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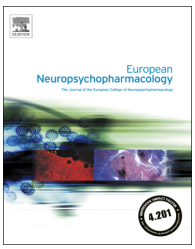

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The electrophysiological effects of the serotonin 1A receptor agonist buspirone in emotional face processing

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Abstract
Emotional face processing is critically modulated by the serotonergic system, and serotonin (5-HT) receptor agonists impair emotional face processing. However, the specific contribution of the 5-HT1A receptor remains poorly understood. Here we investigated the spatiotemporal brain mechanisms underpinning the modulation of emotional face processing induced by buspirone, a partial 5-HT1A receptor agonist. In a psychophysical discrimination of emotional faces task, we observed that the discrimination fearful versus neutral faces were reduced, but not happy versus neutral faces. Electrical neuroimaging analyses were applied to visual evoked potentials elicited by emotional face images, after placebo and buspirone administration. Buspirone modulated response strength (i.e., global field power) in the interval 230–248 ms after stimulus onset. Distributed source estimation over this time interval revealed that buspirone decreased the neural activity in the right dorsolateral prefrontal cortex that was evoked by fearful faces. These results indicate temporal and valence-specific effects of buspirone on the neuronal correlates of emotional face processing. Furthermore, the reduced neural activity in the dorsolateral prefrontal cortex in response to fearful faces suggests a reduced attention to fearful faces. Collectively, these findings provide new insights into the role of 5-HT1A receptors in emotional face processing and have

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implications for affective disorders that are characterized by an increased attention to negative stimuli.
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1. Introduction

Faces provide information about a person's gender, identity, and emotional state. Thus, accurate face processing is essential for appropriate social interaction and behavior. Both single-cells recording in monkey (Sugase et al., 1999) and electrophysiological studies in humans (e.g., Batty and Taylor, 2003), that investigated the processing of basic emotional face (fear, happy, etc.), demonstrated an enhanced response to both face vs. objects and emotional vs. neutral face occurring at ca. 100 ms poststimulus, suggesting a first rapid course categorization of the face. This initial categorization is succeeded by a fine analysis of facial features (e.g. expression detection), occurring at ca. 170 ms poststimulus, as demonstrated by amplitude and latency modulation to fear and happy vs. neutral faces (Vuilleumier and Pourtois, 2007 for a review). A further cognitive analysis of facial expressions occurs approximately 230 ms after stimulus onset (Wong et al., 2009).

Emotional face processing is impaired in individuals with mood disorders, which are characterized by a negative attentional bias and enhanced neural responses to negative stimuli (Disner et al., 2011). Mood disorders are usually treated with antidepressants such as selective serotonin re-uptake inhibitors (SSRIs), which cause an overall increase in the level of serotonin (5-HT) within the brain (Savitz et al., 2009). SSRIs modulate both the behavioral and neurophysiologic responses to emotional faces. For example, recent neuroimaging studies in healthy subjects demonstrated that SSRIs reduced the neural response to fearful faces in the amygdala and lateral prefrontal cortex (PFC) (Brühl et al., 2011). The reported effects of SSRIs on the responses to happy faces are less consistent; some reports show that SSRIs increase neural response activity within the amygdala (Norbury et al., 2009), other reports show no effects of SSRIs on happy face processing. Collectively, these results provide evidence that emotional face processing is modulated by the serotonergic system. Despite the clear role of 5-HT in emotional face processing, the specific contribution of different 5-HT receptors remains poorly understood.

Few studies have investigated the functional role of specific 5-HT receptors on emotional face processing. Psilocybin, a preferential 5-HT2A/1A receptor agonist, selectively impairs the structural encoding of fearful faces, occurring approximately 170 ms after stimulus onset (Bernasconi et al., 2014). Furthermore, Kometer et al. (2012) demonstrated that 5-HT2A receptors contributes to the modulation of fearful face recognition. However, these results do not exclude an influence of 5-HT1A receptors on emotional face processing. In fact, animal studies implicate 5-HT1A receptors in regulating the response to fearful stimuli and the modulation of anxiety. For example, 5-HT1A-receptor-knockout mice are characterized by increased anxiety (Albert et al., 2011), and healthy human subjects with a 5-HT1A receptor polymorphism reacted faster to fearful faces than did unaffected healthy controls. This modulation of threat-related information processing is associated with increased stress and anxiety (Mekli et al., 2011). Furthermore, the density and binding potential of 5-HT1A receptors was significantly reduced in the prefrontal, amygdala, and temporal areas of the brain in patients with anxiety (Lanzenberger et al., 2007); these brain regions are strongly activated during emotional face processing (Dima et al., 2011). In line with these finding, 5-HT1A receptor agonist, such as buspirone, have been used as a treatment of general anxiety disorders (Lee et al., 2005) and as an augmentation of antidepressant drugs (Harvey and Balon, 1995).

Taken together, these findings suggest that 5-HT1A receptors play a role in emotional face processing and that 5-HT1A receptor agonist such as buspirone could decrease the processing of negative face expression. However, the specific contribution of these receptors to emotional face processing is still unknown. Therefore, we investigated the modulation of emotional face processing induced by buspirone, a partial 5-HT1A receptor agonist (Loane and Politis, 2012). Given that buspirone was found to alter prefrontal cortical activity during resting state and cognitive tasks (e.g., Anderer et al., 2000), we hypothesize that buspirone alters emotional face processing, by modulating prefrontal activity. Furthermore, the putative modulation of the negative face expression processing, within the prefrontal areas, should occur ca. 200 ms after the stimulus onset (Luo et al., 2007).

To identify the spatiotemporal brain mechanisms that underlie any modulation of emotional face processing induced by stimulation of 5-HT1A receptors, we conducted electrical neuroimaging analyses of visual evoked potentials (VEPs) elicited by different emotional facial expressions (fear, happiness, and neutral) under placebo and buspirone treatment conditions. Electrical neuroimaging analyses allowed us to differentiate modulations in response strength and topography, and to localize any response changes within the brain using a distributed source model (Murray et al., 2008), thereby providing a detailed description of the likely neurophysiologic mechanisms.

2. Experimental procedures

2.1. Participants

Fifteen healthy participants (11 male; age, 25 ± 0.6 years (mean ± s.e.m.); 14 right-handed) with normal or corrected-to-normal vision participated in the study. Participants were healthy according to medical history, clinical examination, electrocardiography, and blood analysis. To exclude participants with personal and/or family (first-degree relatives) histories of major psychiatric disorders, prospective participants underwent a semi-structured psychiatric interview (DIA-X diagnostic expert system) (Wittchen and Pfister, 1997) and completed the Symptom Checklist-90-R (Derogatis, 1994) and the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). A urine drug screen and a drug consumption questionnaire were used to verify the absence of any history of drug dependence. All participants

were free of any medication for at least 3 weeks before the experiment.

The study was approved by the Ethics Committee of the University Hospital of Psychiatry in Zürich. After receiving a written and oral description of the aim of the study, all participants gave written informed consent prior to enrollment. The use of buspirone was authorized by the Swiss Federal Office for Public Health, Department of Pharmacology and Narcotics, Bern, Switzerland.

2.2. Drug administration

Using a double-blind within-subject design, each participant a placebo (100% maltose) and buspirone (20 mg) in gelatin capsules, which was orally administrated, of identical number and appearance. There was an interval of at least 2 weeks between conditions. Participants were monitored until the drug effects wore off.

2.3. Stimuli and task design

Two experiments were conducted: (1) psychophysical discrimination of emotional faces and (2) passive-viewing of emotional faces. Participants performed both experiments under both treatments (i.e., placebo and buspirone). Backward masking paradigms were started 60 min after placebo/buspirone administration. All target emotional faces were backward-masked with neutral faces. Stimuli comprised black and white images taken from the Ekman and Friesen (1976) series. The target images were neutral and basic emotional expressions (fearful and happy). The masking image was always a neutral face of the same identity. Six different identities were used for each face valence. To limit possible confounders induced by low-level face processing, faces were modified using Adobe Photoshop 2.0 so that task-irrelevant features were removed and the only visible features were the eyes, eyebrows, nose, and mouth. Stimuli were displayed in the center of the monitor and subtended a visual angle of 3 degrees horizontally and 4.4 degrees vertically.

Experiment 1 consisted of two parts: (A) discrimination of fearful faces from neutral faces, and (B) discrimination of happy faces from neutral faces. Both parts involved a two-alternative forced-choice discrimination paradigm and participants were instructed to respond after each "target-mask" pair, by a button-press. No time limit was placed on the response and participants were instructed to respond accurately rather than quickly. At the beginning of each trial, a fixation cross was presented for 1000 ms. Then, the target face was presented for 20, 30, 50, 90, or 170 ms, immediately followed by a mask face (i.e., neutral) presented for 150 ms. Participants completed 5 blocks of 40 trials each (target-mask pairs) for each of both tasks (i.e., fearful vs. neutral and happy vs. neutral). In each block, target faces (emotional or neutral) were randomly presented with equal probability. The experiment was conducted in a sound-attenuated and electrically shielded booth. Eprime 2.0 software (Psychology Software Tools, Pennsylvania, USA) was used to control stimulus delivery and to monitor participant responses. Timing was controlled using an oscilloscope.

Experiment 2 was a passive task. Participants were instructed to passively determine the emotional valence of each face. Each trial began with a fixation cross that was presented for 2000 ms. The target face (i.e., neutral, fearful, or happy) was then presented for either 10 ms (unconscious condition) or 200 ms (conscious condition). Each target face was immediately followed by a mask (i.e., neutral face) presented for 150 ms. A total of 40 trials (i.e., 40 target-mask pairs) was presented for each face valence and for the two target durations, resulting in a total of 240 images. EEG was measured throughout Experiment 2 (similar material and methods can be found in Bernasconi et al., 2014). The conscious and unconscious conditions were part of distinct blocks, one block for the conscious and one block for the unconscious. Only the data from the conscious condition were reported in this study. The EEG data recorded during unconscious face processing will be reported in a future study.

2.4. Behavioral analyses

Behavioral data obtained in Experiment 1 were analyzed according to signal detection theory (Green and Swets, 1966). The discrimination sensitivity index (d') was calculated separately for Experiment 1A (discrimination of fearful from neutral faces) and 1B (discrimination of happy from neutral faces) using the formula $d' = z(\text{Hits}) - z(\text{False Alarms})$ according to Macmillan and Creelman (2005). A two-way ANOVA of treatment (placebo, buspirone) $\times$ target duration (20, 30, 50, 90, 170 ms) was conducted for Experiment 1A and 1B.

2.5. EEG acquisition and preprocessing

Continuous EEG was acquired at 512 Hz throughout Experiment 2 through a 64-channel Biosemi ActiveTwo AD-box referenced to the common mode sense (active electrode). Data preprocessing and analyses were performed using Cartool software (Brunet et al., 2011). Because we were exclusively interested in assessing modulations of the early stages of emotional face processing, the EEG epochs were defined from 100 ms prior to stimulus (i.e., emotional face) onset to 300 ms post stimulus onset. All analyses were conducted over the full epoch.

To calculate VEPs, EEG epochs were averaged for each participant, each treatment (placebo and buspirone), and each face valence (neutral, fearful, and happy), thereby generating a 2×3 within-subject design. A semiautomated $\pm 60\ \mu V$ artifact rejection criterion was applied to reject epochs with eye blinks and/or other sources of transient noise.

Before group-averaging the data obtained for each experimental condition, artifact-contaminated electrodes from each participant were interpolated using 3D splines (Perrin et al., 1987). Next, data were recalculated against the average reference and band-pass filtered (0.18–40 Hz). A Butterworth filter, with -12 db/octave roll-off, was used (implemented in Cartool software; https://sites.google.com/site/fbmlab/cartool). No pre-stimulus baseline correction was applied for the following reasons: (i) we could not assume a priori that the preparatory processes were similar across treatments (placebo and buspirone), and (ii) baseline correction can crucially affect the topography of the dataset and result in a "temporal shift" of the statistical effects (Tzovara et al., 2012). Importantly, our analyses (i.e., both Global Field Power and Global Map Dissimilarity), conducted over the whole epoch length, revealed no significant difference across conditions over the pre-stimulus time period. Therefore, we can exclude the possibility that any post-stimulus effect is due to differences in preparatory processes across conditions (see Section 3 for details).

The mean ($\pm$ SEM) number of accepted EEG epochs in the placebo condition was 35.2 ± 1.35 for neutral faces, 35.4 ± 1.64 for fearful faces, and 34.53 ± 1.49 for happy faces, and that in the buspirone condition was 35.80 ± 1.43 for neutral faces, 36.33 ± 0.92 for fearful faces, and 35.60 ± 1.28 for happy faces (two-way ANOVA treatment $\times$ face valence interaction $F_{(2,28)}=0.144$, $p>0.8$; main effect of treatment: $F_{(1,14)}=0.247$, $p>0.6$; main effect of face valence: $F_{(2,28)}=0.967$, $p>0.4$). Because the number of accepted epochs did not differ across conditions, we can exclude that our results were confounded by differences in signal-to-noise ratio.

2.6. EEG analyses and source estimation

2.6.1. General analysis strategy

The effects of buspirone on emotional face processing were identified using a step-wise analysis procedure, which hereafter will be referred as electrical neuroimaging analysis. Electrical

neuroimaging analyses, which are reference-independent, are implemented in Cartool (Brunet et al., 2011) and allowed us to assess and differentiate the effects of "pure" strength modulations (i.e., modulations in global field power; GFP) that occurred in the absence of topographic modulations and topographic modulations that resulted from changes in the intracranial source configuration. Because each step of the electrical neuroimaging analyses is independent from the others, any combination of these neurophysiologic phenomena can be assessed (Murray et al., 2008). Finally, we used the local autoregressive average distributed linear inverse solution (LAURA; Grave de Peralta Menendez et al., 2004) to estimate the intracranial sources of the neurophysiologic effects identified in the previous steps of the electrical neuroimaging analysis (GFP and/or topographic modulations).

2.6.2. Global electric field analyses

The strength of the electric field at the scalp was evaluated using GFP (Murray et al., 2008), which is independent of the spatial distribution across the electrode montage (Murray et al., 2008). GFP was calculated as the square root of the mean of the squared value recorded at each electrode; thus it represents the spatial standard deviation of the electric field at the scalp. GFP was calculated at each frame of data and analyzed using a two-way nonparametric ANOVA of treatment (placebo, buspirone) and face valence (neutral, fearful, happy). The repeated measures nonparametric *F*-test is a bootstrapping of the subjects label on the one hand, and permutation of the within subjects factors on the other hand. On each cycle, we calculate for each randomization an *F*-value. We repeated this for 5000 cycles, which generated an empirical distribution of *F*-values. From the empirical distribution a corresponding *p*-value can be obtained. This method has the advantage of keeping the intra-variance of the subjects. Finally, for a direct indication of the statistical reliability of an effect/interaction, we must contrast it against the empirical distribution. If our effect/interaction is bigger than the empirical distribution, we can consider our effect as significant and reliable. Only effects with $p<0.05$ that lasted for at least 12 consecutive milliseconds (i.e., 6 consecutive data points) were considered reliable (Guthrie and Buchwald, 1991).

2.6.3. Topographic modulation analyses

Topographic modulations were identified using global map dissimilarity (GMD). GMD is the root mean square of the difference between two strength-normalized vectors (i.e., the voltage of the electrode montage at each instant in time). GMD was calculated time-point by time-point, and analyzed using an empirical distribution determined by a bootstrapping procedure (5000 permutations per data point), based on randomly re-assigning data across conditions for each participant (Koenig and Melie-García, 2010). A GMD modulation is interpreted as a change in the configuration of the intracranial source (Murray et al., 2008). Temporal autocorrelation was corrected through the application of at least 12 contiguous milliseconds as a temporal criterion for the persistence of differential significant effects ($p<0.05$).

2.6.4. Source estimations

LAURA-distributed source estimations (Grave de Peralta Menendez et al., 2004) were calculated over time periods that had a significant treatment × face valence interaction in GFP. To partially correct for multiple testing and temporal autocorrelation, only nodes with two-tailed $p<0.01$ and clusters of at least 21 contiguous nodes were considered (similar criteria have been used elsewhere, e.g., Bernasconi et al., 2014).

3. Results

3.1. Behavior

In Experiment 1A there was a significant treatment × target duration interaction ($F_{(4,56)}=3.54$; $p<0.01$) on the perceptual sensitivity index, but no main effect of treatment ($F_{(1,14)}=1.09$; $p>0.3$; Fig. 1a). Post-hoc *t*-tests indicated a significant effect of treatment when the target was presented for 90 ms (Bonferroni corrected $p<0.01$; Fig. 1a). In fact, the discrimination of fearful vs. neutral faces was reduced under buspirone. In Experiment 1B there was no significant treatment × target duration interaction ($F_{(4,56)}=0.079$; $p>0.9$) and no main effect of treatment ($F_{(1,14)}=2.71$; $p>0.1$; Fig. 1b).

3.2. VEP waveform analysis

To help the reader in assessing the quality of our ERP waveforms, in Fig. 2a, superimposed ERPs from an exemplar electrode (P10), for the six conditions (Placebo and Buspirone, for neutral, happy and fearful faces), are depicted. Electrode P10 was selected according to previous studies which investigated the role of serotonin sub-receptors in emotional face processing.

A first-level analysis of VEPs was performed using individual voltage waveforms. Two-way ANOVA analysis for an exemplar electrode indicated that there was a significant ($p<0.05$ for at least 12 ms) treatment × face valence interaction on the amplitude of the voltage waveform at AEPs at an exemplar electrode (P10) 240–260 ms after stimulus onset (Fig. 2) and a significant ($p<0.05$ for at least 12 ms) main effect of face valence 104–127 ms and 158–300 ms after stimulus onset (results not shown), but no main effect of treatment. The reader should be aware that interpretations are based only on the global, reference-independent analyses of the ERPs.

3.3. Global electric field and topographic analyses

There was a significant modulation in GFP but not in GMD, indicating modulation of the response gain across conditions, but no change in the configuration of the intracranial sources. There was a significant treatment × face valence interaction for GFP 234–248 ms after stimulus onset ($F_{(2,28)}=4.41$; $p<0.01$ for at least 12 ms; Fig. 3a). There was no main effect of treatment on GFP (Fig. 3c), but there was a main effect ($p<0.05$ for at least 12 ms) of face valence 173–248 ms and 259–280 ms after stimulus onset (Fig. 3e). There was no significant treatment × face valence interaction for GMD in the 300 ms post-stimulus period (Fig. 3b). However, there was a main effect ($p<0.05$ for at least 12 ms) of treatment 123–136 ms and 285–300 ms after stimulus onset (Fig. 3d), and a main effect ($p<0.05$ for at least 12 ms) of face valence 162–203 ms, 232–300 ms after stimulus onset (Fig. 3f).

3.4. Source estimations

There was a significant treatment × face valence interaction ($F_{(2,28)}=7.92$; $p<0.01$) for LAURA-distributed source estimations over the right dorsolateral PFC (DLPFC) 234–248 ms after stimulus onset (Fig. 4a). To assess the basis of this interaction,

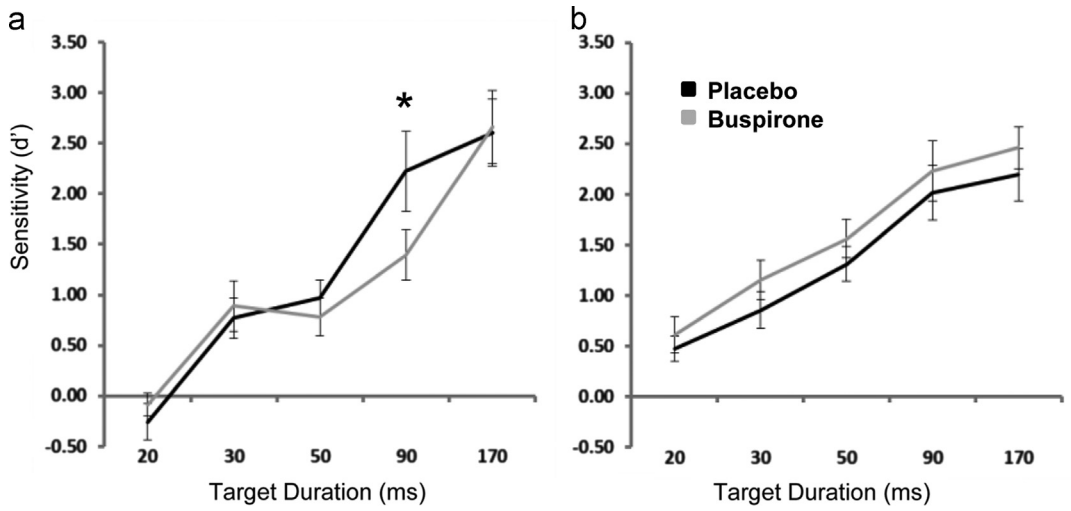

Fig. 1 Behavioral results. Effects of buspirone on discrimination between negative and neutral faces (a) and between positive and neutral faces (b). The black line indicates the perceptual sensitivity index after placebo treatment and the gray line indicates the perceptual sensitivity index after buspirone treatment. Error bars indicate the s.e.m. The asterisk indicates significant differences between treatments.

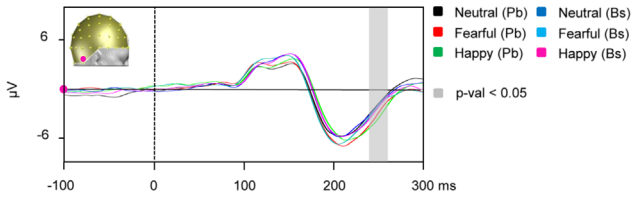

Fig. 2 Exemplar AEP waveform. Representative waveforms (average over all subjects) recorded from electrode P10 in response to images of neutral, fearful, and happy faces presented at time zero (dashed vertical line) after placebo (Pb) and buspirone (Bs) treatment. Gray shading indicates significant treatment × face valance interaction (p value <0.05 for at least 12 contiguous milliseconds).

group-average scalar values of the DLPFC cluster were calculated and are shown in Fig. 4b. Activity within the DLPFC was significantly reduced only for the fearful faces ($p<0.01$).

4. Discussion

In the present study, we explored the time course of neurophysiological modulations induced by buspirone, a 5-HT1A receptor agonist, on emotional face processing. Brain mechanisms associated with such modulations were identified by applying electrical neuroimaging analyses to the VEPs recorded in response to emotional faces as a function of treatment (placebo vs. buspirone). We found that buspirone induced a response strength modulation, of statistically indistinguishable brain generators, over the 230–248 ms post-stimulus time period. Distributed source estimation over this time period indicated a valence-specific effect within the right DLPFC. Collectively, our findings support a model in which 5-HT1A-receptor stimulation has temporal and spatially dissociable effects on the neuronal correlates of emotional face processing.

Behaviorally, we observed that emotional face discrimination of both fearful versus neutral and happy versus neutral faces was not significantly modulated by buspirone, with the exception of fearful versus neutral faces when the image was presented for 90 ms. Under this specific condition, buspirone administration reduced the discrimination of fearful faces. This result is in line with reports showing that acute administration of SSRIs reduced the recognition of fearful faces, suggesting a shift from negative to positive processing bias (Harmer et al., 2003; Norbury et al., 2009). We hypothesize that sub-chronic administration of buspirone would also result in significant modulation of the behavioral response to happy faces, as observed in previous studies (Harmer, 2008). Furthermore, the reduced discrimination of fearful vs. neutral faces observed in the behavioral task, might be due to the modulation of the neurophysiological activity induced by buspirone. In fact, we observed a reduced neural response to fearful faces, within the right DLPFC. However, this conclusion remains highly speculative as the parameters of the behavioral and electrophysiological experiments differed, and therefore needs further investigations.

The strength modulation (i.e., GFP modulation) observed 234–248 ms after stimulus onset suggests that buspirone did not modulate the initial course categorization of faces, i.e., perceptual analysis, which occurs approximately 100 ms after stimulus onset (Vuilleumier and Pourtois, 2007), or the fine categorization of faces, i.e., structural encoding, which occurs approximately 170 ms after stimulus onset (Eimer and Holmes, 2007). Our results suggest that acute stimulation of 5-HT1A receptors modulates the cognitive analysis of fearful faces, i.e., expression decoding, which occurs in prefrontal areas approximately 230 ms after stimulus onset (Nakamura et al., 1999; Wong et al., 2009). These findings extend the results of previous pharmaco-EEG studies showing that SSRIs caused a general increase in 5-HT level and modulated the decoding of emotional face expression at approximately 250 ms after stimulus onset (i.e., the N250 ERPs component) (Kerestes et al., 2009;

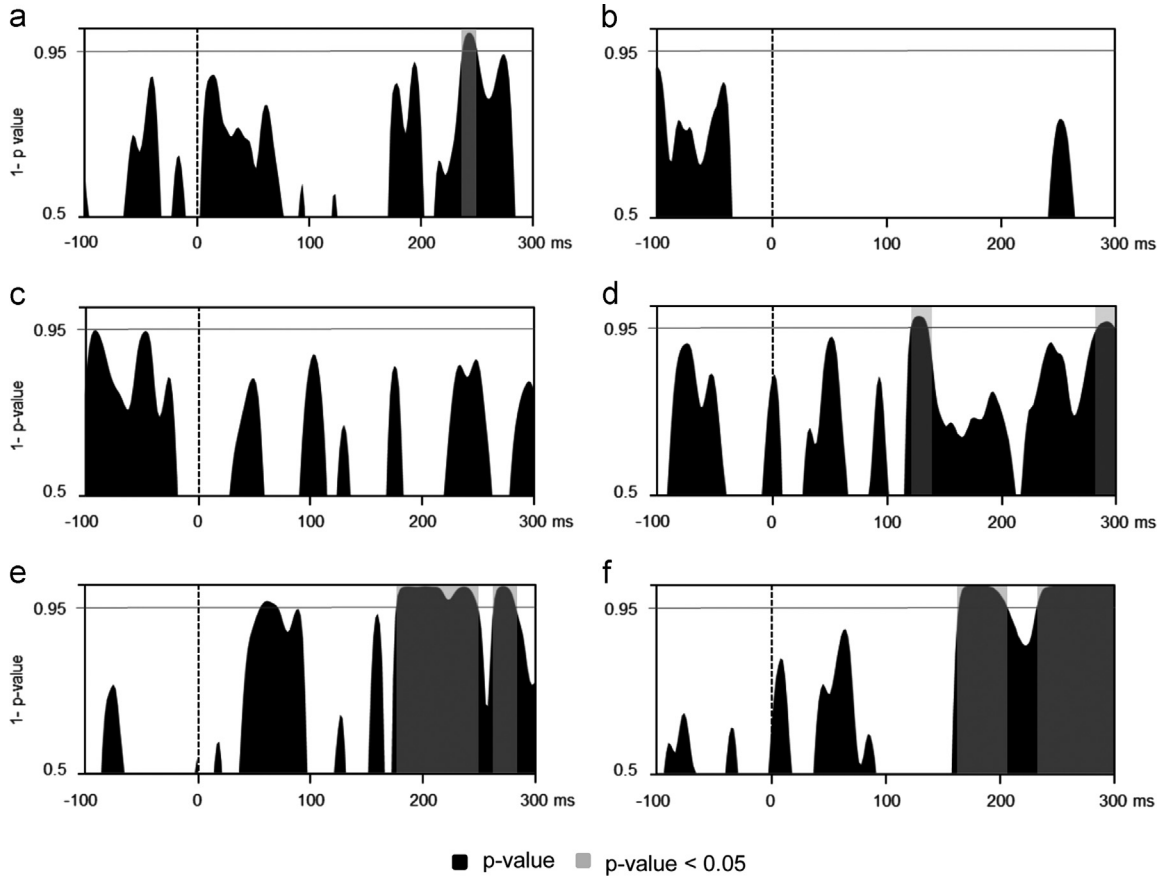

Fig. 3 Electrical neuroimaging results. (a) Significance ($1-p$ value) of the treatment × face valence interaction for global field power, (c) main effect of treatment and (e) main effect of face. (b) Significance ($1-p$ value) treatment × face valence interaction for global dissimilarity, (d) main effect of treatment, and (f) main effect of face. Both global field power and global dissimilarity were assessed time-point by time-point from 100-ms pre-stimulus onset to 300-ms post-stimulus onset. Gray shading indicates a significant treatment × face valence interaction (p-value <0.05 for at least 12 contiguous milliseconds).

Labuschagne et al., 2010), suggesting that the expression decoding that occurs in the PFC approximately 250 ms after stimulus onset is modulated by 5-HT1A receptors rather than by a general increase in 5-HT levels.

There is evidence that the preferential 5-HT2A/1A receptor agonist psilocybin modulates the structural encoding of fearful faces at approximately 170 ms after stimulus onset (Bernasconi et al., 2014). Interestingly, psilocybin-induced reductions in the visual evoked responses during this time period were normalized by the 5-HT2A receptor antagonist, ketanserin (Kometer et al., 2012). Thus, it appears that activation of 5-HT1A and 5-HT2A receptors leads to distinctive temporal effects on fearful face processing: 5-HT2A receptors are probably more involved in the structural encoding of fearful face expressions, whereas 5-HT1A receptor activation seems to influence later processing of facial expressions.

Source localization revealed that buspirone reduced the neural response to fearful faces that occurred in the right DLPFC (BA9) 234–248 ms after stimulus onset. This is in line with the valence-lateralization theory, which suggests that negative emotions are processed predominantly within the right DLPFC and that positive emotions are processed predominantly within the left DLPFC (Fairhall and Ishai, 2007). Furthermore, the reduced neural response to fearful faces supports and extends the crucial role of the serotonergic system in the recognition of emotional faces. In fact, our results demonstrate that the reduced neural response to fearful faces observed after SSRI administration (e.g., Harmer et al., 2003) is likely to be mediated by 5-HT1A receptors, at least over 234–248 ms after stimulus onset.

Several neuroimaging studies have demonstrated that the right DLPFC is associated with attention to emotional judgments and anticipation of negative stimuli (e.g. Ueda et al., 2003), whereas the left DLPFC is involved in the evaluation of emotional stimuli (Grimm et al., 2008). According to this evidence, we can hypothesize that the reduced neural response to fearful faces within the right DLPFC might be due to reduced attention to negative stimuli. This hypothesis is consistent with the reduction in GFP that we observed over this period of time. In fact, modulation of GFP is associated with modulation of attention (e.g., Luck et al., 2000). Additional evidence that buspirone modulates attention to fearful faces is provided by studies of anxiety patients, who have an increased amplitude of ERP present 250 ms after the presentation of images of fearful faces when compared to control subjects (Dennis and Chen, 2007). Because anxiety patients are

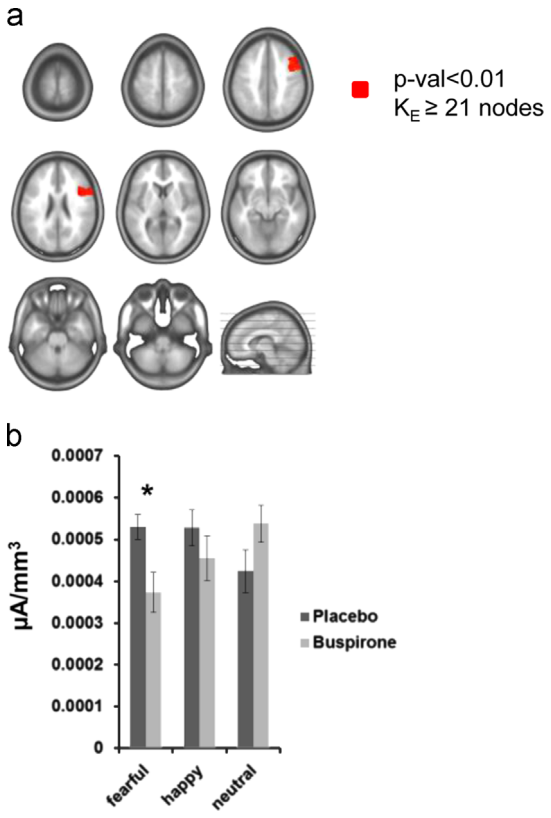

Fig. 4 Statistical analyses of source estimation. (a) Axial slices of the Montreal Neurological Institute template brain. Red indicates regions with a significant treatment × face interaction for source estimation calculated over the time period 230–248 ms after stimulus onset. Only nodes with $p<0.01$ that met the spatial criterion of at least 21 contiguous nodes were considered reliable. (b) The mean scalar value of the neural activity in the DLPFC clusters, error bars indicate s.e.m. Asterisk indicates a significant difference between placebo and buspirone treatment conditions.

characterized by an increased attention to negative stimuli, a correlation between the amplitude of ERPs elicited in response to negative stimuli and anxiety might exist, supporting our hypothesis that 5-HT1A receptors modulate attention to fearful faces 234–248 ms after stimulus onset. Mechanistically, the reduced attention to fearful stimuli might be mediated by both the left and the right DLPFC via top-down control of the amygdala response, which is critically involved in emotional processing (Pourtois et al., 2013). However, the exact interplay between left and right DLPFC in emotional processing is poorly understood.

Neuroimaging studies report an imbalance between left and right DLPFC activation in patients with major depressive disorder. Specifically, the left DLPFC is hypoactive and the right DLPFC is hyperactive during emotional face processing (Fahim et al., 2004). In line with the valence-lateralization theory, hyperactivity in the right DLPFC is associated with excessive attention to fearful stimuli and leads to a state of anxiety and depression (Shackman et al., 2009). Several repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation studies support the critical role of balanced activity within the left and right DLPFC in emotion processing and psychiatric diseases. For instance, modulating neural activity with high-frequency (excitatory) rTMS over the left DLPFC and low-frequency (inhibitory) rTMS over the right DLPFC reduce anxiety and attention to fearful stimuli (van Honk et al., 2002; Grimm et al., 2008). Although not completely elucidated, evidence from both EEG and functional magnetic resonance imaging-rTMS studies indicates that decreased attention to fearful stimuli is due to both reduced activity within the right DLPFC and increased activity within the left DLPFC (Nahas et al., 2003; Schutter et al., 2001). It is likely that the increased activity within the left DLPFC results from decreased inhibitory inputs from the right DLPFC (Schutter et al., 2001). According to these findings, and to our own results, a selective 5-HT1A receptor agonist might reduce the right DLPFC hyperactivity observed in patients with major depressive disorders, eventually reducing the symptoms of the disease. This is in line with the putative antidepressant effects of buspirone (Loane and Politis, 2012). However, this hypothesis remains speculative, and needs further investigation. A possible limitation of the current study is that buspirone is only a partial $5HT_{1A}$ receptors agonist, and that buspirone act as well as an antagonist of D_2 receptors, although its affinity is 15-fold weaker than for the $5HT_{1A}$ receptors (Loane and Politis, 2012).

In conclusion, our results suggest that stimulation of 5-HT1A receptors has a temporal and valence-specific effect on emotional face processing. Furthermore, our results support the view that 5-HT1A receptor agonists may normalize right prefrontal hyperactivity in aberrant emotional processing by reducing attention to negative stimuli, and may thereby alleviate depressive symptoms in affective disorders.

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Contributors

FB performed research, analyzed data and wrote the paper.
FXV and MK designed and wrote the paper.
ES wrote the paper.
TP performed research.
All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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