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Oxytocin and vasopressin hormone genes in children's externalizing problems: A cognitive endophenotype approach

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ABSTRACT

Externalizing problems are among the most common mental health problems of children. Research suggests that these problems are heritable, yet little is known about the specific genes involved in their pathophysiology. The current study examined a genotype-endophenotype-phenotype model of externalizing problems in 320 preschool-aged children. Markers of the oxytocin (*OXT*) and arginine vasopressin (*AVP*) hormone genes were selected as candidates owing to their known association with psychopathology in other domains. We tested whether *OXT* and *AVP* variants were related to children's externalizing problems, as well as two cognitive endophenotypes presumed to underlie these problems: theory of mind (ToM) and executive functioning (EF). Externalizing problems were assessed at age 4.5 using a previously-validated rating scale. ToM and EF were measured with age-appropriate tasks. Using a family-based association design and controlling for non-genomic confounds, support was found for an association between a two-marker *OXT* haplotype (rs2740210–rs2770378) and a two-marker *AVP* haplotype (rs1887854–rs3761249) and externalizing problems. Specific associations of these haplotypes with ToM and EF were also observed. Further, ToM and EF were shown to independently and jointly predict externalizing problems, and to partially mediate the effects of *OXT* and *AVP* on externalizing problems. This study provides the first evidence that genetic variation in *OXT* and *AVP* may contribute to individual differences in childhood externalizing problems, and that these effects may operate through emerging neurocognitive abilities in the preschool period.

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Externalizing problems are among the most common childhood mental health difficulties, with known negative consequences for adult psychiatric health (Kim-Cohen et al., 2003). Externalizing problems include *disruptive behavior* (e.g. aggression, oppositionality, and rule violations), as well as *attention/hyperactivity* problems (e.g., inattention, hyperactivity, and impulsivity; Frick and Nigg, 2012). Family, twin, and adoption studies estimate that 70–75% of the variability in disruptive behavior and attention/hyperactivity problems is genetically influenced (Faraone et al., 2005; Slutske et al., 1997). Evidence also suggests that the comorbidity between these problems is explained by genetic factors (Thapar et al., 2001). To date, most genetic studies of externalizing behavior have focused on genes of the dopaminergic, serotoninergic, and adrenergic systems (Caspi et al., 2008; Comings et al., 2000; Faraone et al., 2005). Significant effects have been reported, but the proportion of variance accounted for by individual single nucleotide polymorphisms (SNPs) is very small, on the order of around 1%. This reflects the common gap between heritability estimates and findings from molecular genetic studies (Plomin, 2013), and suggests a need to broaden the scope of gene targets for externalizing behaviors.

Two sets of genes that are gaining attention in the psychopathology literature are those of the neurohypophysial hormones oxytocin (OXT) and arginine vasopressin (AVP). These hormones are structurally similar, differing by only a couple of amino acids. The *OXT* and *AVP* genes are both located on chromosome 20, suggesting an evolutionary and perhaps functional relation (Gimpl and Fahrenholz, 2001). Behavioral associations with OXT include prosocial behavior (trust, altruism, and generosity), face perception, and the ability to infer other's mental states (MacDonald and MacDonald, 2010). Key behavioral correlates of AVP include aggression, social recognition, nonspatial memory, and attention (Caldwell et al., 2008). These cognitive and behavioral traits may underlie externalizing problems, thus justifying their focus in genetic research on these problems.

Molecular genetic evidence for a link between *OXT/AVP*, child externalizing problems, and underlying cognitive abilities comes from two primary streams of research: (i) genome-wide association studies (GWAS); and (ii) candidate gene association studies. GWAS have been

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quite limited in terms of their success in identifying genes and pathways related to children's mental health problems. In one study of children by Lasky-Su et al. (2008), only two SNPs met criteria for genome-wide significance, one in each of the CDH13 and GFOD1 genes. The former has previously been implicated in substance-abuse problems in adults (Uhl et al., 2008), while the latter is especially relevant given its links with hyperactive/impulsive traits in youth (Salatino-Oliveira et al., 2015). More recently, findings from Mick et al. (2011) demonstrated no statistically significant genome-wide associations in a sample of 6–17 year-olds on a dysregulation score from the Child Behavior Checklist (CBCL) consisting of anxious/depressed, attention, and aggressive symptoms (also see Viding et al., 2013). However, several plausible candidate genes were identified at the $p < 5E-05$ level, including two on chromosome 20, ADRA1D and PRNP. The latter of these has been implicated in cognitive abnormalities in both rodents (Criado et al., 2005; Linden et al., 2008) and humans (Croes et al., 2003; Kachiwala et al., 2005).

Pappa et al. (2015) recently used Genome-wide Complex Trait Analysis in two large samples of 3–9 year-old children and demonstrated significant SNP heritability for attention/hyperactivity problems, externalizing problems, and total problems on the CBCL. They concluded that, although the effect of individual SNPs is small, common SNPs together exert a substantial influence on children's behavioral problems. Using GWAS, Allen-Brady et al. (2009) identified a susceptibility locus for autism near the *OXT-AVP* gene region on chromosome 20. Given that autism is characterized by pronounced deficits in ToM and EF (Kimhi et al., 2014), it may be that genetic variability in *OXT* and *AVP* is associated with psychopathology through disruption of these cognitive abilities. Finally, a recent meta-analysis of over 4500 preschool children showed that 13–43% of the variance in behavior problems was accounted for by genome-wide SNPs (Benke et al., 2014). While the analyses did not yield any genome-wide signals, it was suggestive of a specific association with the *PCSK2* gene, which is also located on chromosome 20. It is interesting to note that enzymatic activity of PCSK2 is involved in processing pro-vasopressin and pro-oxytocin into AVP and OXT, respectively (Gabreëls et al., 1998; Hardiman et al., 2005). These genome-wide findings provide suggestive evidence for a role of *OXT*/*AVP* in the pathogenesis of child psychopathology and underlying cognitive mediators.

Additional evidence for the involvement of the OXT-AVP system in human behavior comes from candidate gene studies that posit particular relationships between specific genes and phenotypes. In general, these studies have reported links with a variety of psychopathological phenotypes. For instance, *OXT* marker rs2740210 has been linked to postpartum depression (Jonas et al., 2013) and schizophrenic symptomatology (Souza et al., 2010) in adults, as well as childhood-onset mood problems (Strauss et al., 2010) and aggression/callous-unemotional traits (Beitchman et al., 2012). *OXT* rs2770378 has been linked to symptoms of autism, including language impairment and restrictive behavior (Hovey et al., 2014). For *AVP*, the rs3761249 marker has been associated with childhood-onset aggression (Malik et al., 2014), as well as risk of schizophrenia (Teltsh et al., 2012) and childhood-onset mood disorders (Dempster et al., 2009). Thus, emerging evidence suggests that genetic variants of both *OXT* and *AVP* are associated with a range of psychopathological conditions in children and adults. The current study extends this work to consider externalizing problems in young children.

The neurodevelopmental correlates of *OXT* and *AVP* may not be exclusive to externalizing problems. One explanation for these broad genetic effects is that *OXT* and *AVP* operate on diverse phenotypes through common endophenotypes that characterize several conditions (Gottesman and Gould, 2003). This is consistent with the Research Domain Criteria (RDoC) initiative of the National Institute of Mental Health, which highlights the importance of identifying genomic aspects of endophenotypes as a means of explicating the genetic architecture and etiology of mental health conditions across the lifespan (Cuthbert, 2014). Accordingly, an additional aim of this study is to examine the link between *OXT*/*AVP* variability and discrete endophenotypes that may underlie externalizing problems. Two endophenotypes for children's externalizing problems are theory of mind (ToM) and executive functioning (EF). ToM is the ability to understand the behavior of other people by inferring the emotions, beliefs, desires, and intentions that motivate behavior. EF reflects a collection of cognitive abilities involved in goal-directed action and problem-solving, such as working memory, inhibition, and cognitive flexibility. Problems in these domains have serious implications for children's psychosocial functioning. Indeed, several studies suggest that deficits in ToM and EF contribute to externalizing problems specifically (Fahie and Symons, 2003; Farrant et al., 2014; Hughes and Ensor, 2006; Olson et al., 2011; Raaijmakers et al., 2008). Thus, these cognitive abilities may carry pathways of genetic risk to externalizing problems (i.e., serve as endophenotypic mediators).

The current study expands previous work by examining the additive and interactive effects of ToM and EF on externalizing problems with a molecular genetic study of *OXT* and *AVP*. This model proposes that variability in *OXT* and *AVP* operate on externalizing problems through ToM and EF, which implies a relationship between *OXT*/*AVP* and these cognitive skills. With respect to hormonal activity, OXT has been shown to facilitate the detection of affect from social cues and the ability to infer others' mental states—these are key indicators of ToM ability (see Gaustella and MacLeod, 2012). AVP has been related to both social information processing and basic cognitive processes such as memory and attention (see Meyer-Lindenberg et al., 2011). Regarding genes within the OXT-AVP network, two prior reports by Wade et al. (2014a, 2015) demonstrated that variability in the OXT receptor gene (*OXTR*) was associated with children's social cognition and ToM, and another showed that variability in the AVP receptor 1A gene (*AVPR1A*) was associated with EF (Wade et al., 2014b). Molecular genetic studies of the genes encoding the OXT/AVP hormones themselves are extremely sparse (Ebstein et al., 2012; Meyer-Lindenberg et al., 2011). Hovey et al. (2014) recently showed that *OXT* rs2770378 was associated with language impairment in 9–12 year-old females with autism, while Bisceglia et al. (2014) showed that *AVP* rs3761249 was associated with behavioral inhibition in children as young as 18 months. Finally, *OXT* rs2740210 has been associated with positive maternal behavior, including infant-directed vocalizations, instrumental care, and breastfeeding duration (Jonas et al., 2013; Mileva-Seitz et al., 2013). This is interesting given that these parenting behaviors have been linked with mothers' own executive and mentalization skills (Deater-Deckard et al., 2012; Ensink et al., 2016). Thus, as with the GWAS literature, these candidate gene studies provide indirect evidence for an association between *OXT* and *AVP* SNPs and cognitive functioning. The current study is the first to directly assess the relationship of these genes with ToM and EF in children.

To summarize, the current study examines a *genotype-endophenotype-phenotype* mediation model of externalizing problems in children. Specifically, we tested whether *OXT* and *AVP* hormone genes are associated with children's externalizing problems (phenotype) and with variation in ToM and EF (endophenotypes). We then test the hypothesis that genetic influences on these endophenotypes mediate the association with the externalizing phenotype.

Material and methods

Study sample

Multiparous women giving birth to infants in the cities of Toronto and Hamilton between 2006 and 2008, who had been contacted by the *Healthy Babies Healthy Children* (*HBHC*) public health program (run by Toronto and Hamilton, Ontario, Public Health Units), were considered for participation. Inclusion criteria for the Kids, Families, Places (KFP) study was: (1) an English-speaking mother; (2) a newborn weighing >1500 g; (3) one or more children <4 years old in the home;

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