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Effect of Escitalopram on Attentional Bias in Panic Disorder an Event-Related Potential Study

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Abstract

Objective: To investigate the effect of treatment with Escitalopram on attentional bias in PD using an ERP dot-probe task of facial expression.

Method: Subjects included 25 patients with PD, and 25 controls. Psychopathology was rated in patients with the HAMA at baseline, after 8-week treatments with Escitalopram. EEG was recorded at Oz when participants perform dot-probe task of facial expression. BESA 5.1.8 was used to perform data analysis.

Result: It showed that 8 week treatments of Escitalopram decreased HAMA scores; patients at baseline showed an attention bias towards threat, however, after 8 week treatments, no significant bias towards happy faces was observed for either group. Patients had a more pronounced (more negative) C1 amplitude than controls in response to the angry–neutral face pairs, however, no differences between patients after 8 week treatments and controls were observed. There was no significant correlation between changes in C1 amplitudes and changes in HAMA scores before and after 8 week treatments of Escitalopram.

Conclusion: Individuals with PD pay more attention to threatening facial expressions, i.e., individuals with PD show a greater bias towards negative stimuli and ERP offers objective evidence that treatment with Escitalopram leads to the improvement of attentional bias.

Keywords: The dot-probe task; Attentional bias; Event-related potentials; Escitalopram; Panic disorder

Introduction

Panic disorder (PD) is a type of anxiety disorder and characterized by the repeated occurrence of unexpected panic attacks, during which the individual experiences a strong fear with anticipation of death. A person with PD often lives in fear of another attack, and may be afraid to be alone or far from medical help. Additionally, individuals who are suffering from PD are often accompanied by somatic symptoms such as palpitations, dyspnoea or faintness. Those suffering from PD have persistent anticipatory fear of recurrent attacks and feel anxious even while they have no occurrence of panic attacks for a certain period. PD can significantly impact individuals' social functions because it leads to avoidance of certain activities and experiences.

The theory of cognitive models is a hypothesis about factor contributing to the development and maintenance of PD. Cognitive models propose that biased information processing plays an important role in the etiology and maintenance of the disorder [1]. Previous many studies have established that individuals with PD tend to pay selective attention to threatening stimuli [2,3], and individuals with PD are more likely to misinterpret internal physiological sensations in catastrophic manner [4]. As opposed to a more general bias towards threatening information, studies showed that individuals with PD show a greater bias mainly towards disorder-relevant stimuli [2]. Undoubtedly, the assessment of the level of cognitive bias is regarded as crucial dimensions of the assessment of treatment outcomes in PD.

Two broad categories of treatment have been shown to be effective in treating PD, one being pharmacotherapy with antidepressants or benzodiazepines, the other being psychotherapy. Escitalopram is one of selective serotonin reuptake inhibitors (SSRIs). Beyond its well-established efficacy in depression with or without anxiety, preclinical studies have demonstrated that Escitalopram has a broad spectrum of anxiolytic activity. Numerous clinical data indicate that Escitalopram is an effective and well-tolerated first-line treatment option for the management of PD [6]. In addition, a study on animal trial indicated that escitalopram treatment attenuated the fear-related behavior in animal model for panic disorder with anticipatory anxiety/agoraphobic symptoms [7].

While there is strong evidence supporting the role of attentional bias in PD, research suggests that this bias may diminish after completing a successful course of cognitive-behavioral treatments [8]. However, there have been still no reports on which the effect of treatment with SSRIs, such as Escitalopram, on attentional bias in PD.

The dot-probe task is widely employed to study attention biases in PD. In this task, two stimuli, one threat-related and one neutral, are shown briefly on each trial, and their offset is followed by a small target in the location just occupied by one of them. Participants are required to respond as fast as possible to the target. Response latencies to the target provide a "snap-shot" of a participants' attention bias,

with faster responses to targets at the attended relative to the unattended location. Faster reaction times (RTs) to targets appearing at the location of threat relative to neutral stimuli are indicative of an attentional bias towards threat and possibly also difficulty to disengage attention from the threatening stimuli [9]. The opposite pattern indicates avoidance of threat. Facial expressions are stimuli with a high arousal effect; therefore, the dot-probe task of facial expression is a useful tool to employ in the study of attentional bias in PD.

The event-related potentials (ERPs) reflect the rapidly changing electrical activity associated with a cognitive event in relatively large synaptic fields containing tens of millions of neurons. Previous studies employed ERP techniques to understand the underlying neural correlates of attentional bias processes and their timing in PD [10-12]. Of particular interest were ERP components known to be modulated by emotion stimuli and spatial attention. ERP dot-probe studies with healthy adults have shown threat related modulation in the C1 component time locked to the faces display. The C1 component (50–100ms post-stimulus) was more intense for displays containing threat faces relative to displays containing nonthreatening faces [10]. The C1 is the first ERP component triggered by the appearance of a stimulus in the visual field, and is thought to be pre-attentive and independent of spatial attention [13].

In the present study, using an ERP dot-probe task of facial expression, we investigated the effect of treatment with Escitalopram on attentional bias in PD. Since Escitalopram is an effective and well-tolerated first-line treatment option for the management of PD, we hypothesize that treatment with Escitalopram may improve the cognitive bias contributing to the recovery process. The main hypotheses of this investigation were: (1) Patients with PD have cognitive bias to threat related facial expression compared to healthy age-matched control subjects. (2) Treatment of patients with Escitalopram improves cognitive bias threat related facial expression. (3) Patients with PD present impaired ERP C1 component compared to control subjects. (4) Treatment of patients with Escitalopram improves ERP C1 component, i.e., successful treatment of PD may have a significant impact on the cognitive processes that characterize and maintain the disorder by measurement of ERP.

Materials and Methods

Time and setting

The experiment was completed in the Department of psychology at Wuxi Mental Health Center, China, from November 2012 to October 2013. All research procedures were approved by the Ethics Committee of Nanjing Medical University, China on Human Studies and conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent to participate. Because patients had a compromised capacity to consent, we gave all research procedures to their next of kins, care takers or guardians, and their next of kins, care takers or guardians consented on the behalf of participants whose capacity to consent was compromised.

Study subjects

Subjects were 25 patients with a Diagnostic and Statistical Manual of Mental Disorders (4th ed, DSM-IV) diagnosis criteria for PD, and 25 matched age and gender controls with no personal or family history of PD. Patients with PD were recruited from Wuxi Mental Health Center of Nanjing Medical University in Jiangsu, China. Controls were recruited from the employees of Wuxi Mental Health Center of Nanjing Medical University. Subjects and controls were excluded from the study if they were smokers; or had a diagnosis of alcohol or substance dependence, neurological disorders, all kinds of head injury; or had received electroconvulsive therapy in the last six months. All participants were Chinese.

Clinical assessments

All participants underwent a clinical assessment by a psychiatrist to collect information on medication, socio-demographic data, and to confirm/exclude a DSM-IV diagnosis. On the day of the ERP recording, the severity of anxiety disorder was rated in patients with Hamilton Anxiety Scale (HAMA) [14]. Handedness was assessed using the Annett handedness scale [15]. Ratings on this scale were recorded into the following definitions of handedness: Annett score (1)=right, (2-7)=mixed, (8)=left. The demographic characteristics of the sample are detailed in Table 1.

	Patients	Controls
Sex ratio (M/F)	25 (10:15)	25 (10:15)
Mean age (S.D.)	39 (12)	39 (12)
Age range	18- 58	18- 58
Handedness		
R/M/L	14 / 6 / 5	12/ 7 / 6
(% R/M/L)	(56%/24%/20%)	(48%/28%/24%)

Table1 : Demographic characteristics of the sample, M: male. F: female. S.D.: standard deviation. R: right. M: mixed. L: left.

Experimental procedure

The dot-probe task: Stimuli: E-Prime software (Edition, 2.0 Psychology Software Tools Inc., Sharpsburg, North Carolina, USA) was used for the trial procedure. The dot-probe task, referred from S. Eldar, et al. [13]. The fixation display was a gray plus sign (2 cm×2 cm) presented in the center of the screen. The face stimuli were 36 pictures that consisted of 12 angry, 12 happy and 12 neutral facial expressions taken from the Chinese Affective Picture System [16]. Each faces display presented at equal distances at the left and right sides of the screen (center-to-center distance of 16.5 cm) and in the upper visual field. There were three types of face pairs: angry–neutral, happy–neutral, and neutral-neutral (36 different pairs in total). The target display consisted of two dots (5mmcenter-to-center). Each dot subtended 2mm in diameter. The dot pair was oriented either horizontally (..) or vertically (:) and appeared at the location of the center of either the left or the right photograph of each face pair. The three types of face pairs (angry-neutral, happy-neutral, and neutral-neutral) made up the three conditions of emotion and were presented in separate blocks. Order of block presentation was counterbalanced across participants. Within the angry-neutral and happy-neutral blocks, the emotional face (angry or happy) was equally likely to be on the left or on the right side of the screen, the target was equally likely to appear at the location of the emotional or the neutral face, and dots orientation was equally likely to be horizontal or vertical. These variables were fully counterbalanced within each block. In the neutral-neutral block, target location and target orientation were counterbalanced.

Dot-probe procedure: Each trial in the dot-probe task began with a 500 ms fixation display followed by the faces display for 500 ms, which was immediately replaced by the target display for 200 ms. Following target display the screen went blank for an inter-trial interval (ITI) of 1300 ms after which a new trial began. Participants had to determine the orientation of the dots by pressing one of two pre-specified buttons.

Derivation of threat bias scores

For the angry-neutral and happy-neutral conditions, attention bias scores were calculated by subtracting the mean RT for targets appearing at the emotion face location (angry or happy) from the mean RT for targets appearing at the neutral face location. Positive bias values reflect an attention bias towards the emotional face, while negative values reflect avoidance of angry/happy faces [13].

Electroencephalographic recordings

According to the 10/20 International System, Electroencephalography (EEG) was recorded with the Stellate Harmonie EEG device (Physiotec Electronics Ltd. Canada) from Oz, left mastoid and right mastoid site using Electro-Cap Electrode System (ECITM Electro-Caps, Electro-cap International, INL USA). Ear electrodes served as a reference and the ground electrode was attached to the forehead. Eye movement artifacts were monitored by recording vertical and horizontal electro oculogram (EOG) from electrodes placed above and below the right eye and at the left outer canthus. Electrode impedance was kept below 5 kΩ. System band pass was 0.1-30 Hz and digitalized continuously at a sampling rate of 250 Hz.

Participants were seated in a comfortable chair 100 cm from the computer screen. In order that the task stimuli appeared in a fixed position within the upper visual field, the horizontal meridian of the screen 3^0 above the eye-line of each participant was set [13]. Participants received 32 practice trials, followed by 6 experimental blocks, two for each emotion condition (angry-neutral, happy-neutral, and neutral-neutral), 96 trials per block, with a total of 576 trials. Short breaks were allowed at the end of each block. EEG was recorded throughout the experiment.

In order to detect the treatment effects on ERPs of attentional bias in Panic Disorder, visual ERPs were recorded at baseline and 8 weeks of Escitalopram treatment. For healthy controls, ERPs were recorded once. At baseline, all patients were neuroleptic naive. After 2 weeks of follow-up, patients received Escitalopram 10-20 mg/day (mean value 16.00, S.D. 3.23)

Data analysis

Brain Electrical Source Analysis program (BESA, Version 5.1.8, Software, Graefelfing, Germany) was used to perform data analysis. Epochs were constructed that consisted of a 100 ms pre-stimulus baseline and a 500 ms post-stimulus interval. All epochs with amplitudes exceeding ± 75 μV at any electrode were excluded automatically. Epochs were averaged offline for each subject and stimulus type and digitally filtered with a low-pass filter of 15 Hz (24 dB down). Trials containing incorrect responses were eliminated from analysis.

According to previous researches [10,17-9], the C1 on Oz electrode site was used as ERP components evoked by the faces displays. Based on the inspection of the grand mean ERPs, the latency windows within 60 ms to 105 ms were selected for analyses. The time windows were the same for all participants and conditions.

Statistical Analyses

Data were analyzed using SPSS (version 10.0 International Business Machines Corporation, New York, USA). Comparisons of HAMA scores were done using independent-sample t-tests. To examine group differences in attention bias scores for each emotion condition, a 2×2 ANOVA was performed with Emotion (angry-neutral, happy-neutral) as a within-subject factor and Group (patients, controls) as a between-subjects factor. One-sample t-tests against zero were used to determine the significance of within-group biases. To examine the valence of the emotional faces in each block affected accuracy and RT as a function of anxiety, two separate 3×2 ANOVAs were conducted on accuracy and RTs with Emotion (angry-neutral, happy-neutral, neutral-neutral) as a within-subject factor and Group (patients, controls) as a between-subjects factor. For ERP component C1, the amplitude at Oz site was subjected to a 3×2 ANOVA with Emotion (angry-neutral, happy-neutral, and neutral-neutral) as a within-subject factor and Group (patients, controls) as a between-subjects factor. Least square difference (LSD) tests were performed as post hoc analyses if indicated. Correlation coefficients between changes in C1 amplitudes and changes in HAMA scores before and after 8 week treatments of Escitalopram were calculated by the Pearson test. Alpha values of .05 were considered significant throughout.

Results

Comparisons of HAMA scores at baseline and after 8 week treatments of Escitalopram: By using independent-sample t-tests, the significant differences for HAMA scores between baseline (18.23(3.52)) and after 8 week treatments of Escitalopram (7.80(2.15)) were observed (t=2.478, p=0.023). 8 week treatments of Escitalopram decreased HAMA scores.

Reaction time data

Comparisons of reaction time data at baseline of patients and controls: A 2×2 ANOVA with Emotion (angry-neutral, happy-neutral) as a within-subject factor and Group (patients at baseline, controls) as a between-subjects factor revealed a main effect of Emotion condition for the attention bias scores (F=4.28, df=1, p=0.015, Cohen's d=0.71), with a larger attention bias towards the emotional face in the angry–neutral condition (7.89) (12.26) than in the happy-neutral condition (-0.03(8.63)). It showed that the bias was significant in the angry–neutral condition (F=6.92, df =1, p=0.011, Cohen's d=0.78), but not in the happy–neutral condition (F=0.00, p=0.89, df=1, Cohen's d=0.00). It revealed no interact effect of Emotion condition for Group (F=0.00, p=0.82, df=1, Cohen's d=0.00). One-sample t-tests showed that the attention bias towards angry faces was significantly greater than zero in the patient group (t=2.869, p=0.008, Cohen's d=1.20), but not in the control group (t=1.863, p=0.35, Cohen's d=0.39). In addition, no significant bias towards happy faces was observed for either group (t=0.85 and -0.68, p=0.36 and 0.42, Cohen's d=0.41 and 0.37), for the patient at baseline and control groups, respectively. To summarize, patients at baseline showed an attention bias towards threat, whereas controls did not. Neither group exhibited an attention bias to happy faces (Table1).

A 3×2 ANOVAs with Emotion condition (angry-neutral, happy–neutral and neutral–neutral) as a within-subject factor and Group

(patients at baseline, controls) as a between-subjects factor for the accuracy scores revealed that these ranged from 89% to 98% across emotion conditions with no significant differences between patient at baseline and control group(p=0.20). However, it revealed a main effect of emotion condition (F=16.34, df=2, p=0.001, Cohen's d=0.85). LSD tests were performed as post hoc analyses and demonstrated significant differences between Accuracy at the neutral–neutral condition (97.28) (2.43)) and those at the happy–neutral condition (96.59(4.83)) (p=0.021) and the angry-neutral condition (94.27(3.59)) (p=0.017). Accuracy was highest for the neutral–neutral condition, followed by the angry–neutral condition, and the angry-neutral condition.

A 3×2 ANOVAs with Emotion condition (angry-neutral, happy-neutral and neutral-neutral) as a within-subject factor and Group (patients at baseline, controls) as a between-subjects factor for the mean RTs did not reveal significant effects, all p>0.05.

Comparisons of the attention bias scores after 8 week treatments of patients and controls: A 2×2 ANOVA with Emotion (angry-neutral, happy-neutral) as a within-subject factor and Group (patients after 8 week treatments, controls) as a between-subjects factor did not revealed a main effect of Emotion condition for the attention bias scores (F=1.26, df=1, p=0.32, Cohen's d=0.01). It showed that the bias was significant neither in the angry–neutral condition (F=1.81, df=1, p=0.29, Cohen's d=0.01), nor in the happy–neutral condition (F=0.00, p=0.77, df=1, Cohen's d=0.00). It revealed no interact effect of Emotion condition for Group (F=0.00, p=0.80, df=1, Cohen's d=0.00). One-sample t-tests showed that the attention bias towards angry faces was neither significantly greater than zero in the patient group (t=1.431, p=0.42, Cohen's d=1.36, nor in the control group (t=1.741, p=0.32, Cohen's d=0.43). In addition, no significant bias towards happy faces was observed for either group (t=0.79 and -0.62, p=0.30 and 0.38, Cohen's d=0.37 and 0.33, for the patient and control groups, respectively. To summarize, both patients and controls did not show an attention bias towards threat or happy faces (Table1).

	Angry-neutral			Happy-neutral			Neutral-neutral
	Target at angry	Target at neutral	Bias score	Target at happy	Target at neutral	Bias score	
Patients (Baseline)	561(63)	570(72)	10(12)	565(64)	568(77)	2(4)	559(62)
Patients (After 8 week treatments)	593(87)	598(79)	5(7)	593(69)	592(72)	-1(2)	594(61)
Controls	597(83)	601(84)	4(8)	596(71)	594(77)	-2(3)	595(58)

Table 2: Mean reaction times, bias scores, and standard deviations in milliseconds for patient (baseline), control and patient (after 8 week treatments) group by each emotion condition

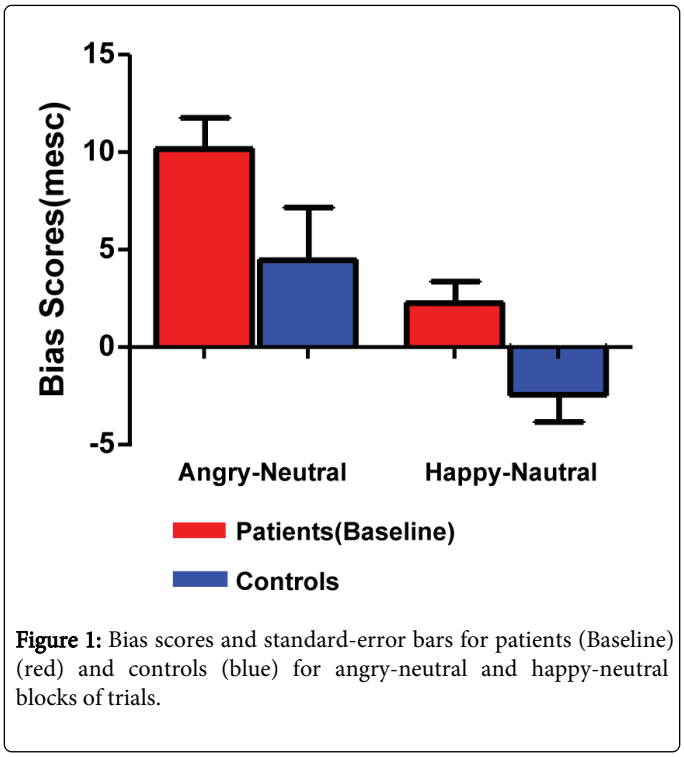

Figure 1: Bias scores and standard-error bars for patients (Baseline) (red) and controls (blue) for angry-neutral and happy-neutral blocks of trials.

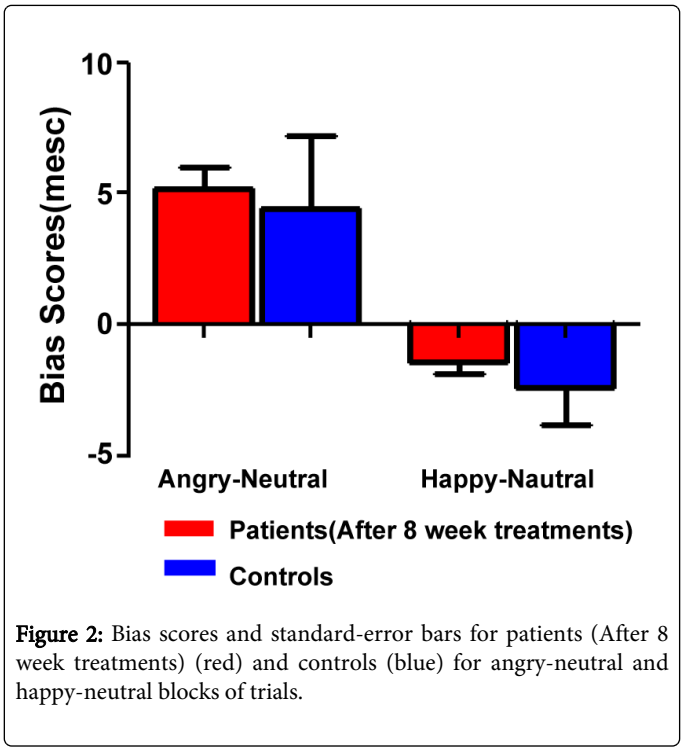

Figure 2: Bias scores and standard-error bars for patients (After 8 week treatments) (red) and controls (blue) for angry-neutral and happy-neutral blocks of trials.

Electrophysiological data

Comparisons between patients at baseline and controls: Using C1 amplitude the dependent measures, a 3×2 ANOVA with Emotion (angry-neutral, happy-neutral and neutral–neutral) as a within-subject factor and Group (patients at baseline, controls) as a between-subjects factor revealed an interact effect of Emotion condition for Group ($F=2.29$, $df=2$, $p=0.04$, Cohen's $d=0.49$). By LSD tests, patients had a more pronounced (more negative) C1 amplitude than controls in response to the angry–neutral face pairs ($t=2.596$, $p=0.028$, Cohen's $d=0.63$). No differences for C1 amplitude in response to the happy–neutral and the neutral–neutral condition between the patient and control were observed (for the happy–neutral condition: $t=0.81$, $p=0.37$; for the neutral-neutral condition: $t=0.92$, $p=0.88$). (Table 2 and 3, Figure 1 and 2).

Comparisons among patients at baseline, after 8 week treatments and controls: Using C1 amplitude as the dependent measures, an one-way ANOVA as Group (patients at baseline, patients after 8 week treatments and controls) as a within-subject factors revealed an main effect ($F=8.91$, $df=2$, $p=0.000$, Cohen's $d=0.70$). LSD tests were performed as post hoc analyses and demonstrated significant differences between C1 amplitudes for patients at baseline and those at both patients after 8 week treatments ($p=0.001$) and controls ($p=0.039$)); however, no differences between patients after 8 week treatments and controls were observed ($p=0.13$), although the C1 amplitude mean of patients after 8 week treatments was less than that of controls (Table 2 and Figure 3).

	Angry-neutral	Happy-neutral	Neutral-neutral
Patients (Baseline)	- 1.93(0.21)	- 0.60(0.25)	- 0.62(0.13)
Patients (After 8 week treatments)	- 0.81(0.41)	- 0.59(0.33)	- 0.59(0.27)
Control	- 0.59(0.23)	- 0.55(0.17)	- 0.58(0.31)

Table 3: The Mean amplitude (μV, presented as mean (SD))of ERP component C1 at Oz site for patient at baseline, control and patient after 8 week treatments group by each emotion condition

Relationship between changes in C1 amplitudes and changes in HAMA scores: There was no significant correlation between changes in C1 amplitudes and changes in HAMA scores before and after 8 week treatments of Escitalopram ($r=0.11$, $P=0.47$).

Discussion

This study is the first to employ an ERP dot-probe task of facial expression to assess cognitive bias in patients with PD treated by Escitalopram. Our results showed that attention bias scores of patients in the angry–neutral condition were more than did controls and no differences on attention bias scores in the happy–neutral condition between two groups were observed. Our study replicated the findings of numerous studies that demonstrated individuals with PD paid more attention to threatening facial expressions, i.e., individuals with PD show a greater bias towards negative stimuli. Additionally, after 8 week Escitalopram treatments, both patients and controls did not show an attention bias towards threat or happy facial expressions, which authenticate previous hypotheses that treatment with Escitalopram leads to the improvement of attentional bias in PD.

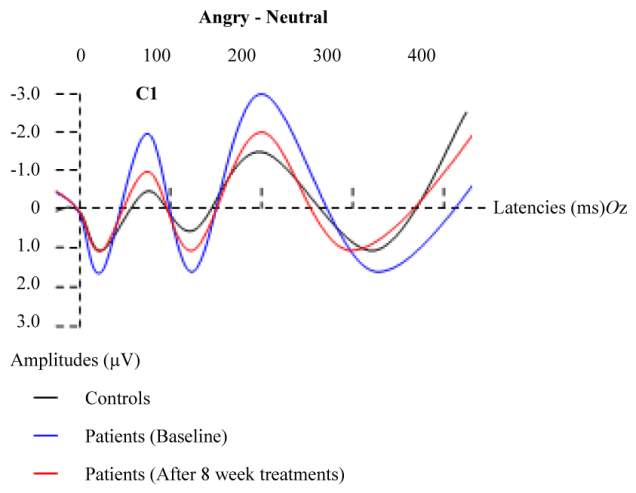

Figure 3(a): Angry-Neutral emotion condition. Grand-averaged ERPs at Oz electrode site for patient (baseline), control and patient (after 8 week treatments) group by each emotion condition during the faces display.

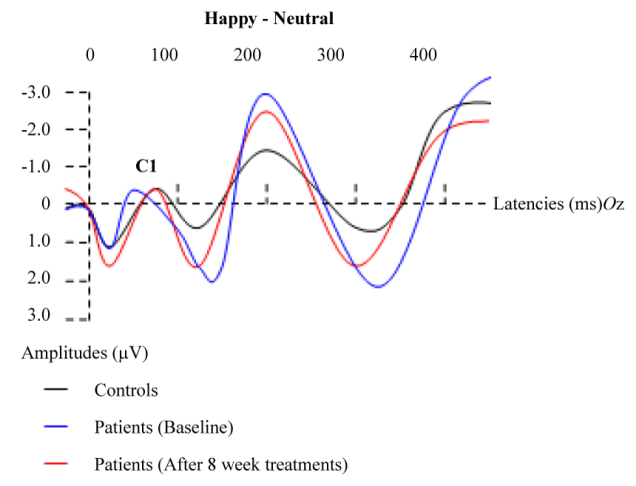

Figure 3(b): Happy-Neutral emotion condition. Grand-averaged ERPs at Oz electrode site for patient (baseline), control and patient (after 8 week treatments) group by each emotion condition during the faces display.

A study indicated that PD is associated with white matter connectivity enhancement in cingulate region, which probably compensate the white matter structural abnormalities derived from PD symptoms [20]. Another study displayed that Escitalopram can increase the cytogenesis of ventral hippocampal formation through its modulation of brain-derived neurotrophic factor (BDNF) release in the chronic stress rat model [21].

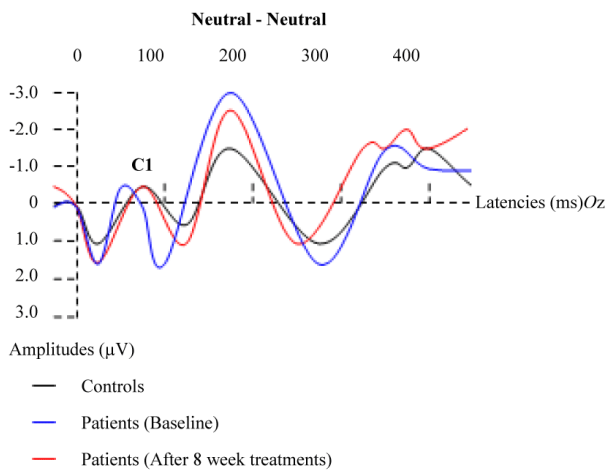

Figure 3(c): Neutral-Neutral emotion condition. Grand-averaged ERPs at Oz electrode site for patient (baseline), control and patient (after 8 week treatments) group by each emotion condition during the faces display.

Furthermore, a previous research showed that Escitalopram contributes to synaptic plasticity through enhancing BDNF calcium-dependent intracellular signal transduction in prefrontal, frontal and hippocampal regions [22]. Above three research results may be accounted for the mechanism of the treatment effect of Escitalopram on PD.

Electrophysiological data revealed that patients had a more pronounced (more negative) C1 amplitude than controls in response to the angry-neutral face pairs, and no differences for C1 amplitude in response to the happy-neutral and the neutral-neutral condition between the patient and control were observed. Consistent with previous researches, patients with PD present abnormalities of ERP C1 component amplitudes. After 8 week Escitalopram treatments, C1 amplitudes for patients were reduced and no differences compared to controls.

A previous study employed event-related functional magnetic resonance imaging (fMRI) to determine how brain responses to a neutral visual target are influenced by the emotional expression of faces appearing at the same location during a covert orienting task [23], and results demonstrated that fearful faces can act as exogenous cues by increasing sensory processing in extrastriate cortex for a subsequent target presented at the same location, but also produce a cost in disengaging towards another location by altering the response of intraparietal sulcus to invalidly cued targets. Neural mechanisms responsible for orienting attention towards emotional vs. nonemotional stimuli are thus partly shared in parietal and visual areas, but also partly distinct.

A recent study that used Positron Emission Tomography (PET) investigated brain baseline glucose metabolism in PD patients in comparison with normal controls and the changes in glucose metabolism after escitalopram treatment [24], and conclude abnormal neocortical function appears to be associated with the pathophysiology of PD and escitalopram exerts its therapeutic action by modulating brain activity at the level of the neocortex and limbic system, notably the amygdala and parahippocampal gyrus.

Above results prove that Escitalopram has an effect on attentional bias in patients with PD. Our electrophysiological results might prove that abnormalities of ERP C1 amplitudes are characters of cognitive bias in PD. Furthermore, ERP C1 amplitude improvement may be a possible biomarker of treatment efficacy. From a neuroelectrophysical standpoint, ERP C1 component offers objective evidence that treatment with the escitalopram ameliorates cognitive bias in PD. However, this study cannot indicate that whether ERP C1 component abnormalities are state-dependent or trait-dependent because of the small sample.

In summary, the present study shows significant effects of Escitalopram treatments on attentional bias in patients with PD as shown by attention bias score and ERP C1 component amplitude results, namely, Escitalopram treatments were able to improve cognitive function for facial identity for negative stimuli. Our research also replicated the findings of previous ERP research results and authenticated previous hypotheses that treatment with Escitalopram may have a significant impact on the cognitive processes that characterize and maintain the disorder by measurement of ERP.

The improvement of this functional marker may indicate an important pathway towards new therapeutic strategies that target cognitive bias in PD. It is important that clinicians understand the benefits and limitations of modern neuroimaging techniques and are also suitably equipped to appraise future developments [25].

In conclusion, the use of ERP C1 in evaluating psychopathology and therapeutic effects is helpful in the clinical management of patients with PD. Therefore, it is necessary to validate this study effect using similar parameters in future studies.

Acknowledgments

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Conflicts of interest

The authors have declared that no competing interests exist.

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