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RELATIONSHIPS AMONG 5-HTT GENOTYPE, LIFE EVENTS AND GENDER IN THE RECOGNITION OF FACIAL EMOTIONS

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Abstract—Accumulating evidence has shown that a polymorphism in the promoter region of the serotonin-transporter (5-HTTLPR) modulates neural activation during the perceptual processing of emotional facial expressions. Furthermore, behavioral research has shown that attentional bias for negative information is increased in s allele carriers. We examined the interactions among 5-HTTLPR (including SNP rs25531), life events and gender on the detection of facial emotions. We found a main effect of genotype, as well as moderating effects of childhood emotional abuse (CEA) and recent life events (RLE). S homozygous participants recognized negative facial expressions at a lower intensity than the other genotype groups. This effect was more evident in female participants and in participants who had experienced life events. The 5-HTTLPR genotype affects facial emotional perception, a process which is linked to a neurobiological response to threat and vulnerability to emotional disorders.

Key words: serotonin transporter gene, stressful life events, facial emotion recognition, gender, gene-environment interaction.

Mood disorders are associated with impairments and biases in the processing of emotional and social stimuli. These impairments may underlie reduced affect regulation and social interaction, and therefore contribute to the development and maintenance of such disorders (Leppanen, 2006). Biases in the perception of emotional face expressions constitute a measurement with face validity since these biases influence social and emotional adaptation. Facial stimuli have also been used in many neuro-imaging studies since they reliably engage the amygdala, a brain region involved in emotional arousal and vigilance (Hariri et al., 2000).

Research has demonstrated that compared with healthy controls, depressed individuals show a bias in the processing of negative emotions in facial recognition tasks (Bouhuys et al., 1999; Gollan et al., 2008; Gur et al., 1992; Mikhailova et al., 1996; Surguladze et al., 2004). Facial emotion recognition bias has also been observed in the remitted state of depression (Bhagwagar et al., 2004; Hayward et al., 2005; Joormann and Gotlib, 2007; Merens et al., 2008b). Furthermore, experimental manipulations of serotonin affect the recognition of emotional face expressions, both in healthy volunteers (Harmer et al., 2003a,b, 2004; Hayward et al., 2005) and in remitted depressed patients (Merens et al., 2008a).

Hasler et al. (2004) have suggested that biased processing of emotional stimuli is a plausible endophenotype for major depression. With respect to the endophenotype criteria, there is evidence for specificity for depression, state-independence and familial association (Hasler et al., 2004). Neurobiological research has examined the association between emotional cognition and a polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) (Canli and Lesch, 2007). The serotonin transporter (5-HTT) is known to be a key regulator of serotonergic neurotransmission (Heils et al., 1996; Lesch et al., 1994). 5-HTTLPR has two variants: short allele (*s*) carriers have reduced transcriptional efficiency of serotonin compared with individuals with two copies of the long allele (*ll*) (Heils et al., 1996). More recently, an A/G single nucleotide polymorphism (rs25531) within 5-HTTLPR has been described (Wendland et al., 2006). The G allele within the *l* variant (L_G) shows lower 5-HTT mRNA expression, similar to the *s* allele (Hu et al., 2006).

Hariri and colleagues (2002) assessed neural activation during perceptual processing of fearful and angry human facial expressions, and found that *s* allele carriers exhibited greater amygdala activity, than *ll* homozygotes (Hariri et al., 2002). This finding has been replicated with larger samples (Hariri et al., 2005), and by independent groups (Canli et al., 2008; Munafo et al., 2008; Pezawas et al., 2005). *S* homozygotes also show greater activation within other brain regions (fusiform gyrus, ventral, lateral prefrontal cortex) in response to fearful faces than *l* carriers (Surguladze et al., 2008).

These studies imply that the short variant of the serotonin transporter gene leads to enhanced reactivity to negative stimuli, which may indicate a genetic-susceptibility mechanism for depression (Pezawas et al., 2005). Parallel behavioral research has shown similar results. In a mixed inpatient psychiatric sample ($n=27$), *s* carriers showed a stronger attentional bias for anxious word stimuli than participants with two long alleles (Beevers et al., 2007). In a healthy sample ($n=144$), *s* homozygotes displayed greater difficulty disengaging attention from sad, happy and fearful facial expressions than *ll* homozygotes (Beevers et al., 2009). In another study, healthy individuals homozygous for the *l* allele ($n=97$) were found to selectively attend to

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Abbreviations: ANOVA, analysis of variance; CEA, childhood emotional abuse; HADS, hospital anxiety and depression scale; RLE, recent life events; 5-HTTLPR, serotonin-transporter-linked promoter region.

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positive affective pictures and avoid negative ones, whereas this pattern was absent among *s* allele carriers (Fox et al., 2009). Among an adolescent sample (n=112), bias for angry faces increased progressively according to 5-HTTLPR status in a dot-probe task, with the *ss* group showing the highest levels of bias. For happy faces, the reverse pattern was found (Perez-Edgar et al., 2009). Children with familial history of depression had greater attentional avoidance of sad faces; a bias which was stronger among children carrying the *s* allele (Gibb et al., 2009). The effects of acute tryptophan depletion on the processing of facial emotional expressions also vary as a function of 5-HTTLPR genotype: depletion impaired the recognition of fear in *s* carriers, but not in *l* homozygotes (Marsh et al., 2006).

In contrast, some studies have shown effects inconsistent with those mentioned above. In an eye-tracking paradigm, healthy *s* allele homozygotes displayed an attentional bias to positive images compared to the other genotype groups (n=45) (Beevers et al., 2010). In another study, among a sample of individuals with familial risk of depression, no effects of allelic variation in the 5HTTLPR were found on measures of facial emotional processing (Mannie et al., 2007).

Most studies so far have used tasks displaying facial expressions of various emotional intensities for only brief periods of time. In daily life however, facial expressions are not seen as static and brief, but as varying in intensity. The ease with which people detect subtle, rather than full-blown, emotional expressions may be related to depression vulnerability. From this perspective, Joormann and Gotlib (2006) introduced a task using real faces that change progressively from a neutral expression to a full emotional expression. They found that depressed participants, in comparison with social anxiety disorder patients or healthy controls, required a greater intensity of happy emotion to correctly identify it as happy. Additionally, social anxiety disorder participants correctly identified angry expressions at a lower intensity than did depressed participants or healthy controls.

The purpose of the present study was to further examine the relationship between the 5-HTTLPR and identification of emotional facial expressions. We used the task introduced by Joormann and Gotlib (2006), which allows for evaluations of facial emotions at varying intensities, as this more closely reflects perceptual communication in real life interpersonal situations. Secondly, previous research involving the 5-HTTLPR and emotional information processing has not explored gender effects (except Beevers et al., 2010, who report no effects). Research has shown differential performance between males and females in facial emotion recognition paradigms. For example, 5-HT depletion impaired the recognition of facial expressions of fear in healthy female volunteers, but not in males (Harmer et al., 2003b). Neuroimaging studies have also reported gender differences in neural responses to facial emotion recognition (Kesler-West et al., 2001; Williams et al., 2005). Men performed worse than women on a task measuring the perception of facial emotional expressions (Montagne et al., 2005). Further, in a study examining gene-environment interaction for depression, males and females showed opposite responses to environmental stressors: *s* allele homozygous females were affected by traumatic conflicts and were more prone to develop depressive symptoms, but *s* allele homozygous males were protected from depression (Sjoberg et al., 2006).

There is mounting research examining gene-environment interactions on depression outcomes, as well as on intermediate phenotypes that are indicators of stress sensitivity (stress hormones, amygdala reactivity) (Caspi et al., 2010). We aimed to examine such a gene-environment interaction on facial emotion perception. We focused on childhood emotional abuse as an environmental stressor, since this type of abuse has been uniquely linked with depression outcomes (Brown and Harris, 2008; Gibb, 2002; Gibb et al., 2001). Emotional problems in adolescents have also been associated with biased recognition of angry and sad faces (Leist and Dadds, 2009). We also examined the influence of recent life events.

We investigated the association between facial emotion identification and 5-HTTLPR, gene-environment interactions and gender differences in these associations. We hypothesized that the *ss* allele group would identify negative emotions (sad, anger, fear) earlier in the emotion intensity sequence than participants in the *sl* and *ll* groups, and that this pattern would be more dominant among females. Furthermore, we hypothesized that life events would moderate this relationship: the *ss* genotype group would identify negative emotions earlier than other genotypes when having had adverse life experiences (early or late). Finally, we aimed to explore the effects of recent life events upon the relationship between 5-HTTLPR and facial emotion perception, to determine whether they (a) have an additive or an inoculation effect upon this relationship among participants with prior childhood emotional abuse, and/or (b) act as a sole moderator of this relationship among participants without a history of childhood emotional abuse.

EXPERIMENTAL PROCEDURES

Participants and procedure

Two hundred and fifty university students of European ancestry were recruited at various sites at Leiden University through advertisements. Participants were included only if both their parents were European. Age range was 18–45 years. On arrival to the laboratory, participants provided written informed consent and completed a number of questionnaires (data reported elsewhere: Antypa and Van der Does, 2010). The participants subsequently provided saliva samples, and finally performed the facial morphing computer task. The procedure lasted about 45 min, and participants received a small monetary reward or course credits for their participation. The research was approved by the Ethics Committee of the Leiden University Medical Center in The Netherlands.

Assessments

Genetic assessment. DNA was obtained using the Oragene Self-Collection Kit—DISC format (DNA Genotek Inc., Ottawa, ON, Canada). 200 μl of saliva was collected in lysis buffer (100 mM NaCl, 10 mM EDTA, 10 mM Tris pH 8, 0.1 mg/ml