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Review articles

Effects of psychotropic drugs used in the treatment of anxiety disorders on the recognition of facial expressions of emotion: Critical analysis of literature

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ABSTRACT

Deficits in recognition of facial expressions of emotion (RFEE) play a central role in the manifestation of anxiety disorders (AD). We systematically reviewed the literature to determine effects of drugs used in AD treatment on RFEE, based on outcomes of accuracy rate, reaction time, and intensity. Electronic databases, including Pubmed, PsycINFO, and Scielo, were used without time constraints. Twenty-six clinical/experimental studies on healthy subjects, focusing on 11 drugs, published in English, Portuguese, and Spanish, were selected. We found that increased recognition of happiness was associated with acute use of citalopram, fluoxetine, duloxetine, and reboxetine. Increased and decreased recognition of negative emotions were associated with the use of selective serotonin and/or norepinephrine reuptake inhibitors, respectively. Benzodiazepine favored recognition of negative emotions. Differences in reaction time were rarely observed. Stimuli with distinct emotion intensities produced similar effects. Specific changes occurred in RFEE depending on the drug, its administration route and dose, and emotion valence. Evidences indicate significant effects on emotional processing relevant to clinical practice, particularly in treating patients with emotional disorders.

Contents

1. Introduction

The ability to recognize facial expressions of emotion (RFEE) is important for social communication and interaction because it provides clues regarding internal emotional states and intentions of other people (Harmer et al., 2003a,b). The precise and accurate processing and identification of these clues are thus essential for social behavior and interaction (Bernasconi et al., 2015).

Most studies that have investigated the relationship between anxiety disorders (AD) and outcome variables of RFEE tasks have shown impairments in individuals with AD compared with healthy individuals (Demenescu et al., 2010). However, this topic is still con-

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troversial in the literature, and some studies have shown otherwise (Yoon et al., 2015). Deficits have mostly been described in studies in which individuals with social anxiety were assessed (Arrais et al., 2010; Button et al., 2013; Rossignol et al., 2007). Considering that specific impairments in the ability to process facial expressions of emotion are associated with AD and can play an important role in the maintenance of various symptoms (Bhagwagar et al., 2004; Grady et al., 2013; Labuschagne et al., 2010), clinical actions that mitigate these deficits should be considered.

The effects of several drugs used in the treatment of AD on RFEE have been the focus of many studies in healthy volunteers, with different results depending on the class of drug tested, and its mechanism of action. The evaluation of these psychotropic drugs on RFEE in healthy volunteers can be considered an important resource to investigate neural and behavioral models of emotional processing. This approach would allow to assess the effects of these drugs on neural circuits without the interference of mood and anxiety present in clinical samples (Pringle and Harmer, 2015). In addition, this analysis could indicate therapeutic possibilities before clinical trials in AD subjects.

It has been hypothesized that the expression and recognition of different emotions are processed by specific neuronal substrates and that differentiated neuronal representations of emotions are accompanied by a selective modulation by neurotransmitters. Therefore, changes in specific neurochemical systems would lead to specific changes in emotional processing, leading to differences in its perception (Harmer et al., 2003a,b). The pharmacological effects of drugs that act on the central nervous system (CNS) could thus cause shifts in emotional processing. Furthermore, RFEE tasks have been identified as predictors of response to drug treatment, especially in studies with depression (Shiroma et al., 2014; Tranter et al., 2009).

Considering that RFEE tasks could be useful as a tool for examining drug effects on anxiety and mood and on the basis of numerous studies that have been published on the subject, this systematic review aims at determining the specific effect of drugs used in the treatment of AD on RFEE according to the following outcome variables: correctness/accuracy rate, reaction time, and intensity.

2. Methods

A systematic review of the literature was performed, with searches conducted in the electronic databases Pubmed, PsycINFO, and Scielo, without time constraints on the date of publication (last search on September 07, 2016) and according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009) and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011).

The guidelines of the World Federation of Societies of Biological Psychiatry (Bandelow et al., 2008) and the Canadian Clinical Practice Guidelines (Zohar et al., 2014) were used to define the drugs used to treat the various AD. Subsequently, searches were performed with the following keywords: (Citalopram OR Escitalopram OR Fluoxetine OR Fluvoxamine OR Paroxetine OR Sertraline OR Duloxetine OR Venlafaxine OR Milnacipran OR Amitriptyline OR Desipramine OR Clomipramine OR Imipramine OR Lofepramine OR Alprazolam OR Clonazepam OR Diazepam OR Lorazepam OR Bromazepam OR Phenelzine OR Tranylcypromine OR Selegiline OR Moclobemide OR Pregabalin OR Gabapentin OR Quetiapini OR Risperidone OR Olanzapine OR Hidroxyzine OR Opipramol OR Buspirone OR Mirtazapine OR Lamotrigine OR Valproate OR ValproicAcid OR Tiagabine OR Topiramate OR Carbomazepine OR Divalproex OR Levitiracetan OR Prazosin OR Reboxetine OR Bupropion OR Agomelatine OR Propanolol OR Atenolol OR Atomoxetine OR Vortioxetine OR Trazodone) AND (Faces OR Facial) AND (Recognition OR Expression OR Emotional).

Criteria for the selection of clinical/experimental studies were the following: studies must be published in English, Portuguese, or Spanish, with healthy adult individuals ($\geq$18 years) of both sexes, whose objective was to determine the effect of selected drugs on RFEE according to the outcome variables correctness/accuracy rate, reaction time, and intensity. Exclusion criteria used as well as the complete process of inclusion and exclusion of articles is shown in Fig. 1.

3. Results

Twenty-six articles were selected from a total of 370 reviewed articles, according to the inclusion and exclusion criteria described (Alves-Neto et al., 2010; Arce et al., 2008; Arnone et al., 2009; Bernasconi et al., 2015; Bhagwagar et al., 2004; Blair and Curran, 1999; Browning et al., 2007; Capitão et al., 2015; Coupland et al., 2003; Del-Ben et al., 2012; Harmer et al., 2013, 2011, 2008, 2006, 2004, 2003a,b, 2001; Kerestes et al., 2009; Labuschagne et al., 2010; Lochner et al., 2012; Murphy et al., 2009, 2008; Paulus et al., 2005; Zangara et al., 2002).

The adequacy of articles was assessed by two independent expert research psychologists.

A total of 28 analyses were performed because two studies presented the independent testing of more than one substance (Harmer et al., 2004; Kerestes et al., 2009). The main characteristics of samples and methods used in the studies are shown in Table 1.

The majority of the articles were published during the last decade (n = 18) by research groups in the United Kingdom (n = 18). The number of individuals in the samples varied between 10 and 28 (with a mean of 14.32 individuals in the experimental groups and 13.22 in the control groups). Nineteen studies included mixed-sex samples, six recruited only men, and three included only women.

The following criteria for the inclusion and exclusion of individuals were used: a) absence of medication use [general: n = 13 studies (50%), psychotropic drugs: n = 6 studies (23%)]; b) absence of substance use [alcohol: n = 6 studies (23%), tobacco: n = 10 studies (38%), illicit/stimulating drugs: n = 10 studies (38%), caffeine: n = 4 studies (15%)]; c) medical condition [general: n = 14 studies (53%), specific neurological disorders: n = 4 studies (15%)]; d) pregnancy: n = 5 studies (19%), e) menstruation n = 4 studies (15%); f) absence of family history of psychiatric disorder: n = 5 studies (19%); and g) intellectual coefficient: n = 2 studies (8%).

Of the 49 researched drugs, only the following 11 drugs were tested (grouped according to their mechanisms of action: a) selective serotonin reuptake inhibitors (SSRIs): citalopram (n = 9), escitalopram (n = 3), fluoxetine (n = 1); b) selective norepinephrine reuptake inhibitors (NRIs): reboxetine (n = 3); c) selective serotonin and norepinephrine reuptake inhibitors: duloxetine (n = 1); d) partial serotonin receptor agonist (5-HT_{1A}): buspirone (n = 1); e) alpha-2 antagonist and serotonin receptor antagonist (5-HT_{2A}, 5-HT_{2C}, and 5-HT_3): mirtazapine (n = 1); f) melatonin receptor agonist and serotonin receptor antagonist (5-HT_{2C}): agomelatine (n = 1); g) benzodiazepines: diazepam (n = 5), lorazepam (n = 2); h) beta blockers: propranolol (n = 1).

From the total of studies reviewed, only four received funding from the pharmaceutical industry: two related to citalopram (Harmer et al., 2013; Labuschagne et al., 2010) and two related to escitalopram (Arce et al., 2008; Lochner et al., 2012). Other studies or do not cite the source of funding (N = 8) or received funds from national research agencies (N = 16).

In most studies (n = 26), these substances were administered via oral route, as a single dose (n = 23) and at different concentrations.