Psychoneuroendocrinology (2015) 58, 23—32

Available online at www.sciencedirect.com

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The association between 2D:4D ratio and cognitive empathy is contingent on a common polymorphism in the oxytocin receptor gene (*OXTR* rs53576)

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Received 25 November 2014; received in revised form 8 April 2015; accepted 8 April 2015

KEYWORDS
Fetal estosterone;
Oxytocin;
2D:4D;
OXTR;
RMET;
Empathy;
Social cognition

Abstract Both testosterone and oxytocin influence an individual's accuracy in inferring another's feelings and emotions. Fetal testosterone, and the second-to-forth digit ratio (2D:4D) as its proxy, plays a role in social cognitive development, often by attenuating socio-affective skill. Conversely, oxytocin generally facilitates socio-affiliative and empathic cognition and behavior. A common polymorphism in the oxytocin receptor gene, *OXTR* rs53576, has been repeatedly linked with psychosocial competence, including empathy, with individuals homozygous for the G allele typically characterized by enhanced socio-cognitive skills compared to A allele carriers. We examined the role of oxytocin and testosterone in collectively contributing to individual differences in cognitive empathy as measured by Baron-Cohen's ''Reading the Mind in the Eyes'' task (RMET). Findings are based on a large cohort of male and female students ($N = 1463$) of Han Chinese ethnicity. In line with existing literature, women outperformed men in the RMET. Men showed significantly lower 2D:4D ratio compared to women, indicating higher exposure to testosterone during the prenatal period. Interestingly, variation in the *OXTR* gene was found to interact with 2D:4D to predict men's (but not

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http://dx.doi.org/10.1016/j.psyneuen.2015.04.007

women's) RMET performance. Among men with GG allelic variation, those with low fetal testosterone performed better on the RMET, compared to men with GG and high fetal testosterone, suggesting greater identification of another's emotional state. Taken together, our data lend unique support to the mutual influence of the oxytocin and testosterone systems in shaping core aspect of human social cognition early in development, further suggesting that this effect is gender-specific.

1. Introduction

Humans are fundamentally social creatures, highly motivated to be with others and to form interpersonal bonds and social structures. In these contexts, the ability to infer another's feelings and emotional states is considered crucial (Frith and Frith, 1999). Both the androgen hormone testosterone and the neuropeptide oxytocin have been identified as markers for the core neuroendocrinological systems underlying our ability to understand others' emotional states, albeit in opposing ways (Bos et al., 2012; Domes et al., 2007; Hermans et al., 2006). Testosterone preprograms the brain during early development (Auyeung et al., 2013), and that programming affects socio-affective adeptness (Auyeung et al., 2009; Baron-Cohen, 2002). The involvement of the oxytocinergic system in supporting behavior, affective states, and cognitions that serve as building blocks of human socio-affiliative and empathic abilities has also been established (Ebstein et al., 2012; Feldman, 2012). Despite mounting evidence linking each of these systems to social cognition, current attempts to test their mutual influence in this respect have been limited.

Fetal testosterone is associated with an established morphological marker that can be indexed after birth: the length ratio of the right hand's second to fourth finger (2D:4D). Males on average have a significantly lower 2D:4D ratio on their right hand and fetal testosterone is thought to underlie this sex difference (Hönekopp et al., 2007; Manning et al., 2000). More so, fetal testosterone is shown to undermine the effect that exogenous testosterone has on diminishing women's cognitive empathy ability (Van Honk et al., 2011). Specifically, females with lower 2D:4D (i.e., higher early testosterone exposure) showed degraded performance on the ''Reading the Mind in the Eyes'' task (RMET), a behavioral paradigm that serves as a proxy of cognitive empathy in humans (Baron-Cohen et al., 2001).

The oxytocinergic system has also been the focus of intense research in recent years, given its role in social motivation and socio-cognitive aptitudes in both men and women (Gordon et al., 2011; McCall and Singer, 2012; Solomon et al., 2014), although often in a sexually-dimorphic manner (Apter-Levi et al., 2013; Carter, 2007; Weisman et al., 2015). Interestingly, the oxytocinergic system is a core mechanism underlying social and affiliative behaviors, including parental care, attachment relationships, and trusting behaviors (Feldman, 2007; Rilling, 2013; Van IJzendoorn and Bakermans-Kranenburg, 2012; Weisman et al., 2012a), mediated in part by its facilitation of the ability to infer the mental state of others (Churchland and Winkielman, 2012), or by enhancing brain activity and gaze duration towards socially meaningful stimuli (Domes et al., 2014; Auyeung et al., 2015).

To examine the role of the brain oxytonergic system in social cognition, many investigations have employed a neurogenetic strategy based on the considerable heritability of the human social repertoire (e.g., Chen et al., 2011). The oxytocin receptor gene (*OXTR*) has emerged as a particularly interesting candidate in this respect. In humans, *OXTR* gene is located on chromosome 3p25, spans 17 kb, contains four exons and three introns (Inoue et al., 1994), and encodes a 389-aa polypeptide with seven transmembrane domains belonging to the class I G-protein-coupled receptor family (Gimpl and Fahrenholz, 2001). Most interestingly, common variation in one *OXTR* single nucleotide polymorphism (SNP), rs53576 G/A, has been consistently associated with individual differences in a range of socio-emotional traits and social cognition abilities (Chen et al., 2011; Lerer et al., 2008; Saphire-Bernstein et al., 2011; Smith et al., 2014; Tost et al., 2010; Wang et al., 2014). The majority of these studies suggest that individuals who are homozygous for the G allele of rs53576 (i.e., GG genotype) are characterized by increased social proficiency and enhanced empathic accuracy or emptional empathy relative to individuals with one or two copies of the A allele (Bakermans-Kranenburg and van Ijzendoorn, 2008; Bradley et al., 2013; Lucht et al., 2013; Uzefovsky et al., 2015).

For example, compared to A allele carriers, GG individuals show greater levels of empathic concern after being presented with a social interaction containing high levels of individual distress and apparent physical pain (Smith et al., 2014). In addition, mothers who carry an A-allele demonstrate lower maternal sensitivity to their child behavior relative to G-allele homozygotes (Bakermans-Kranenburg and van Ijzendoorn, 2008). GG individuals outperformed A allele carriers on the RMET (Rodrigues et al., 2009). Finally, variation in the *OXTR* rs53576 predicts individual differences in structure and function of brain regions associated with social cognitive processes (Tost et al., 2010).

Taken together, the available findings strengthen a provisional role for *OXTR* rs53576 in promoting human social cognition and, particularly, empathic abilities in both men and women. However, complex constructs such as empathy surely engage many neurochemical pathways. The oxytocin receptor likely works in concert with a number of neurobiological systems (Bos et al., 2012; Mokkonen and Crespi, 2015). Interestingly, emerging literature suggests that an interaction between the oxytocin and the testosterone systems contributes to either hypo- or hyper-socio-cognitive manifestations, displays which are commonly evident in