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Modulation of emotional faces processing and its implication for depression and anxiety

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1. Introduction

The recognition of environmental information with emotional valence is crucial for the adjustment and social functioning. Since Darwin (1872), facial expressions of basic emotions have been considered as a fundamental component of the processing of emotions and various studies have provided evidence of a dissociable although interconnected involvement of different neural substrates in the emotional processing. Happiness, sadness, anger, fear and disgust are considered as basic emotions. Although with some controversies, surprise is also considered as a basic emotion.

In spite of some contrary positions (e.g. Russell, 1994) facial expressions of basic emotions have been considered as universal, i.e., identified in a similar way in different cultures, whether they are literate or preliterate (Andrew, 1963; Ekman et al., 1969), as originally proposed by Charles Darwin. The studies carried out by Paul Ekman and his colleagues led to the development of a database of photographs of actors and actresses expressing basic emotions, called Pictures of Facial Affect (Ekman & Friesen, 1976), which has been widely used in different paradigms, such as emotional processing and aversive conditioning and, more recently, psychological paradigms of activation associated with functional neuroimaging. Other sets of images with facial expressions (Gur et al., 2002) have also been used.

The facial musculature is complex, diverse and highly specialized. From an evolutionary perspective, the proliferation and diversification of the facial muscles coincide with the development of language and the period of rapid increase in hominid brain size, when they left the rain forest to live on the savannah. Life in groups led gains to secure food through hunting, and safety from predators. On the other hand, guarantee the survival and breeding in large groups required capacity to recognize emotions of other members of the social organization and, therefore, predict their behavior. If the social cues are important components in this new social organization, the ability to identify and translate these signals must have evolved in parallel with the development of the ability to express and manage, at least partially, the facial expressions. Therefore, humans would not be able to communicate emotional signs, but also to decode them quickly and efficiently (Öhman, 2002).

Our innate ability of decoding emotional signs communicated by our peers can be affected by several conditions, such emotional state, personality traits, diagnosis of mental disorders, drug manipulation, among others. In this chapter we will review results about emotional face processing, obtained through different techniques that can bring some information about the pathophysiology of anxiety and mood disorders.

2. Neural substrates of emotional faces processing

The advance of neuroimaging techniques has provided substantial data for the understanding of the neurobiology of the emotional processing in humans. Several paradigms of psychological activation have been examined by magnetic resonance imaging (fMRI) and positron emission tomography (PET) in order to evaluate specific components of the processing of emotions, such as the conscious or unconscious identification perception of basic emotions, fear conditioning, reward and punishment, among others. Studies of fMRI, applying psychological activation paradigms aimed at verifying the neural responses of healthy volunteers to facial expressions of basic emotions, suggest the activation of specific neural substrates for different emotional expressions.

The face perception in humans is mediated by a neuronal system consisted by multiple and bilateral regions (Haxby et al., 2002). This system has a hierarchical organization, initially composed of a system of visual processing of the face, made up of three distinct regions. The first of these regions is the inferior occipital gyrus that captures the general features of the face perception. This region connects to two other regions, the superior temporal sulcus and the fusiform gyrus. The superior temporal sulcus assesses changing aspects of the face, as the perception of gaze direction of the face and mouth movements. The lateral fusiform gyrus analyzes the invariant aspects of the face, giving the unique identity of each face. This system of visual analysis of the face sends links to an extensive neuronal plot with different cognitive functions that can act in accordance with the visual analysis system to give meaning to the faces. The superior temporal sulcus connects with the intraparietal sulcus, responsible for analyzing the spatial direction, related to head movement and direction of the eyes, and the auditory cortex responsible for processing phonetic content that accompanies the facial stimuli. The fusiform gyrus is connected to the lateral anterior temporal gyrus to process information concerning the identity of the person, name and biographical information. These regions would be connected with the amygdala, insula and other structures of the limbic system.

The activation of the amygdala to fearful faces has been extensively demonstrated in neuroimaging studies with healthy volunteers (Breiter et al., 1996) and studies in patients with neurological injuries show that lesions in the amygdala are associated with impairment in the recognition of facial expressions of fear (Adolphs et al., 1994). Although it is quite significant, the relationship between amygdala activation and the expression of fear seems to be unspecific, since it has also been shown activation of this structure to other emotions such as anger (Hariri et al., 2000), disgust (Sprengelmeyer et al., 1998), sadness (Surguladze et al., 2003), happiness (Breiter et al., 1996; Surguladze et al., 2003) and surprise, when this was interpreted negatively (Kim et al., 2003), suggesting a wider role of the amygdala in different stimuli with emotional valence.

The amygdala seems also to be involved in unconscious emotional processes, because neuronal responses has been observed in this area even when the volunteers did not have an

explicit recognition of emotional expressions (Whalen et al., 1998). Moreover, the activation of the amygdala to negative facial expressions presented in an unconscious perception paradigm (stimulus presentation for 33 milliseconds, followed by a neutral face, with a duration of 333 milliseconds) was followed by a bias for negative evaluation of the faces in a behavioral paradigm similar to that presented in the scanner (Dannlowski et al., 2007). These findings suggest that the increase in the neuronal activation of the amygdala would correlate with increased identification of emotion.

The processing of facial expressions of disgust has been consistently associated with activations in the insular cortex (Phillips et al., 1997), although negative results and activation of the insula by other emotions such as anger have also been reported. In addition, patients with Huntington's disease has an impairment in the recognition of emotional expressions of disgust (Sprengelmeyer et al., 1996), suggesting that fronto-striatal and especially the basal ganglia are also involved in the recognition of facial expressions of disgust, as these regions are involved in Huntington's disease.

Angry faces can be considered as a guide for the others' behavior, in situations where social rules or expectations are violated (Averill, 1982). The orbitofrontal cortex is crucially involved in this kind of function and activations in this region to expressions of anger are reported (Sprengelmeyer et al., 1998). Additionally, patients with lesions in orbitofrontal cortex, who began to show sociopathic behavior, show a generalized impairment in the recognition of facial expressions, but with a more pronounced impairment in the recognition of faces of anger (Blair, 2003) .

Activations of the frontal cortex and the cingulate cortex during the recognition of various facial expressions can be associated with the function of these regions in cognitive and integrative processing of emotions (Lane et al., 1998).

The processing of facial expressions is predominantly involved in identifying emotions, but there is evidence suggesting that viewing of facial expressions would also be able to evoke emotions through a more primitive emotional contagion (Wild et al., 2001). An alternative to the study of evoked emotions is the use of scenes depicting situations which could lead to subjective emotional states, such as the database developed by Lang and his colleagues (Lang et al., 1993), called the International Affective Picture System (IAPS). Hundreds of scenes constituents of this database were evaluated for the valence and the arousal during the validation process. In a study (Britton et al., 2006) comparing the neuronal activation caused by facial expressions of happiness, sadness, fear and anger with the neuronal activation caused by viewing of IAPS pictures with the same emotional content, it has been shown that both stimuli activated brain areas in common, such as the amygdala, posterior hippocampus, prefrontal cortex and medial visual cortex. Moreover, activations in anterior cingulate, insula and superior temporal gyrus were more pronounced for faces than to scenes. In this study it was found that the agreement on the definition of emotion displayed by the stimulus was greater for faces than for scenes, although the later were rated as with greater valence and arousal than the former. A limitation for the use of scenes would be the complexity and amount of information in each picture, which could lead to the recruitment of additional cognitive processing, and recall of prior personal experiences. On the other hand, habituation would be less frequent with the scenes compared to faces.

The neuroimaging findings indicate the existence of specific neural substrates related to the recognition of facial expressions of basic emotions. A meta-analysis (Phan et al., 2002) suggested that the amygdala plays a key role in processing emotions of fear, while the basal

ganglia seem to be particularly involved in processing other emotions such as disgust and happiness. Specifically in regard to the processing of emotional faces, a recent review of 105 fMRI studies with healthy volunteers (Fusar-Poli et al., 2009) has shown activation of amygdala to fearful, happy and sad faces, with a greater sensitivity of the amygdala for fear than happiness or sadness. On the other hand, insular response was observed to angry and disgusted faces, with a greater sensitivity to disgust than to anger. The former meta-analysis also demonstrated that regions of cortex medial prefrontal cortex (areas 9 and 10 of Brodman) extending to the anterior cingulate gyrus (areas 32/33 and 24 of Brodman) are commonly activated by different emotions, strengthening the involvement of these structures in the cognitive aspects of processing of emotions.

Since a considerable body of evidence points to sex differences in the emotional processing (Cahill, 2006), the sexual polymorphism can be a confounding variable in studies looking at the processing of facial expression. Considering the relevance of sex differences in emotional processing, it will be discussed separately.

3. Sexual dimorphism in emotional faces processing

There is a consistent body of evidence of sex differences in the performance of cognitive and emotional functions. In short, women seem to perform better on tasks of verbal fluency, memory and fine motor tasks, while men perform better on tasks related to math and spatial skills (Halpern, 1992). Despite the evidence of sex differences on the cognitive and emotional processes, this issue is still quite controversial and the magnitude, extent and nature of these differences are not fully understood.

Regarding the processing of facial expressions, the results are even more inconsistent. The results of studies comparing the performance of healthy men and women in the identification of basic emotions in facial expressions are controversial, with many pointing to negative results (e.g. Hall et al., 2004), while others point to a difference between the sexes. Among the latter, most of them suggest a better performance of women in the identification of facial expressions, regardless of emotion evaluated (e.g. Hall and Matsumoto, 2004; Rahman et al., 2004; Terracciano et al., 2003). In this direction, physiological parameters suggest a greater responsiveness of women to facial expressions (Campanella et al., 2004; Dimberg, 1990; Orozco & Ehlers, 1998), although negative results have also been reported (Lundqvist, 1995). There are, however, contrary results, showing that men would be faster than women to recognize faces of fear (Campanella et al., 2004) and anger (Williams & Mattingley, 2006).

There is also evidence of sex differences in brain lateralization for the processing of emotions. In general, men use more right hemisphere when processing facial expressions, whereas women use both hemispheres (e.g. Bourne, 2005). Functional neuroimaging studies also suggest a sex difference in the processing of facial expressions (McClure et al., 2004; Williams et al., 2005) and seems to confirm the findings of behavioral lateralization described above. There are, however, reported negative results (Schroeder et al., 2004).

Although neuroimaging studies point to sex differences in neuronal activation caused by emotional faces, results are quite variable, preventing the establishment of a pattern which distinguishes one kind or another. For instance, men showed more pronounced activation of left amygdala in one study (Killgore & Yurgelun-Todd, 2001) but of the right amygdala in other (Williams et al., 2005) to fearful faces. It has also been reported greater activation in

right insula and decreased activation in bilateral hippocampus in men during exposure to faces of fear (Williams et al., 2005). Differences in activation of the anterior cingulate cortex are also controversial, with one study showing activation more pronounced in males (McClure et al., 2004) and another study showing higher activation in females (Williams et al., 2005). There is evidence, however, of an interaction between sex of face and sex of the observer in regard to the activations of the anterior cingulate cortex. Men had a more pronounced activation in this region when looking at male faces, whereas women had more pronounced activations viewing female faces (Fischer et al., 2004). Finally, women had greater hemodynamic responses in the amygdala and right frontal regions to the angry faces (McClure et al., 2004) and men showed more pronounced activation of right amygdala to happy faces (Killgore and Yurgelun-Todd, 2001).

Taken together, the behavioral, physiological and neuroimaging data obtained so far indicate a sexual dimorphism in the processing of facial expressions, although the performance data in the paradigms are less consistent.

The difference in the behavioral data may be related to the lack of control of the phase of the menstrual cycle. There is evidence from cognitive studies pointing to a fluctuating response pattern, related to the phases of the menstrual cycle (Maki et al., 2002). In regard to emotional faces, it has also been shown that women identified facial expressions of fear with greater accuracy during the menstrual cycle characterized by high levels of estrogen (Pearson and Lewis, 2005). In addition, higher levels of progesterone have been associated to a better accuracy in the identification of fearful and disgusted faces with averted gaze as more intense than those with direct gaze (Conway et al., 2007). However, conflicting results have also been reported: women in the follicular phase, characterized by lower levels of progesterone, were more accurate in identifying all emotions than women in luteal phase, characterized by higher levels of progesterone. The behavioral performance was associated to stronger amygdalar activation to emotional faces, measured through functional magnetic resonance imaging (fMRI), with a negative correlation between plasma level of progesterone and amygdalar response to fearful, sad and neutral faces (Derntl et al., 2008a; Derntl et al., 2008b). Recently, we have shown that healthy women in the early follicular phase (day 1 to 5 of the menstrual cycle) recognized angry faces more precisely than women in the ovulatory phase (days 12 to 14) or women in the luteal phase (days 21 to 23). Sadness was more accurately recognized by women in the early follicular phase than by women in the luteal phase. Blood levels of estrogen were negatively correlated to the accuracy in identification of angry faces (Guapo et al., 2009).

Overall, the results of the studies carried out so far support the idea that women process facial expressions more efficiently than men. The results of accuracy in the tasks of identifying emotions are supported by physiological measures. For example, women had EEG (Campanella et al., 2004; Orozco and Ehlers, 1998) and EMG (Dimberg, 1990; Lundqvist, 1995) responses more pronounced, reinforcing the hypothesis that women pay more attention and have somatic reactions more intensively to emotional faces. In addition, women take into account the emotion evoked and emotional valence of the stimulus to evaluate facial expressions, while men consider only the valence component (Thayer and Johnsen, 2000). Evidence from the neuroimaging studies suggest that men and women use different neural networks for the processing of emotions, reinforcing the hypothesis of different strategies for the identification of emotions.

Despite the evidence of sex differences in brain function, this variable is rarely controlled in neuroscience research aimed at the cognitive and emotional processes, both normal and pathological (Cahill, 2006). Many mental disorders have a clear sex differences in the prevalence, clinical presentation and response to treatment, making vital controlling this confounding variable in future studies. The prevalence of depression and anxiety disorders is two times higher in women than in men (Kessler et al., 1993; Weissman et al., 1996). However, little attention has been paid to possible sex differences in emotional and cognitive mechanisms involved in the development and maintenance of depressive and anxious symptoms.

4. Anxiety, depression and emotional faces processing

There is evidence that in healthy subjects, some personality traits, which may represent an increased risk for developing depressive or anxiety disorders, may interfere with the processing of facial expressions. The predisposition to react with more anxiety as measured by the trait form of the Trait Anxiety Inventory-State (STAI) (Spielberger, 1983), was associated with a greater accuracy in identifying facial expressions of fear without interfering with the recognition of other facial expressions (Surcinelli et al., 2006). High scores on the Neuroticism subscale of the Personality Questionnaire developed by Hans Eysenck and colleagues have been considered as a vulnerability factor for the occurrence of depression (revised in Christensen & Kessing, 2006. Healthy subjects of both sexes with high scores on the subscale of Neuroticism were less accurate than individuals with low subscale scores in identifying happy faces (Chan et al., 2007).

Physiological measures also confirm changes in processing of faces of fear in anxious individuals (Rossignol et al., 2005). For example, healthy women with high levels of fear of public speaking had a higher sensitivity to angry faces, as measured by contraction of the corrugator muscles, and to happy faces, as measured by contraction of the zygomaticus, and also attributed a more negative valence the faces of anger than women with low fear of public speaking (Dimberg and Thunberg, 2007). Although dysfunctions of the hypothalamic-pituitary-adrenal axis have been reported in patients with depression and anxiety, there is evidence that acutely, glucocorticoids may reduce fear reactions. Acute administration of 40 mg of cortisol attenuated the unconscious perception of facial expressions of fear, particularly in individuals who self-reported themselves as anxious (Putman et al., 2007).

Neuroimaging studies point to a hyperactivity of the amygdala to expressions of fear in individuals with higher levels of anxiety, measured through the scores on the STAI-T (Etkin et al., 2004). Healthy individuals prone to anxiety showed more pronounced activation of the amygdala and insula to faces of anger, fear and happiness compared to a sensorimotor task, than subjects with low propensity to anxiety. No differences were found between the activation caused by each emotion separately (Stein et al., 2007). There is also evidence of an association between the expression of the short allele of the serotonin transporter, which has been associated to a higher risk to depression and anxiety, and hyperreactivity of the amygdala to faces of fear and anger in healthy volunteers of both sexes (Hariri et al., 2002).

Among patients with established diagnosis of anxiety disorders, there is also evidence of impaired processing of facial expressions. Patients with social phobia had higher skin conductance response than healthy volunteers to fearful faces presented subliminally

(Tsunoda et al., 2008). Functional neuroimaging studies have shown that no medicated social phobics patients had more pronounced activation of the amygdala to aversive faces (anger, fear, disgust) compared with faces of happiness, than healthy volunteers, and that the intensity of the hemodynamic response correlated with the severity of the phobic symptoms (Phan et al., 2006).

Panic disorder without agoraphobia or other comorbidities had an impaired of the identification of facial expressions, particularly the emotions of sadness and anger, in comparison to matched healthy controls. Patients also showed a tendency to mistakenly identify other expressions as anger. However, the presence of depressive symptoms correlated with the performance on the task and the difference between patients and controls disappeared when controlled for depression (Kessler et al., 2007). On the other hand, patients diagnosed with panic disorder and homozygous for the 1019G risk allele of the serotonin receptor 5-HT1A type showed more pronounced activation of the amygdala to faces of happiness and attenuation of the activation of prefrontal regions to fearful faces. The same pattern of increased amygdala activation to happy faces was observed in patients carrying the short allele of the serotonin transporter (Domschke et al., 2006).

Compared with healthy controls, panic patients showed lower intensity of the BOLD (Blood Oxygen Level Dependent) signal in the anterior cingulate cortex and amygdala than healthy controls in response to faces of fear and activations of the cingulate cortex were negatively correlated with subjective measures of anxiety (Pillay et al., 2006). This same group demonstrated that in response to faces of happiness, patients with panic disorder showed more pronounced activation of the anterior cingulate cortex, with no differences between groups in amygdalar activations (Pillay et al., 2007).

Some interesting results about emotional processing in patients with anxiety disorder come from a meta-analysis (Etkin & Wager, 2007) aimed at evaluating the functional neuroimaging studies of patients who underwent paradigms characterized by the contrast of negative emotional stimuli with positive or neutral conditions. They included studies with several paradigms and stimuli such as fear of public speaking for social phobia, memory of traumatic events in posttraumatic stress disorder and presentation of phobic stimuli in specific phobia. The processing of facial expressions was assessed in all anxiety disorders. However, panic disorder and obsessive-compulsive disorder were not included in the meta-analysis because the studies conducted so far have not fulfilled the inclusion criteria established by the authors. Activation of the amygdala and insula to negative stimuli were found in the three disorders studied, suggesting a common involvement of these structures in the pathophysiology of these disorders. Hyperactivity of the amygdala and the insula was more frequently observed in social phobia and specific phobia than in posttraumatic stress disorder, which in turn, presented reduced activations in the ventromedial prefrontal cortex, cingulate cortex and thalamus, which was not observed in other mental disorders study.

Cognitive theories tend to imply negative interpretations in the psychopathology of depression. Depressed individuals, or individuals predisposed to depression, have a tendency to evaluate themselves, others and events of everyday life in a more negative way than healthy controls (Beck, 1979). Patients diagnosed with major depression tend to perceive negative emotional stimuli, including faces of sadness, with greater frequency or accuracy than healthy controls, and tend to pay less attention to positive stimuli, such as happy faces. Some of these abnormalities persist after remission of symptoms and are also

found in non-depressed persons with a high risk of developing depression (revised in Leppanen, 2006).

Depressed subjects had a negative bias in judging facial expressions (Gur et al., 1992), particularly the emotion of sadness, with a strong correlation with the severity of depressive symptoms (Hale, 1998). In addition, the bias for the judgment of ambiguous facial expressions as sadness seems to be a predictor of the persistence of depressive symptoms (Hale, 1998), particularly in women (Bouhuys et al., 1999). Patients in complete remission from depression had a selective attention to facial expressions of sadness, similar to patients with current depression, while healthy volunteers tend to avoid the sad faces and oriented themselves to faces of happiness (Joormann and Gotlib, 2007). Furthermore, the recognition of facial expressions of fear and higher levels of urinary cortisol in depressed patients in complete remission were predictive of the occurrence of relapse (Bouhuys et al., 2006).

Increased neural activity to negative stimuli and decreased neural activity for positive stimuli in brain regions related to the processing of emotions, such as the amygdala and ventral striatum have also been reported in depressed patients (Leppanen, 2006). Depressed patients showed more pronounced activation of the amygdala and ventral striatum to faces of sadness (Fu et al., 2004) and an attenuated response to faces of happiness in the regions of putamen, hippocampus and ventral striatum compared with healthy controls (Fu et al., 2007). Chronic treatment with antidepressants normalized brain activation, attenuating the neuronal response of the left amygdala and ventral striatum to faces of sadness (Fu et al., 2004) and increasing the response of the ventral striatum to faces of happiness (Fu et al., 2007).

There is also evidence of an association between structural brain changes and emotional faces processing in depressed patients. Individuals diagnosed with major depression showed increased amygdalar volume and reduced hippocampal volume compared to controls, in addition to deficits in learning emotional faces, especially with emotions of fear, surprise and disgust. The size of amygdala correlated with the impairment in task performance and presence of symptoms of anxiety. The size of the hippocampus also correlated with the presence of symptoms of anxiety (Weniger et al., 2006).

Taken together, the studies with patients with depression and anxiety disorders suggest impairment in processing facial expressions of basic emotions. Among anxiety disorders, it has been observed a tendency for greater recognition of negative expressions, especially fear and anger, while in the depressive disorders there is a loss of the recognition of positive expressions and increased recognition of negative expressions, with emphasis in sad faces.

In general, neuroimaging studies indicate greater hemodynamic responses in patients than in healthy controls the presentation of facial expressions of basic emotions. The amygdala has been particularly involved in the pathophysiology of depression and anxiety disorders, and changes in their activation to emotional faces have been found in most studies with psychiatric patients.

5. Pharmacological modulation of emotional faces processing

Other evidence pointing to the existence of distinct neurocognitive systems in the emotional processing come from studies that evaluate the effects of psychoactive drugs in the perception of emotional expressions. Pharmacological challenges that interfere with various neurotransmitter systems have been used for the evaluation of their role in identifying facial

expressions, particularly with drugs that act on the serotonergic and GABAergic systems, which will be detailed below.

5.1 Modulation by the serotonergic system

The results of pharmacological challenges that interfere with serotonin function reinforce the role of serotonin (5-HT) in the processing of anxiety and fear (Deakin and Graeff, 1991), and behavioral effects were observed mainly on the recognition of facial expression of fear. Other emotions such as happiness and disgust, also seem to suffer interference in the serotonin levels for processing, though less consistent across studies.

These studies (for review, see Del-Ben et al., 2008) have shown that decreased serotonin function through depletion of the supply of tryptophan in the diet reduced the recognition of facial expressions of fear in women, and in individuals of both sexes carrying the short allele of the serotonin transporter. On the other hand, the acute increase in the dietary intake of tryptophan increased the recognition of expressions of happiness and fear in female volunteers; supplementation of tryptophan for 14 days facilitated the identification of facial expressions of happiness and decreased the recognition of expressions of disgust in women but not in male subjects.

The acute administration of intravenous citalopram, a selective inhibitor of serotonin reuptake inhibitor (SSRI), facilitated the recognition of expressions of happiness and fear in women. A similar effect on faces of fear was obtained after a single dose of citalopram administered orally in healthy volunteers of both sexes. In contrast, the administration for 7 days of oral citalopram (20 mg daily) in healthy volunteers of both sexes has increased the recognition of facial expressions of anger, fear and disgust, compared with the volunteers treated with placebo. A later study from the same group confirmed the reduction of the identification of fearful faces after treatment for 7 days with citalopram (20 mg daily) in both sexes. Euthymic patients with a history of major depression recognized fearful faces more precisely than healthy controls. The acute administration of intravenous citalopram normalized to recognition of expressions of fear in women with a history of depression, but increased the recognition of facial expressions of fear in women with no past history of depression.

These studies also suggest a sexual dimorphism in serotonergic modulation of the perception of facial expressions, since the effects of manipulating serotonin were found mainly in female volunteers. However, it is impossible to explore this hypothesis more deeply, since several studies included only women in their sample.

Acute administration of 3,4-Metilenedioximetamfetamina (MDMA, "ecstasy") in volunteers of both sexes led to an increased recognition of expressions of fear, while in the fourth day of abstinence was observed opposite effect. The drug did not interfere in the recognition of other emotional expressions. Although MDMA causes release of dopamine and norepinephrine, its main mechanism of action is via the serotonergic system, by inhibiting the reuptake of serotonin available in the synaptic cleft and the stimulation of the release of serotonin stored in presynaptic vesicles. In addition, MDMA decreases the synthesis of serotonin by inhibiting the activity of the enzyme tryptophan hydroxylase, leading to a depletion of brain serotonin in the subsequent days of substance use. The acute effect of "ecstasy" facilitated the recognition of facial expressions of fear, but impaired the recognition of facial expressions, four days after use, suggesting that increased 5-HT function facilitates the recognition, while the reduction of 5-HT function enables the perception of facial

expressions of fear. Challenges with tryptophan point to the same direction, at least in female subjects. Dietary supplementation of tryptophan, and consequent increased availability of serotonin, facilitated the recognition of facial expressions of fear, while tryptophan depletion impaired the recognition of facial expressions of fear. Acute administration of citalopram facilitated the recognition of facial expressions of fear, an effect similar to those observed with the supplementation of tryptophan in the diet and the acute use of ecstasy and opposite to that observed with the depletion of tryptophan and four days after the use of ecstasy. Taken together, these data suggest an increase in serotonin function immediately after the acute administration of citalopram.

However, in a recent published study (Alves-Neto et al., 2010), we have found a "depressive" effect of a single dose of escitalopram, the pharmacologically active S-enantiomer of RS-citalopram. The R-enantiomer has been shown to reduce the effects of the S-enantiomer (Sanchez, 2006), probably due to negative allosteric interaction at the level of the 5-HT transporter. As result, escitalopram behaves as a highly potent and selective ligand of the 5-HT transporter and clinical studies have shown that escitalopram causes few side effects and has a relatively fast onset of action (Waugh & Goa, 2003). In a placebo controlled crossover design study with healthy male volunteers we have found that a single dose of escitalopram facilitated the recognition of sadness and inhibited the recognition of happiness, but just when viewing male faces.

The interpretation of the effects of acute administration of SSRIs is not simple, since the clinical response to SSRIs is associated with an increase of the serotonin function, which in turn depends on an accommodation of serotonin receptors, particularly a desensitization of presynaptic receptors type 5-HT1A, which occurs after the use of medication for an average of two weeks. It is, therefore, that early treatment with SSRIs would be a reduction of 5-HT function, which can be associated, with the worsening of symptoms commonly seen in patients with anxiety disorders (Kent et al., 1998). Experimental data showed that after acute administration of SSRIs, there is an increase of serotonin in the raphe nuclei that is higher than in cortex (Bel & Artigas, 1992). Therefore, the acute administration of SSRI preferably would increase the concentration of serotonin around the cell bodies of serotonergic neurons, reducing their shots due to the activation of somatodendritics autoreceptors (Gartside et al., 1995), which would lead to a reduction in the post-synaptic serotonin levels. However, microdialysis studies in animals showed increased concentrations of serotonin in the extracellular space in cortical regions after acute administration of SSRI (David et al., 2003). Furthermore, the acute administration of citalopram in healthy volunteers resulted in increased plasma levels of prolactin and cortisol (Attenburrow et al., 2001; McKie et al., 2005), which is considered as an indirect measure of increased levels of serotonin in the central nervous system.

A possible explanation for these apparently contradictory results comes from studies of the functional neuroanatomy of the serotonergic system. These studies have shown that anatomically distinct serotoninergic pathways differently modulate specific brain circuits. These dissociations suggest that serotonin activity within different regions of the raphe nucleus may be under the influence of different regulatory pathways, being recruited in different ways, depending on specific conditions of the environment and the characteristics of the stimulus (Lowry et al., 2005).

5.2 Modulation of the GABAergic system

There is evidence, albeit in smaller numbers, that the GABAergic system also modulates the recognition of basic emotional expressions. Although benzodiazepines are typical anxiolytic drugs, few studies have been carried out so far investigating their effect on the processing of facial expressions, and they show seemingly contradictory results. It has been that 15 mg of diazepam selectively impair the identification of angry faces (Blair & Curran, 1999). In a further study, however, the same research group (Zangara et al., 2002) reported that the same dose of diazepam affected both angry and fearful faces. To explain these conflicting results, the authors considered that the emotional state of the volunteers could have interfered with the processing of emotional cues, since in the former study, the participants reported more anxiety and discomfort than in the latter. Another study has pointed to a global impairment by diazepam of the identification of emotional faces (Coupland et al., 2003). There is also reported evidence showing no effect of lorazepam (Kamboj & Curran, 2006) or of a low dose of diazepam (Murphy et al., 2008) on the recognition of facial emotional expressions.

The discrepancy in results between the studies described above may be due to differences in the interval between drug administration and implementation of the experimental procedure. In the first (Blair & Curran, 1999) and second (Zangara et al., 2002) studies, the task was initiated 40 minutes after ingestion of the drug, while in the third (Coupland et al., 2003), the task began 75 minutes after drug administration. Therefore, the sedative effects of diazepam may have been responsible for a loss of attention and consequent impaired performance on the task. In addition, the sample of the third study (Coupand et al., 2003) was not balanced by sex, with a majority of women relative to men, which may have affected the results, since, as discussed earlier, there is evidence of a sexual dimorphism in processing of emotion.

Although ethanol acts on different neurotransmitter systems, it is known that the GABAergic system is heavily influenced by this substance and therefore the effects of acute alcohol will be discussed in this session. Alcohol impaired the recognition of emotional expressions of anger in women, while men had reduction in the identification of faces of anger, fear and disgust (Borrill et al., 1987). These data reinforce two points raised earlier: a) the GABAergic system plays an important role in the recognition of emotional expressions of anger and b) there is a sexual dimorphism in the recognition of facial expressions. It has also been shown that low doses of alcohol increased, while higher doses of alcohol decreased the recognition of emotional expressions of happiness by healthy males, suggesting a dose-dependent effect of alcohol on the recognition of facial expressions (Kano et al., 2003).

5.3 Pharmacological challenges and functional neuroimaging

The combination of pharmacological challenges with functional magnetic resonance imaging (Pharmacological Functional Magnetic Resonance Imaging, pharmaco fMRI) is an emerging and promising field of study, which allows the investigation of the effect of drugs on cerebral metabolic activity through measures of changes in the BOLD (Blood Oxygen Level Dependent) signal. However, few studies have investigated the modulation of hemodynamic activation by facial expressions.

So far, only one study (Paulus et al., 2005) examined the effects of pharmacological manipulation with benzodiazepines in neuronal activation, measured by magnetic

resonance functional, caused by facial expressions of basic emotions. Lorazepam was administered orally, at doses of 0.25 mg and 1 mg in 15 healthy volunteers (six women and nine men). The paradigm of psychological activation consisted of presenting a target face (anger, fear or happiness) at the top of the computer screen, being the volunteers asked to paired the emotional expression of the target face with one of the emotional expressions presented in other two faces shown in bottom the of the computer screen by pressing the right and left of a button box. The control task consisted of matching geometric figures. Regardless of the type of emotion, the volunteers showed activation of bilateral amygdala and insula during the task of matching facial expressions, compared to the control task. Lorazepam attenuated the hemodynamic response of the amygdala and the insula, in a dose-dependent way.

The role of the serotonergic system in the emotional faces processing has been a little more investigated through the association of pharmacological challenges and fMRI.

In an unconscious perception paradigm, where volunteers were asked only to recognize the sex of faces during the imaging acquisition, tryptophan depletion in healthy men increased amygdala activation in response to fear faces compared with neutral and happy faces, but just in individuals with high levels of sensitivity to threat, measured by the BIS/BAS (Behavioral Inhibition System / Behavioral Aversive System) scale (Cools et al., 2005). These results have been replicated in healthy women, showing a significant correlation between sensitivity to threats, as measured by the BIS/BAS scale, and more pronounced activation of the amygdala to fearful faces compared to faces of happiness, under the effect of depletion of tryptophan (van der Veen et al., 2007). This later study also showed that mood changes (depressive symptoms) caused by tryptophan depletion in healthy women with a family history of depression was associated with greater impairment in the performance in a task of sex categorization of faces with negative facial expressions (fear, sadness and disgust) and increased right amygdalar activation to faces of fear.

The effects of tryptophan depletion were also evaluated in the processing of faces of sadness and happiness (Fusar-Poli et al., 2007). Independently of the emotional valence of the face, tryptophan depletion attenuated the activations of the right medial/inferior frontal gyrus, the posterior cingulate cortex, the occipital and parietal cortex bilaterally, the right hippocampus, claustrum and insula. Referring specifically to the amygdala, effects were observed only when the emotions were combined and compared with neutral faces. The depletion of tryptophan attenuated amygdala response to emotional faces.

In a paradigm of sex categorization of faces, we found that a low dose of citalopram (7.5 mg), administered intravenously to healthy male volunteers, attenuated the hemodynamic response in right amygdala and right orbitofrontal cortex to aversive faces (anger, disgust and fear) compared to neutral faces in healthy men (Del-Ben et al., 2005). In a study (Anderson et al., 2007) published latter, we reanalyzed the data evaluating the effects of intravenous citalopram on each emotion separately and found that citalopram attenuated the activation of the amygdala to faces of fear and disgust, while increased activation of the insula to disgust faces. No effects of escitalopram on angry faces have been detected.

In this study (Anderson et al., 2007), although citalopram has reduced the activation of the amygdala to faces of fear and disgust, it occurred in different hemispheres. Possibly this is due to the fact that, regardless of treatment, the right amygdala activation was more robust to the faces of fear, while the left amygdala signal intensity was higher at the faces of disgust. A lateralization of the functions of the amygdala has been suggested; the right

amygdala is more associated with arousal and the left with cognitive processes (Skuse et al., 2005). It is possible that the faces of fear have a more immediate emotional salience, while the faces of disgust require the engagement of cognitive functions for their processing. Another possibility would be differences in the time of habituation to the two types of stimuli.

We also observed that, in contrast to the attenuation of the amygdala, citalopram increased the activation of left insula (and on right, at a level below statistical significance), extending to the claustrum, to disgusted faces. The anterior insula has connections with the amygdala and, along with the ventromedial prefrontal cortex, hypothalamus and periaqueductal gray material, is part of a network that modulates the identification and response to threatening stimuli. However, in this study, we found activation of posterior portions of the insula, which seems to be involved with somatosensory processes and pain. Although not specified a priori, citalopram increased the activation of the pulvinar nucleus and occipital cortex, suggesting that serotonin can enhance the function of pathways responsible for the integration of interoceptive and exteroceptive information.

Further studies have confirmed the role of antidepressants in the emotional faces processing. Healthy volunteers of both sexes were subjected to a treatment for seven days with citalopram orally at a dose of 20 mg/day and underwent a paradigm of unconscious perception of facial expressions of fear and happiness marked by the presentation of emotional faces for 17 milliseconds followed by a neutral face with duration of 167 milliseconds. The amygdala was established as a priori region of interest; the treatment caused an attenuation of the activation in the bilateral amygdala to fearful compared with happy faces (Harmer et al., 2006). More recently, the same group has shown that a single dose of citalopram, administered orally, attenuated the amygdalar activation to masked fearful faces (Murphy et al., 2009). Attenuation of amygdala to emotional faces, assessed by a paradigm similar to those used in the lorazepam study (described earlier), has also been obtained with escitalopram, given to health volunteers during 21 days (Arce et al., 2008).

In these neuroimaging studies, effects of the drug in the performance of the tasks performed during the acquisition of neuroimaging were not observed. Also there were no changes in subjective states, except a reduction in self-reported hostility as measured by the Hostility Inventory Buss-Durkee after seven days of use of citalopram.

Given the role of the amygdala in the early stages of coordinating responses to threatening stimuli and the production of emotional states, the effects of citalopram and escitalopram suggest a modulatory role of serotonin in this process, consistent with previous studies showing serotonergic modulation of the amygdala activation to faces of fear by using tryptophan depletion (Cools et al., 2005; van der Veen et al., 2007).

5.4 Combining behavioral data and neuroimaging

To date, few studies have evaluated the modulation of the hemodynamic response caused by facial expressions. In addition, differences in the characteristics of the samples, procedures for acquisition, the analysis of images and paradigms activation employees become even more complex interpreting and conciliating the results of neuroimaging studies.

The interpretation of the modulatory effects of drugs on the findings of fMRI also has its limitations. Increased BOLD signal is considered as an increase rate of neuronal metabolism, as measured by oxygen consumption. The increase in neuronal metabolism caused by the

pharmacological challenge may reflect either an increase in performance ("working better") or the need for an extra effort to achieve the same level of function ("working harder"). The ideal experimental design would be studies correlating behavioral and neuroimaging data and taking into account some confounding variables such as dose, route and time of administration of the pharmacological challenges, as well as sex, age, personality traits, previous history of mental disorders of the participant and his/her relatives and genetics.

The only study so far carried out with benzodiazepines (Paulus et al., 2005) pointed to the attenuation of the amygdala and the insula to emotional faces (positive and positive) compared with a sensorimotor task. These data are in line with behavioral data that show an impairment of the recognition of emotional faces, particularly anger, caused by benzodiazepines (Blair and Curran, 1999; Coupland et al., 2003; Zangara et al., 2002).

Conciliating the results obtained in both behavioral studies and neuroimaging findings that evaluated the serotoninergic function makes the situation even more complex, since the direction of the modulation of neuronal activation is contrary to those of the behavioral studies. If indeed there is a direct correlation between neuronal activation and performance on the task, we would expected that increased serotonergic function would increase neuronal activations and vice versa, but the studies carried out so far point to an increase in neuronal activation of the amygdala (Cools et al., 2005; van der Veen et al., 2007) and reduced accuracy in identifying faces of fear (Harmer et al., 2003b; Marsh et al., 2006) under the effect of depletion of tryptophan. Moreover, behavioral studies point to a facilitation, by acute citalopram, of the recognition of faces of fear (Harmer et al., 2003a) and neuroimaging studies show an attenuation of activation of the amygdala with acute dose (Anderson et al., 2007; Murphy et al., 2009) and of citalopram, given during 7 days (Harmer et al., 2006), and escitalopram, given during 21 days (Arce et al., 2008).

The effects of tryptophan depletion described above were obtained only in volunteers sensitive to threat and therefore these apparently contradictory results may be related to the influence of personality traits. As discussed later, clinical studies show a more pronounced activation of the amygdala to facial expressions in healthy subjects with high traits of anxiety and in patients with anxiety disorders.

With regard to citalopram, it may be that the route of administration has some influence on the effects of drugs on serotonin function. As a part of the study described previously (Del-Ben et al., 2005) images were taken immediately before, during and immediately after infusion of citalopram in order to evaluate the direct effects of the drug in the hemodynamic responses. We observed a pattern of activation of neuronal responses in several brain structures involved in emotional processing (McKie et al., 2005) similar to those observed with the administration of metaclorofenilpiperazina (mCPP), a serotonin agonist (Anderson et al., 2002). Therefore, one may speculate that with the intravenous administration, there is an initial effect of increased serotonin function, before the activation of inhibitory auto-receptors. However, the results obtained with a single dose of citalopram, given orally, has also shown an attenuation of amygdala to fearful faces (Murphy et al., 2009).

An alternative explanation for the initial effects of the antidepressants has been proposed by Catherine Harmer and her colleagues (Harmer et al., 2009). It has been proposed that the clinical effects, particularly in depressed patients, are due to initial changes in the way that the individual processes relevant emotional information, correcting the negative emotional bias normally observed in these patients, which, in turn, lead to mood changes. According

to this view, early changes in emotional processing precede and contribute to later changes in mood and depressive symptoms following antidepressant drug treatment.

6. Final remarks

Emotional faces processing is an innate and socially relevant human ability that can easily be assessed. It can be under the influence of personality traits, genetics and sexual dimorphism, and can be altered by current or past psychiatric diagnosis. Of particular interest, it can be manipulated by drugs largely used in the clinical practice. Relatively simple paradigms composed by facial expressions of basic emotions have contributed significantly for a better understanding of the pathophysiology of several mental disorders. This tool can also have a role for different purposes, such as the prediction of the clinical response, the discovery of new compounds, among others.

7. References

Adolphs, R., Tranel, D., Damasio, H., Damasio, A., 1994. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature 372, 669-672.

Alves-Neto, W.C., Guapo, V.G., Graeff, F.G., Deakin, J.F., Del-Ben, C.M., 2010. Effect of escitalopram on the processing of emotional faces. Braz J Med Biol Res.

Anderson, I.M., Clark, L., Elliott, R., Kulkarni, B., Williams, S.R., Deakin, J.F., 2002. 5-HT(2C) receptor activation by m-chlorophenylpiperazine detected in humans with fMRI. Neuroreport 13, 1547-1551.

Anderson, I.M., Del-Ben, C.M., McKie, S., Richardson, P., Williams, S.R., Elliott, R., Deakin, J.F., 2007. Citalopram modulation of neuronal responses to aversive face emotions: a functional MRI study. Neuroreport 18, 1351-1355.

Andrew, R.J., 1963. Evolution of Facial Expression. Science 142, 1034-1041.

Arce, E., Simmons, A.N., Lovero, K.L., Stein, M.B., Paulus, M.P., 2008. Escitalopram effects on insula and amygdala BOLD activation during emotional processing. Psychopharmacology (Berl) 196, 661-672.

Attenburrow, M.J., Mitter, P.R., Whale, R., Terao, T., Cowen, P.J., 2001. Low-dose citalopram as a 5-HT neuroendocrine probe. Psychopharmacology (Berl) 155, 323-326.

Averill, J.R., 1982. Anger and aggression: an essay of emotion, New York.

Beck, A.T., 1979. Cognitive therapy of depression. Guilford Press, New York.

Bel, N., Artigas, F., 1992. Fluvoxamine preferentially increases extracellular 5-hydroxytryptamine in the raphe nuclei: an in vivo microdialysis study. Eur J Pharmacol 229, 101-103.

Blair, R.J., 2003. Neurobiological basis of psychopathy. Br J Psychiatry 182, 5-7.

Blair, R.J., Curran, H.V., 1999. Selective impairment in the recognition of anger induced by diazepam. Psychopharmacology (Berl) 147, 335-338.

Borrill, J.A., Rosen, B.K., Summerfield, A.B., 1987. The influence of alcohol on judgement of facial expression of emotion. Br J Med Psychol 60 (Pt 1), 71-77.

Bouhuys, A.L., Bos, E.H., Geerts, E., van Os, T.W., Ormel, J., 2006. The association between levels of cortisol secretion and fear perception in patients with remitted depression predicts recurrence. J Nerv Ment Dis 194, 478-484.

Bouhuys, A.L., Geerts, E., Gordijn, M.C., 1999. Depressed patients' perceptions of facial emotions in depressed and remitted states are associated with relapse: a longitudinal study. J Nerv Ment Dis 187, 595-602.

Bourne, V.J., 2005. Lateralised processing of positive facial emotion: sex differences in strength of hemispheric dominance. Neuropsychologia 43, 953-956.

Breiter, H.C., Etcoff, N.L., Whalen, P.J., Kennedy, W.A., Rauch, S.L., Buckner, R.L., Strauss, M.M., Hyman, S.E., Rosen, B.R., 1996. Response and habituation of the human amygdala during visual processing of facial expression. Neuron 17, 875-887.

Britton, J.C., Taylor, S.F., Sudheimer, K.D., Liberzon, I., 2006. Facial expressions and complex IAPS pictures: common and differential networks. Neuroimage 31, 906-919.

Cahill, L., 2006. Why sex matters for neuroscience. Nat Rev Neurosci 7, 477-484.

Campanella, S., Rossignol, M., Mejias, S., Joassin, F., Maurage, P., Debatisse, D., Bruyer, R., Crommelinck, M., Guerit, J.M., 2004. Human gender differences in an emotional visual oddball task: an event-related potentials study. Neurosci Lett 367, 14-18.

Chan, S.W., Goodwin, G.M., Harmer, C.J., 2007. Highly neurotic never-depressed students have negative biases in information processing. Psychol Med 37, 1281-1291.

Christensen, M.V., Kessing, L.V., 2006. Do personality traits predict first onset in depressive and bipolar disorder? Nord J Psychiatry 60, 79-88.

Conway, C.A., Jones, B.C., DeBruine, L.M., Welling, L.L., Law Smith, M.J., Perrett, D.I., Sharp, M.A., Al-Dujaili, E.A., 2007. Salience of emotional displays of danger and contagion in faces is enhanced when progesterone levels are raised. Horm Behav 51, 202-206.

Cools, R., Calder, A.J., Lawrence, A.D., Clark, L., Bullmore, E., Robbins, T.W., 2005. Individual differences in threat sensitivity predict serotonergic modulation of amygdala response to fearful faces. Psychopharmacology (Berl) 180, 670-679.

Coupland, N.J., Singh, A.J., Sustrik, R.A., Ting, P., Blair, R., 2003. Effects of diazepam on facial emotion recognition. J Psychiatry Neurosci 28, 452-463.

Dannlowski, U., Ohrmann, P., Bauer, J., Kugel, H., Arolt, V., Heindel, W., Suslow, T., 2007. Amygdala reactivity predicts automatic negative evaluations for facial emotions. Psychiatry Res 154, 13-20.

Darwin, C., 1872. The expression of the emotions in man and animals. Murray, [S.l.].

David, D.J., Bourin, M., Jego, G., Przybylski, C., Jolliet, P., Gardier, A.M., 2003. Effects of acute treatment with paroxetine, citalopram and venlafaxine in vivo on noradrenaline and serotonin outflow: a microdialysis study in Swiss mice. Br J Pharmacol 140, 1128-1136.

Deakin, J.F.W., Graeff, F.G., 1991. 5-HT and mechanisms of defense. Journal of Psychopharmacology 5, 10.

Del-Ben, C.M., Deakin, J.F., McKie, S., Delvai, N.A., Williams, S.R., Elliott, R., Dolan, M., Anderson, I.M., 2005. The effect of citalopram pretreatment on neuronal responses to neuropsychological tasks in normal volunteers: an FMRI study. Neuropsychopharmacology 30, 1724-1734.

Del-Ben, C.M., Ferreira, C.A., Alves-Neto, W.C., Graeff, F.G., 2008. Serotonergic modulation of face-emotion recognition. Braz J Med Biol Res 41, 263-269.

Derntl, B., Kryspin-Exner, I., Fernbach, E., Moser, E., Habel, U., 2008a. Emotion recognition accuracy in healthy young females is associated with cycle phase. Horm Behav 53, 90-95.

Derntl, B., Windischberger, C., Robinson, S., Lamplmayr, E., Kryspin-Exner, I., Gur, R.C., Moser, E., Habel, U., 2008b. Facial emotion recognition and amygdala activation are associated with menstrual cycle phase. Psychoneuroendocrinology 33, 1031-1040.

Dimberg, U., 1990. Facial electromyography and emotional reactions. Psychophysiology 27, 481-494.

Dimberg, U., Thunberg, M., 2007. Speech anxiety and rapid emotional reactions to angry and happy facial expressions. Scand J Psychol 48, 321-328.

Domschke, K., Braun, M., Ohrmann, P., Suslow, T., Kugel, H., Bauer, J., Hohoff, C., Kersting, A., Engelien, A., Arolt, V., Heindel, W., Deckert, J., 2006. Association of the functional -1019C/G 5-HT1A polymorphism with prefrontal cortex and amygdala activation measured with 3 T fMRI in panic disorder. Int J Neuropsychopharmacol 9, 349-355.

Ekman, P., Friesen, F., 1976. Pictures of Facial Affect. Consulting Psychology, Palo Alto, California.

Ekman, P., Sorenson, E.R., Friesen, W.V., 1969. Pan-cultural elements in facial displays of emotion. Science 164, 86-88.

Etkin, A., Klemenhagen, K.C., Dudman, J.T., Rogan, M.T., Hen, R., Kandel, E.R., Hirsch, J., 2004. Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. Neuron 44, 1043-1055.

Etkin, A., Wager, T.D., 2007. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry 164, 1476-1488.

Fischer, H., Fransson, P., Wright, C.I., Backman, L., 2004. Enhanced occipital and anterior cingulate activation in men but not in women during exposure to angry and fearful male faces. Cogn Affect Behav Neurosci 4, 326-334.

Fu, C.H., Williams, S.C., Brammer, M.J., Suckling, J., Kim, J., Cleare, A.J., Walsh, N.D., Mitterschiffthaler, M.T., Andrew, C.M., Pich, E.M., Bullmore, E.T., 2007. Neural responses to happy facial expressions in major depression following antidepressant treatment. Am J Psychiatry 164, 599-607.

Fu, C.H., Williams, S.C., Cleare, A.J., Brammer, M.J., Walsh, N.D., Kim, J., Andrew, C.M., Pich, E.M., Williams, P.M., Reed, L.J., Mitterschiffthaler, M.T., Suckling, J., Bullmore, E.T., 2004. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. Arch Gen Psychiatry 61, 877-889.

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., Benedetti, F., Abbamonte, M., Gasparotti, R., Barale, F., Perez, J., McGuire, P., Politi, P., 2009. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J Psychiatry Neurosci 34, 418-432.

Gartside, S.E., Umbers, V., Hajos, M., Sharp, T., 1995. Interaction between a selective 5-HT1A receptor antagonist and an SSRI in vivo: effects on 5-HT cell firing and extracellular 5-HT. Br J Pharmacol 115, 1064-1070.

Guapo, V.G., Graeff, F.G., Zani, A.C., Labate, C.M., dos Reis, R.M., Del-Ben, C.M., 2009. Effects of sex hormonal levels and phases of the menstrual cycle in the processing of emotional faces. Psychoneuroendocrinology 34, 1087-1094.

Gur, R.C., Erwin, R.J., Gur, R.E., Zwil, A.S., Heimberg, C., Kraemer, H.C., 1992. Facial emotion discrimination: II. Behavioral findings in depression. Psychiatry Res 42, 241-251.

Gur, R.C., Sara, R., Hagendoorn, M., Marom, O., Hughett, P., Macy, L., Turner, T., Bajcsy, R., Posner, A., Gur, R.E., 2002. A method for obtaining 3-dimensional facial expressions and its standardization for use in neurocognitive studies. J Neurosci Methods 115, 137-143.

Hale, W.W., 3rd, 1998. Judgment of facial expressions and depression persistence. Psychiatry Res 80, 265-274.

Hall, C.W., Gaul, L., Kent, M., 1999. College students' perception of facial expressions. Percept Mot Skills 89, 763-770.

Hall, J.A., Matsumoto, D., 2004. Gender differences in judgments of multiple emotions from facial expressions. Emotion 4, 201-206.

Halpern, D.F., 1992. Sex differences in cognitive abilities, 2nd ed, Hillsdale, NJ.

Hariri, A.R., Bookheimer, S.Y., Mazziotta, J.C., 2000. Modulating emotional responses: effects of a neocortical network on the limbic system. Neuroreport 11, 43-48.

Hariri, A.R., Mattay, V.S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., Egan, M.F., Weinberger, D.R., 2002. Serotonin transporter genetic variation and the response of the human amygdala. Science 297, 400-403.

Harmer, C.J., Bhagwagar, Z., Perrett, D.I., Vollm, B.A., Cowen, P.J., Goodwin, G.M., 2003a. Acute SSRI administration affects the processing of social cues in healthy volunteers. Neuropsychopharmacology 28, 148-152.

Harmer, C.J., Goodwin, G.M., Cowen, P.J., 2009. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. Br J Psychiatry 195, 102-108.

Harmer, C.J., Mackay, C.E., Reid, C.B., Cowen, P.J., Goodwin, G.M., 2006. Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. Biol Psychiatry 59, 816-820.

Harmer, C.J., Rogers, R.D., Tunbridge, E., Cowen, P.J., Goodwin, G.M., 2003b. Tryptophan depletion decreases the recognition of fear in female volunteers. Psychopharmacology (Berl) 167, 411-417.

Haxby, J.V., Hoffman, E.A., Gobbini, M.I., 2002. Human neural systems for face recognition and social communication. Biol Psychiatry 51, 59-67.

Joormann, J., Gotlib, I.H., 2007. Selective attention to emotional faces following recovery from depression. J Abnorm Psychol 116, 80-85.

Kamboj, S.K., Curran, H.V., 2006. Scopolamine induces impairments in the recognition of human facial expressions of anger and disgust. Psychopharmacology (Berl) 185, 529-535.

Kano, M., Gyoba, J., Kamachi, M., Mochizuki, H., Hongo, M., Yanai, K., 2003. Low doses of alcohol have a selective effect on the recognition of happy facial expressions. Hum Psychopharmacol 18, 131-139.

Kent, J.M., Coplan, J.D., Gorman, J.M., 1998. Clinical utility of the selective serotonin reuptake inhibitors in the spectrum of anxiety. Biol Psychiatry 44, 812-824.

Kesler-West, M.L., Andersen, A.H., Smith, C.D., Avison, M.J., Davis, C.E., Kryscio, R.J., Blonder, L.X., 2001. Neural substrates of facial emotion processing using fMRI. Brain Res Cogn Brain Res 11, 213-226.

Kessler, H., Roth, J., von Wietersheim, J., Deighton, R.M., Traue, H.C., 2007. Emotion recognition patterns in patients with panic disorder. Depress Anxiety 24, 223-226.

Kessler, R.C., McGonagle, K.A., Swartz, M., Blazer, D.G., Nelson, C.B., 1993. Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. J Affect Disord 29, 85-96.

Killgore, W.D., Yurgelun-Todd, D.A., 2001. Sex differences in amygdala activation during the perception of facial affect. Neuroreport 12, 2543-2547.

Kim, H., Somerville, L.H., Johnstone, T., Alexander, A.L., Whalen, P.J., 2003. Inverse amygdala and medial prefrontal cortex responses to surprised faces. Neuroreport 14, 2317-2322.

Lane, R.D., Reiman, E.M., Axelrod, B., Yun, L.S., Holmes, A., Schwartz, G.E., 1998. Neural correlates of levels of emotional awareness. Evidence of an interaction between emotion and attention in the anterior cingulate cortex. J Cogn Neurosci 10, 525-535.

Lang, P.J., Greenwald, M.K., Bradley, M.M., Hamm, A.O., 1993. Looking at pictures: affective, facial, visceral, and behavioral reactions. Psychophysiology 30, 261-273.

Leppanen, J.M., 2006. Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. Curr Opin Psychiatry 19, 34-39.

Lowry, C.A., Johnson, P.L., Hay-Schmidt, A., Mikkelsen, J., Shekhar, A., 2005. Modulation of anxiety circuits by serotonergic systems. Stress 8, 233-246.

Lundqvist, L.O., 1995. Facial EMG reactions to facial expressions: a case of facial emotional contagion? Scand J Psychol 36, 130-141.

Maki, P.M., Rich, J.B., Rosenbaum, R.S., 2002. Implicit memory varies across the menstrual cycle: estrogen effects in young women. Neuropsychologia 40, 518-529.

Marsh, A.A., Finger, E.C., Buzas, B., Soliman, N., Richell, R.A., Vythilingham, M., Pine, D.S., Goldman, D., Blair, R.J., 2006. Impaired recognition of fear facial expressions in 5-HTTLPR S-polymorphism carriers following tryptophan depletion. Psychopharmacology (Berl) 189, 387-394.

McClure, E.B., Monk, C.S., Nelson, E.E., Zarahn, E., Leibenluft, E., Bilder, R.M., Charney, D.S., Ernst, M., Pine, D.S., 2004. A developmental examination of gender differences in brain engagement during evaluation of threat. Biol Psychiatry 55, 1047-1055.

McKie, S., Del-Ben, C., Elliott, R., Williams, S., del Vai, N., Anderson, I., Deakin, J.F., 2005. Neuronal effects of acute citalopram detected by pharmacoMRI. Psychopharmacology (Berl) 180, 680-686.

Murphy, S.E., Downham, C., Cowen, P.J., Harmer, C.J., 2008. Direct effects of diazepam on emotional processing in healthy volunteers. Psychopharmacology (Berl) 199, 503-513.

Murphy, S.E., Norbury, R., O'Sullivan, U., Cowen, P.J., Harmer, C.J., 2009. Effect of a single dose of citalopram on amygdala response to emotional faces. Br J Psychiatry 194, 535-540.

Öhman, A., 2002. Automaticity and the Amygdala: Nonconscious Responses to Emotional Faces. Current Directions in Psychological Sciences, p. 5.

Orozco, S., Ehlers, C.L., 1998. Gender differences in electrophysiological responses to facial stimuli. Biol Psychiatry 44, 281-289.

Paulus, M.P., Feinstein, J.S., Castillo, G., Simmons, A.N., Stein, M.B., 2005. Dose-dependent decrease of activation in bilateral amygdala and insula by lorazepam during emotion processing. Arch Gen Psychiatry 62, 282-288.

Pearson, R., Lewis, M.B., 2005. Fear recognition across the menstrual cycle. Horm Behav 47, 267-271.

Phan, K.L., Fitzgerald, D.A., Nathan, P.J., Tancer, M.E., 2006. Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. Biol Psychiatry 59, 424-429.

Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I., 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 16, 331-348.

Phillips, M.L., Young, A.W., Senior, C., Brammer, M., Andrew, C., Calder, A.J., Bullmore, E.T., Perrett, D.I., Rowland, D., Williams, S.C., Gray, J.A., David, A.S., 1997. A specific neural substrate for perceiving facial expressions of disgust. Nature 389, 495-498.

Pillay, S.S., Gruber, S.A., Rogowska, J., Simpson, N., Yurgelun-Todd, D.A., 2006. fMRI of fearful facial affect recognition in panic disorder: the cingulate gyrus-amygdala connection. J Affect Disord 94, 173-181.

Pillay, S.S., Rogowska, J., Gruber, S.A., Simpson, N., Yurgelun-Todd, D.A., 2007. Recognition of happy facial affect in panic disorder: an fMRI study. J Anxiety Disord 21, 381-393.

Putman, P., Hermans, E.J., Koppeschaar, H., van Schijndel, A., van Honk, J., 2007. A single administration of cortisol acutely reduces preconscious attention for fear in anxious young men. Psychoneuroendocrinology 32, 793-802.

Rahman, Q., Wilson, G.D., Abrahams, S., 2004. Sex, sexual orientation, and identification of positive and negative facial affect. Brain Cogn 54, 179-185.

Rossignol, M., Philippot, P., Douilliez, C., Crommelinck, M., Campanella, S., 2005. The perception of fearful and happy facial expression is modulated by anxiety: an event-related potential study. Neurosci Lett 377, 115-120.

Russell, J.A., 1994. Is there universal recognition of emotion from facial expression? A review of the cross-cultural studies. Psychol Bull 115, 102-141.

Sanchez, C., 2006. The pharmacology of citalopram enantiomers: the antagonism by R-citalopram on the effect of S-citalopram. Basic Clin Pharmacol Toxicol 99, 91-95.

Schroeder, U., Hennenlotter, A., Erhard, P., Haslinger, B., Stahl, R., Lange, K.W., Ceballos-Baumann, A.O., 2004. Functional neuroanatomy of perceiving surprised faces. Hum Brain Mapp 23, 181-187.

Skuse, D.H., Morris, J.S., Dolan, R.J., 2005. Functional dissociation of amygdala-modulated arousal and cognitive appraisal, in Turner syndrome. Brain 128, 2084-2096.

Spielberger, C.D., 1983. Manual for the state/trait anxiety inventory (form Y) : (self evaluation questionnaire). Consulting Psychologists Press, Palo Alto.

Sprengelmeyer, R., Rausch, M., Eysel, U.T., Przuntek, H., 1998. Neural structures associated with recognition of facial expressions of basic emotions. Proc Biol Sci 265, 1927-1931.

Sprengelmeyer, R., Young, A.W., Calder, A.J., Karnat, A., Lange, H., Homberg, V., Perrett, D.I., Rowland, D., 1996. Loss of disgust. Perception of faces and emotions in Huntington's disease. Brain 119 (Pt 5), 1647-1665.

Stein, M.B., Simmons, A.N., Feinstein, J.S., Paulus, M.P., 2007. Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. Am J Psychiatry 164, 318-327.

Surcinelli, P., Codispoti, M., Montebarocci, O., Rossi, N., Baldaro, B., 2006. Facial emotion recognition in trait anxiety. J Anxiety Disord 20, 110-117.

Surguladze, S.A., Brammer, M.J., Young, A.W., Andrew, C., Travis, M.J., Williams, S.C., Phillips, M.L., 2003. A preferential increase in the extrastriate response to signals of danger. Neuroimage 19, 1317-1328.

Terracciano, A., Merritt, M., Zonderman, A.B., Evans, M.K., 2003. Personality traits and sex differences in emotion recognition among African Americans and Caucasians. Ann N Y Acad Sci 1000, 309-312.

Thayer, J.F., Johnsen, B.H., 2000. Sex differences in judgement of facial affect: a multivariate analysis of recognition errors. Scand J Psychol 41, 243-246.

Tsunoda, T., Yoshino, A., Furusawa, T., Miyazaki, M., Takahashi, Y., Nomura, S., 2008. Social anxiety predicts unconsciously provoked emotional responses to facial expression. Physiol Behav 93, 172-176.

van der Veen, F.M., Evers, E.A., Deutz, N.E., Schmitt, J.A., 2007. Effects of acute tryptophan depletion on mood and facial emotion perception related brain activation and performance in healthy women with and without a family history of depression. Neuropsychopharmacology 32, 216-224.

Waugh, J., Goa, K.L., 2003. Escitalopram : a review of its use in the management of major depressive and anxiety disorders. CNS Drugs 17, 343-362.

Weissman, M.M., Bland, R.C., Canino, G.J., Faravelli, C., Greenwald, S., Hwu, H.G., Joyce, P.R., Karam, E.G., Lee, C.K., Lellouch, J., Lepine, J.P., Newman, S.C., Rubio-Stipec, M., Wells, J.E., Wickramaratne, P.J., Wittchen, H., Yeh, E.K., 1996. Cross-national epidemiology of major depression and bipolar disorder. JAMA 276, 293-299.

Weniger, G., Lange, C., Irle, E., 2006. Abnormal size of the amygdala predicts impaired emotional memory in major depressive disorder. J Affect Disord 94, 219-229.

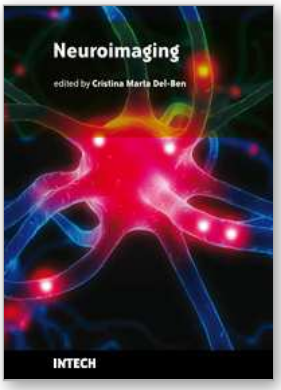
Whalen, P.J., Rauch, S.L., Etcoff, N.L., McInerney, S.C., Lee, M.B., Jenike, M.A., 1998. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J Neurosci 18, 411-418.

Wild, B., Erb, M., Bartels, M., 2001. Are emotions contagious? Evoked emotions while viewing emotionally expressive faces: quality, quantity, time course and gender differences. Psychiatry Res 102, 109-124.

Williams, L.M., Barton, M.J., Kemp, A.H., Liddell, B.J., Peduto, A., Gordon, E., Bryant, R.A., 2005. Distinct amygdala-autonomic arousal profiles in response to fear signals in healthy males and females. Neuroimage 28, 618-626.

Williams, M.A., Mattingley, J.B., 2006. Do angry men get noticed? Curr Biol 16, R402-404.

Zangara, A., Blair, R.J., Curran, H.V., 2002. A comparison of the effects of a beta-adrenergic blocker and a benzodiazepine upon the recognition of human facial expressions. Psychopharmacology (Berl) 163, 36-41.



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Neuroimaging has become a crucial technique for Neurosciences. Different structural, functional and neurochemical methods, developed in recent decades, have allowed a systematic investigation on the role of neural substrates involved in functions performed by the central nervous system, whether normal or pathological. This book includes contributions from the general area of the neuroimaging to the understanding of normal functions and abnormalities of the central nervous system.

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