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The role of oxytocin receptor gene (OXTR) and mother's emotional warmth in predicting adulthood sociability

Henrik Dobewall[a], Christian Hakulinen[a], Laura Pulkki-Råback[a,b], Ilkka Seppälä[c], Terho Lehtimäki[c], Olli T. Raitakari[d,e], Liisa Keltikangas-Järvinen[a], Mirka Hintsanen[f,a,*]

[a] Faculty of Medicine, University of Helsinki, Helsinki, Finland
[b] Helsinki Collegium for Advanced Studies, University of Helsinki, Helsinki, Finland
[c] Department of Clinical Chemistry, Fimlab Laboratories, Finnish Cardiovascular Research Center-Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland
[d] Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland
[e] Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland
[f] Unit of Psychology, University of Oulu, Oulu, Finland

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ABSTRACT

The oxytocin receptor gene (OXTR) may function as a "plasticity gene" that increases or decreases sociability in those individuals susceptible to growing up in a beneficial versus more adverse environment. This study used data from 2289 (55% female) participants from the ongoing prospective Young Finns Study. Maternal emotional warmth was assessed in 1980 when the participants were 3–18 years old. Participants' sociability temperament was measured at five follow-ups, from 1992 to 2012. Emotional warmth in childhood and OXTR genotype were not directly associated with temperamental sociability. We found a nominally significant gene–environment interaction (p = .03) suggesting that participants with a genetic profile of rs1042778 T-allele and rs2254298 A-allele are affected high versus low emotional warmth, whereas homozygotes of both G-alleles are unaffected by the same environmental influence. Our findings should be, however, interpreted as a null result as the interaction effect did not survive correction for multiple testing.

1. Introduction

Temperament traits are regarded as early emerging personality traits that have persistence later in life and are biological in origin (Buss, 1991; Buss & Plomin, 1975). A prominent theory of temperament – which describes inter-individual differences in adulthood temperament – is the Emotionality, Activity, and Sociability (EAS) theory by Buss and Plomin (1986). Emotionality is defined as distress that is accompanied by intense autonomic arousal, activity as the expenditure of physical energy, and sociability as an individual's tendency to prefer the presence of others to being alone (Buss, 1991).

In the current study, we focus on adulthood sociability, as it is a motivational trait that captures preference for social behavior. Individuals with high adulthood sociability socialize whenever possible, are willing to be responsive to others and to cooperate with them, and find it rewarding to spend time with other people (Buss, 1991). More precisely, being sociable is motivated by the intrinsic social rewards of sharing activities, attention from others, and responsivity from others (Buss, 1991). Temperamental sociability has been shown to have moderate (heterotypic) continuity (Katainen, Räikkönen, & Keltikangas-Järvinen, 1998) and the biological sensitivity associated with sociability is associated with how an individual experiences the social environment (Buss & Plomin, 1986). Finally, the study of adulthood sociability development is of clinical relevance, as (lack of) sociability does not only affect close relationships and social behavior but it is also involved in the etiology of various health problems and longevity across the life span (Elovainio et al., 2015; Yang et al., 2016).

1.1. Oxytocin receptor gene (OXTR)

As temperament is thought to be heritable to a large extent (Saudino, 2005), specific candidate genes might play a role in the development of sociability. The neuropeptide oxytocin (OT) has been found to regulate social behavior (Ebstein, Knafo, Mankuta, Chew, & Lai, 2012) and indeed higher plasma levels of the neuropeptide OT are, under most conditions, associated with enhanced social behavior in humans and non-human animals (Bartz, Zaki, Bolger, & Ochsner, 2011; Feldman et al., 2012). Unlike for other hormones, there is only one

* Corresponding author at: Unit of Psychology, University of Oulu, P.O. Box 2000, Yliopistokatu 9, 90014 Oulu, Finland.
E-mail address: mirka.hintsanen@oulu.fi (M. Hintsanen).

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known receptor for OT. Since the first associations were discovered in 2005, allelic variations in the OXTR have been associated with inter-individual differences in a variety of social phenotypes (Ebstein et al., 2012; Li et al., 2015; Peltola et al., 2014; Skuse et al., 2014), yet, a recent meta-analysis of OXTR effects failed to explain a significant part of human social behavior (Bakermans-Kranenburg & van Ijzendoorn, 2014). A recent study of Feldman et al. (2012) connected these two lines of research demonstrating a link between plasma OT levels and single nucleotide polymorphisms (SNPs) in the OXTR (i.e., rs1042778 and rs2254298). A third SNP (rs53576) of the OXTR has been associated with structural alterations of the oxytocinergic regions of the hypothalamus and with amygdala activity during the processing of emotionally salient social cues (Tost et al., 2010). It is further possible that an OXTR SNP has an effect on the initial level of sociability and an effect on changes that occur in this temperament dimension as participants grow older, making it crucial to investigate whether the identified candidate genes have an influence on sociability across the life span.

1.2. Gene–environment (GxE) interactions

Examining genes or environments separately from each other may lead to biased findings because of GxE interactions. Due to their genotypes, some children and adolescents may be more sensitive to the effects of early life experiences—for better or worse— while for others the same environmental influences might have only a weak effect if any (Belsky & Pluess, 2009). Therefore, allelic variation in OXTR might moderate how individuals experience social relationships and situations instead of having a direct effect on sociability. It has been, for instance, argued that biologically elevated sensitivity to social cues might result in higher distress under conditions where individuals' social needs are not met (McQuaid, McInnis, Stead, Matheson, & Anisman, 2013).

Few GxE studies (e.g., Bradley et al., 2011; Hammen, Bower, & Cole, 2015; Hostinar, Cicchetti, & Rogosch, 2014; van Roekel et al., 2013) have investigated whether OXTR variant rs53576 moderates the influence of adverse childhood environments on phenotypes related to sociability (e.g., emotional dysregulation, unstable relationships with close others, loneliness, or perceived social support). Unfortunately, their results are inconclusive as both carriers of the G-allele (Bradley et al., 2011; Hostinar et al., 2014; van Roekel et al., 2013) and the A-allele (Hammen et al., 2015) of rs53576 are found to be more strongly affected by adverse early-environmental influences, dependent on the social phenotype and environmental factor studied. Furthermore, it is not certain whether social phenotypes, including sociability, are influenced by OXTR genotypes in beneficial environments. The only available study did not find significant GxE interactions between rs53576 and perceptions of positive company on loneliness (van Roekel et al., 2013). Children and adolescents might also be differentially susceptible (i.e. more or less sensitive to beneficial as well as adverse environments depending on their OXTR genotypes) to the emotional warmth experienced during childhood (Jokela et al., 2007), potentially accounting for inter-individual differences in sociability development.

Researchers must give a good reason not only for the selection of potential candidate genes, but also the choice of the right environmental factor is important and needs to be justified (Dick et al., 2015). Numerous studies have shown associations between early parental environment and children's development (for a review, see Collins, Maccoby, Steinberg, Hetherington, & Bornstein, 2000). Most theories agree that emotional warmth—sometimes also called closeness or love—is a defining characteristic of an early environment beneficial to the offspring (Clark & Ladd, 2000; MacDonald, 1992; Schaefer, 1959). Also, the EAS approach to temperament agrees that one of the more powerful social rewards is to be liked or loved, especially when offered by parents to their children (Buss, 1991). These intrinsic rewards, in turn, can strengthen the tendency to seek out for others and remain in their company and indeed the maternal warmth in childhood has been associated with children's temperament during adolescence (Katainen et al., 1998). For that reason, it is important to examine GxE interactions in this context.

1.3. The current study

Candidate gene–environment interaction studies have been criticized because it is difficult to justify which environmental and which genetic factor should be studied, and because of several statistical concerns which we tried to address in the current study (Dick et al., 2015; Keller, 2014). In summary, there has been a strong claim in the literature that OXTR variants are responsible for inter-individual differences in a variety of social behaviors. The evidence is sparse for temperament dimensions, with not a single study linking OXTR polymorphisms to the sociability dimension of the Buss–Plomin EAS temperament model (Buss, 1991; Buss & Plomin, 1975). Of the environments that could be studied, the maternal emotional warmth during childhood has been shown to influence the development of temperament (Katainen et al., 1998) and personality traits (Josefsson et al., 2013) and is probably especially important for the development of sociability. We hypothesize, however, that this is only the case if the child carries certain genotypes in the OXTR. The current study, therefore, examined whether or not combinations of the three most promising candidate genes in the OXTR (rs1042778, rs2254298, and rs53576) interact with growing up in a beneficial versus more adverse environment in predicting adulthood sociability. The study is well-powered as it is based on five repeated measurements, assessed 20 years apart in a population-based sample, and uses a well-established scale to measure adulthood sociability.

2. Methods

2.1. Participants

Data were derived from the Young Finns Study (Raitakari et al., 2008), which is a multicenter prospective study monitoring change in cardiovascular risk in representative Finnish birth cohorts, conducted across five university cities with medical schools and their rural surroundings. The initial sample consisted of 3596 children and adolescents (Caucasians), who were 3, 6, 9, 12, 15, and 18 years at the study baseline in 1980 (T0). After the baseline, several follow-up waves have been conducted. Those subjects were excluded for whom no information on their genes or the environmental factor was available and those who had no data from any of the follow-ups, in which our dependent variable was fielded (Fig. 1). The final sample included 2289 participants (1026 male; 1263 female). Participants gave written informed consent, and local ethics committees approved the study. Moreover, the study procedure of each study phase was in accordance with the Helsinki Declaration.

2.2. Measures

2.2.1. Adulthood sociability

The sociability dimension of the Buss–Plomin EAS temperament model (Buss, 1991) was used to measure sociability. Adulthood temperament was assessed in 1992 (T1), 1997 (T2), 2001 (T3), 2007 (T4), and 2012 (T5) with five items, such as, “I like to be with people”. They were rated on a 5-point Likert scale (1, totally disagree; 5, totally agree). Higher scores indicate higher sociability. Cronbach's alpha was generally high, ranging from .78 at T3 to .80 at T5. Note that participants belonging to the youngest age cohort were at T1 still in their adolescence (i.e. 15 years old).

2.2.2. Maternal emotional warmth

Mothers reported their perceptions of the early emotional environment, i.e. the emotional warmth between mother and child with four