Cerebral Processing of Emotions in Phantom Eye Pain Patients: An Event Related Potential Study

Lixia Lou
The Second Affiliated Hospital of Zhejiang University
Yijie Wang
The Second Affiliated Hospital of Zhejiang University
Bingren Zhang
Hangzhou Normal University
Yanli Jia
Tongde Hospital of Zhejiang Province
Wei Wang
Norwegian University of Science and Technology
Juan Ye (yejuan@zju.edu.cn)
The Second Affiliated Hospital of Zhejiang University

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Abstract

Background: Phantom eye pain (PEP) is a major clinical problem after eye removal with no standard treatment protocol to date. As pain is a multidimensional experience associated with emotional and cognitive components, this study aimed to explore the possible neuropsychological mechanisms of PEP in a perspective of emotional cognition, in order to provide a basis for clinical treatment.

Methods: Visual oddball event-related potentials (ERPs) under different external emotional stimuli (Disgust, Fear, Sadness, Happiness, Erotica and Neutral) were tested in 12 patients and 12 healthy volunteers. Participants' affective states were measured with the Mood Disorder Questionnaire (MDQ), the Hypomania Checklist-32 (HCL-32), and the Plutchik–van Praag Depression Inventory (PVP). The amplitudes and latencies of N1, P2, N2 and P3 components were analyzed by three-way ANOVA, i.e., group (2) × emotion (6) × electrode (3). Multiple comparisons were performed using Bonferroni's test.

Results: Longer N1 latencies, increased N1 amplitudes; shorter P2 latencies under Disgust and Happiness, decreased P2 amplitudes; shorter N2 latencies under Erotica, increased N2 amplitudes were found in patients compared with controls. There was no main effect of group or interaction effect on P3 latencies and P3 amplitudes. The MDQ and HCL-32 scores were lower, and the N1 latencies under Sadness were negatively correlated with PVP scores in patients.

Conclusions: PEP patients showed reversed patterns in exogenous attention allocation and enhanced involuntary attention to emotional stimuli compared with controls. This study demonstrated cortical processing of emotions in PEP patients and could provide a basis for developing emotional intervention therapy.

Background

Eye enucleation is often the final option of severe ocular trauma and diseases, such as choroidal melanoma, late-stage glaucoma and endophthalmitis[1]. Although orbital implants and ocular prostheses have been used to restore patients' facial appearance, patients are often suffered from emotional disturbance, such as anxiety and depression[2]. One possible reason is that a common long-term complication of eye removal, namely phantom eye syndrome, is always ignored by clinicians. Phantom eye syndrome is defined as any sensation that the patient reports as originating in the eye despite it being enucleated. The situation is often associated with phantom pain, phantom vision and phantom sensations, occurring several months to years after surgery[3]. Studies reported that 51% of patients who had lost an eye suffered from phantom eye syndrome and 23% experienced phantom eye pain (PEP)[4]. Phantom pain might persist for decades after eye enucleation, and persistent long-term phantom pain would be resistant to any treatment[5]. Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components[6]. Pain could affect working efficiency, social activities, and even lead to mental disorders, if it is not managed timely[7]. Therefore, PEP is an emerging problem that deserves clinical attention both physiologically and psychologically.

Phantom pain is one kind of neuropathic pain, which has been reported following the removal of almost any body part including the eyes, teeth, tongue, nose, limbs, breast and penis[8]. Phantom limb pain is the most studied phantom pain in recent years, and there is a consensus that phantom limb pain is multifactorial and includes peripheral, central, and psychological factors[8]. Cortical reorganization and peripheral input interact to create phantom limb pain[9]. Stress, anxiety and depression seem to contribute to the development of phantom limb pain[10]. Similarly, PEP is recognized to be an interaction of physical and psychological factors[3]. However, the underlying mechanisms of PEP remains unknown and no standard clinical treatment protocol exists to date. Therefore, this study aimed to explore the possible neuropsychological mechanisms of PEP in a perspective of emotional cognition, which might provide a new approach to prevent and control PEP.

In recent years, researchers have put forward feedback loops between pain, emotions and cognition[11]. Chronic pain can have a negative effect on emotions and on cognitive function. Conversely, a negative emotional state can lead to increased pain, whereas a positive state can reduce pain. Similarly, cognitive states such as attention and memory can either increase or decrease pain. Attentional bias to negative information has been found in patients with fibromyalgia syndrome, which is a chronic pain syndrome of unclear pathophysiology[12]. Cerebral event-related potentials (ERPs) are often used to investigate the early cognitive processes of an outside stimulus due to its high temporal resolution. Visual oddball ERPs might be a candidate methodology for elucidating effects of external emotional stimuli on early attentional processes[13]. Several ERP components have been identified, representing different stages of cerebral processing: N1 after the onset of an external stimulus reflects encoding of elementary stimulus features; P2 is attention-related and might be sensitive to emotion; N2 reflects involuntary attention to a stimulus; P3 reflects central resource utilization, that is, voluntary attention and evaluation of a stimulus[14]. Based on previous researches, we have hypothesized attentional bias towards negative emotional stimuli in PEP patients, represented by shorter EPRs latencies and larger EPRs amplitudes. Therefore, a group of patients with PEP as well as a group of healthy volunteers was invited to undergo the ERPs test. In the current study, we tested ERPs under external emotional conditions, including negative (disgust, fear and sadness), positive (happiness and erotica) and neutral emotions. Besides, questionnaires were used to assess phantom pain and affective states in PEP patients.

Methods

Participants

This study enrolled 12 patients with PEP (9 men and 3 women; aged 29.42 years ± 6.60 S.D., ranged 18 ~ 36 years), and 12 healthy volunteers (8 men and 4 women; aged 25.83 years ± 4.65 S.D., ranged 21 ~ 39 years). 7 patients had right eyes enucleated and 5 had left eyes enucleated. All participants, including patients with only one remaining eye, had normal or corrected-to-normal visual acuity. They were all right-handed, had received more than 12 years of education, and were drug and alcohol free for at least 72 hours prior to the test. This study was performed in accordance with the Declaration of Helsinki and was

approved by a local ethics committee. All participants gave their written informed consent to participate in this study.

Questionnaires

Short Form McGill Pain Questionnaire-2 (SF-MPQ-2)

PEP is measured by the “Neuropathic Pain” subscale and “Affective” subscale of SF-MPQ-2. “Neuropathic Pain” subscale consists of 6 different descriptors (hot-burning pain, cold-freezing pain, pain caused by light touch, itching, tingling or pins and needles, numbness) of neuropathic pain. “Affective” subscale consists of 4 affective descriptors (tiring-exhausting, sickening, fearful, punishing-cruel). Each item is rated based on a 0-10 scale with 0 equaling to no pain and 10 equaling to the worst pain. The subscale score is calculated by summing each item scores. The SF-MPQ-2 was demonstrated to be valid with “Neuropathic Pain” and “Affective” subscale internal reliability of 0.74 and 0.77 respectively, in a sample of Chinese individuals[15].

The Mood Disorder Questionnaire (MDQ)

The MDQ is a self-report questionnaire evaluating the symptoms of mania or hypomania[16]. It consists of three parts: one part including 13 forced-choice (yes or no) questions; one part determining whether two or more symptoms have been experienced at the same time; and another part determining the extent to which symptoms have caused functional impairment, on a scale ranging from “no problems” to “serious problems”. The MDQ was demonstrated to be valid with an internal reliability of 0.79 in a sample of Chinese individuals[17].

The Hypomania Checklist-32 (HCL-32)

The HCL-32 is a self-report questionnaire assessing hypomanic symptoms of emotions, thoughts, or behaviors, and questions regarding duration, impact on family, social and work life, or people’s reactions[18]. It consists of 32 forced-choice (yes or no) items. The HCL-32 was demonstrated to be valid with an internal reliability of 0.88 in a sample of Chinese individuals[19].

The Plutchik–van Praag Depression Inventory (PVP)

The PVP is a self-report questionnaire assessing depressive symptoms[20]. It consists of 34 items, with three scale points for each item (0, 1, 2), corresponding with increasing depressive tendencies. If respondents score between 20 and 25, they have “possible depression”; if 25 or above, they have depression. The PVP was demonstrated to be valid with an internal reliability of 0.94 in a sample of Chinese individuals[21].

External emotional stimuli

The external emotional stimuli, which were composed of pictures and sounds of the same domain with high arousal levels of emotional valence, were presented by *eevoke*TM software (ANT Software B.V.,

Enschede, The Netherlands). Pictures were selected from the International Affective Picture System[22], which were horizontally presented (768 × 512 pixels) at a computer screen, sustaining about 19.8° × 13.5° of visual angles. Sounds were selected from the International Affective Digitized Sounds database[23], which were 40 - 50 dB in intensity, delivered through a headphone. The six emotional situations were Disgust (picture code: 9325; sound code: 255), Fear (3053; 275), Sadness (2205; 295), Happiness (2040; 110), Erotica (4680; 205), and Neutral (5390; 172).

ERP designs and recordings

Participants were seated in a dimly lit room, 100 cm away from the computer screen. The experiment consisted of six successive sessions, with an inter-session interval of two minutes. Each session began with a fixation cross for 3000 ms, which was presented in the middle of a black background. Then came 150 ERP trials, with each trial for 2400 ms and an inter-trial interval of 1200 ~ 1500 ms. Within each ERP trial, there was an external emotional stimulus of either Disgust, Fear, Erotica, Happiness, Neutral, or Sadness, lasting 2000 ms for each. Emotional stimuli were presented in a randomized order among participants. Each emotion presentation was followed by either a standard (a square of 40 mm× 40 mm lasting for 400 ms,) or target (a circle of 40 mm in diameter lasting for 400 ms) stimulus in the middle of the black background. The standard stimuli were delivered 120 times (80%) and the target stimuli were 30 times (20%) in a randomized order. Participants were required to actively respond to the target stimuli as soon as possible, by pressing a button with their right index finger.

Three midline electrodes, Fz, Cz, and Pz were chosen for recording. The reference electrodes were attached to the linked mastoids of two sides. Bipolar recordings of the electro-ocular activity were made with electrodes placed at the outer canthus and supraorbitally to the right eye. The impedance of each electrode was kept below 10 kΩ. Potentials were analyzed using ASA software (ANT Software B.V., Enschede, The Netherlands), with a band-pass of .01 ~ 30 Hz. The sampling epoch was 100 ms pre-stimulus and 600 ms post-stimulus. A sweep in which the EEG exceeded ± 70 μV was excluded from averaging. ERP components under external emotional conditions were determined by visual inspection and analyzed in terms of peak latency and baseline-to-peak amplitude. Latency ranges of potentials were: 70 ~ 200 ms for N1, 150 ~300 ms for P2, 180 ~ 400 ms for N2, and 300 ~ 540 ms for P3. In addition, reaction time and response accuracy to the target stimuli under external emotional conditions in each participant were recorded.

Statistical analyses

Ages and scale scores of MDQ, HCL-32, and PVP were compared between the two groups by independent-sample T test, and gender distributions by χ^2 test. Reaction time and response accuracy to target stimuli were analyzed by two-way ANOVA, i.e., group (2) × emotion (6). The amplitudes and latencies of N1, P2, N2 and P3 components were analyzed by three-way ANOVA, i.e., group (2) × emotion (6) × electrode (3). Multiple comparisons were performed using Bonferroni's test. Relationships between ERPs and the affective scale scores were analyzed using the Pearson correlation test, and significant

correlations at no less than two midline electrodes were considered stable and meaningful. The alpha level of significance (p) was set at $\leq .05$. With the present sample size, power to detect an effect was larger than 70% at $p \leq .05$, based on a sample of 12 subjects per group.

Results

3.1 Demographic data, scale and behavioral results

No significant difference was found between patients and controls regarding age (t = 1.54, $p = .14$) and gender ($\chi^2 = .20$, $p = .65$). The mean ± standard deviation (SD) scores of “Neuropathic Pain” subscale and “Affective” subscale were 6.75 ± 3.91, 4.33 ± 3.47 respectively. Itching (6 out of 12), and tingling or “pins and needles” (6 out of 12) are the two most frequent neuropathic pain that patients described. Tiring-exhausting (4 out of 12) is the most frequent affective descriptor.

The mean MDQ scores (t = -3.90, $p = .001$), and the mean HCL-32 (t = -4.67, $p < .001$) scores were lower in patients than that in controls (see Table 1). No group difference was detected regarding PVP scores (t = -1.32, $p = .20$). There was main effect of group on reaction times (F = 11.87, $p = .001$). Reaction times were longer in patients compared with controls. No main effect of emotion, or interaction effect was detected regarding reaction times. No main effect of group and emotion, or interaction effect was detected regarding response accuracies.

Table 1
The scale scores of questionnaires, reaction times and response accuracies to target in two groups.

	Patients (n = 12)	Controls (n = 12)
Mood Disorder Questionnaire	2.67 ± 1.60 ***	7.45 ± 3.26
Hypomania Checklist-32	9.58 ± 6.44 ***	19.55 ± 3.04
Plutchik–van Praag Depression Inventory	8.75 ± 4.41	11.55 ± 7.73
Reaction time to target (ms)		
Under Disgust	539.78 ± 118.29	485.27 ± 95.88
Under Fear	584.96 ± 147.28	474.39 ± 78.86
Under Sadness	532.94 ± 134.12	502.33 ± 59.34
Under Happiness	546.26 ± 132.94	484.94 ± 87.07
Under Erotica	552.33 ± 92.85	489.29 ± 111.55
Under Neutral	535.26 ± 121.59	478.60 ± 76.69
Response accuracy (%)		
Under Disgust	95.5 ± 3.4	98.3 ± 4.8
Under Fear	98.2 ± 4.0	98.1 ± 2.2
Under Sadness	97.9 ± 3.4	98.1 ± 3.3
Under Happiness	98.1 ± 2.7	97.5 ± 3.5
Under Erotica	96.4 ± 6.7	98.1 ± 3.3
Under Neutral	97.0 ± 4.0	99.4 ± 1.3
Note: Mean ± SD, * $p < .05$, *** $p < .001$.		

3.2 Erp Differences Between Groups

There was significant group effect on N1 latencies (F = 7.71, $p = .01$) and N1 amplitudes (F = 6.89, $p = .01$). N1 latencies were prolonged and N1 amplitudes were increased in patients compared with controls. There was significant interaction effect between group and emotion on P2 latencies (F = 3.44, $p = .01$), and group effect on P2 amplitudes (F = 10.50, $p = .01$). Post-hoc testing showed that P2 latencies under Disgust and Happiness were shortened, and P2 amplitudes were decreased in patients compared with controls. There was significant interaction effect between group and emotion on N2 latencies (F = 2.38, $p = .04$) and group effect on N2 amplitudes (F = 10.35, $p = .001$). Post-hoc testing showed that N2 latencies

were prolonged under Neutral and shortened under Erotica, and N2 amplitudes were increased in patients compared with controls. There was no main effect of group or interaction effect on P3 latencies and P3 amplitudes ($p > .05$). For the sake of brevity, only N1 latencies, N1 amplitudes, P2 amplitudes and N2 amplitudes with significant group effect are shown in Table 2. The remaining data are available upon request.

Table 2
N1 latencies, N1 amplitudes, P2 amplitudes and N2 amplitudes in two groups.

		Patients (n = 12)			Controls (n = 12)		
		Fz	Cz	Pz	Fz	Cz	Pz
N1 latency	Disgust	173.70 ± 24.84	170.18 ± 23.51	168.62 ± 22.41	158.30 ± 26.04	155.69 ± 24.89	154.64 ± 22.53
(ms)	Fear	162.22 ± 27.49	160.86 ± 26.56	164.49 ± 26.40	157.78 ± 29.47	158.20 ± 28.36	159.95 ± 27.84
	Sadness	161.10 ± 23.21	163.42 ± 25.09	162.97 ± 25.64	170.18 ± 25.31	168.68 ± 23.99	167.02 ± 25.07
	Happiness	168.54 ± 22.15	167.56 ± 25.43	167.95 ± 23.69	163.08 ± 22.26	165.74 ± 20.25	166.04 ± 21.86
	Erotica	169.06 ± 24.95	168.35 ± 30.82	167.32 ± 28.73	150.09 ± 30.27	153.18 ± 28.63	156.42 ± 26.56
	Neutral	173.91 ± 27.15	173.99 ± 28.41	175.31 ± 26.64	164.17 ± 23.94	163.36 ± 22.12	163.28 ± 23.94
N1 amplitude	Disgust	− .87 ± 6.55	− .43 ± 5.22	-3.78 ± 4.22	.56 ± 4.31	1.42 ± 4.86	-1.27 ± 3.87
(μV)	Fear	-1.35 ± 4.42	-1.53 ± 4.97	-2.23 ± 4.11	-1.67 ± 5.54	.28 ± 6.61	-3.65 ± 5.58
	Sadness	-1.15 ± 4.10	− .43 ± 5.74	-2.80 ± 4.77	2.64 ± 7.65	2.61 ± 9.03	-1.57 ± 8.34
	Happiness	− .74 ± 4.77	− .62 ± 4.77	-3.56 ± 4.55	1.86 ± 9.56	2.00 ± 10.08	-2.38 ± 8.87
	Erotica	-1.01 ± 4.86	-1.83 ± 5.41	-3.81 ± 6.16	3.77 ± 15.48	5.28 ± 18.09	.39 ± 11.90
	Neutral	.08 ± 5.12	− .73 ± 5.81	-3.23 ± 6.16	− .90 ± 6.99	− .45 ± 7.89	-4.86 ± 6.24
P2 amplitude	Disgust	1.01 ± 6.49	.54 ± 5.01	-2.12 ± 4.76	4.33 ± 6.09	4.44 ± 6.78	.14 ± 5.32
(μV)	Fear	1.06 ± 5.47	.36 ± 5.14	-1.00 ± 4.72	2.07 ± 6.43	3.18 ± 8.12	-2.03 ± 6.14
	Sadness	1.05 ± 3.99	1.00 ± 4.60	− .84 ± 3.71	6.52 ± 10.95	6.25 ± 11.43	.98 ± 8.80
	Happiness	1.01 ± 5.42	1.20 ± 5.73	-2.06 ± 5.26	4.06 ± 10.67	2.99 ± 11.28	-2.07 ± 10.41

Note: Mean ± SD.

		Patients (n = 12)			Controls (n = 12)		
	Erotica	1.05 ± 5.47	.32 ± 5.89	-1.73 ± 6.61	7.78 ± 18.01	8.92 ± 20.48	2.68 ± 13.09
	Neutral	2.45 ± 6.41	.87 ± 7.27	-1.74 ± 7.10	1.95 ± 7.63	1.42 ± 8.64	-3.06 ± 6.56
N2 amplitude	Disgust	− .47 ± 5.63	-3.23 ± 4.94	-5.60 ± 5.94	1.42 ± 6.27	.46 ± 6.39	-3.48 ± 6.12
(μV)	Fear	-1.28 ± 6.78	-3.22 ± 6.62	-4.48 ± 5.91	− .57 ± 5.74	-1.47 ± 5.64	-6.18 ± 4.62
	Sadness	− .63 ± 5.03	-2.46 ± 5.56	-4.42 ± 5.27	3.13 ± 9.83	2.15 ± 9.74	-3.01 ± 7.22
	Happiness	-1.37 ± 6.54	-2.66 ± 6.43	-5.99 ± 6.59	1.60 ± 9.89	− .31 ± 11.01	-5.36 ± 10.18
	Erotica	-1.70 ± 5.88	-3.70 ± 6.19	-5.48 ± 7.18	4.44 ± 16.71	4.02 ± 18.13	-1.86 ± 10.56
	Neutral	− .73 ± 6.43	-3.98 ± 7.73	-6.76 ± 8.18	− .22 ± 7.30	-1.46 ± 8.09	-5.88 ± 5.82
Note: Mean ± SD.							

3.3 Relationships Between Erps And Affective States

The N1 latencies under Sadness at middle electrodes (Fz, r = -0.751, p = 0.01; Cz, r = -0.708, p = 0.01; Pz, r = − .721, p = 0.01) were negatively correlated with PVP scores in PEP patients. The N1 latencies under Erotica at middle electrodes (Fz, r = -0.700, p = 0.02; Cz, r = -0.707, p = 0.02; Pz, r = − .747, p = 0.01) were negatively correlated with MDQ scores in controls. No other relationship between ERP components and affective states was found in the two groups.

Discussion

This is the first study to our knowledge addressing the specific effects of external emotional stimuli on cerebral attentional function in PEP patients. We found that N1 latencies were prolonged, N1 amplitudes were increased; P2 latencies under Disgust and Happiness were shortened, P2 amplitudes were decreased; N2 latencies under Erotica were shortened, N2 amplitudes were increased in patients compared with healthy controls. No group differences were detected for P3 components. Indeed, reversed patterns in exogenous attention allocation to emotional stimuli had been found in PEP patients compared with controls, which were different from our initial hypothesis. In addition, the MDQ and HCL-32 scores were lower, and the N1 latencies under Sadness were negatively correlated with PVP scores in PEP patients.

Emotional factors are influential in patients' experience of prolonged phantom pain after eye amputation. On the one hand, it is possible that phantom pain leads to poor health-related quality of life such as mood disorders. On the other hand, it is also likely that poor quality of life attributed to mood disorders induces phantom pain. Interestingly, our study indicated that depression were not more common in PEP patients, which was consistent with the findings in phantom limb pain patients[24]. In a longitudinal study, a dramatic drop in the incidence of psychological symptoms in individuals after amputation had been found by the time of discharge from a rehabilitation ward, which might be owing to emotional adjustment and learning of new skills to adjust to life after amputation[25]. Whereas the association of mood disorders and chronic pain have long been investigated, most studies focused on negative affect such as depression and little attention has been paid to positive affect. Mania and hypomania in full or subsyndromal forms, are central features of bipolar disorders, characterized by elevated mood, decreased need for sleep, increased activity or energy, and so on[26]. A retrospective study revealed that 64.2% of bipolar disorder patients with chronic pain recalled experiencing reduced pain intensity during their most recent manic or hypomanic episode[27]. Similarly, our patients suffering from phantom pain reported lower levels of mania and hypomania than healthy controls. Despite similar levels of depression in two groups, N1 latencies under Sadness were negatively correlated with the levels of depression in PEP patients. A previous study showed tendency toward a negativity bias (faster responses and greater N1 amplitudes) for sad faces in patients with major depressive disorder[28]. The negativity bias under Sadness might be a latent cognitive trait associated with the vulnerability of depression.

ERPs have high temporal resolution and are often used to detect earlier changes of the attentional and cognitive aspects, with latency and amplitude indicating the speed and capacity of cognitive processing of a stimulus respectively[29]. There was no difference in P3 components between two groups, indicating that voluntary attention to emotional stimuli was not impaired in PEP patients. Shorter N2 latencies under Erotica and increased N2 amplitudes in PEP patients implied enhanced involuntary attention to emotional stimuli. These findings were contrary to Troche et al.'s study in which participants performed in an auditory oddball task in a pain-free and a pain condition[30]. They found that voluntary (reflected by P3b amplitude) and involuntary (reflected by P3a amplitude) capture of attention to novel, unexpected stimuli was both impaired by pain. Nevertheless, Veldhuijzen et al.'s study using an ERP probe task with varying task difficulty levels revealed that allocation of attentional resources was deficient in chronic pain patients, instead of attentional capacity[31]. Previous studies did not reach a consistent conclusion on the effects of pain on attentional processing capacity, which still needs further investigation. Exogenous attention has been suggested as an adaptive tool for rapidly detecting salient events and to play a crucial role in conscious perception[32, 33]. Our study reported reversed patterns in N1 and P2 latencies and amplitudes in PEP patients and controls, reflecting different exogenous attention allocation, which is a new finding that worth further exploration.

Several limitations of this study should be noted. Firstly, the sample size was small and eye amputees without phantom pain were not included in control groups. Secondly, we did not include anger and contempt as external emotions, involvements of which might help to show more complicated emotional effects on attentions in PEP. Thirdly, only ERPs at three midline electrodes were recorded, which limits

spatial resolution. Even then, these electrodes position fulfil the minimal requirements for the purposes of this study. Further studies with more rigorous research design are needed to illustrate the cerebral processing of different emotions in PEP patients.

Conclusions

In this study, PEP patients had lower levels of mania and hypomania, and showed reversed patterns in exogenous attention allocation to emotional stimuli compared with controls. In addition, enhanced involuntary attention had been found in PEP patients. The speed of processing Sadness was correlated with the levels of depression. This study demonstrated cortical processing of emotions in PEP patients and could provide a basis for developing emotional intervention therapy. In the management of PEP, strategies aiming at conscious direction of attention may be helpful, e.g., imagery techniques or mindfulness training.

Declarations

Ethics approval and consent to participate

This study has been approved by the Ethics Committees of the Second Affiliated Hospital of Zhejiang University, School of Medicine and were conducted in accordance with the Declaration of Helsinki. Written informed consent of the patients and the healthy individuals was obtained.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LL and YW designed the study. LL, YW, BZ and YJ collected the data. LL and YW analyzed the data and wrote the manuscript. WW and JY revised the manuscript. All authors read and approved the final manuscript.

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References

1. Zhang Y, Zhang M, Wang X, Chen X. Removal of the eye in a tertiary care center of China: a retrospective study on 573 cases in 20 years. International Journal of Ophthalmology. 2015; 8(5):1024-30.
2. Ye J, Lou L, Jin K, Xu Y, Ye X, Moss T *et al*. Vision-Related Quality of Life and Appearance Concerns Are Associated with Anxiety and Depression after Eye Enucleation: A Cross-Sectional Study. PLoS One. 2015; 10(8):e0136460.
3. Andreotti AM, Goiato MC, Pellizzer EP, Pesqueira AA, Guiotti AM, Gennari-Filho H *et al*. Phantom eye syndrome: a review of the literature. ScientificWorldJournal. 2014; 2014:686493.
4. Rasmussen ML. The eye amputated–consequences of eye amputation with emphasis on clinical aspects, phantom eye syndrome and quality of life. Acta Ophthalmologica. 2010; 88(thesis2):1-26.
5. Rasmussen ML, Prause JU, Toft PB. Phantom pain after eye amputation. Acta Ophthalmol. 2011; 89(1):10-6.
6. Williams AC, Craig KD. Updating the definition of pain. Pain. 2016; 157(11):2420-3.
7. Cruccu G, Truini A. A review of Neuropathic Pain: From Guidelines to Clinical Practice. Pain Ther. 2017; 6(Suppl 1):35-42.
8. Luo Y, Anderson TA. Phantom Limb Pain: A Review. Int Anesthesiol Clin. 2016; 54(2):121-39.
9. Andoh J, Milde C, Tsao J, Flor H. Cortical plasticity as a basis of phantom limb pain: Fact or fiction? Neuroscience. 2018; 387:85-91.
10. Subedi B, Grossberg GT. Phantom limb pain: mechanisms and treatment approaches. Pain Res Treat. 2011; 2011:864605.
11. Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. Nature Reviews Neuroscience. 2013; 14(7):502-11.
12. Duschek S, Werner NS, Limbert N, Winkelmann A, Montoya P. Attentional bias toward negative information in patients with fibromyalgia syndrome. Pain Medicine. 2014; 15(4):603-12.
13. Zhang B, Jia Y, Wang C, Shao X, Wang W. Visual event-related potentials in external emotional conditions in bipolar disorders I and II. Neurophysiologie Clinique. 2019; 49(5):359-69.
14. Rugg MD, Coles MG. Electrophysiology of mind: Event-related brain potentials and cognition. NewYork: Oxford University Press; 1995.

15. Li J, Feng Y, Han J, Fan B, Wang J, Wei X *et al*. Multi-centered linguistic adaptation and validation of short-form McGill pain questionnaire-2. Chinese Journal of Pain Medicine. 2013; 19:42-6.
16. Hirschfeld RM, Williams JB, Spitzer RL, Calabrese JR, Flynn L, Keck Jr PE *et al*. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. American Journal of Psychiatry. 2000; 157(11):1873-5.
17. Yang H, Yuan C, Liu T, Li L, Peng H, Rong H *et al*. Validity of the Chinese version Mood Disorder Questionnaire (MDQ) and the optimal cutoff screening bipolar disorders. Psychiatry Research. 2011; 189(3):446-50.
18. Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD *et al*. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. Journal of affective disorders. 2005; 88(2):217-33.
19. Yang H, Yuan C, Liu T, Li L, Peng H, Liao C *et al*. Validity of the 32-item Hypomania Checklist (HCL-32) in a clinical sample with mood disorders in China. BMC Psychiatry. 2011; 11(1):1-7.
20. Plutchik R, Van Praag HM. Interconvertability of five self-report measures of depression. Psychiatry Research. 1987; 22(3):243-56.
21. Wang W, Cao M, Zhu S, Gu J, Liu J, Wang Y. Zuckerman-Kuhlman's personality questionnaire in patients with major depression. Social Behavior and Personality: an international journal. 2002; 30(8):757-64.
22. Lang P, Bradley M, Cuthbert B. International affective picture system (IAPS): affective ratings of pictures and instruction manual. Tech Rep. 2008:A-A8.
23. Bradley MM, Lang PJ. The international affective digitized sounds (IADS-2): affective ratings of sounds and instruction manual. Tech Rep. 2007:B-B3.
24. Kazemi H, Ghassemi S, Fereshtehnejad SM, Amini A, Kolivand PH, Doroudi T. Anxiety and depression in patients with amputated limbs suffering from phantom pain: a comparative study with non-phantom chronic pain. International Journal of Preventive Medicine. 2013; 4(2):218-25.
25. Singh R, Hunter J, Philip A. The rapid resolution of depression and anxiety symptoms after lower limb amputation. Clinical Rehabilitation. 2007; 21(8):754-9.
26. Dubovsky SL. Mania. Continuum (Minneapolis, Minn). 2015; 21(3):737-55.
27. Boggero IA, Cole JD. Mania reduces perceived pain intensity in patients with chronic pain: preliminary evidence from retrospective archival data. Journal of Pain Research. 2016; 9:147-52.
28. Dai Q, Wei J, Shu X, Feng Z. Negativity bias for sad faces in depression: An event-related potential study. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2016; 127(12):3552-60.
29. Hajcak G, MacNamara A, Olvet DM. Event-Related Potentials, Emotion, and Emotion Regulation: An Integrative Review. Developmental Neuropsychology. 2010; 35(2):129-55.
30. Troche SJ, Houlihan ME, Connolly JF, Dick BD, McGrath PJ, Finley GA *et al*. The effect of pain on involuntary and voluntary capture of attention. Eur J Pain. 2015; 19(3):350-7.

31. Veldhuijzen DS, Kenemans JL, van Wijck AJ, Olivier B, Kalkman CJ, Volkerts ER. Processing capacity in chronic pain patients: a visual event-related potentials study. Pain. 2006; 121(1-2):60-8.
32. Carretie L. Exogenous (automatic) attention to emotional stimuli: a review. Cogn Affect Behav Ne. 2014; 14(4):1228-58.
33. Chica AB, Lasaponara S, Lupianez J, Doricchi F, Bartolomeo P. Exogenous attention can capture perceptual consciousness: ERP and behavioural evidence. Neuroimage. 2010; 51(3):1205-12.