Genetics Course
Final Paper

[redacted]

Title: The genetics of behavioural addiction: The neurogenetic pathways that link impulsivity with behavioural addiction risk.

Abstract:

People who are more impulsive tend to act without foresight, which can make them more likely to develop habits such as gambling or excessive gaming. These habits activate the brain's reward system but often lead to lack of control. Currently, there is a lack of research that maps out the system in which genetics influences behavioural addictions. This review paper aims to answer how impulsivity related genes affect brain regions involved with reward and self control. Dopaminergic and serotonergic systems are the neuron networks that use dopamine and serotonin as neurotransmitters, and are crucially involved in reward and motivation. Genetic variants in the aforementioned systems influence neurotransmitter balance, which results in altered signaling across the brain's reward system (which includes the prefrontal cortex, ventral tegmental area (VTA) and neural accumbens (NAc)). This altered signaling leads to increased impulsivity expressed by insufficient inhibition and high reward sensitivity. Because impulsivity serves as a bridge between genetics and addictive behaviour, understanding this neurogenetic pathway is quite important for human health, as it may allow for early identification of at-risk individuals and guide the development of prevention strategies.

Keywords: impulsivity, behavioural addiction, dopamine, serotonin, neurogenetics, reward system.

Introduction:

Addiction is frequently depicted as a cycle, but what compels a person to take that first step? Perhaps people who often struggle with self-control do so not just because of poor choices, but because of a biological predisposition. Behavioural addictions (BA) are chronic conditions in which individuals compulsively partake in specific activities that do not involve the use of substances (such as excessive gambling, gaming, shopping, internet-use, sex, pornography, work, exercise, etc.) which produce immediate reward. Individuals that suffer from these behavioural addictions continue to compulsively engage in these activities despite them having negative consequences on their life, including their mental and physical health. Similar to substance-use disorders, they comprise inhibited self-control, and are stimulated by interactions between neural circuits, genetic predispositions, and environmental factors (Grant et al., 2010). Although most of these disorders are not clinically recognized since they are not included in the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM–V), behavioural addictions are very real conditions that affect countless people around the globe (American Psychiatric Association [APA], 2013).

"Impulsivity, defined as the tendency to act without foresight", (Bevilacqua & Goldman, 2013) could be the factor that pushes someone to engage in addictive behaviours in the first place. Impulsivity is not only psychological, but has a genetic and neurological foundation. There is some compelling evidence that impulsivity is hereditable, with some studies calculating that around 45% of the variance in impulsivity is due to genetic factors (Congdon & Canli, 2008).

Studies have consistently found that multiple brain regions and neurotransmitter systems, particularly the dopaminergic and serotonergic systems, take part in the impulsive behaviours that happen throughout the addiction cycle (Brewer & Potenza, 2008).

Dopaminergic systems are involved in several different brain functions, including learning, reward, and control (Ko & Strafella, 2012). Dopamine (DA) neurons in the ventral tegmental area (VTA) regulate both goal directed and habitual behaviours. Activities that offer instant reward enhance dopamine release and lead to hyperbolic reward signaling, craving and compulsive addiction-seeking (Poisson et al., 2021a). The most relevant dopaminergic pathway genes linked to impulsivity and behavioural addictions include the D2 dopamine receptor (DRD2), D4 dopamine receptor (DRD4), and the dopamine transporter gene (DAT1/SLC6A3) (Bevilacqua & Goldman, 2013; Brewer & Potenza, 2008).

Serotonin (5-HT) is known to have been associated with several motor, cognitive and affective functions, including mood disorders. Various studies have found that reduced levels of 5-HT promote impulsive behaviours, such as impulsive action (failing to repress inappropriate actions) and impulsive choice (choosing immediate rewards over delayed rewards) (Miyazaki et al., 2012a). The most relevant serotonergic pathway genes linked to impulsivity and behavioural addictions include monoamine oxidase A (MAOA), the serotonin transporter gene (SLC6A4) and serotonin receptors such as HTR1B and HTR2C (Bevilacqua & Goldman, 2013; Brewer & Potenza, 2008). The release of 5-HT and DA is especially relevant in the mesolimbic system, as it can influence how reward is processed by the brain.

The mesolimbic system, or reward system, is made up of different brain areas which are in control of processing reward. Reward is defined as the “natural process during which the brain associates diverse stimuli (substances, situations, events, or activities) with a positive or desirable outcome” (Lewis et al., 2021). This process results in changes in a person’s behaviour, eventually causing them to seek that particular positive stimulus (Lewis et al., 2021). There are three specific brain areas that are part of the mesolimbic system which are directly involved with the release of DA and 5-HT; the ventral tegmental area (VTA), the nucleus accumbens (NAc) and the prefrontal cortex (PFC). The VTA is located in the ventral midbrain, and projections from the VTA release DA throughout the neural circuit to the NAc and PFC when reacting to a motivationally significant stimulus. (Kalivas & Volkow, 2005; Pistillo et al., 2015). The NAc is situated in the ventral striatum and plays an integrative role in processing motivation, reinforcement and reward by coordinating inputs from the PRC and the VTA (Bayassi-Jakowicka et al., 2021). The PFC plays an essential role in evaluating motivationally relevant events and predicting rewards. This area is activated by cues associated with reward and determines if a behavioural response will happen (Kalivas & Volkow, 2005). These different factors are linked in a particular pathway in which DA neurons in the VTA project to the NAc and the PFC. (Poisson et al., 2021). Understanding this gene-brain-behaviour pathway may be critical to gain insight into how impulsivity is linked to behavioural addictions, and therefore how to prevent individuals from beginning that addictive cycle due to impulsivity.

Recent literature on behavioural addictions often focuses solely on genes, brain regions or behaviours instead of the pathway as a whole. Research that does have a more

comprehensive outlook is focused on substance use disorders as opposed to behavioural additions (also considered impulse-control disorders or ICDs). Currently, there is a lack of investigation into the genetics, neuroimaging and behavioural factors of behavioural addictions, which generates limited understanding of how genetics shape the vulnerability to these disorders.

This review aims to address how impulsivity related genes (such as DRD2, DRD4, DAT1, MAOA, SLC6A4, HTR1B and HTR2C) affect brain regions involved with reward and self control (such as the VTA, NAc and PFC) and how this contributes to the elaboration of behavioural addictions. This paper argues that understanding how these impulsivity related genes affect these specific brain regions could reveal key mechanisms that are fundamental to behavioural addictions and may aid in early identification and prevention of these disorders.

The scope of Behavioural Addictions:

In the past, behavioural addictions (BAs) have been equated to impulse-control disorders (ICD), due to the similarities in certain characteristics, specifically compulsivity and inhibited impulse regulation (Brewer & Potenza, 2008; Geller, 2008). Nevertheless, as asserted by Grant et. al (2010), this fusion is inaccurate. This is because not all BAs are ICDs and not all ICDs are BAs (illustrated in Figure 1). This difference became apparent when gambling disorder, formerly included in the ICD section in the DSM-IV, was reclassified under the Substance-Related and Addictive Disorders section in the DSM-V (Pinna et al., 2015). This change highlights how BAs are different from ICDs, and that they warrant their own classification.

Currently, the DSM-V does not officially recognize BAs as mental disorders “because at this time there is insufficient peer-reviewed evidence to establish the diagnostic criteria and course descriptions needed to identify these behaviors as mental disorders” (American Psychiatric Association, 2013). However, this lack of official recognition may itself be contributing to the lack of research available on BAs, and this might be creating a futile cycle in which the lack of official recognition deters research and the lack of research impedes clinical recognition. This is why it is imperative to develop further investigations into this matter, as individuals world-wide would benefit from a deep understanding of the disorders at hand.

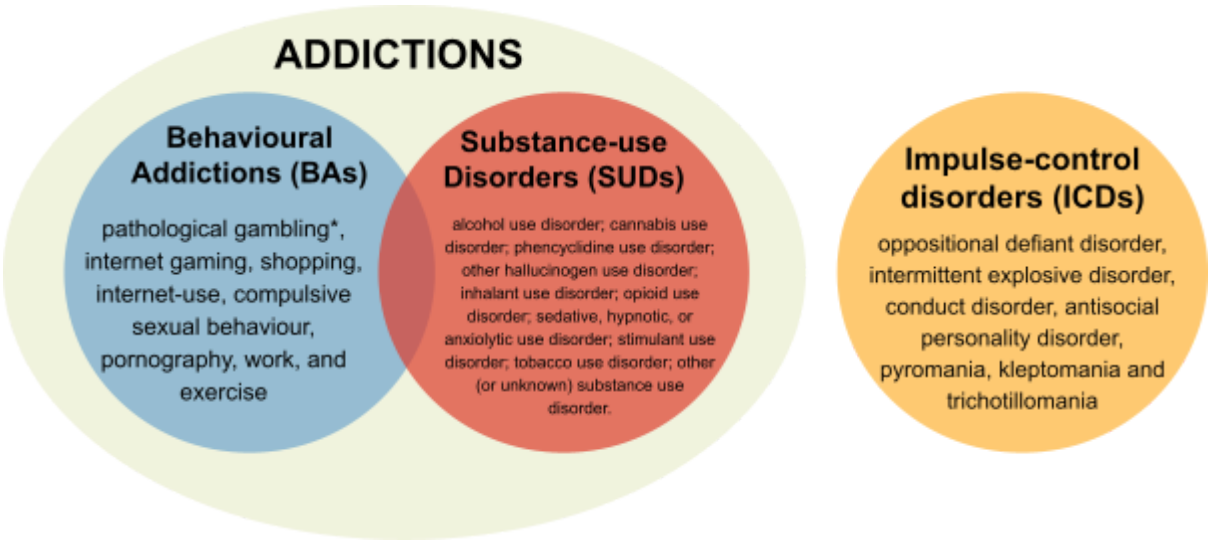
Despite BAs not being widely recognized as clinical disorders beyond pathological gambling, research by Bevilacqua & Goldman (2013) and Congdon & Canli (2008) found genetic underpinnings to these types of impulsive behaviour, involving impulsivity-related genes in the serotonergic and dopaminergic pathways that echo previous findings in SUDs (Poisson et al., 2021). Comprehensive research (such as Brewer & Potenza (2008), Leeman & Potenza (2012) and Lobo & Kennedy (2006)) further demonstrate that BAs have a neurobiological and genetic foundation, in which genes and brain regions alike influence these types of behaviours. Grant et al. (2010) and Pinna et al. (2015) have argued that these disorders should not be ignored, despite their current lack of clinical recognition. For the

most part, the research done on BAs demonstrates the validity of BAs, highlighting the need for further research and recognition.

For the purpose of this review, behavioural addictions (BA) will be defined as chronic conditions in which individuals compulsively partake in activities that do not involve the use of substances. These activities exhibit similar features to addictions such as inhibited self-control, compulsive cravings and persistence to engage in such activities despite them having a negative effect on their lives. This includes pathological gambling, internet gaming, shopping, internet-use, compulsive sexual behaviour, pornography, work, and exercise, as neurological and clinical similarities with substance-use disorders have surfaced (Geller, 2008; Grant et al., 2010; Pinna et al., 2015). Whereas, behaviours such as oppositional defiant disorder, intermittent explosive disorder, conduct disorder, antisocial personality disorder, pyromania, kleptomania and trichotillomania, which are all ICDs (American Psychiatric Association, 2013), will all be excluded from the BA category (as shown in Figure 1) because they lack the similar neuroadaptive mechanisms that are distinctive of addictions (Grant et al., 2010).

Figure 1

The Spectrum of Addictive and Impulsive Disorders.



Note. This diagram demonstrates the classification of addictive and impulsive disorders for the purpose of this review. The outermost circle represents all addictions, divided into two main categories, Behavioural Addictions (BAs) and Substance-use Disorders (SUDs). All SUDs and Impulse-control Disorders (ICDs) shown are based on the DSM-V (American Psychiatric Association, 2013). Pathological gambling (marked with an asterisk) is included in the DSM-V as well. Other BAs are included for this review but are not currently recognized as clinical disorders by the DSM-V.

Key Genes and their role in Impulsivity

The hereditability of impulsivity is a factor that has been demonstrated for both impulsive traits that are included in the DSM categorisation of mental disorders and those outside of

these categories. Evidence from twin studies have calculated that around 45% of self-reported impulsivity is due to genetic factors (Congdon & Canli, 2008). Genes can affect impulsivity by regulating and changing reward sensitivity and inhibitory control. Previous studies have associated neurotransmitters in impulsivity, specifically dopaminergic and serotonergic pathways, which are predominant in brain regions related to impulse control. (Bevilacqua & Goldman, 2013).

Genetic variations in DA receptors (e.g., DRD2 and DRD4) and transporters (e.g., DAT1) have been implicated in impulsive traits (Bevilacqua & Goldman, 2013; Congdon & Canli, 2008), which increase susceptibility to both SUDs and BAs (Albekairi et al., 2025; Brewer & Potenza, 2008). D2 dopamine receptors (DRD2) manage DA neuron activity by creating negative feedback. A large availability of DRD2 reduces compulsive seeking behaviour, while low DRD2 availability is linked to high impulsivity and compulsive behaviours (Poisson et al., 2021; Wise & Jordan, 2021). A lack of DRD2 has been associated with contributing to both compulsive internet gaming and pathological gambling. (Brewer & Potenza, 2008; Leeman & Potenza, 2013). D4 dopamine receptors (DRD4) are expressed in brain regions involved in behavioural inhibition and self control, specifically in the PFC. Knockout studies of DRD4 revealed that mice lacking the receptor show reduced impulsive decision making (Congdon & Canli, 2008). Some studies also found an association between DRD4 and PG (Brewer & Potenza, 2008). DA transporter 1 (DAT1) regulates DA signaling by removing DA from the extracellular space. (Congdon & Canli, 2008). Immoderate levels of DAT1 can excessively reduce DA levels and potentially weaken behavioural inhibition. (Brewer & Potenza, 2008).

Genetic variations in 5-HT receptors (e.g., HTR1B and HTR2B) and transporters (e.g., SLC6A4) have been implicated in impulsive traits (Bevilacqua & Goldman, 2013; Congdon & Canli, 2008), and increase vulnerability to both SUDs and BAs (Brewer & Potenza, 2008). 5-HT enhances motivation via its effects on the NAc, but it inhibits activity in the VTA (Bayassi-Jakowicka et al., 2021). The 5-hydroxytryptamine receptor 1B (HTR1B) inhibits the release of 5-HT and has been implicated in impulsive behaviour by different pharmacological studies (Bevilacqua & Goldman, 2013). It has an involvement in mood regulation and impulsivity, factors that influence addiction vulnerability (Albekairi et al., 2025). The 5-hydroxytryptamine receptor 2B (HTR2B) regulates 5-HT reuptake, and is associated with impulsive violence. HTR3B knockout mice showed increased compulsive seeking and reward reactivity. (Bevilacqua & Goldman, 2013). The 5-hydroxytryptamin transporter gene (SLA6A4) removes 5-HT from extracellular space, managing signal duration and magnitude (Charnay & Léger, 2010). Variation of SLC6A4 is linked to impulsivity, SUDs and ICDs (Brewer & Potenza, 2008). Finally, monoamine oxidase A (MAOA) is an enzyme that breaks down 5-HT and DA (Charnay & Léger, 2010). Higher levels of DA and 5-HT and increased aggressive behaviour were found in MAOA knockout mice (Bevilacqua & Goldman, 2013). Low levels of MAOA predisposes the risk for impulsive aggression because of dysregulated serotonin signaling (da Cunha-Bang & Knudsen, 2021).

Collectively, these genes influence the gene-brain-behaviour pathway by changing the neurotransmitter pathways in the PFC, VTA and NAc. These genetic influences might help understand differences in individual susceptibility to BAs, setting an outline for future research in prevention and treatment strategies.

The Gene-Brain-Behaviour Pathway

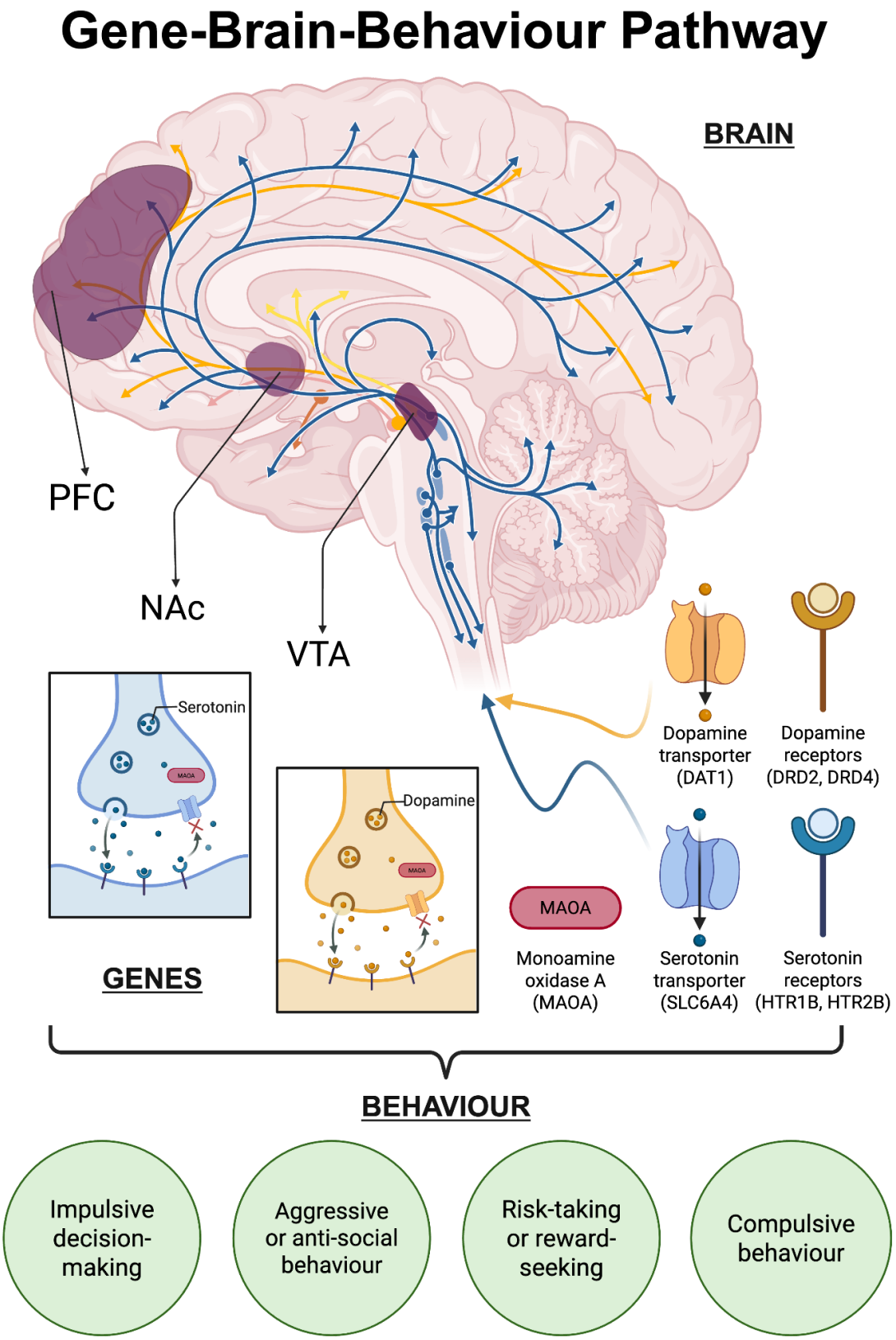
Given what is known about impulsivity-related genes and behavioural addictions (BA), a potential model that explains the way genes ultimately influence the susceptibility of BAs is a gene-brain-behaviour pathway (illustrated in Figure 2). In this model, the genetic variations previously discussed influence the dopaminergic and serotonergic systems, and these systems in turn alter the function of specific brain areas and form impulsive traits. These changes in the brain modify reward processing and decision-making, which manifest as behaviors (such as impulsive traits). Since the environment can alter gene expression, it could also provide an explanation for why environmental factors can also influence addiction susceptibility (Albekairi et al., 2025; Grant et al., 2010; Koob & Volkow, 2010; Lobo & Kennedy, 2006).

The aforementioned serotonergic pathway genes (HTR1B, HTR2B, SLC6A4 and MAOA) manage 5-HT signaling, which influences mood regulation, control inhibition and reward processing (Charnay & Léger, 2010; da Cunha-Bang & Knudsen, 2021; Miyazaki et al., 2012). The dopaminergic pathway genes (DRD2, DRD4, and DAT1), regulate reward processing and sensitivity through the mesolimbic system. This is because of the signaling between the VTA and the NAc (shown in Figure 2) (Ko & Strafella, 2012; Poisson et al., 2021; Wise & Jordan, 2021). These genes can specifically modify PFC activity, which regulates control over impulses (Congdon & Canli, 2008).

The changes in the DA and 5-HT pathways affect the whole mesolimbic system. The PFC, which regulates self-control and determines if there will be a behavioural response to reward cues (Kalivas & Volkow, 2005), is particularly affected by DA transmissions (Congdon & Canli, 2008). Because projections from the VTA release DA to the NAc and the PFC (shown in Figure 2), any change in this brain region can influence the neural reaction to rewarding stimulus (Kalivas & Volkow, 2005; Pistillo et al., 2015). In addition, since the NAc processes motivation, reinforcement and reward by coordinating inputs from the PRC and the VTA (Bayassi-Jakowicka et al., 2021), changes in this region may affect the function of both regions. Understanding this pathway may explain how genetic risk factors translate into behavioural traits.

Figure 2

The Gene-Brain-Behaviour Pathway



Note: Schematic representation of the influence of serotonergic and dopaminergic genes on the PFC, the NAc and the VTA, and the associated behavioural outcomes. Created with BioRender.

Ventral Tegmental Area (VTA) in the BA genetic pathway

The VTA, located in the midbrain, is the beginning of the mesolimbic system, which is linked by neuroimaging studies to reward learning and emotion (Ko & Strafella, 2012). The VTA houses most of the midbrain DA neurons, which mainly project to the NAc and the PFC in the mesostriatal pathway (Poisson et al., 2021). The DA signaling from the VTA to the NAc supports motivation, craving and reward anticipation (Kalivas & Volkow, 2005). Since DA projections from the VTA influence reward learning and motivation, a balanced signaling of this pathway is crucial for adapting reward-seeking and decision-making. Therefore, extreme activity may cause compulsive motivation and impaired learning or motor control (Poisson et al., 2021). Because these DA neurons are essential to generate a behavioural response to addictive activities, gene variants (DRD2, DRD4 and DAT1) that affect the DA firing alters how the brain assigns motivational value to rewarding stimuli (Bayassi-Jakowicka et al., 2021). However, there is currently a lack of investigation into the effects of 5-HT in the VTA and how that may influence BA predisposition.

Nucleus accumbens (NAc) in the BA genetic pathway

The NAc, located in the ventral striatum, is made up of a shell and a core. The NAc shell regulates motivational relevance through its connection with the VTA, because it receives DA from the VTA and regulates mesolimbic reward functions. (Bayassi-Jakowicka et al., 2021). The NAc core handles learned behavioural responses to specific cues by predicting motivationally relevant events (Brewer & Potenza, 2008). The NAc is central to reward processing, evaluation and incentive-based learning, and plays a central role in the acute reinforcing effects of addictive activities because it receives motivational information from the PFC (Kalivas & Volkow, 2005; Koob & Volkow, 2010). Through its connections across the brain, the NAc manages DA release to mesocortical areas, combining reward processing with motor and cognitive functions (Bayassi-Jakowicka et al., 2021).

DA neuron activity from the VTA in the NAc creates a motivational “pull” toward cues and predicted rewards, which is essential for effective reward-seeking and decision making (Poisson et al., 2021). Dopamine released from the NAc is regulated by DRD2 and DRD4, and is essential to forming motivation, reward learning and adaptive behaviours because of synaptic plasticity (Bayassi-Jakowicka et al., 2021). 5-HT receptors, such as HTR1B and HTR2B, modulate the inhibition of premature actions while waiting for rewards, an action that takes place in the core of the NAc. (Miyazaki et al., 2012). Reduced MAOA expression might elevate neural DA levels in the NAc, which influences reward sensitivity (Kalivas & Volkow, 2005). Neurons in the NAc show anticipatory activity in reward delay periods, further implicating the NAc in impulsive traits (Miyazaki et al., 2012).

Over time, chronic addictions induce structural and synaptic changes in neural circuits that regulate reward. In the later stages of addiction, self-control of behaviours can begin to shift from the NAc, where positive reinforcement happens, to the dorsal striatum for habitual use. (Albekairi et al., 2025; Brewer & Potenza, 2008).

It has also been found that BA cue exposure, especially in internet gaming, creates a heightened activation in the NAc (Leeman & Potenza, 2013).

Prefrontal Cortex (PFC) in the BA genetic pathway

The PFC, located in the anterior part of the frontal lobe, mainly modulates DA levels by two routes, the corticonigral and corticostriatal pathways (Ko & Strafella, 2012). Through these pathways, the PFC regulates DA release in the NAc and plays a key role in seeking behaviours (Albekairi et al., 2025). In the course of decision-making tasks, the OFC has increased DA release levels for immediate choices and the lateral PFC and OFC are linked to delayed rewards, with all parts of the PFC being involved in the decision-making process (Bevilacqua & Goldman, 2013). The OFC and mPFC encode reward expectation, which influences the ability to wait for delayed rewards, implicating the PFC with impulsive conditions such as addictions (Miyazaki et al., 2012). Projections from the VTA to the PFC drive risky decision-making, and in risky contexts, these projections decrease with punishment risk (Poisson et al., 2021).

The PFC is crucial in decision-making, reward evaluation, cognitive function and inhibiting intrusive compulsive-seeking thoughts (Brewer & Potenza, 2008). The mPFC and OFC, along with the NAc, modulate patience in the wait to obtain reward through 5-HT signaling (Miyazaki et al., 2012b). The PFC responds to motivationally relevant and reward-predicting events (Kalivas & Volkow, 2005), and dysfunction of the PFC leads to an increase in impulsive choices, as shown in impaired performances in the Iowa Gambling Task (Brewer & Potenza, 2008). Low PFC activity is implicated to impulsive decision-making and greater cue reactivity, similar to abnormalities seen in SUDs and pathological gambling (Brewer & Potenza, 2008; Grant et al., 2010). Cue-induction studies on internet gaming and pathological gambling reveal impaired activity in the PFC and the NAc. While pathological gambling has reduced PFC activity during risk, reward and control tasks, research also found poor white matter integrity in the PFC when suffering from this condition.

Conclusion

The discussion above on the role of the dopaminergic and serotonergic pathway genes on impulsivity has shown that variations in impulsivity-related genes (DRD2, DRD4, DAT1, HTR1B, HTR2B, SLC6A4 and MAOA) alter the neural regions involved in the brain's reward system (the VTA, the NAc and the PFC), which increases impulsivity in individuals and therefore their predisposition to BAs. As behaviours become habitual, addictions begin in the VTA-NAc-PFC circuits, because of their role in reward processing and decisionmaking. This circuit reinforces habitual behaviour through learned stimuli, DA receptor variations and compulsive seeking caused in the NAc (Brewer & Potenza, 2008). Both SUDs and BAs activate the same key regions in the brain (PFC, VTA and NAc) during motivationally relevant event exposure, showing the influence of dopaminergic and serotonergic pathways in these regions due to their overlap (Grant et al., 2010).

The mesolimbic system is central to reward processing in both SUDs and BAs, as found in different brain imaging studies, with reduced activity in these key neural regions leading to impulsive decision-making and heightened cue reactivity (Grant et al., 2010). Variations in the dopaminergic and serotonergic pathways might lead to impaired functioning of the PFC, and are therefore implicated in impulsive decision-making and reward sensitivity in both SUDs and PFCs, with neuroimaging studies finding an overlap between the inhibitory control and reward processing circuits across the spectrum of addictive disorders (Bevilacqua & Goldman, 2013; Congdon & Canli, 2008; Grant et al., 2010). Interactions between the key brain regions of the mesolimbic system regulate the patience an individual has when it comes to waiting for a reward, linking 5-HT and DA pathways to the control of impulsivity. Simultaneously, variations in the VTA, NAc and PFC due to levels of DA and 5-HT genes create a pathway that increases impulsive behaviour, which in turn heightens susceptibility to BAs.

Limitations: Although this review aimed to create a comprehensive report on the potential mapping of BAs, summarising a range of neurobiological reports linking genes related to impulsivity to the mesolimbic system brain regions, several limitations constrain the strength of its conclusions. The review relies heavily on previous reviews done on the matter, which can preserve the biases or methodological gaps of other authors. It also creates a methodological inconsistency across studies, as results may be varied due to these differences in neuroimaging studies, behavioural tasks and others. Most of the included articles are correlational and not longitudinal, and the observed genetic variations in these disorders may be due to the disorders themselves, and not their cause.

When making suggestions for further research, the review takes into account the studies of Lang et. al (2016), and Lind et. al (2013), which aimed to make a genome-wide association study (GWAS) of pathological gambling. Notably, the results of these studies were not included in the review because they found no statistically significant genetic associations of the BA. However, this does not mean that there is no genetic foundation to the disorder, but could be due to the studies' reliance on the candidate gene approach. This review recommends that future GWAS of BAs should avoid this approach by experimenting without a narrow hypothesis and scanning in large and diverse samples. Conducting GWAS in BAs without this potential limitation might lead to more concrete evidence of the influence of dopaminergic and serotonergic pathway genes, or might reveal novel genetic contributions to the literature. The review also recommends further neuroimaging studies using functional magnetic resonance imaging (fMRI) to map the functional changes in reward processing and impulsive decision-making in the proposed gene-brain-behaviour pathway across different types of BAs. Pairing neuroimaging studies with behavioural task studies might also be able to create a link between genetic variation, brain activity and behavioural traits. If further studies are able to provide more concrete evidence that links this proposed pathway, clinical studies could be conducted to develop prevention and treatment strategies for BAs, targeting the specific genes that influence these brain pathways.

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Author 100060

Submission 100055

Reviewer Final Recommendation: Accept with minor revisions

Reviewer Feedback:

Overall, the paper is well written with a clear goal of reviewing select dopaminergic and serotonergic markers involved in behavioral impulsivity across the mesolimbic system in addition to highlighting the importance in understanding the molecular mechanisms driving impulse control disorders (ICDs) to inform upon therapeutics and prognostics. The author has a strong knowledge of the genetic underpinnings and brain regions associated with impulsivity and more broadly ICDs and behavioral addictions (BAs). The included figures are clear and well made to supplement the text. The manuscript does a wonderful job of describing the key molecular components most associated with impulsivity in the current literature and includes some research avenues for future studies to aid in the development of therapeutics and preventative measures for ICDs and BAs. Minor revisions are included below to bolster the manuscript for acceptance:

- Please complete a final readthrough for grammatical and spelling errors as well as condensing sentences to make the main takeaways clear and concise. One example of an acronym error is in the Abstract it states “neural accumbens (NAc)” when this should be nucleus accumbens. Adding in more transition sentences and transition words will help strengthen the logical flow of your ideas throughout the review.
- You outline the role of serotonergic receptors in behavioral impulsivity well, but have you considered the role of HRT2A? There is literature linking this receptor to mood disorders, impulsive behaviors, and maladaptive impulsivity. Adding in a few sentences about this receptor would strengthen your paragraph that reviews the serotonergic system and its link to impulsivity as HRT2A also plays a role in reward processing through its interaction with the dopaminergic system.
- Your review of the mesolimbic system is clear, concise, and detailed in both the introduction as well as in the breakdown of the dopaminergic and serotonergic pathways in the NAc, VTA, and PFC later in your review paper. Fantastic work!
- Great work with setting the stage for the paper through the introduction and ending with the goal of your review paper!
- In your second paragraph of “The scope of behavioral addictions” section, you make a strong argument for why behavioral addictions are underappreciated in the field as well as why it is important to study them. This paragraph can be

made even stronger if you include statistics about the prevalence of these disorders and current therapeutics (or lack of effective therapeutics). Incorporating this information will highlight the health issue at hand to grab the reader's attention then steer their focus on why understanding the genetics is important for innovating preventative care and therapeutics.

- Your two conclusion paragraphs are straightforward and easy to follow. Including a few sentences at the close of the second paragraph highlighting the importance of these pathways in therapeutics (similar to how you closed your final paragraph) prior to going into the limitations and future directions will aid in highlighting the narrative of the paper.

Review of: The genetics of behavioural addiction: The neurogenetic pathways that link impulsivity with behavioural addiction risk.

Final Recommendation: Accept with minor revisions

Overall evaluation:

This review paper is well-researched, clear, and thorough. It tackles an important and emerging topic: the genetic and neurobiological underpinnings of BAs. The author demonstrates strong engagement with the literature on impulsivity, dopaminergic/serotonergic pathways, and brain reward circuits. The paper is well-cited and logically structured, moving from genes to brain regions and linking them through a "gene–brain–behaviour" pathway model.

The manuscript's strength lies in this integrative framework, especially its application to BAs specifically. With sharper focus, stronger synthesis, and more explicit highlighting of the framework in the abstract, introduction, and conclusion, the paper can make a meaningful scholarly contribution.

Major comments:

- The paper sometimes reads as an annotated summary of sources rather than a tightly argued review. To improve flow, add synthesis sentences at the end of evidence-heavy paragraphs (e.g., after describing DA genetic variants, or after each brain-region subsection) that tie findings back into the gene–brain–behaviour framework.
- Introduction:
    - The intro mentions DA/5-HT systems and specific genes in detail, but these are repeated later. Consider condensing this early discussion (no need to go into all genes in intro) and putting detailed information in the gene-focused sections.
- BA vs ICD distinction
    - The paper brings up a good point about the recent distinction made between BAs and ICDs and how it affects research. Since impulsivity is central to both categories, explicitly addressing how impulsivity manifests differently (if it does) in BAs vs ICDs would strengthen the argument.
- Gene–brain–behaviour pathway:
    - The section explaining this pathway is overall well-constructed. To deepen it, consider including an example of an environmental factor that modulates impulsivity and BA risk (e.g., early adversity?).
    - Emphasize your framework as the strength of the paper! This framework linking genetics, brain, and behaviour specifically in BA is the central claim. Highlight this more strongly - particularly in the abstract, introduction, and conclusion.
    - Since the genes and regions described also relate to ICDs and SUDs, consider briefly addressing whether current evidence supports/challenges the separation between BA, ICD, and SUD at the genetic/neural levels.
- Brain region subsections:

    - These sections are clearly written but lean heavily on anatomy and genetic mechanisms. They should be strengthened by adding evidence from human neuroimaging studies showing differences in these regions among individuals with BA's. This would provide evidence that suggests genetic variants lead to functional/structural changes in these regions that worsen/predispose individuals to BA's.
- Scope of BAs
    - The DSM diagnostic history section is slightly long; condense and focus more on what the lack of recognition means for research.

Minor comments:

- Abstract
    - The sentence: *"This review paper aims to answer how impulsivity-related genes affect brain regions involved with reward and self control"* overstates what a review can do. Rephrase to emphasize synthesizing evidence rather than providing causal answers.
    - Don't need abbreviations for VTA or NAc in the abstract; they're used only once and defined later.
    - The phrase *"impulsivity serves as a bridge"* is vague and might overstate impulsivity's role. Consider rephrasing.
- Introduction
    - The quoted definition: *"Impulsivity, defined as the tendency to act without foresight"* is unnecessary. Paraphrase in your own words with the citation.
- Scope of BAs
    - Define SUD (substance use disorder) at first mention.
    - Revise phrasing like *"This is because of the signaling between the VTA and the NAc"* - the meaning is unclear and use caution with the word "because" to avoid implying causality where not established.

Title: The genetics of behavioural addiction: The neurogenetic pathways that link impulsivity with behavioural addiction risk.

Abstract:

People who are more impulsive tend to act without foresight, which can make them more likely to develop habits such as gambling or excessive gaming. These habits activate the brain's reward system but often lead to lack of control. Currently, there is a lack of research that maps out the system in which genetics influences behavioural addictions. This review paper synthesizes evidence on how impulsivity related genes may affect brain regions involved with reward and self control. Dopaminergic and serotonergic systems are the neuron networks that use dopamine and serotonin as neurotransmitters, and are crucially involved in reward and motivation. Genetic variants in the aforementioned systems influence neurotransmitter balance, which results in altered signaling across the brain's reward system (which includes the prefrontal cortex, ventral tegmental area and nucleus accumbens). This altered signaling leads to increased impulsivity expressed by insufficient inhibition and high reward sensitivity. In this way, genetic variation in dopamine and serotonin signaling becomes functionally relevant by altering the neural circuits that mediate reward learning and self control. Because impulsivity may mediate the association between genetic variation and vulnerability to behavioural addictions, understanding this neurogenetic pathway is quite important for human health, as it may allow for early identification of at-risk individuals and guide the development of prevention strategies.

Keywords: impulsivity, behavioural addiction, dopamine, serotonin, neurogenetics, reward system.

Introduction:

Addiction is frequently depicted as a cycle, but what compels a person to take that first step? Perhaps people who often struggle with self-control do so not just because of poor choices, but because of a biological predisposition. Behavioural addictions (BA) are chronic conditions in which individuals compulsively partake in specific activities that do not involve the use of substances (such as excessive gambling, gaming, shopping, internet-use, sex, pornography, work, exercise, etc.) which produce immediate reward. Individuals that suffer from these behavioural addictions continue to compulsively engage in these activities despite them having negative consequences on their life, including their mental and physical health. Similar to substance-use disorders, they comprise inhibited self-control, and are stimulated by interactions between neural circuits, genetic predispositions, and environmental factors (Grant et al., 2010). Although most of these disorders are not clinically recognized since they are not included in the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM–V), behavioural addictions are very real conditions that affect countless people around the globe (American Psychiatric Association [APA], 2013).

Impulsivity, which can be understood as a tendency to initiate actions without evaluating potential consequences, (Bevilacqua & Goldman, 2013) could be the factor that pushes someone to engage in addictive behaviours in the first place. Impulsivity is not only

psychological, but has a genetic and neurological foundation. There is some compelling evidence that impulsivity is hereditable, with some studies calculating that around 45% of the variance in impulsivity is due to genetic factors (Congdon & Canli, 2008). Studies have consistently found that multiple brain regions and neurotransmitter systems, particularly the dopaminergic and serotonergic systems, take part in the impulsive behaviours that happen throughout the addiction cycle (Brewer & Potenza, 2008).

Building on genetic evidence, neurotransmitter studies show that dopaminergic systems are involved in several different brain functions, including learning, reward, and control (Ko & Strafella, 2012). Dopamine (DA) neurons in the ventral tegmental area (VTA) regulate both goal directed and habitual behaviours. Activities that offer instant reward enhance dopamine release and lead to hyperbolic reward signaling, craving and compulsive addiction-seeking (Poisson et al., 2021a). The most relevant dopaminergic pathway genes linked to impulsivity and behavioural addictions include the D2 dopamine receptor (DRD2), D4 dopamine receptor (DRD4), and the dopamine transporter gene (DAT1/SLC6A3) (Bevilacqua & Goldman, 2013; Brewer & Potenza, 2008).

Serotonin (5-HT) is known to have been associated with several motor, cognitive and affective functions, including mood disorders. Various studies have found that reduced levels of 5-HT promote impulsive behaviours, such as impulsive action (failing to repress inappropriate actions) and impulsive choice (choosing immediate rewards over delayed rewards) (Miyazaki et al., 2012a). The most relevant serotonergic pathway genes linked to impulsivity and behavioural addictions include monoamine oxidase A (MAOA), the serotonin transporter gene (SLC6A4) and serotonin receptors such as HTR1B, HTR2C and HTR2A (Bevilacqua & Goldman, 2013; Brewer & Potenza, 2008; Tomson et al., 2016). The release of 5-HT and DA is especially relevant in the mesolimbic system, as it can influence how reward is processed by the brain.

At the neural systems level, these genetic changes converge in the mesolimbic rewards circuitry. The mesolimbic system, or reward system, is made up of different brain areas which are in control of processing reward. Reward is defined as the “natural process during which the brain associates diverse stimuli (substances, situations, events, or activities) with a positive or desirable outcome” (Lewis et al., 2021). This process results in changes in a person’s behaviour, eventually causing them to seek that particular positive stimulus (Lewis et al., 2021). There are three specific brain areas that are part of the mesolimbic system which are directly involved with the release of DA and 5-HT; the ventral tegmental area (VTA), the nucleus accumbens (NAc) and the prefrontal cortex (PFC). The VTA is located in the ventral midbrain, and projections from the VTA release DA throughout the neural circuit to the NAc and PFC when reacting to a motivationally significant stimulus. (Kalivas & Volkow, 2005; Pistillo et al., 2015). The NAc is situated in the ventral striatum and plays an integrative role in processing motivation, reinforcement and reward by coordinating inputs from the PRC and the VTA (Bayassi-Jakowicka et al., 2021). The PFC plays an essential role in evaluating motivationally relevant events and predicting rewards. This area is activated by cues associated with reward and determines if a behavioural response will happen (Kalivas & Volkow, 2005). These different factors are linked in a particular pathway in which DA neurons in the VTA project to the NAc and the PFC. (Poisson et al., 2021). Functionally, alterations in these regions translate into measurable differences in impulsive

behaviour. Understanding this gene-brain-behaviour pathway may be critical to gain insight into how impulsivity is linked to behavioural addictions, and therefore how to prevent individuals from beginning that addictive cycle due to impulsivity.

Recent literature on behavioural addictions often focuses solely on genes, brain regions or behaviours instead of the pathway as a whole. Research that does have a more comprehensive outlook is focused on substance use disorders as opposed to behavioural additions (also considered impulse-control disorders or ICDs). Although both BAs and ICDs involve impairments in inhibitory control, they do not manifest in the same way, as BAs are driven by reward seeking whereas ICDs reflect impulsive actions intended to relieve internal tension. Currently, there is a lack of investigation into the genetics, neuroimaging and behavioural factors of behavioural addictions, which generates limited understanding of how genetics shape the vulnerability to these disorders.

This review aims to address how impulsivity related genes (such as DRD2, DRD4, DAT1, MAOA, SLC6A4, HTR1B, HTR2C and HTR2A) affect brain regions involved with reward and self control (such as the VTA, NAc and PFC) and how this contributes to the elaboration of behavioural addictions. This paper argues that understanding how these impulsivity related genes affect these specific brain regions could reveal key mechanisms that are fundamental to behavioural addictions and may aid in early identification and prevention of these disorders. Taken together, these findings suggest a unified pathway in which genetic variation affects DA and 5-HT signaling, which in turn alters activity in the VTA, NAc and PFC, increasing impulsive actions and ultimately heightening vulnerability to BAs.

The scope of Behavioural Addictions:

In the past, behavioural addictions (BAs) have been equated to impulse-control disorders (ICD), due to the similarities in certain characteristics, specifically compulsivity and inhibited impulse regulation (Brewer & Potenza, 2008; Geller, 2008). Nevertheless, as asserted by Grant et. al (2010), this fusion is inaccurate. This is because not all BAs are ICDs and not all ICDs are BAs (illustrated in Figure 1). This difference became apparent when gambling disorder, formerly included in the ICD section in the DSM-IV, was reclassified under the Substance-Related and Addictive Disorders section in the DSM-V (Pinna et al., 2015). This change highlights how BAs are different from ICDs, and that they warrant their own classification.

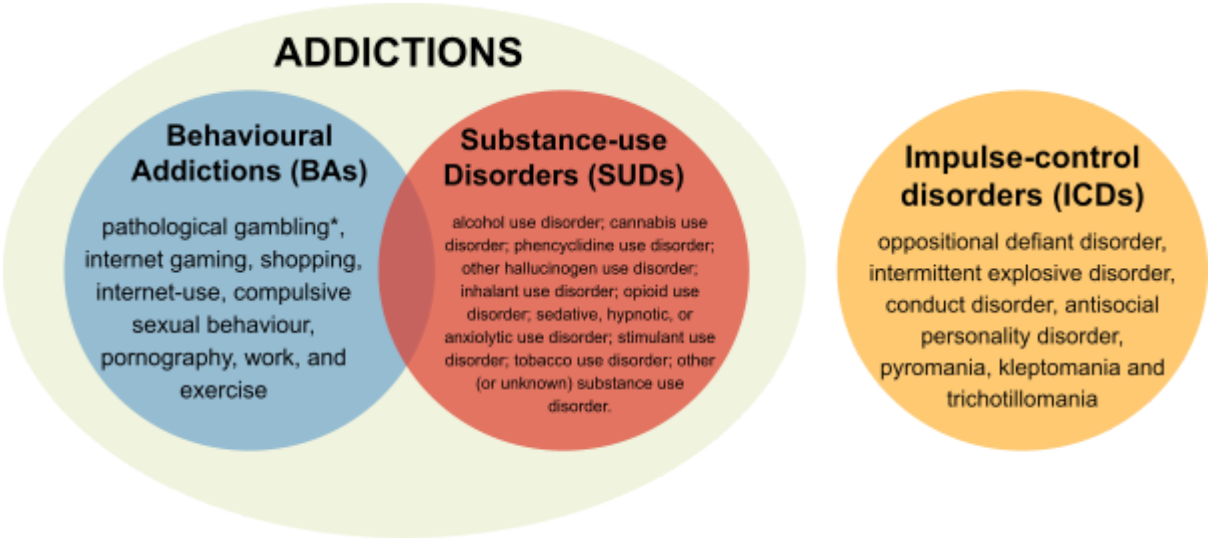
Currently, the DSM-V does not officially recognize BAs as mental disorders “because at this time there is insufficient peer-reviewed evidence to establish the diagnostic criteria and course descriptions needed to identify these behaviors as mental disorders” (American Psychiatric Association, 2013). However, this lack of official recognition may itself be contributing to the lack of research available on BAs, and this might be creating a futile cycle in which the lack of official recognition deters research and the lack of research impedes clinical recognition. This is why it is imperative to develop further investigations into this matter, as individuals world-wide would benefit from a deep understanding of the disorders at hand.

Despite BAs not being widely recognized as clinical disorders beyond pathological gambling, research by Bevilacqua & Goldman (2013) and Congdon & Canli (2008) found genetic underpinnings to these types of impulsive behaviour, involving impulsivity-related genes in the serotonergic and dopaminergic pathways that echo previous findings in substance use disorders (SUDs) (Poisson et al., 2021). Comprehensive research (such as Brewer & Potenza (2008), Leeman & Potenza (2012) and Lobo & Kennedy (2006)) further demonstrate that BAs have a neurobiological and genetic foundation, in which genes and brain regions alike influence these types of behaviours. Grant et al. (2010) and Pinna et al. (2015) have argued that these disorders should not be ignored, despite their current lack of clinical recognition. The public health burden of BAs is substantial. A global meta analysis estimates that between 0.2 and 2.1% of individuals develop BAs like pathological gambling, yet fewer than 15% receive treatment due to limited access and insurance coverage (Petry et al., 2017; Slutske et al., 2010; Stucki & Rihs-Middel, 2007). Similarly, internet gaming addiction affects an estimated 1.7-10% of the US population, but inconsistent diagnostic criteria have impeded clinical interventions (*Video Game Addiction*, n.d.). For the most part, the research done on BAs demonstrates the validity of BAs, yet this lack of approved and accessible treatments highlights the need for further research and recognition that may enable early identification and prevention.

For the purpose of this review, behavioural addictions (BA) will be defined as chronic conditions in which individuals compulsively partake in activities that do not involve the use of substances. These activities exhibit similar features to addictions such as inhibited self-control, compulsive cravings and persistence to engage in such activities despite them having a negative effect on their lives. This includes pathological gambling, internet gaming, shopping, internet-use, compulsive sexual behaviour, pornography, work, and exercise, as neurological and clinical similarities with substance-use disorders have surfaced (Geller, 2008; Grant et al., 2010; Pinna et al., 2015). Whereas, behaviours such as oppositional defiant disorder, intermittent explosive disorder, conduct disorder, antisocial personality disorder, pyromania, kleptomania and trichotillomania, which are all ICDs (American Psychiatric Association, 2013), will all be excluded from the BA category (as shown in Figure 1) because they lack the similar neuroadaptive mechanisms that are distinctive of addictions (Grant et al., 2010).

Figure 1

The Spectrum of Addictive and Impulsive Disorders.



Note. This diagram demonstrates the classification of addictive and impulsive disorders for the purpose of this review. The outermost circle represents all addictions, divided into two main categories, Behavioural Addictions (BAs) and Substance-use Disorders (SUDs). All SUDs and Impulse-control Disorders (ICDs) shown are based on the DSM-V (American Psychiatric Association, 2013). Pathological gambling (marked with an asterisk) is included in the DSM-V as well. Other BAs are included for this review but are not currently recognized as clinical disorders by the DSM-V.

Key Genes and their role in Impulsivity

The hereditability of impulsivity is a factor that has been demonstrated for both impulsive traits that are included in the DSM categorisation of mental disorders and those outside of these categories. Evidence from twin studies have calculated that around 45% of self-reported impulsivity is due to genetic factors (Congdon & Canli, 2008). Genes can affect impulsivity by regulating and changing reward sensitivity and inhibitory control. Previous studies have associated neurotransmitters in impulsivity, specifically dopaminergic and serotonergic pathways, which are predominant in brain regions related to impulse control. (Bevilacqua & Goldman, 2013). Because the DA and 5-HT genes discussed here are also implicated in both ICDs and SUDs, current evidence suggests substantial biological overlap across the three diagnostic categories. This convergence may challenge the idea that BAs are neurologically separate conditions and instead supports a continuum model of addiction vulnerability driven by shared neurogenetic pathways.

Genetic variations in DA receptors (e.g., DRD2 and DRD4) and transporters (e.g., DAT1) have been implicated in impulsive traits (Bevilacqua & Goldman, 2013; Congdon & Canli, 2008), which increase susceptibility to both SUDs and BAs (Albekairi et al., 2025; Brewer & Potenza, 2008). D2 dopamine receptors (DRD2) manage DA neuron activity by creating negative feedback. A large availability of DRD2 reduces compulsive seeking behaviour, while low DRD2 availability is linked to high impulsivity and compulsive behaviours (Poisson et al., 2021; Wise & Jordan, 2021). A lack of DRD2 has been associated with contributing to both compulsive internet gaming and pathological gambling. (Brewer & Potenza, 2008; Leeman & Potenza, 2013). D4 dopamine receptors (DRD4) are expressed in brain regions involved in behavioural inhibition and self control, specifically in the PFC. Knockout studies of DRD4 revealed that mice lacking the receptor show reduced impulsive decision making

(Congdon & Canli, 2008). Some studies also found an association between DRD4 and PG (Brewer & Potenza, 2008). DA transporter 1 (DAT1) regulates DA signaling by removing DA from the extracellular space. (Congdon & Canli, 2008). Immoderate levels of DAT1 can excessively reduce DA levels and potentially weaken behavioural inhibition. (Brewer & Potenza, 2008). Together, these variants converge on altered reward sensitivity and inhibition, forming the first step of the gene-brain behaviour pathway.

Genetic variations in 5-HT receptors (e.g., HTR1B and HTR2B) and transporters (e.g., SLC6A4) have been implicated in impulsive traits (Bevilacqua & Goldman, 2013; Congdon & Canli, 2008), and increase vulnerability to both SUDs and BAs (Brewer & Potenza, 2008). 5-HT enhances motivation via its effects on the NAc, but it inhibits activity in the VTA (Bayassi-Jakowicka et al., 2021). The 5-hydroxytryptamine receptor 1B (HTR1B) inhibits the release of 5-HT and has been implicated in impulsive behaviour by different pharmacological studies (Bevilacqua & Goldman, 2013). It has an involvement in mood regulation and impulsivity, factors that influence addiction vulnerability (Albekairi et al., 2025). The 5-hydroxytryptamine receptor 2B (HTR2B) regulates 5-HT reuptake, and is associated with impulsive violence. HTR3B knockout mice showed increased compulsive seeking and reward reactivity. (Bevilacqua & Goldman, 2013). Another key receptor implicated is the 5-HT2A receptor (HTR2A). Individuals with the prevalent HTR2A -1438A/A genotype displayed significantly higher maladaptive impulsivity scores (Tomson et al., 2016). Because this receptor regulates cortical serotonergic tone, variation in it may influence reward sensitivity and impulse control (Tomson et al., 2016). The 5-hydroxytryptamin transporter gene (SLC6A4) removes 5-HT from extracellular space, managing signal duration and magnitude (Charnay & Léger, 2010). Variation of SLC6A4 is linked to impulsivity, SUDs and ICDs (Brewer & Potenza, 2008). Finally, monoamine oxidase A (MAOA) is an enzyme that breaks down 5-HT and DA (Charnay & Léger, 2010). Higher levels of DA and 5-HT and increased aggressive behaviour were found in MAOA knockout mice (Bevilacqua & Goldman, 2013). Low levels of MAOA predisposes the risk for impulsive aggression because of dysregulated serotonin signaling (da Cunha-Bang & Knudsen, 2021).

Collectively, these genes influence the gene-brain-behaviour pathway by changing the neurotransmitter pathways in the PFC, VTA and NAc. These genetic influences might help understand differences in individual susceptibility to BAs, setting an outline for future research in prevention and treatment strategies.

The Gene-Brain-Behaviour Pathway

Given what is known about impulsivity-related genes and behavioural addictions (BA), a potential model that explains the way genes ultimately influence the susceptibility of BAs is a gene-brain-behaviour pathway (illustrated in Figure 2). In this model, the genetic variations previously discussed influence the dopaminergic and serotonergic systems, and these systems in turn alter the function of specific brain areas and form impulsive traits. These changes in the brain modify reward processing and decision-making, which manifest as behaviors (such as impulsive traits). Since the environment can alter gene expression, it could also provide an explanation for why environmental factors can also influence addiction

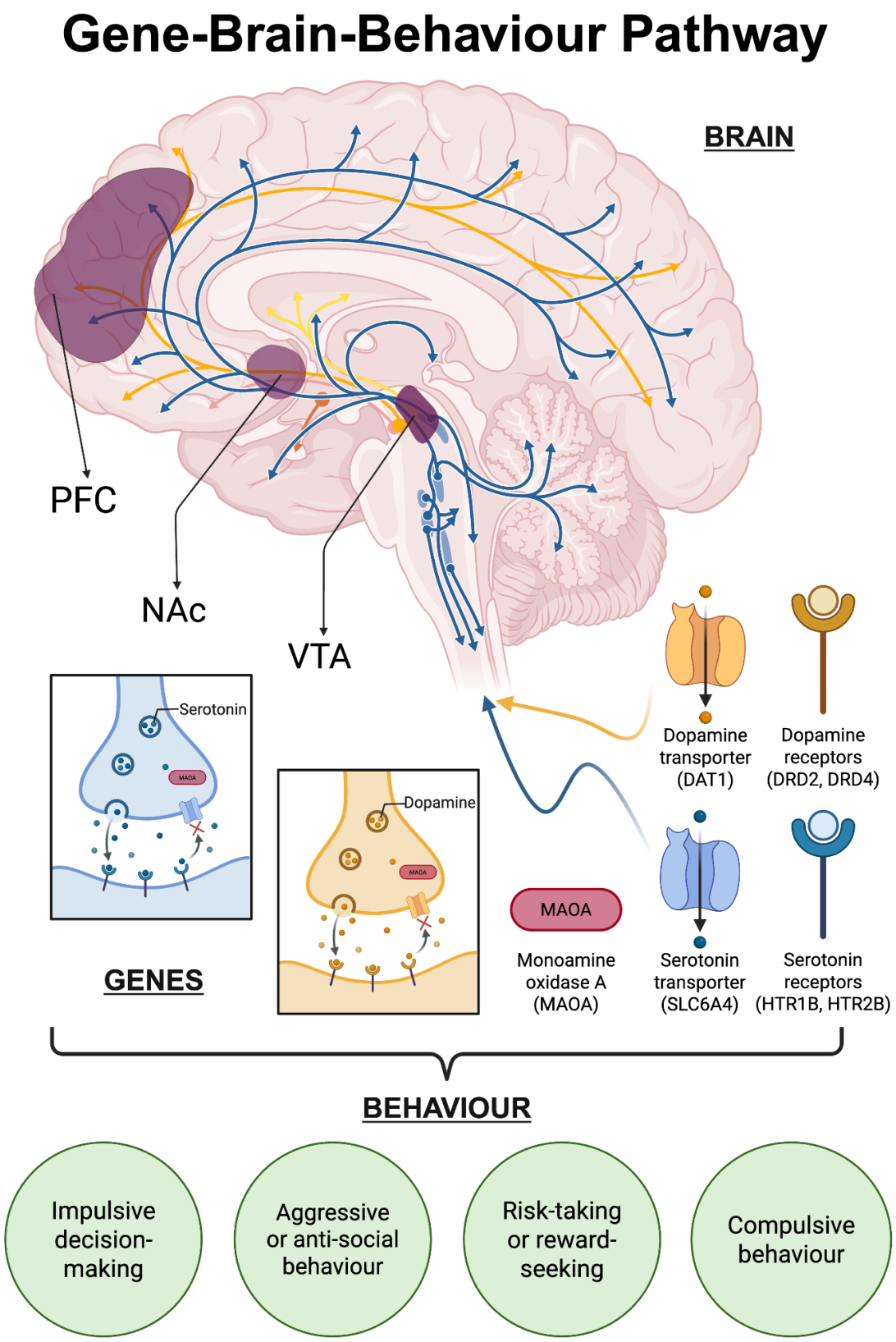
susceptibility (Albekairi et al., 2025; Grant et al., 2010; Koob & Volkow, 2010; Lobo & Kennedy, 2006).

The aforementioned serotonergic pathway genes (HTR1B, HTR2B, SLC6A4 and MAOA) manage 5-HT signaling, which influences mood regulation, control inhibition and reward processing (Charnay & Léger, 2010; da Cunha-Bang & Knudsen, 2021; Miyazaki et al., 2012). Early childhood adversity increases impulsivity risk partly through epigenetic modification of MAOA expression (Charnay & Léger, 2010; da Cunha-Bang & Knudsen, 2021; Miyazaki et al., 2012). Early childhood adversity increases impulsivity risk partly through epigenetic modification of MAOA expression. The dopaminergic pathway genes (DRD2, DRD4, and DAT1), regulate reward processing and sensitivity through the mesolimbic system. One proposed mechanism is the signaling between the VTA and the NAc (shown in Figure 2) (Ko & Strafella, 2012; Poisson et al., 2021; Wise & Jordan, 2021). These genes can specifically modify PFC activity, which regulates control over impulses (Congdon & Canli, 2008).

The changes in the DA and 5-HT pathways affect the whole mesolimbic system. The PFC, which regulates self-control and determines if there will be a behavioural response to reward cues (Kalivas & Volkow, 2005), is particularly affected by DA transmissions (Congdon & Canli, 2008). Because projections from the VTA release DA to the NAc and the PFC (shown in Figure 2), any change in this brain region can influence the neural reaction to rewarding stimulus (Kalivas & Volkow, 2005; Pistillo et al., 2015). In addition, since the NAc processes motivation, reinforcement and reward by coordinating inputs from the PRC and the VTA (Bayassi-Jakowicka et al., 2021), changes in this region may affect the function of both regions. This paper proposes that the gene-brain-behaviour pathway provides a unified model uniquely suited to explaining BAs. Understanding this pathway may explain how genetic risk factors translate into behavioural traits.

Figure 2

The Gene-Brain-Behaviour Pathway



Note: Schematic representation of the influence of serotonergic and dopaminergic genes on the PFC, the NAc and the VTA, and the associated behavioural outcomes. Created with BioRender.

Ventral Tegmental Area (VTA) in the BA genetic pathway

The VTA, located in the midbrain, is the beginning of the mesolimbic system, which is linked by neuroimaging studies to reward learning and emotion (Ko & Strafella, 2012). The VTA houses most of the midbrain DA neurons, which mainly project to the NAc and the PFC in the mesostriatal pathway (Poisson et al., 2021). The DA signaling from the VTA to the NAc supports motivation, craving and reward anticipation (Kalivas & Volkow, 2005). Since DA projections from the VTA influence reward learning and motivation, a balanced signaling of this pathway is crucial for adapting reward-seeking and decision-making. Therefore, extreme activity may cause compulsive motivation and impaired learning or motor control (Poisson et al., 2021). Because these DA neurons are essential to generate a behavioural response to addictive activities, gene variants (DRD2, DRD4 and DAT1) that affect the DA firing alters how the brain assigns motivational value to rewarding stimuli (Bayassi-Jakowicka et al., 2021). Together, these findings suggest genetic variation affecting dopaminergic signaling in the VTA can dysregulate reward prediction and motivation, contributing to the heightened impulsive drive observed in BAs. However, there is currently a lack of investigation into the effects of 5-HT in the VTA and how that may influence BA predisposition.

Nucleus accumbens (NAc) in the BA genetic pathway

The NAc, located in the ventral striatum, is made up of a shell and a core. The NAc shell regulates motivational relevance through its connection with the VTA, because it receives DA from the VTA and regulates mesolimbic reward functions. (Bayassi-Jakowicka et al., 2021). The NAc core handles learned behavioural responses to specific cues by predicting motivationally relevant events (Brewer & Potenza, 2008). The NAc is central to reward processing, evaluation and incentive-based learning, and plays a central role in the acute reinforcing effects of addictive activities because it receives motivational information from the PFC (Kalivas & Volkow, 2005; Koob & Volkow, 2010). Through its connections across the brain, the NAc manages DA release to mesocortical areas, combining reward processing with motor and cognitive functions (Bayassi-Jakowicka et al., 2021).

DA neuron activity from the VTA in the NAc creates a motivational “pull” toward cues and predicted rewards, which is essential for effective reward-seeking and decision making (Poisson et al., 2021). Dopamine released from the NAc is regulated by DRD2 and DRD4, and is essential to forming motivation, reward learning and adaptive behaviours because of synaptic plasticity (Bayassi-Jakowicka et al., 2021). 5-HT receptors, such as HTR1B and HTR2B, modulate the inhibition of premature actions while waiting for rewards, an action that takes place in the core of the NAc. (Miyazaki et al., 2012). Reduced MAOA expression might elevate neural DA levels in the NAc, which influences reward sensitivity (Kalivas & Volkow, 2005). Neurons in the NAc show anticipatory activity in reward delay periods, further implicating the NAc in impulsive traits (Miyazaki et al., 2012).

Over time, chronic addictions induce structural and synaptic changes in neural circuits that regulate reward. In the later stages of addiction, self-control of behaviours can begin to shift

from the NAc, where positive reinforcement happens, to the dorsal striatum for habitual use. (Albekairi et al., 2025; Brewer & Potenza, 2008). It has also been found that BA cue exposure, especially in internet gaming, creates a heightened activation in the NAc (Leeman & Potenza, 2013). Overall, gene-driven variations in DA and 5-HT signaling within the NAc appear to amplify reward sensitivity and cue reactivity, reinforcing compulsive reward-seeking behaviours characteristic of BAs.

Prefrontal Cortex (PFC) in the BA genetic pathway

The PFC, located in the anterior part of the frontal lobe, mainly modulates DA levels by two routes, the corticonigral and corticostriatal pathways (Ko & Strafella, 2012). Through these pathways, the PFC regulates DA release in the NAc and plays a key role in seeking behaviours (Albekairi et al., 2025). In the course of decision-making tasks, the OFC has increased DA release levels for immediate choices and the lateral PFC and OFC are linked to delayed rewards, with all parts of the PFC being involved in the decision-making process (Bevilacqua & Goldman, 2013). The OFC and mPFC encode reward expectation, which influences the ability to wait for delayed rewards, implicating the PFC with impulsive conditions such as addictions (Miyazaki et al., 2012). Projections from the VTA to the PFC drive risky decision-making, and in risky contexts, these projections decrease with punishment risk (Poisson et al., 2021).

The PFC is crucial in decision-making, reward evaluation, cognitive function and inhibiting intrusive compulsive-seeking thoughts (Brewer & Potenza, 2008). The mPFC and OFC, along with the NAc, modulate patience in the wait to obtain reward through 5-HT signaling (Miyazaki et al., 2012b). The PFC responds to motivationally relevant and reward-predicting events (Kalivas & Volkow, 2005), and dysfunction of the PFC leads to an increase in impulsive choices, as shown in impaired performances in the Iowa Gambling Task (Brewer & Potenza, 2008). Low PFC activity is implicated to impulsive decision-making and greater cue reactivity, similar to abnormalities seen in SUDs and pathological gambling (Brewer & Potenza, 2008; Grant et al., 2010). Cue-induction studies on internet gaming and pathological gambling reveal impaired activity in the PFC and the NAc. While pathological gambling has reduced PFC activity during risk, reward and control tasks, research also found poor white matter integrity in the PFC when suffering from this condition. Taken together, evidence that genetic variation impacts neurotransmission in the PFC supports a model in which impaired inhibitory control and risky decision-making increase vulnerability to BAs.

Conclusion

The discussion above on the role of the dopaminergic and serotonergic pathway genes on impulsivity has shown that variations in impulsivity-related genes (DRD2, DRD4, DAT1, HTR1B, HTR2B, SLC6A4 and MAOA) alter the neural regions involved in the brain's reward system (the VTA, the NAc and the PFC), which increases impulsivity in individuals and therefore their predisposition to BAs. As behaviours become habitual, addictions begin in the VTA-NAc-PFC circuits, because of their role in reward processing and decisionmaking. This circuit reinforces habitual behaviour through learned stimuli, DA receptor variations and

compulsive seeking caused in the NAc (Brewer & Potenza, 2008). Both SUDs and BAs activate the same key regions in the brain (PFC, VTA and NAc) during motivationally relevant event exposure, showing the influence of dopaminergic and serotonergic pathways in these regions due to their overlap (Grant et al., 2010).

The mesolimbic system is central to reward processing in both SUDs and BAs, as found in different brain imaging studies, with reduced activity in these key neural regions leading to impulsive decision-making and heightened cue reactivity (Grant et al., 2010). Variations in the dopaminergic and serotonergic pathways might lead to impaired functioning of the PFC, and are therefore implicated in impulsive decision-making and reward sensitivity in both SUDs and PFCs, with neuroimaging studies finding an overlap between the inhibitory control and reward processing circuits across the spectrum of addictive disorders (Bevilacqua & Goldman, 2013; Congdon & Canli, 2008; Grant et al., 2010). Interactions between the key brain regions of the mesolimbic system regulate the patience an individual has when it comes to waiting for a reward, linking 5-HT and DA pathways to the control of impulsivity. Simultaneously, variations in the VTA, NAc and PFC due to levels of DA and 5-HT genes create a pathway that increases impulsive behaviour, which in turn heightens susceptibility to BAs. The strength of this review lies in integrating genetics, brain circuitry and impulsive behaviour into a unified explanatory pathway. Understanding the genetic regulation of DA and 5-HT pathways across the VTA, NAc and PFC offers a potential basis for biomarker development, enabling earlier identification of at-risk individuals. Such mechanistic insight also highlights these neurotransmitter systems as therapeutic targets, suggesting that future interventions may involve correcting pathway specific dysregulation rather than treating behavioural symptoms alone.

Limitations: Although this review aimed to create a comprehensive report on the potential mapping of BAs, summarising a range of neurobiological reports linking genes related to impulsivity to the mesolimbic system brain regions, several limitations constrain the strength of its conclusions. The review relies heavily on previous reviews done on the matter, which can preserve the biases or methodological gaps of other authors. It also creates a methodological inconsistency across studies, as results may be varied due to these differences in neuroimaging studies, behavioural tasks and others. Most of the included articles are correlational and not longitudinal, and the observed genetic variations in these disorders may be due to the disorders themselves, and not their cause.

When making suggestions for further research, the review takes into account the studies of Lang et. al (2016), and Lind et. al (2013), which aimed to make a genome-wide association study (GWAS) of pathological gambling. Notably, the results of these studies were not included in the review because they found no statistically significant genetic associations of the BA. However, this does not mean that there is no genetic foundation to the disorder, but could be due to the studies' reliance on the candidate gene approach. This review recommends that future GWAS of BAs should avoid this approach by experimenting without a narrow hypothesis and scanning in large and diverse samples. Conducting GWAS in BAs without this potential limitation might lead to more concrete evidence of the influence of dopaminergic and serotonergic pathway genes, or might reveal novel genetic contributions to the literature. The review also recommends further neuroimaging studies using functional magnetic resonance imaging (fMRI) to map the functional changes in reward processing and

impulsive decision-making in the proposed gene-brain-behaviour pathway across different types of BAs. Pairing neuroimaging studies with behavioural task studies might also be able to create a link between genetic variation, brain activity and behavioural traits. If further studies are able to provide more concrete evidence that links this proposed pathway, clinical studies could be conducted to develop prevention and treatment strategies for BAs, targeting the specific genes that influence these brain pathways.

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Track Changes for Revised Manuscript [redacted]

Abstract:

- Corrected the “neural accumbens” mistake to "nucleus accumbens”.
- Changed “This review paper aims to answer…” to “This review synthesises evidence on how…”
- Removed VTA and NAc acronyms
- Changed “impulsivity serves as a bridge…” to “impulsivity may mediate the association between genetic variation and vulnerability to behavioural addictions”
- Added “In this way, genetic variation in dopamine and serotonin signaling becomes functionally relevant by altering the neural circuits that mediate reward learning and self control” to improve flow.

Introduction:

- Replaced “Impulsivity, defined as the tendency to act without foresight” quotation with “Impulsivity, which can be understood as a tendency to initiate actions without evaluating potential consequences,”
- Added “Taken together, these findings suggest a unified pathway in which genetic variation affects DA and 5-HT signaling, which in turn alters activity in the VTA, NAc and PFC, increasing impulsive actions and ultimately heightening vulnerability to BAs.” to the end of the introduction to improve flow.
- Added “Although both BAs and ICDs involve impairments in inhibitory control, they do not manifest in the same way, as BAs are driven by reward seeking whereas ICDs reflect impulsive actions intended to relieve internal tension.” to explicitly address how impulsivity manifests differently in BAs vs ICDs.
- Added “Building on genetic evidence, neurotransmitter studies show that” in the transition from genetics to neurotransmitters to improve flow.
- Added “At the neural systems level, these genetic changes converge in the mesolimbic rewards circuitry.” in the transition from neurotransmitters to brain regions to improve flow.
- Added “Functionally, alterations in these regions translate into measurable differences in impulsive behaviour.” in the transition from brain regions to behaviour to improve flow.

Scope of BAs:

- Added “The public health burden of BAs is substantial. A global meta analysis estimates that between 0.2 and 2.1% of individuals develop BAs like pathological gambling, yet fewer than 15% receive treatment due to limited access and insurance coverage (Petry et al., 2017; Slutske et al., 2010; Stucki & Rihs-Middel, 2007). Similarly, internet gaming addiction affects an estimated 1.7-10% of the US population, but inconsistent diagnostic criteria have impeded clinical interventions (Video Game Addiction, n.d.). For the most part, the research done on BAs demonstrates the validity of BAs, yet this lack of approved and accessible treatments highlights the need for further research and recognition that may enable early identification and prevention.” to highlight the health issue at hand to grab the reader’s attention then steer their focus on why understanding genetics is important for innovating preventative care and therapeutics.
- Defined SUDs at first use in this section

Key genes and impulsivity:

- Added discussion on HTR2A gene and its role in impulsivity. “Another key receptor implicated is the 5-HT2A receptor (HTR2A). Individuals with the prevalent HTR2A -1438A/A genotype displayed significantly higher maladaptive impulsivity scores (Tomson et al., 2016). Because this receptor regulates cortical serotonergic tone, variation in it may influence reward sensitivity and impulse control (Tomson et al., 2016).”

- Added “Together, these variants converge on altered reward sensitivity and inhibition, forming the first step of the gene-brain behaviour pathway” after the DA paragraph to improve flow.
- Corrected the “SLA6A4” typo to “SLC6A4”.
- Added “Because the DA and 5-HT genes discussed here are also implicated in both ICDs and SUDs, current evidence suggests substantial biological overlap across the three diagnostic categories. This convergence may challenge the idea that BAs are neurologically separate conditions and instead supports a continuum model of addiction vulnerability driven by shared neurogenetic pathways.” to briefly address whether current evidence supports/challenges the separation between BA, ICD, and SUD at the genetic/neural levels.

Gene-brain-behaviour pathway:

- Changed “this is because…” to “one proposed pathway is…”to avoid implying causation
- Added “Early childhood adversity increases impulsivity risk partly through epigenetic modification of MAOA expression” as an example of an environmental factor.
- Added “This paper proposes that the gene-brain-behaviour pathway provides a unified model uniquely suited to explaining BAs.” to emphasise the framework as the paper’s main contribution.

VTA section:

- Added “Together, these findings suggest genetic variation affecting dopaminergic signaling in the VTA can dysregulate reward prediction and motivation, contributing to the heightened impulsive drive observed in BAs.” to improve flow.

NAc section:

- Added “Overall, gene-driven variations in DA and 5-HT signaling within the NAc appear to amplify reward sensitivity and cue reactivity, reinforcing compulsive reward-seeking behaviours characteristic of BAs.” to improve flow.

PFC section:

- Added “Taken together, evidence that genetic variation impacts neurotransmission in the PFC supports a model in which impaired inhibitory control and risky decision-making increase vulnerability to BAs.” to improve flow.

Conclusion:

- Added “Understanding the genetic regulation of DA and 5-HT pathways across the VTA, NAc and PFC offers a potential basis for biomarker development, enabling earlier identification of at-risk individuals. Such mechanistic insight also highlights these neurotransmitter systems as therapeutic targets, suggesting that future interventions may involve correcting pathway specific dysregulation rather than treating behavioural symptoms alone.” to link to therapeutics and to my proposed pathway.
- Added “The strength of this review lies in integrating genetics, brain circuitry and impulsive behaviour into a unified explanatory pathway.” to explicitly highlight framework contribution.

Referee 1 Review Reply [redacted] [redacted]

Reviewer Feedback:

- Please complete a final readthrough for grammatical and spelling errors as well as condensing sentences to make the main takeaways clear and concise. Adding in more transition sentences and transition words will help strengthen the logical flow of your ideas throughout the review.

Thank you for bringing this to my attention. I completed a full proofreading pass to correct spelling and grammar, shorten overly long sentences and add transitional sentences between paragraphs to improve flow.

- One example of an acronym error is in the Abstract it states “neural accumbens (NAc)” when this should be nucleus accumbens.

Corrected. “Neural accumbens” has been replaced with “nucleus accumbens”.

- You outline the role of serotonergic receptors in behavioral impulsivity well, but have you considered the role of HRT2A? There is literature linking this receptor to mood disorders, impulsive behaviors, and maladaptive impulsivity. Adding in a few sentences about this receptor would strengthen your paragraph that reviews the serotonergic system and its link to impulsivity as HRT2A also plays a role in reward processing through its interaction with the dopaminergic system.

Thank you for pointing this out. Initially I did not find a lot of literature mentioning HTR2A, however upon further research I have added a small discussion on HTR2A and its role in impulsivity.

- Your review of the mesolimbic system is clear, concise, and detailed in both the introduction as well as in the breakdown of the dopaminergic and serotonergic pathways in the NAc, VTA, and PFC later in your review paper. Fantastic work!

Thank you for the positive feedback.

- Great work with setting the stage for the paper through the introduction and ending with the goal of your review paper!

Thank you for the positive feedback. Because of this and the feedback received when elaborating the paper, I have grown confident in the strength of my introduction and will not change it.

- In your second paragraph of “The scope of behavioral addictions” section, you make a strong argument for why behavioral addictions are underappreciated in the field as well as why it is important to study them. This paragraph can be made even stronger if you include statistics about the prevalence of these disorders and current therapeutics (or lack of effective therapeutics). Incorporating this information will highlight the health issue at hand to grab the reader’s attention then steer their focus on why understanding the genetics is important for innovating preventative care and therapeutics.

Agreed. I have added some statistics and clarification on the lack of approved treatments to highlight public health relevance.

- Your two conclusion paragraphs are straightforward and easy to follow. Including a few sentences at the close of the second paragraph highlighting the importance of these pathways in therapeutics (similar to how you closed your final paragraph) prior to going into the limitations and future directions will aid in highlighting the narrative of the paper.

I have revised the conclusion to explicitly connect the gene-brain-behaviour framework to potential prevention and treatment strategies before the limitations section.

Referee 2 Review Reply [redacted]

Major comments:

- The paper sometimes reads as an annotated summary of sources rather than a tightly argued review. To improve flow, add synthesis sentences at the end of evidence-heavy paragraphs (e.g., after describing DA genetic variants, or after each brain-region subsection) that tie findings back into the gene–brain–behaviour framework.

Acknowledged. I have added some synthesis sentences at the end of evidence heavy paragraphs to explicitly link findings to the proposed framework.

Introduction:

- The intro mentions DA/5-HT systems and specific genes in detail, but these are repeated later. Consider condensing this early discussion (no need to go into all genes in intro) and putting detailed information in the gene-focused sections.

Thank you for this suggestion. I understand the concern regarding early detail, however, I have chosen to keep the overview of genes and neurotransmitter systems in the introduction because it provides important context for non-expert readers and prevents cognitive overload later in the manuscript. This structure was intentionally recommended by my mentors during drafting, and the other referee explicitly noted that the introduction "sets the stage" effectively. I have streamlined phrasing to avoid repetition but I believe retaining this information in the introduction strengthens clarity and accessibility.

BA vs ICD distinction

- The paper brings up a good point about the recent distinction made between BAs and ICDs and how it affects research. Since impulsivity is central to both categories, explicitly addressing how impulsivity manifests differently (if it does) in BAs vs ICDs would strengthen the argument.

I have added a brief sentence clarifying that while both involve impaired inhibitory control, BAs tend to reflect reward-seeking impulsivity whereas ICDs involve tension-relief impulsivity.

Gene–brain–behaviour pathway:

- The section explaining this pathway is overall well-constructed. To deepen it, consider including an example of an environmental factor that modulates impulsivity and BA risk (e.g., early adversity?).

I have integrated an example of early adversity to illustrate how the environment interacts with genetic risk.

- Emphasize your framework as the strength of the paper! This framework linking genetics, brain, and behaviour specifically in BA is the central claim. Highlight this more strongly - particularly in the abstract, introduction, and conclusion.

I have strengthened explicit framing language in the mentioned sections stating that the central contribution of the paper is articulating a unified pathway model for BAs.

- Since the genes and regions described also relate to ICDs and SUDs, consider briefly addressing whether current evidence supports/challenges the separation between BA, ICD, and SUD at the genetic/neural levels.

I have added brief sentences acknowledging shared genetic underpinnings and discussing how this complicates the categorical separation.

Brain region subsections:

- These sections are clearly written but lean heavily on anatomy and genetic mechanisms. They should be strengthened by adding evidence from human neuroimaging studies showing differences in these regions among individuals with BA's. This would provide evidence that suggests genetic variants lead to functional/structural changes in these regions that worsen/predispose individuals to BA's.

Thank you for this suggestion. I attempted to incorporate human neuroimaging evidence for the mentioned brain regions, however, after an extensive literature search, I was unable to locate or access human neuroimaging studies explicitly linking these regions to BAs rather than SUDs. My mentor advised that the absence of such studies does not weaken the proposed argument, as this gap highlights the need for further research and reinforces one of the core claims of the review, that BAs remain under investigation at the neurobiological level. I therefore kept the section as written but will clarify that the lack of neuroimaging evidence in BAs represents an important limitation in the field.

Scope of BAs

- The DSM diagnostic history section is slightly long; condense and focus more on what the lack of recognition means for research.

Thank you for this suggestion. I reviewed the DSM discussion in this section and found that only four sentences address the diagnostic history directly, which I believe is a reasonable amount of context to establish why BAs remain underrecognized. The rest of the section already focuses on the consequences of this lack of recognition for research and treatment development. This structure was also positively noted by the other reviewer, who stated that in this section I "make a strong argument for why BAs are underappreciated in the field and why it is important to study them". For these reasons, I will keep the DSM overview as written, while ensuring wording remains concise and focused.

Minor comments:

Abstract:

- The sentence: *"This review paper aims to answer how impulsivity-related genes affect brain regions involved with reward and self control"* overstates what a review can do. Rephrase to emphasize synthesizing evidence rather than providing causal answers.

This has been revised to "this review synthesizes evidence on how…" rather than "aims to answer how..."

- Don't need abbreviations for VTA or NAc in the abstract; they're used only once and defined later.

The abbreviations have been removed

- The phrase *"impulsivity serves as a bridge"* is vague and might overstate impulsivity's role. Consider rephrasing.

This phrase has been replaced with the statement "impulsivity may mediate the association between genetic variation and vulnerability to BAs.

Introduction:

- The quoted definition: *"Impulsivity, defined as the tendency to act without foresight"* is unnecessary. Paraphrase in your own words with the citation.

The definition is now paraphrased and cited.

Scope of BAs:

- Define SUD (substance use disorder) at first mention.

This has been corrected, now reads "substance use disorders (SUDs)"

- Revise phrasing like *"This is because of the signaling between the VTA and the NAc"* - the meaning is unclear and use caution with the word "because" to avoid implying causality where not established.

I have revised phrasing to avoid implying causation by replacing "this is because" with "one proposed pathway is"

11/18/2025

Submission 100055, *"The genetics of behavioural addiction: The neurogenetic pathways that link impulsivity with behavioural addiction risk."*

Post-Revision Critical Review:

Overall, the manuscript is well written and conducts a thorough overview of the molecular mechanisms and genetics that may be driving behavioral addictions (BAs). The revisions to the introduction strengthen the throughline of the review which aims to describe in detail the various genes and brain regions hypothesized to promote BAs. The paragraphs in the introduction describing the dopaminergic and serotonergic systems are well thought out and flow logically to orient the reader to the molecular mechanisms that are discussed later in the paper. A final read through is recommended to identify areas where acronyms that you previously spelled out earlier in the manuscript can be updated to just the acronym (i.e., in this sentence you can just put VTA instead of spelling out ventral tegmental area again as you previously spelled it out fully in your second paragraph of the introduction: “There are three specific brain areas that are part of the mesolimbic system which are directly involved with the release of DA and 5-HT; the ventral tegmental area (VTA), the nucleus accumbens (NAc) and the prefrontal cortex (PFC).”). This sentence should read “…behavioral addictions” instead of additions: “Research that does have a more comprehensive outlook is focused on substance use disorders as opposed to behavioural additions (also considered impulse-control disorders or ICDs).”. The addition of the statistical prevalence of BAs strengthens importance of understanding the genetics and molecular mechanisms of BAs to identify prognostics and therapeutic interventions for BAs. The detailed descriptions of the dopaminergic and serotonergic systems in the “Key genes and their role in impulsivity” section are clear, concise, and the paragraphs flow logically to integrate the studies reviewed. The DA and 5-HT paragraphs tie in nicely with the following paragraphs that integrate the molecular mechanisms and brain regions responsible for modifying behavioral responses and how this relates to BAs. The conclusion and the discussion of limitations along with future research ideas wraps up the manuscript nicely.

Final Decision: Accept with minor revisions

Title: The genetics of behavioural addiction: The neurogenetic pathways that link impulsivity with behavioural addiction risk.

Post Review Response:

Overall, the revisions improve the clarity and organization in several sections, and it is evident that meaningful effort was made to address reviewer comments. Key additions to the manuscript have greatly strengthened and focused key arguments of the paper. That said, a couple areas would benefit from further refinement:

First, although the author chose to retain detailed descriptions of DA/5-HT genes in the introduction, this section is still disproportionately long and repeats material presented (sometimes verbatim) in the genetics section. I understand the intention of supporting laymen readers, but the introduction would be clearer and more focused if it presented only high-level context, reserving detailed gene lists and mechanistic explanations for later sections. This would improve pacing and reduce redundancy.

Second, the response regarding human neuroimaging evidence could be expanded. While the author is correct that it is a growing area of research – there *is* work in neuroimaging studies that suggest the regions in the manuscript are altered in BA. For instance:

- Liu, L., Yip, S. W., Zhang, J. T., Wang, L. J., Shen, Z. J., Liu, B., ... & Fang, X. Y. (2017). Activation of the ventral and dorsal striatum during cue reactivity in Internet gaming disorder. *Addiction biology*, *22*(3), 791-801.
- Limbrick-Oldfield, E. H., Mick, I., Cocks, R. E., McGonigle, J., Sharman, S. P., Goldstone, A. P., ... & Clark, L. (2017). Neural substrates of cue reactivity and craving in gambling disorder. *Translational psychiatry*, *7*(1), e992-e992.
- Fujiwara, H., Tsurumi, K., Shibata, M., Kobayashi, K., Miyagi, T., Ueno, T., ... & Murai, T. (2022). Life habits and mental health: behavioural addiction, health benefits of daily habits, and the reward system. *Frontiers in psychiatry*, *13*, 813507.

While not necessary to go into detail, it would benefit the paper to highlight neuroimaging findings as further evidence of alterations in these regions. It may also strengthen the paper to keep information about gaps in this literature and future work that should be done to further distinguish from SUD.

Third, the paper is well-written and makes a compelling argument but could be more carefully worded to avoid repetition throughout. A careful re-reading of the paper might allow for condensing some points and highlighting novel synthesis rather than repeated wording for the same concepts.

Fourth, the manuscript occasionally shifts back and forth a bit between emphasizing the overlap r the differences between BAs, ICDs, and SUDs. Clearer, more specific claims about how this overlap or distinction manifests would be helpful – ideally in a way that is consistent across all sections of the paper.

One minor note - I might remove this sentence "*The strength of this review lies in integrating genetics, brain circuitry and impulsive behavior into a unified explanatory pathway."* This judgement lies in the eye of the beholder – in other words, your job as the author is to *show not tell* why it's a strong argument and clearly state this pathway as a central claim of the paper.

Overall, the revisions have majorly strengthened the manuscript, but additional tightening and clarification would make it stronger and more persuasive.

Recommendation: Accepted with minor edits