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Addictive Behaviors

Addictive behaviors and addiction-prone personality traits: Associations with a dopamine multilocus genetic profile

Caroline Davis [a,*], Natalie J. Loxton [b]

[a] School of Kinesiology and Health Sciences, York University, Toronto, Canada
[b] School of Psychology, The University of Queensland, Brisbane, Australia

HIGHLIGHTS

- Dopamine signaling positively influences addictive behaviors.
- Personality mediates genetic link to addictive behaviors.
- Quantitative genetics a powerful tool for risk-related research.

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ABSTRACT

The purpose of this study was to examine reward-related genetic risk for addictive behaviors in a healthy community sample (n = 217) of men and women. We tested a mediation model predicting that a quantitative multilocus genetic profile score – reflecting the additive effects of alleles known to confer relatively increased dopamine signaling in the ventral striatum – would relate positively to a composite measure of addictive behaviors, and that this association would be mediated by personality traits consistently associated with addiction disorders. Our model was strongly supported by the data, and accounted for 24% of the variance in addictive behaviors. These data suggest that brain reward processes tend to exert their influence on addiction risk by their role in the development of relatively stable personality traits associated with addictive behaviors.

1. Introduction

The estimated heritability of drug dependence and alcoholism is approximately 50%, indicating that genetic and environmental risk factors play a roughly equivalent role in their development (Buscemi & Turchi, 2011; Enoch, 2012). Moreover, the latter appears to be more influential during adolescence, while the impact of genetic factors tends to increase during the transition to adulthood (Vrieze, McGue, & Iacono, 2012). It is important to note, however, that evidence for the role of common environment on substance abuse/dependence is still relatively limited and instead, largely supports its role in substance *use* (e.g. Fowler et al., 2007; Poelen et al., 2008; White, Hopper, Wearing, & Hill, 2003).

Evidence from population-based transmission studies also suggests that *common* genetic factors contribute to the abuse of a broad range of illicit substances; and that these influences are of equal importance in men and women (Agrawal & Lynskey, 2008). Since all addictive behaviors exert their rewarding effects by increasing dopamine (DA) in the striatum – a central structure in the mesocorticolimbic brain reward pathway – genetic variations affecting the DA system have been a major target for investigating vulnerability to drug abuse (Le Foll, Gallo, Le Strat, Lu, & Gorwood, 2009). It is clear, however, that the relationships between genetic factors on the one hand, and adverse drug-related behaviors on the other, are complex and almost certainly not direct (Volkow & Muenke, 2012). Instead, genetic effects are *mediated* through many developmental processes including individual differences in personality – for instance, a preference for immediately available rewards – and their interaction with equally powerful environmental factors such as exposure to addictive behaviors (Gorwood et al., 2012). Moreover, it is especially difficult to establish causal associations between genetic variation and addiction disorders because they typically develop over a period of time. Therefore, the factors that contribute to initial engagement in the behavior may be quite different from those contributing to its compulsive use and treatment resistance (Dawe & Loxton, 2004).

1.1. Addictive personality

For decades, and across a variety of disciplines, the concept of an '*addictive personality*' has been discussed and debated (e.g. Berglund et al., 2011; Eysenck, 1997; Lester & Narkunski, 1978; Nathan, 1988;

* Corresponding author at: 343 Bethune College, York University, 4700 Keele Street, Toronto, ON, M3J 1P3. Tel.: +1 416 736 2100x77327; fax: +1 416 923 3067.
E-mail address: cdavis@yorku.ca (C. Davis).

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VanKaam, 1965). During this time, the principal strategy for identifying whether there is indeed a set of etiologically significant and enduring traits that predispose to addiction has relied largely on empirical methods. For example, various psychometric measures have been developed by selecting items from extant personality tests that differentiate those with drug addictions from non-affected control subjects. The first prominent example was the *MacAndrews Alcoholism Scale* (MacAndrew, 1965) based on discriminating items from the *Minnesota Multiphasic Personality Inventory*. Problematic, however, has been the evidence of a pronounced sex bias to this scale (Kagan & Albertson, 1986). The *Addiction Scale* of the *Eysenck Personality Inventory-R* (Eysenck & Eysenck, 1975) has had better psychometric success. It comprises items that differentiated ($p < 0.001$) those with drug addictions from normal controls, and which collectively reflect elevated levels of emotional reactivity, proneness to stress, impulsivity, and negative affect (Gossop & Eysenck, 1980). Since its development, this scale has also been successfully validated with groups of problem drinkers (Ogden, Dundas, & Bhat, 1988), pathological gamblers (Clarke, 2003), and compulsive overeaters (Davis et al., 2011; Lent & Swencionis, 2012), all of whom demonstrated significantly elevated scores compared to the general population.

1.2. Quantitative genetics

Recognition, over the past several years, that complex traits and behaviors are influenced by multiple genes has prompted the view that common disorders are more appropriately considered in quantitative terms – as opposed to discreet qualitative entities – whereby their relevant genetic variants can be aggregated into composites that reflect a polygenic liability (Plomin, Haworth, & Davis, 2009). The value of this perspective is strengthened by evidence that individual polymorphic loci normally contribute only a small proportion of phenotypic variance, and their independent effects typically do not reach statistical significance, especially in relatively small clinical samples where the population prevalence of a disorder is low (Nikolova, Ferrell, Manuck, & Hariri, 2011). A quantitative genetic approach has been used successfully, for example, in a study which identified the aggregated effect of multiple DA single nucleotide polymorphisms (SNPs) associated with sensation-seeking behavior (Derringer et al., 2010). Recently, Nikolova et al. (2011) extended this research in an innovative direction. They were the first to use a biologically informed "multilocus genetic profile (MLGP) score" – a composite measure comprising multiple *functional* polymorphic DA markers, which individually had been associated with variation in striatal DA signaling – to demonstrate that the MLGP score accounted for a greater proportion of variance in ventral striatum reactivity than did each locus considered independently. Specifically, they employed a card guessing game including a monetary reward, with the aim of strongly engaging the ventral striatum so that variation in the responsiveness of this brain area could be recorded via functional magnetic resonance imaging (BOLD fMRI) and correlated with genetic-marker data.

1.3. The present study

The aim of the present study was to employ the novel MLGP procedure described by Nikolova et al. (2011) to assess its association with addictive behaviors in a non-clinical sample of adults. Following the arguments of Plomin et al. (2009) – that disorders can be interpreted as the extremes of quantitative dimensions – and based on clinical evidence that addictive behaviors are linked and do not tend to occur singly in individuals (Haylett, Stephenson, & Lefever, 2004), we employed an aggregated measure of engagement in a variety of addictive behaviors. We also used a statistical methodology that allows us to test a theoretical mediation model (see Fig. 1) predicting that genetic variability related to DA signaling strength renders its influence on addictive behaviors via its positive association with addiction-prone personality traits. The advantage of employing this mechanism-based genetic-risk approach in healthy adults is that our findings are not confounded by the presence of an existing addiction disorder. This is important given the well-established neuro-adaptations – such as down-regulation of receptor activation – and the consequent psychobehavioral changes associated with abuse of DA-stimulating activities and substances (Koob & Simon, 2009).

2. Methods

2.1. Participants

Adults (women = 158 and men = 59) between the ages of 24 and 47 years took part in the study. Eighty percent of the sample was Caucasian and 15% was of African descent. Participants were required to be fluent in English and to have lived in North America for at least five years prior to their enrolment. Exclusion criteria included a current diagnosis of any psychotic disorder, substance abuse, alcoholism, or a serious medical/physical illness such as cancer, heart disease, or paralysis. Participants were recruited from posters placed at universities, local hospitals, and other public institutions. Advertisements were also placed in local newspapers and online sites like CraigsList. The procedures employed in this study were approved by the university Research Ethics Board, and were carried out in accordance with the Declaration of Helsinki. As an initial step in the screening procedure, a short telephone interview was carried out to confirm basic eligibility criteria.

2.2. Measures

2.2.1. Multilocus genetic profile (MLGP)

Multilocus genetic profile (MLGP) scores were based on six known DA-related polymorphisms, all of which have been linked to functional changes in brain DA transmission and/or responsiveness of the ventral striatum. According to the scoring method used by Nikolova et al. (2011), genotypes associated with relatively increased striatal DA signaling strength were given a score of 1; those associated with relatively low signaling a score of 0; and in the case where a genotype is associated with intermediate signaling strength, a score of 0.5 was given. The MLGP score for each participant is then the sum of his/her score at each of the six loci, with a possible range from 0 to 6 (Table 1).

Taq1A is a C/T SNP (rs1800497) located in the ankyrin repeat and kinase-domain containing 1 gene (ANKK1), downstream of the DRD2 region on chromosome 11. Relative to the T (A1) allele, the C (A2) has been associated with relatively increased DA signaling (Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991) and increased striatal glucose metabolism (Noble, Gottschalk, Fallon, Ritchie, & Wu, 1997) due to the relationship of the A1 allele with reduced D2 receptor binding affinity (Noble, 2003) and lower striatal receptor densities (Jonsson et al., 1999). The A1 allele is frequently reported to be inherited dominantly, so both the A1/A1 and A1/A2 genotypes were given a score of 0 (Lawford et al., 1997; Voisey et al., 2012.)

−141C Ins/Del is a SNP (rs1799732) located in the promoter region of DRD2. The DelC minor allele has been associated with significantly less promoter activity and protein expression of DRD2 (Arinami, Gao,

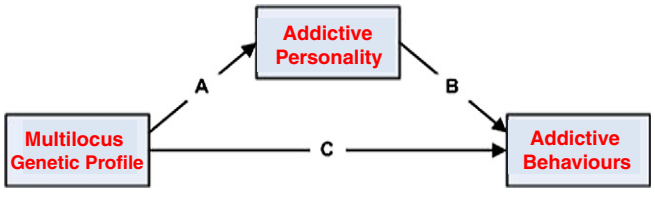

Fig. 1. Mediational path diagram for relationships among a *multilocus genetic profile*, *addictive personality traits*, and a composite measure of *addictive behaviors*.