ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 22 (2004) 1084–1096

Augmentation of serotonin enhances pleasant and suppresses unpleasant cortical electrophysiological responses to visual emotional stimuli in humans

Andrew H. Kemp, Marcus A. Gray, Richard B. Silberstein, Stuart M. Armstrong, and Pradeep J. Nathan*

Neuropsychopharmacology Laboratory, Brain Sciences Institute, Swinburne University of Technology, Hawthorn VIC 3122, Australia

Received 8 October 2003; revised 11 March 2004; accepted 11 March 2004

The serotonergic system is one of the major systems targeted in the pharmacological treatment of a wide range of mood disorders including depression; however, little is known about the neurophysiological mechanisms underlying the effects of serotonin (5-HT) on affective phenomena including emotional behaviours, mood and emotional processing. The aim of the current study was to investigate how 5-HT acutely modulates steady-state visually evoked potentials (SSVEP), heart rate (HR) and verbal ratings associated with the viewing of differently valent emotional images. In a randomised double-blind, placebo-controlled design, 17 healthy subjects were tested under two acute treatment conditions: placebo and citalopram (20 mg) (a selective serotonin re-uptake inhibitor, or SSRI). Participants were tested 2 h post treatment whilst viewing 75 images (categorised as pleasant, neutral or unpleasant). Results indicate that under placebo treatment, processing of unpleasant valence [unpleasant (−) neutral images] was associated with decreases in SSVEP amplitude and latency in frontal and occipital cortices, whereas processing of pleasant valence [pleasant (−) neutral images] was associated with amplitude decreases and latency increases within frontal and left temporoparietal cortices. Decreases in both amplitude and latency are both interpreted as surrogate measures of cortical activation or excitation. Citalopram relative to placebo attenuated the electrophysiological activation to unpleasant valence within frontal and occipital cortices, but potentiated electrophysiological activation (amplitude only) to pleasant valence within parietooccipital cortices. Citalopram relative to placebo also suppressed differences in heart rate associated with the viewing of pleasant and unpleasant images, but did not alter subject's subjective responses to emotional images. Results suggest that responsiveness to pleasant and unpleasant stimuli following neurochemical modulation may vary across different response systems (i.e. self-report, HR and SSVEP). Electrophysiological findings suggest that acute serotonergic augmentation with citalopram modulates cortical processing of emotionally valent stimuli such that response to pleasant valence is potentiated and response to unpleasant valence is suppressed. The findings suggest a possible neurophysiological mechanism underlying antidepressant drug action on emotion.

Keywords: Serotonin; Serotonin re-uptake inhibitors; SSRI; Antidepressants; Emotion; Emotional valence; Emotional processing; International Affective Picture System; IAPS; Electrophysiology; SSPT; Brain imaging; Healthy human participants; Mood disorders

Introduction

The indoleamine, 5-hydroxytryptamine, or serotonin (5-HT) was discovered over 50 years ago (Erspamer and Asero, 1952; Rapport et al., 1948; Twarog and Page, 1953), and since then, its role in the pathophysiology of emotional disorders and mechanism of action of antidepressants has been subject to considerable research. Selective serotonin re-uptake inhibitors (SSRIs) augment 5-HT in the brain and are now one of the major pharmacological treatments of a wide range of mood disorders including depression. Studies have demonstrated that enhancement of 5-HT with antidepressants such as the SSRIs is associated with a decreasing magnitude of negative emotional states in psychiatric patients (e.g. Salzman et al., 1995; Steiner et al., 1995; van Vliet et al., 1994; see also Delgado et al., 1990). Although SSRIs are now widely used for the treatment of many emotional disorders, little is known about the neurophysiological mechanisms underlying the effects of serotonin on affective phenomena including emotional behaviours, mood and emotional processing, which may contribute towards their therapeutic mechanism of action.

Early correlational research on emotional behaviours and mood suggested that serotonergic abnormalities are associated with a variety of psychiatric and personality disturbances involving emotional dysfunction, including depression and impulse control disorders (see Coccaro et al., 1989; Heninger, 1995). Low 5-HT has been shown to be associated with violent and impulsive suicidal behaviour (Cremniter et al., 1999; Spreux-Varoquaux et al., 2001), impulsive aggression (Spoont, 1992) and personality measures of hostility and aggression (Cleare and Bond, 1997; Manuck et al., 1998). In contrast, high 5-HT has been shown to be associated with

* Corresponding author. Neuropsychopharmacology Laboratory, Brain Sciences Institute, Swinburne University of Technology, 400 Burwood Road, Hawthorn VIC 3122, Australia. Fax: +61-3-9214-5525.
E-mail address: pnathan@bsi.swin.edu.au (P.J. Nathan).
Available online on ScienceDirect (www.sciencedirect.com.)

1053-8119/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2004.03.022

harm avoidance, behavioural inhibition and reduced levels of positive and negative affect (Depue, 1995; Hansenne and Ansseau, 1999; Hennig et al., 2000; Zald and Depue, 2001). This has lead to the proposal that 5-HT may act as a general constraint system, where its primary function is to inhibit the information flow of neural systems that mediate affective and motivational processes (Depue and Spoont, 1986; Spoont, 1992; Zald and Depue, 2001).

Recent studies have directly compared the effects of serotonergic manipulation via 5-HT precursor depletion (see reviews: Moore et al., 2000; Reilly et al., 1997; Van der Does, 2001) or serotonin enhancing agents (e.g. SSRIs) (Knutson et al., 1998) on mood and emotional behaviour. 5-HT depletion via 5-HT precursor depletion (i.e. tryptophan depletion) has been shown to reduce mood in those with a genetic predisposition to affective disorders in several studies (Benkelfat et al., 1994; Ellenbogen et al., 1996; Klaassen et al., 1999; Quintin et al., 2001). In contrast, chronic (4-week) serotonergic enhancement with the SSRI paroxetine was correlated negatively with measures of hostility, assaultiveness and negative affect, and positively with social affiliation (Knutson et al., 1998). Furthermore, chronic (2-week) ingestion of the serotonin precursor, L-tryptophan, enhanced social functioning by decreasing quarrelsome behaviour and increasing dominant behaviour in normal volunteers (Moskowitz et al., 2001).

Although most studies have examined 5-HT-mediated changes over long time frames (such as mood and personality traits), and have used questionnaire- and behavioural-based measures, little is known about the role of 5-HT in the mechanisms involved in the processing and responding to emotional stimuli. Recently, Harmer et al. (2003a) reported that acute administration of the SSRI, citalopram (10 mg iv), facilitated the processing of happy facial expressions as evidenced by greater accuracy and reduced response times under citalopram relative to the placebo treatment. This finding was replicated in a subsequent study by the same authors after administration of tryptophan (Attenburrow et al., 2003). In addition, repeated administration of citalopram was associated with reduced recognition of the negative facial expressions, fear and disgust (Harmer et al., 2002). These findings, together with those from studies investigating emotional behaviour and mood, suggest a negative association between serotonin and unpleasant affect and a positive association with positive affect.

An alternative method for examining effects of neurochemical manipulation on emotional processing is neurophysiological methods incorporating brain imaging. For example, a recent study employing functional magnetic resonance imaging (fMRI) found that acute administration of lorazepam (a GABA-A/benzodiazepine receptor agonist) decreased the activation associated with negative affective stimulation (both intensity of signal and number of voxels), but increased the activation associated with positive affective stimulation within the orbitofrontal cortex (Northoff et al., 2002). Similarly, a preliminary fMRI study in depressed subjects reported that global brain activation to unpleasant images was decreased, but the activation to pleasant images was enhanced within the right secondary visual cortex following chronic venlafaxine (a combined noradrenaline and 5-HT re-uptake inhibitor) (Kalin et al., 1997). However, these findings were not reported in a subsequent article based on the same study/sample (Davidson et al., 2003). In this latter study, activations associated with the negative vs. neutral stimuli trial only were modified by chronic venlafaxine in depressed subjects (decreased activations in the insular and anterior cingulate cortex). It is important to note however that these latter two studies were conducted in depressed patients and not control subjects and there was no placebo comparison making it difficult to interpret the findings. These findings do however suggest possible system- or network-based neurophysiological mechanisms for the modulation of emotional processes by antidepressants.

The mechanisms involved in the modulatory effects of serotonin on emotional processing are yet to be examined. This is particularly relevant given that the cortical regions affected by serotonergic manipulation also overlap with those regions associated with emotion (Smith et al., 2002). The current study therefore examined the effects of acute serotonergic augmentation (with the SSRI, citalopram) on cortical electrophysiological responses to the processing of pleasant and unpleasant visual emotional stimuli. Emotional responses are phasic in nature, and consequently require a technique that is able to track transient electrophysiological changes associated with the processing of emotional stimuli. Therefore, steady-state probe topography (SSPT) was used. This technique offers the ability to track transient cortical electrophysiological changes with relatively high temporal resolution (usually 0.77 s) (Silberstein et al., 1995, 1998). SSPT examines changes in 13 Hz steady-state visually evoked potentials (SSVEPs) which comprises two components: amplitude and latency (phase), and previous work has demonstrated that these components are sensitive to emotional manipulation (Kemp et al., 2002, 2004). These studies demonstrated that transient widespread and bilateral frontal SSVEP latency and occipital amplitude reductions are associated with the cortical processing of pleasant and unpleasant emotional stimuli. Based on the literature, it was hypothesised that following citalopram, unpleasant images relative to neutral images will be associated with a reduction in significantly activated cortical brain regions (especially within the frontal and occipital regions) whereas pleasant images relative to neutral images will be associated with enhancement of activation.

Methods

Participants

Seventeen healthy subjects (eight males and nine females) participated in the current study (mean age, 22.88; SD, 4.61; mean education, 15.69; SD, 1.30). All participants were right-handed, (the Edinburgh Inventory, Oldfield, 1971), nonsmokers, not on any medication (minimum 1 month drug-free) or illicit drugs. All successfully completed a medical examination involving physical- and question-based assessment, conducted by a physician who screened and excluded individuals with a history of past and present cardiovascular, hepatic, gastrointestinal, endocrine, neurological or psychiatric conditions. Participants were recruited by advertising on university notice boards and gave informed consent to take part in the study, which was approved by the Swinburne Research Ethics Committee.

Procedure

The study employed a randomised double-blind, placebo controlled design, in which subjects were tested under two acute treatment conditions: oral administration of placebo and citalopram (20 mg), each of which was separated by a minimum washout period of 1 week. The study involved presentation of a series of images, selected from the International Affective Picture System (IAPS) (Lang et al., 1999), under both treatment conditions. These images were chosen based on standardised valence and arousal

ratings published in the IAPS Instruction Manual. Images selected were categorised as unpleasant, neutral and pleasant, and standardised ratings for valence ranged between 1.8 and 3.47, 4.46 and 5.46, 7.02 and 8.34, respectively, whereas standardised ratings of arousal ranged between 3.52 and 5.5, 1.55 and 4.27, 2.67 and 5.94, respectively. A more detailed description of task construction has been described previously (Kemp et al., 2002).

Subjects were instructed to focus on emotional content, to refrain from emotive inhibition, and to be prepared to rate each image on valence and arousal dimensions using the Self-Assessment Manikin (SAM) (Lang et al., 1999). The task involved presentation of selected images for a duration of 6 s, with each image followed by a valence, then an arousal rating scale to obtain verbal responses as to how subjects felt whilst they viewed the presented images. Images were categorised according to the predefined valence of the images [unpleasant (U), neutral (N) and pleasant (P); with each block containing 25 images] and presented to participants in three blocks (P,N,U or U,N,P).

Subjects arrived for testing on each of the two testing days at approximately 8 am, after which a standard breakfast was provided. Subjects were then brought to the recording room, which was soundproofed and dimly lit and instructed on how to complete the IAPS task. Subjects were tested 2 h following administration of either placebo or citalopram. This 2-h delay was chosen to coincide with approximate peak plasma levels of citalopram (Noble and Benfield, 1997). The administration of either placebo or citalopram on a particular day was counterbalanced across subjects.

A diffuse 13-Hz sinusoidal white flicker, which was superimposed onto the visual field, elicited the SSVEPs whilst images and rating scales were presented to subjects from a computer monitor. The visual flicker was presented through a set of modified goggles and subtended a horizontal angle of 160° and a vertical angle of 90°, and had a modulation depth of 45% when viewed against the background. Brain electrical activity was recorded by 64 monopolar leads (impedances generally <5 kΩ), positioned in International 10/20 positions and sites between these positions, using a lycra electrode cap. Linked ear electrodes were used as a reference and a nose electrode was used for ground. One of the monopolar leads was sacrificed to record the electrocardiogram (ECG) from the upper left arm, which was also referenced to the linked ear electrodes. Recorded activity was bandpass filtered from 0.74 to 74 Hz and digitised at a rate of 500 Hz with 16-bit accuracy.

Signal processing

The key features of SSPT signal processing analysis and associated artifact detection procedures have been described previously (e.g. Silberstein et al., 1995). SSVEPs were produced for all electrodes by calculating the 13-Hz Fourier coefficients (FC) for each cycle and then smoothing the FC time series by averaging overlapping blocks of 10 FCs. This methodology was applied to all image categories and for each treatment condition. A target averaging technique was used to select the SSVEP associated with each image and then, average all epochs for each category. Epochs for each individual were then averaged to form a cross-subject-averaged 6-s epoch for each image category. The SSVEP epoch corresponding to the neutral images was then subtracted from both emotional categories yielding activity interpreted as being associated with pleasant or unpleasant valence.

The functional significance of the SSVEP amplitude and latency modulations has been discussed previously (Silberstein, 1995b, 1998; Silberstein et al., 2001). To summarise, re-entrant feedback and feed-forward cortico-cortico and thalamo-cortico fibres have been proposed to underlie the generation of the SSVEP. In this framework, decreases in the number of synchronised neural elements (or increases in the number of desynchronised neural elements) within the re-entrant loop (loop gain) will be associated with decreases in SSVEP amplitude, whereas decreases in the synaptic and axonal transmission times of the re-entrant loop (loop-time) will be associated with SSVEP latency decreases.

Presentation of data

SSVEP results are initially presented in terms of amplitude and latency time series plots, as well as Hotellings T statistical cluster plots (Fig. 2). Electrodes (presented on the y-axis of these time series and cluster plots) are compartmentalised into regions approximately associated with frontal (electrodes 0–20, including Fp1, Fp2, F7, F3, Fz, F4 and F8), centro-parieto-temporal (electrodes 21–52, including T3, C3, Cz, C4, T4, T5, P3, Pz, P4 and T6) and occipital (electrodes 53–63, including O1, Oz and O2) electrode placement to aid interpretation of these plots. Display of statistical cluster plots have been used previously to efficiently summarise the comparison of multiple data sets as well as determine robust effects through identification of consecutive statistical spatiotemporal clusters (Gray et al., 2003; Kemp et al., 2004; Murray et al., 2002). These plots illustrate levels of statistical significance (indicated by colour values) across the two treatment conditions (placebo, citalopram) for all electrodes across all time points.

Based on this initial examination, we then averaged the SSPT into different time periods (identified in the cluster plots) and present these averaged time periods as topographic maps using a spherical spline interpolation procedure (Nunez et al., 1994). These maps display the two components of the SSVEP: amplitude and latency for each emotional condition relative to the neutral images, and the statistical strength of the differences (Hotellings T statistic). The SSVEP topographic maps are scaled to the highest/lowest values for each valence category (pleasant, unpleasant) and each SSVEP component (amplitude, latency), as the purpose of the current paper is to explore the differences between treatment conditions (placebo, citalopram).

Statistical issues

Behavioural SAM ratings were analysed using a within-subjects Treatment × Category repeated-measures analysis of variance (RANOVA) for valence and arousal (separately) to determine whether treatment modified participant's emotional ratings of the presented images. In addition, analysis of heart rate corresponding with the presentation of all image categories within placebo and citalopram conditions was conducted in the following way. Cardiac interbeat intervals (ibi) during picture presentation were converted to beats per minute (bpm) in half-second bins. In the current study, we averaged these half-second bins for each 6-s epoch associated with the three valenced categories and conducted a within-subjects Treatment (placebo, citalopram) × Category (unpleasant, neutral, pleasant) RANOVA to allow investigation of treatment effects.

The statistical strength of the SSVEP differences between the emotional images (unpleasant, pleasant) and the neutral images were examined using the Hotellings T^2 parameter and presented in statistical cluster plots as well as topographic maps. An alpha

criterion for the Hotellings T was arbitrarily set at $P = 0.01$ (uncorrected for multiple comparisons) for the SSVEP data as used previously (Gray et al., 2003; Kemp et al., 2004). In addition to Hotellings statistics, a series of post hoc RANOVA tests were conducted to directly test differences between the two drug conditions. Eighteen electrodes (nine within the left hemisphere and nine within the right hemisphere) were entered for both frontal and posterior locations and included Fp1, Fp2, F3, F4, F7 and F8 for frontal locations, and T5, T6, P3, P4, O1 and O2 for posterior electrode locations as well as electrode locations midway between these standard positions. Midline electrode sites were excluded. As the within-subject factors of Drug (placebo, citalopram), Category (neutral, pleasant, unpleasant image categories) and Hemisphere were of primary a priori interest, RANOVAs employing a customised experimental design were applied (separately) for amplitude and latency SSVEP components. Applying a customised experimental design allows for selection of fewer effects to be reported regardless of the number of factors entered. This method therefore minimises the generation of false positive findings (Type 1 error) whilst focusing on the effects of most interest. The within-subject factors of Drug, Category, Hemisphere and Electrode and a between-subjects factor of gender were defined; however, the within-subjects model included only Drug × Category and Drug × Category × Hemisphere interactions. The between-subjects factor of gender was also included in the model to investigate possible confounding effects of gender on the basis of our recent study which reports on electrophysiological gender effects following presentation of identical images to those presented in the current study (Kemp et al., 2004).

Results

Behavioural data

The means and standard deviations for ratings of valence and arousal made by subjects are presented below in Table 1.

Significant category effects were found for both valence [$F(1.17,18.77) = 110.38$, $P < 0.001$, partial eta squared = 0.87] (Greenhouse–Geisser adjusted) and arousal [$F(2,32) = 26.41$, $P < 0.001$, partial eta squared = 0.62]. For the valence dimension, planned comparisons revealed that participant's ratings of both pleasant and unpleasant images were significantly different from ratings of neutral images [$F(1,16) = 95.92$, $P < 0.001$, partial eta squared = 0.86 and $F(1,16) = 93.72$, $P < 0.001$, partial eta squared = 0.85, respectively]. For the arousal dimension, planned comparisons revealed that ratings of arousal for both pleasant and unpleasant images were significantly different from ratings of neutral images [$F(1,16) = 15.93$, $P = 0.001$, partial eta squared = 0.50 and $F(1,16) = 51.05$, $P < 0.001$, partial eta squared = 0.76, respectively]. In addition, ratings of arousal for unpleasant images were significantly different to those of pleasant images [$F(1,16) = 10.49$, $P = 0.005$, partial eta squared = 0.40]. No main effects for treatment were demonstrated, nor were participant's ratings of valence or arousal modified by treatment.

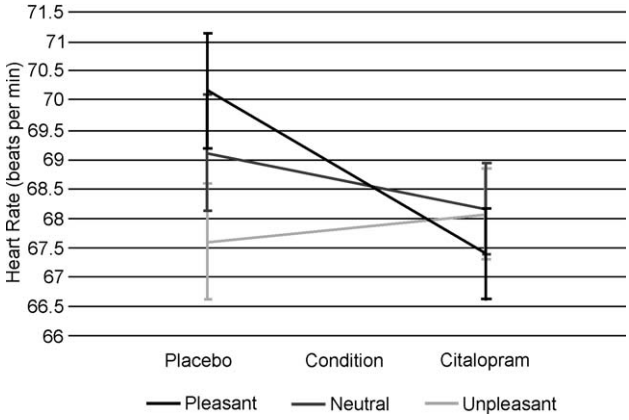

Fig. 1. Average heart rate (beats per minute or bpm) for each image-category (pleasant, neutral, unpleasant) for both treatment conditions (placebo, citalopram).

ECG data

Analysis of heart rate (HR) using a 2 (Treatment) × 3 (Category) within-subject, RANOVA design revealed a significant main effect for category [$F(2,32) = 3.39$, $P = 0.046$, partial eta squared = 0.18], and although the main effect for treatment was not significant, treatment was found to modify the main effect for category [$F(1.43,22.80) = 4.12$, $P = 0.042$, partial eta squared = 0.21] (Greenhouse–Geisser adjusted) (see Fig. 1 for a visual display of this interaction). Planned comparisons for category revealed that HR during viewing of unpleasant images was significantly different from HR during viewing of pleasant images [$F(1,16) = 6.79$, $P = 0.019$, partial eta squared = 0.30]; a trend towards statistical significance for HR during viewing of unpleasant images relative to HR during viewing of neutral images [$F(1,16) = 4.16$, $P = 0.058$, partial eta squared = 0.21]; and no statistical difference between HR during pleasant images and HR during viewing of neutral images.

RANOVA post hoc tests were conducted on the placebo and citalopram treatment groups to further understand the category × treatment interaction effect. Previous literature suggests that heart rate is able to discriminate differently valenced images (e.g. Lang et al., 1993; Palomba et al., 1997); therefore, RANOVAs were chosen to investigate this interaction rather than paired-sample t tests on each of the valenced categories because we were interested in (1) whether heart rate was able to discriminate the three valenced

Table 1
Means and standard deviation are presented for valence and arousal SAM ratings, for pleasant, neutral and unpleasant categories in placebo and citalopram treatment conditions

	Pleasant		Neutral		Unpleasant	
	Placebo	Citalopram	Placebo	Citalopram	Placebo	Citalopram
Valence	6.37 ± 0.62	6.12 ± 0.51	5.04 ± 0.22	5.09 ± 0.23	3.50 ± 0.68	3.51 ± 0.62
Arousal	3.31 ± 1.70	2.82 ± 1.30	1.88 ± 0.94	1.87 ± 0.84	3.96 ± 1.56	3.80 ± 1.57

categories of images in placebo treatment and (2) how citalopram altered this effect.

Significant category effects were found for the placebo treatment condition [$F(2,32) = 5.70$, $P = 0.008$, partial eta squared = 0.26], but not for the citalopram condition [$F(2,32) = 0.96$, $P = 0.394$], suggesting that the ability for heart rate to distinguish between differently valenced images under no drug condition was suppressed by the citalopram treatment condition. Planned comparisons for category within the placebo treatment condition revealed that heart rate during viewing of unpleasant images was significantly less than heart rate during viewing of pleasant images [$F(1,16) = 7.38$, $P = 0.015$, partial eta squared = 0.32]; a trend towards a statistically significant reduction in heart rate during viewing of unpleasant images relative to neutral images [$F(1,16) = 4.51$, $P = 0.05$, partial eta squared = 0.22]; no significant differences between neutral and pleasant images.

SSVEP data

Amplitude and latency time series plots, representing the differences between emotional and neutral categories (emotional valence), as well as the statistical significance of these differences are presented in Fig. 2. The Hotellings T time series plots display significant clusters of electrodes and time points during the processing of both pleasant and unpleasant valence under placebo and citalopram conditions. Fig. 2 indicates that, for pleasant valence, the placebo condition is associated with a smaller number of significant time points relative to the citalopram condition during the middle and late time components (visual comparison between the first and second statistical cluster plots). In addition, Fig. 2 indicates for unpleasant valence that the placebo condition is associated with a greater number of significant time points relative to the citalopram condition, during all three components (early, middle, late), particularly within the posterior region (visual

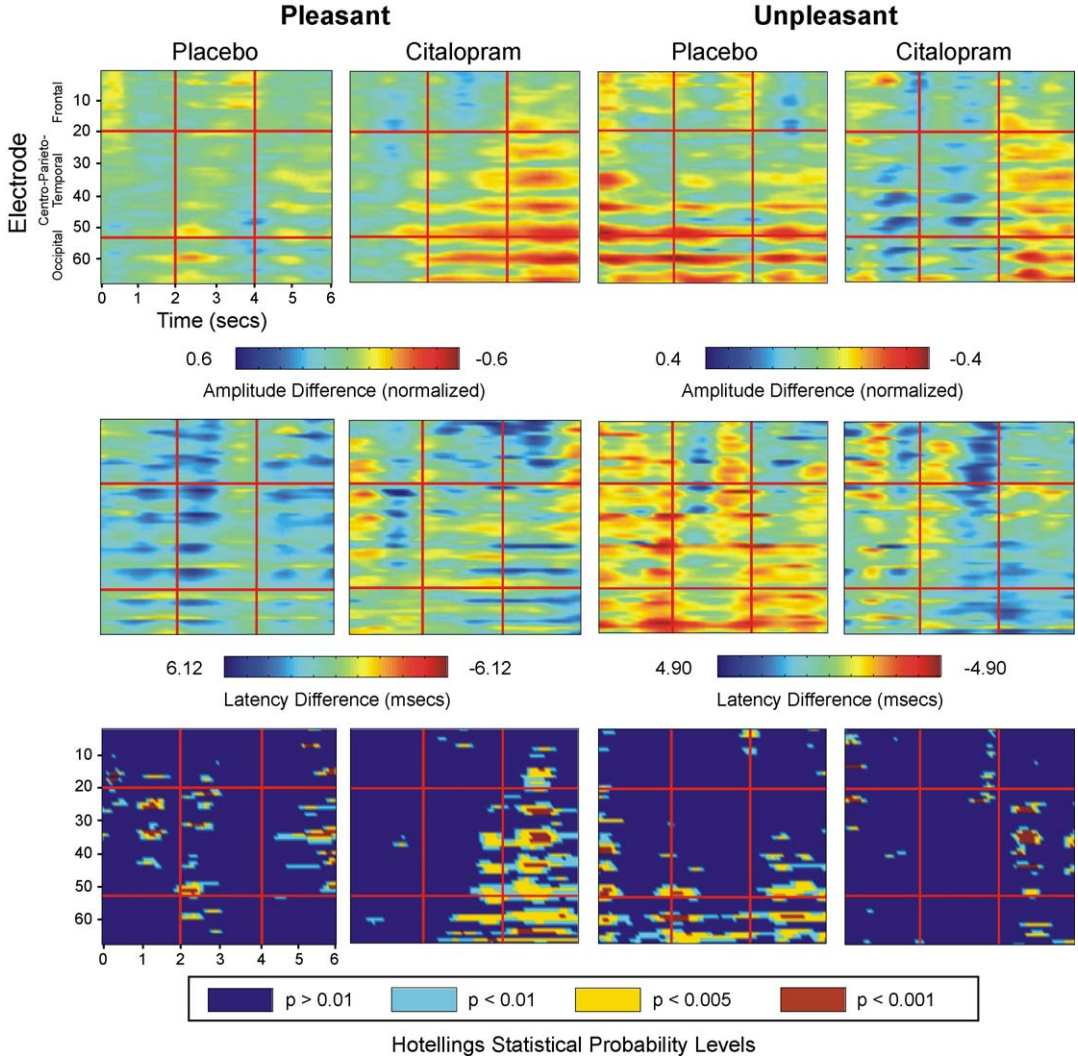

Fig. 2. Amplitude (row 1) and latency (row 2) time series plots for placebo and citalopram conditions illustrate the difference between both emotional categories (pleasant and unpleasant) and the neutral category across time (x-axis) for each of the 64 electrode positions (y-axis). Warmer colours in these plots represent reduced amplitude and reduced latency during the presentation of affective images. The Hotellings statistical cluster plots (row 3) illustrate the results of point-wise Hotellings T tests, which evaluated the differences between the emotional categories and neutral category. For clarity, P values have been colour-coded for four levels of probability (see legend). Each plot has been divided into early (0–2 s), middle (2–4 s) and late (4–6 s) time periods.

comparison between the first and second statistical cluster plots). The locations of these differences as well as statistical significance of these differences are displayed in topographic maps and examined in three equal 2-s time periods (Figs. 3a and b).

The effects of placebo and citalopram on the processing of pleasant valence are illustrated in Fig. 3a. After administration of placebo, the processing of pleasant valence is associated with amplitude decreases and latency increases in frontal regions throughout the 6-s epoch and in posterior regions during the middle component. After administration of citalopram, the effects observed under placebo condition during the early and middle epochs were attenuated, although there was an augmentation reflected by a large parietooccipital amplitude decrease suggesting increased activation within this region. This amplitude decrease begins within the 2- to 4-s epoch and extends into frontal regions during the 4- to 6-s epoch. The associated Hotellings *T* topographic map revealed widespread significant posterior activations for the 4- to 6-s epoch. In summary, although citalopram reduces the significant differences between pleasant and neutral images within early and middle components of processing pleasant stimuli, the greatest effects (amplitude

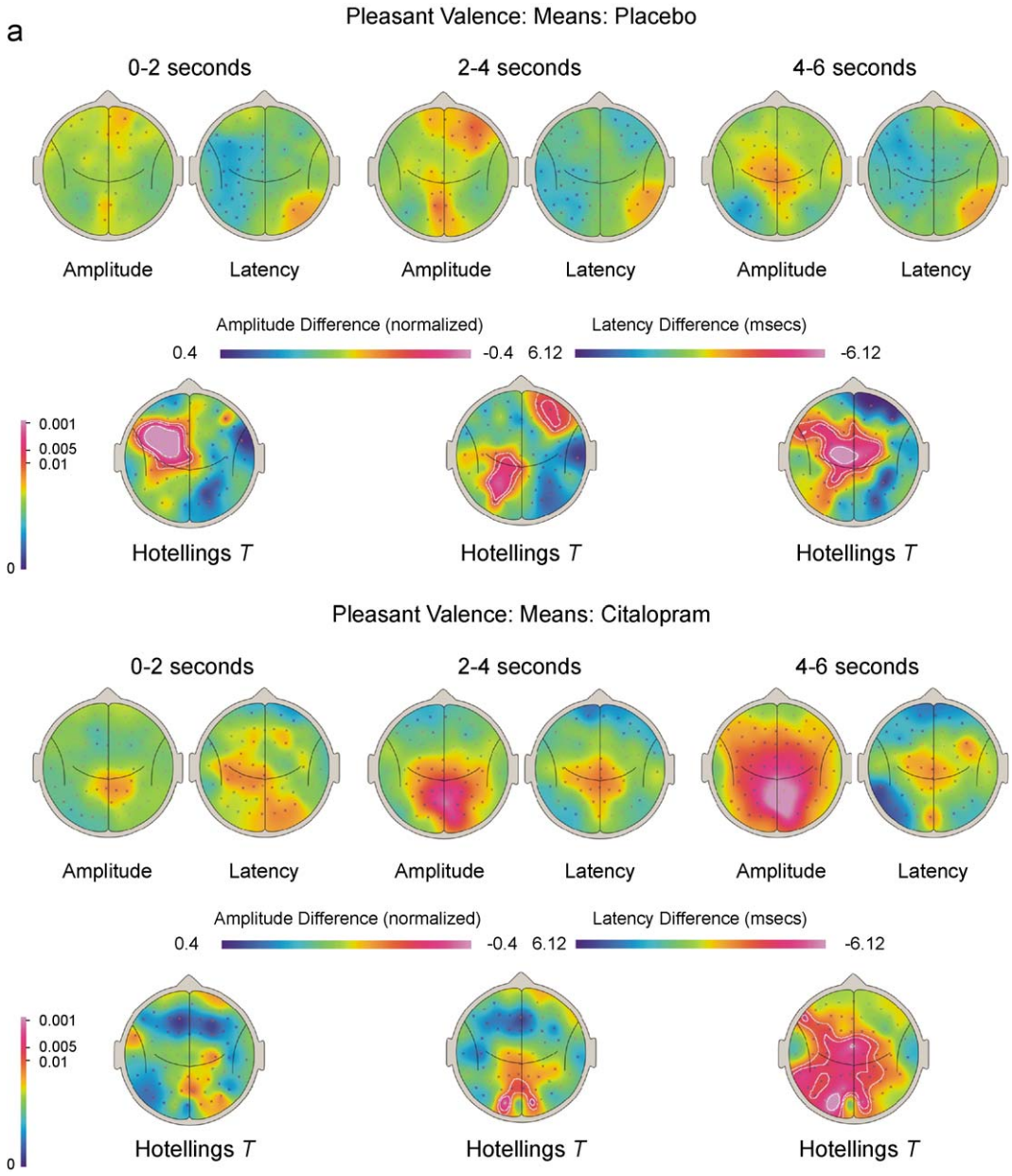

Fig. 3. (a) Topographic maps associated with pleasant valence are presented which display the 13-Hz SSVEP data (amplitude and latency) in addition to Hotellings *T* statistics for placebo and citalopram conditions. Three time periods are presented which relate to early (0–2 s), middle (2–4 s) and late (4–6 s) components of image viewing. Warmer colours represent reductions in amplitude and latency during pleasant images relative to neutral images, and larger *T* values in the Hotellings *T* maps. (b) Topographic maps associated with unpleasant valence are presented which display the 13-Hz SSVEP data (amplitude and latency) in addition to Hotellings *T* statistics for placebo and citalopram conditions. Three time periods are presented which relate to early (0–2 s), middle (2–4 s) and late (4–6 s) components of image viewing. Warmer colours represent reductions in amplitude and latency during unpleasant images relative to neutral images, and larger *T* values in the Hotellings *T* maps.

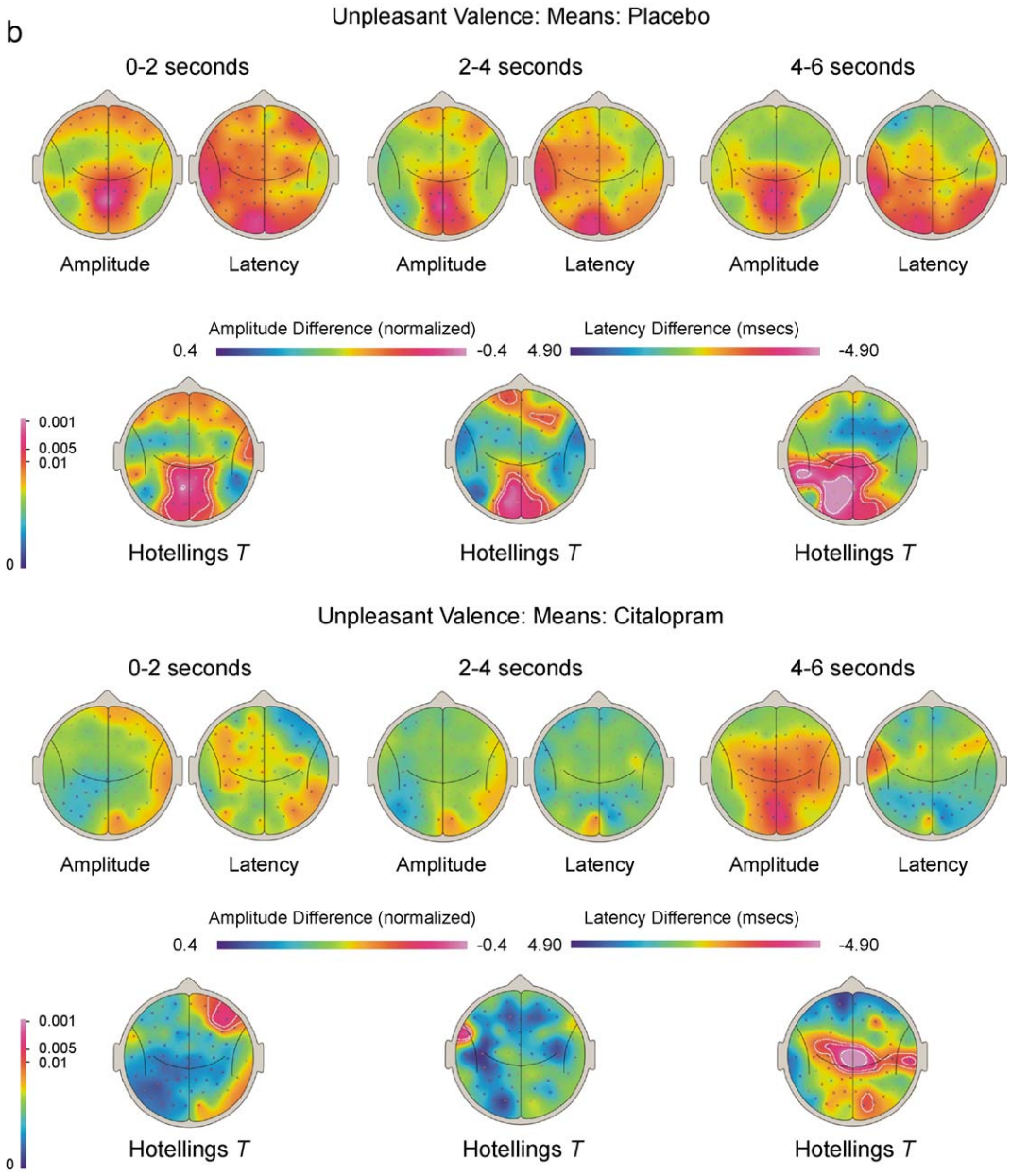

Fig. 3 (*continued*).

reductions) are displayed within the late component, suggesting increased activity within parietooccipital regions.

The effects of placebo and citalopram on the processing of unpleasant valence are illustrated in Fig. 3b. After administration of placebo, the processing of unpleasant valence is associated with widespread significant reductions in amplitude and latency, particularly within the posterior region. After administration of citalopram, unpleasant valence is associated with a suppression of these amplitude and latency reductions (reduced activity), within both frontal and posterior regions, and this suppression is particularly prominent during the early and middle epochs. In addition, latency is noted to demonstrate significant latency increases within the right anterior frontal (early epoch), left anterior temporal regions (middle epoch) and occipital regions (late epoch) during the citalopram condition. Finally, the late component of the citalopram condition is characterised by significant and widespread decreases in posterior amplitude. In summary, administration of citalopram is associated with a suppression of the frontal and posterior amplitude and latency reductions (reduced activity) as well as latency increases (reversal of activity seen under placebo) when compared with the placebo condition.

A preliminary analysis was conducted to examine whether males (n = 8) and females (n = 9) differ in the processing of pleasant and unpleasant valence and the effects on this processing following acute administration of citalopram. Results of this preliminary investigation are displayed in Fig. 4 and suggest that following citalopram, pleasant valence is associated with greater reductions in amplitude within centro-parieto-temporal and occipital regions in males (also corresponding with an increase in the number and size of statistical clusters within these regions). This

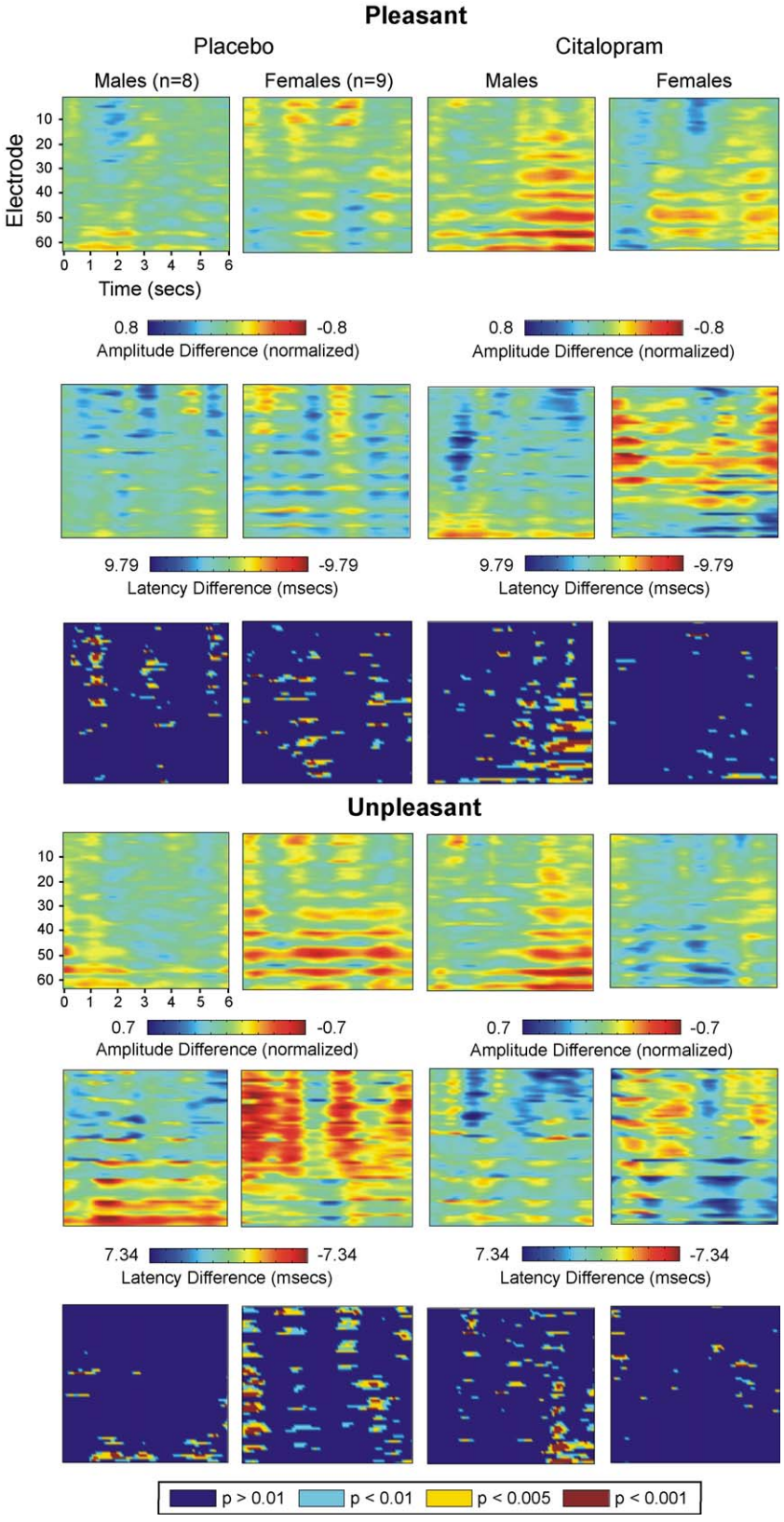

Fig. 4. Unpleasant and pleasant time series plots for placebo and citalopram conditions associated with male and female genders.

profile, however, was not displayed by females. Results also suggest that following administration of citalopram, unpleasant valence is associated with a suppression of both amplitude and latency reductions in females (also corresponding with a reduction in the number and size of statistical clusters). This profile, however, was not displayed by males. In summary, the effects of citalopram on pleasant valence (when males and females are combined) appear to be predominantly influenced by males, whereas effects of citalopram on unpleasant valence (when males and females are combined) appear to be predominantly influenced by females.

Finally, a series of RANOVAs were conducted on both anterior and posterior electrode locations to more directly test for statistical differences between placebo and citalopram. Frontal effects during the early time period were investigated because the most interesting effects, according to the Hotellings maps, appear to occur during this epoch, particularly for the latency component in the unpleasant (−) neutral comparison and citalopram condition. In contrast, posterior effects during the late time period were investigated because the most interesting effects, according to the Hotellings maps, appear to occur during this epoch, particularly for the amplitude component in the pleasant (−) neutral comparison and citalopram condition. The RANOVAs conducted on amplitude and latency in anterior locations during the early time period revealed no Drug × Category, Drug × Category × Gender, Drug × Category × Hemisphere, Drug × Category × Hemisphere × Gender interactions, suggesting that Drug condition does not modify the effects of Category at anterior electrode locations. The RANOVA conducted on amplitude in posterior locations for the late time period revealed no statistically significant effects although the Drug × Category × Hemisphere [$F(2,30) = 2.869$, $P = 0.072$, partial eta squared = 0.161] reached trend levels of significance. The RANOVA conducted on latency in posterior locations for the late time period revealed a significant Drug × Category interaction [$F(2,30) = 3.845$, $P = 0.033$, partial eta squared = 0.204]. Tests of within-subjects contrasts identified a significant effect of drug for the contrast of unpleasant images vs. neutral images [$F(1,15) = 5.926$, $P = 0.028$, partial eta squared = 0.283] but not for pleasant images vs. neutral images [$F(1,15) = 1.627$, $P = 0.221$]. To explore this finding further, a follow-up, repeated-measures ANOVA was conducted for the placebo and citalopram conditions separately, for the difference between unpleasant and neutral images across all 18 posterior electrodes. Only the within-subjects factor of Category was included in the model, therefore exploring the effects of Category after collapsing across Electrode. Findings suggest that posterior latency in the placebo condition during presentation of unpleasant images is less than that during presentation of neutral images [$F(1,16) = 5.794$, $P = 0.029$, partial eta squared = 0.266]. By contrast, posterior latency in the citalopram condition during presentation of unpleasant images did not significantly differ from that during presentation of neutral images [$F(1,16) = 0.573$, $P = 0.460$]. Gender was not found to modify the Drug × Category or Drug × Category × Hemisphere interactions for either anterior or posterior electrode locations. In summary, RANOVA results confirm the Hotellings findings that latency reductions during the processing of unpleasant images (relative to neutral images) within posterior regions are suppressed in the citalopram condition, and suggest a trend for a modifying role of citalopram on the processing of pleasant images (relative to neutral images) within posterior regions but failed to confirm any effects of citalopram within anterior electrode locations.

Discussion

Acute augmentation of serotonin with citalopram was found to differentially affect the electrophysiological responsiveness to pleasant and unpleasant images relative to neutral images. Two key findings in terms of the SSVEPs should be highlighted. Firstly, in the citalopram condition in contrast to the placebo condition, processing of pleasant valence was predominantly associated with increased parietooccipital activity (characterised by widespread reductions in amplitude), whereas processing of unpleasant valence was predominantly associated with a suppression of anterior–frontal and occipital activity (characterised by suppression of amplitude and latency reductions). Secondly, different spatiotemporal statistically significant patterns emerge following administration of citalopram in contrast to placebo. In particular, the processing of unpleasant valence (i.e. in the placebo condition) was associated with significant parietooccipital activations (amplitude and latency reductions) throughout the three time periods and frontal activations during the middle time period. Citalopram's predominant effects were the attenuation of these findings. The processing of pleasant valence, however, was associated with significant frontal activations (amplitude reductions) throughout the three time periods and left temporoparietal activations during the middle time period. Citalopram's predominant effect was to enhance processing within parietooccipital regions in the middle and late time points.

The present study employed SSPT to examine the effects of citalopram on emotional processing. This technique examines changes in 13 Hz SSVEPs, which primarily reflect neuronal activity within pyramidal cells of the neocortex (which are the principal source of cortical glutamate). SSVEP is composed of two components, amplitude and phase (latency) and previous work has demonstrated that these components are sensitive to cognitive and emotional manipulation (e.g. Gray et al., 2003; Kemp et al., 2002, 2004; Silberstein et al., 1996, 2000). We have suggested that amplitude may be compared to alpha activity in association with cognitive tasks (Silberstein, 1995a,b), whereas latency reductions (or increased processing speed) may be a consequence of increased synaptic excitatory processes in these networks, and conversely, latency increases may be a consequence of reduced synaptic excitation (or increased synaptic inhibition) (Silberstein et al., 2000, 2001). Hence, amplitude and latency reductions are interpreted as increased cortical activation. Although the exact mechanisms associated with SSVEP changes are not known, there is strong evidence for interactions between serotonin and glutamate in neocortical pyramidal cells (see Marek and Aghajanian, 1998, for a review). In addition, it is possible that the responsiveness to serotonergic augmentation, of certain excitatory (5-HT_{2A}) and inhibitory (5-HT_{1A}) receptors within pyramidal cells may vary depending on the emotional circuitry involved in the processing of pleasant or unpleasant valence. Consequently, activation of these excitatory and inhibitory receptors may lead to amplitude and latency changes observed during the processing of pleasant and unpleasant valence, respectively. These mechanisms are supported by evidence that most antidepressants enhance postsynaptic 5-HT_{1A} hyperpolarisation (see Barnes and Sharp, 1999, for a review of central 5-HT receptors) and the finding that 5-HT induces a marked increase in excitatory postsynaptic currents within layer V of the pyramidal cells through activation of 5-HT_{2A} receptors (Marek and Aghajanian, 1998).

In the present study, the processing of pleasant valence after citalopram (relative to placebo) was characterised by diffuse, amplitude reductions within parietooccipital regions which are suggestive of increased activity. We have previously reported that amplitude reductions within occipital regions are associated with increases in visual attention (e.g. Silberstein et al., 1990). In addition, a study using fMRI reported increased activity in response to positive stimuli within the right occipital region, following chronic administration of venlafaxine (Kalin et al., 1997). These authors suggested that the increased responsiveness to positive stimuli following venlafaxine treatment may be associated with an increase in attention. Harmer et al. have recently reported that enhanced perception of affiliative signals occurring with citalopram administration may be an aspect particular to the action of SSRIs (Harmer et al., 2003a). The authors suggest that enhanced perception of affiliative signals may facilitate approach behaviours such as social affiliation and dominance. This interpretation supports earlier studies which reported an enhancement of these behaviours following chronic SSRI administration (Knutson et al., 1998; Moskowitz et al., 2001). These previous findings suggest that the strong amplitude reductions displayed after citalopram in the present study may reflect a cortical neurophysiological mechanism relating to enhanced perception to or orienting towards the pleasant images.

The processing of unpleasant valence after citalopram was associated with an attenuation of the cortical activation seen during placebo treatment (i.e. amplitude and latency reductions) within anterior frontal and occipital regions. This attenuation with citalopram was more pronounced within right anterior frontal and left anterior temporal regions in which latency increases were observed (decreased activation). Interestingly, the right prefrontal cortex has been previously implicated in both transient and chronic changes in negative mood (e.g. Kemp et al., 2004; Mayberg et al., 1999, respectively) as well as withdrawal-related behaviour (e.g. Davidson and Irwin, 1999). Our findings are consistent with studies that have reported that antidepressant treatment decreases activation within the orbital cortex and ventrolateral PFC (Brody et al., 2001b; Drevets and Raichle, 1992; Drevets et al., 1999; Mayberg et al., 1999; Nobler et al., 1994). In addition, it has been previously reported that antidepressant treatment is associated with a reversal of pretreatment brain activity in depressed patients (Brody et al., 2001a; Drevets et al., 2002; Mayberg et al., 1999). The increased activation within the occipital cortex (observed under placebo) is likely a function of feedback from the amygdala (Amaral et al., 1992; Davidson et al., 2003) and may relate to a heightened sensitivity to visual stimuli with emotional relevance (Lane et al., 1999; Lang et al., 1998). Findings suggest the citalopram may reduce this sensitivity possibly by modulating the amygdala response to negative stimuli. Decreases in activation within frontal and occipital areas may be related to the theory that reduced excitatory transmission within limbic-thalamo-cortical (LTC) and limbic-cortical-striatal-pallidal-thalamic (KCSPT) circuitry plays a role in the mechanisms of antidepressant treatment (Drevets et al., 2002).

The findings of this study may demonstrate a neurophysiological mechanism for the effects of serotonergic antidepressants such that increasing 5-HT leads to an enhancement of pleasant but a suppression of unpleasant cortical electrophysiological responses to visual emotional stimuli. As discussed in the introduction of this paper, theoretical models have suggested that increases in 5-HT are associated with the behavioural dimensions of harm avoidance and constraint. Results from the current study suggest that increased levels of 5-HT may "constrain" neurophysiological processing of unpleasant stimuli. The results also suggest that initial processing of pleasant stimuli may be enhanced. Harmer et al. (2003c) have posited a tentative hypothesis for antidepressant action that suggests enhanced perception of affiliative signals may precede and even facilitate approach behaviour and social interaction. It is possible therefore that antidepressants such as SSRIs shift the attentional bias from negative to positive stimuli and that these effects are apparent even after an acute dosage. Our findings also suggest that the use of brain imaging techniques may better explain immediate responsiveness to affective stimuli than simply correlating the association between 5-HT functioning and subjective responses (i.e. questionnaires) (e.g. Zald and Depue, 2001).

Gender differences have been previously reported in studies on emotional processing (e.g. Bremner et al., 2001; Kemp et al., 2004; Killgore, 2000; Lee et al., 2002; Pendergrass et al., 2003; Wrase et al., 2003). Therefore, preliminary gender differences in the processing of pleasant and unpleasant valence and the effects on this processing following acute administration of citalopram were examined in the current study. Results suggest that the effects of citalopram on pleasant valence (when males and females are combined) appear to be predominantly influenced by males, whereas the effects of citalopram on unpleasant valence (when males and females are combined) appear to be predominantly influenced by females. This suggests that citalopram may potentiate male's responsiveness to pleasant stimuli, although suppressing female's responsiveness to unpleasant stimuli. These findings are consistent with our previously published study that reported that whereas males may be more responsive (electrophysiologically) to pleasant images (relative to neutral images), females may be more responsive (electrophysiologically) to unpleasant images (relative to neutral images) (Kemp et al., 2004). It should be noted however, that the gender differences (reported in the current study) are preliminary findings and based on a small sample size. Future studies should further investigate therefore not only how males and females differ on emotional processing, but neurochemical modulation of this processing.

Although differences in the electrophysiological responses to emotional valence were observed in the current study, no changes were observed in subjective behavioural ratings (SAM ratings). This finding supports observations of a previous study that showed changes on objective measures (i.e. detection of a higher number of facial expressions of happiness with reduced response times), but lack of changes in subjective state (using visual analogue scales and the Befindlichkeits Scale) following acute serotonergic enhancement with citalopram (Harmer et al., 2003a). These findings suggest that emotional processing may occur independently or at a lower threshold, than overt changes in mood. In contrast to the subjective behavioural findings, physiological heart rate was shown to be modulated by citalopram. More specifically, the findings in the placebo condition demonstrate that heart rate during the viewing of unpleasant images was less than that during the viewing of pleasant images (supporting previous findings, e.g., Aftanas et al., 2001; Lang et al., 1993; Palomba et al., 1997), and that this effect disappeared following administration of citalopram. Importantly, our heart rate data provide another physiological measure of emotional responsiveness to the presented images, and in addition, that this emotional responsiveness is eliminated by serotonergic enhancement with an antidepressant. Although it is uncertain what the exact mechanism responsible for this effect is, it is likely that the effects of citalopram on emotion-modulated HR may occur through descending influences of regions known to be involved in emotional

processing, such as the prefrontal cortex and amygdala (see Thayer and Lane, 2000, for a discussion of the functional networks which mediate psychophysiological resources in attention and emotion).

We have previously reported that transient, widespread and bilateral frontal SSVEP latency and occipital amplitude reductions are associated with the cortical processing of pleasant and unpleasant valence in 16 participants using the same IAPS stimuli (Kemp et al., 2002). More recently, we confirmed the finding that frontal latency and occipital amplitude reductions are associated with the processing of pleasant and unpleasant valence in 30 participants (Kemp et al., 2004). Previous studies in healthy subjects using fMRI and PET imaging have reported increased activity within the medial prefrontal cortex and visual cortical areas during tasks that examine emotional processing (see recent meta-analyses, Phan et al., 2002; Wager et al., 2003). It is important to note however that increased activity within the medial prefrontal cortex is in contrast to the findings of mood induction and depressed state in which decreased activation is reported within dorsomedial/dorsolateral regions (e.g. Drevets et al., 2002; Mayberg et al., 1999). It is likely that such a discrepancy relates to differences between emotional processing and emotional induction paradigms, internally and externally generated emotions as well as the modulatory effects of cognitive processes.

In the current study, the processing of unpleasant valence was associated with a decrease in SSVEP amplitude and latency in frontal and occipital cortices, whereas pleasant valence was associated with widespread amplitude decreases within frontal and temporoparietal cortices. Although the findings reported in the current study relating to the processing of unpleasant valence under placebo are generally consistent with our two previously published studies (under drug-free conditions), the SSVEP latency increases during the processing of pleasant valence was not. It is possible that this difference may relate to several factors. Firstly, compared to our previous studies, the current study examined emotional processing after the administration of placebo. Indeed, administration of placebo has been reported to produce specific brain-modulated activation (Mayberg et al., 2002). It is possible that the differences observed in the processing of pleasant valence between this study and our previous studies may be related to a placebo effect. Secondly, there were differences in experimental design (i.e. participants in the two previous studies had only viewed the IAPS stimuli once, whereas participants in the current study may have seen the images up to three times, which included prior baseline and treatment recordings). Interestingly, Phan et al. (2003) have suggested that the rostral anterior cingulate cortex, medial prefrontal cortex, hippocampus and amygdala activations may habituate with repeated exposure. It is possible that participants under placebo had habituated to the pleasant stimuli as the present study presented images that were classified as low on the arousal dimension. In addition, participants may have been less likely to habituate to unpleasant images due to a heightened sensitivity to negative stimuli, a phenomenon known as the negativity bias (see Cacioppo and Gardner, 1999, for discussion).

Finally, several limitations of the study are worth noting. Firstly, although participants were instructed to refrain from emotive inhibition, it should be recognised that the SSPT technique examines the conscious, ongoing processing of emotion (see Kemp et al., 2002, for discussion). Therefore the results within frontal locations may reflect conscious, cognitive regulatory processes in addition to affective elicitation. Secondly, the SSPT technique used in the present study only provides information on modulation of amplitude and latency components of the 13-Hz frequency; therefore, the specificity of these findings is unclear. Thirdly, RANOVA statistics confirm the Hotellings findings that latency reductions during the processing of unpleasant images (relative to neutral images) within posterior regions are suppressed in the citalopram condition and suggest a trend for a modifying role of citalopram on the processing of pleasant images (relative to neutral images) within posterior regions. However, RANOVA statistics failed to confirm any effects of citalopram within anterior electrode locations as is suggested by the Hotellings statistics from a visual comparison between placebo and citalopram conditions. It is important to note that although the Hotellings T statistics were conducted on complex numbers (combination of amplitude and phase) using in-house software, no in-house software is available at present for conducting repeated-measures statistics on such data. RANOVA statistics were therefore conducted on amplitude and latency data separately to allow for tests to be run using SPSS V.10 (SPSS Inc., 1999). These procedural differences may in part account for differences between the results of the two statistical tests reported in the current study. It is also possible that the failure to confirm any effects of citalopram within frontal regions by the RANOVA may indicate that frontal changes are more pronounced following chronic administration.

Overall, our findings suggest that acute enhancement of serotonergic function with the SSRI, citalopram, modulates neurophysiological processing of emotionally valent stimuli such that cortical response to pleasant valence is potentiated and cortical response to unpleasant valence is suppressed. These findings are consistent with the interpretation that antidepressants may enhance perception of affiliative signals, although constraining perception of negative signals even after an acute dosage (Harmer et al., 2003c). Our study moves beyond the examination of cellular and neurochemical mechanisms of antidepressant action and employs a more systems-based approach to the study of antidepressant action, through examination of the neurophysiological responses to visual emotional stimuli (Harmer et al., 2003b; Nathan et al., 2003). This approach may lead to greater understanding of the functional consequences of neurochemical modulation on cortical networks involved in emotional processing.

Acknowledgments

The commentary and cooperation of many colleagues is gratefully acknowledged. In particular, thanks go to Jim Thompson, Peter Line and Cindy Van Roy for help with computer programming and analysis.

References

Aftanas, L., Varlamov, A., Pavlov, S., Makhnev, V., Reva, N., 2001. Event-related synchronization and desynchronization during affective processing: emergence of valence-related time-dependent hemispheric asymmetries in theta and upper alpha band. Int. J. Neurosci. 110, 197–219.

Amaral, D.G., Price, J.L., Pitkanen, A., Carmichael, S.T., 1992. Anatomical organization of the primate amygdaloid complex. In: Aggleton, J.P. (Ed.), The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction. Wiley-Liss, New York, pp. 1–66.

Attenburrow, M.J., Williams, C., Odontiadis, J., Reed, A., Powell, J., Cowen, P.J., et al., 2003. Acute administration of nutritionally sourced tryptophan increases fear recognition. Psychopharmacology (Berl.) 169, 104–107.

Barnes, N.M., Sharp, T., 1999. A review of central 5-HT receptors and their function. Neuropharmacology 38, 1083–1152.

Benkelfat, C., Ellenbogen, M.A., Dean, P., Palmour, R.M., Young, S.N., 1994. Mood-lowering effect of tryptophan depletion. Arch. Gen. Psychiatry 51, 687–697.

Bremner, J.D., Soufer, R., McCarthy, G., Delaney, R., Staib, L.H., Duncan, J.S., et al., 2001. Gender differences in cognitive and neural correlates of remembrance of emotional words. Psychopharmacol. Bull. 35, 55–78.

Brody, A.L., Barsom, M.W., Bota, R.G., Saxena, S., et al., 2001a. Prefrontal–subcortical and limbic circuit mediation of major depressive disorder. Semin. Clin. Neuropsychiatry 6, 102–112.

Brody, A.L., Saxena, S., Stoessel, P., Gillies, L.A., Fairbanks, L.A., Alborzian, S., et al., 2001b. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: preliminary findings. Arch. Gen. Psychiatry 58, 631–640.

Cacioppo, J.T., Gardner, W.L., 1999. Emotion. Annu. Rev. Psychol. 50, 191–214.

Cleare, A.J., Bond, A.J., 1997. Does central serotonergic function correlate inversely with aggression? A study using D-fenfluramine in healthy subjects. Psychiatry Res. 69, 89–95.

Coccaro, E.F., Siever, L.J., Klar, H.M., Maurer, G., Cochrane, K., Cooper, T.B., et al., 1989. Serotonergic studies in patients with affective and personality disorders. Arch. Gen. Psychiatry 46, 587–598.

Cremniter, D., Jamain, S., Kollenbach, K., Alvarez, J.C., Lecrubier, Y., Gilton, A., et al., 1999. CSF 5-HIAA levels are lower in impulsive as compared to nonimpulsive violent suicide attempters and control subjects. Biol. Psychiatry 45, 1572–1579.

Davidson, R.J., Irwin, W., 1999. The functional neuroanatomy of emotion and affective style. Trends Cogn. Sci. 3, 11–21.

Davidson, R.J., Irwin, W., Anderle, M.J., Kalin, N.H., 2003. The neural substrates of affective processing in depressed patients treated with venlafaxine. Am. J. Psychiatry 160, 64–75.

Delgado, P.L., Charney, D.S., Price, L.H., Aghajanian, G.K., Landis, H., Heninger, G.R., 1990. Serotonin function and the mechanism of antidepressant action. Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. Arch. Gen. Psychiatry 47, 411–418.

Depue, R.A., 1995. Neurobiological factors in personality. Eur. J. Pers. 9, 413–439.

Depue, R.A., Spoont, M.R., 1986. Conceptualizing a serotonin trait. A behavioural dimension of constraint. Ann. N.Y. Acad. Sci. 487, 47–62.

Drevets, W.C., Raichle, M.E., 1992. Neuroanatomical circuits in depression: impressions for treatment mechanisms. Psychopharmacol. Bull. 28, 261–274.

Drevets, W.C., Gadde, K., Krishnan, R., 1999. Neuroimaging studies of depression. In: Charney, D.S., Nestler, E.J., Bunney, B.J. (Eds.), Neurobiology of Mental Illness. Oxford Univ. Press, New York, pp. 394–418.

Drevets, W.C., Bogers, W., Raichle, M.E., 2002. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. Eur. Neuropsychopharmacol. 12, 527–544.

Ellenbogen, M.A., Young, S.N., Dean, P., Palmour, R.M., Benkelfat, C., 1996. Mood response to acute tryptophan depletion in healthy volunteers: sex differences and temporal stability. Neuropsychopharmacology 15, 465–474.

Erspamer, V., Asero, B., 1952. Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. Nature 169, 800–801.

Gray, M., Kemp, A.H., Silberstein, R.J., Nathan, P.J., 2003. Cortical neurophysiology of anticipatory anxiety: an investigation utilizing steady state probe topography (SSPT). NeuroImage 20, 975–986.

Hansenne, M., Ansseau, M., 1999. Harm avoidance and serotonin. Biol. Psychol. 51, 77–81.

Harmer, C.J., Shelley, N.C., Harrison, P.J., Cowen, P.J., Goodwin, G.M., 2002. Repeated administration of citalopram or reboxetine reduces the perception of negative emotions from facial expressions. J. Psychopharmacol. S16, A70.

Harmer, C.F., Bhagwagar, Z., Perrett, D.I., Völlm, 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., Cowen, P.J., Goodwin, G.M., 2003b. Antidepressants and emotional processing. Neuropsychopharmacology 28, 1384–1385.

Harmer, C.J., Hill, S.A., Taylor, M.J., Cowen, P.J., Goodwin, G.M., 2003c. Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. Am. J. Psychiatry 160, 990–992.

Heninger, G.R., 1995. Indoleamines: the role of serotonin in clinical disorders. In: Bloom, F.E., Kupfer, D.J. (Eds.), Psychopharmacology: The Fourth Generation of Progress. Raven, New York, pp. 471–482.

Hennig, J., Toll, C., Schonlau, P., Rohrmann, S., Netter, P., 2000. Endocrine responses after D-fenfluramine and ipsapirone challenge: further support for Cloninger's tridimensional model of personality. Neurophysiology 41, 38–47.

Kalin, N.H., Davidson, R.J., Irwin, W., Warner, G., Orendi, J.L., Sutton, S.K., Mock, B.J., et al., 1997. Functional magnetic resonance imaging studies of emotional processing in normal and depressed patients: effects of venlafaxine. J. Clin. Psychiatry 58, 32–39.

Kemp, A.H., Gray, M.A., Eide, P., Silberstein, R.B., Nathan, P.J., 2002. Steady-state visually evoked potential (SSVEP) topography during processing of emotional valence in healthy subjects. NeuroImage 17, 1684–1692.

Kemp, A.H., Silberstein, R.B., Armstrong, S.M., Nathan, P.J., 2004. Gender differences in the cortical electrophysiological processing of visual emotional stimuli. NeuroImage. 16, 632–646.

Killgore, W.D., 2000. Sex differences in identifying the facial affect of normal and mirror-reversed faces. Percept. Mot. Skills 91, 525–530.

Klaassen, T., Riedel, W.J., van Someren, A., Deutz, N.E.P., Honig, A., van Praag, H.M., 1999. Mood effects of 24-hour tryptophan depletion in healthy first-degree relatives of patients with affective disorders. Biol. Psychiatry 46, 489–497.

Knutson, B., Wolkowitz, O.M., Cole, S.W., Chan, T., Moore, E.A., Johnson, R.C., Terpstra, J., et al., 1998. Selective alteration of personality and social behaviour by serotonergic intervention. Am. J. Psychiatry 155, 373–379.

Lane, R.D., Chua, P.M., Dolan, R.J., 1999. Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures. Neuropsychologia 37, 989–997.

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

Lang, P.J., Bradley, M.M., Fitzsimmons, J.R., Cuthbert, B.N., Scott, J.D., Moulder, B., et al., 1998. Emotional arousal and activation of the visual cortex: an fMRI analysis. Psychophysiology 35, 199–210.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 1999. International affective picture system (IAPS): instruction manual and affective ratings. Technical Report A-4. The Center for Research in Psychophysiology; University of Florida.

Lee, T.M., Liu, H.L., Hoosain, R., Liao, W.T., Wu, C.T., Yuen, K.S., et al., 2002. Gender differences in neural correlates of recognition of happy and sad faces in humans assessed by functional magnetic resonance imaging. Neurosci. Lett. 333, 13–16.

Manuck, S.B., Flory, J.D., McCaffery, J.M., Matthews, K.A., Mann, J.J., Muldoon, M.F., 1998. Aggression, impulsivity and central nervous system serotonergic responsivity in a nonpatient sample. Neuropsychopharmacology 19, 287–299.

Marek, G.J., Aghajanian, G.K., 1998. The electrophysiology of prefrontal serotonin systems: therapeutic implications for mood and psychosis. Biol. Psychiatry 44, 1118–1127.

Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin, R.K., Jerabek, P.A., et al., 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am. J. Psychiatry 156, 675–682.

Mayberg, H.S., Silva, J.A., Brannan, S.K., Tekell, J.L., Mahurin, R.K., McGinnis, S., et al., 2002. The functional neuroanatomy of the placebo effect. Am. J. Psychiatry 159, 728–737.

Moore, P., Landholt, H.P., Seifritx, E., Clark, C., Bhatti, T., Kelsoe, J., et al., 2000. Clinical and physiological consequences of rapid tryptophan depletion. Neuropsychopharmacology 23, 601–622.

Moskowitz, D.S., Pinard, G., Zuroff, D.C., Annable, L., Young, S.N., 2001. The effect of tryptophan on social interaction in everyday life. Neuropsychopharmacology 25, 277–289.

Murray, M.M., Wylie, G.R., Higgins, B.A., Javitt, D.C., Schroeder, C.E., Foxe, J.J., 2002. The spatiotemporal dynamics of illusory contour processing: combined high-density electrical mapping, source analysis, and functional magnetic resonance imaging. J. Neurosci. 22, 5055–5073.

Nathan, P.J., Kemp, A.H., Harrison, B.J., 2003. Antidepressants and emotional processing. Neuropsychopharmacology 28, 1383.

Noble, S., Benfield, P., 1997. Citalopram: a review of its pharmacology, clinical efficacy and tolerability in the treatment of depression. CNS Drugs 8, 410–431.

Nobler, M.S., Sackeim, H.A., Prohovnik, I., Moeller, J.R., Mukherjee, S., Schnur, D.B., et al., 1994. Regional cerebral BF in mood disorders: III. Treatment and clinical response. Arch. Gen. Psychiatry 51, 884–897.

Northoff, G.W., Thomas, R.A., Gessner, M., Schlagenhauf, F., Fell, J., Baumgart, F., et al., 2002. GABA-ergic modulation of prefrontal spatio-temporal activation pattern during emotional processing: a combined fMRI/MEG study with placebo and lorazepam. J. Cogn. Neurosci. 14, 348–370.

Nunez, P.L., Silberstein, R.B., Cadusch, P.J., Wijesinghe, R.S., Westdorp, A.F., Srinivasan, R., 1994. A theoretical and experimental study of high resolution EEG based on surface Laplacians and cortical imaging. Electroencephalogr. Clin. Neurophysiol. 90, 40–57.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Palomba, D., Angrilli, A., Mini, A., 1997. Visual evoked potentials, heart rate responses and memory to emotional pictorial stimuli. Int. J. Psychophysiol. 27, 55–67.

Pendergrass, J.C., Ross, T.J., Garavan, H., Stein, E.A., Risinger, R.C., 2003. Differential neural responses to emotional stimuli in females and males: a functional magnetic resonance imaging study in humans. Brain Cogn. 51, 195–196.

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.

Phan, K.L., Liberzon, I., Welsh, R.C., Britton, J.C., Taylor, S.F., 2003. Habituation of rostral anterior cingulate cortex to repeated emotionally salient pictures. Neuropsychopharmacology 28, 1344–1350.

Quintin, P., Benkelfat, C., Launay, J.M., Arnulf, I., Poinereau-Bellenger, A., Barbault, S., et al., 2001. Clinical and neurochemical effect of acute tryptophan depletion in unaffected relatives of patients with bipolar affective disorder. Biol. Psychiatry 50, 184–190.

Rapport, M.M., Green, A.A., Page, J.H., 1948. Serum vasoconstrictor (serotonin). Isolation and characterisation. J. Biol. Chem. 179, 1243–1251.

Reilly, J.G., McTavish, S.F., Young, A.H., 1997. Rapid depletion of plasma tryptophan: a review of studies and experimental methodology. J. Psychopharmacol. 11, 381–392.

Salzman, C., Wolfson, A.N., Schatzberg, A., Looper, J., Henke, R., Albanese, M., et al., 1995. Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. J. Clin. Psychopharmacol. 15, 23–29.

Silberstein, R.B., 1995a. Steady-state visually evoked potentials, brain resonances, and cognitive processes. In: Nunez, P.L. (Ed.), Neocortical Dynamics and Human EEG Rhythms. Oxford Univ. Press, New York, pp. 272–303.

Silberstein, R.B., 1995b. Neuromodulation of neocortical dynamics. In: Nunez, P.L. (Ed.), Neocortical Dynamics and Human EEG Rhythms. Oxford Univ. Press, New York, pp. 591–627.

Silberstein, R.B., 1998. Neocortical resonances and holding memory. In: Koga, Y., Nagata, K., Hirata, K. (Eds.), Brain Topography Today. Elsevier Science, Amsterdam, pp. 34–38.

Silberstein, R.B., Schier, M.A., Pipingas, A., Ciorciari, J., Wood, S.R., Simpson, D.G., 1990. Steady-state visually evoked potential topography associated with a visual vigilance task. Brain Topogr. 3, 337–347.

Silberstein, R.B., Ciorciari, J., Pipingas, A., 1995. Steady-state visually evoked potential topography during the Wisconsin card sorting test. Electroencephalogr. Clin. Neurophysiol. 96, 24–35.

Silberstein, R.B., Cadusch, P.J., Nield, G., Pipingas, A., Simpson, D.G., 1996. Steady state visually evoked potential topography dynamics and cognition. The Eleventh International Conference on Event-Related Potentials of the Brain, Excerpta Medica International Congress Series, pp. 379–385.

Silberstein, R.B., Farrow, M., Levy, F., Pipingas, A., Hay, D.A., Jarman, F.C., 1998. Functional brain electrical activity mapping in boys with attention-deficit/hyperactivity disorder. Arch. Gen. Psychiatry 55, 1105–1112.

Silberstein, R.B., Line, P., Pipingas, A., Copolov, D., Harris, P., 2000. Steady-state visually evoked potential topography during the continuous performance task in normal controls and schizophrenia. Clin. Neurophysiol. 111, 850–857.

Silberstein, R.B., Nunez, P.L., Pipingas, A., Harris, P., Danieli, F., 2001. Steady state visually evoked potential (SSVEP) topography in a graded working memory task. Int. J. Psychophysiol. 42, 125–138.

Smith, G.S., Ma, Y., Dhawan, V., Gunduz, H., Carbon, M., Kirshner, M., et al., 2002. Serotonin modulation of cerebral glucose metabolism measured with positron emission tomography (PET) in human subjects. Synapse 45, 105–112.

Spoont, M.R., 1992. Modulatory role of serotonin in neural information processing: implications for human psychopathology. Psychol. Bull. 112, 330–350.

Spreux-Varoquaux, O., Alvarez, J.-C., Berlin, I., Batista, G., Despierre, P.-G., Gilton, A., et al., 2001. Differential abnormalities in plasma 5-HIAA and platelet serotonin concentrations in violent suicide attempters: relationships with impulsivity and depression. Life Sci. 69, 647–657.

Steiner, M., Steinberg, S., Stewart, D., Carter, D., Berger, C., Reid, R., et al., 1995. Fluoxetine in the treatment of premenstrual dysphoria. N. Engl. J. Med. 332, 1529–1534.

Thayer, J.F., Lane, R.D., 2000. A model of neurovisceral integration in emotion regulation and dysregulation. J. Affect. Disord. 61, 201–216.

Twarog, B.M., Page, J.H., 1953. Serotonin content of some mammalian tissues and urine and a method for its determination. Am. J. Physiol. 175, 157–161.

Van der Does, A.J.W., 2001. The effects of tryptophan depletion on mood and psychiatric symptoms. J. Affect. Disord. 64, 107–119.

van Vliet, I.M., den Boer, J.A., Westenberg, H.G., 1994. Psychopharmacological treatment of social phobia; a double blind placebo controlled study with fluvoxamine. Psychopharmacology (Berl.) 115, 128–134.

Wager, T.D., Phan, K.L., Liberzon, I., Taylor, S.F., 2003. Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. NeuroImage 19, 431–513.

Wrase, J., Klein, S., Gruesser, S.M., Hermann, D., Flor, H., Mann, K., Braus, D.F., Heinz, A., 2003. Gender differences in the processing of standardized emotional visual stimuli in humans: a functional magnetic resonance imaging study. Neurosci. Lett. 348, 41–45.

Zald, D.H., Depue, R.A., 2001. Serotonergic functioning correlates with positive and negative affect in psychiatrically healthy males. Pers. Individ. Differ. 30, 71–86.