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Influence of DRD4 Receptor Gene Polymorphism on Aspirational Quality and Approach Motivation

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INFLUENCE OF DRD4 RECEPTOR GENE POLYMORPHISM ON ASPIRATIONAL QUALITY AND APPROACH MOTIVATION

By

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Thesis Approval

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Abstract

The present study investigates the presence of a molecular genetic basis of the quality of aspiration and motivation for behavior described by Ryan and Deci's self-determination theory and Gray's biopsychological theory of personality respectively. In this study, investigation was carried out to determine the impact of DRD4 receptor gene polymorphism on intrinsic and extrinsic aspiration as well as approach motivation using the Aspiration Index scales and Behavioral Inhibition and Activation (BIS/BAS) scales as our psychometric instrument of evaluation. In a pilot study consisting of 9 healthy subjects, the 7R allele of DRD4 receptor gene was associated with higher mean score of extrinsic motivation. Furthermore, the 7R allele of the DRD4 gene had a higher mean value for the relative centrality of extrinsic motivation in the aspiration index of participants. The findings of this study suggest that the presence of certain allelic expressions of DRD4 receptor gene may predict aspirational quality. However, a full study comprising a large sample of participants is required to establish the accuracy our hypothesis.

Keywords: DRD4, aspiration index, BIS/BAS, motivation, polymorphism

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Introduction

Specific Aims of the Present Study

Dopamine regulating and receptor genes have considerable impact on the construct of personality and behavioral traits (Reuter et al., 2006; Light et al., 2007). By coding for the receptors and enzymes that regulate the activities of dopamine neurotransmitter in the brain, these genes play a critical role in the determination of personality type and regulation of behavior. More so, certain polymorphic expressions of these genes have been associated with personality types and behavioral tendencies that are heavily reward-dependent (Alfimova et al, 2019). However, scientific studies aimed at establishing the nexus between these genetic polymorphisms and variations in personality are insufficient. Firstly, the number of studies exploring this relationship are few. Secondly, the studies that have been conducted did not focus on a single dopamine regulation gene but rather on epistatic interactions between different dopaminergic genes. While Reuter et al (2006) examined the effects of COMT and DRD2 interactions on approach behaviors, Alfimova et al (2019) studied ANKK1/DRD2 and HTR2C cys23ser interactions on approach motivations. Other studies (Light et al., 2007; Guo et al., 2008) have also looked at the impact of these genes on non-reward centered behaviors. The present study fills the gap by examining the influence of a single dopamine regulating gene (DRD4) on human aspirations and approach motivation.

This study throws more light on the role played by one of such dopaminergic gene, i.e. DRD4 gene, in determining aspirational quality, and by extension its behavioral/emotional health consequences. The predominance of extrinsic motivation relative to intrinsic motivation and extreme behavioral pursuits of rewards have been linked to poor mental health, drug addiction,

and depression (Schmuck et al., 2000; Auerbach et al., 2011). Meanwhile, both drug addiction and depression constitute a national health burden with immense cost to the government, and most importantly to the sufferer (Alcohol and Drug Use Collaborators, 2018). Currently, treatment of these disorders lacks sufficient preventative measures and are therefore largely reactive. In conclusion, this study contributes towards understanding the influence of dopaminergic genes on the quality of life aspirations. In the same vein, certain genetic components of behavioral instincts associated with overly reward-sensitive personalities may be uncovered.

Hypothesis

The central hypothesis of this study is that polymorphic expressions of the DRD4 receptor gene contributes significantly to scores generated on the aspiration index and BIS/BAS scales. Particularly, we postulated that the effect of these polymorphic expressions will mainly be observed on extrinsic motivation and approach motivation as measured by aspiration index and BIS/BAS scales respectively. Genetic studies geared towards examining this blend of relationship between aspiration index and BIS/BAS scales are scanty, hence the innovatory impact of this study. Therefore, our specific aim tested the hypothesis that polymorphism in DRD4 receptor gene influence scores on the aspiration index scale (extrinsic motivation) and BIS/BAS (BAS sub-scale) scale.

Aim of the Study

The aim of the present study was to determine whether polymorphism in DRD4 receptor gene influences scores on the aspiration index (extrinsic motivation) and BIS/BAS (BAS sub-scale) scales.

Expected Outcome

We predicted a positive correlation between measured approach motivation using BIS/BAS and the 7R and 2R alleles of DRD4. Additionally, we expected to observe a positive correlation between these allelic expressions and a predominance of extrinsic motivation measured using the aspiration index scales. Overall, we hypothesized that participants expressing one or more of these alleles would present with higher scores of reward sensitivity and responsiveness when compared to those without these allelic expressions.

Literature Review

Dopamine neuro-regulation and behavior

Personality theories explain differences in human behavior as a function of variation in underlying neurobiological processes (Gray, 1982; Di Domenico & Ryan, 2017). One of such processes involves the regulation of dopamine in the brain. The regulation of dopamine availability in the brain happens at several stages of the neurotransmitter's release and metabolism. These stages include dopamine release from storage vesicles via exocytosis, binding to and activation of dopamine receptors, and dopamine reuptake.

As a neurotransmitter, dopamine is involved in motor control, the experience of pleasure, executive functions and arousal (Kruger et al., 2005; Berridge, 2006; Schacht, 2016).

Accordingly, neuronal functioning and systems that are sensitive to dopamine exerts a predetermining impact on human mental states and behavioral tendencies (Depue & Collins, 1999; Depue & Fu, 2013). Some of these tendencies such as behavioral adjustments to the presence of rewards and punishments constitutes the bedrock of certain features of our personality. Thus, processes occurring in dopaminergic circuits in the brain are often reflected behaviorally in the quality (intrinsic or extrinsic) and the direction (approach or avoidance) of motivation (He et al., 2018). On account of this, individual differences in dopamine regulation will result in personality variations with an attendant dissimilarity in assimilation of and interaction with the environment (Smillie et al., 2010).

Effects of dopamine dysregulation on behavior

In dysfunctional states, dopamine neurotransmitter has been associated with impulsiveness, and addictions related to sex, gambling and drugs (Manuck et al., 2000; Worsley et al., 2000; Ceravolo et al., 2010). This is attributable to dopamine's capacity to stimulate appetitive behavior and promote the experience of pleasure (Friedel, 2004; Nemoda et al., 2010). According to the prevailing theories offering explanations about the involvement of dopamine in the experience of pleasure, it is stated that dopamine confers motivational salience. In other words, dopamine does not only cause individuals to feel pleasure, but in addition, it kindles the expectation of pleasure as a reward for the achievement of a particular goal (Schultz, 2015). Consequently, the expectation of pleasure as potential reward upon attaining a particular goal triggers approach behaviors and goal-oriented actions. In the same way, expectation of negative rewarding stimuli can induce avoidance behaviors (Richter et al., 2013).

Dysfunctions in dopamine regulation may result from several biological events including a). Epigenetically through the exposure of fetuses to alcohol and drugs, b). Changes to dopamine circuitry and molecular processes caused by addiction, and c). Genetic polymorphism.

The expression of genetic information programmed into dopaminergic genes can be altered by chronic exposure of a fetus to alcohol (Laufer et al., 2013; Lussier et al., 2018). DNA methylation is one way by which this alteration can occur (Zhang et al., 2013). DNA methylation which is the addition of methyl groups to DNA molecules is a normal biological process associated with aging, cancer development, and repression of gene transcription. Also, it represents an epigenetic means by which excessive alcohol consumption can effect genetic alterations. By undergoing the process of DNA methylation, the suppression of genetic information in dopamine genes e.g. DRD2 & DRD4 is an observed consequence of maternal alcohol use (Fransquet et al, 2016). Pathologically, the abnormal methylation of these genes is manifested as psychiatric illnesses and neurodevelopmental disorders such as fetal alcohol spectrum disorder (FASD) (Laufer et al., 2013). As such, patients who suffer from alcohol related neurodevelopmental disorder which is a less severe form of FASD present with neurobehavioral deficits including impulse control and attention deficit hyperactive disorder (ADHD) (Lussier et al., 2018).

In similar fashion, disruptions in brain dopamine system have been implicated in the emotional changes associated with borderline personality disorder (BPD) and dopamine dysregulation syndrome (DDS) in Parkinson disease patients (Ceravolo, 2010). In both conditions, sufferers engage in impulsive behaviors such as drug use, dangerous sex, and reckless spending. However, whereas in BPD, one of the investigated causes is genetic

variability (Lis et al., 2007), DDS is a condition that results from long-term intake of dopaminergic drugs while treating brain diseases such as Parkinson's (O'Sullivan et al., 2009). The appetitive motivation and strong craving for pleasurable incentives that characterizes these two conditions indicates that alterations in the genetic template of the brain's dopamine network may translate into strong behavioral hunting of pleasurable rewards.

Genetically, variation in dopamine regulation is attributed to polymorphisms in dopamine regulating and receptor genes such as Catechol-O-methyl transferase (COMT), Dopamine receptors (D1, D2 and D4), Dopamine transporter (DAT) and Mono-amine oxidase (MAO) (Balci et al., 2013; Felten, 2011). These genes code for receptors and enzymes responsible for dopamine production, vesicle release, storage, receptor binding and reuptake in the central nervous system. Although not all polymorphic expressions in dopamine genes lead to significant changes in dopamine neurotransmission, some anomalies in dopamine transmission processes are traceable to genetic variance. As an example, the types of mutations that can be expressed by the DRD4 gene includes Val194Gly substitution, 13 base pair deletion, 12 base pair repeat in exon 1, tandem duplication of 48 base pairs, C-521T, and 48 base pair VNTR in exon 3. Of all these, only the 48bp VNTR and to a lesser extent the C-521T are notably associated with novelty seeking. Additionally, of the nine repeats (2 – 11) constituting the 48bp VNTR of DRD4, only the 2 and 7 repeats are considered relevant to behavioral phenotypes (Bookman et al., 2002; He et al., 2018).

Dopaminergic genes and mental disorders

In terms of mental health and behavior, certain variants of dopamine regulating and receptor genes are associated with anti-social and delinquent behaviors, psychiatric illnesses such

as bipolar disorder and depression, as well as personality traits such as risk-taking, impulsiveness and addiction (Greenwood et al., 2001; Guo et al., 2008). The growing number of studies with evidence linking these psychiatric and behavioral illnesses to genetics has served as a reasonable basis for scientific theories and investigations seeking to define the degree to which personality differences can be predicted by genetic constitution.

Dopaminergic gene polymorphs, personality theories, types, and evaluation

Indeed, polymorphic expressions of dopamine genes have been demonstrated as one factor influencing the different personality types measured by psychometric instruments such as aspiration index and BIS/BAS (Reuter et al., 2006; Smillie et al., 2010; Montag & Reuter, 2014). Meanwhile, the development of these psychometric instruments is founded on the need to scale the classification of personality types expounded by personality theories. Hence, the nature of the different personality types and psychological tendencies evaluated by these instruments is the focus of personality theories.

Self-determination theory

One of such theories is the Self-Determination Theory (SDT). Developed by Edward Deci and Richard Ryan, SDT holds that humans are motivated to accomplish life goals in order to fulfil the basic psychological need for autonomy, competence and affiliation. This motivation may be internally or externally driven in which case they are referred to as intrinsic and extrinsic motivation respectively. Competence – the attainment of expert levels in a given activity, and autonomy which is described as maintaining control over one's actions are preconditions for intrinsic motivation. Accordingly, intrinsically motivated individuals engage in goal-oriented

actions for its own sake, i.e., the satisfaction derived from such actions are inherent in its performance (Deci & Ryan, 2012).

On the other hand, extrinsically motivated individuals are sprung into goal-oriented behaviors because of the potential of achieving external rewards such as fame, praise and financial gains. However, it should be noted that generally, aspirations of individuals usually comprise both intrinsic and extrinsic targets (Kasser et al., 2004). That is for example, the behavior of an individual may be simultaneously motivated by the need to achieve competence as well as garner financial gains.

Although as specified by self-determination theory, these basic psychological needs (autonomy, competence, and affiliation) can only be met by intrinsic motivation, the ideal and most common state maintains a balance of both intrinsic and extrinsic motivation (Deci & Ryan, 2012). In the other extreme, a preponderance of extrinsic motivation in an individual's aspirational conduct will cause autonomy to be sacrificed. Likewise, the introduction of rewards even when a behavior is already intrinsically motivated engenders loss of autonomy and may affect performance or competence. Thus, the relative predominance of extrinsic motivation in an individual's aspirational conduct is associated with emotional stress and depression (Kasser & Ryan, 1996).

Biopsychological theory of personality

Another recognized personality theory is Gray's biopsychological theory of personality. Gray asserts that human behavioral responses to environmental or external cues are controlled by two systems namely Behavioral Activation System (BAS) and Behavioral Inhibition System

(BIS) (Gray, 1982). Behavioral Activation System promotes movement towards a goal due to its high sensitivity to reward stimuli, and with each activity rewarded with pleasure, there is reinforcement of approach motivation. In addition, when BAS is in operation, an individual is impulsive, motivated into action by the possibility of obtaining reward and engages in risky behaviors. The twin personality subtype is regulated by the Behavioral Inhibition System (BIS). Under the control of BIS, an individual will display high sensitivity to punishment and seek to avoid it, is risk-averse and anxiety prone. When BAS also known as approach motivation is high, impulsivity is also high as well as the tendency to engage in alcohol and drug abuse, on the other hand, high BIS or avoidance motivation is associated with negative emotions and clinical states such as fear, anxiety and depression (Gray, 1982; Gray & McNaughton, 2000).

In the central nervous system, the currency for BAS operations is dopamine. BAS neural components have been identified as the dopaminergic fibers proceeding from the ventral tegmental area (substantia nigra & nucleus A10) to the frontal cortex and the limbic system (Depue & Collins, 1999; Barrós-Loscertales et al., 2010; Krebs, 2011; Depue & Fu, 2013). As for BIS, Gray asserted that the system regulating sensitivity to threats is mediated by noradrenergic and serotonergic activities in the brain (Gray & McNaughton, 2000).

Personality type assessments

In an effort to measure the traits described by the self-determination theory and Gray's bio-psychological theory of personality, the Aspiration Index (AI) and Behavioral Inhibition and Behavioral Activation System (BIS/BAS) scales which are two distinct and standardized psychometric measures are often employed (Kasser & Ryan, 1996; Carver & White, 1994). While BIS/BAS developed by Carver and White measures the sensitivity of individuals to

reward and punishment cues, aspiration index scale determines whether an individual is intrinsically or extrinsically motivated. Scores attained on the BIS/BAS 24-item questionnaire are currently used as a clinical marker to foretell manic and depressive episodes in bipolar patients (Meyer et al., 1999). Several studies have suggested that extreme sensitivity to reward and punishment cues may be related to mental disorders. For example, high BAS and low BIS have been associated with manic episodes while high BIS have been observed to cause anxiety (Meyer et al., 1999; Corr, 2002).

Equally, scores generated from the aspiration index questionnaire are strongly associated with mental health indicators (Kasser & Ryan, 1996). Specifically, numerous studies have shown that the achievement of intrinsic aspirations relative to extrinsic aspiration is strongly associated with psychological wellbeing (Sebire et al., 2009). More so, this is due to the observation that the basic psychological needs of autonomy, competence, and affiliation are rarely fulfilled by pursuing extrinsic aspirations. Studies carried out with newly graduated college students show that pursuit of extrinsic aspirations can promote dissatisfaction with life and affect mental health (Deci et al., 1999; Shamloo & Cox, 2009).

Presently, differences in dopamine regulation has been pinpointed by a number of studies as a major component impacting the fun-seeking and reward responsiveness exhibited by BAS sub-scale personality types (Light et al., 2007; Smillie et al., 2010; Wacker et al., 2013). Nonetheless, the implication of these genetic polymorphic expressions as the force behind the reward-dependent extrinsically motivated personality described in the self-determination theory and appraised by the aspiration index scale has not been sufficiently examined.

Furthermore, the neuronal correlates of aspiration index and BIS/BAS as instruments used for evaluating approach motivation and aspirations are not as clear and distinct. Although, studies have revealed that resting pre-frontal EEG activity asymmetry predicts lateralized response to BIS/BAS, and task-elicited (state emotion manipulations) pre-frontal EEG asymmetry is a better predictor of individual differences in BIS/BAS (Balconi et al., 2011, 2017), similar efforts in functional studies have been lacking for aspiration index scale.

Dopaminergic gene polymorphs

In the pursuit to identify the neuronal correlates of the reward-dependent goal-oriented actions captured by the extrinsic aspect of the aspiration index scales as well as the impulsivity and reward responsiveness that characterizes the Bas scale, dopamine regulation in the CNS have been largely implicated by studies conducted in this regard (Light et al., 2007; Smillie et al., 2010; Wacker et al., 2013).

Dopamine regulation is genetically controlled by a set of genes that regulates the degradation, receptor binding, transport and uptake of dopamine. As discussed earlier, variations in the structural architecture of these genes will often impact functional differences on the activities of receptors and enzymes involved in these processes. One such enzyme controlled by these genes is the Catechol-O-methyl transferase (COMT) enzyme, which is encoded by the COMT gene, and is involved in the degradation of catechol neurotransmitters like dopamine and epinephrine through the addition of a methyl group (Grossman et al., 1992). The COMT gene expresses functional polymorphism of a single nucleotide, a G to A transition in codon 158 of the COMT gene, leading to the substitution of valine with methionine (Val158Met). The

methionine variant has up to four-fold reduced enzyme activity, causing a prolonged presence of dopamine at dopamine receptor sites due to the slow rate of degradation (Lachman et al., 1996).

Reduction of enzymatic activity in COMT Met allele has been exploited in the management of Parkinson's disease where COMT inhibitors are combined with dopaminergic drugs like levodopa to boost dopamine availability at the D1 and D2 receptors (Rivest et al., 1999; Jankovic & Aguilar, 2008). Also, studies found the Met allele to be associated with psychiatric conditions such as ADHD and schizophrenia, with its role identified as enhancing a decline in cognitive functioning (Lachman et al., 1996). Unsurprisingly, a significant effect of anti-psychotic medications among those with Met allele is the improvement of cognitive functioning. Expectedly, the prolonged dopamine availability promoted by the COMT Met allele is thought to be responsible for high scores in novelty-seeking among carriers of the gene (Reuter et al., 2006; He et al., 2018).

Another dopamine metabolizing enzyme with significant control on dopamine regulation is Monoamine Oxidase (MAO) comprising of A and B subtypes; these are metabolizing enzymes with regional distribution in the brain especially the hypothalamus, striatum, global pallidus and the cortex (Tong et al., 2013). MAOs catalyze the oxidative deamination of monoamines including dopamine in the brain (Sabol et al., 1998; Edmondson et al., 2004). As such, the presence of MAO genetic variants may lead to dysfunctions in metabolism of dopamine neurotransmitter.

In humans, the 2R, 3R, 3.5R, 4R and 5R alleles of the 30-base repeat sequence displays different levels of transcriptional activity of the MAOA gene promoter. Among the alleles, the 2R allele has been linked severally with anti-social and delinquent behaviors with a particular study showing higher levels of self-reported violent misconduct (Guo et al., 2008; Tiihonen,

2014). Before discovery of the 2R allele and its effect on behavior, studies have demonstrated that the 3R and 5R alleles of the gene are associated with aggressive and violent behaviors under stressful conditions (Manuck et al., 2000).

Dopamine Transporter (DAT) is a membrane protein with established presence in the nigro-striatal, mesolimbic and meso-cortical pathways, areas rich in dopaminergic networks (Ciliax et al., 1999). DAT actively pumps dopamine out of the synapses back into the cytosol, a re-uptake process that extinguishes the neurotransmission of dopamine. The DAT1 gene is located on human chromosome 5 and consists of 15 coding exons, manifesting a 40 base pair Variable Number Tandem Repeat (VNTR) genetic polymorphism with 7R, 9R, 10R, and 11R alleles (Vandenbergh et al., 1992). Polymorphisms and alterations in the activity of DAT have considerable impact on behavioral health as it has been identified as a risk factor in bipolar disorder and clinical depression (Laasonen-Balk et al., 1999; Greenwood et al., 2001). The role played by DAT in these mental conditions can be observed through the actions of psychostimulants such as cocaine and amphetamine on dopamine neurotransmission. Psychostimulants inhibit the actions of DAT, hence, the re-uptake of dopamine from the synapses back into presynaptic terminals is suppressed. The resultant increase in availability of dopamine for neurotransmission provokes psychosis in normal individuals, and mania episodes in bipolar patients (Kalivas, 2007; Vaughan & Foster, 2013).

Dopamine Receptors DRD2 and DRD4 are subtypes of a family of G-coupled protein receptors activated by dopamine. Both DRD2 and DRD4 are now known to be involved in various psychiatric conditions and serves as receptor sites for a number of anti-psychotic drugs like clozapine (Van Tol et al., 1991). Up to three polymorphisms have been identified with the DRD2 gene including Taq1A, C957T, and -141C ins/del. Of these three, the DRD2 Taq1A

which is associated with lower D2 receptor density has been the most studied. Carriers of the Taq1A gene demonstrate a higher risk of drug abuse and addiction (Comings et al., 1994; Munafo et al., 2007). This tendency is founded upon the sensitivity to dopamine that is bound to occur due to insufficient D2 receptors in the brain. In a study, carriers of the A1 allele showed higher sensitivity and increased performance when bromocriptine a D2 receptor agonist was administered (Kirsch, 2006). Therefore, the proneness to seek for and identify activities capable of increasing neural dopamine availability by carriers of the A1 allele strongly predisposes carriers of the gene to drug addiction (Comings et al., 1994; Munafo et al., 2007). A similar finding was observed in another study where DRD2 gene was found to influence the vigorous pleasure-seeking that characterizes approach motivation in schizophrenia (Alfimova et al., 2019).

In human DRD4 gene, an important polymorphism is the 48 base pair Variable Number Tandem Repeat (VNTR) in exon 3 consisting of 2 – 11 repeats. Although it consists of 2 – 11 repeats, the most common variants are the 2R, 4R, and 7R (Inoue et al., 1993). It should also be noted that dopamine is considered more potent at the 2R and 7R alleles than the other allelic repeats. The 7R allele shows less affinity and sensitivity to dopamine and has been associated with several psychological disorders including ADHD and personality traits such as novelty seeking and drug abuse (He et al., 2014). Further, DRD4 alleles influence responses to anti-psychotics (Van Tol et al., 1991). While recent evidence suggests that DRD4 receptor has high affinity for clozapine, other studies point out that carriers of the 7R allele may require higher doses of stimulants like methylphenidate in ADHD treatment (Hamarman et al., 2004).

Although polymorphism in dopamine regulating and receptor genes (COMT, DRD, DAT, MAO) have been indicated by quite a number of studies as the genetic cause of observable variations in approach motivation, it is less so for aspiration index, especially extrinsic

motivation. Nonetheless, few genetic studies have presented results that indicates a link between these genes and quality of aspiration (Söderqvist et al., 2014; Di Domenico & Ryan, 2017). Finding the genetic alterations that precipitate life aspirations that are extremely dominated by extrinsic motivation may require a change from an approach that treats Gray's biopsychological theory and self-determination theory as mutual exclusives.

Moreover, the specific roles played by each gene, and the effect of gene-gene interactions in determining the expressions of behavior measured by the Aspiration index and BIS/BAS are yet to be fully determined. Already, recent studies suggest that interaction between COMT Met allele and DRD2 Taq1A influences response timing to large rewards (Balci et al., 2013).

Significance of this Study

Outcomes of aspirational quality assessment using the aspiration index scale portrays the balance of intrinsic and extrinsic motivation. Measurement scores hugely swayed towards extrinsic motivation indicates a central guiding principle dominated and informed by external rewards. Emotional health consequence often results from such predisposition (Kasser & Ryan, 1996). Among such consequences are self-report of unhappiness as well as the lack of determination to accomplish established individual goals once the expected rewards are removed (Kasser et al., 2004; Deci & Ryan, 2012). For example, college students with dominant extrinsic motivations are more likely to quit schooling. This is because rewards for academics are not immediate, and the expectation of its eventual achievement can easily be lost in the didactics of everyday schooling.

Behavioral activation system on the other hand governs the tendency to be stimulated and attracted towards ventures that are rewarding. This trait is also characterized by poor risk assessments, impulsiveness, drug use and risky enterprises (Gray & McNaughton, 2000).

This study attempts to identify neuronal correlates of extrinsic motivation and behavioral activation by examining the influence of DRD4 receptor gene on aspiration index and BIS/BAS scores. Consequently, the genetic components for Behavioral activation system and extrinsic motivation may be identified.

Pinpointing the extent to which the identified polymorphic expressions affect Aspiration index and BIS/BAS scores lends scientific support to the suggestion that these genetic polymorphs may be culpable in certain psychiatric and mental health conditions, especially those that present with addictions and dysfunctional reward systems. As a result, the likelihood of these receptors to be employed as drug targets in the treatment of mental disorders is substantial.

Innovation

Current studies on aspirational quality are largely focused on how the predominance of extrinsic motivation impacts emotional and mental health. Moreover, the link between the predominance of extrinsic motivation and mental health have been established. This predominance is observed in the tendency to be easily and only most likely stimulated towards a particular goal when external rewards are in view and obtainable. So far to our knowledge, no studies have tried to pin the propensity to be motivated mostly by external rewards unto the regulation of dopamine neurotransmitter in the brain. This study plays an innovatory role amongst scientific inquiries into the nature of human aspirations by looking at the possible influences of polymorphic genetic expressions of DRD4 receptor gene on extrinsic motivation.

Secondly, in a few studies, COMT and DRD2 genes have been linked with certain personality types and behaviors captured by BAS, this study extends the approach to DRD4. This study also proposes a potential link between BAS and extrinsic motivation. It is likely that dopamine receptor and regulating genes provides the connection between behavioral activation and a predominance of extrinsic motivation. The rationale for our study aim is that identifying a link between DRD4 receptor gene and scores obtained on the aspiration index and BIS/BAS scales may reveal the extent to which motivation and behavior are genetically controlled. Besides that, uncovering a link between DRD4 receptor gene and personality assessment scores further reflects how much of behavioral health is genetically determined. Already, DAT and DRD2 receptors are implicated in bipolar disorder, clinical depression and emotional dysregulation syndrome.

Methodology

The aim of this study was to investigate whether there is an association between DRD4 receptor genes and BIS/BAS (BAS sub-scale) and AI (extrinsic motivation) scores. To achieve this aim, DNA samples from participants alongside completed BIS/BAS and AI questionnaires were employed to investigate the role played by genetics in determining aspirational quality and approach motivation.

The population sampled comprised college students and healthy adults at least 18 years old. Participants were invited through emails, text messages, and/or face-to-face meetings. This study was carried out on Arkansas Tech University campus. In compliance with ATU COVID-19 procedures, participants were required to fill out COVID screening forms the day of their appointment. Participants ‘also had their body temperature taken before commencement of the experiment.

Personality Assessment

Participants were given the Behavioral Inhibition and Activation (BIS/BAS) and Aspiration Index questionnaires to fill. The Behavioral Inhibition and Activation (BIS/BAS) scales is a 24 item self-report instrument which is rated on a four-point Likert scale. The questionnaire consists of 7 BIS items, 13 BAS items (includes 3 subscales), and four fillers. The BIS/BAS reveals the sensitivity of an individual to punishment and reward cues. Higher scores on the BAS sub-scales (fun, drive, and reward responsiveness) indicates proneness to fun-seeking behaviors and high responsiveness to rewards.

The Aspiration Index (AI) questionnaire evaluates quality of motivation and indicates whether an individual is relatively more driven by intrinsic factors such as affiliation, community feeling, health, and personal growth, or extrinsic factors such as money, fame, and recognition. It consists of 35 aspiration items which are grouped into seven categories namely personal growth, health, affiliation, community feeling wealth, fame, and image. Each category comprises about 4 or 5 items. Participants will rate these items based on (a) personal importance and (b) the chances of attaining them in the future, with responses rated on a 7-point scale. The predominance of extrinsic motivation in a participant's AI score points towards an aspirational quality sensitive to external motivating factors.

The BIS/BAS and AI questionnaires allows us to evaluate and determine the direction and quality of participants' motivation and by extension those likely to possess the genes under examination.

Genotyping

To carry out DNA extraction and genotyping, saliva samples of participants were collected via passive drool. Saliva DNA was isolated using the Chelex extraction protocol developed in the IBNS lab at Arkansas Tech University. Amplification of the VNTR polymorphism in DRD4 genes was carried out using exon III specific primers in a total volume of 50ul containing 25ul of 2X master-mix solution, 1ul each of forward (5' GCGACTACGTGGTCTACTCG 3') and reverse (5' AGGACCCTCATGGCCTTG 3') primers, 10ul of the extracted DNA sample, and 13ul of nuclease free water. The PCR protocol employed for DRD4 consist of 15 minutes of initial denaturation at 95ºC, followed by 40 cycles of denaturation at 94ºC for 1 minute, annealing at 55ºC for 1 minute, extension at 72ºC for 90 seconds, and final extension at 72ºC for 10 minutes.

Products of PCR amplification were visualized under ultraviolet light after resolution in 2% agarose gel subjected to electrophoresis and stained with ethidium bromide. Sample DNA sizes were determined by comparison with 100bp DNA ladder. A 4-repeat PCR product has a predicted length of 475bp.

Statistical Analysis

Statistical analysis of the study results was performed using IBM SPSS (version 25). The percentage of each DRD4 allelic repeats present in the participant pool (allele frequency) was calculated. For the aspiration index questionnaires completed by participants, the mean corrected score (MCS) of each aspiration subscale was calculated by adding the scores of all the sub-scales to get the total sub-scale scores, dividing the total sub-scale scores by seven (number of sub-scales in the aspiration index) to get the average total sub-scale score, and then subtracting the

average of the total sub-scales scores from each sub-scale score. The average of the extrinsic sub-scales MCS provided the summary extrinsic motivation scores. Relative intrinsic/extrinsic orientation of aspirations, which is the relative dominance of intrinsic motivation in an individual's aspiration index was determined by subtracting extrinsic motivation scores from intrinsic motivation scores. Higher values of relative orientation scores signify the predominance of intrinsic motivation in a participants' aspirational quality, while lower scores point towards an extrinsically motivated individual. As for the BIS/BAS questionnaires, total BAS scores were calculated from the total average of the BAS sub-scales (Schmuck et al., 2000).

In order to analyze any associations between DRD4 receptor gene polymorphisms and extrinsic motivation, DRD4 gene alleles with the highest mean score of extrinsic motivation was determined, furthermore, the DRD4 gene polymorph with the lowest mean score of intrinsic/extrinsic orientation of aspiration was also determined. To ascertain the relationship between approach motivation and DRD4 gene alleles, correlative analysis between participants' extrinsic scores and measures of approach motivation was calculated.

Results

Table 1

DRD4 alleles, aspiration index scores and BAS scores

Repeats	Frequency	Summary Extrinsic Scores	Intrinsic/ Extrinsic Orientation	Reward Responsiveness	Total BAS
2R	33%	-1.2452	2.1792	16.33	39
5R	78%	-1.1107	1.9437	16.8571	41.4
7R	44%	-1.0292	1.8010	17.00	40.33

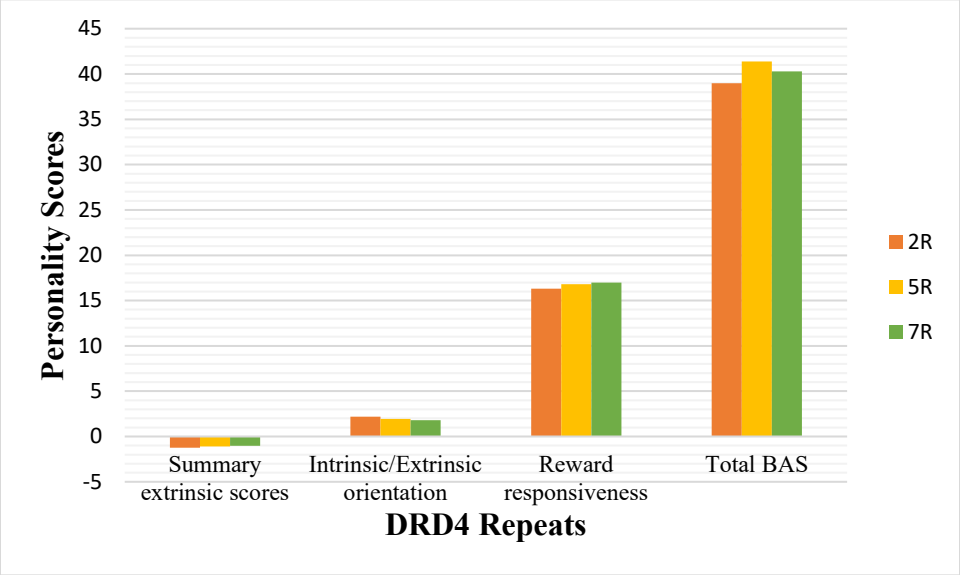
In this study, allele frequencies of DRD4 polymorphism were distributed among the participants such that three out of the nine participants possessed 2R alleles, four participants possessed 7R alleles, seven participants possessed 5R, and one participant possessed the 4R allele.

Associations between DRD4 allelic expressions and personality

According to results of the aspiration index questionnaire completed by participants, those possessing the 7R allele of DRD4 gene had the highest mean score of summary extrinsic aspiration score (Table 1). Additionally, participants with the 7R allele had the lowest mean score of intrinsic/extrinsic orientation of aspirations, demonstrating relatively higher values of extrinsic motivation in their aspirational quality.

Figure 1

DRD4 alleles, summary extrinsic scores, intrinsic/extrinsic orientation, reward responsiveness, and total BAS scores



In the BAS sub-scale scores, the 7R polymorphism had the highest mean score for reward responsiveness. However, all the alleles present demonstrated comparable total BAS scores.

Figure 2

Error bars for summary extrinsic scores, intrinsic/extrinsic orientation, reward responsiveness, and total BAS scores

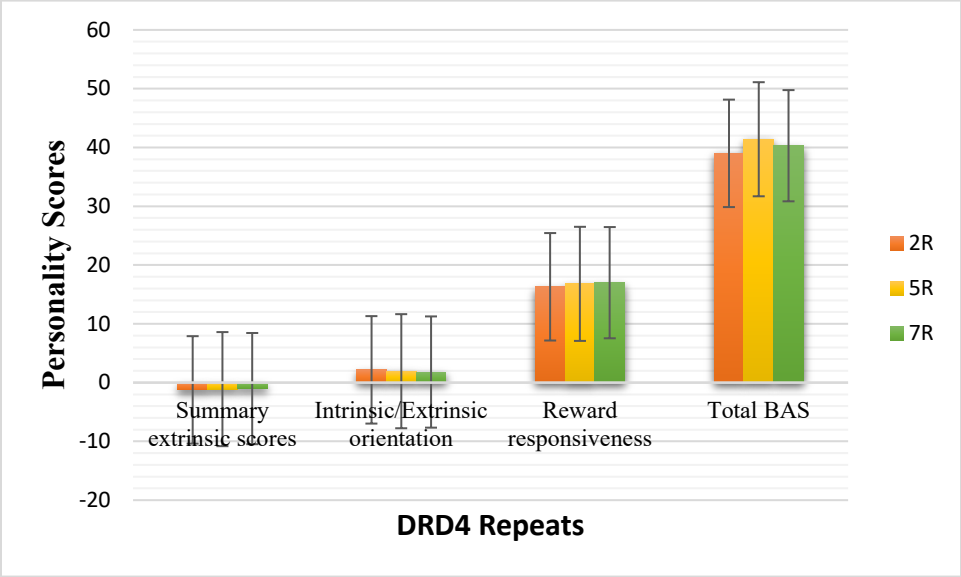


Table 2

Correlations of DRD4 allelic repeats with aspirational quality and approach motivation

Repeats	Summary Extrinsic Scores	Intrinsic/ Extrinsic Orientation	Reward Responsiveness	Total BAS
2R	-.263	.263	-.428	-.296
5R	.142	-.142	-.369	-.211
7R	.338	-.338	-.077	-.213

Going further, tests of correlation was performed between DRD4 repeat alleles and personality scores obtained from participants of the study. This test was conducted to observe whether there are any relationships between participants' extrinsic scores and those of reward responsiveness and total BAS. As shown in Table 2 above, the 7R allele of DRD4 receptor gene shows weak but positive correlation with the summary extrinsic motivation scores, and the highest correlative value with reward responsiveness.

However, the tests of correlation showed no positive association between extrinsic motivation scores and those of reward responsiveness and total BAS.

Table 3

Correlations between extrinsic scores and measures of approach motivation

	Reward responsiveness	Total BAS Score
Summary Extrinsic Scores	-.101	-.501

Discussion

This study tested the hypothesis that certain polymorphic expressions of DRD4 receptor gene are associated with a predominance of extrinsic motivation in aspiration index scores as well as high approach motivation in BIS/BAS scales. DRD4 is a dopamine receptor coded for by the DRD4 gene, and its binding affinity to, and activation by dopamine varies according to the gene variant that is expressed. In light of the scientific evidence that regulation of dopamine

neurotransmission constitutes the underlying neurobiological mechanism of reward-sensitivity, the DRD4 receptor gene easily comes under examination as one of the genes that may influence reward-centered behaviors. Additionally, this study directs its focus towards evaluating a possible underlying similarity in the neural correlates that governs the behavioral manifestations measured by aspiration index and BIS/BAS scales.

According to the findings of the present study, the 7R allele of DRD4 receptor gene correlated with higher relative centrality of extrinsic motivation in aspiration index scores, reward-responsiveness scores (BAS sub-scale) and total BAS scores.

The effect of dopamine regulation on extrinsic motivation may arise from the pleasurable experience that is attached to the attainment of extrinsic goals i.e. fame, money and recognition. It is plausible that the anticipation of these rewards alongside the pleasurable feelings they confer upon their attainment will activate approach behaviors, more so, this may likely be the case when polymorphic expressions in dopaminergic genes cause dysfunctions in dopamine neurotransmission.

The fact that individuals with aspirational quality dominated by extrinsic motivation construct life goals around external rewards and may pursue those goals in the expectation of experiencing the pleasures attached to those rewards suggests a fundamental link between the behavioral activation system (BAS) of the biopsychological theory of personality and extrinsic motivation of self-determination theory. As noted earlier, individuals with a predominance of extrinsic motivation and those high in approach motivation (BAS) engage in behavioral pursuits of highly rewarding goals. This was indicated in the results of the study which showed that the DRD4 7R allele was associated with the highest extrinsic motivation scores and reward responsiveness. Therefore, it is not unlikely that the same neuro-mechanism and brain dopamine

rewarding system responsible for BAS activity is equally in charge and directs the neuro-biological processes of extrinsic motivation.

However, the idea that BAS and extrinsic motivation may share the same genetic and neurobiological basis will be limited to individuals who possess the variants of dopaminergic genes that are associated with high reward sensitivity. Since the predominance of extrinsic motivation in individuals is not only characterized by the urge to obtain external rewards but can also be reflected in the desire to avoid punishments, some of the individuals with high scores in extrinsic motivation relative to intrinsic motivation may not be high in approach motivation (BAS), but rather show high avoidance motivation. Thus, being high in extrinsic motivation without possessing the genetic variants that predisposes one to extreme reward-seeking behaviors suggests the existence of another neurobiological pathway for extrinsic motivation that does not utilize the dopamine reward system and likely not influenced by dopamine regulation genes.

The implication of this pilot study is that it directs scientific interests towards the influence of dopaminergic genes on human aspirations, and in this particular case, DRD4 receptor gene on extrinsic motivation. Already, there is an abundance of studies demonstrating that dopamine regulation and its impact on approach motivation depends in large part on the activity of DRD4 receptors. Consequently, certain genetic variants of this gene such as the 7R and 2R have often been associated with high reward sensitivity. Likewise, from the outcome of the present study, the 7R allele of DRD4 gene receptor demonstrated a measure of relationship with the predominance of extrinsic motivation relative to intrinsic motivation in participants' aspiration index scores.

The differences in correlation between the DRD4 alleles and scores obtained from the personality measures ranged from small to large depending on the particular alleles under comparison. For the summary extrinsic scores and intrinsic/extrinsic orientation scores, there was a small difference (.196) between the 5R and 7R DRD4 alleles, but a large and significant difference (.601) between 2R and 7R alleles. On reward responsiveness, differences in effect sizes between 5R and 7R alleles, and 2R and 7R alleles were moderate i.e., .292 and .351 respectively. However, the differences in effect sizes among the alleles (2R and 7R, 5R and 7R) for the total BAS scores were insignificant, ranging between .002 and .083.

In addition to the effects of DRD4 receptor gene polymorphism on extrinsic motivation as indicated by the outcome of the present study, there are also potential clinical applications. The predominance of extrinsic motivation relative to intrinsic motivation has already been linked with depression and life-dissatisfaction. The identification of the specific underlying genetic polymorphism that may give rise to unhealthy aspirations that are heavily dependent on external rewards is crucial to an early recognition of individuals predisposed to the ill-effects thereof.

Further studies are needed to determine if other dopaminergic genes such as Catechol-O-methyltransferase (COMT), DRD2, mono-amine oxidase (MAO), and dopamine transporter (DAT) have similar influences on extrinsic motivation as is hypothesized in the present study about DRD4 receptor gene. On top of that, these studies should determine if there are specific epistatic interactions between these genes that may shape the outcome of scores generated on the aspiration index (extrinsic motivation) and BIS/BAS (BAS sub-scale) scales. That is, if certain polymorphic expressions of COMT, DRD2, MOA, and DAT affects scores on the AI and BIS/BAS scales, then it is not only important to ascertain the specific genetic polymorphs

involved, but also to determine the effect that epistatic interactions among these genes may exert on the scores obtained from these personality measures.

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Appendix A

Aspiration Index Scale

W1 To be a very wealthy person

W2 To have many expensive possessions

W3 To be financially successful

W4 To be rich

W5 To have enough money to buy everything I want

F1 To have my name known by many people

F2 To be admired by many people

F3 To be famous

F4 To have my name appear frequently in the media

I1 To successfully hide signs of aging

I2 To have people comment often about how attractive I look

I3 To keep up with fashions in hair and clothing

I4 To achieve the ‘‘look’’ I’ve been after

PG1 To grow and learn new things

PG2 At the end of my life, to be able to look back on my life as meaningful and complete

PG3 To choose what I do, instead of being pushed along by life

PG4 To know and accept who I really am

A1 To have good friends that I can count on

A2 To share my life with someone I love

A3 To have committed, intimate relationships

A4 To feel that there are people who really love me, and whom I love

C1 To work for a better society

C2 To assist people who need it, asking nothing in return

C3 To work to make the world a better place

C4 To help others improve their lives

H1 To be physically healthy

H2 To feel good about my level of physical fitness

H3 To keep myself healthy and well

H4 To be relatively free from sickness

Appendix B

BIS/BAS Scale

1. A person's family is the most important thing in life.
2. Even if something bad is about to happen to me, I rarely experience fear or nervousness.
3. I go out of my way to get things I want.
4. When I'm doing well at something I love to keep at it.
5. I'm always willing to try something new if I think it will be fun.
6. How I dress is important to me.
7. When I get something I want, I feel excited and energized.
8. Criticism or scolding hurts me quite a bit.
9. When I want something I usually go all-out to get it.
10. I will often do things for no other reason than that they might be fun.
11. It's hard for me to find the time to do things such as get a haircut.
12. If I see a chance to get something I want I move on it right away.
13. I feel pretty worried or upset when I think or know somebody is angry at me.
14. When I see an opportunity for something I like I get excited right away.
15. I often act on the spur of the moment.
16. If I think something unpleasant is going to happen I usually get pretty "worked up."

17. I often wonder why people act the way they do.

18. When good things happen to me, it affects me strongly.

19. I feel worried when I think I have done poorly at something important.

20. I crave excitement and new sensations.

21. When I go after something I use a "no holds barred" approach.

22. I have very few fears compared to my friends.

23. It would excite me to win a contest.

24. I worry about making mistakes.