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EEG Correlates of Emotional Experience in Huntington's Disease

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Abstract

Recognizing negative emotions is impaired in Huntington's disease (HD), while the subjective emotional involvement in affective pictures images is not completely known in these patients. We aimed to further evaluate emotional reaction in early HD patients, by means of subjective arousal and valence rating and EEG changes induced by International Affective Pictures (IAPS).

We recruited 16 consecutive genetically confirmed HD outpatients, and 16 sex and age matched controls. Eighty-four color slides, 28 pleasant, 28 unpleasant and 28 neutral images, in random presentation, were chosen from the International Affective Picture System. EEG was recorded by 32 scalp electrodes.

HD patients judged negative and positive affective images respectively more unpleasant and pleasant than controls. They also exhibited higher arousal for pictures, independently from their affective content. However, in HD patients we observed a reduced positivity in the 400-700 m.sec intervals during unpleasant pictures viewing.

Present findings may suggest that emotional impact related to affective images is preserved in HD, but it coexists with impairment of late cortical processing following unpleasant stimuli.

Keywords: Huntington's disease; Emotion experience; Affective pictures; Late cortical potential

Introduction

Huntington's disease (HD) is an autosomal dominant, fully penetrant, neurodegenerative disorder, characterized by a progressive neuronal loss in the striatum that results in a characteristic triad of symptoms, commonly including movement disorders (usually chorea), cognitive involvement (dementia) and psychiatric symptoms [1].

Recent studies confirm that psychiatric disorders, in particular Major Depression Disorder (MDD), anxiety, irritability, and apathy [2,3] frequently occur in patients with HD. Changes in personality and emotional impairment are usually reported during the progress of disease, and may even precede motor features onset [4].

Recognition of others' emotions was specially studied in HD patients, and a selective disgust recognition deficit was identified even in preclinical gene-carriers [5-7], associated to impairment in recognizing anger and fear [8]. The impaired recognition of various negative emotions, observed in both symptomatic and pre-symptomatic HD patients samples [9,10], was associated to striatal volume loss [11].

While the recognition of others' emotions was largely studied in HD, the subjective emotional impact under different affective stimuli received less attention. A recent study found a differential impairment in others' emotion recognition and subjective emotional involvement in HD, the former being reduced and the latter enhanced in respect to controls [12].

The International Affective Picture System (IAPS; Center for the Study of Emotion and Attention [CSEA-NIMH], 1995) is a standardized set of affective picture stimuli varying on the emotional dimensions of valence and arousal, for affect induction [13]. Although emotional expression is highly varied, many theorists view its motivational basis as having a much simpler, two-factor organization: a bipolar dimension of affective valence-from attraction and pleasure to aversion and displeasure, and a dimension of activation-from calm to aroused [13]. In addition, it is known that the vision of affective images induces a late positive potential (LPP, 400-700 ms) over central-parietal regions. This component may provide an objective measure of affective arousal [14], expressing a relatively high level of visual processing, in which sustained attention is allocated to motivationally relevant and emotionally salient cues, able to trigger arousal reactions [15]. Affective stimuli may therefore elicit not only attention and perceptual processes but also motor effects [16], which functions may be compromised in basal ganglia disorders [17]. This hypothesis is also supported by Functional Magnetic Resonance (FMRI) findings in regard to the activation of caudate under negative pictures, as a key element in social withdrawal [18,19]. Event related potentials may be an easy and cheap method to explore cognitive deficit in the course of HD [20], and additional information may come from EEG activity related to affective stimuli processing.

In order to go better inside the subjective emotional impact under standardized affective stimuli, we aimed to evaluate valence and arousal ratings and late EEG positive potential induced by IAPS pictures in early not demented HD patients compared to controls.

Methods

Cases

This study enrolled 16 consecutive out-patients (Table 1), affected by genetically confirmed HD, attending the Ambulatory for Huntington's chorea of the Neurological Science Department of Bari University. They were recruited during their first visit. The study was approved

CASES	AGE	SEX	DURATION (years)	CAG	UHDRSM	CHOREA	TFC	MMSE	BECKS
1	37	M	0,5	45	10	2	13	25	10
2	64	F	5	41	33	10	4	25	5
3	50	F	3	44	29	6	6	25	27
4	55	F	1	43	19	2	6	26	28
5	63	F	4	42	33	4	5	25	13
6	33	M	4	56	22	10	7	25	10
7	62	M	5	42	21	10	7	25	16
8	48	F	0,5	44	4	1	11	28	11
9	51	M	5	44	32	12	5	25	4
10	63	F	4	40	6	2	13	30	4
11	42	M	0,5	47	30	6	12	30	25
12	45	F	4	45	51	9	5	25	9
13	54	F	2	41	9	1	13	30	8
14	43	M	0,5	45	15	4	12	30	13
15	41	F	3	44	32	8	5	27	10
16	32	F	1	47	10	2	13	30	16
Controls	M 48.75 SD 9.8 (36-55) F=0.13 n.s.	9 F 7 M chi square 0.13 n.s.							

Table 1: Demographic and clinical features in Huntington's disease patients and controls. The results of one way ANOVA for age and chi square for sex between patients and controls are reported.
Duration: the time from the first diagnosis of HD, based on motor symptoms.
UHDRSM: Motor Section of Unified Huntington's Disease Rating Scale
TFC: Total Functional Capacity Scale
MMSE: Mini Mental State Examination
Becks: Beck Depression Inventory
M: Mean
SD: Standard Deviation
n.s. not significant

by the local Ethics Committee of Bari Policlinico General Hospital. The inclusion criteria in patients group was: genetically confirmed HD. Exclusion criteria were: cognitive impairment (Mini-Mental State Examination < 24) [21], less than 8 education years, and neuroleptics or other CNS acting drugs treatments. Patients underwent the motor section of Unified Huntington's Disease Rating Scales (UHDRSM) [22], the Total Functional Capacity Scale [23] and the Beck Depression Inventory [24] (Table 1).

Sixteen age and sex matched controls were also selected, on the basis of the exclusion of any neurological, psychiatric and general medical disorders, or CNS acting drugs use (Table 1).

Experimental procedure

After arriving at the laboratory, participants read and signed an informed consent and electrodes were attached. Patients and controls were informed on the characteristics of images and the meaning of valence and arousal rating they should assigned. They were then asked to pay attention to images, which were randomly presented. After the experimental session, participants were asked to rate all test pictures on two separate scales for valence and arousal ranging from 1 (very unpleasant, no arousal) to 9 (very pleasant, very strong arousal). Both rating scales were presented consecutively and simultaneously with the test picture on the monitor. Participants made their ratings by pressing one of the designated keys on the computer keyboard. We did not

perform valence and arousal ratings during the EEG, in order to avoid movement artifacts.

EEG recording

EEG was obtained by 32 scalp electrodes, by means of Micromed System Plus apparatus (Micromed, Mogliano Veneto, Italy; www.micromed-it.com) according to the international 10/20 system and the x–y–z coordinates provided by the ASA software (ASA version 4.8.1; ANT software Software, Enschede, Netherlands: http://www.ant-neuro.com). The reference electrode was placed on the nose, the ground electrode was in Fpz, and one electrode was placed above the right eyebrow for electrooculogram (EOG) recording. Impedance was kept at 10 kΩ or less. The EEG and EOG signals were digitized at 250 Hz.

Stimulation

Eighty-four color slides were chosen from the International Affective Picture System [25], depicting 28 unpleasant, 28 pleasant and 28 neutral objects or scenes, resulting in three different picture content categories[1]. Pictures were randomly presented on a 19-in computer screen. Each presentation lasted 1.5 s, and a black panel with a central white point was interposed between the images for 1.5 s. Subjects were initially invited to look at the central white point, and to pay attention to the different images. We avoided longer experimental procedure

[1]Criteria for the choice of the pictures were normative ratings (Lang, Bradley, & Cuthbert, 1997) on the dimensions of affective valence and arousal (on a scale ranging from 1 to 9, with low scores indicating low arousal and low pleasure and high scores indicating high arousal and high pleasure).Negative and positive pictures had comparable arousal ratings (6.13 vs. 6.09, respectively). Neutral pictures had low arousal (2.57) and intermediate valence ratings (5.09).
The slide numbers were as follows:
positive:
1440,2040,2030,2080,2154,2209,2260,2332,2360,2550,2660,4220,4235,4279,4290,4610,4626,4660,5626,5833,7270,7502,8080,8170,8185,8190,8370, 8501; neu tr al:1616,4520,5533,7000,7004,7052,7057,7058,7060,7100,7140,7150,7170,7207,7238,7242,7490,7493,7495,7504,7506,7546,7620,7820,7830,8160,8241, 8645;
negative:1050,1052,1111,1220,1274,10,1300,2053,2095,2120,2141,2205,2455,2703,2730,2799,2800,2811,3010,3120,3180,3215.3220,3530,9570,9250,9910,9921.).

employing more slides presentation, which would be stressful for our patients.

EEG analysis

EEG recordings were analyzed by an EEG expert who was blind to the experimental conditions. Trials contaminated by ocular or muscle artifacts were excluded from the analysis. An automatic artifact rejection system excluded all runs containing transient signals exceeding 65 uV on any recording channel, including the EOG, from the average. The ASA software, vers- 4.8.1 was employed to average at least 20 artifacts-free trials, corresponding to the vision of Pleasant (P), Unpleasant (U) and Neutral (N) pictures. For the averaging, only the EEG recorded during the subjectively evaluated pleasant pictures (rating 7-9), unpleasant (rating 1-4) and neutral (rating 5-6) were considered. Given that all the IAPS images, corresponding to the EEG trials selected for the averaging on the basis of the absence of artifacts, were judged by patients and controls in terms of their affective category, we were able to average 20-22 artifact-free trials for Pleasant (20.93 ± 0.74 in patients, 21.06 ± 0.82 in controls), Unpleasant (21 ± 0.79 in patients; 20.93 ± 0.89) and Neutral (20.87 ± 0.82 in patients; 21.18 ± 0.94 in controls) conditions. The considered time for LLP averaging was in the 1.5 sec following pictures onset, with 100 msec pre-stimulus analysis, 256 Hz sampling rate and 0.01-30 hz digital filter. In order to measure the LPP on the considered derivations, an automatic wave scoring detection, provided by ASA software, was employed, after a visual inspection. This program computed the maximal positivity in the 400-700 msec time range, after baseline correction. We selected this time analysis in accord to Pastor [14] and our previous studies [26].

Statistical Analysis

Arousal and valence rating

After the application of the Kolmogorov-Smirnov test to assure the normal distribution of data, the arousal and valence attributed to images, were compared between patients and controls, by means of two-ways ANOVA, considering main effect of diagnosis and affective category (P,U or N). The Bonferroni test was then performed in the single groups.

Late EEG potential

The Kolmogorov-Smirnov test was applied also to EEG data to assure the normal distribution of data. For LPP amplitude, we choose to run out repeated measures ANOVA separately on Fz, CZ and Pz derivations, considering the affective categories as the within and the diagnosis as the between factors, in order to better evaluate the possible EEG changes linked with different emotional impacts in the single group and the possible different behavior in the two groups. The Bonferroni test was then performed in the single groups.

In order to perform Statistical Probabilities Maps (SPMs), the results of t test between patients and controls, corrected for multiple comparisons, was applied to LPPs evoked by P,U and N pictures viewing by means of ASA software.
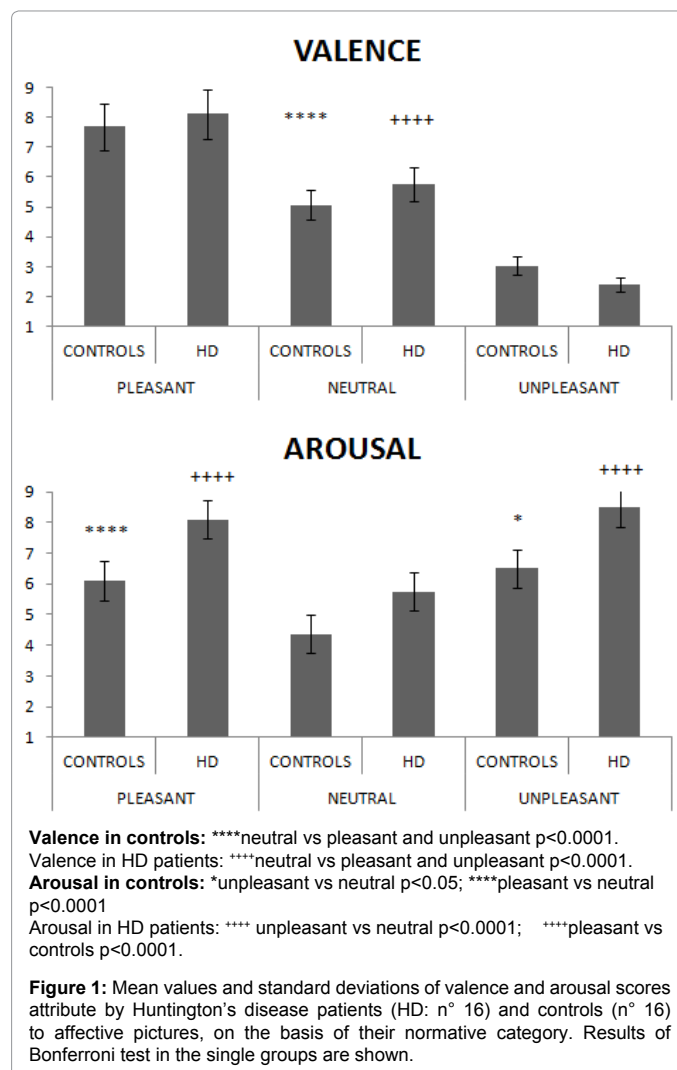
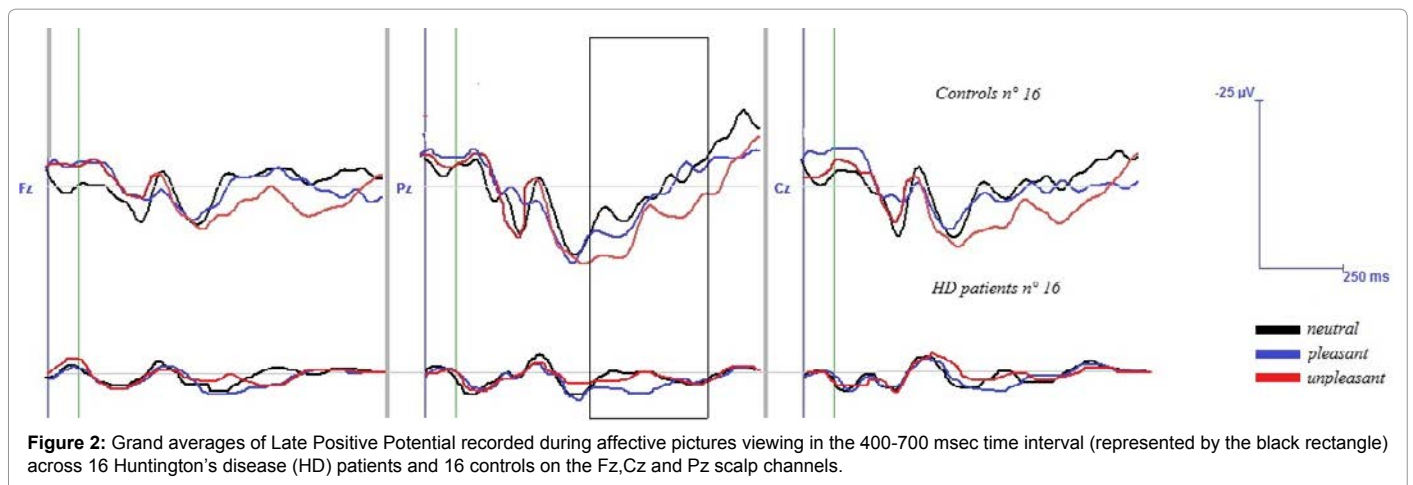### Correlation with clinical features

In HD patients, the valence and arousal scores and LPP amplitudes were correlated with main clinical features by means of Spearman correlation test. LPP amplitude was also correlated with arousal rating in both patients and control groups.

Results

Valence and arousal rating

Considering valence rating, results of two way ANOVA showed no significant effect for diagnosis (F=0.93 DF 1 p=0.33), a significant effect for affective category (F=392.32 DF 2 p<0.0001) and for the interaction diagnosis for affective category (F=8.82 DF 2 p<0.0001). Summarizing, HD patients attributed to unpleasant pictures lower and to pleasant pictures higher valence scores compared to controls (Figure 1). Considering arousal rating, results of two ways ANOVA showed a significant effect for diagnosis (F=135 DF 1 p<0.0001), and for affective category (F= 45.48 DF 2 p<0.0001), while the interaction diagnosis x affective category was not significant (F=1.77 DF 2 p= 0.17), so HD patients exhibited higher arousal for pictures viewing, independently from their affective content (Figure 1). Considering the single groups, we found that the valence rating of neutral pictures was significantly higher in respect to unpleasant and lower in respect to pleasant pictures in both HD patients and controls (Bonferroni test: N vs. P p<0.0001; N vs. U p<0.0001). Considering the arousal, there was no difference between pleasant and unpleasant conditions, while neutral pictures determined less arousal when compared to both pleasant and unpleasant ones in both groups (Bonferroni test in HD group, P vs. N:

Valence in controls: ****neutral vs pleasant and unpleasant p<0.0001.
Valence in HD patients: ++++neutral vs pleasant and unpleasant p<0.0001.
Arousal in controls: *unpleasant vs neutral p<0.05; ****pleasant vs neutral p<0.0001
Arousal in HD patients: ++++ unpleasant vs neutral p<0.0001; ++++pleasant vs controls p<0.0001.

Figure 1: Mean values and standard deviations of valence and arousal scores attribute by Huntington's disease patients (HD: n° 16) and controls (n° 16) to affective pictures, on the basis of their normative category. Results of Bonferroni test in the single groups are shown.

Figure 2: Grand averages of Late Positive Potential recorded during affective pictures viewing in the 400-700 msec time interval (represented by the black rectangle) across 16 Huntington's disease (HD) patients and 16 controls on the Fz,Cz and Pz scalp channels.

p<0.0001; U vs. N p<0.0001; in control group: P vs N p<0.0001; U vs N p=0.043) (Figure 1).

Late EEG potential (LPP)

The repeated measures ANOVA analysis showed no significant effect for the within factor pictures valence on the Fz derivation (F=2.34 DF 2 p=0.1) and a significant effect for Cz (F=4.23 DF 2 p=0.048) and Pz (F=4.43 DF 2 p=0.04) derivations. The between factor diagnosis had no significant effect either on Fz (F=2.31 DF 1 p=0.14), or Cz (F=2.15 DF 1 p=0.15) and Pz (F=2.34 DF 1 p=0.14). There was a significant effect for the interaction valence for diagnosis on the Cz (F=4.23 DF 1 p=0.048) and Pz (F 4.43 DF 1 p=0.04) derivations, while this was not significant on Fz (F=2.34 DF 1 p=0.13) (Figure 2).

In the single groups, the Bonferroni test showed a significant lower amplitude of LPP recorded over Pz in neutral condition compared to the pleasant one (controls: p=0.023: patients=0.048). In normal group, the comparison between neutral and unpleasant conditions was also significant (p=0.012), while it was not significant in HD patients (p=0.12). Summarizing, we observed main effect of pictures valence on Cz and Pz derivations, with a different behavior in HD and control group, for a lack of significant LPP amplitude changes in U vs. N conditions in patients group.

The SPMs, revealed reduced amplitude of LPP recorded during unpleasant pictures viewing on centro-temporal-parietal regions in HD patients compared to controls (Figure 3).

The mean valence rating attributed by each patient to pleasant and unpleasant pictures was significantly correlated with Beck Depression Inventory scores (Results of Spearman correlation test: valence rating attributed to Pleasant pictures vs. Beck Depression Scores: 0.819 p=0.002; Unpleasant Pictures: -0.736 p=0.003), while the arousal levels did not display any correlation with clinical features.

In normal subjects the arousal level was correlated with LPP amplitude (Pz derivation) for both pleasant (Spearman test 0.51 p=0.041) and unpleasant pictures (0.72 p=0.003), while in HD this correlation was absent for unpleasant pictures (0.12 p=0.13) and present for the pleasant condition (0.52 p=0.046).

No significant correlation was found between the LPP amplitude recorded in unpleasant condition and main clinical features, as age, duration of illness, UHDRSM, Chorea, TFC and Becks Depression Inventory.

Discussion

Valence and arousal rating

Our results indicate that HD patients experience subjective affective impact for both pleasant and unpleasant pictures more intensively than controls. The coherence of the subjective rating with the affective categories of images we observed in our HD patients could be compatible with the mild cognitive impairment they presented. In fact, patients with mild dementia could correctly respond to affective pictures [27]. Considering the deficit in others' negative emotion recognition generally observed in HD patients [9], we can argue that emotion recognition and subjective emotion experience processing are differently impaired in HD. The affective impact of both pleasant and unpleasant pictures, were correlated to depression severity in HD patients. However, the affective and arousal rating expressed by HD patients did not correspond to that generally described in major depressed patients, who exhibited reduced emotional involvement by pleasant pictures and by anhedonia [28] and high affective impact only under sad pictures [29-31]. Our HD patients were not homogenous in regard to depressive symptoms, so an enlargement of the studied group may contribute to confirm the role of depression in the subjective impact toward both positive and negative affective stimuli.

LPP amplitude

At the best of our knowledge, this is the first study on EEG correlates of affective images in HD, while few studies evaluated valence and arousal ratings in the same patients [12]. The late positivity we evaluated in the 400-700 msec range corresponds in healthy controls to the cortical processing following the recognition and discrimination of pictures content, expressed in the 200-400 range, and it is subtended by a specific involvement of brain areas sustaining attentive processing toward motivational significance, emotional stimuli [32]. In our healthy controls, both pleasant and unpleasant pictures induced a positivity in the time range, according to the high arousal they induced: however, the unpleasant pictures viewing evoked a positive potential more diffused on the central regions, suggesting an extensive cortical recruitment toward images with negative emotional content. The EEG response in HD consisted of a mild positivity during pleasant pictures viewing, which was correlated with arousal, and an absence of response for unpleasant pictures, despite the high arousal expressed by patients. So far the correlation between LPP amplitude and arousal, which was present for controls in unpleasant and pleasant condition, was lost in HD only in regard to negative pictures.
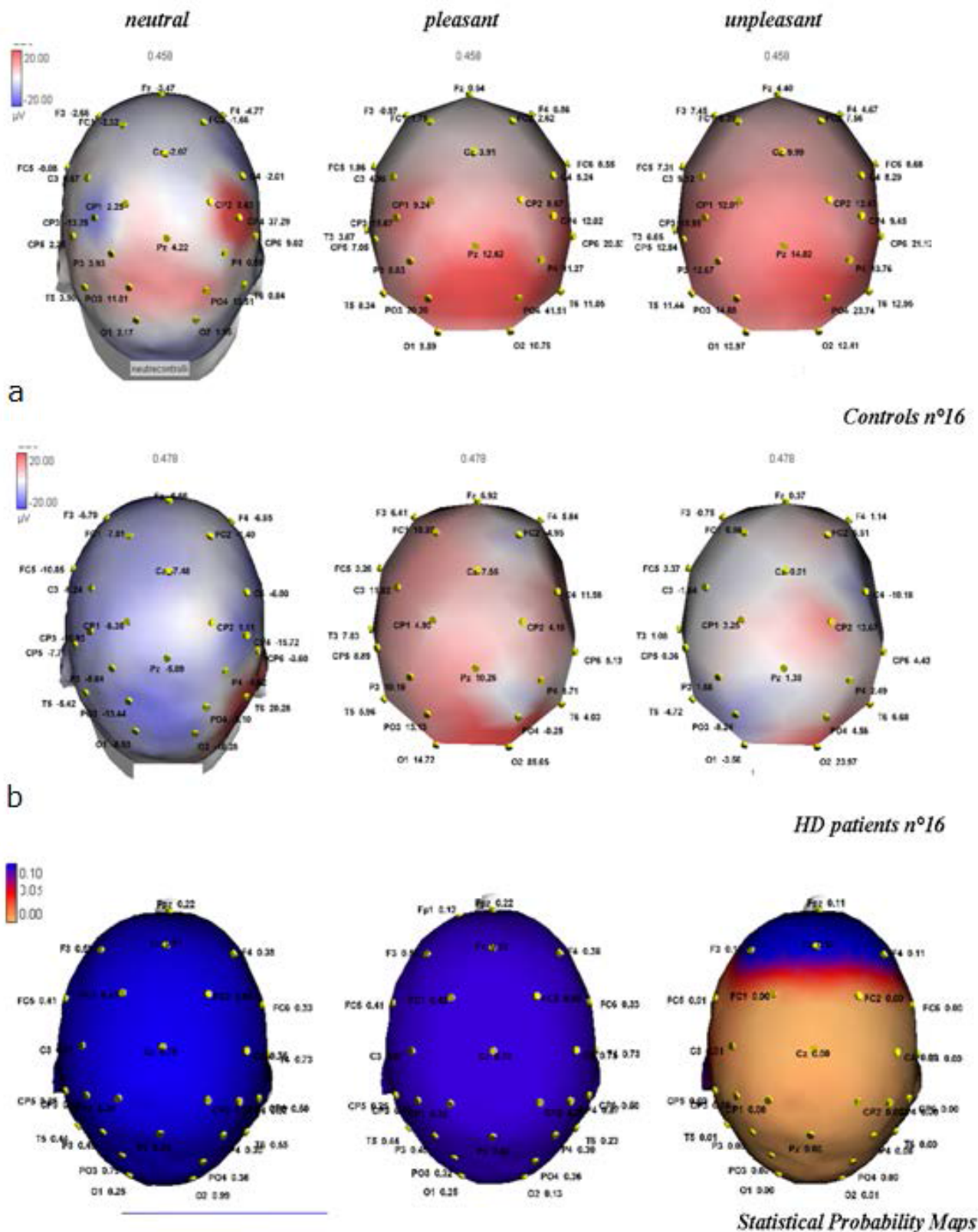
Figure 3: Amplitude maps of the grand average of Late Positive Potential recorded during affective picture viewing in 16 patients (a) and 16 controls (b). At the bottom, the statistical probability maps report the results of the application of Student's t test, corrected for multiple comparisons, between patients and control group. The red color signs the significance threshold at 0.05 p level; the yellow color p levels below 0.01, the blue color represent no significant result. HD patients show a significantly reduced LPP during unpleasant pictures viewing on the centro-temporal-parietal derivations.

Findings from EEG analyses of emotional pictures viewing suggest that the exposition to emotionally engaging stimuli is associated with the activation of visual cortex and the cortical regions underlying attention modulation and preparation for action, in temporal (left middle/inferior temporal gyrus), parietal (bilateral parietal lobules), and frontal (left middle/inferior frontal gyrus) structures [33,34], as also confirmed by the results of the topographic analysis obtained in our healthy volunteers. The Statistical Probability Maps confirmed that in HD patients there was a reduced activation of cortical zones which were recruited in healthy controls during the exposition to unpleasant pictures. The dissociation between the subjective expression of negative emotional impact and EEG related changes may be due to different reasons. The LPP expresses the processing of sustained attention against high relevant stimuli, preparing to motor response [32]. HD patients may be emotionally involved in negative pictures, but unable to activate cortical networks elaborating relevant visual stimuli in order to maintain attention and prepare motor reaction. In the case of neutral and pleasant pictures, the related cortical events appeared only slightly and not significantly reduced, so a deficit in late attentive processing of visual stimuli may emerge in HD patients when an avoidance behavior should be prepared. Basal ganglia dysfunction may involve the multiple circuits that connect them with the rest of the brain for a wide variety of functions including affective processes [35]. In fact in healthy volunteers, both positive and negative stimuli determining rewarding and aversive processing induced a clear activation of striatal nuclei. The striatum is the first station of the main subcortical output system of the emotional brain [36] and it is able to activate motor programs (some of them innate) such as those associated with emotional expressions or withdrawal behaviors [37]. In particular the caudate nucleus seemed sensitive to negative visual stimuli in a normal sample [19]. The striatal dysfunction characterizing HD patients [4], may cause an altered activation of cortical areas subtending motor response preparation under unpleasant emotional processing. A recent study reported reduced LPP amplitude specifically when viewing unpleasant, compared to pleasant, pictures in non demented Parkinson's disease patients, consistent with specific difference in aversive processing between patients and healthy controls [17]. A dysfunction of cortical response to unpleasant pictures and the impairment in aversive processing may be related to the abnormal basal ganglia modulation, more than to the psychiatric features characterizing HD patients. In fact, depression was not correlated to LPP amplitude, but only to the valence attributed to positive and negative pictures. In depressed patients, reduced amplitude of the late positive component evoked under both positive and negative trials was found in respect to healthy controls [38]. In a group of adolescents affected by mental health problems, a larger sustained late positive potential in response to targets that followed negative emotional pictures compared to targets that followed neutral pictures was observed [39].

Conclusions

Our study suggests that in HD patients there is a preservation of emotion recognition with an impairment of late cortical processing subtending sustained attention toward unpleasant pictures. Considering previous studies on a reduction of the cortical response related to painful stimuli, without abnormalities of subjective pain rating [40] and higher threshold for the motor reaction against pain [41], impairment in cortical processing toward negative stimuli potentially related to motor aversive behavior may be supposed in genetically confirmed patients. The significance of our results is limited by several factors, first of all the small HD series and the lack of pre-symptomatic

individuals, then the weakness of visual and automatic analysis for movement-related artifacts exclusion, as well as the coexistence of mild cognitive impairment, even with high Mini Mental State scores, and the scarce homogeneity of patients in regard to depressive symptoms. The absence of central nervous system acting drugs therapies was an advantage of the present study, though it limited the patient's inclusion. On the other hand, multicenter studies on event related potentials, are also difficult to be conducted, for the scarce homogeneity of different laboratories, so in our opinion such results may be taken into account, adding something to the knowledge of emotive status of HD patients.

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