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Original article

Genetic modulation of the response bias towards facial displays of anger and happiness

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ABSTRACT

Background: Investigating genetic modulation of emotion processing may contribute to the understanding of heritable mechanisms of emotional disorders. The aim of the present study was to test the effects of catechol-*O*-methyltransferase (*COMT*) *val158met* and serotonin-transporter-linked promoter region (5-HTTLPR) polymorphisms on facial emotion processing in healthy individuals.
Methods: Two hundred and seventy five (167 female) participants were asked to complete a computerized facial affect recognition task, which involved four experimental conditions, each containing one type of emotional face (fearful, angry, sad or happy) intermixed with neutral faces. Participants were asked to indicate whether the face displayed an emotion or was neutral. The *COMT-val158met* and 5-HTTLPR polymorphisms were genotyped.
Results: Met homozygotes (*COMT*) showed a stronger bias to perceive neutral faces as expressions of anger, compared with *val* homozygotes. However, the *S*-homozygotes (5-HTTLPR) showed a reduced bias to perceive neutral faces as expressions of happiness, compared to *L*-homozygotes. No interaction between 5-HTTLPR and *COMT* was found.
Conclusions: These results add to the knowledge of individual differences in social cognition that are modulated via serotonergic and dopaminergic systems. This potentially could contribute to the understanding of the mechanisms of susceptibility to emotional disorders.

1. Introduction

Identification of the genetic mechanisms that drive the processing of emotions may help in establishing the mechanisms of susceptibility to emotional disorders [6]. As well as searching the whole genome for associations with affective disorder symptomatology [10,42], investigators have been looking for biologically meaningful associations between specific candidate genes conferring the risk for emotional disorders [21] – the approach adopted by the current study.

Compared to the recent surge in neuroimaging genetics research, there has been markedly less empirical interest in behavioral research on the genetic effects on emotion processing in healthy individuals. This could, in part, be due to the higher sensitivity of the neuroimaging approach that may provide for stronger effects even on smaller samples compared with behavioral genetic studies [24]. However, the importance of behavioral studies in highlighting the effects of genetic influences on cognitive and emotional processing should not be dismissed. Indeed, the recognition bias towards negative facial expressions, such as sadness has been detected, not only in people suffering from depression [23], but also in first-degree relatives of depressed individuals [25,29], including their infants [7], which strongly suggests the heritability of a biased cognitive mechanism underpinning recognition of these affects. It remains to be shown whether the particular genes potentially involved in emotional

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disorders have any impact on emotion processing in healthy individuals [19].

In this study, we investigated the effect of two genetic markers on the processing of facial emotional expressions in healthy participants. One of the genetic markers of interest in the regulation of emotion processing is the serotonin-transporter gene (*SLC6A4*), in particular, the short (*S*) allele of the serotonin-transporter-linked promoter region (5-HTTLPR) of this gene conferring lower expression levels compared with the long (*L*) allele. In humans, *S*-allele carriers show behavioral characteristics of negative emotionality in comparison to *L*-allele homozygotes [30]. This has been suggested to underlie a higher risk of developing clinical depression in the *S*-allele carriers when exposed to stressful life events, which demonstrates a significant gene *x* environment interaction [26].

Another marker that has been implicated in emotion processing is a gene coding for catechol-*O*-methyltransferase (*COMT*) that modulates the catabolism of catecholamines. A relatively frequent *val-158-met* polymorphism (a methionine to valine substitution at codon 158) results in lower levels of *COMT* enzymatic activity in the synaptic cleft compared with the *val* polymorphism [28]. The *met*-allele has been associated with the enhanced vulnerability to anxiety [15], panic disorder [13,53], as well as bipolar affective disorder [36,38]. While links between *COMT* and major depressive disorder (MDD) are not universally recognized [32], an interaction between *COMT* and 5-HTTLPR genotypes has been shown to predispose individuals with a history of stressful life events to MDD [33]. Perhaps more importantly, Conway et al. [8] described a gene *x* gene *x* environment interaction where in the presence of at least one *met*-allele, both 5-HTTLPR genotype groups predicted a vulnerability to depressogenic stressors.

Neuroimaging genetic studies have contributed significantly to the search for intermediate phenotypes for emotional disorders, showing increased limbic activation for the 5-HTTLPR (*S*) and *COMT* (*met*) carriers in response to negatively valenced emotional signals (for review see [41]). Importantly, an additive effect of these polymorphisms has been described, resulting in exaggerated limbic activity during the processing of emotionally unpleasant pictures [43]. Furthermore, in our recent study [47], we showed that an interaction between 5-HTTLPR (*S*) and *COMT-met* genotypes was associated with reduced effective connectivity within an emotion processing circuit. This was suggested to underlie inefficiency of cortical networks, regulating emotion processing in individuals with this particular configuration of genetic markers.

An interaction of 5-HTTLPR and *COMT* genes has also been observed in a study of fear learning and fear-extinction in healthy individuals [31]. These authors reported enhanced fear conditioning and a loss of fear control in *S*-allele carriers of the 5-HTTLPR gene, who were also homozygous for the *met*-allele of the *COMT* gene.

Behavioral studies of the modulatory effects of 5-HTTLPR have so far reliably demonstrated greater attentional bias in the *S*-allele carriers toward negatively valenced stimuli [3,4,50]. Antypa et al. [1] found that *S*-homozygotes recognized negative facial expressions at a lower intensity and this effect was more pronounced with individuals who had experienced a significant history of negative life events. Studies have also demonstrated reduced bias toward positively valenced stimuli in 5-HTTLPR *S*-allele carriers [19,27,40]. Taken together, these studies suggest that the *S*-allele is associated with greater bias toward emotionally negative and a correspondingly smaller bias to emotionally positive stimuli, compared to the *L*-allele. Moreover, Stollstorff et al. [45] demonstrated that the effect of 5-HTTLPR was not confined to emotional/perceptual processes, but also extended to the other cognitive domains. In their study, the *S*-allele homozygotes were less accurate in evaluating emotional (mostly negative) relational reasoning problems with belief-logic conflict, relative to *L*-homozygotes.

There has been little research on *COMT* gene and the studies of associated off-line emotion processing are inconsistent. For example, it has been shown that *met* homozygotes were less efficient in the recognition of sad facial expressions and had longer response times than *val* homozygotes [51]. The only study to date testing a joint effect of *COMT* and 5-HTTLPR on the processing of facial displays of emotion [11] have described significantly poorer recognition of facial expressions of happiness in *S*-allele carriers, together with a better recognition of fearful faces, compared with *L*-homozygotes of 5-HTTLPR. The study failed to report any significant effect of *COMT* gene on emotion recognition, and could not find any interaction between the *COMT* and 5-HTTLPR genes. The lack of a significant interaction may have been due to the sample characteristics as the effect was examined on 88 female participants and was based on the raw scores of recognition accuracy.

In the present study, the effects of *COMT* and 5-HTTLPR and their potential interactions on the perception of facial displays of emotion were explored in a large group of healthy individuals of both sexes. Part of this sample (91 individuals), previously underwent a series of fMRI procedures with fearful facial emotional expressions, which demonstrated an interaction of *S*- and *met*-alleles with effective connectivity and is reported elsewhere [47]. We have employed a statistically robust two-high threshold approach [9] that provides for the measures of both the discrimination accuracy and the response bias. We hypothesized that the *met* and *S*-alleles will be associated with a greater recognition bias towards negatively (sadness, anger and fear) but not the positively (happy) valenced facial expressions. That is, these effects will manifest as a main effect of each genotype as well as an interaction between the two genes.

2. Methods and materials

2.1. Participants

Two hundred and seventy-five right-handed volunteers (167 female; 108 male) participated in the study. All were white Caucasians aged between 18 and 55 years whose first language was English. Exclusion criteria were current or past substance abuse, head injury or any pre-existing neuropsychiatric disorder, screened out by the Structured Clinical Interview for DSM-IV-TR Axis I disorders [17] (see Table 1 for a full description of the participants). All the participants with family history of psychiatric disorder declared were excluded. The study was conducted in compliance with the Code of ethical principles for medical research involving human subjects of the World Medical Association (Declaration of Helsinki) and approved by the local ethics review committee. After providing written informed consent, cognitive abilities, mood and personality characteristics of all the participants were assessed with rating scales and questionnaires as shown in Table 1. On completion of this battery, a buccal swab was taken for subsequent assay.

2.2. Genotyping

The genotype of the *COMT-val*158*met* (rs4680) SNP was determined by allelic discrimination assay (C__25746809_50) based on fluorogenic 5′ nuclease activity: a TaqMan SNP genotyping assay was performed with the ABI Prism 7900HT and analyzed with Sequence Detection System software according to the manufacturer's instructions (Applied Biosystems, Warrington, UK). To determine the genotypes of the 5-HTTLPR insertion/