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The impulsive horse: Comparing genetic, physiological and behavioral indicators to those of human addiction.

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ABSTRACT

Stress and genotype elicit changes in impulse control in a range of species that are attributable to adaptations in both the central and peripheral nervous system. We examined aspects of this mechanism in the horse by assessing the effect of a dopamine receptor genotype (DRD4) and central dopaminergic tone (measured via spontaneous blink rate [SBR] and behavioral initiation rate [BIR]), on measures of impulsivity, compulsivity (3-choice serial reaction time task) and sympathetic/parasympathetic system balance (heart rate variability [HRV]). Genotype did not have a significant effect on any of the parameters measured. SBR but not BIR correlated significantly with levels of impulsivity. There was no clear association of HRV parameters with either measures of central dopaminergic activity or impulsivity/compulsivity. Overall, some elements of the data suggest that the horse may be a useful animal model for assessing the genetic and environmental factors that lead to the physiological and behavioral phenotype of human addiction, particularly when considering the relationship between central dopaminergic tone and impulsivity.

1. Introduction

Early life stress (ELS) and genotype interact to remodel dopamine systems in a range of species that can set different behavioral trajectories via different physiological (e.g. hypoactive parasympathetic/hyperactive sympathetic nervous systems) [1–3] and behavioral endpoints (e.g. reduced impulse control, food and drug addiction) [4–11]. In humans, the administration of certain psychostimulant drugs through the individual's lifetime can also further alter dopamine systems to exacerbate these changes in behavior [12, 13]. Increasingly, evidence suggests that a very similar model of dopamine and behavioral dysregulation exists in domestic animal species as a result of how these animals are managed and kept in the domestic environment. Specifically, ELS (e.g. weaning, restricted environments) increases susceptibility to develop spontaneous stereotypic behaviors in a range of domestic animal species [14–20] and these behaviors have been strongly linked to: (a) dysregulation of basal ganglia dopaminergic systems [21–23]; (b) reduced impulse control (e.g. impulsivity, compulsivity, perseverance) [24–28]; and (c) reduced sympathovagal tone, reflecting increased sympathetic nervous system (SNS) over parasympathetic nervous system (PNS) activity [29]. Similar

to the effects of certain psychostimulant drugs in humans, highly palatable food substrates (particularly high fat/glucose/carbohydrate content) activate, in a range of species, the SNS [30], dopamine and opioid systems [31, 32] and exacerbate behavioral endpoints associated with reduced impulse control [33–35].

Here, we aimed to explore whether genetic and functional changes in central dopaminergic activity affect variation in impulse control, compulsive behavior and sympathovagal balance in a domestic animal species known to develop spontaneous stereotypies, the horse (*equus caballus*) (Fig. 1).

Polymorphisms of the dopamine receptor gene *DRD4* (variable numbers of tandem repeats [VNTR] in exon III) in humans have been reported to determine levels of novelty seeking [36], impulsivity [37] and the risk of addiction-type behaviors [38, 39]. Polymorphisms in *DRD4* exon III (VNTR and a single nucleotide polymorphism [SNP; A-G substitution]), have also been identified in the horse [40–42] and the A-G substitution (SNP G292A) has been shown to be associated with increased 'wanting' type behaviors in the form of locomotory appetitive response (e.g. vertical head movement) in the horse during cue-elicited reward seeking [43]. *DRD4* gene variants thus appear to produce a

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similar effect on impulse control across species and this was therefore considered to be a reasonable candidate gene for examining the physiological and behavioral consequences of an altered central dopaminergic system within this study. In order to measure impulsivity/compulsivity and central dopaminergic tone in the horse, we used the serial reaction time task and spontaneous blink rate (SBR) (e.g. [44, 45]), both of which have previously been validated in this domestic species [46, 47].

2. Methods

2.1. Subjects

One hundred horses were initially screened for spontaneous blink rate (SBR) Section 2.2 and 26 of these animals were subsequently selected based on their SBR results (8 low blink rate animals [440 blinks/30mins], 9 middle blink rate animals [441–622 blinks/30 min] and 9 high blink rate animals [>623 blinks/30mins]) to go through for cognitive and genetic measurement within the trial. The selected horses were of mixed breeds, age (average 11.1, 2–27 [min-max] years) and sex ($n = 11$ geldings, $n = 15$ mares) from 7 equine yards in Gloucestershire and Wiltshire area of the UK. All horses were in good health and fed to meet individual dietary requirements for maintenance according to the National Research Council (2007). None of the horses performed stereotypic behavior at the time of the study. All horses were tested in their normal stable environment.

2.2. Spontaneous blink rate (SBR)

SBR was measured as previously described [48]. Briefly, following a 10-min habituation to the presence of an observer, unilateral (left-hand-side only) full blinks (continuous paroxysmal brief repetitive eye closures; Karson 1983) were quantified on a mechanical sequential counter for 30 min. Measurements were taken mid-morning or mid-afternoon during periods when the horse would not normally be fed. This procedure was repeated three times per horse (on three separate days) and from this, the mean SBR/30 min was calculated for each

animal.

2.3. Behavioral initiation rate (BIR)

BIR was measured as previously described [48]. Briefly, following a 10-min habituation to the presence of an observer, every behavior initiation was recorded with a mechanical counter for 30 min. All behaviors were defined by a pre-determined ethogram [49], though only the number of behavioral transitions were recorded and not type of behavior. Each bout of behavior was recorded as a new initiation irrespective of the previous behavior; for example, the sequence 'Feeding [Starting point]–Standing [Initiation 1]–Feeding [Initiation 2]–Drinking [Initiation 3]–Standing [Initiation 4]' was recorded as four initiations. Importantly, sub-movements of behavior – for example, raising of the head whilst still undergoing mastication as part of feeding – was not recorded as an initiation of a new behavior. All horses were observed on three separate occasions, and an overall mean calculated to give the average BIR (initiations/min) for each horse.

2.4. Genomic sample collection, preparation and analysis

Samples of 20 mane/tail hairs were taken from each animal and stored in a labelled zip-lock bag at 4 °C until sample preparation. Genomic DNA was isolated from each hair sample using a DNA extraction kit (ISOHAIR; Nippon Gene Co. Ltd., Toyama, Japan). Analysis of the G292A SNP was conducted as previously described [50] at Gifu University. In brief, the PCR was conducted on a T100™ thermal cycler (BIO-RAD, California, USA) and PCR primer pairs were F1 (5'-CCGCTCATGCTGCTGCTCTACTGG 3') and R1 (5'-TGCGCTCCCGCCGGTGATCTT 3') with Ampli-taq Gold 360 Master Mix (Applied Biosystems, California, USA) used as a PCR polymerase. The PCR protocol was run per PCR kit instructions and each PCR product was purified with MonoFas DNA Purification Kit I (GL Sciences Inc. Tokyo, Japan) for DNA sequencing. DNA sequencing was conducted on an ABI Prism 3100 and 3130 Genetic Analyzer (Applied Biosystems) using primers, F2 (5'-CTCATGCTGCTGCTCTAC-3') or R2 (5'-GGTGATCTTGGCGCCT-3') to identify the A-G substitution from the DNA sequence of each horse.

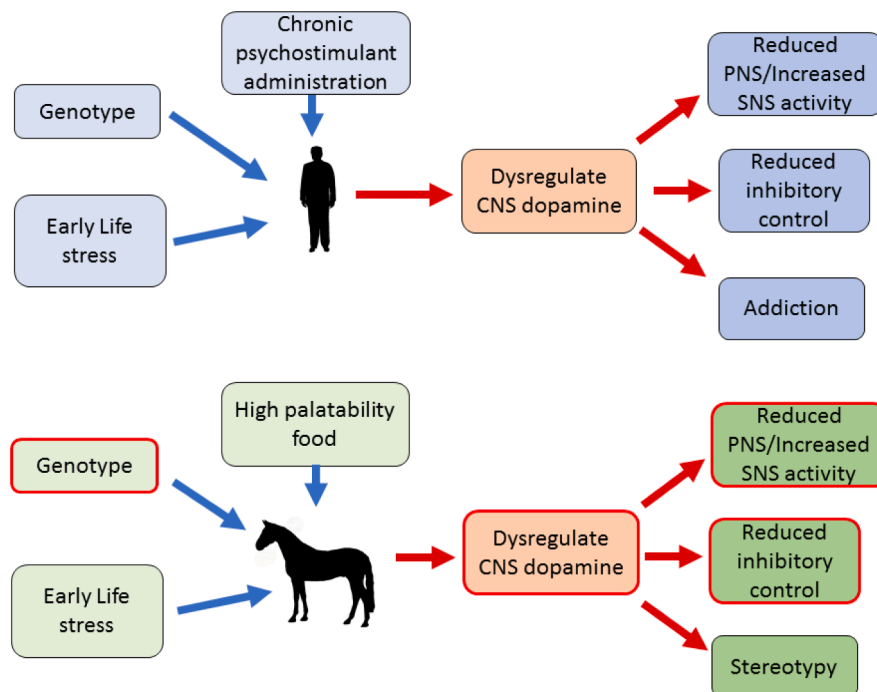


Fig. 1. Comparison of factors leading to reduced inhibitory control in human and animals. Boxes outlined in red indicate factors being tested within the equine model in this study.

2.5. Three choice serial reaction time task procedure

The three-choice serial reaction time task (3CSRTT) was fully automated, and carried out using a purpose-built testing system described in detail elsewhere [47]. Horses were all trained in their own stable. During all training, horses were loosely held by the owner (who was, in all cases, naïve to the aims and objectives of the research and unable to see the presentation of stimuli on the apparatus, to avoid any bias or unconscious signaling to the animal) using a head-collar and lead rope. Training was split into discrete phases, during which animals were initially habituated to the equipment, and then trained on an increasingly challenging series of tasks in order to gain access to a food reinforcer. Each animal was trained and tested for 1 session per day.

2.5.1. Pretraining

The 4 stages of pre-training has been described in detail elsewhere [47]. In Phase 1, the initial Pavlovian training phase, food (5 g of pony nuts) was released from the apparatus according to a fixed time (FT) 30-second schedule for 15 trials within 1 session. During Phase 2, horses were exposed to an auditory stimulus (400 Hz, 0.15 s, 75 dB), designed to induce an orienting response in the animals at the beginning of each trial. During this phase, all three screens were illuminated white. A response (nose press) on any of the white screens within a 30-sec illumination period was reinforced with a delivery of food. In this phase, if the horse failed to respond within 30-sec, the trial ended with release of food. After the trials timed out, or a correct response, there was a 15-sec inter-trial interval (ITI), followed by commencement of the next trial. A total of 15 trials was presented to each animal per session. Learning criterion was set at one session with at least 50% of trials correct (i.e. responding within the 30-sec period). In Phase 3, the Phase 2 protocol was repeated, but without non-contingent release of food. Following criteria (at least 50% correct), Phase 4 comprised a repeat of Phase 3, but with only one of the three stimulus screens being illuminated, the location of which was randomised between trials (5 trials in each of 3 locations/session). During Phase 4, the time limit was removed, but the horse was required to press the correct screen to move to the next trial (no non-contingent release of food). In Phase 5, the same protocol as Phase 4 was carried out, except this time the stimulus only remained for 20-sec, followed by a 5-sec 'limited hold' (LH), during which the horse was still reinforced for a correct response. Incorrect choices, and omissions (no response, or responding after the LH), were signaled with an auditory stimulus (1000 Hz, 0.5 s, 75 dB). In addition, in order to progress, horses were required to achieve an 80% correct response rate. In Phase 6, the stimulus duration was reduced to 10-sec (10-sec LH). Finally, in Phase 7, the stimulus duration was reduced to 5-sec (5-sec LH).

2.5.2. Task training and testing

During 3CSRTT training, a pre-stimulus interval (PSI) was introduced, which comprised a delay between the auditory stimulus signaling the start of the trial, and the initiation of one of the three stimulus lights (5-sec followed by 5-sec LH). Correct choices within the 5-sec stimulus presentation or the 5-sec LH were reinforced. Incorrect responses during the stimulus presentation or LH (nose poke to an incorrect stimulus), responses during the PSI (premature responses), and omissions (no response within the 5-sec PSI, 5-sec stimulus or 5-sec LH) resulted in an 'incorrect' signal (100 Hz auditory stimulus, 75 dB), and a 15-sec ITI. Any repeated responses after a correct response (termed 'compulsive' responses) were recorded but not punished. 3CSRTT continued for 12 sessions for each horse. 3CSRTT data were recorded as accuracy [correct/(correct+incorrect)], impulsivity [premature/(correct+incorrect+premature)]; compulsive (*n* compulsive responses), and were calculated as a mean for each animal across all 3CSRTT sessions.

2.6. Heart rate variability (HRV)

Vagally mediated heart rate variability (vmHRV) was obtained

utilizing the Polar® Equine V800 Science system. The electrode belt was applied to the horse according to the manufacturer's instructions. To improve contact between the electrodes and horse skin, a water-based lubricant (KY Jelly) was applied to the electrodes prior to placement of the belt on the horse. Data were downloaded via Polar Flow®, with further analysis with regards to the LF/HF ratio (frequency domain) being undertaken utilizing Kubios HRV version 2.2 software. Time domain measurements of HRV were calculated using the root mean square of successive differences of NN intervals (rMSSD). Data were detrended utilizing the 'smoothness priors' function, with the smoothness parameter set at 500 ms [51]. Artefact filtering was also conducted utilizing the custom setting at 0.3, removing RR intervals which differ from the RR interval immediately prior by more than 30% as artefacts (Schmidt et al., 2010). Finally, the HRV was processed via a fast fourier transformation (FFT) [52, 53]. HRV measurements were taken at rest and also during the 3CSRTT task and a mean HRV value derived for each horse from those values.

2.7. Statistical analysis

Statistical analyses were conducted using jamovi (v 1.22.2.0) for Macintosh (<https://www.jamovi.org/>). Following genotyping, horses were organised according to DRD4 genotype (A-allele absent vs A-allele present) for the purpose of statistical analyses as per previous studies [50]. One-way ANOVA (unequal variances assumed [Welch's]) and independent T-tests were carried out to examine the effect of genotype, and A-absent vs A-present, respectively, on SBR, BIR, impulsivity, compulsivity and accuracy on the 3CSRTT and the HRV (RMSSD) data. A correlation matrix was also carried out using the SBR, BIR impulsivity, compulsivity and accuracy on the 3CSRTT, and the HRV (rMSSD, LF/HF) data. Descriptive statistics are reported as mean ± standard deviation. Type I error rates were $\alpha = 0.05$.

2.8. Ethical approval

The research undertaken was granted ethical approval by the Ethics Committee at the Royal Agricultural University.

3. Results

Genotype frequencies for the groups are displayed in Table 1. The allele frequencies did not deviate from Hardy Weinberg ($\chi^2 = 0.33, P = 0.85$).

There was no significant main effect of genotype (AA, AG, GG) on inferred measures of dopamine tone (SBR [$F_{2,23} = 1.35, p = 0.279$]; BIR [$F_{2,23} < 1$]), HRV measures (rMSSD [$F_{2,23} = 1.2, p = 0.319$]; LH/HF [$F_{2,23} = 2.28, p = 0.125$]) or on any of the 3CSRT endpoints (accuracy [$F_{2,23} < 1$]; impulsivity [$F_{2,23} < 1$]; compulsivity [$F_{2,23} < 1$]). There were similarly no significant main effects of A-absent vs A-present genotype on any of the measures (*t*-tests, p 's > 0.17).

Table 2 presents a correlation matrix of all measured variables. There was a strong positive correlation between the two inferred measures of dopamine tone, SBR and BIR (Fig. 2). SBR was positively correlated with impulsivity (Fig. 2), but there was no significant correlation between BIR and impulsivity. There was a moderate positive correlation between the frequency HRV domain measure (LF/HF) and compulsive responses on the 3-CSRT (Fig. 2). There were no correlations with time domain (rMSSD) indices and any of the measured endpoints. Impulsive and compulsive responses were strongly positively correlated, and accuracy

Table 1
Allele frequencies of the DRD4 gene variant.

DRD4 gene variant		
AA	AG	GG
7	14	5

Table 2
Correlation matrix of the measured variables.

	rMSSD	LF/HF	SBR	BIR	Accuracy	Impulsivity	Compulsivity
rMSSD	—						
LF/HF	-0.133	—					
SBR	0.052	0.135	—				
BIR	0.056	0.113	0.446*	—			
Accuracy	-0.244	-0.036	-0.288	-0.030	—		
Impulsivity	0.292	0.300	0.427*	0.068	-0.724***	—	
Compulsivity	0.196	0.460*	0.368	0.105	-0.569**	0.854***	—

Note.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

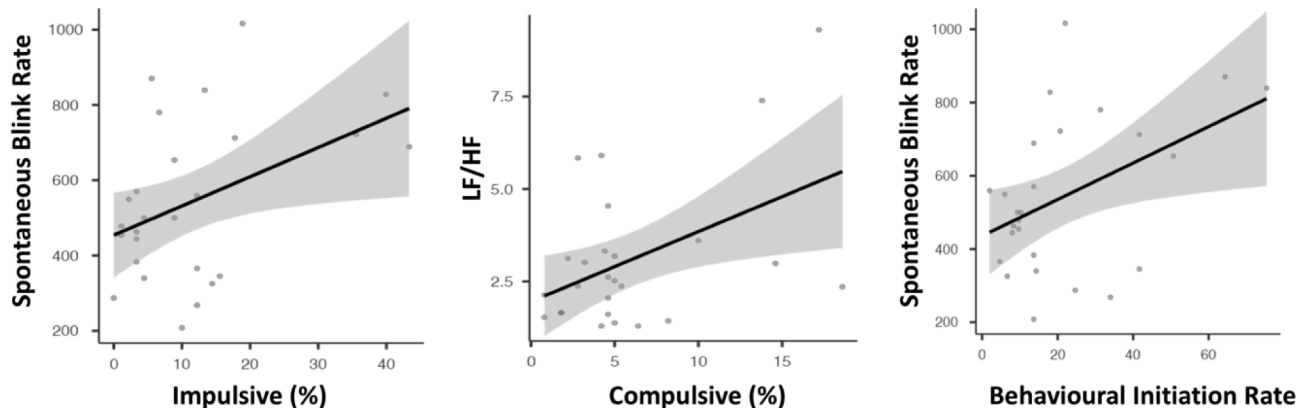


Fig. 2. Scatter plots (line of best fit \pm 95%CI) of significant correlations between variables.

was strongly negatively correlated with both impulsive and compulsive responses.

4. Discussion

The two variants of the G292A SNP (A-G substitution) were identified as previously described [50] with genotype frequencies aligning with Hardy-Weinberg equilibrium. Out of the 26 animals, 5 were A-absent for the G292A SNP group whereas 21 animals were A-present. There were no significant differences between genotypes or between A-allele present versus A-allele absent groups for any of the measured parameters. This is at odds with previous studies where DRD4 polymorphisms have been linked with increased impulsivity [54, 55] and SBR [56] but may simply reflect the low number of A-absent individuals ($n = 5$) within the sampled group making a type II statistical error more likely.

Impulsivity and compulsivity were positively inter-correlated, and both measures were negatively correlated with accuracy during the 3CSRTT. Although originally considered to be two conditions at the opposite end of the same spectrum [57], more recent statistical modeling of impulsivity and compulsivity has demonstrated substantial co-occurrence [58] with similar environmental and genetic factors driving the two conditions [59]. Across animal models, impulsivity is known to be mediated by cortico-striatal circuitry involving regions of the prefrontal cortex and striatum (nucleus accumbens, caudate/putamen) [60]. Compulsivity is mediated by similar circuitry but more recently a distinction has been made between these two forms of response inhibition with impulsivity associated with increased connectivity of the prefrontal cortex with the ventral striatum and reduced connectivity with dorsal striatum, whereas compulsivity is only associated with reduced connectivity of the prefrontal cortex and the dorsal striatum [61]. The high correlation between the two measures reported here (0.854) suggests that, in horses, there is overlap and co-occurrence

of the two psychological traits. However, the significant correlation of SBR with impulsivity but not compulsivity that was also reported suggests that there are still differences in the underlying mechanism. The correlation of central dopaminergic activity (as measured by SBR) and impulsivity in this study aligns with studies in other species (humans and rodents) [60]. Interestingly, BIR did not correlate with impulsivity but did moderately correlate with SBR. BIR has previously been used as an inferred measure of direct over indirect pathway dominance running through the basal ganglia [24] whereas SBR is considered to be a more generalised measure of central dopaminergic tone [45]. In this sense, BIR may reflect activity in dorsal (caudate-putamen) cortico-striatal loops but not be a relevant measure of the overactivation of the ventral (nucleus accumbens) cortico-striatal loops and basal levels of impulsivity [60].

Addictive phenotypes have been associated with reduced parasympathetic nervous system activity, as measured through a reduction in vagally mediated (vm) HRV [1]. Here, we predicted that if an addictive phenotype was identified in the horse, via levels of impulsivity and central dopamine levels, that this would be linked with a significant reduction in vmHRV levels. The data were not conclusive in this respect, with only the frequency-domain (LF/HF) HRV parameter being significantly associated with compulsivity. These findings are at odds with pharmacological and neuroimaging studies that have shown a positive relationship between higher resting levels of HRV and the inhibitory capacity of prefrontal-subcortical circuits [62–66]. However, it should also be noted that the relationship between HRV and impulsivity [67–69] is often variable (see [2] for review) with HRV in some human clinical groups being state-dependent. For example, in patients with bipolar disorder, HRV is elevated (compared to healthy controls) during manic states but decreased during depressed states [70]. This can be explained by what is currently known about central dopamine physiology during these states with upregulation in D2/D3 receptors during the manic phase and increased striatal dopamine transporter (DAT)

reducing neurotransmitter availability during the depressive phase [71]. Further studies are thus needed to assess longitudinal transient changes in HRV alongside impulsivity/compulsivity as well as inferred measures of dopaminergic tone (SBR) in order to get a full understanding of the relationship between these parameters.

5. Conclusion

In relation the hypotheses set out in Fig. 1, DRD4 genotype did not make a significant contribution to impulsivity or compulsivity levels in the horse or explain the variance in dopamine-related parameters such as SBR or BIR, or parasympathetic/sympathetic activity. This conclusion is made with some caution due to the limited number of A-absent allele horses within the sampled population of this study. SBR, as an inferred measure of central dopaminergic tone, however, was correlated with impulsivity but not compulsivity. Impulsivity and compulsivity in the horse appear to be linked and this seems to align with current thinking about these two psychological constructs. However, the different relationship of these two measures of response inhibition with SBR also suggests that there are neurophysiological differences underlying the two conditions. There was also no clear association between HRV parameters and measures of central dopaminergic activity and impulsivity/compulsivity but more data over greater time periods may be required in order to elucidate this relationship.

Overall, some elements of the predicted model of the genetic and environmental factors producing a physiological and behavioral phenotype similar to human addiction appear to be valid, particularly the relationship between central dopaminergic tone and impulsivity. Further research is required to investigate other aspects of the model, particularly the physiological and behavioral consequences of early life stress and highly palatable food substrates and how this relates to the stereotypy phenotype.

6. Data availability statement

The data that support the findings of this study are openly available in [OFS at <https://osf.io/s5h47/files/>].

Data Availability

The data are available via an online repository. The repository link is given in the data availability statement at the end of the manuscript.

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