Thinking and doing: the effects of dopamine and oxytocin genes and executive function on mothering behaviours

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Animal and human studies suggest that initial expression of maternal behaviour depends on oxytocin and dopamine systems. However, the mechanism by which these systems affect parenting behaviours and the timing of these effects are not well understood. This article explores the role of mothers’ executive function in mediating the relation between oxytocin and dopamine gene variants and maternal responsiveness at 48 months post-partum. Participants (n = 157) were mothers recruited in the Maternal Adversity, Vulnerability and Neurodevelopment Study, which assesses longitudinally two cohorts of mothers and children in Canada. We examined single nucleotide polymorphisms (SNPs) related to the dopamine and oxytocin systems (DRD1 rs866, DRD1 rs265976, OXTR rs237885 and OXTR rs2254298), assessed mothers’ decision-making at 48 months using the Cambridge Neurological Automated Testing Battery (CANTAB) and evaluated maternal responsiveness from videotaped interactions during the Etch-A-Sketch co-operation task. Mediation analyses showed that OXTR rs2254298 A-carriers had an indirect effect on positive parenting which was mediated by mothers’ performance on decision-making task (estimate = 0.115, P < 0.005), while OXTR rs2254298 A-carriers had both direct and indirect effects on physically controlling parenting, also mediated through enhanced performance on decision-making (estimate = −0.059, P < 0.005). Dopamine SNPs were not associated with any measure of executive function or parenting (all P > 0.05). While oxytocin has previously been associated with only the early onset of maternal behaviour, we show that an OXTR polymorphism is involved in maternal behaviour at 48 months post-partum through mothers’ executive function. This research highlights the importance of the oxytocin system to maternal parenting beyond infancy.

Keywords: CANTAB, decision-making, dopamine, Etch-A-Sketch, executive functions, mediation, oxytocin, physically controlling parenting, positive parenting, SNP

Mothering is a dynamic and complex process, relying on myriad skills and multiple systems interacting as the mother develops and hones parenting skills to meet the challenges inherent to child development. Much research has been conducted to understand the biological systems that underlie adaptive and sensitive parenting. While animal and human studies suggest that some components of maternal behaviour depend on the oxytocin and dopamine systems, the neurocognitive mechanisms linking these biological systems with maternal behaviour are not fully understood. Oxytocin is a neuropeptide that was first characterized for its effects on parturition and milk ejection; more recently, it has been implicated in the expression of maternal behaviour in rats, sheep, rhesus macaques and humans (Feldman et al. 2012). The oxytocin system, as quantified by salivary and plasma levels of the peptide and single nucleotide polymorphisms (SNPs) in both the ligand and receptor, has also been associated with social and emotional behaviours (Feldman et al. 2012). Several reports have focused on the effects of oxytocin ligand gene polymorphisms on maternal behaviour in the early life of the infant, finding associations between oxytocin SNPs and infant-directed speech and instrumental care (Jonas et al. 2013; Mileva-Seitz et al. 2013). Oxytocin SNPs also associate with breastfeeding duration (Jonas et al. 2013; Mileva-Seitz et al. 2013). Similarly, SNPs in the oxytocin receptor gene are also implicated in maternal behaviour, associating with affectionate maternal touch (Apter-Levy et al. 2013), maternal depression (Apter-Levy et al. 2013; Mendlewicz et al. 2012) and quality of early maternal care (Feldman et al. 2013).
While the connection between early parental behaviours and oxytocin may be well established, the extent to which differences in oxytocin system function affects differences in later parenting has not been resolved.

The animal literature has broadly showed the role of oxytocin in the initiation of maternal behaviours. In rats (Fahrbach et al. 1985; Pedersen et al. 1982, 1985, 1994; van Leengoed et al. 1987), sheep (as reviewed by Kendrick et al. 1997) and mice (Rich et al. 2014), the initiation of maternal behaviour depends on the functional central oxytergic system. Although many studies have shown that oxytocin is not necessary for the maintenance of maternal behaviour (Carter et al. 1997; Fahrbach et al. 1985; Numan & Corodimas 1985; Numan et al. 2006), some work suggests that oxytocin is still important in regulating some aspects of later maternal behaviour. Pedersen and Boccia (2003) found that in rats, even after the establishment of maternal behaviour, infusions of an oxytocin antagonist reduced licking and grooming of pups, kyphotic nursing and high-arched nursing. A study on mice also found that oxytocin was required for nursing, but that no differences between oxytocin knockout mice and wild type in any other maternal behaviour were apparent (Nishimori et al. 1996). While most animal literature agrees that oxytocin is involved in the initiation but not in the maintenance of maternal behaviours, there is abundant evidence from antagonist or genetic manipulation studies that dopamine is involved in both initiation and maintenance of maternal behaviours in model species (as reviewed by Bridges 2015). Despite these studies being conducted in animals, there are similarities in the physiological processes of the initiation and maintenance of maternal behaviour between model species and humans. In addition, model species and humans are both influenced by environmental and experiential factors in the expression of maternal behaviours (as reviewed by Lonstein et al. 2015).

The dopaminergic system and polymorphisms in dopamine ligands and receptors have been implicated in impulsivity, addiction and gambling (Caldu et al. 2007; Chen et al. 2011; Comings et al. 1997; Seeger et al. 2004; Smith et al. 2008; Stice et al. 2008; Styn et al. 2009). Intriguingly, these psychopathologies involve reward circuits, which might have evolved to support social attachment and parent–child bonding (Insel 2003). Indeed, past research has already shown a link between dopamine polymorphisms and maternal behaviour in the first 6 months of life involving neurocognitive mechanisms (Mileva-Seitz et al. 2012). Specifically, maternal attention was associated with two dopamine receptor (DRD1) SNPs. Alleles in these two SNPs were associated with a decrease in the amount of time mothers spent attending to their infants. The DRD1 might influence attention towards the infant by modulating infant salience. Moreover, genes of the dopaminergic system might also influence maternal sensitivity. The SNPs in both genes encoding for COMT and DRD4 are associated with the efficiency of dopamine transmission and with decreased maternal sensitivity in mothers with high levels of daily hassles (Lee et al. 2010; van Ijzendoorn et al. 2008). Mothers with a 7-repeat DRD4 variant had increased sensitivity to fussy infants compared with mothers without the 7-repeat variant DRD4. Furthermore, differences in maternal vocalization and speaking to the infant were associated with two dopamine receptor (DRD2) haplotypes (Kaitz et al. 2010; Mileva-Seitz et al. 2012). The frequency of maternal verbal commands was also associated with dopamine transporter (DAT) polymorphisms (Lee et al. 2010). While previous research has focused on the effects of dopamine system polymorphisms on maternal behaviour in the early life of the infant, little is known about how dopamine polymorphisms might affect maternal cognition and behaviour as the child becomes more mobile, fluent and independent. As the child develops new skills and abilities, the mother must also develop her parenting skills and abilities in parallel with the child.

Previous studies on the neurocognitive processes associated with maternal sensitivity and maternal cognition have shown a link between attention and spatial working memory tasks and maternal responsiveness to their 2–6-month-old infants (Atkinson et al. 2009; Gonzalez et al. 2012). Furthermore, teen mothers with poorer performance on a cognitive flexibility task also showed lower maternal sensitivity (Chico et al. 2014). Adult mothers with greater cognitive flexibility, specifically the ability to switch attention and change strategies, displayed higher sensitivity towards their 2–6-month-old infants (Gonzalez et al. 2009). Additionally, we have found substantial associations between maternal sensitivity at 3–18 months and spatial working memory, cognitive flexibility and decision-making (A. Plamondon et al. submitted). Executive functions may represent a possible mechanism through which the oxytocin and dopamine genes affect maternal behaviours. Quality parenting necessarily involves selective attention, sensitivity and synchrony, processes that are all controlled by the mother and require attention, cognitive flexibility and decision-making (Crandall et al. 2015; Deater-Deckard et al. 2010, 2012; Rutherford et al. 2015). Executive functions, as a global construct of top-down control of inhibition, working memory, planning and problem-solving, are involved in all aspects of daily living, whether achievement-oriented, health-related or in social interactions (as reviewed by Diamond 2013). Given the importance of executive functions in social contexts, the evidence from animal studies that the maintenance of maternal behaviours is less dependent on hormones, and in particular the demands associated with child development of self-regulation and autonomy for a parent (Bridgett et al. 2015; Chang et al. 2014; Cuevas et al. 2014), we expect the relationship between maternal responsiveness and maternal executive function to become more salient during the offspring’s childhood as compared with infancy.

Both dopamine and oxytocin have been implicated in cognitive functions. Dopamine activity in the prefrontal cortex is critical for executive function, attention and cognitive flexibility (Afonso et al. 2007; Arnsten 2006; Goldman-Rakic 1998). Attention in humans is central to maternal sensitivity, and the logical question yet to be addressed is whether genetic predictors of human attentional processes are also associated with differences in maternal behaviour and responsiveness. Although not conducted with post-partum populations, polymorphisms in several dopamine receptor genes have been associated with differences in cognitive tasks, working memory and attentional function and/or in prefrontal activation (Bobb et al. 2005; Brookes et al. 2006; Caldu et al. 2007;
Lasky-Su et al. 2007; Misener et al. 2004; Ribases et al. 2012; Wilkosc et al. 2010). While dopamine has been associated with executive functions, oxytocin has been related to memory. Several studies have reported that oxytocin suppresses some types of memory in both rats (de Wied 1980; van Ree et al. 1978) and humans (Heinrichs et al. 2004; Herzmann et al. 2012; Wirth 2015). Furthermore, the likelihood that oxytocin, due to its evolutionarily ancient origins and its presence in non-social species, is involved in cognition apart from social interaction and/or cognition as a foundation of social interaction has been previously developed as a theory to explain the mnemonic effects of oxytocin (Wirth 2015). One study considered oxytocin system polymorphisms in the context of cognitive function and memory, Skuse et al. (2014) reported A-carriers of OXTR rs237887 had impaired recognition memory compared with non-A-carriers. In addition, dopamine and oxytocin are good candidate systems in the study of cognitive processes underlying maternal behaviours.

The current study

The current study aims to understand the relationship between dopamine and oxytocin SNPs, executive functions such as cognitive flexibility, working memory, decision-making, motor inhibition and maternal behaviour at 48 months post-partum. We first predicted that one of the mechanisms through which oxytocin and/or dopamine genes would affect maternal behaviour is through enhancing mothers’ executive function. We narrowed the genes of interest to the oxytocin receptor gene, known for its relation to plasma oxytocin levels, maternal behaviours and social cognition (Bakermans-Kranenburg & van IJzendoorn 2008; Feldman et al. 2012; Jonas et al. 2013; Lucht et al. 2013; Massey et al. 2015; Mileva-Seitz et al. 2013; Park et al. 2010; Slane et al. 2014; Wu et al. 2012) and the dopamine receptor 1 gene known for its relation to maternal orienting away, visuospatial working memory in human females, brain metabolism, executive functioning (Bobb et al. 2005; Misener et al. 2004; Ribases et al. 2012; Wilkosc et al. 2010) and attention-deficit (hyperactivity) disorder (Bobb et al. 2005; Mileva-Seitz et al. 2012; Misener et al. 2004; Ribases et al. 2012; Wilkosc et al. 2010). We then predicted that mothers carrying variants on the OXTR gene (rs2254298 and rs237885) that have been associated with increased empathy, positive maternal behaviours and increased plasma oxytocin, and DRD1 variants (DRD1 rs686 and DRD1 rs265976) that have been associated with less maternal orienting away, would show greater maternal flexibility and more attentiveness towards their children in a contingent and sensitive manner.

Materials and methods

Participants

Participants were part of the Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) Study, which longitudinally follows two cohorts of mothers and children in Hamilton, Ontario and Montreal, Quebec in Canada. The data in the primary analyses were restricted to the Hamilton sample, in which maternal cognitive functions were assessed. Genetic data were available for 157 participants. A partial replication was performed with the Montreal sample.

Age of mother at delivery and SES

Demographic characteristics, such as age at delivery and socio-economic status (SES), were collected during the second trimester of pregnancy with the health and well-being of mothers and their newborns questionnaire, a composite questionnaire including short validated versions of a variety of questionnaires (O’Donnell et al. 2014). The SES variable was calculated to include both income and education, with two groups represented, based on national census data (Statistics Canada 2008): 1 = low SES, low education or low SES and high education or high SES, low education; 2 = high SES, high education. Based on the national census data, low SES is defined as <$21,358 total family income after tax, while high SES is defined as >$21,359 total family income after tax. Low education is defined as less than high school graduation (Statistics Canada 2011; Wendland et al. 2014).

Edinburgh Postnatal Depression Scale

The Edinburgh Postnatal Depression Scale (EPDS) is a questionnaire with 10 items to screen for post-partum depression. The EPDS has high sensitivity (86%) and high specificity (78%) (Cox et al. 1987) and is considered the gold standard to assess maternal symptoms of depression during pregnancy and the early post-partum. Participants completed the EPDS during the second trimester and at 3, 6, 12 and 18 months post-partum. Because of the stability of the scores across time (r = 0.585–0.774, n = 191, P < 0.001), the five scores were used to compute a mean maternal depression score.

Genotyping

Participants’ DNA was collected by using buccal swabs (Epican, Madison, Wisconsin, U.S.A.). We selected SNPs based on the literature on executive function and parenting behaviours. The genotypes were determined using the Taqman assay on the ABI Prism 7000 (Applied Biosystems, Foster City, CA, USA). We tested the tagged SNPs in the dopamine receptor (DRD1 rs686 and DRD1 rs265976) and oxytocin receptor (OXT rs237885; OXTR rs2254298, both in intron 3). Genotypes were tested for Hardy–Weinberg equilibrium (HWE; calculator for two alleles) and linkage disequilibrium (LD) within the OXTR and DRD1 genes (HaploReg v2). A total of 10% of samples were genotyped. All data were checked for clustering, assay quality and blanks. Poorly performing SNPs/assays were disqualified. Our sample has over 80% power to detect an R2 of as low as 0.048, 0.040, 0.037 and 0.041, respectively, for rs2254298, rs237885, rs686 and rs265976 (taking into account their correspond- ing minor allele frequencies (MAFs), sample sizes, α of 0.05, additive genetic model and using a two-tailed analysis to detect effects in either direction) (Guadernan & Morrison 2008).

Executive function

Executive function at 48 months was assessed with the Cambridge Neuropsychological Automated Testing Battery (CANTAB, Cambridge Cognition, Ltd., Cambridge, UK). Four tests were administered on a touch-screen computer:

Motor inhibition was tested with the stop-signal task. Scores were computed as an average of the standardized scores on the proportion of time the subject was able to successfully stop and the stop-signal reaction time, which measured the average length of time the subject was able to inhibit the response in 50% of the trials. Higher scores indicate better motor inhibition.

Cognitive flexibility was tested with the intra/extra-dimensional task. Scores were obtained by reversing the standardized number of errors on the extra-dimensional shift condition. Higher scores indicate higher cognitive flexibility.

Working memory was tested with the spatial working memory task. Scores were computed as averages of the reversed standardized scores for the number of times a search strategy was used and the number of errors (visiting the same square twice within or
between searches). Higher scores indicate better usage of working memory strategies and better working memory.

Decision-making was tested with the information sampling task. Boxes opened is a measure of information gathering prior to making a decision and is the averaged standardized score on the number of boxes opened in both a fixed and decreasing points conditions. Higher scores on boxes opened indicate more information gathering and thereby better decision-making. Henceforth, decision-making ability is reflected in number of boxes opened.

**Observed parenting behaviours**

Behaviour was observed at 48 months post-partum while the mother–child dyad engaged with the Etch-A-Sketch task, which necessitates mother and child co-operation to reproduce a series of five images, increasing in difficulty. This task is useful to observe parent–child interaction in a challenging, co-operative and goal-directed activity. The mother was instructed to use only the left knob (to make horizontal lines) while the child was instructed to use only the right knob (to make vertical lines). The interaction was recorded and coded for the observed behaviours of the mother and the child on 16 scales. The scores were standardized and subjected to principle components analysis applying varimax rotations into four reliable factors: positive parenting, physically controlling behaviour, parental negativity and parental instruction, all with eigenvalues > 1. Parental instruction had low intraclass correlations for both intrarater and interrater reliability. Neither parental instruction nor parental negativity had good validity, largely because the items that comprised the factors were more reflective of mothers' general mood and not to the interactions or parenting per se. In contrast, the factors, positive parenting and physically controlling parenting, had good face validity and good cohesion. To establish the latter, we computed a mean score on the standardized scales loading on the respective factor. Both factors had good cohesion as measured by Cronbach's alpha: positive parenting (α = 0.767) explained 16.81% of the variance and physically controlling parenting (α = 0.531) explained 18.05% of the variance. The intraclass correlations for the measures included had high intrarater reliability (0.77–1.00) and higher interrater reliability (0.71–1.00).

**Positive parenting**

Positive parenting includes parent's verbal personalized approval of the child, verbal approval and encouragement of the child's actions, the extent to which the parent engages with the child to complete the task through looking, listening and reciprocity, the general atmosphere of the parent–child interaction, parental attunement to provide an atmosphere to guide the child to take on his/her own role in the task. Higher scores indicate more positive parenting.

**Physically controlling**

Physically controlling includes parent's restraint of the child, such as physically restraining the child's actions, taking over the Etch-A-Sketch or touching the right knob, as well as parent's rough-handling such as smacking, forcefully pulling or pushing or roughly removing things from the child. Higher scores indicate more physical control.

**Statistical analysis**

In the first step, data were visually inspected for normality distribution and outliers. Then, we considered correlations between variables to construct a model. We then examined the four selected SNPs for OXTR and DRD1 for each measure of executive function in a stepwise multiple regression model adjusting for basic demographics (SES and maternal age) and maternal depression. The SNPs that were significant after Bonferroni correction for multiple testing were investigated further. Each regression was confirmed with all outliers removed from analysis. Data preprocessing and multiple regression models were performed using the IBM SPSS Statistics software, version 22.

In the second step with R version 3.0.1, we ran a multiple imputation on a data set including all participants with available data for the significant SNPs using the predictive mean matching algorithm as a measure of information gathering prior to making a decision and is the averaged standardized score on the number of boxes opened in both a fixed and decreasing points conditions. Higher scores on boxes opened indicate more information gathering and thereby better decision-making. Henceforth, decision-making ability is reflected in number of boxes opened.

**Results**

**Genotypes**

All SNPs were in HWE in our sample. All SNPs were in low LD (r² < 0.20) with the other SNPs on the same gene (HaploReg v2). When groups were small (representing <5% of the sample), minor homozygotes were combined with heterozygotes to create two groups for each genotype. Table 1 summarizes the HWE, MAF and genotype data.

**Covariates**

The mean age for all mothers at delivery was 30.50 years (SD = 4.57), with a minimum of 18 and a maximum of 43 years. As testing was conducted 4 years after delivery, mothers would be between 22 and 47 years of age at the time of cognitive testing and behavioural observations. For the combined measure of SES and education, 36 women reported low income and low or high education or high income and low education while 103 women reported high income and high education. The mean score on EPDS was 6.808 (4.339) with a range of 0–21.33.
Table 1: Genotype information and participant ethnicity within each analysis

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>HWE n (%)</th>
<th>P-value</th>
<th>Genotype distributions</th>
<th>Location</th>
<th>% Caucasian</th>
<th>% Mixed or non-Caucasian</th>
<th>% Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>OXTR</td>
<td>rs2254298</td>
<td>160</td>
<td>0.417</td>
<td>11.25</td>
<td>AA = 1</td>
<td>90.4</td>
<td>4.5</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AG = 34</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GG = 125</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Intronic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OXTR</td>
<td>rs237885</td>
<td>187</td>
<td>0.611</td>
<td>49.20</td>
<td>AA = 47</td>
<td>93.6</td>
<td>5.3</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AC = 90</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Intronic</td>
<td></td>
<td></td>
<td>CC = 50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD1</td>
<td>rs686</td>
<td>214</td>
<td>0.681</td>
<td>38.32</td>
<td>AA = 80</td>
<td>84.1</td>
<td>4.7</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GA = 104</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>3'−Untranslated region</td>
<td></td>
<td></td>
<td>GG = 30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD1</td>
<td>rs265976</td>
<td>189</td>
<td>0.37</td>
<td>21.96</td>
<td>CC = 113</td>
<td>84.4</td>
<td>4.6</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GC = 69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Downstream region</td>
<td></td>
<td></td>
<td>GG = 7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Correlation matrix with cognitive and behavioural phenotypes and maternal genotypes

<table>
<thead>
<tr>
<th></th>
<th>Motor inhibition</th>
<th>Cognitive flexibility</th>
<th>Working memory</th>
<th>Decision-making</th>
<th>Positive parenting</th>
<th>Physically controlling parenting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor inhibition</td>
<td>1</td>
<td>0.81</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>−0.014</td>
<td>1</td>
<td>−0.136</td>
<td>−0.020</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td>−0.155 (P = 0.039)</td>
<td>1</td>
<td>0.113</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decision-making</td>
<td>−0.008</td>
<td>−0.149 (P = 0.017)</td>
<td>0.217</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive parenting</td>
<td>−0.127</td>
<td>−0.202 (P = 0.011)</td>
<td>0.104</td>
<td>0.298 (P = 0.011)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Physically controlling parenting</td>
<td>−0.031</td>
<td>0.216 (P = 0.001)</td>
<td>−0.121</td>
<td>−0.277 (P = 0.001)</td>
<td>−0.600 (P = 0.000151)</td>
<td>1</td>
</tr>
<tr>
<td>DRD1 rs686</td>
<td>−0.057</td>
<td>−0.101 (P = 0.044)</td>
<td>0.131</td>
<td>0.079</td>
<td>−0.049</td>
<td>−0.014</td>
</tr>
<tr>
<td>DRD1 rs265976</td>
<td>−0.013</td>
<td>−0.095 (P = 0.004)</td>
<td>0.059</td>
<td>0.114</td>
<td>0.023</td>
<td>0.002</td>
</tr>
<tr>
<td>OXTR rs237885</td>
<td>−0.028</td>
<td>−0.021 (P = 0.004)</td>
<td>−0.049</td>
<td>0.202</td>
<td>−0.078</td>
<td>0.155</td>
</tr>
<tr>
<td>OXTR rs2254298</td>
<td>−0.026</td>
<td>−0.027 (P = 0.004)</td>
<td>0.094</td>
<td>−0.291 (P = 0.004)</td>
<td>−0.006</td>
<td>−0.136</td>
</tr>
</tbody>
</table>

Data preprocessing

One subject from Hamilton was excluded as an extreme value in the behavioural measures (>3 SDs from the mean). In the stepwise multiple regression of the four genotypes on the four measures of executive function, only OXTR rs2254298 significantly predicted the decision-making variable (P = 0.004) after the Bonferroni correction. Thus, subsequent analysis focused on OXTR rs2254298. The correlations between cognitive and behavioural phenotypes and maternal genotypes support the results of the stepwise regression (Table 2).

Mediation analyses

In the Hamilton cohort, the effects of OXTR rs2254298 on positive parenting were fully mediated by decision-making (estimate = 0.115, P < 0.005). There were no significant direct effects of genotype on positive parenting (P = 0.78). In contrast, there was both a direct and an indirect effect of OXTR rs2254298 on mothers’ physically controlling behaviour, with an incomplete and inconsistent mediation by mothers’ decision-making (estimate = −0.059, P < 0.005). The direct effect of genotype on this physically controlling behaviour measure was positive, with A-carriers exerting more physical control over their children than non-A-carriers (estimate = 0.186, P = 0.03). Mediation results are summarized in Table 3 and Fig. 1.

To exclude the possibility of a moderation of genotype on the association between executive function and maternal parenting, we ran moderation models with each measure of executive function as the independent variable, genotype as the moderator and each dimension of parenting behaviours as the outcome. None of these models were significant (data not shown).

Replication

We were able to partially replicate our findings in the Montreal cohort, who did not receive executive function testing, but for whom there was both genotyping and Etch-A-Sketch behavioural observations (n = 152). We found a non-significant total effect of the genotype on physically controlling behaviour (P = 0.15) with an estimated effect size of r = 0.242. We used Fisher’s r-to-z transformation to test if the total effect sizes were comparable in both Hamilton and Montreal samples, which was indeed the case (P = 0.204), providing a partial replication of our findings (Lowry 2015).
Table 3: Mediation of genotype by decision-making on positive parenting and physically controlling parenting by model, where $ab =$ the mediated effect, $c' =$ the direct effect when the mediated effect has been partialled out and $c =$ the total effect (direct effect + mediated effect)

<table>
<thead>
<tr>
<th>Model</th>
<th>Estimate</th>
<th>95% CI (lower)</th>
<th>95% CI (upper)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OXTR rs2254298 Decision-making</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive parenting (Fig. 1a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average causal mediation effect ($ab$)</td>
<td>0.1145</td>
<td>0.032</td>
<td>0.221</td>
<td>0.01*</td>
</tr>
<tr>
<td>Average direct effect ($c'$)</td>
<td>0.0468</td>
<td>−0.260</td>
<td>0.341</td>
<td>0.74</td>
</tr>
<tr>
<td>Total effect ($c$)</td>
<td>0.1613</td>
<td>−0.150</td>
<td>0.4523</td>
<td>0.33</td>
</tr>
<tr>
<td>Proportion mediated</td>
<td>0.7097</td>
<td>−6.732</td>
<td>6.090</td>
<td>0.33</td>
</tr>
<tr>
<td>OXTR rs2254298 Decision-making</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physically controlling parenting (Fig. 1b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average causal mediation effect ($ab$)</td>
<td>−0.059</td>
<td>−0.122</td>
<td>−0.015</td>
<td>0.01*</td>
</tr>
<tr>
<td>Average direct effect ($c'$)</td>
<td>0.186</td>
<td>0.025</td>
<td>0.349</td>
<td>0.02*</td>
</tr>
<tr>
<td>Total effect ($c$)</td>
<td>0.1272</td>
<td>−0.035</td>
<td>0.291</td>
<td>0.13</td>
</tr>
<tr>
<td>Proportion mediated</td>
<td>−0.461</td>
<td>−4.626</td>
<td>2.453</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*a* $P < 0.05$.

Figure 1: Mediation of genotype by decision-making on positive parenting and physically controlling parenting by model. *$P < 0.05$; **$P < 0.001$.

Discussion

Summary of results

The OXTR rs2254298 was related to non-social decision-making, with A-carriers displaying more information gathering, measured by boxes opened, in a decision-making task than non-A-carriers. We did not find dopamine system SNPs to be related to either executive function or parenting behaviours in our sample. These null findings may be due to an underpowered analysis based on extremely small effect sizes. Conversely, it may be that other SNPs within the dopamine system are more strongly associated with executive functions and/or parenting behaviours. Furthermore, the selected SNPs may not be functional variants. Also, our tests of executive functions may not accurately reflect aspects of executive functions in which dopamine is dominant. Finally, our study includes children, rather than infants, which may place emphasis on different brain network of the mothers.

In regard to our OXTR findings, the relationship between OXTR rs2254298 and positive parenting behaviours was mediated by non-social decision-making, in whom A-carriers who displayed more information gathering in a decision-making task display more positive parenting behaviours. We also found a direct effect of OXTR rs2254298 on physically controlling behaviours, with A-carriers displaying higher levels of physically controlling behaviours. There was also a mediated relationship between OXTR rs2254298 and physically controlling behaviours, with OXTR rs2254298 predicting more information gathering in a decision-making task, which in turn predicted lower physically controlling behaviours. The analyses showed an inconsistent mediation: the OXTR rs2254298 A-carriers had increasing parental aggression towards the child as shown by increased physically controlling behaviours and also increased executive functioning during decision-making, which suppressed parental aggression of physically controlling behaviours. Thus, the mediation is inconsistent, in that the effects in the OXTR rs2254298 A-carriers were in opposite directions from the non-A-carriers: both increase physically controlling behaviours directly, but to also decrease physically controlling behaviours indirectly through increasing decision-making. The inconsistent mediation hints at the pleiotropic effects of OXTR (Meyer-Lindenberg & Tost 2012). Our results can be considered in the context of three intersecting literatures: the relationship of oxytocin to parenting behaviours, to social cognition and to aggression as well as decision-making in social interactions.

Oxytocin and parenting

Previous studies have found a relationship between OXTR rs2254298 non-A-carriers and parental behaviours, including reduced early parental care and engagement with their infants compared with rs2254298 A-carriers (Feldman et al. 2013). Furthermore, non-A-carrier mothers were more likely
to be depressed than A-carrier mothers (67% compared with 34%; Apter-Levy et al. 2013). In non-maternal participants, non-A-carriers also have an increased frequency of major depressive disorder (Mendlewicz et al. 2012). This may be partially explained by an association between non-A-carriers and lower plasma oxytocin levels (Feldman et al. 2012). Although it is important to note that plasma oxytocin levels are not central oxytocin levels, recent work shows that plasma and central oxytocin are strongly positively correlated (Carson et al. 2015). Moreover, rs2254298 genotype appears to interact with the experience of early adversity, with girls who are heterozygous (GA) having higher levels of social anxiety and depression as compared with homozygotes (Kurmsta & Heinrichs 2013). Finally, non-A-carriers have increased unipolar depression and high levels of adult separation anxiety (Costa et al. 2009). In addition, previous research consistently shows a link between A-carriers and increased parental care and involvement, possibly through differences in oxytocin levels and interaction with parental mood and early adversity. Our current findings add to this literature, showing a significant direct association between A-carriers and higher physically controlling parental behaviour towards the child and an indirect association between A-carriers and more positive parenting through higher scores on decision-making as an executive function.

Oxytocin and social cognition
Oxytocin is most often studied through intranasal administration and genetic polymorphisms in the context of social cognition, and has been linked to an array of prosocial behaviours such as empathy, generosity and co-operation (for comprehensive reviews, see Love 2014; Olff et al. 2013). In the parenting literature, higher oxytocin levels and SNPs that are thought to functionally enhance oxytocin are associated with more approach behaviours and interaction with the infant (Apter-Levy et al. 2013; Feldman et al. 2012, 2013; Mileva-Seitz et al. 2013; Wittfoth-Sbardt et al. 2012). While most research on social cognition and oxytocin uses an experimental approach with intranasal oxytocin administration, some studies have considered genotypes. Specifically, on reading the mind in the eyes task, A-carriers did not recognize positive emotional pictures as often as G-carriers (Lucht et al. 2013) and also had marginally lower verbal intelligence scores (Lucht et al. 2009). Although rs2254298 was not associated with generosity, trustworthiness or trusting behaviours in a dictator game (Apicella et al. 2010), an earlier study found a marginal association with A-carrier males and increased generosity (Israel et al. 2009). Within the context of social cognition, our results should be considered in the classic definition of maternal sensitivity, as a mother’s awareness of the child’s signals, an accurate interpretation of the signals and a prompt and appropriate response to the signals. While our measure of observed parenting is not sensitivity per se, it does invoke the components of maternal sensitivity. In this study, A-carriers, who have previously been shown to have higher plasma oxytocin levels than non-A-carriers (Feldman et al. 2012), display higher levels of physically controlling behaviours, which may relate to inaccurate interpretation of the child’s signals. A study that measured oxytocin plasma concentrations reported that low sensitivity mothers had higher baseline levels of oxytocin compared with high sensitivity mothers (Elmadh et al. 2014). A study using intranasal oxytocin administration found that women given oxytocin had lower accuracy on identifying emotions in infant faces than women who had been given a placebo (Voorthuis et al. 2014), which may be the mechanism by which higher oxytocin has been associated with lower sensitivity in our and others’ studies (Elmadh et al. 2014). However, further research is required to understand the role of rs2254298 in social cognition and whether these effects are related to higher levels of plasma oxytocin.

Oxytocin and aggression
While oxytocin has for a long time been characterized as a ‘love hormone’, more recent research now characterizes oxytocin as a ‘double-edged sword’, acting to increase some affiliative behaviours and also some aggressive behaviours. While the idea of divergent effects of oxytocin may seem irreconcilable, previous work has come to a similar conclusion with regard to attribution of emotional state in physiological arousal (Schachter & Singer 1962). Animal literature has consistently found an association between elevated oxytocin and maternal aggression (Bosch & Neumann 2012). However, other factors may also be involved in whether oxytocin increases aggression. In a factor analysis of contextual effects interacting with OXTR genetics, the factors of alcohol, provocation and ‘winning the task’ interacted with OXTR genotype to increase aggression (LoParo et al. 2016). Finally, a recent review sheds light on the importance of situational context as a factor that can moderate the effects of oxytocin (Olff et al. 2013). In situational circumstances deemed ‘safe’ by the participant, oxytocin can facilitate prosocial behaviours, whereas in situations perceived as ‘unsafe’ by the participant, oxytocin may increase the tendency towards antisocial behaviours (Olff et al. 2013). Furthermore, both situational context and oxytocin can interact with personal psychological characteristics. It is possible that some participants perceived the videotaped mother–child interaction as ‘unsafe’, thereby increasing ‘antisocial’ behaviours, such as physically controlling parenting. However, this effect of oxytocin on parental behaviour might have been tempered by higher executive functions, as shown on the CANTAB decision-making task. In addition, our results corroborate the idea of oxytocin as a double-edged sword, with A-carriers displaying increased physically controlling behaviours, better performance on a decision-making task and indirectly more positive parenting than non-A-carriers.

Social interactions as decisions
While the idea of social interactions as a series of decisions may seem a bit calculated, the interpretation of the affective state of another person requires a decision, not only on what mental state to attribute to the other person, but also on how to respond to that perceived emotion in the particular present context (Lynn et al. 2014). In this characterization of social interactions as a series of decisions, there is a close overlap with Ainsworth et al.’s (1978) description of maternal sensitivity: to perceive infant cues, to correctly
interpret them and to respond contingently. Each aspect of maternal sensitivity therefore requires a decision to attend to the child instead of some other stimuli such as the television or a smartphone. For example, a decision as to how much information in terms of child-generated cues to gather and how to interpret that information, and finally a decision on if, when or how to act on that information. While most of the experimental paradigms researching oxytocin have thus far involved a social context, our work shows that even in a non-social, non-verbal task, one oxytocin receptor SNP is associated with differences in decision-making, which may be a major root of social interactions and an important fundamental component of mother–child interactions.

Limitations
As this study was conducted in a longitudinal manner, there are some limitations inherent to longitudinal data collection, such as sample biasing due to drop outs. Here, we attempt to control for drop out by using imputed data. We found no significant differences between included participants and excluded participants in SES, age, depression scores, positive parenting or physically controlling parenting (data not shown). Also, while the SNPs selected for study have previously been associated with parenting behaviours and/or executive functions, there are no data to support a functional difference in genotypes for any of the SNPs within this study. Finally, we might have been underpowered in our analysis to detect very small but significant effect sizes, as these findings should be considered with caution. Also, our sample size is relatively modest for genetic studies, thus replication is important to substantiate these findings.

Conclusions
Previous research has shown that the oxytocin system is associated with the onset of maternal behaviour, maternal motivation and warmth, and is involved in bonding, close contact and nursing. We extend this literature by showing that the oxytocin system, through receptor polymorphisms, is involved in maternal behaviour at 48 months post-partum through executive functions. However, the relationships between oxytocin, executive functions and parenting behaviours are complex. The results suggest that an OXTR SNP related to increased oxytocin functioning is associated with improved decision-making, which in turn is associated with increased positive parenting and decreased physically controlling parenting. However, the OXTR SNP is also associated with increased physically controlling behaviour, when the variance associated with executive functions has been partialled out.

References


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