Research Square

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The dysfunction of affective picture processing in pituitary patients: an ERPs study

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Research

Keywords: Pituitary adenoma, ERPs, emotional processing, LPP

Posted Date: April 8th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-20708/v1

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Abstract

Background: Cognitive impairments have been reported in patients with pituitary adenoma; however, there is a lack of knowledge of investigating the emotional stimuli processing in pituitary patients. Thus, we aimed to investigate whether there is emotional processing dysfunction in pituitary patients by recording and analyzing the late positive potential (LPP) elicited by affective stimuli.

Methods: Evaluation of emotional stimuli processing by LPP Event related potentials (ERPs) was carried out through central- parietal electrode sites (C3, Cz, C4, P3, Pz, P4) on the head of the patients and healthy controls (HCs).

Results: In the negative stimuli, the amplitude of LPP was 2.435 ± 0.419μV for HCs and 0.656 ± 0.427μV for patient group respectively ($p = 0.005$). In the positive stimuli, the elicited electric potential 1.450 ± 0.316μV for HCs and 0.495 ± 0.322μV for patient group respectively ($p = 0.040$). Moreover, the most obvious difference of LPP amplitude between the two groups existed in the right parietal region. On the right hemisphere (at the P4 site), the elicited electric potential was 1.993 ± 0.299μV for HCs and 0.269 ± 0.305μV for patient group respectively($p = 0.001$).

Conclusion: There are functional dysfunction of emotional stimuli processing in pituitary adenoma patients. Our research provides the electrophysiological evidence for the presence of cognitive dysfunction which need to be intervened in the pituitary adenoma patients.

Background

Pituitary adenomas are the most common intracranial tumors following meningiomas, accounting for about 16.5% of central nervous system tumors [1]. The mechanical pressure from tumor mass on adjacent neuroanatomical regions such as inferior frontal lobe, diencephalon, optic chiasma, and pituitary stalk could disrupt the tissue structures [2]-[4], which might decrease the endocrine functions of hypothalamus or pituitary stalk. On the other hand, the pituitary may secrete abnormally high hormones than usual. Therefore, apart from the physical damages, abnormal cognition appears commonly in pituitary adenoma patients. Substantial evidence has shown that pituitary patients frequently complain about problems in attention [5], working memory [6], executive function [7], depression [8], and emotion processing [9], which affect the quality of patients' life [10][11].

Cognitive functions refer to the information processing, storage and extraction in the brain [12]. Recent literature on affective neuroscience has identified neural networks in perceptual procession of emotional expressions on face [13]. These networks are involved in regions performing emotional discrimination and affective semantic processing. The specific areas of the brain were damaged in patients, whose emotion recognition would also be affected. LPP is the positive potential that appears 400 ms after affective stimuli [14], which is influenced by affective words, pictures, and faces [15]-[19] with a centro-parietal distribution [20]. However, up to now, no study that investigated the emotional processing function in pituitary adenoma patients has been reported. In this study, emotional processing function in

pituitary adenoma patients was explored by recording and analyzing LPP elicited by affective stimuli. We hypothesize that pituitary adenoma patients may suffer from the dysfunction of emotional processing owing to the pressure on the cognitive function areas of the brain or hormone imbalance.

Methods

Subjects

Pituitary adenomas patients were were recruited in the Department of Neurosurgery, Wuhan School of Clinical Medicine, Southern Medical University (China) during diagnostic hospitalization. The inclusion criteria for patients were as follows: (1) the tumors were pathologically and immunohistochemically diagnosed as pituitary adenoma; (2) No history of craniotomy and radiation therapy; (3) they did not have any severe heart, liver and kidney failure; (4) Participants could cooperate to complete ERPs tests. Exclusion criteria for patients were as follows: (1) A history of neurologic or psychiatric disorders; (2) No drug or alcohol abuse [subjects who drink alcohol over 2.0 standard drinks (10 g of pure alcohol) on days and meet any 2 of the 11 criteria under the DSM-V in the past year] [21], and medication intake (including oral contraceptives). All patients and healthy controls (HCs) had visual acuity and hearing ability sufficient to take part in the test. Cognition evaluation (ERPs study) was conducted to investigate the affective picture processing before the surgery. There were 26 patients that have prolactinoma, growth hormone (GH) pituitary adenoma or non-functional pituitary adenoma separately meeting the above-mentioned conditions (female,15; 27.9±2.8 y). 26 healthy people matched to the patients of observation group with age, sex, education, and handedness (female, 15; 27.2±2.9 y) were selected as the HCs. People in the HCs were in good health, without mental disease and history of psychoactive substance abuse as well as family history of mental illness. There was no significant difference in age, gender, educational level between the two groups (p 0.05). The study was approved by the ethics committee of Wuhan School of Clinical Medicine, Southern Medical University, and informed consents were explained carefully and obtained from all participants.

Radiological assessment

All participants underwent preoperative coronal and sagittal Magnetic Resonance Imaging (MRI) scanning by a 1.5T GE scanner (GE EXCITE, Milwaukee, WI, USA) with a head coil. Participants lied on their back with cushions around their head to inhibit their head motion, and earplugs (29 dB) in their ears to reduce scanner noise. Adenoma and the size were recognized through MRI image by two experienced neurosurgeon blinded to patients' clinical features. Median adenoma diameter on sagittal imaging was about 21.0mm (mean 21.0 ± 4.4mm). Median suprasellar tumor extension scored 8.4 mm (mean 8.4 ± 3.3 mm). The compression of frontal lobe parenchyma was present in all cases. There were no abnormalities in the MRI image of control people evaluated by the same two neurosurgeons.

Endocrinological assessment

Endocrinological levels on the whole pituitary axes were measured from 8:00 a.m. to 9:30 a.m. on the day of LPP testing considering circadian variation in hormone levels. Clotted or heparinized blood was delivered in ice boxes to the clinical laboratory of Chinese People's Liberation Army General Hospital of Central War Zone. 14 patients with prolactinomas manifested hyper- prolactin (PRL) soley. 2 patients with prolactinomas were hyper- PRL and hyper-GH. 10 patients with non-functional pituitary adenoma had normal hormonal status. All the 26 people in HCs had normal hormonal levels.

Stimuli and procedure

Sixty pictures were selected from the International Affective Picture System (IAPS) [22]. Visual stimuli used IAPS pictures in the center of a computer screen (light degree = 60 cd/m^2). The examinee was seated in a semi-dark room, watching the screen 100 cm from their eyes, with a visual angle of 4°×4°. Stimuli consisted of 20 positive images including babies and animals, 20 neutral images including objects, and 20 negative images including attack scenes, violence, and wild animals. Affective stimuli were matched on arousal (See Table 1). One-way repeated-measures ANOVAs were computed for valence and for arousal dimensions. Post-hoc contrasts indicated that positive stimuli and negative stimuli showed distinct valence but not distinct arousal. Positive stimuli and negative stimuli differed from neutral stimuli both in arousal and valence. The trial began with a fixation mark (+) on the black screen for 1000 ms, and then a random image appeared for 2000 ms. The images were presented in a pseudo-random order, with the constraint that a specific image appeared no more than three times consecutively. One trial contains 45 negative, 45 neutral, and 45 positive stimuli so that one trial takes 405 seconds. The stimulus presentation was controlled with the E-prime (Psychology Software Tools). During the trial, the subjects were instructed to look passively at the pictures, and reduce eye blinks and body movements as much as they can. We just instruct participants to mentally categorize these stimuli and without any pressing button, only in order to pay their attention on these stimuli.

EEG recording and analysis

The electroencephalography (EEG) signals were continuously recorded (band pass 0.05-200Hz, sampling rate 1000Hz) at central- parietal electrode sites (C3, Cz, C4, P3, Pz, P4; 10-20 International System) referenced to the left mastoid (right mastoid as recording site). The EEG data were off-line re-referenced to the bio-mastoids reference. The EEG was from 200 ms pre-stimulus to 800 ms post-stimulus, and the baseline corrected to the mean amplitude 200 ms before the stimulus. The EEG were segmened separately for positive, negative and neutral stimuli. The artifact-free EEG with positive, negative and neutral conditions were averaged respectively and at least 50 trials were available for each subject and condition. For further analysis, the ERPs data were digitally low-pass filtered at 30 Hz (24 dB/octave).

Compared with ERPs induced by neutral stimuli, positive and negative stimuli produced larger parietal LPP, regardless of pituitary adenoma or control group. The measurements of amplitudes of LPP was computed for time windows: 300□550 ms. Analyses were conducted using a 3 (type of stimuli picture: positive, negative and neutral) × 6 (electrode site: C3, Cz, C4, P3, Pz, P4) × 2 (patient group and HCs)

repeated-measures analysis of variance (ANOVA) to acquire effects of different stimulus picture and whether these effects are different among the electrode site of the LPP and between the two groups. The degree of freedom was corrected with Greenhouse–Geisser epsilon.

Result

Figure 1 showed the affective stimuli and neutral stimuli elicited robust LPP components. Compared with the ERPs waveform elicited by neutral stimuli, affective stimuli elicited larger parietal LPP components, regardless of pituitary adenoma or control group. Figure 2 showed the ERP waveforms elicited by control group were larger than those by patient group. These sites(C3, Cz, C4, Pz) were not detainled because there was no statistical difference.

Overall analysis showed that the main effects for emotional stimuli ($F (2, 100) = 19.814$, $p = 0.001$, $\eta^2P = 0.288$), region ($F (1, 50) = 6.102$, $p = 0.0173$, $\eta^2P = 0.111$), and group ($F (1, 50) = 7.113$, $p = 0.010$, $\eta^2P = 0.127$) all reached significant. Interestingly, the two-way interaction of Group * emotional stimuli was significant ($F (2, 100) = 5.009$, $p = 0.008$, $\eta^2P = 0.093$), showing that, in the case of negative stimuli, the group effect was statistically different (2.435 ± 0.419μV for control group and 0.656 ± 0.427μV for observation group, respectively; $p = 0.005$); in the case of positive stimuli, the group effect was statistically different (1.450 ± 0.316μV for control group and 0.495 ± 0.322μV for observation group, respectively; $p = 0.040$). There was also a statistical difference between region and group type ($F = 13.790$, $p = 0.001$, $\eta^2P = 0.220$), suggesting that, on the right hemisphere (at the P4 site), the group effect was different with statistical significance (1.993 ± 0.299μV for control group and 0.269 ± 0.305μV for observation group, respectively; $p = 0.001$) .

Discussion

There is evidence that neurobehavioral disorders are common in pituitary adenoma patients, but most of them are ignored in the actual clinic treatment in neurosurgery treatment. In our study, parietal LPP elicited by affective stimuli was significant larger than those elicited by neutral stimuli in both patient group and HCs. Compared with the LPP amplitudes in the HCs, the LPP amplitudes elicited by both negative and positive pictures in the patient group were less. Importantly, the most obvious difference of LPP amplitude between the two groups appears in the right parietal region (at the P4 site).

Previous study showed the right cerebral hemisphere has a special role in both the posed and spontaneous expression of emotion and the dominant emotional expression in the right hemisphere, especially the prosodic and lexical expression in patients with brain impairment, and the facial expressions of normal subjects [23]. Interestingly, the posterior regions of the right hemisphere has been found to be more important in the expression of emotion [24]. Resent study has ruled out the right hemisphere is specialized for processing all emotional information compared to the left hemisphere [25]. One possibility is that emotional processing involves strategies (e.g., integrative and holistic) and functions (e.g., nonverbal and visuospatial) for which the right hemisphere is specialized. Gardner et al.

[26] believed that the key need to participate in the emotional processing of the right hemisphere was the demand of space. In addition, the right hemisphere was described as having greater capabilities of multimodal integration and organization, inter-lobular organization [27], and larger inter-regional interconnections [28]. These features of the right hemisphere may be particularly suited to the complex multimodal nature of emotional processing [23]. In line with previous findings, the emotional modulation of LPP component was significantly less on the right hemisphere in patients than in the HCs. These data indicated that the right brain hemisphere has a pivotal role in emotion and there was a dysfunction of emotional processing in pituitary adenoma patients.

To date, evidences have indicated that the amplitude of the LPP is modulated by emotion instructions [29]. LPP is a relevant component of affective picture processing [30]. LPP reflects an automatic increase in attention to visual emotional stimuli [31] and is mediated by task demands [32] and personality traits [33] as well as by the arousal and valence levels of affective pictures. In adults, highly arousing pictures elicited greater LPP potienal than less-arousing pictures when the pictures were passively viewed [34]. Both positive and negative pictures elicited larger LPP amplitudes than neutral pictures [32]-[36]. In this research, we also found both patient group and HCs manifested enhanced LPP for emotional stimuli, compared with neutral stimuli. However, smaller LPP amplitude for emotional stimuli in patients than HCs, indicating the impaired affective picture processing in pituitary patients. The impaired affective picture processing can be due to the compression to the brain, or effects of hormonal imbalance on sensitive structures. However, up to now, there is no consensus on the cause of cognitive impairments [37]. It was once believed that the cognitive function of pituitary adenoma patient was closely related with hormone, because excessive secretion of pituitary hormones can cause various metabolic disorders or organ damage. Receptors for glucocorticoids particularly are abundant in the limbic system and glucocorticoid-associated brain impaired, cognitive impairments, especially memory loss can be seen in excess glucocorticoid hormone production [38]. For example, higher levels of anxiety and depression phenomenon were observed more in people with Cushing's disease than with acromegaly [39], it is not only the body image change but also the specific hormone abnormality that is responsible for the mood disturbance. Greater hyperprolactinemia was associated with a larger decrease in cognitive performance [5]. Impairment of executive function is also closely related with hyperprolactinemia with a negative effect on cognitive ability [41]-[43]. These cognitive dysfunctions are related to the lesion of the prefrontal cortex, a structure that we also found abnormalities in patients with prolactinomas. Our previous study found that patients with prolactinomas showed decrease in gray matter volume (GMV) in prefrontal cortex including the right middle frontal cortex (MFC), and the right inferior frontal cortex (IFC) [44], suggesting that abnormal high PRL levels may have an adverse effect on cognitive function.

However, recent studies have found that there is no significant difference in the cognitive dysfunction between nonfunctioning adenoma and growth hormone adenoma [45]. Nonfunctioning adenoma (Nonsecreting pituitary adenoma) generally grows slowly, producing no endocrine symptom. The cognitive dysfunction of affective picture processing in the present study can be attributed to compression to the important brain structures, such as the optic chiasma and pituitary, hypothalamus. Moreover, suprasellar extension may directly replace or indirectly interrupt (due to local high intracranial

pressure) adjacent neuro-anatomical structures such as the diencephalic structures, hypothalamus, mammillary bodies, or parts of the inferior frontal lobes, which can leads to decreased vision, cranial nerve palsy, and hypopituitarism, hypogonadism, hypothyroidism, and deficit of adrenal function. A recent study showed that the fluctuations in hormone level are not relevant to the degree of cognitive dysfunction. In their study, the cognitive function of nonfunctioning adenoma patients was impaired most significantly [46]. The study provides evidence that cognitive dysfunction may exist, even if there was no excess biochemical problem. This may reflect where structural hippocampal, neurovascular, or electrophysiologic changes caused by the tumor or excess GH [47][48].

Several limitations should be addressed. First, although there was a significantly decreased LPP amplitude in preoperative group, the relatively small sample size should be increased in our future study to validate the generalization of this finding. Second, the age of the patient at the time may play a role in the cognitive function because older adolescents are more vulnerable to suffer cognitive impairments compared to young patients [49]. Third, this research involved a mix of prolactinoma, GH pituitary adenoma and non-functional pituitary adenoma. Comparison of cognitive function for each type of pituitary tumor can be studied in future.

Conclusion

In sum, the present study investigated the function of emotional processing in pituitary adenoma patients by analyzing LPP component. Compared with the LPP in healthy people, LPP related to emotional stimuli in patients was smaller, especially in the right parietal regions, whereas the LPP related to neutral stimuli did not differ between healthy people and pituitary adenoma patients. These data suggested the dysfunction of emotional processing, which proved necessity for the treatment of the impaired affective stimuli processing in pituitary adenoma patients.

Abbreviations

ERPs: Event related potentials

LPP: late positive potential

HCs: healthy controls

GH: growth hormone

MRI: Magnetic Resonance Imaging

PRL: prolactin

EEG: electroencephalography

GMV: gray matter volume

MFC: middle frontal cortex

IFC: inferior frontal cortex

Declarations

Ethics approval and consent to participate

All procedures followed the Declaration of Helsinki and were approved by the Ethical Committee of Wuhan School of Clinical Medicine, Southern Medical University (China). The number of the approved ethical statement is “[2014] 024-1.” All subjects were fully informed of the nature of the study protocol and all gave their written consents regarding participation.

Consent for publication

Written informed consents were obtained from all patients or their legally authorized representatives, and privacy of patients was effectively protected.

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.

Authors contributions

Guozheng Xu and Jian Song were responsible for the study concept and design. Chenglong Cao contributed to the interpretation and manuscript revision. Binbin Liu, Jianren Yue and Yuzhao Lu collected the EEG data and revised the first draft of the manuscript. Jian Song and Chenglong Cao assisted with data analysis and interpretation of findings. Cheng Huang and Huichao Ding performed the statistical analysis. Jian Song and Chenglong Cao drafted the manuscript. All authors have reviewed the content and approved the final version for publication.

Acknowledgments

We would like to thank the financial support of National Natural Science Foundation of China (No81571049).

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Table

Table 1. Means and standard deviations for arousal and valence for each IAPS

Mean valence and arousal ratings	IAPS			
	Positive	Neutral	Negative	P
Valence	6.1540±1.7842	4.9400±0.1812	3.188±0.6594	0.01
Arousal	5.4160±0.3135[a]	2.5673±0.5062	5.4887±0.3905[a]	0.01

a*P*<0.05compared with neutral stimuli

Figures

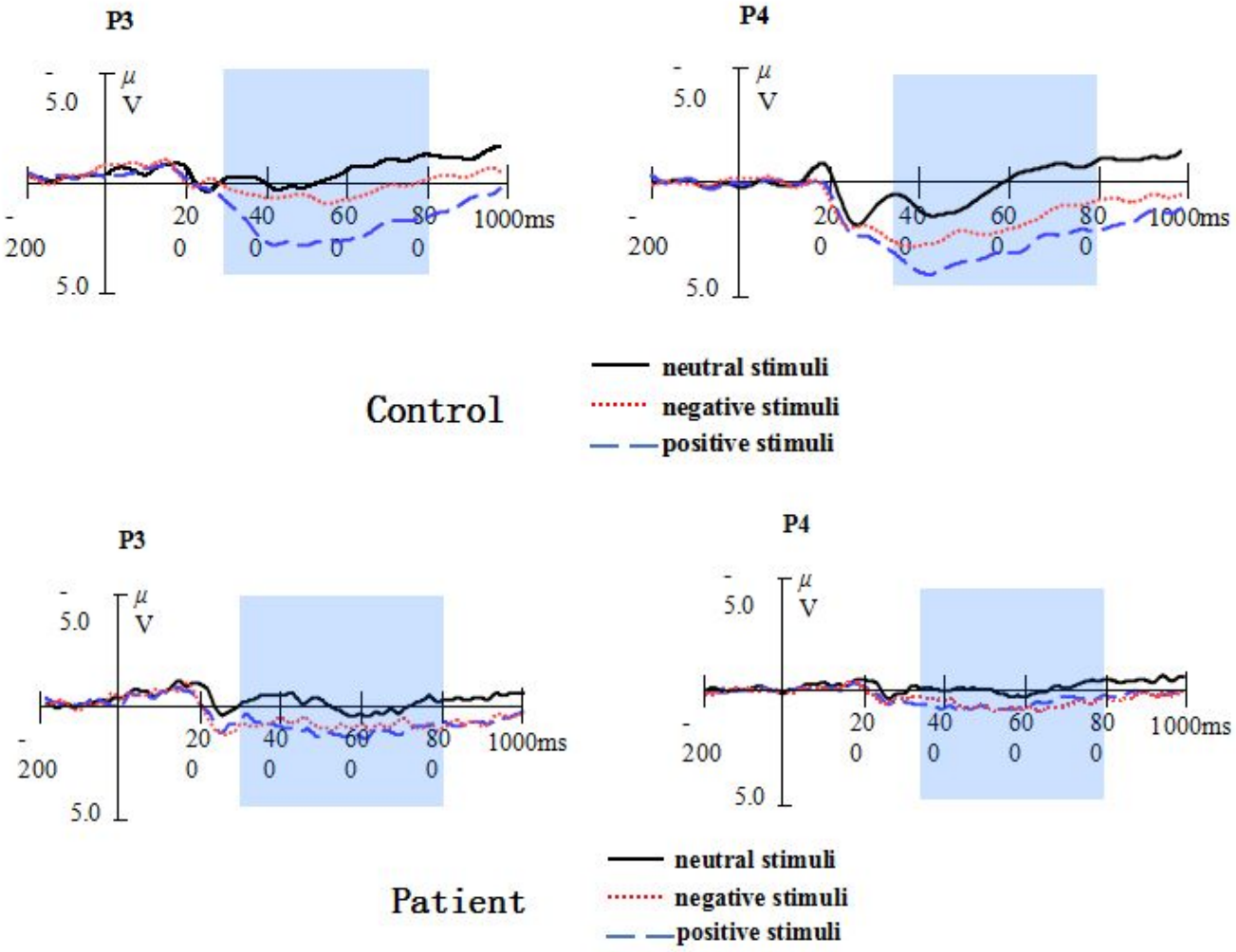


Figure 1

The average waveforms elicited by affective and neutral stimuli in two groups, respectively.

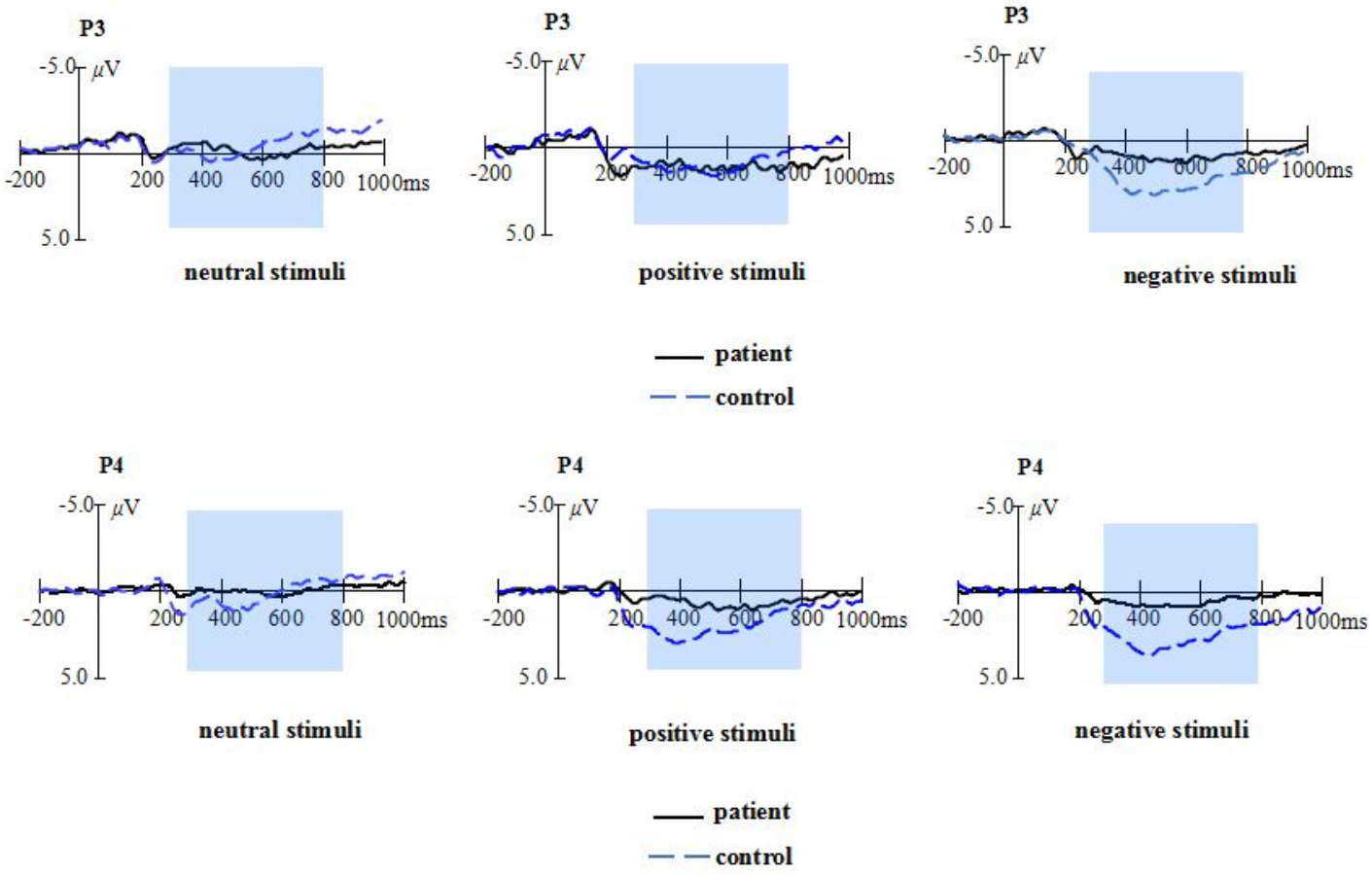


Figure 2

LPP amplitudes elicited by negative, positive and neutral IAPS pictures in parietal regions (P3 and P4 sites).