2   **Genetic differences between sport groups**

While it was important to demonstrate that high- and low-risk athletes differed on measures of sensation seeking to provide rationale for grouping based on sport participation, the primary goal of the study described in the current chapter was to investigate the differences in allele frequencies between genetic variants that have previously been implicated in approach-related or risk-taking phenotypes. Although none of the genetic differences between high- and low-risk sports groups remained significant after applying a stringent correction factor, there

were marginal differences in allele frequencies at two loci (*STMN1* rs182455 and *BDNF* Val66Met) in the full samples, and the same trends were present when tested in small subsets matched for sex and recruitment location.

STMN1 is a gene that has been associated with fearlessness in mice and humans. Mice lacking the *Stathmin1* gene spent more time on a raised platform than wild-type mice, possibly indicative of reduced fear of heights, and the knockout mice also showed impairments in conditioned fear, which the authors also referred to as reduced anxiety (Shumyatsky et al., 2005). The phenotype exhibited by these mice is similar to the motivational tendency for weak-avoidance in response to a stressful stimulus (e.g., Elliot & Thrash, 2002). *STMN1* (located on chromosome 1 in humans) is highly expressed in the lateral nucleus of the amygdala (Shumyatsky et al., 2002), a region of the brain that is thought to play a key role in emotional learning and fear (Phelps & LeDoux, 2005). More recently, *STMN1* has been associated with startle and stress response in humans (Brocke et al., 2010). An acoustic startle paradigm was used to elicit a fear response in a sample of healthy adults and the *STMN1* rs182455 T allele was significantly associated with startle and cortisol response but the direction of the response differed for males and females (Brocke et al., 2010). Female carriers of the T allele showed reduced startle and cortisol responses, whereas male carriers of the T allele showed the opposite. The rs182455 is located approximately 2 kbp[35] upstream from *STMN1* and in the current study it appeared to be in almost perfect linkage disequilibrium with rs213641, a variant located in either the 5' UTR or exon 1 (depending on the trascribed version of the gene; UCSC, 2013) (Brocke et al., 2010). In the current study, the high-risk sport group had a higher frequency of the T allele compared to the low-risk sport group. When males and females were analyzed separately, the

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[35] UCSC shows variations in its position between -1615 to -2339 bp dependent on mRNA transcript (UCSC Genome Browser, accessed February 21, 2013)(UCSC, 2013).

frequency of the T allele in males was higher ($p = .008$) in the high-risk sport group, but the allele frequencies did not differ in the females (though the female sample size was too small to be conclusive). When the analysis between high- and low-risk sports groups was restricted to males recruited only from France, the same trends for an increased frequency of the T allele among the high-risk sport group were present ($p < .05$), though again, the sample size is far too small to be conclusive. It is interesting that a SNP that was associated with fear response (possibly indicative of a weak avoidance system) in a previous study differed significantly in frequencies between athletes actively seeking out activities that many individuals might consider fearful and those athletes participating in low-risk sports (that are not likely to be fearful). In contrast to the previous *STMN1* association study that found the T allele was associated with a decreased fear response in *females*, the current results suggest that the T allele may be associated with participation in high-risk sports in *males*. After exclusions, the number of participants in the genetic analyses described in this chapter was small, and a similarly small sample size was used in the Brocke et al. (2010) (total $n = 106$) study; therefore, these findings need to be replicated and sex should be considered in the analysis.

A trend for differences in allele frequencies between sports groups was also observed in a coding polymorphism (Val66Met) in the gene encoding brain-derived neurotrophic factor (*BDNF*). The trends were present when tested in a small subset matched for sex and recruitment location. The difference in allele frequencies between high- and low-risk sport participants was only significant in females ($p = .007$); there was a higher frequency of the C allele (coding for the Val amino acid) in the high-risk sport group. When only females recruited in France were included in the analysis, again frequency of Val carriers was higher ($p = .04$), even in the drastically reduced sample. The Val allele has previously been associated with high scores on

boredom susceptibility (a subscale in the Sensation Seeking Scale) (Kang et al., 2010), and has also been associated with high extraversion scores (Terracciano, Tanaka, et al., 2010); therefore, although the differences observed between sports group was not significant after correction, it is encouraging that the findings are in the same direction as previous associations. No other SNPs from genes that have previously been implicated in approach-related traits were significantly overrepresented in the high-risk sport group.

The sample sizes of the groups used in the genetic analyses were insufficient to discern small changes in allele frequencies; however, due to the challenges in recruiting highly specialized groups outside of university or clinical settings, sample sizes involving such subjects are often small (e.g., Ma et al., 2013). To improve statistical power, future studies investigating genetic and personality differences between high- and low-risk sport participants would benefit from much larger samples. In addition to increasing statistical power, larger samples would allow for separate subgroup analyses (e.g., genetic analyses grouped by sex). The only SNPs that were analyzed separately for males and females were the *MAO-A* rs6323, located on the X-chromosome, and the additional analyses following the marginally significant results in *STMN1* rs182455 and *BDNF* rs6265.

8.5.3   **Sex differences**

The proportions of males and females differed between high- and low-risk sports groups; however, males and females in their respective sport groups did not score differently on sensation seeking in the study described in the current chapter. Males generally score higher on sensation seeking than females in healthy control populations (Cross et al., 2011; Zuckerman & Kuhlman, 2000), but there is little research as to whether athletic females score on par with athletic males. Llewellyn and colleagues (2008) discussed the lack of research on gender

differences in high-risk sports and reported no significant gender differences in sensation seeking or impulsivity (as measured by the ZKPQ ImpSS) in their study on risk-taking behaviours in rock climbing. Female surfers and golfers (the study combined high- and low-risk groups for the gender analysis) score on par with males on SSS subscales of experience seeking and thrill and adventure seeking, but males scored higher than females on the disinhibition scale (Diehm & Armatas, 2004). Differences in sensation seeking between males and females participating in low-risk sports have been observed, although the margin of difference between sexes narrows when comparing higher-level athletes (i.e., athletes competing at national and international levels) (Braathen & Svebak, 1992).

Although no differences in personality traits were observed between the sexes, the trends for different allele frequencies between sport groups varied between males and females. A marginal association between sport participation and the Val66Met in *BDNF* was only observed in females, and the trend in rs182455 in *STMN1* was only observed in males. The sample sizes are too small to be conclusive, but other studies have reported sex-specific results (e.g., Brocke eet al., 2010). Future genetic studies should recruit samples large enough to allow for separate analyses in males and females, and future personality studies should explore the relationship between gender and sensation seeking in high-performing athletes in both high- and low-risk sports.

8.5.4 ADHD

Exclusions due to high scores on the ADHD adult self-report checklist further reduced the number of participants included in the genetic analyses. A number of the genes proposed as candidates for approach-related traits are also implicated in ADHD (Gizer et al., 2009); therefore, any positive screens (based on self-report symptom checklist) were excluded from the

genetic analysis. Over a quarter of athletes from both sport-cohorts reported scores suggesting the presence of ADHD-like symptoms. Although no formal diagnostic interview was included in the current study, the self-report checklist is commonly used as a screen for ADHD and the ASRS-V1.1 has strong concordance with clinician diagnoses (Kessler et al., 2007). To my knowledge, there are no studies to date that have investigated the incidence of ADHD (or ADHD-like symptoms) among proficient adult athletes. A commentary by Parr (2011) discusses trends for a higher incidence of ADHD in athletes; he suggests that sports may provide an outlet for individuals to focus their energy and to quiet distractions (Parr, 2011), but these comments were based on personal observation and no study was carried out. The only other study on ADHD in athletes reported a high incidence (5 out of 7 athletes) of ADHD within a boys' gymnastics team[36] (Kaufmann, Bajaj, & Schiltz, 2011); but the gymnast sample is too small to make inferences about ADHD incidence in athletes. Clearly, there is a need for more research in this area.

8.5.5 **Limitations and conclusions**

This chapter contributes valuable information to the field of high-risk recreation, an area of research that is greatly underrepresented in the literature. High- and low-risk athletes in the current study differed on a number of variables, including measures of personality, patterns of disinhibited behaviour, and there was a trend towards differences in two genetic variants (though the findings were not significant after correction for multiple tests). The in-depth characterization of these athletes described in the current chapter will hopefully provide insight for potential confounding variables that should be considered when comparing athletes differing

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[36] The gymnasts were described as "boys", but no ages were specified. ADHD classification was based on a questionnaire about ADHD diagnosis and stimulant medication use that was completed by parents.

in their choice of recreation; however, while the results are intriguing, for the reasons discussed below, all of the findings presented should be considered preliminary and require replication in larger, more homogeneous samples.

The results should be interpreted with caution, as there are a number of limitations stemming mainly from the challenge of recruiting large numbers of athletes participating in high-risk sports at a proficient level. Despite the burgeoning popularity of high-risk recreation, many of the sports described in Table 8-3 are still practiced by relatively few individuals (compared to low-risk sports). There are also geopolitical issues to contend with when designing studies, including practical considerations (sports may be restricted to specific environments and climates) and cultural constraints (e.g., B.A.S.E. jumping is illegal in most countries, but is legal in France). The effect of these types of issues contributed to the unplanned sample heterogeneity. Chamonix is a mountain town in the French Alps that is known for attracting adventurers (this is apparent from the number of offices offering adventure sport lessons, compared to Canadian mountain towns like Whistler or Squamish), and the town is also home to the first and largest mountain guide school in the world (www.chamonix-guides.com). For these reasons a majority of high-risk athletes were recruited in France, but unfortunately, recruitment of an equal number of athletes participating regularly in low-risk sports from France was met with difficulties. Sports membership in France is organized at the municipal level and there were no "University of Bordeaux" sports teams (e.g., golf, badminton, etc.) from which to recruit. Although the high- and low-risk groups differed systematically in terms of location of recruitment, all analyses of psychological variables accounted for these differences by comparing matched subsamples at the cost of reducing statistical power. The majority of the genetic analyses did not take recruitment location into account; however, the genotype distributions

between recruitment locations were the same across a majority of the SNPs tested and all participants reported three generations of European ancestry. Based on these results it is unlikely there was population stratification present within this sample; though this cannot be ruled out unless the samples were genotyped for a panel of ancestral informative markers. Another major limitation of the genetic results is that participants in the high- and low-risk groups may have experienced different sociocultural pressures that could have influenced the choice of sport participation. The high-risk sport group was a European-based international sample of Caucasian athletes, whereas the low-risk sport group was mostly from Western Canada. Obtaining large samples of culturally homogeneous high-risk athletes would be preferable but may be very difficult as many of the best recruitment sites include festivals, competitions, or tourist-filled mountain towns – all of which often attract international clientele.

Chapter 9: General discussion

9.1 Review of project findings

The series of research projects described in this thesis contributes valuable information on molecular genetics, personality, and demographics to the field of high-risk recreation, an area of study that is greatly underrepresented in the literature. The findings are not only of interest to researchers studying high-risk sports, but potentially to a wider audience of researchers in personality and behavioural genetics. The research focused on infrequently studied populations of healthy adults seeking risks through prosocial outlets (i.e., sports) rather than the more commonly studied community or clinical populations seeking risks through antisocial outlets (i.e., drugs, alcohol). The research combined the development of a domain-specific tool (Project 1) with an in-depth exploration of molecular variants associated with sensation seeking (Projects 2 and 3) and investigations of covariates associated with sensation seeking and sport participation (all projects, but with an emphasis in Project 3).

Specifically, the first project involved the development and validation of a new tool (the CSSQ-S) to measure sensation seeking in skiers and snowboarders. Strong psychometric properties and high re-test reliability of the instrument were shown in multiple independent populations. The CSSQ-S tool showed stronger predictive utility in predicting injury frequency compared to the broader trait measure, impulsive sensation seeking. The CSSQ was later generalized to contain items suitable for any of the following downhill sports: skiing, snowboarding, mountain biking, and kayaking. To facilitate research in France, a hub of high-risk recreation, a French version of the CSSQ was created for Project 3. Both the translated and generalized versions had reliabilities similar to original CSSQ-S described in Chapter 3. Phenotypes in Projects 2 and 3 were defined using the CSSQ and the ZKPQ Imp-SS scale(s), and

interestingly, there were associations in two studies between the CSSQ and genetic variants, but not with the broader trait measures.

The second project involved multiple investigations of variants in candidate genes for approach-related traits. The first study found a significant association between alleles at a SNP in *DRD4* (-521 C/T) and contextual sensation seeking in skiing, which was consistent with previous findings between the SNP and novelty seeking. This study was followed by a multi-SNP analysis in several candidate genes in a larger sample of skiers and snowboarders. The two-stage, joint-analysis study revealed a significant association with a single SNP in the *DRD3* (rs167771) and sensation seeking, which had previously only been investigated in a handful of studies on psychiatric phenotypes. The final study in Project 2 revealed no significant associations between sensation seeking and four *DRD4* promoter SNPs nor with a 120-bp tandem duplication (also in the promoter).

The final project involved an in-depth analysis of practitioners of high- and low-risk sports. The sport groups differed in sensation seeking, demographic characteristics, and disinhibited behaviours, and there were differences in allele frequencies between sport groups at two loci (*STMN1* rs182455 and *BDNF* rs6265) although the differences were not significant after correction for multiple tests. Among the sport participants reporting proficient skiing and snowboarding ability, there was an interaction between the *DRD4* exon III 48-bp VNTR and -521 C/T that was associated with domain-specific sensation seeking (CSSQ). Although the main effects of the -521 C/T polymorphisms were not significant in this sample, there was a trend for higher CSSQ scores in CC homozygotes (Chapter 7), which was consistent with the findings described in Project 2 (Chapter 4).

Discussions pertaining to the specific results of each study are described in respective chapters (Chapters 3 to 8). This final chapter will: 1) relate key findings to the broader field of approach-related traits and behavioural genetics; 2) highlight evolutionary mechanisms that may influence sensation seeking; 3) discuss sensation seeking as it relates to sport; 4) propose physiological mechanisms to explain the most significant findings (e.g., pertaining to the *DRD4*); and 5) discuss factors that may influence high-risk sport participation. Finally, this chapter includes a brief discussion of limitations of the present research and ideas for future directions.

9.2   Key findings

Patterns of sport-related behaviours, as measured by the CSSQ, are associated with the *DRD4*. There is strong support for the -521 C/T in association with contextual sensation seeking in downhill sports, but the VNTR may modulate the relationship. There is also support for the involvement of three other genes, *BDNF, DRD3*, and *STMN1,* in sensation seeking based on a quantitative trait analysis and a comparison of athletes participating in high- and low-risk sports. The data supporting the involvement of *BDNF* and *STMN1* in high-risk recreation participation are weaker than the relationships observed between the dopamine receptors (*DRD3* and *DRD4*) and sensation seeking; therefore, the following discussion focuses on latter findings (for a more detailed discussion of *BDNF* and *STMN1*, please see Chapter 8, section 8.5.2).

The associations with *DRD4* variants were only significant when the phenotype was defined by the CSSQ and the variant in *DRD3* was only associated with a sensation-seeking phenotype as defined by the ZKPQ subscale. There were no genetic associations with total scores on impulsivity or with impulsive-sensation seeking. It has been well documented that impulsivity is a heterogeneous trait (Evenden, 1999); therefore, combining scores from subscales

that contain both impulsivity and sensation seeking may result in a more heterogeneous phenotype. Genetic association studies commonly aim to define aetiologically homogeneous phenotypes (Noble, 2003), and the aetiology of impulsivity is not considered unitary (Evenden, 1999). Using narrow phenotypes defined by instruments that dissociate impulsivity and sensation seeking may be preferable to using constructs that contain "impulsive" items across multiple facets or that use total scores from heterogeneous subscales.

Variants in the *DRD4* have inconsistently been associated with novelty seeking (reviewed by M. R. Munafo et al., 2008; Oak et al., 2000; Paterson et al., 1999), but perhaps the novelty seeking phenotype, as measured using the Temperament and Character Inventory (TCI), is more heterogeneous (Gana & Trouillet, 2003; U. E. Lang et al., 2007) than either of the sensation-seeking measures used in the work described in this thesis. As discussed in Chapter 3, narrower traits like domain-specific sensation seeking may predict variance in specific outcomes not accounted for by more general traits (e.g., Paunonen & Ashton, 2001). The CSSQ showed stronger predictive utility (with respect to injury frequency) and defines a more focused phenotype than the ZKPQ ImpSS (combined scale). The components of the ZKPQ ImpSS scale can be divided into narrower phenotypes and the analyses described in Chapter 5 revealed an association between the ZKPQ sensation seeking subscale and a variant in *DRD3* that was not associated with the impulsivity subscale. The TCI novelty seeking scale similarly consists of multiple facets (four, each containing between 9 and 11 items), and factor analysis revealed only six (out of 40) items loaded significantly (>.40) onto a single factor solution (Gana & Trouillet, 2003), yet a majority of *DRD4* genetic association studies define the phenotype using the *total* novelty seeking score (M.R. Munafo et al., 2008). This phenotypic heterogeneity might imply

underlying genotypic heterogeneity, which would make it more difficult to find associations between the variables.

The definition of a precise phenotype is essential to genetic association studies, as demonstrated by the inconsistencies in the literature linking the serotonin transporter variable length polymorphism to avoidance-related traits. Genetic associations have been inconsistently reported, and a meta-analysis that grouped the phenotypes by personality instruments found significant results only in one subset that measured anxiety using the TCI harm avoidance subscale, but not when measured using the Five Factor neuroticism subscale (M. R. Munafo, Clark, & Flint, 2005). The scores derived from the two measures are moderately correlated (r = .54; De Fruyt, Van de Wiele, & Van Heeringen, 2000), and are usually grouped for meta-analysis, but subtle differences in phenotypic definition appear to influence whether or not genetic associations are observed (M. R. Munafo et al., 2005).

The *DRD4* and other genes involved in dopaminergic and serotonergic neurotransmission have not only been investigated in association with personality traits (e.g., Ebstein & Israel, 2009; M. R. Munafo et al., 2003; M. R. Munafo et al., 2008), but have more commonly been investigated in association with externalizing disorders, including, but not limited to: ADHD, substance use disorder, alcoholism, and gambling (Nernoda et al., 2011). Many of the above-mentioned disorders have heterogeneous aetiologies, which may account for some of the inconsistencies in the results of genetic association studies (J. E. McGeary et al., 2007; Sher et al., 2005; Sonuga-Barke, 2003). McGreary (2009) recommends the use of "intermediary phenotypes"[37] in the form of personality traits, lab-based assays, and neuroimaging techniques as a preferable way to explore the genetic underpinnings associated with potentially heterogeneous

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[37] Based on the "endophenotype" concept (reviewed by Gottesman & Gould, 2003).

psychopathologies. Subtypes of the above-mentioned disorders and co-morbidities between

disorders have been linked to high levels of impulsivity and sensation seeking (reviewed in J. S.

Kotler & McMahon, 2005; Sher et al., 2005; Verdejo-Garcia et al., 2008), but the two traits may

have distinct neurobiological influences (Dick et al., 2010; Magid et al., 2007) and the respective

genetic contributions may vary. High-risk athletes who do not report problematic substance use

may represent a unique population of very high sensation seekers free from the potentially

confounding heterogeneity of high impulsivity. High-risk athletes have been called the "true

arousal seekers", and were found to habituate more rapidly to visual stimuli (measured by event-

related potentials) compared to non-athletic extreme scorers on impulsive sensation seeking

(Fjell et al., 2007). Athletes who participate in high-risk sports might represent a homogeneous

group to study the complex genetic influences associated with extreme manifestations of the

sensation-seeking trait.

9.3   Evolutionary mechanisms

Today, high sensation seeking is most commonly associated with deviant behaviours but

in ancient times, sensation-seeking behaviour was both advantageous and potentially lethal.

High sensation seekers may have been more inclined to seek out new resources, which could

lead to increased survival and reproductive success, but these activities could also lead the high

sensation seeker towards danger and premature death. On the other end of the spectrum, a low

sensation seeker may not be able to obtain sufficient resources during hard times (thus limiting

personal survival), but may provide better care for their offspring (thus increasing offspring

survival rate). From an evolutionary perspective, the two patterns of behaviour may have been

differentially selected for depending on environmental conditions, resulting in balancing

selection and favouring the maintenance of both high- and low-sensation seeking in the species. As human survival is highly dependent on our culture, even traits that may have put an individual at risk could have been selected for if they greatly benefited his/her extended family. An optimal level of sensation seeking is necessary for survival, but too little or too much is less advantageous. Compared to the daily lives of our ancestors, the amenities of urban, modern life have limited routine natural outlets for thrill and adventure possibly leading individuals to satisfy a potentially innate need for stimulation through alternative risk-taking activities (e.g., drug use, gambling, sports).

One particular variant, the *DRD4* 48-bp VNTR, has been associated with approach-related traits (M. R. Munafo et al., 2008) and there is strong evidence for balancing selection acting on the locus based on the worldwide allelic distribution of the polymorphism (Ding et al., 2002; Wang et al., 2004). The ancestral and most common allele for the VNTR is the 4-repeat (4R) allele; and the 7-repeat (7R) allele, which arose from a series of spontaneous mutations, dates back to approximately 40,000 to 50,000 years ago (Wang et al., 2004). There is evidence of strong linkage disequilibrium in the regions surrounding the 7R allele, but there is significantly lower linkage disequilibrium in the region surrounding the 4R allele. Interestingly, there is a distinct breakdown of linkage within a ~300-bp region in the promoter that contains the -521 C/T SNP, that is not likely to be caused by a higher probability for mutations, since the 300-bp region does not differ in G-C content compared to surrounding regions (Wang et al., 2004). Both the VNTR and the -521 C/T have been associated with approach-related traits (e.g., novelty seeking), but low linkage between the variants in most European samples suggests that each variant may contribute to the phenotype independently.

In the European samples described in Chapter 7, the 4R allele was the most common, followed by the 7R, then the 2R. The 2R allele is less common in European populations, but is more common in Asian populations and is the youngest allele, putatively derived from the 7R morph (Wang et al., 2004). The pressures from balancing selection have resulted in relatively high frequencies of multiple alleles worldwide. The 7R allele, which is most commonly the allele associated with high novelty seeking (e.g., M. R. Munafo et al., 2008), may have been selected for during the out-of-Africa exodus leading to an increased frequency of the newer morph (Ding et al., 2002). Individuals with a greater ability to respond to novelty and willingness to take risks (characteristics of sensation seeking) might be considered "response ready" in environments demanding such adaptations, and this may have conferred a greater chance of survival (Wang et al., 2004). Such behaviours may be considered maladaptive in some environments (e.g., present-day classroom/work settings), but would have been advantageous in other environments (e.g., exploration, sport) (Ding et al., 2002).

9.4   Sensation seeking in athletes

9.4.1   Sensation seeking and performance

High sensation seeking *and* impulsivity are traits that are commonly associated with deviant risk-taking behaviours (Roberti, 2004), but high sensation seeking in the absence of impulsivity may be important for attaining peak performance in sport. For example, an alpine ski racer that places a high value on reward and is willing to take risks (i.e., part of the definition of sensation seeking), straddling the line between control and loss thereof, has the potential to achieve better results. A current example of this "all or fall" attitude is demonstrated by Lindsey Vonn, an American female alpine skier ranked among the top in the world, who is commonly

distinguished for her risk-all attitude approach to ski racing: often she either gets on the podium or she falls. Such patterns of sensation seeking and risk-taking associated with elite status do not just apply to high-risk sports. A large study on high-level national athletes (participating in all types of sports) in France found that elite athletes score significantly higher on sensation seeking (and measures of psychological well-being and self-confidence) than recreational athletes or non-athletic controls (Samadzadeh, Abbasi, & Shahbazzadegan, 2011). Similarly, elite springboard divers scored higher on sensation seeking than non-diving controls (Hinton-Bayre & Hanrahan, 1999), and high-level athletes across a range of sports scored higher on sensation seeking than moderate-level athletes (Braathen & Svebak, 1992). Sensation seeking may not only be a pre-requisite for participation in high-risk sports (Goma-i-Freixanet et al., 2012), it may be essential for attaining elite status in a variety of sports. Increased difficulty of a sport skill is often accompanied by a risk, but is generally rewarded with higher scores (in judged sports); athletes willing to take risks have the potential to achieve higher scores (or faster times in race-sports). For example, a figure skater high in sensation seeking may risk falling by attempting a harder element (i.e., quadruple jump) because the potential reward (i.e., points for difficulty) is deemed worth the risk. A low sensation seeker may not be willing to take the risk, choosing to skate a more conservative program. Although the benefit will not always exceed the cost (integral to the definition of risk), the athlete who never takes a chance by pushing to the limit of his/her physical ability may achieve less success.

In the final project described in this thesis, there was a difference in sensation-seeking scores between high- and low-risk athletes; which is consistent with the literature (Goma-i-Freixanet et al., 2012). The athletes studied, though proficient, were not "elite" athletes, and no comparisons were made with non-athletic controls; therefore it is not known whether elite high-

risk athletes score higher on sensation seeking or on par with elite low-risk athletes. This would

be an interesting question to pursue. While extreme sensation-seeking scores may sometimes be

viewed as maladaptive, extreme manifestations of the trait may be beneficial to sport

performance.

9.4.2   **Gender differences in sensation seeking**

Gender differences in sensation seeking typically seen in non-athletic populations (Cross

et al., 2011; Zuckerman & Kuhlman, 2000) may be absent or there may be smaller differences

between males and females in proficient athletic samples. In the studies described in this thesis,

males scored higher than females on global and domain-specific sensation seeking but only in

the projects limited to skiers and snowboarders. The observed gender differences are

comparable to the literature in healthy control populations (Cross et al., 2011; Zuckerman &

Kuhlman, 2000) and to other samples of skiers (Bouter et al., 1988; Cherpitel et al., 1998).

Interestingly, there were no differences in sensation seeking between the sexes in either the high-

or low-risk samples described in Chapter 8. Skiers and snowboarders were proficient (at least

intermediate), but the participants were not recruited on the basis of practicing their sport

regularly. On the other hand, both the high- and low-risk sport cohorts were selected because

they were proficient *and* regular practitioners of their sport. A study on mountaineers similarly

found no gender differences in sensation seeking (Burnik, Jug, & Kajtna, 2008) and female

surfers scored on par with male surfers on all but the disinhibition subscale from the Sensation

Seeking Scale (Diehm & Armatas, 2004). There are fewer studies that have measured sensation

seeking in low-risk sports, and while gender differences have been observed in low-risk sports,

the margin of difference between sexes narrows when comparing higher-level athletes (i.e.,

athletes competing at national and international levels) (Braathen & Svebak, 1992). Although no information about competition level was obtained, a number of the athletes in the low-risk sport group in the studies described in this thesis were members of university varsity or competitive adult teams. Future studies should include not only measures of ability, but rank or performance level in the sports surveyed.

9.5   Proposed mechanisms

While each of the three main projects described in this thesis aimed to investigate sensation-seeking trends in athletes, the primary goals of Projects 2 and 3 were to investigate whether genetic variants were associated with sensation seeking and/or recreation choice. There were significant associations between sensation seeking and *DRD4* alleles in two studies, but there are few hypothesized mechanisms in the literature to explain how the alleles might contribute to the sensation seeking phenotype. In particular, few studies have proposed a hypothesis as to why the *DRD4* -521 C allele, which may potentially increase D4 receptor density due to increased transcriptional efficiency (Okuyama et al., 2000), might predispose an individual to sensation seeking (see Table 4-1, Chapter 4 showing a list of -521 C/T studies to date). In fact most theories surrounding dopamine receptors hypothesize the opposite, for example: a decrease in D2-like (D2 and D3) receptor density has been associated with increased sensation and reward seeking (Buckholtz et al., 2010; Volkow et al., 2006; Zald et al., 2008). Most commonly, however, the decrease in receptor density associated with reward seeking that has been observed in other studies is with respect to the density of *autoreceptors* (which act via negative feedback on the dopaminergic neuron to decrease dopamine release) (reviewed in Beaulieu & Gainetdinov, 2011), and most studies refer to pre-synaptic D2 or D3 receptors only.

There are studies reporting the existence of pre-synaptic D4 receptors (Svingos, Periasamy, & Pickel, 2000), but they are not likely to have a role in modulating neurons in the nucleus accumbens (a major site of action of dopamine) (Mizuno, Schmauss, & Rayport, 2007). A mechanism linking increased *post*-synaptic D4 receptor density to approach-related traits, to my knowledge, has not been proposed. Therefore, the following mechanism should be considered highly speculative and is based on the available literature on D4-receptor-related neurotransmission.

The D4 receptor subtype is inhibitory as the binding of agonists on post-synaptic D4 receptors results in a decrease in cellular cAMP. Inhibition of an inhibitory synapse results in potentiation, and this mechanism has been proposed for the D4 receptors located in the prefrontal cortex (PFC) and the nucleus accumbens. There is a preferential distribution of D4 receptors on GABAergic (inhibitory) interneurons in the PFC (Mrzljak et al., 1996), and dopaminergic projections originating from the ventral tegmental area synapse with GABAergic neurons in the nucleus accumbens (Depue & Collins, 1999; Pierce & Kumaresan, 2006); these types of "feed-forward inhibition" of inhibitory pathways results in overall excitation (Lauzon & Laviolette, 2010). In other words, D4 activation can remove inhibitory influences in the PFC and the striatum thereby altering limbic and cortical function (Lauzon & Laviolette, 2010). Hypersensitive mesocortical and mesolimbic dopamine projections have been associated with drug craving in response to stimuli (Floresco & Tse, 2007; Pierce & Kumaresan, 2006). Perhaps the feed-forward inhibition of GABA neurons via D4 receptors also contributes to the sensation-seeking trait.

It is also important to understand that phasic bursts of dopamine are related to positive reinforcers (Tripp & Wickens, 2009) and may be involved in approach behaviour and in forming

associations between cues and reward; whereas, tonic dopamine levels may influence

generalized motivational dispositions towards reward (Luciana, Wahlstrom, Porter, & Collins,

2012). The dopamine-firing modes exert influences on each other, but how they interact to

regulate incentive motivation is less well understood (Luciana et al., 2012); although increased

dopaminergic tone purportedly decreases reward-related phasic bursts (Grace, 2000). Many

researchers have suggested that sensation seeking is a hyperdopaminergic trait, in that

individuals who report high sensation seeking have increased dopaminergic transmission (e.g.,

Cloninger, 1987; Gjedde, Kumakura, Cumming, Linnet, & Moller, 2010; Zuckerman, 2007a),

which perhaps translates to an increased motivational tendency to seek out reward. Similar

trends have been observed in animals; for example, hyperdopaminergic mice exhibit increased

sensation seeking (Pecina et al., 2003). Further in line with these findings, dopaminergic

neurotransmission was altered in *Drd4*-knockout mice, and the modified animals exhibited

reduced novelty seeking in the form of exploration (Rubinstein et al., 1997). If a lack of D4

receptors in mice results in reduced novelty seeking, then an increased density of receptors (if the

functional effects of the -521 C allele also occur *in vivo*) may result in increased novelty seeking.

Increased tonic dopaminergic transmission due to increased receptor density may lead to

increased motivational tendencies to seek out reward.

In comparison to the sparse literature on how the *DRD4* -521 C allele might contribute to

an approach-related phenotype, a number of theories have been proposed to explain associations

observed between the exon III 7R allele and novelty seeking. Exon III of the *DRD4* codes for

the third cytoplasmic loop of the G-protein coupled receptor (Van Tol et al., 1992). D4 receptors

expressing the 7R allele have blunted function compared to those with a 4R allele (Asghari et al.,

1995; Asghari et al., 1994). Wang et al. (2004) proposed that there is a "suboptimal" response

associated with novel stimuli (i.e., phasic burst) in carriers of the blunted 7R allele, and that

carriers would require increased dopamine to function normally, which they might obtain by

seeking novelty or taking risks. How the -521 C/T and VNTR alleles may interact to influence

sensation seeking is not known.

9.6   Potential factors influencing high-risk sport participation

9.6.1   Physiological factors

The previous section suggested possible mechanisms to relate sensation seeking and

genetic variants at the molecular level. While the molecular biology underlying this relationship

is not understood, a number of broader arousal theories to explain motivation for participation in

high-risk sports have been discussed in the literature. While the high-risk sports studied in the

current thesis range from seemingly "intense" gravity sports to potentially less intense downhill

sports, all of the sports involve either high speeds, heights, and/or risk-exposure – all factors that

might increase a person's level of arousal. Both of the above-mentioned hypothesized molecular

mechanisms fit nicely with the "optimal level of arousal" theory often associated with sensation

seeking. According to this theory, high sensation seekers are chronically under-aroused and seek

out increased stimulation to attain "normal" levels of arousal (Zuckerman, 2007a). Alternatively,

(or possibly jointly) the reward-related phasic burst in high sensation seekers may be greater

(i.e., they are hypersensitive to reward) than that in low-sensation seekers, further reinforcing

them to repeat the behaviours (Depue & Collins, 1999; Pickering, 2004). Perhaps the motivation

for sensation seeking in sport stems from a combination of these two mechanisms. People who

take up high-risk sports may have lower basal levels of arousal, and thus seek out intense stimuli

to reach an optimal set-point (I. H. Franken et al., 2006; Pain & Pain, 2005) and when they

experience reward in the form of an exciting experience the "exploration bonus" is perceived as positive (hedonic), making them more likely to repeat the activity. Low sensation seekers on the other hand, are less motivated to seek out arousal-inducing experiences, perhaps because they are closer to their optimal "set-point" while carrying out day-to-day activities. When faced with an exciting experience, the low sensation seeker may be pushed beyond his/her comfort zone and actually experience more anxiety (heightened avoidance systems), discouraging them from repeating the activity (i.e., inverted U-theory of arousal, Figure 1-2) (Cross et al., 2011; Zuckerman, 1994). These individual differences may be influenced by genetic variation and the *DRD4* is a promising candidate based on the findings from the research described in this thesis, but little is known about the molecular mechanisms involved.

9.6.2 **Environmental factors**

Genetic factors may influences an individual's reward-related motivational tendencies which may in turn affect recreation choice, but environmental factors are likely important as well. Environment factors, including peer-group, family, and culture, may influence a person's participation in high-risk sport; however, friends are more likely to influence the motivation to try a *new* sport (e.g., Celsi et al., 1993); whereas, the motivation for continued participation in a sport may be more intrinsically driven (this is seen in youth sport; (e.g., Coté & Hay, 2002)). Personality and intrinsic motivation may be especially important for extremely arousing sports, like skydiving and paragliding, where a person motivated by strong avoidance (and weak approach) may perceive the activity as highly aversive decreasing the likelihood of repeated participation.

The sensation-seeking trait has moderate heritability (.60), and heritability estimates for exercise habits (e.g., participation, frequency, duration) are as high as .85 (reviewed by De Geus & de Moor, 2008). Environmental influences on exercise habits play a role in childhood, but genetic factors explain a greater portion of variance in exercise participation in adolescence and both environmental and genetic factors appear to contribute equally to the variance in adulthood (reviewed by De Geus & de Moor, 2008). Although the twin studies reviewed on exercise habits did not provide details about the heritability of specific types of exercise, similar trends might be observed with respect to exercise in the form of high-risk sport. Genetic factors appear to play a role in exercise participation, but interactions between genotype and environment are likely important and such interactions have been found for genes implicated in sensation seeking in the current studies.

9.6.3   Gene-environment interplay

Gene-by-environment (GxE) associations have been reported for the *DRD4* exon III VNTR. A Finnish longitudinal study that followed children over 14 years found that those carrying the 2R or 5R of the *DRD4* 48-bp VNTR had higher novelty seeking scores if they had been raised in hostile environments, whereas no association between novelty seeking and the *DRD4* genotype was observed in children raised in non-hostile environments (Keltikangas-Jarvinen, Raikkonen, Ekelund, & Peltonen, 2004). Other studies exploring interactions between negative life events ranging from low socio-economic status to quality of parental interaction in infants found that individuals carrying the 7R allele (commonly considered the "risk" allele for externalizing disorders and approach-related traits) were more likely to exhibit externalizing phenotypes (aggressive behaviours; Nobile et al., 2007) or increased reward sensitivity

(sensation seeking; Sheese, Voelker, Rothbart, & Posner, 2007; delayed discounting task; Sweitzer et al., 2012) when confronted with adverse life events. The Finnish researchers mentioned above similarly reported a moderating effect of socio-economic status on the association between the *DRD4* VNTR variant and novelty seeking; however, oddly, children from higher socio-economic status carrying 2 or 5 repeat alleles scored the highest on novelty seeking (Lahti et al., 2006), contrary to previous studies reporting a link between the 7R allele and novelty seeking. It is important to note that the Finnish studies (Keltikangas-Jarvinen et al., 2003; Lahti et al., 2006) that observed associations with the 2R and 5R alleles were carried out in the *same* participants (a population-based sample of Finnish children).

Recently, a meta-analysis provided support for GxE interactions between dopaminergic genes and childhood rearing playing a significant role in influencing externalizing phenotypes. Bakerman et al. (2011) proposed that children exhibit differential susceptibility to environmental effects of rearing depending on their genotype, in that genetically "vulnerable" children are more susceptible to environmental influences, either positive or negative (Bakermans-Kranenburg & van Ijzendoorn, 2011). A challenge with gene-environment studies is that many involve longitudinal or observation-based designs, which are costly and differ in feasibility compared to cross-sectional association studies. The GxE studies that are not longitudinal may be subject to recall bias if, for example, the researchers inquire about negative life events by questionnaire (e.g., Reiner & Spangler, 2011; Adverse Life Events Scale). Future studies on associations between genetic variants and sensation seeking through sport might benefit from considering the influence of the environment. More extensive history, especially concerning quality of mentor relationships and socioeconomic status would be interesting variables to consider. A positive mentor may reinforce sensation seeking through sport in carriers of a "risk" allele, but may have

no effect on carriers of the alternate allele; alternatively, the absence of positive reinforcement may lead carriers to other, more deviant risk-taking behaviours.

9.7   Limitations of the current research

Personality is a difficult phenotype to measure since it is often based on self-report questionnaires. The "common-method bias" (when the dependent variable is measured using one source, e.g., self report) is a potential threat to a study's internal validity (Podsakoff et al., 2003). A peer-questionnaire was included in Projects 1 and 2 in an attempt to verify the accuracy of the self-report; however, this questionnaire applies only to the domain-specific sensation seeking measure (not the ZKPQ), and was not included in all of the studies. It was also not included as a phenotypic measure for the genetic association studies because too few peers were present at the time of sampling. Future studies would benefit from creating an aggregate score for a phenotype based on a combination of self-report sport measures (M. R. Munafo et al., 2003) and actual behavioural measures. Examples of behavioural measures include a laboratory task on risk taking like the BART[38] or behaviours could be observed in the field (e.g., film skiers taking part in a freeride competition and code behaviours based on level of "sensation seeking" or "risk").

In addition to strong phenotypic measures, genetic associations strive for large, ethnically homogeneous samples. Participants were recruited outside university and clinical settings (common sources for large samples), and due to the limited inclusion criteria (i.e., relating to proficiency and frequency of sport participation) the pool of subjects from which to draw participants was small in comparison to general population-based personality and genetics

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[38] Balloon analogue risk task.

studies. As such, the sample sizes are smaller than ideal for genetic association studies. Genetic studies also strive for homogeneous samples, and though all participants were self-reported Caucasians, the sport groups were culturally heterogeneous. A large number of athletes recruited in Western Canada were travellers living in ski towns for a season, similarly, a number of athletes recruited in Chamonix were high-risk sport enthusiasts that had moved to the mountains to pursue their sport. This uncontrolled variability between participants may have impacted the results. A majority of the high-risk sports described in the current thesis take place in mountain towns, places that draw a large percentage of international seasonal workers (e.g., a substantial portion of Whistler's population is composed of transient, seasonal workers based on a report by Whistler Municipality (2005)); therefore, there are benefits (e.g., greater potential participant pool) and drawbacks (e.g., cultural heterogeneity) to sampling from these mountain towns.

The studies described in this thesis did not take environmental factors into account when studying genetic associations, and the variance due to cultural differences cannot be estimated, but attempts were made to ensure that participants were ethnically homogeneous. All participants included in the genetic analyses in the current thesis reported being of European descent. Self-reported European ancestry has been shown to be a proxy for genetic ancestry (Attia et al., 2009; Divers et al., 2011; Dumitrescu et al., 2010). For example, within a large sample ($n = 170,000$) of individuals reporting European descent recruited from Britain there were small differences in allele frequencies between geographic regions, but large differences in allele frequencies were only observed in thirteen genomic regions, most of which were situated in known genes (none of which are included in this dissertation) (Burton et al., 2007). Furthermore, studies comparing self-reported ancestry with ancestry obtained using ancestral informative markers found that there were no significant differences between the two measures

(Divers et al., 2011; Dumitrescu et al., 2010). While it would have been ideal to use a panel of ancestral markers to test for deviations in population structure, the number of markers required to adequately test (96 to 300+) for population stratification far exceeded the number of variants analyzed (Divers et al., 2011). Limited by financial constraints, the studies described in this dissertation did not include such markers. Because the genetic studies only included Caucasian participants, the results have limited generalizability and studies should be replicated in other populations.

9.8   Future directions

The high-risk sport literature is relatively sparse compared to the literature on other forms of risk-taking and there are many avenues of research that would be interesting to pursue. Areas of study that have little or no research relating to high-risk recreation include: gene by environment interactions, epigenetics, neuroimagery, and psychophysiology, to name a few. The field of epigenetics would be an especially intriguing field for studying sensation seeking, because to my knowledge, there are very few studies that have explored epigenetic influences relating to personality.

9.8.1   Epigenetics

While a majority of behavioural genetic studies have has centred on candidate gene association studies, in recent years there has been increased interest in epigenetics among the psychiatric community, and this field represents a promising future direction for genetic studies on sensation-seeking phenotypes. Epigenetics refers to non-sequence modifications of DNA, either at the nucleotide or the nucleoprotein (e.g., histones) level. These modifications affect the

accessibility of the DNA to polymerases and therefore are often involved in gene regulation. In mammals, DNA-base epi-modification involves the addition of a methyl group (methylation) to cytosines; however, only when the cytosine is followed by a guanine (i.e., CpG dinucleotides). CpG sites are often found in clusters (called CpG islands) in or near the regulatory regions of genes and, when methylated, tend to suppress expression of the gene (Hanna et al., 2012).

DRD4 is of particular interest for epigenetic studies because the promoter region has a very rich G-C content (71%), and contains two CpG islands in the 5' region between bases at -900 and +500 (Kamakura, Iwaki, Matsumoto, & Fukumaki, 1997). Methylation profiles at the *DRD4* promoter were concordant between mono- and di-zygotic twins (DNA extracted from buccal cells), suggesting the importance of the family environment and that *DRD4* methylation is not necessarily heritable (Wong et al., 2010), and these differences in methylation were apparent at a young age and varied between time points (twins were assessed at 5 and 10 years of age). Very few studies have investigated methylation profiles of the *DRD4* promoter, and to my knowledge none have examined *DRD4* methylation in association with personality traits. There have, however, been studies on epigenetic influences on externalizing disorders. A recent study on alcohol dependence examined 382 CpG sites in peripheral tissue cells (lymphocytes) across 82 candidate genes for alcoholism, including multiple neurotransmitter pathway genes (i.e., genes encoding receptors and transporters for serotonin, dopamine, GABA, glutamate) and found hypermethylation at multiple loci in the alcohol dependent group compared to controls. Notably, there was hypermethylation at a single CpG site in the *DRD4* promoter and multiple sites in serotonin receptor subtype 3A (H. P. Zhang et al., 2013). The influence of polymorphisms on *DRD4* methylation has been investigated and differences in methylation were observed between genotypes at multiple *DRD4* promoter loci, particularly at the -906 T/C (dbSNP rs3758653)

(Docherty et al., 2012). A number of reviews propose epigenetic mechanisms, to explain GxE interactions, and to account for the "missing heritability" in psychiatric phenotypes; however, it appears that there is still large gap in the literature with regards to epigenetic influences on personality and psychiatric phenotypes.

9.8.2 Personality and disinhibited behaviours in risky recreation

The bulk of studies on high-risk recreation have focused on personality traits; however, there are other avenues relating to personality and/or employing longitudinal research designs that warrant further study. For example, it would be interesting to investigate impulsivity in high-risk sport both in general and as it relates to sport injury or other disinhibited behaviours (e.g., substance use, alcohol use). Studies on personality traits in high-level athletes are limited, and it would be interesting to investigate gender differences in traits among high-level athletes practicing either high- or low-risk sports and to investigate whether high-sensation seeking is related to performance in elite athletes. Finally, longitudinal studies that investigate whether youth designated as "at-risk" (either based on personality assessments or the presence of externalizing symptoms) would benefit from exposure to high-risk sports – potentially as an alternative outlet for sensation seeking.

A Vancouver-based program called Take a Hike (TAH, an established adventure-based learning program for at-risk youth) represents a potential application for the proposed research. At-risk youth in the program are introduced to wilderness sports through weekly excursions that combine academics and adventure. Improvements on a number of psychological and fitness measures were observed between two time-points (4 months apart) in a small pilot study, and an 8-month longitudinal study is currently underway (Burr & Thomson, 2013). The students in the

TAH program are not necessarily all high sensation seekers, but if engagement in stimulating sports results in reduced disinhibited behaviours and improved well-being among a small group of at-risk youth, the potential benefits in a group of adolescents and young adults exhibiting high sensation-seeking tendencies may be even greater.

9.9   Conclusions

The results described in this thesis provide support for using a narrow, domain specific measure of sensation seeking to characterize phenotypes for genetic association studies in downhill sports participants. The new phenotypic tool is moderately correlated with sport ability, a factor that should be considered for future studies. The results also provide support for associations between genetic variants from *DRD3* and *DRD4* and contextual and global sensation seeking. Many of the results were consistent with previous studies on variants in the dopamine receptor genes, although numerous other genes that had previously been associated with approach-related traits were not associated with sensation seeking in the current thesis. Athletes participating in high-risk sports score higher on sensation-seeking measures than their low-risk counterparts, but do not differ in impulsivity. High-risk recreation enthusiasts represent an interesting group in which to study correlates of sensation seeking, potentially unconfounded by impulsivity.

The willingness to take risks, which is a facet of the sensation-seeking trait is essential to attaining high levels of competitiveness in many sports. That this behaviour is, to some degree, predicted by genetic background provides a novel insight into the potential antecedents of performance. Numerous studies have shown that high sensation seekers choose high-risk pastimes, but there has been little research into physiological and genetic variables in high-risk

athletes. Researchers have commonly studied sensation seeking by including practitioners of deviant thrill seeking outlets (e.g., gambling and drug use), yet high-risk sports create a novel setting to investigate correlates between sensation-seeking behaviours and biological variables in the laboratory or in the field. Understanding that some athletes are naturally more risk-seeking than others can inform sports/school programs to better engage high sensation seekers in sports that satisfy their desires for risk taking while fostering discipline and physical fitness – potential "positive side effects" of high-risk recreation through sport.

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Appendices

Appendix A   Descriptions of high-risk sports

Sport	Description
Adventure racing	An endurance race typically involving orienteering, trail running, mountain biking, white-water kayaking, and/or rappelling.
BASE jumping	A gravity sport that involves jumping with a parachute off of Buildings, Antennas, Spans (bridges), or Earth (cliffs, abysses).
BMX	A cycling sport that involves racing bicycles in motocross style (riders in heats racing at the same time) on a dirt track riddled with jumps and obstacles.
Bungee jumping	A gravity sport that involves jumping from a span while attached by a harness to a long elastic cord.
Car (auto) racing	Involves racing cars on a track.
Cave diving	A water sport that involves scuba diving in underwater (or partially underwater) caves.
Caving (spelunking or potholing)	A land sport that involves squeezing through narrow tunnels, exploring unknown territory in caves.
Cliff jumping	A water/gravity sport that involves jumping off a cliff into water.
Climbing (rock)	A mountain sport that involves ascending a rock face. There are multiple styles: Bouldering – climbing short routes (< 3-5 meters) without a rope. Top-roping – climbing with a rope already secured above. Lead climbing – bringing the rope and securing it to the wall on the way up. Traditional climbing – placing protection in natural features of the rock. Soloing – climbing walls without any protection. Deep water soloing – climbing without protection above water.
Dirt biking (motocross in EU)	Riding a motorcycle off-road.
Freeride skiing or snowboarding (Big mountain)	A form of off-piste skiing that involves navigating natural hazards (cliffs, tree stumps, avalanches). Sometimes called "big mountain"
Freestyle skiing or snowboarding	A form of skiing devoted to moguls and aerials. Today freestyle skiing does not always include moguls and occurs mostly in terrain parks.
Hang gliding	A gravity sport similar to paragliding, however the glider has a more structured frame. Take-off most often involves running off a high piece of land in order to catch a draft.
High lining*	A mountain sport that involves walking across a nylon cord winched tightly between two high points spanning a gap.
Ice climbing	A mountain sport that involves ascending frozen waterfalls.
Kite surfing	A water sport that combines paragliding and surfing: riders are harnessed to a kite and they ride a surfboard (on water) propelled by the wind.
Luge	A sliding sport that involves lying supine on a sled and sliding down an iced, serpentine downward-sloping track.
Mountaineering (alpinism in EU)	A mountain sport that involves ascending mountains. Typically includes a combination of rock and ice climbing, and rappelling. *note: hiking is not the same as mountaineering.
Mountain biking (VTT in France)	A cycling sport that involves riding on dirt trails. Most popular types include downhill riding and cross country riding. Both involve navigating natural or man-made obstacles (tree stumps, rocks, planks, bridges) at high speeds.
Paragliding	A gravity sport that involves flying while suspended by a lightweight fabric "wing" attached to flier via strings to a harness. Typically launched by foot from a high point of land.
Parkours (free-running)	A form of urban running that involves jumping off structures (e.g., roof top to roof top) or creating an obstacle course from urban structures (benches, railing, walls,

Sport	Description
	roofs). Involves a combination of balance, acrobatics, and endurance.
Rappelling (abseiling in UK)	A gravity sport that involves the descent from a rock face (or mountain route) using a rope. Climbers use this method to descend from a climb, but rappelling is also a sport practiced by non-climbers.
Sailing	Navigating a vessel propelled by the wind.
Skateboarding or longboarding	An urban sport involving balancing on a small plank mounted with 4 wheels. Typically involves riding ramps and combining speed with acrobatic moves. Longboarding is a subgenre of skateboarding in which the boards are longer, and the primary goal is to ride down paved hills.
Ski or snow cross	Similar to motocross, but on snow. Multiple riders race simultaneously around a ski/snowboard track riddle with jumps and turns.
Skydiving	A gravity sport that involves jumping from a plane with a parachute.
Speed riding or speed flying	A combination of skiing and paragliding. Sometime done on flat open terrain (e.g., frozen lake), sometimes down slopes. Skier alternates between skiing and flying.
Speed skiing	Skiing at very high speeds (speed skiers do not turn, they go straight and are most commonly in tuck position). Current world record is 251km/h (wikipedia).
Steep skiing (pente-raide in EU)	A genre of skiing that mixes mountaineering and skiing. The mountaineering skills are required to ascend to the peak of a mountain, the skier then descends on skis and commonly has to navigate narrow, steep chutes.
Street luge	Similar to luge described above, but instead of sliding on ice, the sled has wheels and the athletes slide down paved hills.
Surfing	A water sport that involves standing on a surfboard and riding waves.
Whitewater kayaking	A water sport that involves paddling down moving water (i.e., rivers, waterfalls).
Wind surfing	A water sport that combines surfing and sailing. The surfboard is powered by the wind.
Wing-suit flying	A gravity sport that occurs that involves a special suit to create a wing between a person's arms and torso. Can be combined with either skydiving (from a plane) or BASE-jumping. Wing-suit flying allows the diver to slow down (prolong air-time) or to navigate through cliffs and obstacles (in BASE jumping).

Note: common categories: gravity sports (downhill sports like skiing, biking, sliding are sometimes included in this category), mountain sports (could be called anti-gravity sports, involves ascension), water sports (includes under and over water). EU = European Union.

Appendix B Relationships between impulsive sensation seeking and other approach measures

Data shown in Tables B1 and B2 below are taken from a study that was done in collaboration with Dr. Scott Carlson through the UBC Department of Psychology "subject pool". University students completed a series of questionnaires on disinhibited behaviours and personality traits. Table B1 shows participant demographics, and Table B2 shows the correlations between various personality measures.

Table B1

Descriptive statistics for participant demographics

Variable	
Sex, m/f	144/140
Ethnicity, *n* (%)	
East Asian	107 (38)
European	117 (42)
Other	58 (20)
Age (years)	20.93 ± 0.14
Years in university	2.83 ± 0.07

Note. Mean ± standard error. Ethnic groups representing less than 5% of the group composition were combined in the "other" ethnicity group.

Table B2

Pearson correlations involving Personality Scales with Reward and Punishment Sensitivity and Rash Impulsivity

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1	BAS-D																	
2	BAS-FS	.38**																
3	BAS-RR	.48**	.47**															
4	E	.36**	.36**	.28**														
5	SS	.26**	.60**	.21**	.43**													
6	SS-Z	.16**	.60**	.14*	.30**	.68**												
7	SR	.36**	.52**	.24**	.39**	.45**	.41*											
8	N	-.15*	-.17**	-.15*	-.47**	-.31**	-.14*	-.06										
9	BIS	-.04	-.14*	.31**	-.21**	-.36**	-.30**	-.04	.41**									
10	SP	-.30**	-.32**	-.11	-.56**	-.47**	-.36**	-.11	.54**	.52**								
11	C-rev	-.28**	.09	-.22**	-.29**	-.01	.14*	.12*	.39**	.03	.28**							
12	Imp-Z	.01	.43**	-.04	.09	.33**	.56**	.40**	.15*	-.15*	-.07	.50**						
13	NU	.09	.25**	-.02	-.04	.15*	.26**	.38**	.50**	.11	.25**	.46**	.59**					
14	PU	.03	.32**	-.09	.06	.26**	.39**	.45**	.24**	-.06	.11	.38**	.61**	.73**				
15	Pers-rev	-.29**	.04	-.31**	-.26**	-.13*	.09	.07	.39**	.00	.27**	.76**	.48**	.45**	.37**			
16	Pre-rev	.02	.33**	-.12*	.15*	.26**	.45**	.30**	.09	-.25**	-.23**	.38**	.67**	.40**	.43**	.43**		
17	ImpSS-Z	.10	.60**	.07	.26**	.63**	.94**	.46**	-.03	-.26**	-.28**	.31**	.82**	.45**	.54**	.28**	.60**	

Note. n = 279. BAS-D = BAS Drive, BAS-FS = BAS Fun Seeking, BAS-RR = BAS Reward Responsiveness E = Extraversion, SS = UPPS-P Sensation

Seeking, SS-Z = ZKPQ Sensation Seeking, SR = SPSRQ Sensitivity to Reward, N =IPIP Neuroticism, SP = SPSRQ Sensitivity to Punishment, C = IPIP

Conscientiousness, Imp-Z = ZKPQ Impulsivity, NU = UPPS-P Negative Urgency, PU = UPPS-P Positive Urgency, Pers = UPPS-P Perseverance, Pre = UPPS-P

Premeditation, ImpSS-Z = ZKPQ Impulsive sensation seeking, Rev = reverse scored scales.

*p < .05, **p < .01

Appendix C Zuckerman Kuhlman Personality Questionnaire (full version, Zuckerman

et al., 1993)

ITEM		TRUE	FALSE
1	I tend to begin a new job without much planning on how I will do it	A	B
2	I do not worry about unimportant things.	A	B
3	I enjoy seeing someone I don't care for humiliated before other people.	A	B
4	I never met a person that I didn't like.	A	B
5	I do not like to waste time just sitting around and relaxing.	A	B
6	I usually think about what I am going to do before doing it.	A	B
7	I am not very confident about myself or my abilities.	A	B
8	When I get mad, I say ugly things.	A	B
9	I tend to start conversations at parties.	A	B
10	I have always told the truth.	A	B
11	It's natural for me to curse when I am mad.	A	B
12	I do not mind going out alone and usually prefer it to being out in a large group.	A	B
13	I lead a busier life than most people.	A	B
14	I often do things on impulse.	A	B
15	I often feel restless for no apparent reason.	A	B
16	I almost never litter the streets.	A	B
17	I would not mind being alone in a place for some days without any human contacts.	A	B
18	I like complicated jobs that require a lot of effort and concentration.	A	B
19	I very seldom spend much time on the details of planning ahead.	A	B
20	I sometimes feel edgy and tense.	A	B
21	I almost never feel like I would like to hit someone.	A	B
22	I spend as much time with my friends as I can.	A	B
23	I do not have a great deal of energy for life's more demanding tasks.	A	B
24	I like to have new and exciting experiences and sensations even if they are a little frightening.	A	B
25	My body often feels all tightened up for no apparent reason.	A	B
26	I always win at games.	A	B
27	I often find myself being "the life of the party".	A	B
28	I like a challenging task much more than a routine one.	A	B
29	Before I begin a complicated job, I make careful plans.	A	B
30	I frequently get emotionally upset.	A	B
31	If someone offends me, I just try not to think about it.	A	B
32	I have never been bored.	A	B
33	I like to be doing things all of the time.	A	B
34	I would like to take off on a trip with no pre-planned or definite routes or timetables.	A	B

ITEM		TRUE	FALSE
35	I tend to be oversensitive and easily hurt by thoughtless remarks and actions of others.	A	B
36	In many stores you just cannot get served unless you push yourself in front of other people.	A	B
37	I do not need a large number of casual friends.	A	B
38	I can enjoy myself just lying around and not doing anything active.	A	B
39	I enjoy getting into new situations where you can't predict how things will turn out.	A	B
40	I never get lost, even in unfamiliar places.	A	B
41	I am easily frightened.	A	B
42	If people annoy me I do not hesitate to tell them so.	A	B
43	I tend to be uncomfortable at big parties.	A	B
44	I do not feel the need to be doing things all of the time.	A	B
45	I like doing things just for the thrill of it.	A	B
46	I sometimes feel panicky.	A	B
47	When I am angry with people I do not try to hide it from them.	A	B
48	At parties, I enjoy mingling with many people whether I already know them or not.	A	B
49	I would like a job that provided a maximum of leisure time.	A	B
50	I tend to change interests frequently.	A	B
51	I often think people I meet are better than I am.	A	B
52	I never get annoyed when people cut ahead of me in line.	A	B
53	I tend to start my social weekends on Thursdays.	A	B
54	I usually seem to be in a hurry.	A	B
55	I sometimes like to do things that are a little frightening.	A	B
56	Sometimes when emotionally upset, I suddenly feel as if my legs are unsteady.	A	B
57	I generally do not use strong curse words even when I am angry.	A	B
58	I would rather "hang out" with friends rather than work on something by myself.	A	B
59	When on vacation I like to engage in active sports rather than just lie around.	A	B
60	I'll try anything once.	A	B
61	I often feel unsure of myself.	A	B
62	I can easily forgive people who have insulted me or hurt my feelings.	A	B
63	I would not mind being socially isolated in some place for some period of time.	A	B
64	I like to wear myself out with hard work or exercise.	A	B
65	I would like the kind of life where one is on the move and travelling a lot, with lots of change and excitement.	A	B
66	I often worry about things that other people think are unimportant.	A	B
67	When people disagree with me I cannot help getting into an argument with them.	A	B
68	Generally, I like to be alone so I can do things I want to do without	A	B

ITEM		TRUE	FALSE
	social distractions.		
69	I never have any trouble understanding anything I read the first time I read it.	A	B
70	I sometimes do "crazy" things just for fun.	A	B
71	I often have trouble trying to make choices.	A	B
72	I have a very strong temper.	A	B
73	I have never lost anything.	A	B
74	I like to be active as soon as I wake up in the morning.	A	B
75	I like to explore a strange city or section of town by myself, even if it means getting lost.	A	B
76	My muscles are so tense that I feel tired much of the time.	A	B
77	I can't help being a little rude to people I do not like.	A	B
78	I am a very sociable person.	A	B
79	I prefer friends who are excitingly unpredictable.	A	B
80	I often feel like crying sometimes without a reason.	A	B
81	No matter how hot or cold it gets, I am always quite comfortable.	A	B
82	I need to feel that I am a vital part of a group.	A	B
83	I like to keep busy all the time.	A	B
84	I often get so carried away by new and exciting things and ideas that I never think of possible complications.	A	B
85	I don't let a lot of trivial things irritate me.	A	B
86	I am always patient with others even when they are irritating.	A	B
87	I usually prefer to do things alone.	A	B
88	I can enjoy routine activities that do not require much concentration or effort.	A	B
89	I am an impulsive person.	A	B
90	I often feel uncomfortable and ill at ease for no real reason.	A	B
91	I often quarrel with others.	A	B
92	I probably spend more time than I should socializing with friends.	A	B
93	It doesn't bother me if someone takes advantage of me.	A	B
94	When I do things, I do them with lots of energy.	A	B
95	I like "wild" uninhibited parties.	A	B
96	After buying something I often worry about having made the wrong choice.	A	B
97	When people shout at me, I shout back.	A	B
98	I have more friends than most people do.	A	B
99	Other people often urge me to "take it easy	A	B

Appendix D ImpSS subscale from the ZKPQ, from Zuckerman et al., 1993

Please rate the extent to which you agree or disagree with the following statements.
Circle the appropriate answer. A = True, B = False.

ITEM		TRUE	FALSE
1	I tend to begin a new job without much planning on how I will do it.	A	B
2	I usually think about what I am going to do before doing it.	A	B
3	I often do things on impulse.	A	B
4	I very seldom spend much time on the details of planning ahead.	A	B
5	I like to have new and exciting experiences and sensations even if they are a little frightening.	A	B
6	Before I begin a complicated job, I make careful plans.	A	B
7	I would like to take off on a trip with no preplanned or definite routes or timetables.	A	B
8	I enjoy getting into new situations where you can't predict how things will turn out.	A	B
9	I like doing things just for the thrill of it.	A	B
10	I tend to change interests frequently.	A	B
11	I sometimes like to do things that are a little frightening.	A	B
12	I'll try anything once.	A	B
13	I would like the kind of life where one is on the move and traveling a lot, with lots of change and excitement.	A	B
14	I sometimes do "crazy" things just for fun.	A	B
15	I like to explore a strange city or section of town by myself, even if it means getting lost.	A	B
16	I prefer friends who are excitingly unpredictable.	A	B
17	I often get so carried away by new and exciting things and ideas that I never think of possible complications.	A	B
18	I am an impulsive person.	A	B
19	I like "wild" uninhibited parties.	A	B

Items 1, 2 (reverse-scored), 3, 4, 6 (reverse scored), 10, 17, 18 represent the impulsivity

factor. Items 5, 7, 8, 9, 11, 12, 13, 14, 15, 16, 19 represent the sensation seeking factor.

Appendix E Summary of variants previously studied in association with approach- or avoidance phenotypes

Gene	Polymorphism	dbSNP ID	Location	Allele frequency		Phenotypes	References
BDNF	Val66Met	rs6265	Exon 2	.80G	.20A	E, I, N, SS	(Frustaci et al., 2008*; Kang et al., 2010*; Terracciano, Tanaka, et al., 2010*)
COMT	Val158Met	rs4680	Exon 3	.48G	.52A	BPD, E, Imp, NS, RD, SS, startle, SUD (cocaine, meth), sexual RT	(Benjamin et al., 2000*; Gallinat et al., 2003; Strobel et al., 2003*; Tsai et al., 2004*; Reuter and Hennig 2005*; Golimbet et al., 2007*; Hosak et al., 2007*; Ishii et al., 2007; Lang et al., 2007*; Yacubian et al., 2007*; Lohoff et al., 2008*; Montag et al., 2008*; Nemoda et al., 2010; Bousman et al., 2010*)
COMT	C/T	rs4633	Exon 3	.60C	.40C	ADHD, NS	(Choudhry et al., 2012; Halleland et al., 2009; Roe et al., 2009*)
COMT	A/G	rs6269	upstream	.60A	.40G	ADHD, financial RT	(Choudhry et al., 2012; Halleland et al., 2009*)
DAT1	1343 A/G	rs6347	Exon 9	.90A	.10G	ADHD, SUD (meth)	(Feng et al., 2003; Ujike et al., 2003)
DAT1	C/T	rs27072	3' UTR	.80C	.20T	ADHD, Imp	(Ouellet-Morin et al., 2008*)
DAT1	40-bp VNTR (9 or 10 repeats)	-	3' UTR	.90 10R	.10 9R	ADHD, AUD, BART, BPD, ODD, NS, smoking, SUD	(Comings et al., 1996*; Blum et al., 1997*; Jorm et al., 2000; Bau et al., 2001*; Hong et al., 2003; Ujike et al., 2003*; Yacubian et al., 2007*; Hou and Li, 2009; Nemoda et al., 2010; Mata et al., 2012*)
DBH	-1021 C/T (-970 C/T)	rs1611115	upstream	.80C	.20T	ADHD, AUD, CD, ODD, TS,	(Comings et al., 1996; Kamata et al., 2009*)
DRD2	Taq1A (in ANKK1)	rs1800497	downstream	.74G	.26A	ADHD, BPD, CD, ODD, gambling, Imp, NS, SS, smoking,	(Comings et al., 1996*; Blum et al., 1997*; Comings et al., 1997*; Noble et al., 1998*; Ratsma, van der Stelt, Schoffelmeer, Westerveld, & Gunning, 2001*; Berman, Ozkaragoz, Young, & Noble, 2002; Eisenberg et al., 2007*; Shanahan, Erickson, Vaisey, & Smolen, 2007*; Esposito-Smythers et al. 2009*; Hou & Li, 2009*; Nemoda et al. 2010; Moyer et al., 2011*)
DRD2	Taq1B	rs1079597	Intron 1	.85G	.15A	BPD	(Nemoda et al., 2010)
DRD2	Taq1D	rs1800498	Intron 2	.60T	.40C	BPD	(Nemoda et al., 2010)
DRD3	Ser9Gly	rs6280	Exon 2	.55T	.45C	AUD, NS, OCD	(Duaux et al., 1998*; Staner et al., 1998*; Gorwood et al., 2001*; Joyce et al., 2003; Vandenbergh et al., 2007*)
DRD3	A/G	rs167771	Intron 2	.65A	.35A	ASP	(deKrom et al., 2009*; Staal et al, 2011*)
DRD3	DdeI (A-48G)	rs686	5' UTR exon 2	.60A	.40G	AUD, Nicotine dep, SS, SUD, Scz	(Comings et al., 1997*; Limosin et al., 2003*; Liu et al., 2006*; Batel et al., 2008*; Huang, H.Y., et al., 2010*; Zhu et al., 2011*)

Gene	Polymorphism	dbSNP ID	Location	Allele frequency		Phenotypes	References
DRD4	48 bp VNTR 'S' short < 6R; 'L' long >5R		Exon 3	.82 S	.18 L	AUD, BPD, E, HA, Imp, NS, financial RT, sexual RT, rxn time, SS, SUD	(Benjamin et al., 1996*; Ebstein et al., 1996*; Muramatsu, Higuchi, Murayama, Matsushita, & Hayashida, 1996*; Ono et al., 1997*; Noble et al., 1998*; Ekelund, Lichtermann, Jarvelin, & Peltonen, 1999*; Benjamin et al., 2000*; M. Kotler et al., 2000; Bau et al., 2001; Mitsuyasu et al., 2001; Szekely et al., 2004; Eisenberg et al., 2007*; McGeary et al., 2007*; Congdon, et al., 2008*; Kang, Nanikoong, & Kim, 2008*; B. C. Campbell et al., 2010; Dreber et al., 2009*; Kuhnen and Chiao, 2009*; Roussos et al., 2009*; Garcia et al., 2010*; Nemoda et al., 2010; Dreber et al., 2011*; Szekely et al., 2011*)
DRD4	120-bp repeat	rs4646984	~1.2 kb upstream	.80 L	.20 S	ADHD, BDP, Imp, Scz	(McCracken et al., 2001*; Rogers et al., 2004*; Kereszturi et al., 2007*; Nakajima et al., 2007; Gizer et al., 2009; Lai et al., 2010; Nemoda et al., 2010; Sanchez-Mora et al., 2011)
DRD4	-1106 T/C	rs936460	upstream			Scz	(Mitsuyasu et al., 2007; Nakajima et al., 2007)
DRD4	-906 T/C	rs3758653	upstream	.80T	.20C	NS, SS, Scz	(Mitsuyasu et al., 2007; Nakajima et al., 2007; Heck et al., 2009; Derringer et al., 2010)
DRD4	-809 G/A	rs936461	upstream	.65G	.35A	Scz	(Mitsuyasu et al., 2007; Nakajima et al., 2007*)
DRD4	-616 G/C	rs747302	upstream	.53G	.47C	BPD, Scz	(Mitsuyasu et al., 2001; Bookman et al., 2002; Nakajima et al., 2007; Nemoda et al., 2010*)
DRD4	-521 C/T	rs1800955	upstream	.60 T	.40 C	BPD, E, NS, OD	(Okuyama et al., 2000*; Ekelund et al., 2001; Mitsuyasu et al., 2001; Ronai et al., 2001*; Bookman et al., 2002*; Jonsson et al., 2002; Strobel et al., 2002; Lee et al., 2003*; Eichhammer et al., 2005; Golimbet et al., 2005; Golimbet et al., 2007*; Nemoda et al., 2010)
MAOB	A/G	rs1799836	Intron 13, X chromosome	.55A	.45G	Enzyme activity	(Garpenstrand et al. 2000*; Pivac et al. 2006)
SLC6A4	5-HTTLPR (long vs short)	-	upstream	.57L	.43S	Anx, AUD, CD, Dis, HA, Imp, Meth dep., NS	(Lesch et al., 1996; Benjamin et al., 2000*; Hong et al., 2003; Strobel et al., 2003*; Szekely et al., 2004; Kang et al., 2008; Malmberg et al., 2008*; Aluja et al., 2009*; Kuhnen et al., 2009*)
STMN	tag SNP	rs182455	upstream	.60C	.40T	Imp, startle	(Brocke et al., 2010*; Ehlis et al., 2011*)

Note. * *indicates a positive association.* ADHD = attention deficit hyperactivity disorder, Anx = anxiety, ASP = autism spectrum disorder, AUD = alcohol use disorder, BART = balloon analogue risk task, BPD = bipolar disorder, CD = conduct disorder, dep. = dependence, Dis = disinhibition, E = extraversion, HA = harm avoidance, I = introversion, Imp = impulsivity, Meth = methamphetamine, N = neuroticism, NS = novelty seeking, OCD = obsessive compulsive disorder, OD = opiod dependent, ODD = operational defiant disorder, RT = risk taking, Scz = schizophrenia, SS = sensation seeking, startle = laboratory startle paradigms, SUD = substance use disorder.

Appendix F Contextual Sensation Seeking Questionnaire for skiing and snowboarding

GENETICS OF SPORTS BEHAVIOURS

Age: _____   Gender: ☐ Male   ☐ Female

Cigarette smoker? ☐ Yes, currently ☐ No, but was.   ☐ No.   **How many years have/did you smoke?** _____

Marital Status: _____   **Dependents:** ☐ Yes   ☐ No

Occupation: _____   **City of residence:** _____

Highest level of education: ☐ High school ☐ Post-secondary diploma or degree

Ethnicity (Based on genetic groups):

☐ White (European descent) ☐ First Nations descent   ☐ Black (Caribbean)   ☐ Black (African)

☐ Black (other)   ☐ Asian (Indian)   ☐ Asian (Pakistani)   ☐ Asian (Japanese)

☐ Asian (Chinese)   ☐ Other, please specify: _____

Sport of choice: ☐ Skiing   ☐ Snowboarding   ☐ Telemark

Level of ability: ☐ Beginner ☐ Novice   ☐ Intermediate ☐ Advanced ☐ Expert *any terrain/condition

Number of days at the hill per season: ☐ < 10   ☐ 10-25   ☐ 25-40 ☐ >40

Please rate the extent to which you agree or disagree with the following statements. Circle the appropriate answer.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

	1	2	3	4	5
1. I like to ski/ride fast.	1	2	3	4	5
2. I like to ski/ride down runs that I have never been down before.	1	2	3	4	5
3. I like to start a run even if I cannot see what lies ahead (i.e. big cornice).	1	2	3	4	5
4. I like to ski/ride out of bounds.	1	2	3	4	5
5. I like to attempt jumps even if I'm not sure of the quality of the landing area.	1	2	3	4	5
6. I like to push my boundaries when I ski/ride.	1	2	3	4	5
7. If I lose control, I don't try to immediately slow down, I just go with it.	1	2	3	4	5
8. If the only way down is a straight line through a narrow pass, I go for it without hesitation even if I know I will have to go fast.	1	2	3	4	5
9. I am always trying to find new and exciting ways down a run.	1	2	3	4	5
10. A 15-foot high drop off a cliff isn't too high a jump for me.	1	2	3	4	5

Appendix G Contextual Sensation Seeking Questionnaire for skiing: Peer version

Genetics of sport-behaviours: Peer Review Form

Name: will peel off this portion   **Name of Friend/Participant:** will peel off this portion

(We are only asking you to provide your name to match this questionnaire with an identification code. Once the match has been made, your responses will be made anonymous (coded by ID number) your answers will not be shared with the subject whom you are reviewing.)

PLEASE ANSWER THE FOLLOWING QUESTIONS ABOUT YOUR FRIEND (NOT ABOUT YOURSELF).

Peer's sport of choice: ☐ Skiing   ☐ Snowboarding

Peer's level of ability:

☐ Beginner   ☐ Novice   ☐ Intermediate   ☐ Advanced   ☐ Expert *
                                                                        (*any terrain, *any condition)

Average number of runs skied by your friend in a day per difficulty grade:
● _____   ■ _____   ◆ _____   ◆◆ _____

How many times have you skied/snowboarded with the subject?
☐ <5   ☐ 5-10   ☐ >10   ☐ Not sure.

Please complete the following questionnaire. It is a sport-specific questionnaire containing 13 specific questions about the skiing/snowboarding behaviours of your friend. Please take your time to read the questions and answer truthfully. There are no right or wrong answers to any of these questions, so please just give your immediate response to the questions. You may feel that in some cases questions are repetitive but please answer every question (unless you feel uncomfortable doing so). Remember that your responses will remain confidential and no one other than the researchers involved in this study will have access to your data.

SECTION I:

Please rate the extent to which you agree or disagree with the following statements. Circle the appropriate answer.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

1. He/she likes to ski/ride fast.
   1   2   3   4   5

2. He/she likes to ski/ride down runs that he/she has never been down before.
   1   2   3   4   5

3. He/she likes to start a run even if he/she cannot see what lies ahead (*e.g.* big cornice).
   1   2   3   4   5

4. He/she likes to ski/ride out of bounds.

      1   2   3   4   5

5. He/she likes to attempt jumps even if he/she is not sure of the quality of the landing area.

      1   2   3   4   5

6. He/she likes to push his/her boundaries when skiing/riding.

      1   2   3   4   5

7. If he/she loses control, he/she doesn't seem to immediately slow down, he/she just appears go with it.

      1   2   3   4   5

8. If the only way down is a straight line through a narrow pass, he/she would go for it without hesitation even if it means going fast.

      1   2   3   4   5

9. He/she is always trying to find new and exciting ways down a run.

      1   2   3   4   5

10. A 15-foot high drop off a cliff isn't too high a jump for my friend.

      1   2   3   4   5

Appendix H Sample consent form

SUBJECT INFORMATION AND CONSENT FORM FOR <u>MINORS</u>

Project: The relationship between genetics and sports behaviours: variants in dopamine pathway genes.

Principal investigator: Jim Rupert

Other investigators: Cynthia Thomson, M.Sc.; UBC Human Kinetics; Scott Carlson, PH.D.; UBC Psychology

Goals: The goals of this project are to analyze whether an association exists between common genetic variants in the dopamine pathway genes and general and sport-specific sensation seeking behaviours. Specifically, these genes include dopamine receptor genes (DRD1, DRD2, DRD3, DRD4, DRD5), dopamine transporter gene (DAT1), enzymes that breakdown dopamine (COMT, MAO-B), the serotonin transporter/receptors (another neurotransmitter involved in approach-related behaviours).

Your participation is voluntary: If you wish to participate, sign the form. Please take time to read the additional information provided carefully. You are free to withdraw at any time and without giving any reasons for your decision.

Who can participate in the study?
Men and women between 17 and 40 years of age who are at least intermediate skiers or snowboarders and other intermediate level or greater high-risk sport participants. The questionnaires are available in English.

What does the study involve?
The questionnaire component (stage 1) involves filling out a brief questionnaire on sports behaviours and a standardized personality questionnaire (ZKPQ), DNA sample (stage 2): You will use a cytobrush (Med) to swab cells from the inner cheek. This will feel similar to rubbing a firm toothbrush against your inner cheek.

Will my taking part in this study be kept confidential?
Your confidentiality will be respected. Everything (questionnaires, DNA samples, results) are coded and the key stored separately. No information that discloses your identity will be released or published without your specific consent to the disclosure.

Who do I contact if I have any questions or concerns about my rights as a subject during the study?
f you have any concerns about your rights as a research subject and/or your experiences while participating in this study, contact the Research Subject Information Line in the University of British Columbia Office of Research Services.

Funding: This project is funded in part by a BC Mental Health and Addictions Research Network seed grant, the Faculty of Education Student Research Grant, and the Canadian Institute for Health Research (CIHR).

SUBJECT CONSENT TO PARTICIPATE

Project: The relationship between genetics and sports behaviours: variants in Dopamine pathway genes.

Principal investigator: Dr. Jim Rupert, School of Human Kinetics, UBC

Please initial the component(s) of the project in which you wish to participate.

I am consenting to participate in the questionnaire component of this project _____
I would like a copy of the results (provide an E-mail address to which the results can be sent)_____

To participate in this study, please read the box below.

- I understand that by signing this form, I am consenting to participate in the study.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I understand that all of the information collected will be kept confidential.
- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate, or to withdraw from this study at any time.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.

Printed name of subject:_____ Signature:_____Date_____

Printed name of witness:_____ Signature:_____ Date_____

Printed name of principal
investigator/representative:_____ Signature:_____ Date_____

Appendix I Correlations between CSSQ-S and ZKPQ subscales

	Subscale	1	2	3	4	5	6
1	CSSQ-S	-					
2	ImpSS	.49**	-				
3	Agg-Hos	.21*	.20*	-			
4	Activity	.19*	.19*	.09	-		
5	Neur-Anx	-.25**	-.08	.21*	.08	-	
6	Soc	-.06	.26**	.07	.07	.07	-

Note. n = 192, MSc sample completed the full ZKPQ. CSSQ-S = Contextual Sensation

Seeking Questionnaire for skiing and snowboarding, ImpSS = impulsive sensation seeking, Agg-

Hos = aggression-hostility, Neur-Anx = neuroticism-anxiety, Soc = sociability.

*p < .01.

**p < .001.

Appendix J DNA concentrations obtained using various techniques and cell types

Sample type	Technique	Range	M (SD)
Buccal swab	Purelink kit[a] (n = 16)	6-38 ng/ul	14.8 (11.1) ng/ul
Buccal swab	Alcohol based method[b] (n = 12)	26-103 ng/ul	55.5 (24.3) ng/ul
Saliva	Oragene[a] (n = 9)	55-401 ng/ul	304.2(108.8) ng/ul

Note. Purelink Genomic DNA kit (Invitrogen Corporation, Carlsbad, CA, USA); Oragene-DNA

(DNA Genotek Inc., Ottawa, ON, Canada).

[a]Isolated as per manufacturers protocol, [b]Alcohol-based isolation from Saftlas et al., (2004).

Appendix K Buccal swab instructions
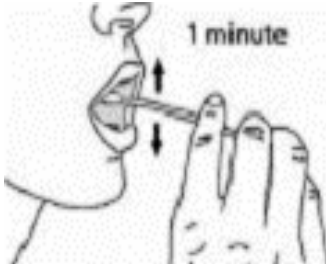
* If possible swab first thing in the morning, or at least not after a drink/meal.

1. Rub vigorously inside cheek.
2. Rub in crevasses where cheek meets gums (but don't stab yourself!)
3. Rub for 1 minute to ensure we get cells.
4. Place in envelope provided, do not lick the seal – air must enter.

Appendix L DNA Isolation from buccal cells

Protocol based on Saftlas et al., (2004).

Day 1:

1) Cut off brush heads and put in 1.8 ml tubes (cut brushes so tubes will close).
2) Incubate brush heads at 55°C for 8 hrs/overnight in 700 *u*l lysis buffer + 3.8 *u*l Proteinase K solution (20 mg/ml).
   a. Lysis buffer: 100 mM NaCl, 10 mM TrisCl (pH 8.0), 25 mM EDTA, 0.5% SDS

Day 2

1) Centrifuge tubes with brush heads for about 1 min at 13 000 RPM at 4°C (to pull the cells off of the bristles), remove and discard the brush heads.
2) Add 2.3 *u*l RNAase solution (10mg/ml) and incubate 60 minutes at 55°C.
3) Add 320 protein precipitation buffer (5 M KOAc (potassium acetate) solution – see Maniatis book for recipe)).
4) Incubate on ice for 10 minutes (*longer is better, i.e., 20-30 minutes).*
5) Centrifuge 5 minutes at 13 000 RPM at 4°C (pellets proteins).
6) Transfer supernatant containing DNA to fresh tube, discard pellet.
7) Add 510 *u*l isopropanol and 2.5 *u*l glycogen (this will participate the DNA).
8) Incubate on ice minimum 10 minutes *(longer is better, usually at least 20 minutes).*
9) Centrifuge 10 minutes at 13 000 RPM at 4°C (pellets are DNA).
10) Carefully discard the supernatant – KEEP PELLET (EDNA will be small/tiny whiteish pellet in bottom of tube).
11) Rinse carefully with 70% ethanol to remove any remaining salt (*e.g.* add 200 *u*l EtOH, invert gently a couple of times to wash pellet, centrifuge 1 min. at 13 000 RPM) (*I do this twice, using 500 ul on first rinse, 200 ul on second).*
12) Let dry (overnight), then re-suspend in 100*u*l TE buffer (10 mM Tris/Cl, 1mm EDTA pH 8.0) and freeze *(* volume is variable and depends on desired concentration. I use 50 ul).*
13) For important samples, divide into two 50 *ul* aliquots and store one as a backup in -80°C freezer.

Quantifying the yield is usually unnecessary. **0.5 to 1.0 *ul* of this DNA prep should PCR amplify.**

Appendix M Laboratory recipes

Ingredients for DNA Isolation
Buccal Lysis Buffer (50 mL)

1	mL	NaCl (5 M)
0.5	mL	TrisCl (1M)
2.5	mL	EDTA (0.5M)
1.25	mL	SDS (20%)
44.75	mL	H_2O

Protein Precipitation Buffer (KOAc)

60	mL	KOAc (5M)
11.5	mL	Acetic Acid
28.5	mL	H_2O

To make 5M KOAc

29.45 g of KOAc (s)
60   mL water
TE Buffer pH 8.0 (10x)

10 mM Tris; bring to pH 8.0 with HCl
1 mM EDTA

To make 100 mL solution:

1	mL	Tris HCl (1M), pH 8
0.2	mL	EDTA (0.5M)

Top to 100 mL with double distilled water

EDTA 0.5M pH 8.0

Dissolve 186.1 g Na2EDTA.2H2O in 700 mL of H2O
Adjust pH to 8.0 with 10M NaOH (~50 mL)
Add ddH2O to a volume of 1L

Appendix N Sample plate layout for Genome Quebec

TOTAL VOLUME 30.00 UL   PLATE 2

20.00 NG/U

TOTAL CONC 20.00 L   ORGANIZED BY CONCENTRATION

	1	2	3	4	5	6	7	8	9	10	11	12
A SAMPLE ID	1025	872	681	751	516	711	700	631	538	571	480	642
CONC.	27.10	18.15	19.56	19.84	20.28	20.30	20.94	21.04	22.03	22.29	22.74	23.16
VOL. DNA	24.35	36.36	33.74	33.27	32.54	32.51	31.52	31.37	29.96	29.61	29.02	28.50
VOL. H_2O	8.65	-3.36	-0.74	-0.27	0.46	0.49	1.48	1.63	3.04	3.39	3.98	4.50
B	633	748	573	721	684	869	521	736	580	610	870	495
	23.35	23.41	24.04	24.27	24.38	24.96	25.09	25.13	25.59	25.71	25.73	26.34
	28.27	28.19	27.45	27.19	27.07	26.44	26.31	26.26	25.79	25.67	25.65	25.06
	4.73	4.81	5.55	5.81	5.93	6.56	6.69	6.74	7.21	7.33	7.35	7.94
C	1051	565	725	597	499	636	1028	765	754	1032	733	NTC
	32.60	26.49	26.57	26.95	27.42	27.57	28.12	28.60	28.89	28.99	29.53	
	20.25	24.92	24.84	24.49	24.07	23.94	23.47	23.08	22.85	22.77	22.35	
	12.75	8.08	8.16	8.51	8.93	9.06	9.53	9.92	10.15	10.23	10.65	
D	550	1026	487	543	750	548	542	762	738	852	714	NTC
	29.80	30.23	30.39	30.95	31.16	31.78	31.94	32.57	32.94	33.14	33.16	
	22.15	21.83	21.72	21.32	21.18	20.77	20.66	20.26	20.04	19.92	19.90	
	10.85	11.17	11.28	11.68	11.82	12.23	12.34	12.74	12.96	13.08	13.10	
E	613	626	579	489	607	498	690	729	645	654	716	1050
	33.33	35.70	33.74	33.90	33.92	34.20	34.24	34.35	34.40	34.80	35.27	35.38
	19.80	18.49	19.56	19.47	19.46	19.30	19.28	19.21	19.19	18.97	18.71	18.65
	13.20	14.51	13.44	13.53	13.54	13.70	13.72	13.79	13.81	14.03	14.29	14.35
F	1022	652	537	1023	504	544	680	662	554	624	561	632
	35.64	33.44	37.12	37.18	37.28	38.01	38.38	38.58	39.16	40.14	40.66	40.77
	18.52	19.74	17.78	17.75	17.70	17.36	17.20	17.11	16.85	16.44	16.23	16.19
	14.48	13.26	15.22	15.25	15.30	15.64	15.80	15.89	16.15	16.56	16.77	16.81
G	529	718	744	694	734	650	611	838	619	572	717	NTC
	41.27	41.57	41.78	42.42	42.50	44.00	44.41	44.43	44.86	45.34	46.09	
	15.99	15.88	15.80	15.56	15.53	15.00	14.86	14.85	14.71	14.56	14.32	
	17.01	17.12	17.20	17.44	17.47	18.00	18.14	18.15	18.29	18.44	18.68	
H	485	551	742	641	840	582	567	497	482	635	515	NTC
	46.37	46.52	47.53	48.92	49.11	49.26	49.30	49.79	50.39	50.49	50.76	
	14.23	14.19	13.89	13.49	13.44	13.40	13.39	13.26	13.10	13.07	13.00	
	18.77	18.81	19.11	19.51	19.56	19.60	19.61	19.74	19.90	19.93	20.00	

Appendix O Primers sequences for PCR amplification of various regions

Gene	Primer name	Sequence	Product size	Reference	Success?
SLC6A4	5HTTCook-F	5' TGA ATG CCA GCA CCT AAC CC 3'	406 bp short 450 bp long	(Cook et al., 1997)	Failed
	5HTTCook-R	5' TTC TGG TGC CAC CTA GAC GC 3'	406 bp short 450 bp long		
	5HTT-Heils-F	5'GGC GTT GCC GCT CTG AAT GC 3'	484 bp short 528 bp long	(Heils et al., 1996)	Failed
	5HTT-Heils-R	5' GAG GGA CTG AGC TGG ACA ACC AC 3'	484 bp short 528 bp long		
SLC6A3 (DAT1)	DAT1-F	5' TGT GGT GTA GGG AAC GGC CTG AG 3'	360-520 bp	(Jorm et al., 2000)	Failed
	DAT1-R	5' CCT TGA GCC GTG ACC TC AGG AA 3'	379-811 bp		
DRD4	D4VNTR-F	5'(HEX) AGG ACC CTC ATG GCC TTG 3'		(Smolen et al., 2002)	Success
	D4VNTR-R	5' GCG ACT ACG TGG TCT ACT CG 3'			
	D4dup-F	5' GTT GTC TCT CTT TTC TCA TTG 3'	429 bp short 549 bp long	(Seaman et al., 1999)	Success
	D4dup-R	5' GAA GGA GCA GGC ACC GTG AGC 3'			

Note. Multiple attempts at optimization failed for the 5HTTLPR and DAT1 40-bp VNTR. *SLC6A4* = serotonin transporter, *DAT1* = dopamine transporter, *DRD4* = D4 dopamine receptor, F = forward primers, R = reverse primers.

Appendix P Skiers ZKPQ scores shown with "norms" from Zuckerman et al., 1993

| | Skiers | | | | | Zuckerman Norms | | | | | |
| | | Males (*n* = 98) | | Females (*n* = 97) | | Males (*n* = 1144) | | | Females (*n* = 1825) | | |
Subscale	Alpha	*M*	*SD*	*M*	*SD*	Alpha	*M*	*SD*	*Alpha*	*M*	*SD*
ImpSS	.83	12.84*	3.30	10.80*	4.66	.77	10.99	3.87	0.81	9.68	4.16
Agg-Host	.71	7.08*	3.17	6.46*	3.20	.76	8.83	3.69	0.76	7.89	3.61
Neur-Anx	.83	4.40*	3.42	7.63*	4.14	.82	7.18	4.23	0.84	10.49	4.51
Soc	.76	8.42*	3.39	9.78	3.58	.77	9.86	3.75	0.79	10.26	3.78
Activity	.99	9.79*	3.56	10.16*	3.57	.74	7.71	3.50	0.77	7.31	3.65

Note. Data obtained from (Zuckerman et al., 1993).

M = mean, *SD* = standard deviation, Alpha = Cronbach alpha as a measure of internal reliability.

* *p* < .05 for sex-matched comparisons.

Appendix Q Path diagram for confirmation factor analysis of the CSSQ

Chi-Square=140.43, df=35, P-value=0.00000, RMSEA=0.075
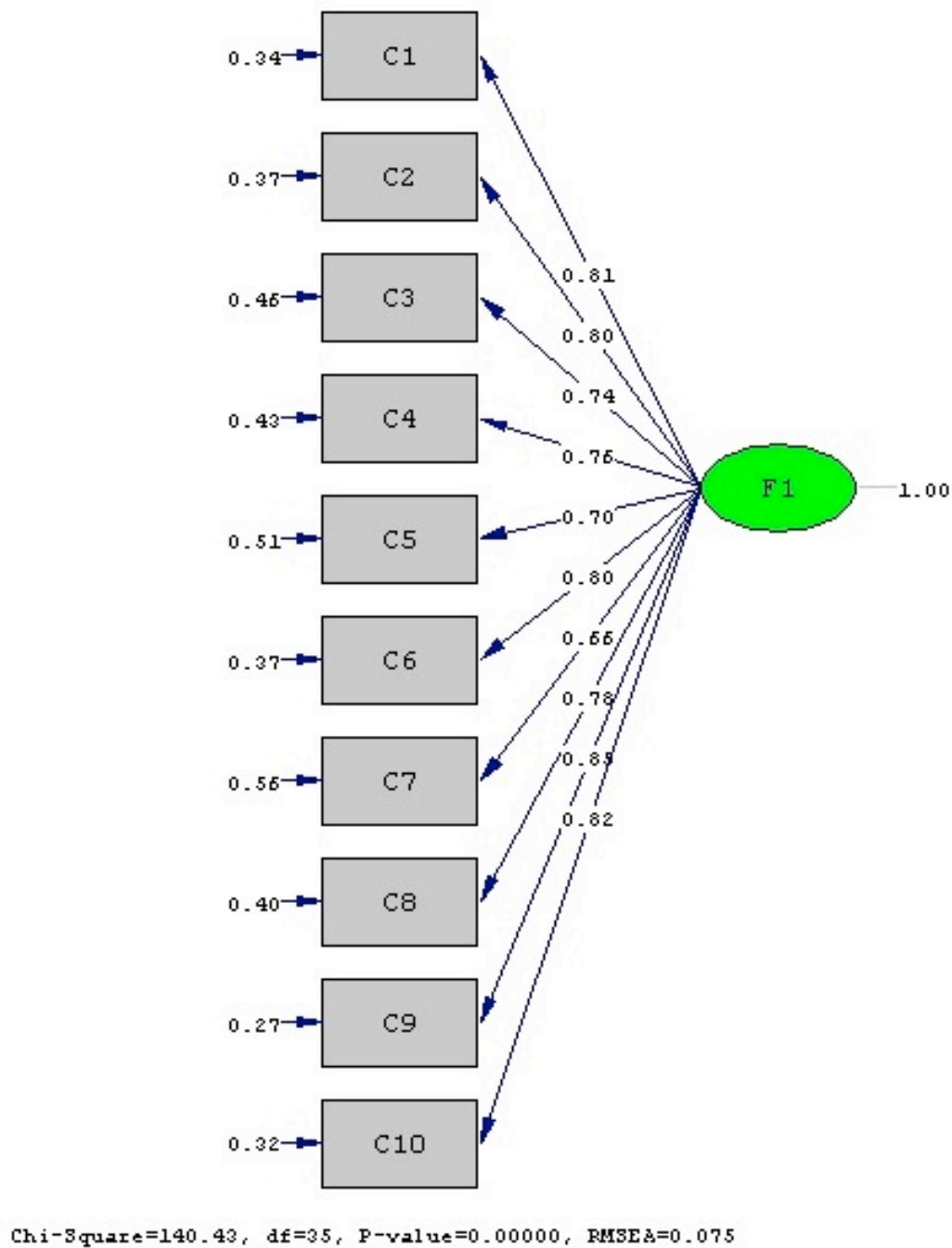
Figure P-1. Path diagram from confirmatory analysis using LISREL 8.8. A weighted least squares estimation was employed. C1 through C10 represent items 1 to 10 on the CSSQ-S. F1 = contextual sensation seeking factor (unidimensional structure).

Appendix R Sample PyroQ result for *DRD4* -521 C/T

A segment of the *DRD4* promoter sequence is shown below. The following sequence (obtained

from UCSC Blat: www.genome.ucsc.edu) was used to design primers surrounding the -521 C/T

locus (depicted by Y*). Primers are underlined and shown in Table Q-1.

```
TCGYYCGCTCAGCTGTCCGCSCAGTTTCGGAGGCGGCCACGCGAGGATCAACTGTGCAACGGGTGGGGCCGCGGCTG

ACCGTGGTGGTCGCGGGGGCTGASVRCCAGAGGCTGNKMSGSGGNNNCGGCGGGATGAGCTAGGCGTCGGCGGTTGA

GTCGGGCGCGGAGTCGGGGGCAGGGGGAGCGGGCYYGGAGGYY*GCGCACGAGGTCGAGGCGAGTCCGCGGGGGAGG

CGGGCAGAGCCTGAGCTCAGGTCTTTCTGCGTCTGGCGGAACGGGCCTGGGAGGGAGGTTTTGCCAGATACCAGGTG

GACTAGGGTGAGCGCCCGAGGGCCGGGACGCACYYACGGGCCGGGRRGGATGGCGCTGGCGTCGATGCCCGCGCGCT

TCAGGGCCTGGTCTGGCCGCCCCTCCATCCTTGTCGGTTTCYYGGGTCGCGGACCCC
```


Table Q-1

Primer design output

Primer	Id	Sequence	Bp	Tm, °C	%GC
⟍PCR	F1	TAGGCGTCGGCGGTTGAG	18	74.7	66.7
⟋PCR	R1	GACTCGCCTCGACCTCGTG	19	73.5	68.4
→Sequencing	S1	TCGGGGGCAGGGGGA	15	69.6	80.0
Sequence to Analyze: GCGGGCYYGG AGGYY*GCGCA CGAGGTCGAG GCGAGTCCGC					

Note. Primer design using Biotage AB PSQ Assay Design Software (Version 1.0.6, USA).

Score given to the primer set = 92, indicating a "high" quality primer according to the software

program. *Target polymorphism is at position "15".
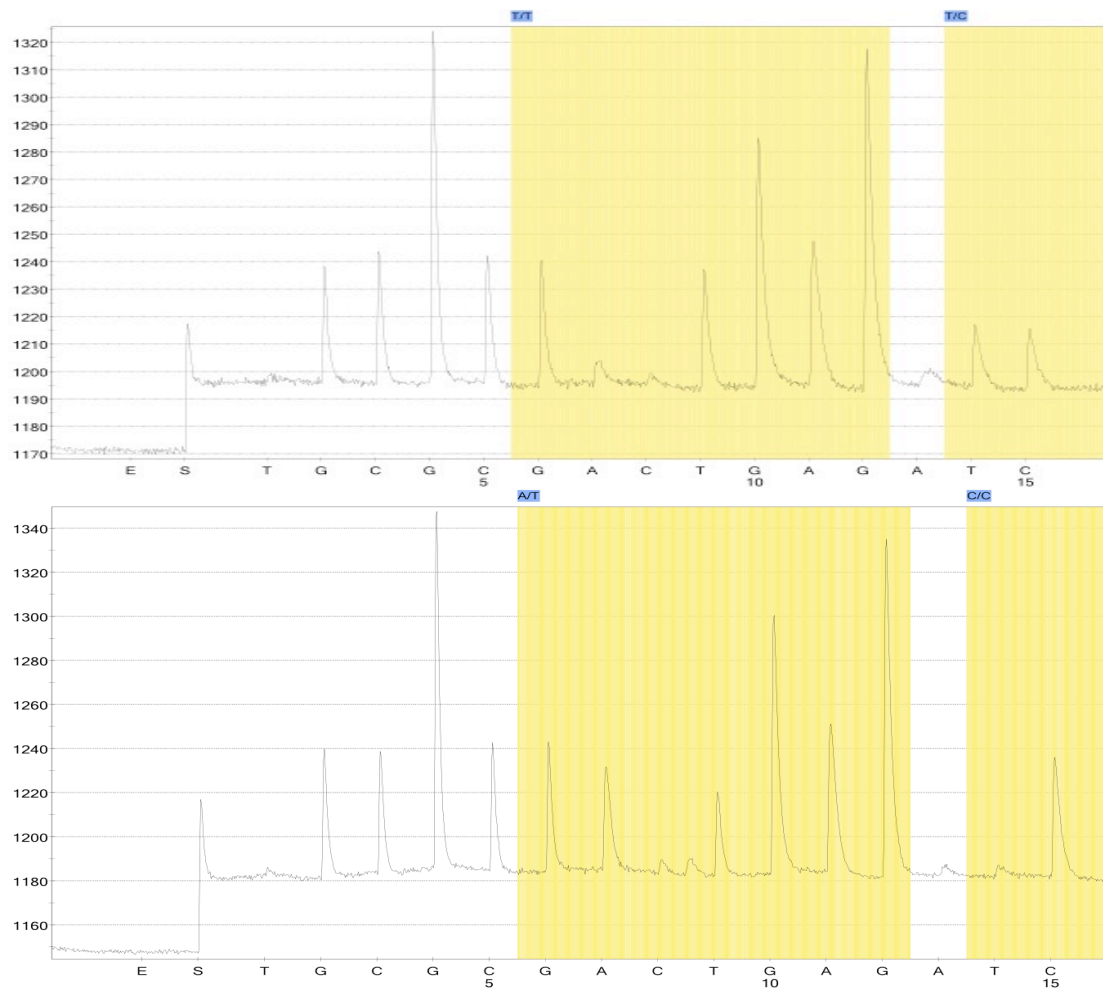
Figure Q-2. The last two bases (shown to the far right) represent the -521 C/T SNP. The top

image shows a CT genotype based on spikes of equal amplitudes following the addition of a T

and C base; the bottom image shows a high-amplitude peak following the addition of a C

nucleotide only, indicative of a CC genotype.
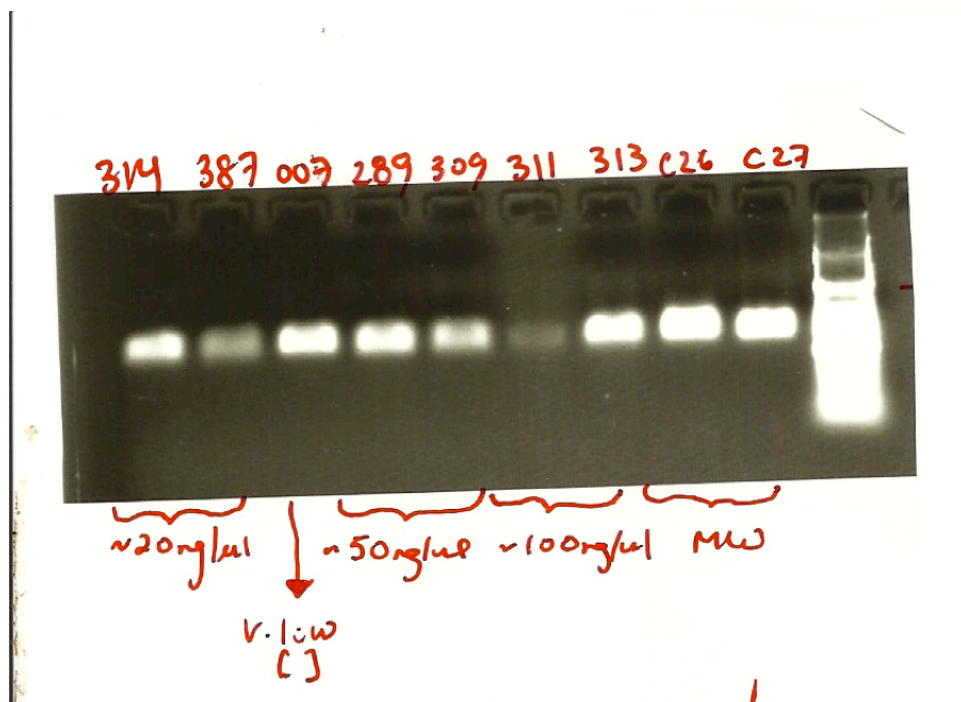
Figure Q-3. Picture of uncut -521 C/T PCR products. Testing a range of concentrations to use for pyrosequencing.

Sample ID shown above image, approximate DNA template concentrations shown below image.

From left to right: ~20 ng/ul, low concentration sample, ~50 ng/ul, ~100 ng/ul, high concentration mouthwash samples, DNA ladder.

Appendix S Fisher's method for combining probabilities

Fisher's method (1932) is a method for combining p-values from independent samples. It is commonly used in meta-analysis or for combining results from multiple studies (see example from molecular biology: (Hess & Iyer, 2007)). The formula gives a *Chi*-square statistic, from which you can determine a joint-p-value based on the *Chi*-square distribution:

$\chi^2_{2k} = -2 \sum^i \ln(p_i)$, where degrees of freedom for two tests $\chi^2_{,} 2k = 2*2 = 4$

Appendix T Genome Quebec marker list and project report for Festival sample

Table T-1

Marker list given to Genome Québec for genotyping of the samples described in Chapters 5 & 6

Priority	Locus_Name	Notes (if any)	H	dbSNP	Type	Removal?
1	COMT Val158Met	Functional	.46	rs4680	SNP	
2	DRD4 -906 T/C	*DRD4* promoter	.31	rs3758653	SNP	
3	MAOB Intron 13	Functional	.48	rs1799836	SNP	
4	DBH -1021 C/T	Functional	.28	rs1611115	SNP	
5	DRD2 Taq1A	Functional	.40	rs1800497	SNP	
6	DRD4 -616 G/C	*DRD4* promoter	.50	rs747302	SNP	Failed
7	DRD4 -603 G/del	*DRD4* promoter	n/a	rs747303	INDEL	Failed[a]
8	DRD4 -809 G/A	*DRD4* promoter	.50	rs936461	SNP	
9	DRD4 -521 C/T	Functional	.41	rs1800955	SNP	Failed
10	DRD2 Taq1B (A/G)		.34	rs1079597	SNP	
11	DRD1 A-48G (DdeI)	Functional	.46	rs686	SNP	
12	DRD2 intron A/C	Functional	.34	rs1076560	SNP	
13	DRD4 intron		.50	rs7124601	SNP	
14	DRD2 intron G/T	Functional	.40	rs2283265	SNP	
15	DRD3 Ser9Gly (A/G)	Functional	.50	rs6280	SNP	
16	COMT C/T His62	Tag	.42	rs4633	SNP	
17	DRD2 Taq1D (T/C)		.28	rs1800498	SNP	
18	DAT1 -67 A/T		.50	rs2975226	SNP	Failed
19	DRD4 -1106 C/T	*DRD4* promoter	.67	rs936460	SNP	
20	DAT1 1343 A/G		.28	rs6347	SNP	
21	5HTTLPR SNP A/G	Functional	.19	rs25531	SNP	Failed[b]
22	DAT1 1821 G/A		.45	rs2937639	SNP	
23	DRD2 C/T	Tag	.35	rs6277	SNP	
24	5HT2A -1438A/G	Tag	.50	rs6311	SNP	
25	DAT1 2319 A/G	Functional	.33	rs27072	SNP	
26	DRD2 A/C	Tag	.36	rs2734831	SNP	
27	DRD4 -291 C/T	*DRD4* promoter	.22	rs916457	SNP	
28	DAT1 intron 4 C/G		.48	rs463379	SNP	
29	DRD1 C/T	Tag	.47	rs251937	SNP	
30	DRD2 C/G	Tag	.27	rs17601612	SNP	
31	DRD2 C/T	Tag	.50	rs4245147	SNP	
32	DRD2 A/C	Tag	.50	rs7131056	SNP	
33	COMT C/T		.28	rs737865	SNP	
34	COMT A/G		.42	rs165599	SNP	Failed
35	DRD1	Tag	.49	rs4867798	SNP	
36	DRD1		.24	rs4532	SNP	
37	DRD3		.47	rs167771	SNP	

Notes. [a]Amplification of G/del was not possible because the multiplex technique was specific to SNP genotyping.

[b]This SNP is located within an insertion, and therefore it was not possible to genotype using the multiplex technique.

SNPs were prioritized based on purported functional differences between alleles (based on the literature) and previous associations with approach-related phenotypes.

Table T-2

The Genome Quebec project report is shown below

Samples		Good	Failed	Total	% Good
	Total	651	117	768	84.77
	Reference	618	117	735	84.08
	Replicate	0	0	0	0
	Control Reference	19	0	19	100
	Control Replicate	14	0	14	100
Assays		Good	Failed	Total	% Good
	Total	32	5	37	86.49
	Reference	30	4	34	88.24
	Replicate	2	1	3	66.67
	Control Reference	0	0	0	0
	Control Replicate	0	0	0	0
	Panels			1	
Genotypes		Good	Failed	Total	% Good
	Genotypes Recorded	20834	6953	27787	74.98
	Reference Genotypes Recorded	19026	5964	24990	76.13
	Good Reference Genotypes Recorded	18347	193	18540	98.96
		Total	% Assay		
	MAF=0	0	0		
	0 < MAF < 0.05	0	0		
	MAF >= 0.05	30	100		
Inconsistencies		Assay	Total Error	Total Comp.	% Error Rate
	Mendelian Errors	0	0	0	0
	Sample Reproducibility Errors	0	0	371	0
					0
	Assay Reproducibility Errors	0	0	596	

Note. Project report from February 25th, 2011. MAF = minor allele frequency.

Appendix U Descriptive statistics for analyses at Stages 1 and 2 (chapter 5)

Table U-1

Descriptive Statistics by genotype for Stage 1 analyses in the discovery sample (n = 291,

Chapter 5)

SNP	Gene	Ref Allele	*n*	ImpSS *M*	*SD*	Imp *M*	*SD*	SS *M*	*SD*	*n*	CSSQ-S *M*	*SD*
rs4633	*COMT*	CC	61	13.05	4.14	4.00	2.53	9.05	2.09	60	37.26	7.11
		TC	145	12.42	3.68	3.63	2.09	8.79	2.16	142	36.30	7.07
		TT	83	13.19	3.85	4.06	2.41	9.13	2.03	80	37.61	7.06
rs4680	*COMT*	GG	61	13.05	4.14	4.00	2.53	9.05	2.09	60	37.26	7.11
		GA	147	12.49	3.71	3.67	2.11	8.82	2.16	144	36.34	7.08
		AA	81	13.05	3.89	3.99	2.41	9.06	2.08	79	37.61	7.01
rs737865	*COMT*	CC	20	13.00	5.14	4.30	2.39	8.70	3.08	19	39.85	6.07
		TC	102	12.66	3.68	3.79	2.15	8.86	2.05	100	35.18	7.22
		TT	134	12.61	3.90	3.77	2.42	8.84	2.08	130	37.08	6.64
rs1611115	*DBH*	TT	11	13.64	3.47	4.55	1.81	9.09	2.17	11	36.52	7.22
		CT	98	12.96	3.66	4.02	2.24	8.94	2.03	98	36.64	7.31
		CC	182	12.60	3.98	3.69	2.33	8.91	2.17	175	37.05	6.93
rs686	*DRD1*	GG	49	13.00	4.35	4.14	2.45	8.86	2.34	48	36.82	6.90
		AG	126	12.97	3.74	3.96	2.19	9.01	2.06	124	37.04	7.72
		AA	115	12.42	3.77	3.55	2.33	8.87	2.11	111	36.84	6.33
rs4532	*DRD1*	TT	116	12.47	3.79	3.58	2.34	8.89	2.11	112	36.90	6.33
		TC	127	12.95	3.71	3.96	2.18	8.99	2.06	125	37.02	7.67
		CC	48	12.96	4.39	4.10	2.44	8.85	2.32	47	36.54	7.11
rs251937	*DRD1*	CC	17	13.94	4.25	4.71	2.17	9.24	2.70	17	41.54	4.99
		TC	135	12.71	3.95	3.80	2.35	8.91	2.12	132	36.46	6.75
		TT	127	12.76	3.73	3.87	2.22	8.89	2.09	123	36.89	7.50
rs4867798	*DRD1*	CC	31	12.42	3.43	3.81	1.94	8.61	2.33	31	36.64	6.71
		TC	112	13.13	3.61	3.92	2.25	9.21	1.89	109	37.69	6.74
		TT	144	12.51	4.13	3.75	2.40	8.76	2.24	140	36.26	7.34
rs6277	*DRD2*	CC	62	12.81	3.58	3.81	2.44	9.00	1.76	62	37.41	6.56
		TC	145	12.76	3.97	3.88	2.24	8.88	2.28	142	37.37	7.37
		TT	84	12.73	3.88	3.76	2.28	8.96	2.09	80	35.63	6.77
rs1076560	*DRD2*	CC	195	12.94	3.78	3.89	2.31	9.06	2.01	190	37.11	7.33
		CA	82	12.71	4.02	3.88	2.24	8.83	2.36	80	36.67	6.24
		AA	14	10.50	3.32	2.79	2.22	7.71	1.90	14	35.17	7.70
rs1079597	*DRD2*	AA	13	10.38	3.43	2.85	2.30	7.54	1.85	13	34.56	7.67
		GA	82	12.63	3.98	3.82	2.22	8.82	2.35	80	36.72	6.28
		GG	195	12.95	3.79	3.89	2.31	9.06	2.01	190	37.16	7.32

			ImpSS			Imp		SS		CSSQ-S		
SNP	Gene	Ref Allele	*n*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*n*	*M*	*SD*
rs1800497	*DRD2*[a]	TT	18	10.33	3.55	2.61	2.17	7.72	2.14	18	34.99	7.49
		CT	98	12.82	4.00	3.92	2.30	8.90	2.25	95	36.96	6.81
		CC	174	13.03	3.68	3.93	2.26	9.10	1.98	170	37.06	7.17
rs1800498	*DRD2*	TT	108	12.95	3.72	3.76	2.23	9.19	1.95	104	37.98	7.28
		TC	137	12.66	3.83	3.87	2.19	8.79	2.18	134	36.39	6.99
		CC	45	12.51	4.28	3.82	2.72	8.69	2.33	45	36.03	6.54
rs2283265	*DRD2*	TT	13	10.38	3.43	2.85	2.30	7.54	1.85	13	34.56	7.67
		GT	82	12.63	3.98	3.82	2.22	8.82	2.35	80	36.72	6.28
		GG	195	12.98	3.79	3.91	2.32	9.07	2.01	190	37.11	7.34
rs2734831	*DRD2*	AA	45	12.51	4.28	3.82	2.72	8.69	2.33	45	36.03	6.54
		CA	137	12.66	3.83	3.87	2.19	8.79	2.18	134	36.39	6.99
		CC	108	12.95	3.72	3.76	2.23	9.19	1.95	104	37.98	7.28
rs4245147	*DRD2*	CC	63	12.32	4.02	3.62	2.39	8.70	2.15	63	37.56	8.19
		TC	151	12.63	3.91	3.69	2.30	8.94	2.19	147	36.68	6.50
		TT	76	13.33	3.56	4.25	2.13	9.08	1.96	73	36.84	7.13
rs7131056	*DRD2*	AA	49	12.73	3.30	3.88	1.99	8.86	1.88	47	34.96	6.95
		CA	127	12.52	4.00	3.69	2.24	8.83	2.26	125	37.10	6.94
		CC	112	12.97	3.88	3.93	2.44	9.04	2.07	109	37.49	7.05
rs17601612	*DRD2*	CC	42	12.50	3.76	3.45	2.38	9.05	1.85	42	37.01	8.40
		GC	141	12.26	3.90	3.57	2.19	8.69	2.29	136	36.80	6.82
		GG	107	13.54	3.74	4.35	2.30	9.20	1.97	105	36.90	6.85
rs6280	*DRD3*	CC	33	12.73	3.55	3.61	2.03	9.12	1.98	32	34.04	6.91
		TC	140	12.83	3.91	3.88	2.39	8.95	2.15	138	37.88	7.53
		TT	117	12.63	3.87	3.80	2.23	8.83	2.13	113	36.42	6.22
rs167771	*DRD3*	AA	203	13.07	3.75	4.01	2.29	9.05	1.97	199	37.21	6.82
		AG	77	12.38	3.85	3.56	2.25	8.82	2.23	74	36.78	7.30
		GG	11	9.73	4.56	2.36	1.86	7.36	3.26	11	31.93	8.25
rs6311	*HTR2A*	CC	93	12.54	4.02	3.62	2.29	8.91	2.25	91	37.15	6.74
		CT	152	12.97	3.83	3.99	2.26	8.98	2.14	147	36.95	7.10
		TT	45	12.60	3.65	3.78	2.40	8.82	1.80	45	36.46	7.41
rs1799836[c]	*MAO-B*[b]	GG	81	13.05	3.78	3.80	2.35	9.25	2.07	78	39.26	5.46
		AA	99	13.20	3.52	3.80	2.30	9.23	1.78	98	39.80	6.41
rs1799836[d]	*MAO-B*	GG	23	11.26	4.99	3.74	2.56	7.52	2.68	22	33.30	6.15
		AG	59	12.58	3.50	3.74	2.09	8.80	2.02	58	33.05	6.29
		AA	29	12.00	4.60	3.74	2.48	8.38	2.54	28	30.86	6.98
rs6347	*SLC6A3*	GG	22	13.77	3.04	4.09	1.82	9.68	1.67	22	38.82	6.31
		AG	125	12.56	3.75	3.66	2.39	8.90	1.97	120	36.78	7.08
		AA	142	12.73	4.05	3.93	2.27	8.80	2.29	140	36.57	7.10
rs27072	*SLC6A3*	CC	201	12.62	3.87	3.77	2.29	8.85	2.13	194	36.74	7.13
		CT	77	13.34	3.62	4.12	2.18	9.22	1.93	77	37.10	7.03
		TT	11	11.18	4.81	3.00	2.68	8.18	3.06	11	37.82	6.76

SNP	Gene	Ref Allele	ImpSS			Imp		SS		CSSQ-S		
			n	*M*	*SD*	*M*	*SD*	*M*	*SD*	*n*	*M*	*SD*
rs463379	*SLC6A3*	CC	25	12.28	3.71	3.12	2.09	9.16	2.21	24	38.04	6.85
		GC	95	13.32	3.46	4.15	2.15	9.17	1.97	92	37.74	6.86
		GG	168	12.55	4.01	3.76	2.36	8.79	2.16	165	36.26	7.10
rs2937639	*SLC6A3*	AA	51	12.80	4.23	3.94	2.66	8.86	2.05	50	37.41	7.65
		GA	124	12.83	3.54	3.82	2.19	9.01	1.99	122	36.93	6.98
		GG	111	12.66	4.05	3.79	2.23	8.86	2.33	107	36.61	7.01

Note. Numbers vary between ZKPQ (ImpSS, Imp, and SS) and CSSQ-S due to exclusions for ability. *M* = mean,

SD = standard deviation.

[a]rs18004997 is located in *ANKK1 (*downstream from *DRD2*) but is often considered a *DRD2* polymorphism.

[b]*MAO-B* is on the X-chromosome so males and females were analyzed separately.

[c]Male scores by genotype for rs1799836.

[d]Female scores by genotype for rs1799836.

Table U-2

Descriptive statistics by genotype for Stage 2 analyses (replication sample, n = 308, Chapter 5)

SNP	Gene	Ref Allele	ImpSS n	ImpSS M	ImpSS SD	Imp M	Imp SD	SS M	SS SD	CSSQ-S n	CSSQ-S M	CSSQ-S SD
rs1800497	*DRD2*[a]	TT	9	12.44	5.05	3.56	2.60	8.89	2.89	9	36.22	6.55
		CT	113	12.60	3.78	3.72	2.32	8.89	2.06	107	36.77	6.74
		CC	186	12.31	3.90	3.72	2.17	8.59	2.33	176	35.24	8.19
rs17601612	*DRD2*	CC	53	12.06	4.03	3.62	2.19	8.42	2.44	50	35.30	8.75
		GC	150	12.65	3.61	3.73	2.19	8.92	2.00	143	36.38	7.42
		GG	105	12.28	4.19	3.73	2.32	8.54	2.47	99	35.31	7.42
rs167771	*DRD3*	AA	216	12.68	3.81	3.76	2.25	8.91	2.17	204	36.23	7.72
		AG	85	11.86	4.05	3.60	2.23	8.26	2.35	81	35.08	7.46
		GG	7	11.29	3.90	3.57	1.99	7.71	2.50	7	32.86	7.76

Note. Numbers vary between ZKPQ (ImpSS, Imp, and SS) and CSSQ-S due to exclusions for ability. *M* = mean, *SD* = standard deviation.

[a]rs18004997 is located in *ANKK1 (*downstream from *DRD2*) but is often considered a *DRD2* polymorphism.

Appendix V Sample gel photographs for *DRD4* 120-bp tandem duplication

James Rupert 2011-08-23 15hr 56min

1-10. Ⓐ
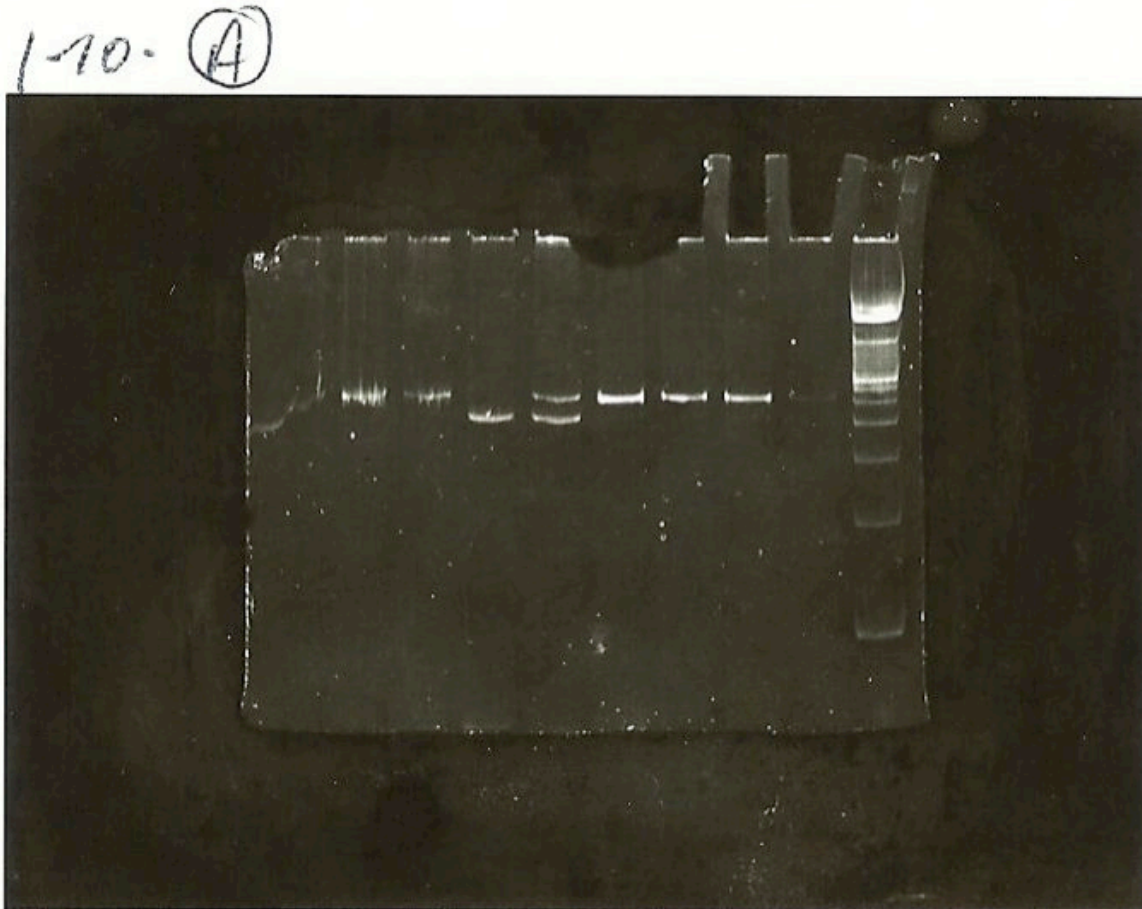
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Figure V-1. Sample picture showing genotypes for the *DRD4* 120-bp tandem duplication.

PAGE gel stained with Sybr Safe gel stain (Life Technologies, Burlington, ON, Canada). Gel

electrophoresis ran at 130V for 75 minutes.

Genotypes lanes 1-10 (left to right): no call, LL, LL, SS, LS, LL, LL, LL, no call, 100-bp ladder.

11-20 . (B)
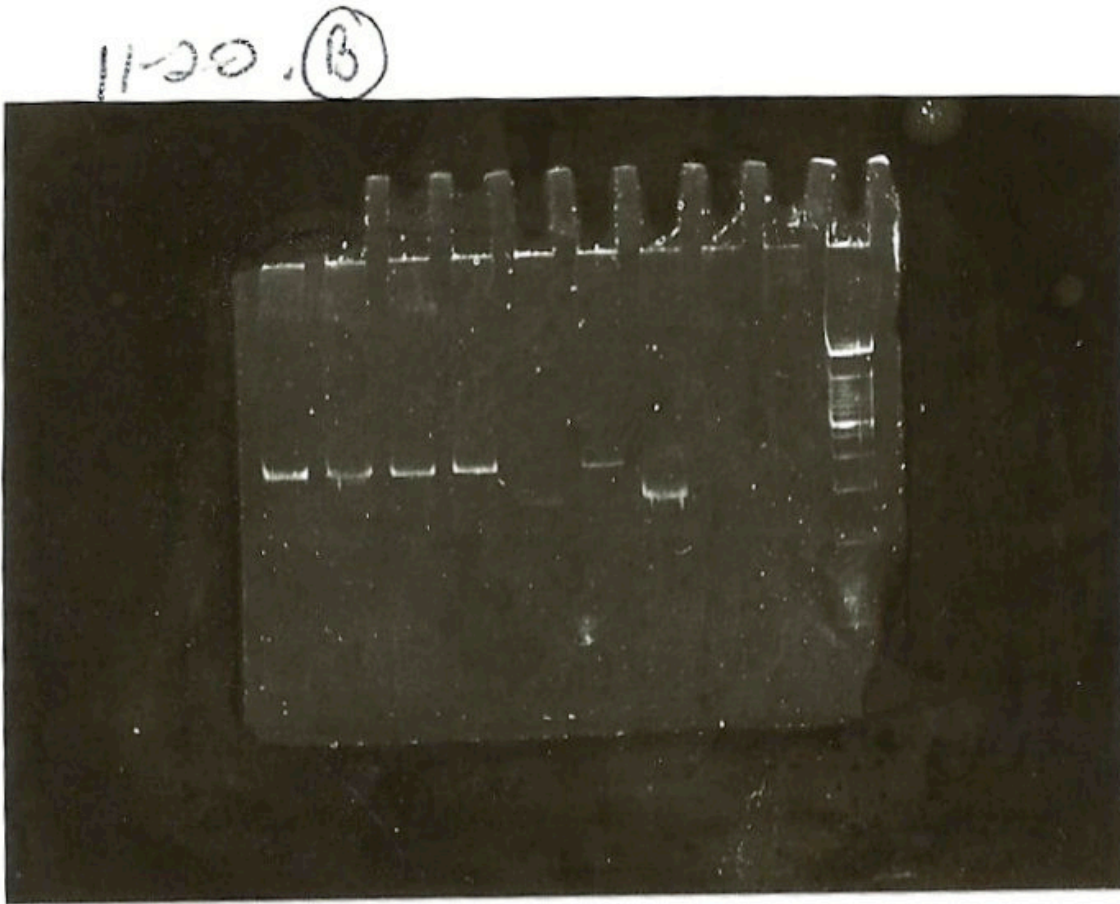
Figure V-2. Sample picture showing genotypes for the *DRD4* 120-bp tandem duplication.

PAGE gel stained with Sybr Safe gel stain (Life Technologies, Burlington, ON, Canada). Gel

electrophoresis ran at 130V for 75 minutes.

Genotypes lanes 11-20 (left to right): LL, LL, LL, LL, (L)S*, LL*, SS*, NTC, no call, 100-bp

ladder.

*Ambiguous genotype, PCR redone and/or products re-run.

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Appendix W Additional analyses for impulsivity and sensation seeking as separate scales (Chapter 6)

Marker	dbSNP	Genotype	n	Imp		SS	
				M	*SD*	*M*	*SD*
120-bp repeat	-	LL	296	3.87	2.27	8.91	2.13
		LS	126	3.87	2.18	8.66	2.32
		SS	14	3.86	2.14	9.21	2.19
		LS + SS	140	3.87	2.17	8.71	2.31
		F_{add}, F_{grp}		0.02,	0.01	0.29,	0.34
		p_{add}, p_{grp}		.98,	.94	.75,	.56
-1106 T/C	rs936460	TT	272	3.86	2.13	8.89	2.18
		TC	244	3.80	2.41	8.80	2.24
		CC	61	3.29	2.19	8.52	2.00
		F_{add}, F_{grp}		1.61,	0.64	1.18,	0.60
		P		.20,	.42	.31,	.44
-906 T/C	rs3758653	TT	393	3.80	2.30	8.78	2.22
		TC	163	3.69	2.10	8.90	2.07
		CC	21	3.90	2.72	8.90	2.42
		F_{add}, F_{grp}		0.14,	0.21	0.20,	0.36
		p		.87,	.65	.81,	.55
-809 G/A	rs936461	GG	225	3.85	2.23	8.85	2.34
		GA	274	3.67	2.27	8.80	2.07
		AA	74	3.91	2.38	8.77	2.19
		F_{add}, F_{grp}		0.51,	0.48	0.26,	0.47
		p		.60,	.49	.76,	.49
-291 C/T	rs916457	CC	507	3.75	2.28	8.77	2.22
		CT	51	3.97	2.18	9.03	1.92
		TT	5	3.80	2.17	9.60	1.34
		F_{add}, F_{grp}		0.27,	0.46	0.41,	0.77
		p		.77,	.50	.67,	.38

Note. *F*-statistics and *p*-values for both additive and grouped models are shown (minor genotype grouped with heterozygote). F_A = additive model, F_G = grouped model, M = mean, *SD* = standard deviation. [†]Homogeneity of variances violated, test not performed.

Appendix X Psychiatric screening based on medications

Please consult the list of medications provided by the researcher.
Are you currently taking any of the medications listed on the sheet provided?

❑ Yes ❑ No

If you are currently taking any medications (related to behaviours) that are not listed above, please specify:
_____
Note: if you do not feel comfortable answering this question, you may proceed to the next question.

A)   Have you ever been prescribed a medication for *anxiety*? (*anxiolytic*)
     ❑ Yes   ❑ No (If No, please skip to B →*)

- For how long (in days) were you taking the medication? _____
- Reason(s) for use:
     ❑ To relax during the day   ❑ To help with sleep
     ❑ Other (please specify)_____
- Who prescribed the medication?
❑ General practitioner   ❑ Psychiatrist   ❑ Other (please specify)_____

→*B
B)   Have you ever been prescribed a medication for *depression*? (*anti-depresssant*)
  ❑ Yes   ❑ No (If No, please
  skip to C →)

- For how long (in days) were you taking the medication? _____
- Reason(s) for use:
     ❑ To relax during the day   ❑ To help with sleep
     ❑ Other (please specify)_____
- Who prescribed the medication?
     ❑ General practitioner   ❑ Psychiatrist   ❑ Other (please specify)_____

→*C
C)   Have you ever been prescribed a *neuroleptic*?
  ❑ Yes   ❑ No (If No, please skip to the next page →)

- For how long (in days) were you taking the medication? _____
- Reason(s) for use:
     ❑ To relax during the day   ❑ To help with sleep
     ❑ Other (please specify)_____
- Who prescribed the medication?
     ❑ General practitioner   ❑ Psychiatrist   ❑ Other (please specify)_____

List of medications:

Anxiolytics	Antidepressants	Neuroleptics
alprazolam	Amitriptyline	Amisulpride
Ativan	Anafranil	Carbamazepine
anxyrex	Buproprion	Chlorpromazine
bromazepam	Celexa	Clozapine
buspar	Citalopram	Clozaril
buspirone	Clomipramine	Depakene
chlordiazepoxide	Desyrel	Haldol
clonazepam	Effexor	Haloperidol
clorazepate	Elavil	Largectil
Dalmane	Fluvoxamine	Lithium
diazepam	Fluoxetine	Navane
flurazepam	Imipramine	Olanzapine
Halcion	Lithium	Quetiapine
Klonopin	Luvox	Reserpine
Librium	Nardil	Risperdal
lorazepam	Paroxetine	Risperidone
oxazepam	Paxil	Seroquel
Restoril	Phenelzine	Serpasil
Serax	Prozac	Solian
temazepam	Sertraline	Tegretol
Tranxene	Tofranil	Thiothixene
triazolam	Trazodone	Thorazine
Valium	Venlafaxine	Valproic Acid
Xanax	Wellbutrin	Zyprexa
	Zoloft	

Appendix Y CSSQ generalized for "downhill" sports

SPORT: ❏ **Alpine skiing** ❏**Snowboarding** ❏ **Mountain Biking**
Level of ability for sport chosen above:

❏**Beginner** ❏**Novice** ❏ **Intermediate** ❏ **Advanced** ❏ **Expert** *(*any terrain, *any condition)

Number of days spent doing sport per year:
    ❏**< 10**   ❏ **10-25**   ❏ **25-40**   ❏ **>40**

Please complete the following questionnaire. It is a sport-specific questionnaire containing 10 specific questions about skiing/snowboarding/biking behaviours.

Please rate the extent to which you agree or disagree with the following statements. Circle the appropriate answer.	Strongly disagree	Disagree	Neutral	Agree	Strongly Agree
1 I like to ski/ride fast.	**1**	**2**	**3**	**4**	**5**
2 I like to ski/ride down runs that I have never been down before.	**1**	**2**	**3**	**4**	**5**
3 I like to start a 'run' even if I cannot see what lies ahead (i.e. cornice, rock, tree, stump).	**1**	**2**	**3**	**4**	**5**
4 I like to ski/ride out of bounds (applies to snowsports only).	**1**	**2**	**3**	**4**	**5**
5 I like to attempt jumps even if I'm not sure of the quality of the landing area.	**1**	**2**	**3**	**4**	**5**
6 I like to push my boundaries when I play my sport.	**1**	**2**	**3**	**4**	**5**
7 If I lose control, I don't try to immediately slow down, I just go with it.	**1**	**2**	**3**	**4**	**5**
8 If the only way down is a straight line through a narrow pass/chute/trail, I go for it without hesitation even if I know I will have to go fast.	**1**	**2**	**3**	**4**	**5**
9 I am always trying to find new and exciting ways down a 'run'.	**1**	**2**	**3**	**4**	**5**
10 A 15-foot (skiers)/10-foot (bikers/kayakers) high drop off a cliff isn't too high a jump for me. *15 feet = 4.5 m; *10 feet = 3 m	**1**	**2**	**3**	**4**	**5**

Appendix Z CSSQ in French

SPORT : ☐ **Ski Alpin**   ☐ **Snowboarding**   ☐ **Vélo de montagne (VTT)**

Niveau de capacité pour le sport choisi ci-dessus :

☐ **Débutant** ☐ **Novice**   ☐ **Intermédiaires**   ☐ **Avancée**   ☐ **Expert** *(*tout terrain, *toute condition)

Nombres de jours par années faisant le sport choisi :

☐ **< 10**   ☐ **10-25**   ☐ **25-40**   ☐ **>40**

S'il vous plait, compléter le questionnaire suivant. C'est un questionnaire spécifique aux sports de montagnes.

Répondez aux questions suivantes en vous auto évaluant sur chacun des critères à l'aide de l'échelle à droite de la page. Encercle le numéro qui vous correspond 1 a 5.	Fortement en désaccord	En désaccord	Neutre ou indifférent	En accord	Fortement en accord
1 J'aime skier/descendre vite.	**1**	**2**	**3**	**4**	**5**
2 J'aime faire du ski/VTT à des endroits où je ne suis jamais allé.	**1**	**2**	**3**	**4**	**5**
3 J'aime me lancer dans une descente même si je ne vois pas ce qui nous attend (ex : corniche, roche, arbre, souche).	**1**	**2**	**3**	**4**	**5**
4 J'aime faire du hors piste.	**1**	**2**	**3**	**4**	**5**
5 J'aime tenter des sauts même si je ne suis pas sûr de la qualité de l'aire d'atterrissage.	**1**	**2**	**3**	**4**	**5**
6 J'aime repousser mes limites lorsque je fais mon sport.	**1**	**2**	**3**	**4**	**5**
7 Si je perds le contrôle, je ne cherche pas à ralentir, je fais avec.	**1**	**2**	**3**	**4**	**5**
8 Si le seul moyen pour descendre est d'aller tout droit au travers d'un passage étroit ou une goulotte, j'y vais sans hésiter, même si je sais que je devrais aller vite.	**1**	**2**	**3**	**4**	**5**
9 J'essaie toujours de trouver des façons nouvelles et excitantes de descendre.	**1**	**2**	**3**	**4**	**5**
10 Un saut du haut d'une falaise de 4.5 mètres en ski ou 3.5 mètres en vélo n'est pas trop élevée pour moi.	**1**	**2**	**3**	**4**	**5**

Appendix AA Sample gel photographs for *DRD4* exon III VNTR
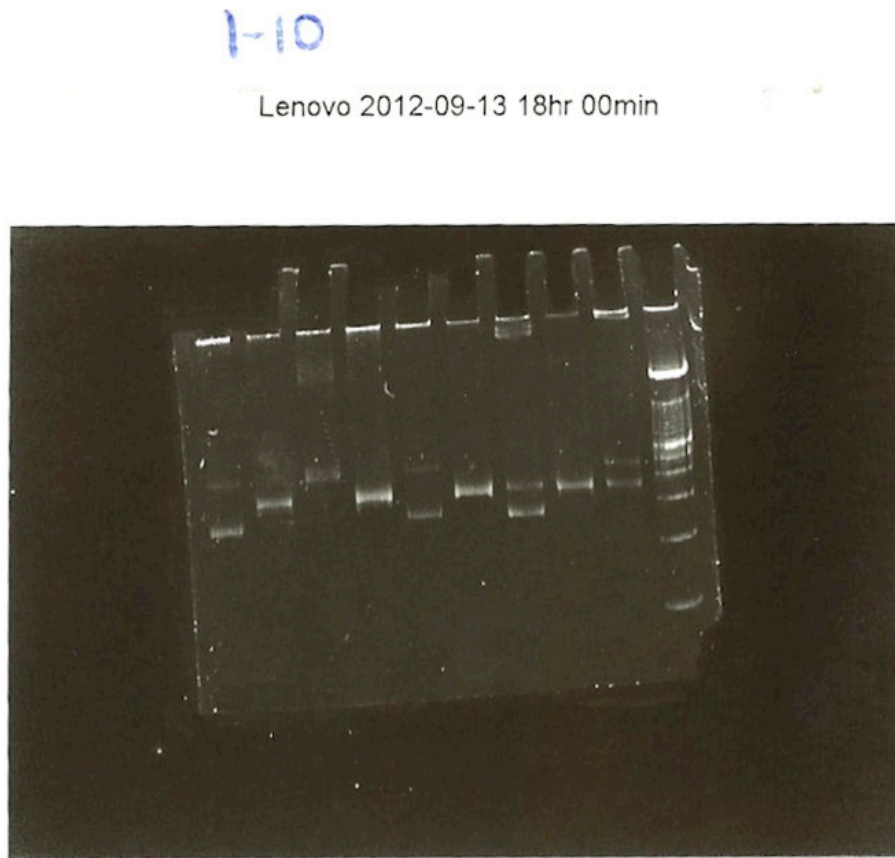
Figure AA-1. Sample picture showing genotypes for the *DRD4* 48-bp VNTR. PAGE gel stained

with Sybr Safe gel stain (Life Technologies, Burlington, ON, Canada). Gel electrophoresis ran

at 125V for 95 minutes.

Genotypes lanes 1-10 (left to right): 27, 44, 77, 44, 27[‡], 44, 42, 44, 47, 100-bp ladder.

[‡]Reference genotype from ABI prism analyzer.

2 = 2-repeats, 4 = 4 repeats, 7 = 7 repeats.

Location: C:/Users/Lenovo/Documents/Cynthia
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Page 1 of 1

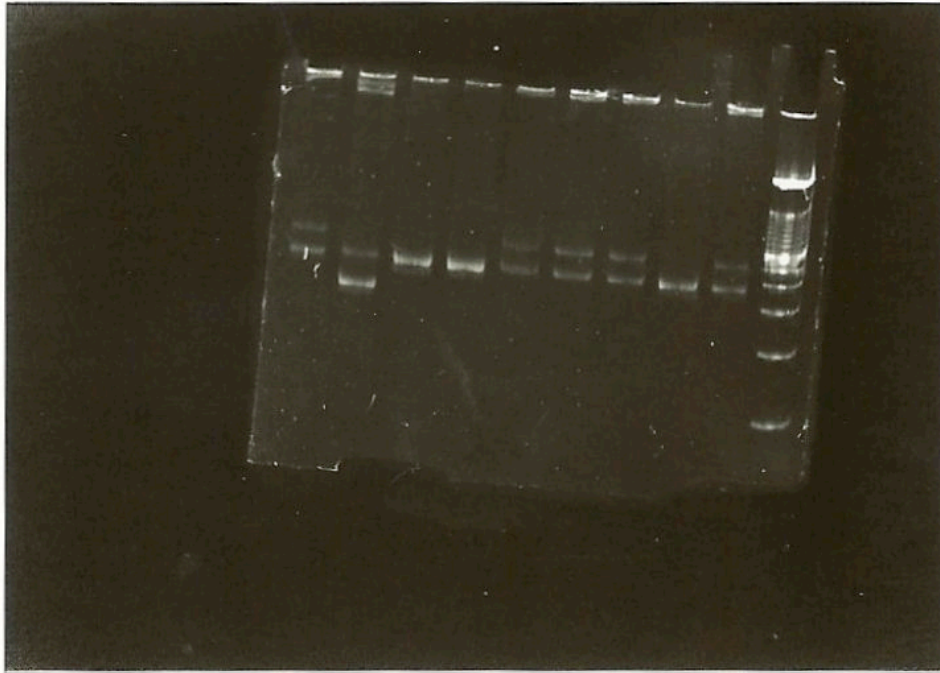*Figure AA-2.* Sample picture showing genotypes for the *DRD4* 48-bp VNTR. PAGE gel stained

with Sybr Safe gel stain (Life Technologies, Burlington, ON, Canada). Gel electrophoresis ran

at 125V for 95 minutes.

Genotypes lanes 21-30 (left to right): 47, 42, 44, 44, 47[‡], 47, 47, 44, 47, 100-bp ladder.

‡Reference genotype from ABI prism analyzer.

2 = 2-repeats, 4 = 4 repeats, 7 = 7 repeats.

Appendix BB *DRD4* **120-bp tandem duplication data for high- and low-risk athletic samples**

Gene	Sex	Recruitment location	SNP		Genotype counts		Allele frequencies				Between sport-groups	
					High	Low	High		Low			
							Maj	Min	Maj	Min	χ^2	*p*
DRD4	Combined	Combined	120-bp	LL	47	30	.90	.10	.90	.10		1.0
				LS	10	7						
				SS	1	1						
	Males	Combined	120-bp	LL	38	14	.88	.12	.84	.16		1.0
				LS	10	4						
				SS	1	1						
	Females	Combined	120-bp	LL	9	16	1.0	0	.82	.08		.54
				LS	0	3						
				SS	0	0						

Note. A total of 150 genotypes for the *DRD4* 120-bp tandem duplication were obtained, but after applying the exclusions used in Chapter 8, the number of genotypes included for high- and low-risk sport groups were 58 and 38, respectively. Genotyping methods are described in Chapter 6 (section 6.3.3). For a sample photograph, see Appendix V. Maj = major allele frequency, Min = minor allele frequency, L = long allele (240-bp), S = short allele (120-bp).

Appendix CC Questionnaire used in Project 3

1 - Demographics:

Age: _____ *if you are under 17 yrs of age please do not proceed with the questionnaire.*

Sex: ❑ Male ❑ Female

Marital status: ❑ Single ❑ cohabitating with partner ❑ married
  ❑ Separate ❑ divorced ❑ other: _____

Dependents (children who rely on you for support/security): ❑Yes ❑ No

Occupation:_____ **City of residence:** _____

Highest level of education:

  ❑ High School ❑ Trade /college diploma ❑ University degree ❑ Graduate degree

2 a) Ethnicity: (Based on genetic groups):

  ❑ White (European descent)
    ❑ Northern ❑ Eastern
    ❑ Southern ❑ Western
  ❑ Indiginous nations descent
  ❑ Black (Carribean)
  ❑ Black (African)
  ❑ Black (other)
  ❑ Asian (Indian)
  ❑ Asian (Pakistani)
  ❑ Asian (Japanese)
  ❑ Asian (Chinese)
  ❑ Other, please specify:

2b) Please list the ethnicity of your grandparents on each side of your family (if known):	*If same as 2a) please put a check (√) if unknown put "X"*
	Mother's mother: _____
	Mother's father: _____
	Father's mother: _____
	Father's father: _____

3 – Language: First language: _____

"Fluency" – I am able to fully understand both written and spoken English.
3 a)   Are you fluent in English? ❑ Yes ❑ No

3 b)   How many years have your been speaking English?
   ❑ less than 10 years   ❑ 10 to 15   ❑ 16 to 20   ❑ more than 20 years

** If you have answered "No" to 3 a) you do not need to proceed with the rest of the questionnaires. Thank you for your time.

4 – Smoking: Do you smoke cigarettes?
❑ Yes, regularly   ❑ Yes, occasionally (includes "social" smokers)
If yes, for how many years? _____   Approximately how many cigarettes per day? _____

❑ No, I used to, but quit
For how many years did you smoke? _____ How many per day? _____

❑ No, never smoked *(if you have tried smoking you may still check this box)* → *SKIP TO #5*

→ If you smoke regularly, how long after you wake up do you wait before having your first cigarette?
*IF NOT → GO TO #5 _____
   ❑ Less than 5 min   ❑ 6 to 30 min   ❑ 31 to 60 min   ❑ Over 60 min

Do you find it hard to not smoke in non-smoking areas?   ❑ Yes ❑ No

Do you smoke when you are sick and on bed-rest?   ❑ Yes ❑ No

5 – Alcohol: Have you ever drunk alcohol?   ❑ Yes ❑ No   → **IF NO, GO TO #6*

How often do you typically consume alcohol?
   ❑ Occasionally
   ❑ At least once a week
   ❑ A few days a week
   ❑ Every day

Do you typically consume alcohol: ❑ Alone   ❑ With others   ❑ Both

*Please respond to the following statements considering your behaviours over **the past 12 months:***

Have you ever felt that you need to decrease your consumption of alcoholic beverages?   ❑ Yes ❑ No

Have your peers ever made remarks about your levels of consumption?   ❑ Yes ❑ No

Have you ever felt like you drank too much?   ❑ Yes ❑ No

Have you ever needed more alcohol in the morning to help you feel better?   ❑ Yes ❑ No

6 - Have you ever tried any illicit substances? (e.g. cannabis, cocaine...) ❑ Yes ❑ No → *IF NO, GO TO THE NEXT PAGE*

Which substances from the list below do you *currently* use?_____ **OR**,
❑ I have tried one/some of the substances listed, but no longer use any of them.
→ *GO TO THE NEXT PAGE*

Amphetamines (e.g., Speed)	Ectasy (MDMA)	Opiates (e.g., opium, morphine)
Barbiturates (e.g., Quaaludes, downers)	Hallucinogenes (e.g., LSD, Acid, Peyote, mushrooms)	Valium, other tranquilizers
Cannabis (marijuana)	Hashish	
Cocaine	Heroine	

How often do you typically consume the substance(s) chosen above?
❑ Occasionally
❑ At least once a week
❑ A few days a week
❑ Every day

Do you typically consume: ❑ Alone   ❑ With others   ❑ Both

*Please respond to the following statements considering your behaviours over **the past 12 months:***

Have you ever used any of the drugs chosen before noon? ❑ Yes ❑ No

Have you ever used any of the drugs while alone? ❑ Yes ❑ No

Have you ever had problems remembering things while under the influence? ❑ Yes ❑ No

Have friends and family ever suggested you reduce your intake? ❑ Yes ❑ No

Have you ever tried to reduce your drug intake without success? ❑ Yes ❑ No

Have you ever had problems because of your drug consumption (arguments, accidents, etc.) ❑ Yes ❑ No

Appendix DD Sport questionnaire used in Project 3 (high-risk sport version)

Genetics of risk behaviours: sports questionnaire

The pages that follow ask about your involvement in high-risk sports (e.g. mountaineering, surfing, paragliding) and downhill sports (i.e., skiing, snow boarding, or mountain biking).

3.0 Sports:

NOTE: If you do <u>not</u> participate in any sport listed below, or a sport that might be considered "high-risk" please check this box: ❏

3.1 Please check if you participate in any of the following sports:

☐ *Adventure racing*	☐ *Kite surfing*	☐ *Snowboard cross*
☐ *B.A.S.E. jumping*	☐ *Luge*	☐ *Speed riding*
☐ *BMX*	☐ *Mountaineering*	☐ *Speed skiing*
☐ *Bungee jumping*	☐ *Mountain Biking*	☐ *Street Luge*
☐ *Car racing*	☐ *Paragliding*	☐ *Surfing*
☐ *Cliff jumping*	☐ *Parkour (freerunning)*	☐ *Whitewater kayaking*
☐ *Climbing*	☐ *Rappelling*	☐ *Wing-suit flying*
☐ *Dirt biking*	☐ *Sailing Skateboarding *pipes & structures*	***Not listed? Please specify:***
☐ *Freeride skiing*		☐ *Other:* _____
☐ *Freeride snowboarding*	☐ *Ski cross*	☐ *Other:* _____
☐ *Ice Climbing*	☐ *Sky diving*	☐ *Other:* _____

3.2 Please list any sports from the list above that you participate on a regular basis (more than *twice* per year):

_____

_____

3.3 Please choose your most proficient sport out of the ones listed in 3.2:

_____

_____

3.4 Level of ability for sport chosen in 3.3 _____(please fill in sport)

❏ Beginner   ❏ Novice   ❏ Intermediate   ❏ Advanced   ❏ Expert *(*any terrain, *any condition)

3.5 Number of days spent doing sport per year: _____

If you are also proficient at **Skiing, Snowboarding, or Mountain Biking**. Please take the time to fill out the questions on the following page. If not, please proceed to PAGE 7. →

SPORT: ❑ Alpine skiing ❑Snowboarding ❑ Mountain Biking

Level of ability for sport chosen above:
❑Beginner❑Novice ❑ Intermediate ❑ Advanced ❑ Expert *(*any terrain, *any condition)

Number of days spent doing sport per year:
❑< 10 ❑ 10-25 ❑ 25-40 ❑ >40

Please complete the following questionnaire. It is a sport-specific questionnaire containing 10 specific questions about skiing/snowboarding/biking behaviours.

Please rate the extent to which you agree or disagree with the following statements. Circle the appropriate answer.	Strongly disagree	Disagree	Neutral	Agree	Strongly Agree
1 I like to ski/ride fast.	1	2	3	4	5
2 I like to ski/ride down runs that I have never been down before.	1	2	3	4	5
3 I like to start a 'run' even if I cannot see what lies ahead (i.e. cornice, rock, tree, stump).	1	2	3	4	5
4 I like to ski/ride out of bounds (applies to snowsports only).	1	2	3	4	5
5 I like to attempt jumps even if I'm not sure of the quality of the landing area.	1	2	3	4	5
6 I like to push my boundaries when I play my sport.	1	2	3	4	5
7 If I lose control, I don't try to immediately slow down, I just go with it.	1	2	3	4	5
8 If the only way down is a straight line through a narrow pass/chute/trail, I go for it without hesitation even if I know I will have to go fast.	1	2	3	4	5
9 I am always trying to find new and exciting ways down a 'run'.	1	2	3	4	5
10 A 15-foot (skiers)/10-foot (bikers/kayakers) high drop off a cliff isn't too high a jump for me. *15 feet = 4.5 m; *10 feet = 3 m	1	2	3	4	5

Appendix EE Adult Self Report Scale V1.1 (Kessler et al., 2005)

→ CODE : _____

	Never	Rarely	Sometimes	Often	Very Often
Please tick the selection from the right-hand scale that best reflects how each statement applies to you. The items below refer to how you have felt and conducted yourself over the past 6 months.					
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?	❑	❑	❑	❑	❑
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?	❑	❑	❑	❑	❑
3. How often do you have problems remembering appointments or obligations?	❑	❑	❑	❑	❑
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?	❑	❑	❑	❑	❑
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?	❑	❑	❑	❑	❑
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?	❑	❑	❑	❑	❑

Note. One point per item is given if participant chooses "sometimes", "often", or "very often"

for items 1, 2, 3; and one point per item is given if participant chooses "often" or "very often" for

items 4, 5, 6 for a maximum score of 6. If the patient scores four or higher, the participant has

symptoms "highly consistent with ADHD in adults" (Kessler et al., 2005).

Appendix FF Genome Quebec marker list and project report for high- and low-risk sport samples

Table FF-1

Marker list for Chapter 8 high- and low-risk sport group comparison

	Locus Name	Marker	Position	Maj	Min	Strand	MAF	H	Call rate
1	BDNF val66met	rs6265	chr11:27679916	C	T	R	0.21	.35	1.00
2	COMT A/G	rs6269	chr22:19949952	A	G	F	0.43	.53	1.00
3	COMT C/G	rs4818	chr22:19951207	G	C	R	0.00	.00	**0**[a]
4	COMT C/T His62	rs4633	chr22:19950235	C	T	F	0.48	.51	.99
5	COMT val158met	rs4680	chr22:19951271	C	T	R	0.48	.50	1.00
6	DAT1 -67 A/T	rs2975226	chr5:1445616	T	A	F	0.00	.00	**0**[a]
7	DAT1 -839C/T	rs2652511	chr5:1446389	G	A	R	0.39	.44	0.99
8	DAT1 1343 A/G (DdeI)	rs6347	chr5:1411412	A	G	F	0.25	.35	1.00
9	DAT1 2319 A/G	rs27072	chr5:1394522	T	C	F	0.00	.00	**0**[a]
10	DBH -1021 C/T	rs161115	chr1:96499830	T	A	R	0.40	.49	.94
11	DBH 1654 C/T Arg549Cys	rs6271	chr9:136522274	G	A	R	0.08	.15	1.00
12	DBH C/G	rs1611122	chr9:136508932	C	G	F	0.46	.50	.99
13	DRD1 utr 2348 A/G	rs686	chr5:174868700	T	C	R	0.40	.45	1.00
14	DRD1 utr 898 C/T	rs4532	chr5:174870150	T	C	F	0.39	.46	.99
15	DRD1utr A/G	rs265981	chr5:174870902	C	T	R	0.39	.46	1.00
16	DRD2 intron A/C	rs1076560	chr11:113283688	G	T	R	0.18	.31	1.00
17	DRD2 INTRON G/T	rs2283265	chr11:113285536	G	T	F	0.18	.31	.99
18	DRD2 TAG C/T	rs6277	chr11:113283459	T	C	F	0.48	.48	1.00
19	DRD2 TAQ1A	rs1800497	chr11:113270828	C	T	F	0.22	.38	.99
20	DRD3 intron A/G	rs1167771	chr3:113876275	A	G	F	0.19	.31	1.00
21	DRD3 ser9gly	rs6280	chr3:113890815	T	C	F	0.34	.49	.99
22	DRD4 -1106 C/T	rs936460	chr11:636199	A	G	R	0.30	.41	1.00
23	DRD4 -291 C/T	rs916457	chr11:637014	G	A	R	0.05	.09	1.00
24	DRD4 -521 C/T	rs1800955	chr11:636784	A	G	R	0.45	.49	.97
25	DRD4 -616 G/C	rs747302					Failed pre-optimization[b]		
26	DRD4 -809 G/A	rs936461	chr11:636496	C	T	R	0.35	.43	1.00
27	DRD4 -906 T/C	rs3758653	chr11:636399	A	G	R	0.18	.26	.99
28	DRD4 870 C/T	rs762502	chr11:640119	T	C	F	0.00	.00	**0**[a]
29	DRD4 int A/C	rs11246226	chr11:641191	C	A	F	0.49	.53	1.00
30	HTR1A C/G	rs6295	chr5:63258565	C	G	R	0.49	.53	1.00
31	HTR2A -1438A/G	rs6311	chr13:47471478	G	A	R	0.42	.50	.98
32	HTR2A 346 G/A Asp49Asn	rs6312	chr13:47470824	T	C	R	0.07	.12	.99
33	HTR2A C/T his452Tyr	rs6314	chr13:47409034	G	A	R	0.10	.18	1.00
34	MAOA 1072G/T	rs6323	chrX:43591036	A	C	R	0.27	.14	1.00
35	SLC6A4 upst C/T	rs25532	chr17:28564170	C	T	F	0.11	.21	.97
36	STMN1 C/G	rs182455	chr1:26234983	G	A	R	0.39	.46	1.00
37	STMN1 utr 289 G/T	rs213641	chr1:26232356	A	C	R	0.40	.47	.98
38	TH A/G	rs10770141	chr11:2193840	G	A	F	0.38	.49	.99

Note. Maj = major allele, Min = minor allele, Strand = orientation: F = forward, R = reverse, MAF = minor allele frequency, H = heterozygosity. [a]Four SNPs failed amplification (0% call rates). [b]the rs747302 failed to amplify during the assay optimization phase and was removed from the assay

Table FF-2

Genome Quebec project report

Samples		Good	Failed	Total	% Good
	Total	276	12	288	95.83
	Reference	270	7	277	97.47
	Replicate	0	0	0	0
	Control Reference	2	5	7	28.57
	Control Replicate	4	0	4	100

Assays (number of markers)		Good	Failed	Total	% Good
	Total	33	4	37	89.19
	Reference	33	4	37	89.19
	Replicate	0	0	0	0
	Control Reference	0	0	0	0
	Control Replicate	0	0	0	0
	Panels			1	
				Total	% Assay
	MAF=0			0	0
	0 < MAF < 0.05			0	0
	MAF >= 0.05			33	100

Genotypes		Good	Failed	Total	% Good
	Genotypes Recorded	9040	1616	10656	84.83
	Reference Genotypes Recorded	8842	1407	10249	86.27
	Good Reference Genotypes Recorded	8835	75	8910	99.16

Inconsistencies	Sample	Assay	Total Error	Total Comp.	% Error Rate
Mendelian Errors	0	0	0	0	0
Sample Reproducibility Errors	0	0	0	132	0
Assay Reproducibility Errors	0	0	0	0	0

Note. Report date: May 17, 2012. MAF = minor allele frequency.

Appendix GG Genotype distributions that differed between samples recruited in France and Canada

SNP	Genotype	Recruitment country		Statistical test	
		Canada	France		*p*
rs6271	1	1	4	Fisher's	**.00005**
	2	10	20		
	3	67	24		
rs6314	1	1	3	Fisher's	**.0004**
	2	13	21		
	3	64	24		

Note. Chi-square tests were used when 80% of the cells had counts greater than 5, otherwise results were results were obtained using a Fisher's exact test.

Appendix HH Genotype and allele frequencies for *BDNF* and *STMN*1

Gene	Sex	Recruitment location	SNP		Genotype counts		Allele frequencies			
					High	Low	High		Low	
							Maj	Min	Maj	Min
BDNF	Females	Combined	rs6265	GG	14	13	.91	.09	.66	.34
				GA	3	15				
				AA	0	3				
		France		GG	14	3	.91	.09	.67	.33
				GA	3	2				
				AA	0	1				
STMN1	Males	Combined	rs182455	CC	13	3	.47	.53	.27	.73
				CT	30	11				
				TT	17	18				
		France		CC	9	1	.44	.56	.09	.90
				CT	30	0				
				TT	16	10				

Note. Samples were split by sex, and only details from significant associations are shown.

Maj = major allele, Min = minor allele.