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Variation in the μ-opioid receptor gene (*OPRM1*) moderates the influence of early maternal care on fearful attachment

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There is evidence that both early experience and genetic variation play a role in influencing sensitivity to social rejection. In this study, we aimed at ascertaining if the A118G polymorphism of the μ-opioid receptor gene (*OPRM1*) moderates the impact of early maternal care on fearful attachment, a personality trait strongly related to rejection sensitivity. In 112 psychiatric patients, early maternal care and fearful attachment were measured using the Parental Bonding Inventory and the Relationship Questionnaire (RQ), respectively. The pattern emerging from the RQ data was a crossover interaction between genotype and maternal care-giving. Participants expressing the minor 118 G allele had similar and relatively high scores on fearful attachment regardless of the quality of maternal care. By contrast, early experience made a major difference for participants carrying the A/A genotype. Those who recalled higher levels of maternal care reported the lowest levels of fearful attachment whereas those who recalled lower levels of maternal care scored highest on fearful attachment. Our data fit well with the differential susceptibility model which stipulates that plasticity genes would make some individuals more responsive than others to the negative consequences of adversity and to the benefits of environmental support and enrichment.

Keywords: *OPRM1* gene; maternal care; fearful attachment; rejection sensitivity

INTRODUCTION

For social animals, being socially excluded is often equivalent to death. As a result, in species with complex social organizations, the process of natural selection favored the evolution of physiological and psychological mechanisms designed to recognize and react to threats of social exclusion in an efficient manner (MacDonald and Leary, 2005). Human beings are no exception to this evolutionary trend. Baumeister and Leary (1995) have proposed that as humans we possess a need to belong which constitutes a fundamental motivation—driving our thoughts, emotions and interpersonal behavior. This need to belong comprises 'a pervasive desire to form and maintain at least a minimum quantity of lasting, positive, and significant interpersonal relationships' (Baumeister and Leary, 1995, p. 497). Consequently, people who experience persistent difficulties in establishing and maintaining satisfying relationships with others, and thus have difficulty satisfying their belongingness needs, are likely to experience a distressing sense of deprivation, arising from the perception of actual or potential psychological distance from close others or a social group.

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The affective states experienced in response to rejection, exclusion or ostracism have been collectively subsumed under the term 'social pain'. The concept of social pain was first suggested by Panksepp and colleagues. They provided evidence that the social attachment system was built up from more primitive regulation systems such as those involved in place attachment, thermoregulation and physical pain (Panksepp, 1998; Stein *et al.*, 2007). Such an overlap would be evolutionarily adaptive. Because of the prolonged period of immaturity and the critical need for maternal care in mammalian infants, the pain mechanisms involved in detecting and preventing physical danger were co-opted by the more recently evolved social attachment system to detect and prevent social separation (Eisenberger and Lieberman, 2004). Indeed, research has begun to reveal similarities in the neurocognitive processes underlying physical pain and social pain. Recent neuroimaging work has revealed that the dorsal anterior cingulate cortex, commonly associated with the 'unpleasantness' of physical pain, is also activated during the distressing experience of social rejection, and its activity correlates strongly with self-reported social distress (Eisenberger *et al.*, 2003).

Psychological studies focusing on individual differences in sensitivity to and fear of social rejection have emphasized the importance of adult attachment patterns. Bartholomew and Horowitz (1991) described an adult attachment pattern that

they called 'fearful avoidant' (commonly referred to as 'fearful' in the attachment literature.) Fearfully avoidant people distance themselves from relationship partners because they consciously fear the possible negative consequences of closeness to and reliance on others, but they also wish they did not have to feel this way. They score high on both the dimensions that characterize insecure attachment: anxiety (i.e. a strong need for care and attention from attachment figures coupled with a pervasive uncertainty about the willingness of attachment figures to respond to such needs) and avoidance (i.e. discomfort with psychological intimacy and the desire to maintain psychological independence). Rejection sensitivity is a crucial aspect of fearful attachment. In persons with this style of adult attachment, avoidance of intimacy is strictly linked with a negative working model of self and fear of rejection. Life is especially difficult for a person with a fearful attachment pattern. Fearfully avoidant people are more likely than others to be involved in highly distressed and violent couple relationships, are cognitively closed and rigid, and have the most severe personality disorders and the poorest mental health (see Mikulincer and Shaver, 2007 for a review).

Retrospective (Priel and Besser, 2000; Irons *et al.*, 2006) and longitudinal (Roisman *et al.*, 2001; Grossmann *et al.*, 2005) studies examining the association between parental care during infancy and childhood and attachment patterns during adulthood have provided convergent evidence for the formative influence of early experience on later adult attachment. In particular, there is evidence that lower levels of early maternal care are associated with more fearful attachment late in adolescence and adulthood (Gittleman *et al.*, 1998). Although early experience is likely to make a major contribution to individual differences in fearful attachment during adulthood, genetic factors might also be involved in influencing sensitivity to social rejection, as showed by a recent study (Way *et al.*, 2009) of the A118G polymorphism of the μ-opioid receptor gene (*OPRM1*) in healthy volunteers. Participants completed a self-report inventory of dispositional sensitivity to social rejection and a subsample completed a functional magnetic resonance imaging (fMRI) session in which they were rejected from an online ball-tossing game played with two supposed others. The A118G polymorphism was associated with dispositional sensitivity to rejection in the entire sample and in the fMRI subsample. G allele carriers showed greater reactivity to social rejection in neural regions previously shown to be involved in processing social pain as well as the unpleasantness of physical pain, particularly the dorsal anterior cingulate cortex and anterior insula.

Based on the findings reported above, it is likely that both early experience and genetic variation play a role in influencing sensitivity to social rejection. However, to our knowledge, no study has addressed the question if the causative role of these variables implies gene x environment interactions. Such a question is justified by growing evidence that genes and environment often interact to shape behavior and development, including vulnerability to dysfunctional personality traits (Seabrook and Avison, 2010). Thus, in this study, we aimed at ascertaining if the A118G polymorphism of the μ-opioid receptor gene (*OPRM1*) moderates the impact of early maternal care on fearful attachment.

Because this is the first study investigating a possible gene x environment interaction in the etiology of fearful attachment, we decided to enroll a clinical sample rather than a community sample. The rationale was that fearful attachment (Levy *et al.*, 2005) and poor maternal care (Parker *et al.*, 1995) are overrepresented in psychiatric patients with high levels of negative affectivity but relatively rare among healthy volunteers.

METHOD

Participants

The sample of this study consisted of 112 patients (74% women; mean ± s.d. age: 34.81 ± 10.5 years) consecutively admitted to the day hospital of the psychiatric clinic at the University of Rome Tor Vergata. Diagnostic assessment was made by experienced clinical psychiatrists using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-CV) (First *et al.*, 1997) and the Schedule for Interviewing DSM-IV Personality Disorders-IV (SIDP-IV) (Pfohl *et al.*, 1997). Patients with medical or neurological disorders, mental retardation, or psychotic disorders were excluded from the sample. The diagnostic composition of the sample was as follows: major depressive disorder, 31%; eating disorders, 25%; anxiety disorders, 21%; bipolar disorder, 14%; cluster B personality disorders, 9%. All data were obtained under informed consent and using procedures and protocols approved by the University of Rome Tor Vergata Intramural Ethics Committee and the EMBL Bioethics Internal Advisory Committee (BIAC).

Psychometric assessment

To measure fearful attachment, we used the Relationship Questionnaire (RQ; Bartholomew and Horowitz, 1991). Participants were instructed to interpret the attachment questionnaire as referring to all their close relationships with peers (whether romantic or not). The RQ is a single-item measure made up of four short paragraphs, each describing a prototypical attachment pattern as it applies in close adult peer relationships. Participants are asked to rate their degree of correspondence to each prototype on a 7-point scale. The four attachment patterns (i.e. secure, preoccupied, fearful and dismissing) are defined in terms of two dimensions: anxiety (i.e. a strong need for care and attention from attachment figures coupled with a pervasive uncertainty about the willingness of attachment figures to respond to such needs) and avoidance (i.e. discomfort with psychological intimacy and the desire to maintain psychological independence). The RQ paragraph

describing fearful attachment reads as follows: 'I am uncomfortable getting close to others. I want emotionally close relationships, but I find it difficult to trust others completely, or to depend on them. I worry that I will be hurt if I allow myself to become too close to others.' A cross-cultural study of the RQ conducted on a convenience sample of college students reported that the mean ± s.d. score for the Italian population was 3.09 ± 2.01 (Schmitt *et al.*, 2004).

Maternal care experienced in childhood was measured using the Parental Bonding Inventory (PBI) (Parker *et al.*, 1979). The questionnaire is retrospective, meaning that adults (over 16 years) complete the measure for how they remember their parents during their first 16 years. The PBI includes a subscale assessing maternal warmth/care. This scale consists of 12 items querying the quality of subjects' relationship with their mother during childhood (e.g. 'My mother spoke to me in a warm and friendly voice.') Participants report on a four-point scale how true each statement was of their own experiences. The participants of this study were assigned to 'low care' or 'high care' groups based on their maternal care scores, using the suggested cutoff score of 27 by Parker and Lipscombe (1979). The PBI has been found to have good reliability and validity, long-term stability, satisfactory construct and convergent validity, and to be independent of mood effects (Parker, 1989; Murphy *et al.*, 2010).

The Profile of Mood States (POMS; McNair *et al.*, 1992) is a self-administered questionnaire designed to assess current mood states. Participants were asked to carefully read each of 65 items, then respond to a 5-point Likert scale ranging from 1 (not at all) to 5 (extremely) based on how they were feeling the day they completed the inventory. The total mood disturbance score (POMS-TMD) was calculated by summation of the five negative affect scales (fatigue, depression, tension, anger and confusion) and subtraction of the vigor scale. A higher POMS-TMD corresponds to higher levels of mood disturbance.

Genotyping

Genomic DNA was extracted from buccal swabs using a standard phenol/chloroform isolation procedure. Sequences from exon 1 of the human μ-opioid receptor gene were amplified by PCR using primers surrounding the A118G polymorphism: 5′-CCGTCAGTACCATGGACAGCAGCG GTG and 5′-GTTCGGACCGCATGGGTCGGACAGGAT (Bond *et al.*, 1998). The reactions were performed in a total volume of 25 μl containing 10 mM Tris pH 8.3 50 mM KCl, 0.2 mM dNTP, 1.5 mM $MgCl_2$, 10 pmol of each primer, 0.5 U Taq (Promega, Madison, WI) and 50–100 ng of genomic DNA. PCR was carried out using the following conditions: 5 min at 95.0 C, 30 cycles of 94.0 C for 30 sec, 63 C for 30 sec and 72 C for 30 sec, and a final elongation phase at 72 C for 10 min. PCR products were subsequently cut with *Dpn II* and run on a 3% agarose gel to determine genotype. Fragments of 154 and 129 bp corresponded to the A *(Asn)* and G *(Asp)* alleles, respectively. Genotype was confirmed in 47 samples using a Taqman assay (Catalog #C8950074, Applied Biosystems, Forster, CA).

Statistical analysis

Two-way analyses of variance (ANOVA) and covariance (ANCOVA) were used to calculate the effects of early maternal care and genotype on fearful attachment scores. Homogeneity of variance was tested by the Levene's test. Partial η^2 was used as a measure of effect size. Pairwise comparisons between subgroups of participants were made by using Bonferroni post-hoc tests. Analysis was performed on a personal computer using SPSS for Windows, version 17.0 (SPSS, Inc., Chicago, Ill.).

RESULTS

The frequency distribution of the *OPRM1* genotypes was as follows: 69% A/A, 29% A/G, 2% G/G. Genotype frequencies were in Hardy-Weinberg equilibrium and did not significantly diverge from those reported in other Caucasian populations (chi-square = 0.52, df = 1, $P = 0.83$). Due to the small number of G allele homozygotes, the G/G and A/G groups were combined in the data analysis to form the group of G allele carriers. Genotype was associated with neither gender (chi-square = 0.92, df = 1, $P = 0.34$) nor quality of maternal care in childhood (chi-square = 0.41, df = 1, $P = 0.52$). Using the categorical classification of the RQ, 24% of the participants described themselves as having a fearful style of attachment. Such a percentage is much higher than that reported in non-clinical populations (e.g. Scharfe and Bartholomew, 1994).

There was a significant main effect of the reported quality of maternal care in childhood on fearful attachment [$F(1, 108) = 5.64$, $P < 0.02$, partial $\eta^2 = 0.05$]. Participants who recalled lower levels of maternal care scored higher on the RQ scale measuring fearful attachment. There was a non-significant main effect of the genotype on fearful attachment [$F(1, 108) = 0.28$, NS]. Participants expressing the minor 118 G allele and those carrying the A/A genotype did not differ on the RQ scale measuring fearful attachment.

There was a highly significant interaction effect between quality of maternal care and genotype on fearful attachment [$F(1, 108) = 12.50$, $P < 0.001$, partial $\eta^2 = 0.10$] (Figure 1). This indicates that participants expressing the minor 118 G allele and those carrying the A/A genotype were affected differently by the quality of maternal care experienced in childhood. Specifically, participants expressing the minor 118 G allele had similar and relatively high scores on the RQ scale measuring fearful attachment regardless of the quality of maternal care (Bonferroni post-hoc test: $P = 1$). By contrast, the quality of maternal care made a big difference for participants carrying the A/A genotype (Bonferroni post-hoc test: $P < 0.0001$). Those who recalled higher levels of maternal care reported the lowest levels of fearful

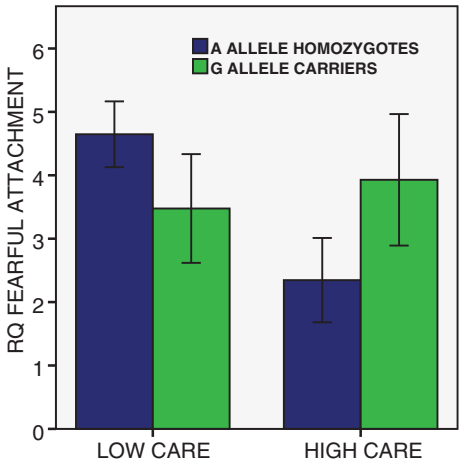

Fig. 1 Fearful attachment scores (mean ± 2 S.E.M.) for participants classified by levels of maternal care in early childhood (low care *vs* high care) and A118G genotype (A allele homozygotes: blue bar; G allele carriers: green bar).

attachment. However, those who recalled lower levels of maternal care formed the subgroup of participants with the highest levels of fearful attachment. We repeated the analysis including the POMS-TMD as a covariate into an ANCOVA model to control for the possible confounding effect of mood state on the assessment of fearful attachment. The interaction effect between quality of maternal care and genotype on fearful attachment remained highly significant ($F(1, 106) = 14.87$, $P < 0.0001$). The cumulative variance in the fearful attachment score explained by the interaction effect was 12.3%.

DISCUSSION

Previous studies of the A118G polymorphism of the *OPRM1* gene in human subjects have shown that genetic differences in μ-opioid neurotransmission are associated with individual differences in sensitivity to both social pain and social reward. The important role of the opioid system in modulating both pain and pleasure, and the extensive similarities in the anatomical substrates of painful and pleasant sensations may explain why some individuals are more sensitive to both the pain of social rejection and the pleasure of social attachment (Leknes and Tracey, 2008).

Evidence for an association between the A118G polymorphism and sensitivity to social reward is currently limited to a single study including a subset of the participants enrolled into the present study and conducted in a mixed sample of 214 adult healthy volunteers and psychiatric patients (Troisi *et al.*, 2010). Compared to individuals expressing only the major allele A, subjects expressing the minor allele G had an increased tendency to become engaged in affectionate relationships and experienced more pleasure in social situations. Data on sensitivity to social rejection are more abundant and derive from studies employing different methodologies, including neuroimaging and animal models. In a sample of 122 healthy volunteers, Way *et al.* (2009) found that G allele carriers showed greater reactivity to social rejection in neural regions previously shown to be involved in processing social pain as well as the unpleasantness of physical pain, particularly the dorsal anterior cingulate cortex and anterior insula. These findings are consistent with those reported by Zubieta *et al.* (2003) who found that μ-opioid neurotransmission within the anterior cingulate cortex was negatively correlated with self-reported negative affect during the recollection of the death of a loved one or the ending of a romantic relationship. In rhesus monkeys, Barr *et al.* (2008) found that a functional variant in the μ-opioid receptor gene (*OPRM1* C77G), which parallels the functional effects of the A118G polymorphism in humans (Vallender *et al.*, 2008), is associated with more prolonged distress in infants separated from their mothers during the weaning period.

In accord with the findings reported above, the results of the present study confirm that the A118G polymorphism of the *OPRM1* gene plays a role in modulating sensitivity to social rejection. Two findings makes the present study an original contribution to this area of research. First, we focused on fearful attachment, a personality trait which is strongly related to sensitivity to social rejection but that has not been previously studied. Second, we found that the A118G polymorphism interacts with early maternal care in influencing the development of a fearful style of adult attachment. After controlling for current levels of mood disturbance, the gene-environment interaction on fearful attachment became stronger. Since there was no significant difference in early maternal care by subject genotype, we can exclude that genotype was a proxy for the quality of early experience. Considering that previous studies of fearful attachment have focused almost exclusively on the impact of early experiences (Gittleman *et al.*, 1998; Irons *et al.*, 2006), this finding may lead attachment researchers to reconsider the contribution of genetic factors. Such a change of perspective toward a more complex view of pathways to fearful attachment would be in line with growing evidence showing the importance of various genetic polymorphisms for the development of adult attachment styles (Gillath *et al.*, 2008; Costa *et al.*, 2009).

In psychiatric research on gene-environment interaction, the finding that some individuals are particularly vulnerable to adversity has been classically explained by the diathesis-stress model, which is based on the search for those 'vulnerability genes' that increase susceptibility to negative environmental conditions (Belsky *et al.*, 2009). Does the diathesis-stress model explain our results? As reported above, previous studies have identified the G allele as the 'at-risk' variant of the A118G polymorphism. Thus, the diathesis-stress model would predict that G carriers exposed to lower levels of early maternal care should score highest in fearful attachment. In contrast, G carriers exposed to higher levels of maternal care and participants with the A/A

genotype (i.e. those with the 'protective' genetic makeup) should score lower in fearful attachment. Our data do not confirm such a prediction. Participants scoring highest in fearful attachment were those carrying the A/A genotype and experiencing lower levels of early maternal care. On the other hand, when exposed to higher levels of maternal care, participants with A/A genotype scored lowest in fearful attachment. Thus, the pattern emerging from the RQ data was a crossover interaction between genotype and maternal caregiving.

In a study of the A118G polymorphism, Copeland *et al.* (2011) have recently reported that child genotype interacted with parent behavior such that there were no genotype differences for those with low levels of parent problems; however, when a history of parent problems was reported, the G allele carriers had more enjoyment of parent-child interactions and fewer arguments. These findings show that, in the context of having a parent with a history of mental health problems, substance problems, or criminality, children carrying the G allele were advantaged across two measures of parent-child relations when compared with A/A subjects. These data converge with our results that G allele carriers are less sensitive to negative rearing experiences.

Clearly, the diathesis-stress model is not applicable to our results because it is difficult to determine which is the 'at-risk' allele of the A118G polymorphism associated with fearful attachment. Yet, our data fit well with the differential susceptibility model proposed by Belsky *et al.* (2009). According to this new framework for interpreting gene-environment interactions, vulnerability genes may actually function more like plasticity genes, resulting in certain individuals being more responsive than others to both positive and negative environmental experiences. Unlike vulnerability genes that would only cause some individuals to be more susceptible than others to adversity, plasticity genes would make some individuals more responsive than others to the negative consequences of adversity and to the benefits of environmental support and enrichment. Applied to the interaction between the A118G polymorphism and early maternal care, the differential susceptibility model would conceptualize the A/A genotype as the plastic allelic variant, making individuals simultaneously more vulnerable to the negative consequences of lower levels of maternal care (as reflected by highest levels of fearful attachment) and more responsive to the benefits of higher levels of maternal care (as reflected by lowest levels of fearful attachment).

The differential susceptibility model accords well with evolutionary hypotheses (Wang *et al.*, 2004; Ebstein, 2006) explaining the relative frequency of those genetic polymorphisms that differ widely across human populations, as is the case for the A118G polymorphism (Arias *et al.*, 2006). It is possible that the maintenance of this polymorphism in human evolution is related to the need for diverse behavioral phenotypes in ancestral human populations living in different environments selecting for or against an increased tendency toward social sensitivity (Way and Lieberman, 2010).

Limitations of the present study include the use of self-report measures to assess fearful attachment and maternal behavior. In molecular genetic research, a well-founded criticism against self-report scales is that they are a long way from actual social behavior (Hamer, 2002; Ebstein, 2006). However, there is evidence that the self-report measure of fearful attachment used in this study is predictably related to interpersonal behavior (Haggerthy *et al.*, 2009). Persons who score high on the RQ fearful attachment scale are more likely than others to be involved in highly distressed and violent couple relationships, are cognitively closed and rigid, and have the most severe personality disorders and the poorest mental health (Mikulincer and Shaver, 2007). An additional concern related to the use of self-report measures is the accuracy of childhood recollections reported by participants. Previous studies of the PBI did demonstrate significant correlations between subject reports and independent reports of parental behavior (Parker, 1981), and also did show highly significant correlations between twins in how they rate their parents (Parker, 1986). Nevertheless, it is impossible to be sure if participants really experienced their reported rearing practices. Another limitation is that our sample is not representative of the general population. Ebstein (2006) has argued for the inclusion of subjects with extreme phenotypes as a complimentary strategy in unraveling the complexity of personality genetics. It is likely that the peculiar characteristics of our sample in terms of adult attachment style and early experience were instrumental in revealing the impact of the combined interaction between genotype and maternal caregiving on sensitivity to social rejection. However, the generalizability of our findings remains to be investigated.

If replicated, our results show that the strength of the association between early maternal care and an adult style of fearful attachment partly depends on the moderating effect of the A118G polymorphism. In our clinical sample, the A/A genotype acted as a plastic allelic variant making A allele homozygotes more responsive than G allele carriers to both positive and negative environmental experiences. Ideally, future studies aimed at replicating our findings should assess simultaneously the role of functional variants of different genes influencing social sensitivity (Way and Lieberman, 2010) and combine self-report measures with direct observation of attachment behavior in both clinical and non-clinical populations.

Conflict of Interest

None declared.

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