Interactive effects of *DRD2* rs6277 polymorphism, environment and sex on impulsivity in a population-representative study

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Abstract

Previous research has shown that dopaminergic dysregulation and early life stress interact to impact on aspects of impulse control. This study aimed to explore the potentially interactive effects of the rs6277 polymorphism of the dopamine D2 receptor gene (*DRD2*), stressful or supportive environment and sex on behavioural and self-reported measures of impulsivity, as well as alcohol use – a condition characterised by a deficit in impulse control. The sample consisted of the younger cohort (*n*=583) of the longitudinal Estonian Children Personality, Behaviour and Health Study. The results showed that the CC homozygotes (suggested to have decreased striatal D2 receptor availability) who had experienced stressful life events (SLE) or maltreatment in the family prior to age 15 showed higher self-reported maladaptive impulsivity at age 15. The genotype-SLE interaction and further association with sex was also evident in the frequency of alcohol use at age 15. Lack of warmth in the family contributed to significantly higher levels of thoughtlessness and more frequent alcohol use in CC carriers at age 25, whereas family support was associated with lower thoughtlessness scores in CC males, which may suggest a protective effect of supportive family environment in this group. Together the findings suggest that *DRD2* rs6277 polymorphism, in interaction with environmental factors experienced in childhood and youth may affect facets of impulsivity. Future work should aim to further clarify the sex and age-specific effects of stressful and supportive environment on the development of neuronal systems that are compromised in disorders characterised by deficits in impulse control.

Keywords: Receptors, dopamine D2; impulsive behaviour; stress; family relations; alcohol

1. Introduction

Impulsivity is a multidimensional behavioural and personality construct, characterised by thoughtlessness and the tendency to engage in rapid, unplanned action (Chamberlain & Sahakian, 2007). Impulsive behaviours are thought to arise from compromised executive functioning, as a result of dysfunctional inhibitory processes and strong impulses (otherwise known as desires, urges or habits), triggered and modulated by situational and dispositional factors (Bari & Robbins, 2013; Hofmann, Friese, & Strack, 2009; Metcalfe & Mischel, 1999). The tendency to engage in impulsive behaviours is seen in psychopathologies such as substance use disorders, attention-deficit/hyperactivity disorder (ADHD), borderline and antisocial personality disorders (Whiteside & Lynam, 2001) and schizophrenia (Hoptman, Antonius, Mauro, Parker, & Javitt, 2014). Furthermore, problems with emotional and behavioural self-control are at the core of the conditions characterised in the subsection of Disruptive, Impulse-Control, and Conduct Disorders in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013).

The impulsivity construct proposed by Dickman (1990) distinguishes between dysfunctional (maladaptive) and functional (adaptive) impulsivity subtypes, which have been supported by results from psychometric tests and animal studies (Brunas-Wagstaff, Bergquist, Richardson, & Connor, 1995; J. W. Dalley, Mar, Economidou, & Robbins, 2008; Miller, Joseph, & Tudway, 2004). Whereas both types of impulsivity are characterised by rapid, error-prone processing and the tendency to act in a non-reflective manner, they differ in their adaptive value, consequences and cognitive correlates. Adaptively impulsive individuals engage in rapid action without forethought when such a strategy is deemed appropriate by the individual's other personality traits. As a result, these individuals tend to gain from fast decision-making and information processing abilities (Dickman, 1990) and creativity (Harnishfeger & Bjorklund, 1994). On the other hand, dysfunctional impulsivity

involves acting thoughtlessly in spite of the negative consequences due to the inability to inhibit such action tendencies and the incapability to engage in slow methodical approaches (Dickman, 1990).

Impulsive behaviours are likely to be modulated by several brain neurotransmitter systems, including serotonergic, noradrenergic, cholinergic and dopaminergic systems (J. W. Dalley et al., 2008), with striatal and frontal dopaminergic abnormalities being most commonly investigated (Volkow, Fowler, Wang, Swanson, & Telang, 2007). Evidence from animal studies has demonstrated that highly impulsive rats have fewer D2/3 receptors available in the ventral striatum and acquire cocaine self-administration more easily, which may provide a partial explanation to the individual differences in the likelihood of engaging in addictive behaviours (J. W. Dalley et al., 2007). Furthermore, the blocking of dopamine D2 receptors in dorsal striatum impairs the performance on a response inhibition task (Eagle et al., 2011) and striatal reward-related dopamine activity has been shown to correlate with self-reported impulsivity in a community sample of healthy volunteers (Forbes et al., 2009). Striatal D2 receptor activity may also induce secondary prefrontal dysfunction, as reductions in the striatal D2 receptors are associated with diminished activity of orbitofrontal cortex and cingulate gyrus - brain areas that play an important role in compulsive behaviours and inhibitory control, respectively (Volkow et al., 2007).

Impulsivity has a substantial genetic component, with the genetic effects generally being stronger in children than in adults and in males compared to females (Bezdjian, Baker, & Tuvblad, 2011). Genetic studies provide further evidence for the role of dopaminergic neurotransmission in impulsive behaviours. More specifically gene variants associated with striatal and prefrontal dopamine receptor availability, dopamine release and extracellular dopamine levels, such as the dopamine receptor D2 encoding gene *DRD2* -141C deletion, the dopamine transporter encoding gene *DAT1* 9-repeat, and the ankyrin repeat and kinase

domain containing 1 encoding *ANKK1* Taq1A (Laakso et al., 2005) were implicated in impulsivity. These gene variants are associated with reward-related ventral striatum activity (Forbes et al., 2009), with performance on response inhibition and cognitive control tasks (Markett, Montag, Walter, Plieger, & Reuter, 2011; White, Morris, Lawford, & Young, 2008), and with impulsivity-related disorders such as alcoholism (Bowirrat & Oscar-Berman, 2005), gambling (Comings et al., 1996) and schizophrenia (Gluskin & Mickey, 2017). More recently, genome-wide association studies have provided further support for dopaminergic genes, including *DRD2* in nicotine and alcohol consumption and alcohol use disorder (e.g. Kranzler et al., 2019; M. Liu et al., 2019; Thompson et al., 2020; Zhou et al., 2020), schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), and personality traits such as neuroticism (Nagel, Watanabe, Stringer, Posthuma, & Van Der Sluis, 2018).

The synonymous rs6277 single nucleotide polymorphism (SNP; 957C > T; Pro319Pro) within *DRD2* has gained considerable research interest in psychiatric genetics, with recent GWAS studies implicating this polymorphism in neuroticism (Nagel et al., 2018), alcohol use (although falling short of genome-wide significance, https://atlas.ctglab.nl/PheWAS) and candidate gene studies showing the role of rs6277 in schizophrenia (L. Liu et al., 2014). Positron emission tomography studies have shown that the schizophrenia risk genotype CC (L. Liu et al., 2014) is associated with lower striatal (Smith et al., 2017), but higher extrastriatal D2 receptor availability (Hirvonen et al., 2009). A recent study by Beste, Stock, Epplen, and Arning (2016) found that CC homozygotes of the *DRD2* rs6277 polymorphism showed elevated rates of false alarms on a Go/No-Go task compared to CT and TT homozygotes, whereas the latter two groups did not differ from each other. C allele and CC genotype carriers have also been shown to be over-represented amongst the alcohol dependent patient groups, compared to healthy controls (Swagell et al.,

2012). However, other researchers have found T allele carriers to exhibit less effective response inhibition on a stop-signal task (Colzato, van den Wildenberg, & Hommel, 2013) and higher impulsivity scores on a delay discounting task compared to CC homozygotes (Kawamura et al., 2013). TT homozygotes have also exhibited higher scores of self-reported dysfunctional, but not functional impulsivity (Colzato, van den Wildenberg, Van der Does, & Hommel, 2010). However, some studies have failed to find an association between *DRD2* rs6277 and response inhibition altogether (C Gurvich & Rossell, 2014), or the effects have been apparent in interaction with other genotypes (Rincón-Pérez et al., 2020). Although the reasons for these divergent findings are yet to be established, it has been suggested that in addition to the variety of behavioural tasks used (Rincon-Perez, Sanchez-Carmona, Albert, & Hinojosa, 2018), factors such as environmental stressors and gender may also play a role. In support of this argument, it has previously been shown that acute stress leads to increased impulsivity in CC homozygotes in both reward responsiveness and delay discounting tasks (White, Lawford, Morris, & Young, 2009). The research findings on the effects of *DRD2* and environment interactions on impulsivity and related constructs (e.g. externalising behaviours, alcohol use and misuse) is accumulating, as shown in recent review papers (Kim & Park, 2018; Weeland, Overbeek, de Castro, & Matthys, 2015). However, until now, Taq1A has been the most commonly investigated polymorphism in such studies and further research on other polymorphisms is needed.

In our previous study we demonstrated that *DRD2* rs6277 polymorphism and its interaction with early life stress (ELS) appears to affect performance on the Rapid Visual Information Processing test (RVP), a complex measure of selective and sustained attention. Further investigation into the subcomponents of the RVP test revealed a particularly strong *DRD2*×ELS interaction on the measure of response inhibition (Klaus et al., 2017), whereby CC carriers who had experienced ELS showed impaired performance compared to the CC

carriers without significant ELS experiences. However, this study focused on only adverse experiences, whereas the neurodevelopmental view of impulsivity proposes that the brain is wired to be impulsive at birth, but supportive family relations improve self-regulatory skills and impulse-management (Daruna & Barnes, 1993). The individuals genetically most vulnerable to stress may therefore show the greatest benefit when raised in a supportive environment (Belsky & Pluess, 2009). Secondly, our previous study focused on only male participants, and there is some evidence that the effects of rs6277 on cognitive abilities are sex-dependent (C Gurvich & Rossell, 2015).

Sex differences have been documented in the onset and symptomatology of disorders characterised by deficits in impulse control and attention, such as ADHD, drug addiction, autism and schizophrenia, with males generally showing a more severe course of illness (Canuso & Pandina, 2007; Trent & Davies, 2012). The neurobiological basis of these differences likely involve genetic factors, HPA-axis dynamics, neurotransmitter function (particularly dopamine and gamma-aminobutyric acid) and ovarian hormones (Carroll & Anker, 2010). It has been noted that oestrogen affects dopamine release in both striatal (Czoty et al., 2009) and prefrontal regions, and increases the expression of dopaminergic genes, including *DRD2* in the prefrontal cortex (PFC; Sarvari et al., 2014). Evidence from animal models suggests that females have significantly more dopaminergic cells in the mesocortical pathway (Kritzer & Creutz, 2008), and dopamine neurotransmission and dopaminergic receptor expression fluctuates together with the changing levels of oestrogen (Di Paolo, 1994; Nordström, Olsson, & Halldin, 1998). However, another line of evidence suggests that oestrodial provides a neuroprotective effect against mental health problems, particularly schizophrenia, by downregulating dopamine receptor sensitivity similarly to D2 antagonists (Hafner, 2003). This may also explain why women with schizophrenia have lower levels of oestrogen overall, and are likely to develop a psychotic episode during

periods of low oestrogen, such as post-partum and post-menopause (Markham, 2012). Furthermore, a study by Conner and colleagues (2010) demonstrated that the presence of hypodopaminergic genetic risk predicted the number of drugs tried in males, whereas negative life events predict the drug use in females, suggesting that sex, genetic, and environmental factors need to be considered in concert in impulsivity research.

The aim of this study was to elaborate on our previous findings on the *DRD2*×ELS interaction on response inhibition (Klaus et al., 2017) by further investigating the association between *DRD2* rs6277 and early adversity on behavioural and self-reported impulsivity, as well as on alcohol use in a population-representative sample. We additionally aimed to investigate the mediating effect of sex on the aforementioned outcomes. We hypothesised that being a CC homozygote of the *DRD2* rs6277 polymorphism and having experienced a high number of stressful life events (SLE) and/or maltreatment in the family before the age of 15 leads to: 1) higher self-reported maladaptive impulsivity, 2) decreased adaptive impulsivity, and 3) poorer performance on the behavioural impulsivity tests. Secondly, we hypothesised that warm family relations contribute to: 1) lower maladaptive impulsivity, 2) higher adaptive impulsivity scores, and 3) better performance in the behavioural impulsivity tests in the CC homozygotes compared to other groups. However, as oestrogen may provide a neuroprotective effect (Hafner, 2003), we expected females to show a less pronounced effect of environmental events on behavioural and self-reported impulsivity measures than males. We expected the alcohol use data to follow a pattern similar to that of behavioural and self-reported maladaptive impulsivity. As a secondary aim, we explored the association between *DRD2* rs6277 genotype and personality traits, as it has been suggested that impulsivity may be impacted upon by the individual's other personality traits (Dickman, 1990).

2. Materials and methods

2.1 Participants

The participants investigated in this study formed the younger cohort of the European Youth Heart Study conducted in Estonia in 1998/1999, later incorporated into the longitudinal Estonian Children Personality, Behaviour and Health Study (Harro et al., 2001). The mean age of the younger cohort during the first study wave was 9.6 years (*SD*=0.5, 278 males, 305 females). Follow-ups were conducted in 2004 (*n*=483, M_{Age}=15.3±0.5, 222 males, 261 females), 2007 (*n*=454, M_{Age}=18.3±0.5, 202 males, 252 females) and 2014 (*n*=440, M_{Age}=25.3±0.5, 193 males, 247 females). All subjects were of Caucasian origin based on their self-report on ethnicity. Written informed consent was obtained from the children's parents and children themselves. Permission for the study was obtained from the Ethics Review Committee on Human Research of the University of Tartu.

2.2 Impulsivity measures

2.2.1 Self-report measures.

The Adaptive and Maladaptive Impulsivity Scale (AMIS; Laas et al., 2010) was used for measuring self-reported facets of impulsivity at each study wave. AMIS is a 24-item modified measure of the Dickman Impulsivity Inventory (Dickman, 1990) and the impulsivity-related facets of the Neuroticism Extraversion Openness Personality Inventory (P. T. Costa & McCrae, 1989). AMIS distinguishes four facets of impulsivity: Fast Decision-making, Excitement-seeking, Thoughtlessness and Disinhibition. Each of these subscales consist of six items, measured on a five-point Likert scale, with a maximum score of 30 points for each subscale. A measure of Adaptive Impulsivity was obtained by adding together the scores from Fast Decision-making and Excitement-seeking subscales, while a measure of

Maladaptive Impulsivity was obtained using the composite score of Disinhibition and Thoughtlessness (Eensoo, Harro, Pullmann, Allik, & Harro, 2007).

2.2.2 Behavioural measures.

The Visual Comparison Test (VCT) was carried out by 378 children at the age of 15. The computer-based stimuli (based on Dickman and Meyer, 1988) composed of geometric figures made up of multiple Xs. The figure was paired with another figure to form either the same or a different figure pair. In the same pair, the two figures were identical. In different pairs, the position of a single X was changed in the periphery of the figure. The participant had to decide whether the figure pairs were the same or different as quickly and as accurately as possible. The twenty pairs of figures were randomly intermixed and the test lasted for approximately 15 min. For a detailed description of the procedure used in VCT, see Paaver and colleagues (2007). Impulsivity score (I-score), an estimate of speed–accuracy trade-off was calculated by subtracting the standard score of the mean latency from the standard score of the total number of errors committed.

The stop-signal task was performed by the participants at age 18. Based on the stop-signal paradigm described by Logan, Schachar, and Tannock (1997), a blue ball was presented on the computer screen on each trial. On Go trials, the subject had to respond as quickly as possible by pressing the space bar. On Stop trials (25% of the trials), a red cross appeared right after the blue ball and the participant had to inhibit the Go impulse. The stop signal appeared at variable delays (100, 150, 200, 250 ms). The test consisted of 160 trials and the outcome measures consisted of commission errors (false hits on No-Go trials), omission errors (missed Go responses), average Go reaction time, and the stop signal reaction time (SSRT, Stop signal delay subtracted from Go reaction time). Stop signal delay was obtained based on a logistic regression model predicting the delay value, where 50% of the

subject's trials were successful. The analyses are based on the data from 398 participants (and from 363 participants in the case of the SSRT).

2.3 Stressful life events and family environment

Childhood and youth SLE were self-reported at age 15. The list of SLE consisted of 21 adverse experiences, such as parental death and divorce/separation, unemployed parent, absence of both parents, financial problems, poor living conditions and poverty in the household, poor health, chronic diseases, death of a close relative, serious illness of a family member, humiliation at home, fear of school and bullying at school. The events were recorded dichotomously as present/absent and the number of adverse experiences were added together to form the total number of experienced adverse life events (Kiive, Laas, Vaht, Veidebaum, & Harro, 2017). The participants were divided into Low SLE and High SLE groups based on median split (MS; 0-2 and 3-17 events, respectively).

Relationships in the family were measured with a child-report Tartu Family Relationships Scale (M. Paaver, Kurrikoff, Nordquist, Oreland, & Harro, 2008), with the four subscales measuring Closeness, Support, Misprize, and (emotional and physical) Abuse. Due to the relatedness of the scores between subscales, Closeness and Support can be added together to form a higher order subscale called Warmth in the family, and Abuse and Misprize subscales may be pooled under the common name Maltreatment. The participants were divided into Low/High Maltreatment and Low/High Warmth groups based on the MS of the scores (Maltreatment MS: 17-26, 27-70; Warmth MS: 27-77, 78-103). The subcomponents (Closeness, Support, Misprize, Abuse) were further analysed using MS (Closeness MS: 17-54, 55-73; Support MS: 8-24, 25-30; Misprize MS: 10-14; 15-38; Abuse MS: 7-12, 13-32).

2.4 Alcohol consumption

Subjects reported the age when they first consumed half a unit of alcohol during follow-up studies. One unit of alcohol was defined as a glass of light wine or champagne (12 cl), a shot of vodka (4 cl), or a bottle (33 cl) of light alcohol (beer, long drink, cider, etc.). Alcohol intake was measured based on the most frequently consumed type of alcoholic beverage. A five point scale was used at ages 18 and 25: *1* = never, *2* = less than once a month, *3* = at least once a month, *4* = at least once a week, *5* = every day. At age 15, a four point scale was used, without the option *5* = every day (Vaht, Kurrikoff, Laas, Veidebaum, & Harro, 2016).

In order to determine the lifetime prevalence of alcohol use disorder, psychiatric assessment was carried out at age 25 by experienced clinical psychologists using the Mini-International Neuropsychiatric Interview (M.I.N.I.5.0.0.; Sheehan et al., 1998; Estonian version: Shlik et al., 1999).

2.5 Personality

All implemented personality scales measured the five basic personality dimensions: extraversion, neuroticism, openness, agreeableness, and conscientiousness (P. Costa & McCrae, 1992). At the age of 9, the personality traits were measured using a 40-item Estonian Brief Big Five Inventory using teacher and parental report (EBBFI; Laidra, Allik, Harro, Merenäkk, & Harro, 2006). During the follow-up study waves, personality traits were measured using self-report measures as described in Vaht, Kiive, Veidebaum, and Harro (2016).

2.6 Genotyping

The real-time polymerase chain reaction (RT-PCR) for genotyping the *DRD2* rs6277 SNP was performed using a TaqMan Pre-Designed SNP Genotyping Assay C__11339240_10 (Applied Biosystems; Foster City, CA, USA) containing primers and fluorescent probes. Genotyping reactions were performed in a total volume of 10 ml with ~25 ng of template DNA. RT-PCR reaction components and final concentrations were as follows: 1:5 5 x HOT FIREPol® Probe qPCR Mix Plus (ROX) (Solis BioDyne) and 1:20 80 x TaqMan Primers Probe. Context sequence [VIC/FAM] was as follows:

TCTTCTCTGGTTTGGCGGGGCTGTC[A/G]GGAGTGCTGTGGAGACCATGGTGGG.

Reactions were performed on the Applied Biosystems ViiA™ 7 Real-Time PCR System. The amplification procedure consisted of an initial denaturation step at 95 °C for 12 min and 40 cycles of 95 °C for 15 s and 60 °C for 1 min. Positive and negative controls were added to each reaction plate. No inconsistencies occurred. Genotyping was performed blind to all phenotypic data. Allele frequencies agreed with National Center for Biotechnology Information database and published reports.

2.7 Data analysis

All self-report and behavioural impulsivity data were standardised into z-scores, which indicates how far and in what direction the group deviates from the whole sample's mean, according to the formula $Z_x=(X-M_x)/SD_x$, where Z_x denotes the z-score, X the raw score, M the sample's mean, and SD the standard deviation of the mean. IBM® SPSS® Statistics, Version 25 was used for all statistical analyses. The effect of *DRD2* genotype on the number of SLE and on the scores on Family Relationship questionnaires was investigated using one-way ANOVA and Kruskal-Wallis tests. Longitudinal effects of *DRD2* genotype, Sex and the median split of SLE of Family Relations scores on the impulsivity and alcohol use data (age

at first consumption, frequency of alcohol use, lifetime prevalence of AUD) were investigated using Generalised Estimating Equations. Data within each study wave were analysed using 3×2×2 analysis of variance (ANOVA) with *DRD2* genotype, Sex and median split of SLE or Family Relations scores as independent variables (IV). The self-reported and behavioural impulsivity scores and alcohol use data (age at first consumption, frequency of alcohol use) were treated as dependent variables (DV). Where initial analyses yielded significant interactions between three IVs, follow-up two-way ANOVAs were carried out by splitting the groups by Sex. Family Relations subcomponents were investigated further only if the higher order subscale (Warmth or Maltreatment) analyses yielded significant results. For the ANOVA models, we will present *F*-values, *p*-values, effect sizes (partial η^2) and *post hoc* power (π). *Post hoc* power was calculated because the sample had already been formed in the past. Fisher's LSD was used for *post hoc* comparisons. In the case of a dichotomous dependent variable (prevalence of AUD), binary logistic regression analyses were used. We used one-way ANOVA to carry out exploratory analyses on the main effect of *DRD2* genotype on personality traits for the whole sample, as well as for males and females separately. The level of significance was set at $p<0.05$.

3. Results

Genotype could not be determined for one participant. Overall, the genotype distributions did not deviate from Hardy-Weinberg Equilibrium (*TT*=157, *TC*=273, *CC*=149; $X^2 = 1.87$, df=1, $p=.17$). As the main effects of SLE, Family Relations and Sex on impulsivity have been described in previous papers (Laas et al., 2014; M. Paaver et al., 2008; Reif et al., 2011), these will not be discussed here. There were no significant associations between the *DRD2* genotype and the number of SLE or the scores on Family Relations questionnaires ($p>.05$ in all cases). Neither did we find any significant main effects of *DRD2* on the

impulsivity or alcohol use measures. An overview of the number of participants whose data were used in the current analyses is shown in Supplementary table 1.

3.1 The effects of *DRD2*, SLE and Sex interactions on self-reported impulsivity

The complete results from GEE analyses with *DRD2* rs6277 genotype, Sex and SLE on self-reported impulsivity measures across three study waves are shown in Supplementary Table 2, and the results from three-way ANOVAs within each study wave are presented in Supplementary table 4. The significant results will be outlined here. GEE analyses showed a marginally significant three-way interaction (χ^2=5.567, p=.062) on Thoughtlessness across three study waves, and ANOVA analyses on separate study waves showed a significant three-way *DRD2*×SLE×Sex interaction on Thoughtlessness scores at age 25, F(2, 366)=3.260, p=.040, partial η^2=.018, π=.618. Further division of the participants by Sex did not reveal any significant *DRD2*×ELS interactions, p>.05 in both cases. Marginally significant two-way *DRD2*×SLE interaction on Maladaptive Impulsivity was found across all study waves (GEE; χ^2=5.537, p=.063), and such interaction was most pronounced at age 15, F(2, 460)=4.585, p=.011, partial η^2=.020, π=.776. *Post hoc* comparisons showed that CC/High SLE and TT/High SLE groups scored significantly higher on Maladaptive Impulsivity compared to the respective Low SLE groups, and CC/High SLE group additionally scored higher than TC heterozygotes on Maladaptive Impulsivity. The *DRD2*×SLE interaction was also apparent at ages 18 and 25, although the analyses did not reach statistical significance, p>.05 in both cases (see Figure 1). The *DRD2*×SLE interaction on Maladaptive Impulsivity at age 15 was driven by Thoughtlessness subscale, F(2, 460)=6.221, p=.002, partial η^2=.026, π=.893, (Supplementary table 2), with the scores following a pattern similar to the *DRD2*×SLE interaction on Maladaptive Impulsivity (see Supplementary figure 1).

GEE analyses also showed a marginally significant *DRD2*×Sex interaction on Maladaptive Impulsivity (χ^2=5.918, p=.052), and particularly on the Disinhibition subscale across the study waves (χ^2=7.067, p=.029). ANOVA analyses showed that this effect was particularly pronounced at age 18, F(2, 383)=3.742, p=.025, partial η^2=.019, π=.683. *Post hoc* analyses indicated that female TC heterozygotes scored significantly higher on Maladaptive Impulsivity compared to male TC heterozygotes at age 18 (see Supplementary figure 2).

Figure 1

3.2 The effects of *DRD2,* Maltreatment and Sex interactions on self-reported impulsivity

The results from longitudinal GEE analyses focussing on the effects of *DRD2* genotype, Sex and Family Relations on self-reported impulsivity can be seen in Supplementary Table 3 and the results from three-way ANOVA analyses on individual study waves are shown in Supplementary table 5. No significant three-way interactions emerged from the GEE, but the results showed a *DRD2*×Maltreatment effect on Maladaptive Impulsivity (χ^2=7.732, p=.021), and its subcomponents Thoughtlessness (χ^2=6.317, p=.042) and Disinhibition (χ^2=9.007, p=.011). ANOVA analyses showed that the interaction was particularly apparent at age 15, F(2, 452)=3.902, p=.021, partial η^2=.017, π=.703, and driven by Thoughtlessness subscale, F(2, 452)=3.941, p=.020, partial η^2=.017, π=.708. *Post hoc* analyses showed that CC/High Maltreatment group generally scored higher on the composite Maladaptive Impulsivity scale (see Figure 2), as well as on the Thoughtlessness subscale (see Supplementary figure 3) compared to other groups. Figure 2 further shows that the differential sensitivity to Maltreatment in CC homozygotes can shows a similar pattern at

ages 18 and 25. Further analyses on the Family Relations subcomponents showed a *DRD2*×Abuse interaction on Maladaptive Impulsivity, $F(2, 459)=5.418$, $p=.005$, partial $\eta^2=.023$, $\pi=.845$, and especially on Thoughtlessness subscale at age 15, $F(2, 459)=5.693$, $p=.004$, partial $\eta^2=.024$, $\pi=.863$. *Post hoc* analyses showed that TT and CC homozygotes (particularly the latter), from the High Abuse group had heightened Maladaptive Impulsivity scores compared to the same genotype Low Abuse groups (see Supplementary figure 4). Thoughtlessness scores followed a similar pattern (see Supplementary figure 5).

Figure 2

Additionally, a *DRD2*×Maltreatment interaction on the Adaptive Impulsivity subcomponent of Excitement Seeking was seen at age 25, $F(2, 360)=3.447$, p=.033, partial $\eta^2=.019$, $\pi=.644$, with TT/High Maltreatment group showing reduced Excitement-seeking scores compared to TT/Low Maltreatment, TC/Low Maltreatment, and CC/High Maltreatment groups (see Supplementary figure 6), but GEE analysis results were non-significant, $p>.05$.

3.3 The effects of *DRD2*, Warmth and Sex interactions on self-reported impulsivity

No significant three-way interactions of *DRD2* genotype, Sex and Warmth emerged on the composite scores of Maladaptive or Adaptive impulsivity (Supplementary Tables 3 and 5). However, a marginally significant *DRD2*×Warmth interaction on the Thoughtlessness subscale was found across the study waves ($\chi^2=4.871$, $p=.088$), and ANOVA analyses on the separate study waves showed that this interaction was most pronounced at age 25, $F(2, 360)=3.491$, $p=.032$, partial $\eta^2=.019$, $\pi=.650$, whereby Low Warmth was associated with higher scores of Thoughtlessness in CC carriers when compared to CC and TT homozygotes

from the High Warmth groups (Figure 3). Further analyses on Warmth subcomponents showed a *DRD2*×Support interaction on Thoughtlessness at age 25, $F(2, 366)=3.520$, $p=.031$, partial $\eta^2=.019$, $\pi=.654$, and a three-way *DRD2*×Support×Sex interaction, $F(2, 366)=3.940$, $p=.020$, partial $\eta^2=.021$, $\pi=.707$. Follow-up two-way ANOVA on the male subsample showed a significant main effect of Support, $F(1, 157)=4.465$, $p=.036$, partial $\eta^2=.028$, $\pi=.556$, and a significant *DRD2*×Support interaction, $F(2, 157)=3.846$, $p=.023$, partial $\eta^2=.047$, $\pi=.691$, whereby most notably the CC/High Support group males displayed decreased Thoughtlessness scores compared to other groups. In the female subsample, the two-way ANOVA also showed a significant *DRD2*×Support interaction, $F(2, 209)=3.612$, $p=.029$, partial $\eta^2=.033$, $\pi=.633$, with *post hoc* pairwise comparisons showing that TT/High Support group showed lower Thoughtlessness scores compared to TT/Low Support and TC/High support groups (Figure 4).

Figure 3

Figure 4

3.4 The effects of *DRD2*, SLE/Family Relations and Sex interactions on behavioural measures of impulsivity

Analyses of the SST outcomes showed a marginally significant *DRD2*×SLE interaction on commission errors, $F(2, 338)=2.438$, $p=.089$, partial $\eta^2=.014$, $\pi=.489$ (Figure 5a) and on SSRT, $F(2, 308)=2.677$, $p=.070$, partial $\eta^2=.017$, $\pi=.529$ (Figure 5c). There was also a marginally significant main effect of *DRD2* genotype, $F(2, 338)=2.591$, $p=.076$, partial $\eta^2=.017$, $\pi=.515$, on the mean Go reaction time, with CC homozygotes being slower than TC heterozygotes and TT homozygotes. A significant *DRD2*×Sex interaction also emerged, $F(2, 338)=2.845$, $p=.030$, partial $\eta^2=.021$, $\pi=.659$, whereby TT homozygous males had faster

reaction times than all other groups, $p<.05$ in all cases. Additionally, the results showed a marginally significant *DRD2*×SLE interaction on the mean Go reaction time, $F(2, 338)=2.845$, $p=.060$, partial $\eta^2=.017$, $\pi=.556$ (Figure 5d). Similarly, a marginally significant *DRD2*xMaltreatment interaction occurred on the mean Go reaction time, $F(2, 336)=2.703$, $p=.068$, partial $\eta^2=.016$, $\pi=.533$, which followed a pattern similar to that seen in the case of *DRD2*×SLE interaction on Figure 5d. No significant main effects of *DRD2* or its interactions with Sex, SLE, or Family Relations emerged on omission errors (Figure 5b), $p>.05$ in all cases. No significant main effects of *DRD2* or its interactions with Sex, SLE or Family Relations emerged from the VCT, $p>.05$ in all cases.

Figure 5

3.5 The effects of *DRD2*, SLE/Family Relations and Sex on alcohol use

GEE with *DRD2* genotype, SLE and Sex as predictor variables showed a marginally significant *DRD*2×SLE interaction ($\chi^2=4.971$, $p=.083$), as well as a three-way *DRD2*×SLE×Sex interaction ($\chi^2=5.007$, $p=.082$) on the frequency of alcohol use across study waves. Three-way ANOVAs on separate study waves showed that the *DRD2*×SLE and *DRD2*×SLE×Sex interactions were most pronounced at age 15 ($F(2, 440)=4.239$, $p=.015$, partial $\eta^2=.019$, $\pi=.741$, and $F(2, 440)=3.234$, $p=.040$, partial $\eta^2=.014$, $\pi=.615$, respectively). Follow-up two-way ANOVA on the male subsample only showed a significant main effect of SLE, $F(1, 200)=15.885$, $p<.001$, partial $\eta^2=.069$, $\pi=.978$, whereby males who had experienced a higher number of SLE generally consumed more alcohol than the low SLE males. Follow-up two-way ANOVA in the female subsample showed a significant main effect of SLE, $F(1, 240)=15.068$, $p<.001$, partial $\eta^2=.059$, $\pi=.972$, and a significant

DRD2×SLE interaction, $F(2, 240)=9.584$, $p<.001$, partial $\eta^2=.074$, $\pi=.980$. *Post hoc* comparisons indicated that TT/High SLE and CC/High SLE groups consumed significantly more alcohol than the respective low SLE groups (Figure 6).

Figure 6

There was a significant *DRD2*×Warmth interaction on the frequency of alcohol use at age 25, $F(2, 358)=3.412$, $p=.034$, partial $\eta^2=.019$, $\pi=640$. *Post hoc* comparisons showed that the difference emerged from the CC genotype group, whereby CC/Low Warmth group engaged in drinking significantly more frequently, compared to the CC/High Warmth group (Figure 7). Follow-up investigations into the warmth subcomponents produced interactions only at a marginal significance level, *DRD2*×Closeness, $F(2, 360)=2.893$, $p=.057$, partial $\eta^2=.016$, $\pi=.564$, *DRD2*×Support, $F(2, 364)=2.497$, $p=.084$, partial $\eta^2=.014$, $\pi=.500$. GEE and ANOVA analyses the age of first consumption and lifetime prevalence of AUD did not reach statistical significance, $p>.05$ in all cases.

Figure 7

3.6 The effects of *DRD2* and Sex on personality traits

The secondary, exploratory analyses on the effect of *DRD2* genotype on personality traits showed a significant effect of *DRD2* rs6277 genotype on Agreeableness, $F(2,260)=4.8$, $p=.009$, Conscientiousness, $F(2, 260)=4.8$, $p=.009$, and Neuroticism, $F(2,260)=3.7$, $p=.027$ in the female subsample at age 9. The results showed a possible heterozygosity effect, whereby the TC carriers showed highest Neuroticism scores, and lowest Agreeableness and

Conscientiousness scores compared to other genotype carriers. However, there were no consistent associations between *DRD2* rs6277 and personality traits in the follow-up analyses. More information on these analyses can be seen in a Supplementary Table 6.

4. Discussion

The aim of this study was to further explore the previously found *DRD2* rs6277 and childhood adversity interaction on response inhibition (Klaus et al., 2017) by investigating the *DRD2*×environment×sex interactions on measures of behavioural and self-reported impulsivity in a population-representative sample. We first hypothesised that the experience of SLE and family maltreatment before the age of 15 leads to higher self-reported maladaptive and lower adaptive impulsivity scores, and to poorer performance on the behavioural impulsivity tests in the *DRD2* rs6277 CC homozygotes compared to other groups, and that the genotype-stress interaction is more pronounced in males compared to females. No consistent pattern of three-way interactions on the self-reported or behavioural impulsivity measures was seen. However, two-way *DRD2*×environment analyses showed that either CC genotype carriers, or both CC and TT carriers were most sensitive to the effects of adverse environment. We found that a higher number of SLE were associated with elevated maladaptive impulsivity and thoughtlessness scores in CC and TT homozygotes at age 15. A higher level of abusive family relations resulted in elevated maladaptive impulsivity and thoughtlessness primarily in CC homozygotes at age 15. These scores followed a similar pattern at ages 18 and 25. We further detected a marginally significant *DRD2*×SLE interaction on the measure of commission errors, SSRT and mean Go reaction time in SST. The mean number of commission errors, which is equivalent to the measure of false alarms in the RVP, followed a pattern similar to that found in our previous study (Klaus

et al., 2017), whereby the CC/High SLE group showed slightly inferior performance compared to the CC/Low SLE group. Altogether, these findings from the current study suggest that *DRD2* and childhood or youth adversity interact to affect facets of impulsivity, but the interactions were more pronounced for the self-report measures and our first hypothesis was therefore only partially supported.

The marginally significant findings from the SST and the non-significant findings from VCT are in line with those found by White and colleagues (2009), who reported a non-significant rs6277 and acute stress interaction from a GoStop task, despite significant interactions on a reward responsiveness and delay discounting tasks. The discordance with the findings from our own previous study (Klaus et al., 2017) may partly be explained by the age of the participant population. The mean age of the participants used in White and colleagues' study (2009) study was 19.3 years (*SD*=1.89), rather similarly to the current study population. On the other hand, our previous study population had the mean age of 35.2 years (*SD*=11.32; Klaus et al., 2017) and it has been suggested that the effect of *DRD2* rs6277 on response inhibition may be magnified by ageing (Colzato et al., 2013). A general decline in the dopaminergic functioning takes place from early to late adulthood, with gradual reductions seen in the number of dopaminergic cell bodies, synapses, as well as brain dopamine levels (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006). Furthermore, age-related decreases in D2 receptor binding have been noted throughout the brain, including the striatum and neocortex (Li, Lindenberger, Nyberg, Heekeren, & Bäckman, 2009). On behavioural level, reduced striatal D2 receptor availability has been associated with impaired behavioural inhibition in animal (Eagle et al., 2011) and human studies (Hamidovic, Dlugos, Skol, Palmer, & de Wit, 2009), perhaps via indirect effects on PFC dopaminergic signalling (Kellendonk et al., 2006). The *DRD2* rs6277 CC homozygotes have fewer available striatal D2 receptors and potentially higher striatal dopamine levels compared to TT and TC carriers

(Smith et al., 2017) and environmental stressors additionally increase the striatal (Pruessner, Champagne, Meaney, & Dagher, 2004) and decrease prefrontal dopamine levels (Mizoguchi, Shoji, Ikeda, Tanaka, & Tabira, 2008). It may be therefore proposed that further age-related decreases in D2 receptor availability may be progressively unfavourable to CC homozygotes with advancing age, leading to impaired response inhibition. Indeed, further investigations into the age-related factors in our previous study showed that the effects of *DRD2* genotype on executive function test outcomes (Spatial Working Memory and RVP) were driven by the participants over 40 years of age (data not shown; Klaus et al., 2017). The findings may therefore suggest that age-related decreases in dopamine function push the CC homozygotes further towards the far end of the inverted U-shaped dopamine curve (Cools & D'Esposito, 2011).

According to our second hypothesis, we expected warm family relations to contribute to decreased maladaptive impulsivity, increased adaptive impulsivity, and better performance on the behavioural impulsivity tests in the CC homozygotes compared to other groups, but that the male CC carriers would benefit more from family warmth. The mean self-reported thoughtlessness scores at age 25 indeed followed the expected direction. Further investigation into warmth subcomponents showed a *DRD2*×familial support×sex interaction, whereby a high level of family support was associated with reduced thoughtlessness in CC males. However, in the female subsample, the High Support group exhibited thoughtlessness scores indicative of a U-shaped dopamine function (discussed below). Altogether, these findings may provide some evidence for the theory that learning and positive parenting develop self-regulatory skills for managing emotions and impulses (Daruna & Barnes, 1993), and the individuals genetically most susceptible to stress may show the greatest benefit from these positive experiences (Belsky & Pluess, 2009). However, the lack of *DRD2*×warmth×sex interactions on adaptive impulsivity measures suggests that supportive environment reduces

dysfunctional impulsivity traits, it does not enhance functional impulsivity. Furthermore, no significant three-way interactions, nor *DRD2*×favourable environment interactions emerged from the behavioural impulsivity tests and the second hypothesis is therefore also partially supported.

We hypothesised that the findings on alcohol use would follow in a similar vein to the results from the behavioural and self-reported maladaptive impulsivity measures. In line with the results on self-reported thoughtlessness, we found a *DRD2*×SLE×Sex interaction on alcohol use frequency across three study waves, which was most apparent at age 15. Further inspection of male and female samples showed that the *DRD2*×SLE interaction was only seen in the female subsample, with the findings potentially being indicative of the inverted U-shaped dopamine function in the High SLE group, and the opposite pattern being exhibited by the Low SLE group. As with the findings on thoughtlessness, there was also some evidence of warmer family relations being associated with reduced alcohol consumption in CC carriers at the age of 25 (although no sex differences were seen here). The similar pattern of findings in self-reported impulsivity and alcohol use data is perhaps not surprising, as the link between impulsive behaviour and alcohol use (and AUD) is well-established, whereby AUD is associated with higher levels of impulsivity (Dick et al., 2010). It has been proposed that this association may stem from a bidirectional relationship between the two constructs, whereby impulsivity leads to alcohol abuse, but dysregulated alcohol intake may also enhance impulsivity (Perry & Carroll, 2008).

As noted above, TT homozygotes with a history of SLE and/or maltreatment followed a pattern similar to the CC homozygotes in many of the self-reported impulsivity outcomes and in alcohol use frequency (and a possible rs6277 heterozygosity effect was also seen in the personality data). These findings further provide evidence for the non-linear nature of dopamine function, which suggests that intermediate levels of dopamine may be needed for

optimal cognitive function (Cools & D'Esposito, 2011). The similar findings in CC and TT carriers, and the further interaction with environmental stressors may partly explain why studies investigating the effects of *DRD2* rs6277 genotype on cognitive outcomes have produced inconsistent results with some studies reporting TT homozygotes showing inferior performance (Colzato, van den Wildenberg, et al., 2010; Kawamura et al., 2013) and other studies reporting poorer performance in CC homozygotes (Klaus et al., 2017; Rodriguez-Jimenez et al., 2006; Xu et al., 2007).

Whereas some genotype×environment×sex interactions were detected, overall the three-way interactions were not consistently seen. Although oestrogen affects dopamine release in both striatal (Czoty et al., 2009) and prefrontal regions, and impacts on *DRD2* expression in the PFC (Sarvari et al., 2014), the results from the current study suggest that the effects of sex hormones on D2 receptor availability may not be sufficient to produce a strong impact on behavioural and personality measures. This is perhaps not unexpected, as no differences or only small differences have been noted in the basal D2 receptor binding potential in the striatum when comparing males and females (Munro et al., 2006; Pohjalainen, Rinne, Nagren, Syvalahti, & Hietala, 1998) and no significant differences have been detected between males and females in the response inhibition task performance (Colzato, Hertsig, van den Wildenberg, & Hommel, 2010). However, it could also be that the results presented here lacked sufficient statistical power to detect sex differences. In the cases where *DRD2*×environment×sex and *DRD2*xSex interactions were detected (in the context of Maladaptive impulsivity and alcohol use), the findings point to the non-linear nature of dopamine function, particularly in the female sample, which warrants further investigation in future studies.

Interestingly, there were no correlations between the self-reported and behavioural impulsivity measures in our findings (see Supplementary Tables 7a and 7b) similarly to

previous studies (e.g., Lane, Cherek, Rhoades, Pietras, & Tcheremissine, 2003; Mitchell, 1999; Reynolds, Ortengren, Richards, & de Wit, 2006), and it might be argued that these methods measure fundamentally different facets or traits. Indeed, behavioural impulsivity measures are objective, whereas self-report measures rely on one's perception of oneself in relation to other people and these self-perceptions may sometimes be inaccurate (Reynolds et al., 2006). Our findings may therefore suggest that CC carriers who have experienced adverse events in childhood perceive themselves as being more maladaptively impulsive, whereas the opposite is true if the CC carriers have been reared in a supportive family environment.

Some limitations should be considered. Firstly, in the absence of information on other dopaminergic gene variants and basal dopamine levels, *DRD2* rs6277 gives only an approximate idea of the individual's dopaminergic function and their position on the inverted U. Furthermore, the inverted U hypothesis mentioned throughout the manuscript is a part of the bigger picture, since the relationship between dopamine, different brain areas and cognitive functioning is not yet clear – dopaminergic function differs depending on the brain regions, neural circuits, polymorphisms and cognitive functions under investigation (Jeffrey W Dalley & Robbins, 2017; Floresco, 2013). Secondly, the self-report method for measuring SLE and family relations may have resulted in underreporting of the life experiences (Laas et al., 2014), and would therefore need further attention in future studies. Also, the difference in the cognitive tasks used in this and previous study (VCT and SST vs RVP) prevented direct comparison of the results across the two samples. This limitation was partly overcome by separately investigating the outcome measure of commission errors (false hits on a No-Go trial) in the SST, which is thought to be similar to the measure of false alarms in the RVP task. However, future studies could implement tasks more comparable to the one used in our previous study (Klaus et al., 2017) such as RVP. Finally, as the participants' age might have contributed to the differential findings from the behavioural tests between this and the

previous study, future studies are also needed to investigate the moderating effect of age on the association between the *DRD2* rs6277 genotype, stress and impulsivity.

In sum, this study extended our previous findings (Klaus et al., 2017) and showed that *DRD2* rs6277 polymorphism interacts with SLE and family environment in affecting aspects of self-reported impulsivity, with CC homozygotes generally showing heightened maladaptive impulsivity in the context of adverse environment. On the other hand, there was some evidence of CC carrier males benefitting from supportive family relations by showing lower levels of thoughtlessness. Genotype-environment interactive effects, and further interaction with sex was also evident in alcohol drinking habits. Results from the behavioural impulsivity tests showed only marginally significant *DRD2*×SLE interactions. Overall, these results expand our previous findings (Klaus et al., 2017) by showing that *DRD2* rs6277 polymorphism interacts with childhood and youth adverse and supportive experiences to affect facets of impulsivity.

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References

1. American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. Washington, DC: American Psychiatric Association.
2. Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.-C., & Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: current status and future prospects. *Neuroscience & Biobehavioral Reviews, 30*(6), 791-807. doi:10.1016/j.neubiorev.2006.06.005
3. Bari, A., & Robbins, T. W. (2013). Inhibition and impulsivity: behavioral and neural basis of response control. *Progress in Neurobiology, 108*(Supplement C), 44-79. doi:10.1016/j.pneurobio.2013.06.005
4. Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: differential susceptibility to environmental influences. *Psychological Bulletin, 135*(6), 885-908. doi:10.1037/a0017376
5. Beste, C., Stock, A. K., Epplen, J. T., & Arning, L. (2016). Dissociable electrophysiological subprocesses during response inhibition are differentially modulated by dopamine D1 and D2 receptors. *European Neuropsychopharmacology, 26*(6), 1029-1036. doi:10.1016/j.euroneuro.2016.03.002
6. Bezdjian, S., Baker, L. A., & Tuvblad, C. (2011). Genetic and environmental influences on impulsivity: a meta-analysis of twin, family and adoption studies. *Clinical Psychology Review, 31*(7), 1209-1223. doi:10.1016/j.cpr.2011.07.005
7. Bowirrat, A., & Oscar-Berman, M. (2005). Relationship between dopaminergic neurotransmission, alcoholism, and Reward Deficiency syndrome. *American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics, 132B*(1), 29-37. doi:10.1002/ajmg.b.30080

8. Brunas-Wagstaff, J., Bergquist, A., Richardson, P., & Connor, A. (1995). The relationships between functional and dysfunctional impulsivity and the Eysenck personality questionnaire. *Personality and Individual Differences, 18*(5), 681-683.

9. Canuso, C. M., & Pandina, G. (2007). Gender and schizophrenia. *Psychopharmacology Bulletin, 40*(4), 178-190.

10. Carroll, M. E., & Anker, J. J. (2010). Sex differences and ovarian hormones in animal models of drug dependence. *Hormones and Behavior, 58*(1), 44-56. doi:10.1016/j.yhbeh.2009.10.001

11. Chamberlain, S. R., & Sahakian, B. J. (2007). The neuropsychiatry of impulsivity. *Current opinion in psychiatry, 20*(3), 255-261. doi:10.1097/YCO.0b013e3280ba4989

12. Colzato, L. S., Hertsig, G., van den Wildenberg, W. P., & Hommel, B. (2010). Estrogen modulates inhibitory control in healthy human females: evidence from the stop-signal paradigm. *Neuroscience, 167*(3), 709-715. doi:10.1016/j.neuroscience.2010.02.029

13. Colzato, L. S., van den Wildenberg, W. P., & Hommel, B. (2013). The genetic impact (C957T-DRD2) on inhibitory control is magnified by aging. *Neuropsychologia, 51*(7), 1377-1381. doi:10.1016/j.neuropsychologia.2013.01.014

14. Colzato, L. S., van den Wildenberg, W. P., Van der Does, A. J., & Hommel, B. (2010). Genetic markers of striatal dopamine predict individual differences in dysfunctional, but not functional impulsivity. *Neuroscience, 170*(3), 782-788. doi:10.1016/j.neuroscience.2010.07.050

15. Comings, D. E., Rosenthal, R. J., Lesieur, H. R., Rugle, L. J., Muhleman, D., Chiu, C., . . . Gade, R. (1996). A study of the dopamine D2 receptor gene in pathological gambling. *Pharmacogenetics, 6*(3), 223-234.

16. Conner, B. T., Hellemann, G. S., Ritchie, T. L., & Noble, E. P. (2010). Genetic, personality, and environmental predictors of drug use in adolescents. *Journal of Substance Abuse Treatment, 38*(2), 178-190. doi:10.1016/j.jsat.2009.07.004

17. Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry, 69*(12), e113-125. doi:10.1016/j.biopsych.2011.03.028

18. Costa, P., & McCrae, R. (1992). *The Revised NEO Personality Inventory (NEO PI-R)*

19. *and NEO Five-Factor Inventory (NEO-FFI) professional manual. .* Odessa, FL.

20. Costa, P. T., & McCrae, R. R. (1989). Neo PI/FFI manual supplement. *Odessa, FL: Psychological Assessment Resources, 40*.

21. Czoty, P. W., Riddick, N. V., Gage, H. D., Sandridge, M., Nader, S. H., Garg, S., . . . Nader, M. A. (2009). Effect of menstrual cycle phase on dopamine D2 receptor availability in female cynomolgus monkeys. *Neuropsychopharmacology, 34*(3), 548-554. doi:10.1038/npp.2008.3

22. Dalley, J. W., Fryer, T. D., Brichard, L., Robinson, E. S., Theobald, D. E., Laane, K., . . . Robbins, T. W. (2007). Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science, 315*(5816), 1267-1270. doi:10.1126/science.1137073

23. Dalley, J. W., Mar, A. C., Economidou, D., & Robbins, T. W. (2008). Neurobehavioral mechanisms of impulsivity: fronto-striatal systems and functional neurochemistry. *Pharmacology, Biochemistry and Behavior, 90*(2), 250-260. doi:10.1016/j.pbb.2007.12.021

24. Dalley, J. W., & Robbins, T. W. (2017). Fractionating impulsivity: neuropsychiatric implications. *Nature Reviews Neuroscience, 18*(3), 158. doi:doi:10.1038/nrn.2017.8

25. Daruna, J. H., & Barnes, P. A. (1993). A neurodevelopmental view of impulsivity.

26. Di Paolo, T. (1994). Modulation of brain dopamine transmission by sex steroids. *Reviews in the Neurosciences, 5*(1), 27-41.

27. Dick, D. M., Smith, G., Olausson, P., Mitchell, S. H., Leeman, R. F., O'Malley, S. S., & Sher, K. (2010). Understanding the construct of impulsivity and its relationship to alcohol use disorders. *Addiction biology, 15*(2), 217-226. doi:doi:10.1111/j.1369-1600.2009.00190.x

28. Dickman, S. J. (1990). Functional and dysfunctional impulsivity: personality and cognitive correlates. *Journal of Personality and Social Psychology, 58*(1), 95-102.

29. Dickman, S. J., & Meyer, D. E. (1988). Impulsivity and speed-accuracy tradeoffs in information processing. *Journal of Personality and Social Psychology, 54*(2), 274-290.

30. Eagle, D. M., Wong, J. C., Allan, M. E., Mar, A. C., Theobald, D. E., & Robbins, T. W. (2011). Contrasting roles for dopamine D1 and D2 receptor subtypes in the dorsomedial striatum but not the nucleus accumbens core during behavioral inhibition in the stop-signal task in rats. *Journal of Neuroscience, 31*(20), 7349-7356.

31. Eensoo, D., Harro, M., Pullmann, H., Allik, J., & Harro, J. (2007). Association of traffic behavior with personality and platelet monoamine oxidase activity in schoolchildren. *Journal of Adolescent Health, 40*(4), 311-317. doi:10.1016/j.jadohealth.2006.10.011

32. Floresco, S. B. (2013). Prefrontal dopamine and behavioral flexibility: shifting from an "inverted-U" toward a family of functions. *Frontiers in neuroscience, 7*. Retrieved from doi:https://doi.org/10.3389/fnins.2013.00062

33. Forbes, E. E., Brown, S. M., Kimak, M., Ferrell, R. E., Manuck, S. B., & Hariri, A. R. (2009). Genetic variation in components of dopamine neurotransmission impacts

ventral striatal reactivity associated with impulsivity. *Molecular Psychiatry, 14*(1), 60-70. doi:10.1038/sj.mp.4002086

34. Gluskin, B., & Mickey, B. (2017). Genetic variation and dopamine D2 receptor availability: a systematic review and meta-analysis of human in vivo molecular imaging studies. *Translational psychiatry, 6*(3), e747.

35. Gurvich, C., & Rossell, S. L. (2014). Genetic variations in dopamine and inhibitory control: Lack of influence on action restraint. *Behavioural Brain Research, 267*, 12-16. doi:https://doi.org/10.1016/j.bbr.2014.03.015

36. Gurvich, C., & Rossell, S. L. (2015). Dopamine and cognitive control: sex-by-genotype interactions influence the capacity to switch attention. *Behavioural Brain Research, 281*, 96-101. doi:https://doi.org/10.1016/j.bbr.2014.11.045

37. Hafner, H. (2003). Gender differences in schizophrenia. *Psychoneuroendocrinology, 28 Suppl 2*, 17-54.

38. Hamidovic, A., Dlugos, A., Skol, A., Palmer, A. A., & de Wit, H. (2009). Evaluation of genetic variability in the dopamine receptor D2 in relation to behavioral inhibition and impulsivity/sensation seeking: an exploratory study with d-amphetamine in healthy participants. *Experimental and Clinical Psychopharmacology, 17*(6), 374-383. doi:10.1037/a0017840

39. Harnishfeger, K. K., & Bjorklund, D. F. (1994). A Developmental Perspective on Individual-Differences in Inhibition. *Learning and individual differences, 6*(3), 331-355. doi:Doi 10.1016/1041-6080(94)90021-3

40. Harro, M., Eensoo, D., Kiive, E., Merenakk, L., Alep, J., Oreland, L., & Harro, J. (2001). Platelet monoamine oxidase in healthy 9- and 15-years old children: the effect of gender, smoking and puberty. *Progress in Neuro-Psychopharmacology and*

Biological Psychiatry, 25(8), 1497-1511. doi:https://doi.org/10.1016/S0278-5846(01)00212-3

41. Hirvonen, M. M., Lumme, V., Hirvonen, J., Pesonen, U., Nagren, K., Vahlberg, T., . . . Hietala, J. (2009). C957T polymorphism of the human dopamine D2 receptor gene predicts extrastriatal dopamine receptor availability in vivo. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 33*(4), 630-636. doi:10.1016/j.pnpbp.2009.02.021

42. Hofmann, W., Friese, M., & Strack, F. (2009). Impulse and Self-Control From a Dual-Systems Perspective. *Perspectives on Psychological Science, 4*(2), 162-176. doi:10.1111/j.1745-6924.2009.01116.x

43. Hoptman, M. J., Antonius, D., Mauro, C. J., Parker, E. M., & Javitt, D. C. (2014). Cortical thinning, functional connectivity, and mood-related impulsivity in schizophrenia: relationship to aggressive attitudes and behavior. *American Journal of Psychiatry, 171*(9), 939-948. doi:10.1176/appi.ajp.2014.13111553

44. Kawamura, Y., Takahashi, T., Liu, X., Nishida, N., Noda, Y., Yoshikawa, A., . . . Sasaki, T. (2013). Variation in the DRD2 gene affects impulsivity in intertemporal choice. *Open Journal of Psychiatry, 3*(01), 26.

45. Kellendonk, C., Simpson, E. H., Polan, H. J., Malleret, G., Vronskaya, S., Winiger, V., . . . Kandel, E. R. (2006). Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. *Neuron, 49*(4), 603-615. doi:10.1016/j.neuron.2006.01.023

46. Kiive, E., Laas, K., Vaht, M., Veidebaum, T., & Harro, J. (2017). Stressful life events increase aggression and alcohol use in young carriers of the GABRA2 rs279826/rs279858 A-allele. *European Neuropsychopharmacology, 27*(8), 816-827. doi:10.1016/j.euroneuro.2017.02.003

47. Kim, J., & Park, A. (2018). A systematic review: Candidate gene and environment interaction on alcohol use and misuse among adolescents and young adults. *The American journal on addictions*, *27*(5), 345-363. doi:https://doi.org/10.1111/ajad.12755

48. Klaus, K., Butler, K., Durrant, S. J., Ali, M., Inglehearn, C. F., Hodgson, T. L., . . . Pennington, K. (2017). The effect of COMT Val158Met and DRD 2 C957T polymorphisms on executive function and the impact of early life stress. *Brain and behavior*, *7*(5), e00695. doi: https://doi.org/10.1002/brb3.695

49. Kranzler, H. R., Zhou, H., Kember, R. L., Smith, R. V., Justice, A. C., Damrauer, S., . . . Reid, J. (2019). Genome-wide association study of alcohol consumption and use disorder in 274,424 individuals from multiple populations. *Nature communications*, *10*(1), 1-11. doi:https://doi.org/10.1038/s41467-019-09480-8

50. Kritzer, M. F., & Creutz, L. M. (2008). Region and sex differences in constituent dopamine neurons and immunoreactivity for intracellular estrogen and androgen receptors in mesocortical projections in rats. *Journal of Neuroscience*, *28*(38), 9525-9535. doi:10.1523/JNEUROSCI.2637-08.2008

51. Laakso, A., Pohjalainen, T., Bergman, J., Kajander, J., Haaparanta, M., Solin, O., . . . Hietala, J. (2005). The A1 allele of the human D2 dopamine receptor gene is associated with increased activity of striatal L-amino acid decarboxylase in healthy subjects. *Pharmacogenetics and Genomics*, *15*(6), 387-391.

52. Laas, K., Reif, A., Herterich, S., Eensoo, D., Lesch, K.-P., & Harro, J. (2010). The effect of a functional NOS1 promoter polymorphism on impulsivity is moderated by platelet MAO activity. *Psychopharmacology*, *209*(3), 255-261. doi:10.1007/s00213-010-1793-z

53. Laas, K., Reif, A., Kiive, E., Domschke, K., Lesch, K. P., Veidebaum, T., & Harro, J. (2014). A functional NPSR1 gene variant and environment shape personality and impulsive action: a longitudinal study. *J Psychopharmacol, 28*(3), 227-236. doi:10.1177/0269881112472562

54. Laidra, K., Allik, J., Harro, M., Merenäkk, L., & Harro, J. (2006). Agreement among adolescents, parents, and teachers on adolescent personality. *Assessment, 13*(2), 187-196. doi:10.1177/1073191106287125

55. Lane, S. D., Cherek, D. R., Rhoades, H. M., Pietras, C. J., & Tcheremissine, O. V. (2003). Relationships among laboratory and psychometric measures of impulsivity: Implications in substance abuse and dependence. *Addictive Disorders & Their Treatment, 2*(2), 33-40.

56. Li, S.-C., Lindenberger, U., Nyberg, L., Heekeren, H. R., & Bäckman, L. (2009). Dopaminergic modulation of cognition in human aging *Imaging the aging brain* (pp. 71-91): Oxford University Press.

57. Liu, L., Fan, D., Ding, N., Hu, Y., Cai, G., Wang, L., . . . Pan, F. (2014). The relationship between DRD2 gene polymorphisms (C957T and C939T) and schizophrenia: a meta-analysis. *Neuroscience Letters, 583*, 43-48. doi:10.1016/j.neulet.2014.09.024

58. Liu, M., Jiang, Y., Wedow, R., Li, Y., Brazel, D. M., Chen, F., . . . Tian, C. (2019). Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nature genetics, 51*(2), 237-244. doi:https://doi.org/10.1038/s41588-018-0307-5

59. Logan, G. D., Schachar, R. J., & Tannock, R. (1997). Impulsivity and inhibitory control. *Psychological Science, 8*(1), 60-64. doi:DOI 10.1111/j.1467-9280.1997.tb00545.x

60. Markett, S., Montag, C., Walter, N. T., Plieger, T., & Reuter, M. (2011). On the molecular genetics of flexibility: the case of task-switching, inhibitory control and genetic variants. *Cognitive, Affective & Behavioral Neuroscience, 11*(4), 644-651. doi:10.3758/s13415-011-0058-6

61. Markham, J. A. (2012). Sex steroids and schizophrenia. *Reviews in Endocrine & Metabolic Disorders, 13*(3), 187-207. doi:10.1007/s11154-011-9184-2

62. Metcalfe, J., & Mischel, W. (1999). A hot/cool-system analysis of delay of gratification: dynamics of willpower. *Psychological Review, 106*(1), 3-19.

63. Miller, E., Joseph, S., & Tudway, J. (2004). Assessing the component structure of four self-report measures of impulsivity. *Personality and Individual Differences, 37*(2), 349-358. doi:10.1016/j.paid.2003.09.008

64. Mitchell, S. H. (1999). Measures of impulsivity in cigarette smokers and non-smokers. *Psychopharmacology, 146*(4), 455-464.

65. Mizoguchi, K., Shoji, H., Ikeda, R., Tanaka, Y., & Tabira, T. (2008). Persistent depressive state after chronic stress in rats is accompanied by HPA axis dysregulation and reduced prefrontal dopaminergic neurotransmission. *Pharmacology Biochemistry and Behavior, 91*(1), 170-175. doi:10.1016/j.pbb.2008.07.002

66. Munro, C. A., McCaul, M. E., Wong, D. F., Oswald, L. M., Zhou, Y., Brasic, J., . . . Wand, G. S. (2006). Sex differences in striatal dopamine release in healthy adults. *Biological Psychiatry, 59*(10), 966-974. doi:10.1016/j.biopsych.2006.01.008

67. Nagel, M., Watanabe, K., Stringer, S., Posthuma, D., & Van Der Sluis, S. (2018). Item-level analyses reveal genetic heterogeneity in neuroticism. *Nature communications, 9*(1), 1-10. doi:https://doi.org/10.1038/s41467-018-03242-8

68. Nordström, A.-L., Olsson, H., & Halldin, C. (1998). A PET study of D2 dopamine receptor density at different phases of the menstrual cycle. *Psychiatry Research: Neuroimaging, 83*(1), 1-6.

69. Paaver, M., Kurrikoff, T., Nordquist, N., Oreland, L., & Harro, J. (2008). The effect of 5-HTT gene promoter polymorphism on impulsivity depends on family relations in girls. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 32*(5), 1263-1268. doi:10.1016/j.pnpbp.2008.03.021

70. Paaver, M., Nordquist, N., Parik, J., Harro, M., Oreland, L., & Harro, J. (2007). Platelet MAO activity and the 5-HTT gene promoter polymorphism are associated with impulsivity and cognitive style in visual information processing. *Psychopharmacology, 194*(4), 545-554. doi:10.1007/s00213-007-0867-z

71. Perry, J. L., & Carroll, M. E. (2008). The role of impulsive behavior in drug abuse. *Psychopharmacology, 200*(1), 1-26. doi:https://doi.org/10.1007/s00213-008-1173-0

72. Pohjalainen, T., Rinne, J. O., Nagren, K., Syvalahti, E., & Hietala, J. (1998). Sex differences in the striatal dopamine D2 receptor binding characteristics in vivo. *American Journal of Psychiatry, 155*(6), 768-773. doi:10.1176/ajp.155.6.768

73. Pruessner, J. C., Champagne, F., Meaney, M. J., & Dagher, A. (2004). Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [11C] raclopride. *Journal of Neuroscience, 24*(11), 2825-2831.

74. Reif, A., Kiive, E., Kurrikoff, T., Paaver, M., Herterich, S., Konstabel, K., . . . Harro, J. (2011). A functional NOS1 promoter polymorphism interacts with adverse environment on functional and dysfunctional impulsivity. *Psychopharmacology, 214*(1), 239-248. doi:10.1007/s00213-010-1915-7

75. Reynolds, B., Ortengren, A., Richards, J. B., & de Wit, H. (2006). Dimensions of impulsive behavior: Personality and behavioral measures. *Personality and Individual Differences, 40*(2), 305-315. doi:10.1016/j.paid.2005.03.024

76. Rincón-Pérez, I., Echeverry-Alzate, V., Sánchez-Carmona, A., Bühler, K., Hinojosa, J., López-Moreno, J., & Albert, J. (2020). The influence of dopaminergic polymorphisms on selective stopping. *Behavioural Brain Research, 381*, 112441. doi:https://doi.org/10.1016/j.bbr.2019.112441

77. Rincon-Perez, I., Sanchez-Carmona, A. J., Albert, J., & Hinojosa, J. A. (2018). The association of monoamine-related gene polymorphisms with behavioural correlates of response inhibition: A meta-analytic review. *Neuroscience and Biobehavioral Reviews, 84*(Supplement C), 49-62. doi:10.1016/j.neubiorev.2017.11.009

78. Rodriguez-Jimenez, R., Hoenicka, J., Jimenez-Arriero, M. A., Ponce, G., Bagney, A., Aragues, M., & Palomo, T. (2006). Performance in the Wisconsin Card Sorting Test and the C957T polymorphism of the DRD2 gene in healthy volunteers. *Neuropsychobiology, 54*(3), 166-170. doi:10.1159/000098652

79. Sarvari, M., Deli, L., Kocsis, P., Mark, L., Maasz, G., Hrabovszky, E., . . . Liposits, Z. (2014). Estradiol and isotype-selective estrogen receptor agonists modulate the mesocortical dopaminergic system in gonadectomized female rats. *Brain Research, 1583*, 1-11. doi:10.1016/j.brainres.2014.06.020

80. Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature, 511*(7510), 421-427. doi:https://doi.org/10.1038/nature13595

81. Smith, C. T., Dang, L. C., Buckholtz, J. W., Tetreault, A. M., Cowan, R. L., Kessler, R. M., & Zald, D. H. (2017). The impact of common dopamine D2 receptor gene

polymorphisms on D2/3 receptor availability: C957T as a key determinant in putamen and ventral striatum. *Translational psychiatry, 7*, e1091. doi:10.1038/tp.2017.45

82. Swagell, C. D., Lawford, B. R., Hughes, I. P., Voisey, J., Feeney, G. F., van Daal, A., . . . Young, R. M. (2012). DRD2 C957T and Taq IA genotyping reveals gender effects and unique low-risk and high-risk genotypes in alcohol dependence. *Alcohol and alcoholism, 47*(4), 397-403. doi:10.1093/alcalc/ags047

83. Thompson, A., Cook, J., Choquet, H., Jorgenson, E., Yin, J., Kinnunen, T., . . . Pirmohamed, M. (2020). Functional validity, role, and implications of heavy alcohol consumption genetic loci. *Science advances*, *6*(3), eaay5034. doi:10.1126/sciadv.aay5034

84. Trent, S., & Davies, W. (2012). The influence of sex-linked genetic mechanisms on attention and impulsivity. *Biological Psychology*, *89*(1), 1-13. doi:10.1016/j.biopsycho.2011.09.011

85. Vaht, M., Kiive, E., Veidebaum, T., & Harro, J. (2016). A functional vesicular monoamine transporter 1 (VMAT1) gene variant is associated with affect and the prevalence of anxiety, affective, and alcohol use disorders in a longitudinal population-representative birth cohort study. *International Journal of Neuropsychopharmacology, 19*(7). doi:10.1093/ijnp/pyw013

86. Vaht, M., Kurrikoff, T., Laas, K., Veidebaum, T., & Harro, J. (2016). Oxytocin receptor gene variation rs53576 and alcohol abuse in a longitudinal population representative study. *Psychoneuroendocrinology, 74*, 333-341. doi:https://doi.org/10.1016/j.psyneuen.2016.09.018

87. Volkow, N. D., Fowler, J. S., Wang, G. J., Swanson, J. M., & Telang, F. (2007). Dopamine in drug abuse and addiction: results of imaging studies and treatment

implications. *Archives of Neurology, 64*(11), 1575-1579. doi:10.1001/archneur.64.11.1575

88. Weeland, J., Overbeek, G., de Castro, B. O., & Matthys, W. (2015). Underlying mechanisms of gene–environment interactions in externalizing behavior: A systematic review and search for theoretical mechanisms. *Clinical child and family psychology review, 18*(4), 413-442. doi:https://doi.org/10.1007/s10567-015-0196-4

89. White, M. J., Lawford, B. R., Morris, C. P., & Young, R. M. (2009). Interaction between DRD2 C957T polymorphism and an acute psychosocial stressor on reward-related behavioral impulsivity. *Behavior Genetics, 39*(3), 285-295. doi:10.1007/s10519-008-9255-7

90. White, M. J., Morris, C. P., Lawford, B. R., & Young, R. M. (2008). Behavioral phenotypes of impulsivity related to the ANKK1 gene are independent of an acute stressor. *Behav Brain Funct, 4*, 54. doi:10.1186/1744-9081-4-54

91. Whiteside, S. P., & Lynam, D. R. (2001). The Five Factor Model and impulsivity: using a structural model of personality to understand impulsivity. *Personality and Individual Differences, 30*(4), 669-689. doi:Doi 10.1016/S0191-8869(00)00064-7

92. Xu, H., Kellendonk, C. B., Simpson, E. H., Keilp, J. G., Bruder, G. E., Polan, H. J., . . . Gilliam, T. C. (2007). DRD2 C957T polymorphism interacts with the COMT Val158Met polymorphism in human working memory ability. *Schizophrenia Research, 90*(1-3), 104-107. doi:10.1016/j.schres.2006.10.001

93. Zhou, H., Sealock, J. M., Sanchez-Roige, S., Clarke, T.-K., Levey, D. F., Cheng, Z., . . . Smith, R. V. (2020). Genome-wide meta-analysis of problematic alcohol use in 435,563 individuals yields insights into biology and relationships with other traits. *Nature Neuroscience*, 1-10. doi:https://doi.org/10.1038/s41593-020-0643-5

Supplementary Table 1

Supplementary Table 2

Supplementary Table 3

Supplementary Table 4

Supplementary Table 5

Supplementary figure 1

Supplementary figure 2

Supplementary figure 3

Supplementary figure 4

Supplementary figure 5

Supplementary figure 6

Supplementary Table 6

Supplementary Table 7a and 7b