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Research Article

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Keywords

Disorganized attachment: caused by abusive treatment of the child by the part of the primary caregiver; child displays fear and disorientation in the context of separation and stress

DRD4: A G protein-coupled receptor activated by the neurotransmitter dopamine; associated with psychiatric and neurological disorders

Low birthweight: defined as less than 2500 g in newborns

Endophenotype: a concept in psychiatry used to describe hereditary traits associated but not delineated by a genotype

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Preschool Children Without 7-repeat DRD4 Gene More Likely to Develop Disorganized Attachment Style

Abstract

Background: A disorganized attachment style is characterized by fearful and disoriented behaviours when a child is separated from their caregiver. Its presence is an early predictor of the later development of psychopathology, including depression. This study seeks to determine the effects of one environmental factor – the incidence of low birth weight – and one genetic factor – the presence of the long (7-repeat) polymorphism of the dopamine D4 receptor (DRD4) gene – on the development of disorganized attachment between the child and the mother.

Methods: We sampled 251 mother-child dyads from the Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) project. We measured birth weight and DRD4 genotype, and assessed attachment style using modified separation-reunion procedure.

Results: Birth weight did not have a significant effect on disorganized attachment (b=-0.001, t(230)=0.006, p=0.910). Presence of DRD4 7-repeat polymorphism had a significant negative effect on presence of disorganized attachment style (b=-1.196, t(230)=0.411, p=0.004).

Conclusion: Children without the DRD4 7-repeat allele were more likely to display a disorganized attachment style compared to children with the DRD4 7-repeat allele. This indicates that the 7-repeat allele of the DRD4 gene may serve as a protective factor against disorganized attachment.

Introduction

Overview - Attachment Theory and Psychopathology

It has long been known that the interaction between a child and his or her caregiver has a significant effect on later behavioural and psychological development. (1) In numerous studies, it has been shown that the nature of the early nurturance between caregiver and child has a significantly predictive relationship with outcomes such as infant physiological responsiveness to stressors as well as later cognitive and social development. (2-5)

The original conceptualization of attachment described an evolutionary-based, innate predisposition of the child to seek proximity to and contact with a specific caregiver, most notably when the child is frightened, tired, or ill. (7, 8) Attachment is a dyadic process whereby both the parent and the offspring provide cues and behaviours which strengthen the bond. Ainsworth's research indicated that children may be classified as having one of three primary attachment styles: secure, insecure-avoidant and insecure-resistant. (8) A fourth attachment style has emerged and has been added to this typology: disorganized attachment. (9) Children who are classified as exhibiting disorganized attachment tend to demonstrate fearful and disoriented behaviours in the context of separation and stress. This behaviour is thought to reflect the inability of these children to resolve anxiety. (9)

Disorganized attachment is an early predictor of the development of psychopathology in childhood and adolescence. (10) It is associated with externalizing behaviours such as aggression and anti-social personality types, and internalizing disorders such as depression and anxiety. (11) It has been hypothesized that children with disorganized attachment may develop particular schemas that can lead to depression, such as being overwhelmed by particular difficulties or viewing oneself as incapable when facing challenges. (12) Accordingly, recent research finds disorganized attachment to be a potential endophenotype for internalizing disorders such as adult onset depression. (13)

Environmental Factor of Interest – Birth Weight

There has been a significant amount of research conducted on the effects of fetal and infant growth on developmental outcomes. Most of this research focuses on the survival outcomes of 'at risk' infants born with lower birth weights, though research also has looked at effects of very low birth weight (VLBW) on motor, cognitive, behavioural, and emotional development. (14) Risks for later neurological impairments or behavioural problems are heightened and are widely discussed for such infants. (15-22) As well, significant differences in the behavioural and emotional self-regula-

tion of these 'at risk' infants have been reported, with findings of decreased attention, reduced positive affect, and prolonged reaction time to stimuli. (23-27)

Birth weight has been considered to reflect pressures on personal growth and stress exposure during pregnancy. There is a large body of evidence specifically examining the influence of prematurity and VLBW. Low birth weight (LBW) is defined as infant weight that is below 2500 grams while VLBW is defined as infant weight that is below 1500 grams. Children who are born before the typical gestation period of 38-42 weeks are termed preterm infants. VLBW and preterm infants are typically placed in Neonatal Intensive Care Units (NICU) after birth and are separated from their parents almost immediately. Much of the current research on birth weight and attachment has investigated infants who are either VLBW or preterm.

Interestingly, a review reports that the effects of preterm birth and VLBW are inconsistent. (23, 28) Several studies find no difference in the attachment quality between full-term and preterm infants. (29-33) One study, looking specifically at VLBW infants, finds that birthweight does not associate with attachment quality. (34) Finally, studies looking at both preterm and VLBW infants find no significant difference in attachment quality when compared to full term infants. (14, 23, 35, 36) Only three studies report positive findings, including an association between preterm birth and increased frequency of insecure type attachment. (37) The other two studies compare VLBW children to regular birth weight children, finding positive results for the association between birthweight and attachment style. (38, 39)

Birth weight exists on a continuum. A slight decrease in birth weight, even if it is still considered to be in the normal range, has been shown to predict psychopathology. (40) There exists no research which examines the association between birth weight in the normal continuum and attachment. Due to the high correlation existing between prematurity and low birth weight, it has not been possible to distinguish the effect of growth from that of shortened gestational period.

Gene of Interest - DRD4 Gene

The dopamine D4 receptor (DRD4) is critical for the cognitive and emotional processes that are sub-served by neural circuits in the prefrontal cortex. (41) The DRD4 gene and its variants affect the dopamine receptor efficiency in the brain. It is well established that the DRD4 gene is associated with a child's ability to pay attention, with variants of the gene being associated with ADHD. (42-45) Since a child's attention is an integral part of how they may react to their mother and/or guardian, researchers have begun to look into the mechanisms of how the DRD4 gene can affect the attachment between a child and a mother. The association between DRD4 polymorphisms and disorganized attachment is of particular interest.

The DRD4 gene has two functional polymorphisms: a 48 base-pair variable number tandem repeat (VNTR) in Exon III and the −521C/T polymorphism in the promoter of the gene. In the VNTR, the common functional variants range from 2 to 11 copies (46), with the most common ones seen in humans being the 4-repeat (short) and the 7-repeat (long) alleles. (47)

One of the first studies evaluating the association between disorganized attachment and the DRD4 gene found that disorganized attachment is four times more frequent among infant carriers of at least one 7-repeat DRD4 allele. (48) Additionally, in the same sample, the -521 thymine allele is associated with disorganized attachment, with a ten-fold increase in the rate in association with the 7-repeat allele of DRD4. (49) However, the -521 thymine variant does not show a significant effect without the presence of the 7-repeat allele. (49)

Out of several attempts, few studies have replicated the significant association between the 7-repeat allele of the DRD4 gene and disorganized attachment. Since 2001, five studies have reported that the 7-repeat allele is not significantly associated with disorganized attachment in children. (50-54) Two studies report positive results, with one based on the same original sample. (48, 49, 55, 56) Collectively, with the exception of one study, all positive results showing association between the 7-repeat allele with disorganized attachment have been from the same sample of infants. (48, 49, 56, 55)

Hypothesis

Given the inconsistent findings concerning the association between birth weight and the development of disorganized attachment between the child and mother, the current research seeks to confirm that there is no association between birth weight and disorganized attachment. Additionally, it is predicted that the DRD4 receptor gene polymorphisms would serve as a risk factor and have a positive main effect on the development of disorganized attachment between the child and mother.

Methods and Materials

The MAVAN Sample

The study sample comes from the Maternal Adversity Vulnerability and Neurodevelopment (MAVAN) project, an established cohort of mothers and children recruited between 2003 and 2009. (57) Please view the Online Supplementary Methods Page for a detailed description of the MAVAN project.

Inclusion / Exclusion Criteria

Eligibility criteria included mother's age ≥18 years at the expected date of delivery, singleton gestation, and babies born at 37 weeks or longer of gestational age. We excluded women with severe chronic illness, placenta previa, a history of incompetent cervix diagnosed in a previous pregnancy, or impending delivery of an infant affected by a major anomaly.

Procedure

We followed the women during pregnancy. Birth outcomes were assessed at time of delivery. Mothers and their child were seen at 6, 12, 18, and 24 months and yearly subsequently.

Measures (Independent)

Birth weight: Adjusted using Canadian normative data.
Genotype: We coded DRD4 as 7-repeat vs. other genotypes from oral-buccal swab samples.

Measures (Dependent)

Attachment Style: We administered the modified separation–reunion procedure as previously described for preschool-age children. Administration occurred at 36 months, from which Disorganized classification (D) was obtained. (58)

Measures (Adjustment – Covariates)

Child: gender

Maternal: We obtained maternal education from a prenatal questionnaire and trichotomized (Table 1). (59)

Analysis

We present descriptive data for child and maternal variables. Univariate analyses examined the association between predictors, covariates, and disorganized attachment. We conducted a logistic regression model to test for the independent effects of the predictors.

Results

Descriptive

There was an almost equal distribution of boys and girls. For DRD4, 34.6% were carriers of at least one 7-repeat allele, while 65.4% were not. For disorganized attachment, 22.9% were categorized as disorganized, while 77.1% were not. The distribution of mothers included 15.6% with a high school degree or a partial college education, 32.0% with a college degree or some university education, and 52.4% with at least a university degree (Table 1).

Covariates

Males and females did not differ in their distributions of disorganized attachment, (χ^2 (DF = 1, N = 231) = 0.557, p = .455) (Table 2). The frequency of disorganized attachment in children differed according to their mother's education status. (χ^2 (DF = 2, N = 231) = 18.99, p = .000).

Environmental Factor of Interest – Birth Weight

Birth weight was not significantly associated with the development of disorganized attachment, ((DF = 1, N = 231) = 0.113, p = 0.738) (Table 2).

Gene of Interest - DRD4 Gene

The genotype was significantly associated with disorganized attachment, (χ^2 (DF = 1, N = 231) = 9.47, p = 0.02) (Table 2). Children without the 7-repeat allele were significantly associated with the development of disorganized attachment (Fig. 1). Children with the 7-repeat allele were 0.31 times as likely to develop disorganized attachment style when compared to children without the 7-repeat allele (Table 3).

Adjusted Analyses

Given that maternal education was found to be a significant covariate, a Logistic Regression Test was used to assess whether the associations were independent of the covariates. Birth weight remained unassociated with the development of disorganized attachment, (b = -0.002, p = 0.998) (Table 3). On the other hand, DRD4 genotype was still significantly associated with the development of disorganized attachment, (b = -1.120, p = 0.004).

Discussion

Birth weight did not have a significant effect on attachment type. This result is consistent with the majority of prior research on preterm/VLBW and attachment. It should be noted that one key distinction of our study is that birth weight percentile was used instead of length of term (preterm) or birth weight (VLBW). Prior literature has been limited by an inability to determine whether the birth weight of recorded infants was small due to actual low birth weight or simply because of prematurity. To ensure results were clear in the present study, infants who were born prior to 37 weeks of gestational age were excluded from the MAVAN sample.

Consistent with our second hypothesis, we found the DRD4 7-repeat polymorphism to be significantly associated with disorganized attachment. Contrary to expectations, results indicate that children with the DRD4 7-repeat allele are less likely to have disorganized attachment than children without the DRD4 7-repeat allele. Although statistical significance was achieved, the direction of the association was unexpected and opposite to our originally hypothesised relationship.

Our finding that children with the DRD4 7-repeat allele were less likely to have disorganized attachment is consistent with only one study. (55) In a sample including children with maltreatment, child maltreatment was found to interact with the DRD4 genotype to predict disorganized attachment. The researchers found that at 12 months of age, the maltreated group who received experimental intervention (but not the maltreated children who did not receive intervention nor the normal control group) showed an association between DRD4 genotype and disorganized attachment. They found that children in this group who had the 7-repeat allele were less likely to display disorganized attachment as only 17.5% of those showing disorganized attachment had the 7-repeat allele while 82.5% of those showing disorganized attachment lacked the 7-repeat allele. While a sample examining maltreated children is very different from the MAVAN sample, this does provide intriguing reinforcement of the results found in this study. It should be noted that the children tested in this group were tested again at 2 years of age, and the results were not replicated. We note this to be the only other example of the DRD4 7-repeat allele being negatively associated with disorganized attachment. However, complementary findings indicate the 7-repeat allele may act as a protective factor very early in infancy (1–2 months of age) suggesting that the DRD4 7-repeat allele is associated with an easy temperament and more adaptive behaviour. (60 -62)

While much of the attention in prior research has been on the negative implications of the DRD4 7-repeat allele, very little focus has been on the positive aspects. Previous research commonly emphasizes the cumulative negative effects of specific "risk genes" and an adverse rearing environment, whereas potentially cumulative positive effects of the same risk genes interacting with positive rearing environments remain understudied. (54, 63) Accordingly, a theoretical construct of 'differential susceptibility' has been tested to examine whether children with the "risk genes" are more susceptible not only to the effects of adverse environments, but also the beneficial effects of supportive rearing. (64, 65) The DRD4 could potentially operate as one such susceptible gene with meta-analytic findings providing validation. (63, 66) For example, children with the DRD4 7-repeat allele exposed to unresponsive maternal care displayed more externalizing behaviour problems than children without the DRD4 7-repeat allele, but children with the DRD4 7-repeat allele exposed to responsive maternal care showed the lowest levels of externalizing problem behaviour. (54)

In some instances, it may be the case that the DRD4 7-repeat allele does indeed function as a protective factor. Considering the 7-repeat allele originated as a rare mutation whose frequency increased in human populations by positive selection, there has arisen increased speculation about its contribution to the evolution and adaptability of human development. (41, 67) Such a possibility supports the need to go beyond the common labelling of the DRD4 7-repeat allele as merely a risk factor for various internalizing and externalizing disorders. – it may well have protective properties.

Our results support that such an influence may exist between the DRD4 7-repeat allele and disorganized attachment. It is well established that the 7-repeat allele is associated with ADHD and decreased attention. (42-45) Lower dopaminergic signalling impedes negative feedback-based learning and is associated with stronger preference for immediate reinforcers. (68, 69) However, this may be advantageous or disadvantageous depending on specific environmental characteristics. (70) In our study sample, infants with the 7-repeat allele were less attentive to their environment and the parenting style of their caregivers during early years; this genotype may thus serve as a protective factor. However, conclusions as to why this might occur cannot be deduced until maternal sensitivity is measured alongside this genotype.

From the contradictory results accumulated for both birth weight and DRD4 genotype in terms of attachment, it is clear that several factors are at play. It is important that gene x environment interaction studies with various different factors are conducted. Rates of disorganized attachment are high when compared to other endophenotypes, reaching a frequency of one in six children in low-risk populations. Having significant numbers of a population exhibit endophenotypes for any type of psychopathology is not only a psychological problem for the individual, but also poses a significant social and economic challenge. The burden of assisting those with depression and other psychopathologies put strain on our social service and health care resources. Such challenges can be addressed by study designs which consider genetic influences, neural pathways and environmental factors potentially implicated in the mother-child relationship.

Limitations

The subsample used to test the hypotheses reflects a significant drop-out rate. Not all of the children have been genotyped or tested for attachment yet. In addition, attachment style and disorganized attachment is a very complex psychological dynamic that is likely affected by multiple different genetic and environmental factors. Several other genetic and environmental factors from both the mother's and the child's experience could have an effect with the development of disorganized attachment. When compared to other genetic studies, the MAVAN has a relatively smaller number of participants. Our power, however, is strengthened by the accuracy of our genotyping method, precise functional sub-categorization of the DRD4 allele (the presence of at least one 7-repeat allele), and the experimental measure of attachment. (71) Finally, we only examined a monogenic model. There is growing evidence for the interaction of genes (GxG) and specifically the association of DRD4 with 5HTTLPR but also with MAO. One interesting possibility, for example, would involve norepenephrine-related genes, given that norepenephrine acts in concert with dopamine to influence attentional processes and likely attachment disorganization. (72)

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Figures and Tables

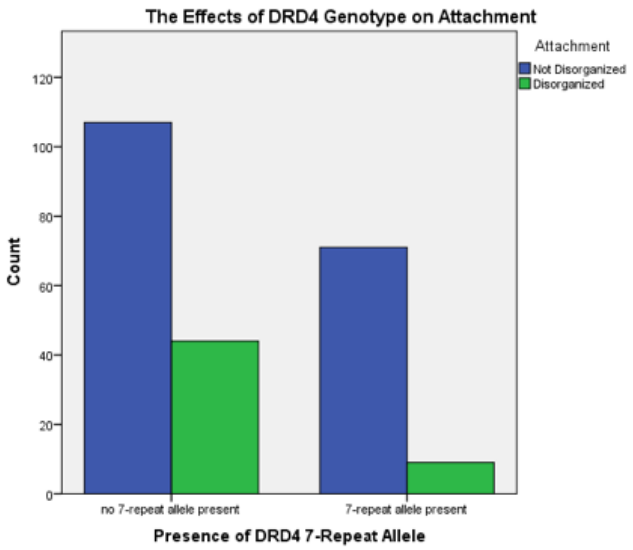

Figure 1. The Effects of DRD4 Genotype on Attachment. The darker bars represent not disorganized attachment, while the lighter colour represents disorganized attachment.

Variables	Montreal and Hamilton (N = 231) N (%)
Mothers	
Education	
High school or partial college education	36(15.6%)
Completed college degree or partial university education	74(32.0%)
University graduate degree or more	121(52.4%)
Children	
Gender:	
Male	115(49.8%)
Female	116 (50.2%)
Birth Weight (grams):	Mean: 3353.20 Std. Deviation: 467.157
Birth Weight (percentile):	Mean: 45.49 Std. Deviation: 27.987
Birth Weight:	
Low Birth Weight (< 2500 g)	6 (2.60%)
> Low Birth Weight (> 2500 g)	225 (97.4%)
Genotype DRD4:	
Presence of at least one 7-repeat allele	80(34.6%)
No 7-repeat allele	151(65.4%)
Attachment:	
Disorganized	53(22.9%)
Not disorganized	178(77.1%)

Table 1. Demographic Characteristics of subjects from MAVAN

	Mean	Disorganized N (%)	X^2	T-test	DF	Sig
Birth weight (percentile)	45.49			0.113	229	0.738
Disorganized	45.79					
Not disorganized	44.47					
DRD4			9.47		1	0.02
7-Repeat Allele		9 (3.9%)				
Other Allele		44 (19%)				
Gender			0.557		1	0.455
Male		29 (12.6 %)				
Female		24 (10.4 %)				
Maternal education			18.99		2	0.000
High school or partial College education		18 (7.80%)				
Completed college or partial University education		10 (4.30%)				
University graduate degree or more		25 (10.8%)				

Table 2. The prediction of Disorganized Attachment from birth weight and DRD4 – Univariate analysis

Predictors	B	SE	Exp(B)	Odds Ratio	Confidence Interval (95%)	Sig.
Birth weight (percentile)	-0.002	0.006	1.363			0.998
DRD4	-1.120	0.402	0.326	0.308	0.142-0.671	0.004
Covariates						
Maternal Education	-0.521	0.213	0.594			0.014
Gender	0.310	0.327	1.363	1.26	0.683-2.34	0.344

Table 3. The prediction of Disorganized Attachment from birth weight and DRD4 using a logistic regression model

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