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DRD2 and *SLC6A3* moderate impact of maternal depressive symptoms on infant cortisol

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ABSTRACT

Both maternal depressive symptoms and infants' dopamine-related genetic characteristics have been linked to infants' hypothalamic-pituitary-adrenal (HPA) functioning. This study investigated the interactive influence of maternal depressive symptoms and infant *DRD2* and *SLC6A3* genotypes on infant cortisol reactivity; whether this interaction reflects diathesis-stress or differential susceptibility; and whether this interaction influences the flexibility of the infant cortisol response across challenges known to exert differential effects on infant cortisol reactivity. A community sample of 314 mother-infant dyads participated in toy frustration (age 16 months) and maternal separation (age 17 months) challenges, and salivary cortisol was collected at baseline, +20, and +40 min. Maternal depressive symptoms were assessed with the Beck Depression Inventory-II at infant age 16 months. Infant buccal cells were collected at both time points for genotyping. *DRD2* and *SLC6A3* genotypes moderated the relation between maternal depressive symptomatology and infant cortisol reactivity in a diathesis-stress manner in the context of toy frustration, and in a differential susceptibility manner in the context of maternal separation. Higher levels of maternal depressive symptoms predicted reduced cortisol flexibility across challenges for infants with at least one A1 allele of *DRD2* and infants with the 10/10 genotype of *SLC6A3*. Results suggest that maternal depressive symptomatology is related to infants' cortisol reactivity and to the flexibility of that reactivity across psychosocial challenges, but this relation is dependent on the infant's genetic characteristics.

1. Introduction

Infant exposure to maternal depression (Brennan et al., 2008) and depressive symptoms (among non-clinically depressed mothers, Laurent et al., 2011) are associated with dysregulated hypothalamic-pituitary-adrenal (HPA) function, a biobehavioral vulnerability for subsequent depressive symptomatology (Halligan et al., 2007). Specifically, prenatal and postnatal maternal depression (Brennan et al., 2008; Feldman et al., 2009) and depressive symptomatology (Laurent et al., 2011), as well as the insensitive parenting associated with depressive symptoms (Albers et al., 2008; Hatzinikolaou and Murray, 2010), are linked to infant cortisol dysregulation (although findings are not entirely consistent; e.g., Brennan et al., 2008; Luijk et al., 2010). Such dysregulation is characterized by elevated levels of cortisol (Azak et al., 2013), but, after repeated overstimulation, the HPA-axis may become hyporesponsive to psychosocial and acute stress (Fernald et al., 2008; Gump et al., 2009).

An infant's genetic characteristics also influence HPA function. Genes related to dopaminergic function may be particularly relevant, given that i) neonates of depressed mothers have lower dopamine levels (Diego et al., 2004), ii) dopamine is critical to the pathophysiology of depression (Dunlop and Nemeroff, 2007), and iii) dopamine influences the medial prefrontal cortex (mPFC) and amygdala, which regulate HPA functioning (Zhang et al., 2005). Accordingly, dopamine-related genes may moderate the degree to which HPA function is influenced by the caregiving environment (Bakermans-Kranenburg et al., 2008). However, the nature of this moderation is unclear. Here we assess two models of interaction, diathesis-stress and differential susceptibility.

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The diathesis-stress model suggests that genetically "vulnerable" children experience the worst outcomes if reared in impoverished environments. In contrast, the differential susceptibility model suggests that genetically "susceptible" children experience both the worst outcomes if reared in impoverished environments and the best outcomes if reared in enriched environments (Belsky and Pluess, 2009). Interestingly, both diathesis-stress and differential susceptibility may operate for the same gene x environment (GxE) interaction but within different contexts (e.g., Roisman et al., 2012; Dalton et al., 2014), i.e., a particular gene may interact with a particular environmental factor in one way in the context of one challenge and in another in the context of a different challenge. Research pertinent to how differential context associates with diathesis-stress or differential susceptibility is extremely rare, such that it is impossible to make specific hypotheses in this regard.

Here we assess influences of the dopamine transporter *SLC6A3* and dopamine D2 receptor *DRD2* genes, selected a priori on the basis of associations with HPA functioning (Belda and Armario, 2009; Alexander et al., 2011), diathesis-stress (Laucht et al., 2007; Propper et al., 2008), and differential susceptibility (Bakermans-Kranenburg and van IJzendoorn, 2011). A 40-base pair VNTR downstream of *SLC6A3* alters the density of the dopamine transporter protein in vitro differentially based on the presence of 9- or 10-repeat alleles. The 10-repeat allele, and 10/10 genotype specifically, is associated with dysregulated HPA function (Alexander et al., 2011) and heightened susceptibility to environmental influences with respect to several outcomes linked to HPA function (e.g., externalizing problems, Kahn et al., 2003; Sonuga-Barke et al., 2009). The *DRD2* gene is localized to chromosome 11q23 and the single nucleotide polymorphism rs1800497 (Taq1A) involves a C to T substitution. The presence of an A1 allele is associated with dysregulated HPA function (Belda and Armario, 2009) and heightened susceptibility to environmental influences with respect to several outcomes related to HPA function (e.g., affective problems, respiratory sinus arrhythmia; Mills-Koonce et al., 2007; Propper et al., 2008). Thus, maternal depressive symptoms may impact HPA function the most in infants carrying an Al allele of *DRD2* and in infants with the 10/10 genotype of *SLC6A3* (Belsky and Pluess, 2009).

Current statistical guidelines for assessing diathesis-stress/differential susceptibility bin alleles in groups of susceptibility genotypes (e.g., A1/A2 and A1/A1 are "susceptible", but A2/A2 is "resilient", Bakermans-Kranenburg and van IJzendoorn, 2011), a practice that unjustifiably assumes allele dominance in cases of heterozygosity. To address this potential ambiguity, we repeat analyses for both genes without "binning", i.e., by tallying the number of susceptibility alleles (so that, e.g., A1/A1 genotypes are most susceptible, followed by A1/A2, with A2/A2 being least susceptible).

In addition to diathesis stress and differential susceptibility, we examine intra-individual, between-challenge cortisol variability (Laurent et al., 2012; Atkinson et al., 2013). We incorporated two challenges known to provoke differential cortisol responsivity, the toy frustration procedure (TFP, maternal denial of access to an attractive toy; Braungart-Rieker and Stifter, 1996), and the strange situation procedure (SSP, mother-infant separation paradigm; Ainsworth et al., 1978). Atkinson et al. (2013) found that infants typically responded to the TFP with a *decrease* in cortisol secretion, attributed to the probability that infants came to the procedure with anticipatory anxiety but they downregulated in the context of the nonstressful TFP. By contrast, the SSP provoked an increase in cortisol secretion (Atkinson et al., 2013; Fig. 1). Atkinson et al. (2013) found further that infants of more sensitive mothers showed more robust cortisol decreases in the TFP, and more robust increases in the SSP, than did the infants of less sensitive mothers. Based on these findings, Atkinson et al. (2013) argued that healthy HPA function involves flexible reactivity, with cortisol response titrated to challenge. To our knowledge, intra-individual, between-challenge cortisol variability has not been examined in relation to maternal depressive symptoms or infant genotype.

Thus, the aims of this study were threefold. (i) We assessed the hypothesis that infant *DRD2* and *SLC6A3* genotypes moderate the relation between maternal depressive symptoms and infant cortisol reactivity. (ii) We assessed diathesis-stress and differential susceptibility models for each of these genetic markers in the context of differentially effective challenges, the TFP and SSP. (iii) Based on the discrepant effectiveness of the TFP and SSP, we assessed influence of GxE interactions on flexibility of cortisol response. In this regard, we hypothesized that higher, relative to lower, maternal depressive symptoms predict reduced cortisol flexibility across challenges (i.e., less robust declines in the TFP and less robust increases in the SSP; Atkinson et al., 2013), particularly for infants carrying at least one A1 allele of *DRD2* and infants with the 10/10 genotype of *SLC6A3*.

2. Methods and materials

2.1. Participants

A community sample of 314 demographically low risk mother-infant dyads (52% male infants) was recruited through postings in community centers and in-person visits to activity centers in Toronto (Atkinson et al., 2013). This study examines data collected when infants were 16 (M = 15.97; SD = 1.34) and 17 (M = 17.25; SD = 1.92) months. Maternal age at the 16-month visit ranged from 21 to 46 years (M = 32.94; SD = 4.51). Median family income was $114,000–149,999Canadian (25th and 75th percentiles were $92,000–113,999 and $150,000–199,999). Mothers self reported their highest level of education as primary (n = 3, 1%), secondary (n = 24, 7.7%), community college (n = 70, 22.4%), university (n = 149, 47.8%), and post-graduate degree (n = 66, 21.2%). Eleven mothers (4.5%) were smokers. Most (95%) mothers were in a relationship. Number of hours in out-of-home care ranged from zero to 35 (Median = 2, Interquartile Range = 8). Participants self-reported their ancestry as Caucasian (n = 229, 74.8%), Asian (n = 26, 8.5%), African American (n = 11, 3.5%), Hispanic (n = 7, 2.2%) and Other (including Mixed, East Indian, Middle Eastern, Persian; n = 41, 13.06%).

2.2. Procedure

The Research Ethics Boards at the Centre for Addiction and Mental Health and Ryerson University granted approval for this study and all procedures were performed in accordance with relevant guidelines. At infant age 16-months, two female experimenters observed the mother and infant in the home, coordinated the TFP, and administered maternal inventories. The SSP was conducted at 17 months in the laboratory. At the end of each visit, buccal cells were collected. Saliva was collected at baseline, 20, and 40 min post TFP and SSP. All visits commenced between 0900 h and 1000 h; morning cortisol collection is recommended for infants so as to exclude the confounding influence of naps, irregular feeding times, etc. (Goldberg et al., 2003).

2.3. Measures

2.3.1. Maternal depression

The Beck Depression Inventory-II (BDI-II, Beck et al., 1996) is commonly used to assess the presence and severity of depressive symptomatology in mothers sampled from the community (e.g.,