Does Parkinson’s disease lead to alterations in the facial expression of pain?

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1. Introduction

A considerable percentage (50%–90%) of patients with Parkinson’s disease (PD) suffer from pain which can be classified in pain related to motor problems or central pain [2,7,44,19,10]. The latter might be due to the PD-specific dopaminergic deficiencies and especially occurs in the Off-phase [15,7,17,41,35]. Adequate pain communication is crucial for PD patients when presenting with pain to inform their social environment, trigger empathy and receive sufficient pain treatment [8,45,25].

An important tool to communicate pain is the facial expression [20, 38]. Evidence suggests that characteristic facial movements (e.g. eye-narrowing, movements of eyebrows and the upper lip) are involved in the expression of pain [28,26,36]. Since hypomimia which refers to a reduced level of facial expressiveness is a common sign in PD [23], the facial expression of pain might be altered in PD patients, as it has already been shown for classical emotions [22,42,43].

The alterations in the facial expression of pain in PD might derive from PD induced disturbances in the activation of the extrapyramidal motor system. Due to a loss of the dopaminergic neurons in the substantia nigra, the motor basal ganglia loops get imbalanced which leads to attenuated activation of the facial nuclei in the brainstem [43, 46]. In line with this, the basal ganglia have also been shown to be involved in the regulation of the facial expression of pain in healthy participants [27].

Next to (more quantitative) changes in the degree of facial expression of pain, it is possible that PD might also lead to (more qualitative) changes with regard to the types of facial movements being displayed. We consider that hypomimia in PD might not be obvious in all facial muscles to the same extent. There might be facial areas in which the motor control is preserved while other areas are affected. Therefore, PD patients might still be in control of certain elements of the facial language in response to pain while other elements are no longer accessible.

Furthermore, it is almost compelling to test whether the facial expression of pain normalizes in the On along with the motor symptoms. It is conceivable that PD patients have adjusted to not using the facial expression for pain communication like patients in other non-use syndromes and still show less facial expression of pain despite reestablished motor functions.

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The aim of the present study was to comprehensively explore the facial expression of pain in PD patients. Therefore, facial expressions of PD patients and matched controls in response to phasic heat-pain were recorded in the Off and On and were analyzed using the Facial Action Coding System (FACS). The FACS is seen as the gold standard when analyzing and quantifying facial expressions and has already been successfully used in emotional PD research (for example [43]). In addition to phasic heat stimuli we used a temporal summation procedure in order to study the facial expression of pain under short-term and long-term stimulus conditions.

We hypothesize that (i) the pain-specific facial activity is reduced in PD patients compared to controls, especially in the Off. Moreover, (ii) specific elements of the facial language in response to pain might also be altered in PD patients (e.g. specific facial actions might be more or less affected by hypomimia).

2. Methods

2.1. Subjects

Twenty-three patients with idiopathic Parkinson syndrome (ICD-10: G20) (3 female, mean age = 67.1, SD = ±9.9, mean disease duration = 8.1 years, SD = ±5.7 years) and 23 age and sex matched controls (3 female, mean age = 68.2, SD = ±7.8 years) participated in the study. PD patients were outpatients addressed via regional self-help groups. Inclusion criteria for patients were (1) diagnosis of idiopathic PD (disease duration 1–25 years), which affected both body sides to a similar degree (no hemi-PD), (2) therapy with dopaminergic medication (levodopa and/or DA agonists) and (3) significant relief of PD symptoms one hour after DA medication intake, based on self-report. PD patients were excluded from the study if they suffered from (1) other neurological and psychiatric diseases, especially depression (PD patients were interviewed and psychiatric history was examined) and/or (2) further severe physical disorders (for example acute cardiovascular diseases) and/or (3) severe pain which was not related to PD and/or (4) indications of dementia (mini-mental status examination (MMSE) < 24). The control group was recruited via advertisements in local newspapers. Control subjects had to meet the same criteria like the PD patients – except the diagnosis of PD. Moreover, healthy subjects with a history of chronic or central pain, as well as acute pain on the test day were not included.

The study was a cooperation of the Department of Neurology, Sozialstiftung Bamberg, and the Department of Physiological Psychology, University of Bamberg. The Department of Neurology was in charge of the medical, especially neurological diagnostics while the pain testing was conducted in the Department of Physiological Psychology.

All sessions took place in the morning. PD patients were asked to discontinue their dopaminergic medication for the 14–15 h leading up to the investigation. If treated with prolonged released medications, participants did not take these medications for the 24 h prior to the investigation in order to at least reduce retarded pharmacological activity. Likewise, other PD medications, like COMT or MAO inhibitors, DA uptake inhibitors or NMDA receptor blockers were also discontinued for 24 h.

On the test day between 8 and 9 am, PD patients in the Off were examined by experienced neurologists (PR or CM, who are chief or senior physicians) in the Department of Neurology, Sozialstiftung Bamberg, for inclusion and exclusion criteria as well as for the severity of the PD. For this purpose the 3rd scale (motor examination) of the Unified Parkinson’s disease Rating Scale (UPDRS) was used. Afterwards, the actual experiment was conducted in the Department of Physiological Psychology, University of Bamberg, starting between 9 and 10 am. The study protocol was approved by the ethics committee of the University of Erlangen. All participants gave their written informed consent. For their participation all participants received 60 Euros and travel expenses.

2.2. Apparatus and stimuli

Heat stimuli were generated and applied by a contact-heat evoked potential stimulator (CHEPS, Medoc, Israel) with a round 27 mm-diameter surface thermode, which contains a heating-thermofoil covered by thermoconductive plastic. Additionally, a pair of thermocouples is embedded in the lamination which provides an estimation of the skin temperature at the stimulated area.

Facial recording during heat stimulation was accomplished by a video camera (Sony handycam, 2 megapixels resolution). For coding of the facial data a Software designed for the analysis of observational data (ObserverXT; Noldus Information Technology, Wageningen, Netherlands) was used.

2.3. General procedure

In order to test the facial expression of pain both in the Off and On, the experimental session consisted of two identical blocks. Each block consisted of the determination of the heat-pain threshold and the subsequent pain test in which facial expressions of pain were supposed to be evoked and recorded. After the first block, all participants took a one-hour break during which no pain measurements were accomplished. At the beginning of the break, PD patients took their individual dopaminergic medication and also completed a set of questionnaires (cognitive functioning, non-motor PD symptoms in the last 4 weeks, see below).

Prior to the second experimental block patients were asked to rate their motor performance. The On-phase was reached during the first hour after medication intake, which is good practice in comparable studies investigating pain processing in PD patients both in the Off and On [41,17,7,18,41]. In addition, PD patients were asked to estimate whether the severity of the potentially persisting PD symptoms after the medication intake was of the common degree. After the break, PD patients and controls completed the second experimental block. For simplifying the terminology, “Off” always refers to the first test block in PD patients and in controls, while “On” refers to the second block both in PD patients and in controls throughout the paper (in the latter group of course without pharmacological treatment). Duration of the experimental session was about 2.5 h (45 min for each block and 1 h break). Participants were carefully familiarized with the methods. For the measurements participants were comfortably seated in a chair.

2.4. Threshold determination

Participants’ heat-pain threshold was determined using the method of limits. Site of stimulation was the volar site of the left forearm, 2–4 cm beneath the cubital joint, where the contact thermode was held by an experimenter. For assessment of the heat-pain threshold, the thermode temperature increased from a baseline of 35 °C at a rate of 0.7 °C/s until the participants felt a first pain sensation and responded by pressing a button. Each time they pressed the button, the temperature returned to baseline temperature, which was held constant until the next trial. Overall, there were 8 trials and pain thresholds were determined as the average of the last 5 trials.

The determination of the heat-pain threshold served two purposes. First, we were interested in differences in the pain sensitivity between PD patients and controls both in the Off and On. Second, this allowed us to tailor supra-threshold painful stimulation to the individual pain sensitivity. By doing so, we can exclude that potential differences in facial expressions of pain between both groups are simply due to differences in the perceived pain intensity between groups. Additionally, since the individual pain sensitivity is considered in each participant, a too intensive pain stimulation is prevented which minimizes the risk for tissue damage.
2.5. Supra-threshold stimulation and assessment of the facial expression of pain

After threshold determination, facial expressions during painful stimulation were assessed. We did this by applying (i) phasic heat-pain as well as (ii) a temporal summation protocol to study the facial expression of pain under short-term and long-term stimulus conditions. Stimulations were always applied to the volar site of the left forearm while the thermode was held by an experimenter and baseline temperature set to 35 °C.

(i) Phasic heat-pain: participants were exposed to 2 phasic heat stimuli (plateau duration of 5 s, rate of rise/fall: 10 °C/s). First a sub-threshold non-painful heat stimulus (−3 °C below pain threshold) was applied in order to familiarize subjects to the stimulation. After an inter-stimulus interval (ISI) of one minute, a supra-threshold painful heat stimulus (+3 °C above pain threshold) was administered. Both stimuli were announced by an experimenter 10 s before onset. After the offset of the stimulus the participants were asked to rate the painfulness of their sensation using an 11-points numerical pain rating scale (NRS) (0 = “no pain at all” – 10 = “highest pain imaginable”).

(ii) One minute after the second phasic heat stimulus the temporal summation procedure started. Temporal summation was tested by comparing sensations evoked by single pulses of heat stimulation to sensations evoked by a series of 10 pulses (only the last pulse was rated), which were applied with a repetition frequency of 0.5 Hz. The series of 10 pulses was always delivered 60 s after the single pulse. Temperature of stimuli in the summation procedure was 3 °C above the individual pain threshold (rate of rise/fall 10 °C/s). The stimuli were saw-tooth shaped. The three runs of single pulses and pulse series were separated by intervals of 60 s.

Like the phasic stimuli, both the single pulses and the series of pulses were announced by an experimenter 10 s before onset. After the offset of the stimuli/stimulus series the participants were asked to rate the painfulness of their sensation using an 11-points numerical pain rating scale (NRS) (0 = “no pain at all” – 10 = “highest pain imaginable”). Regarding the series of 10 pulses, participants were instructed only to rate the painfulness of the 10th pulse. The difference between the rating of the 10th pulse in the series and the single pulse indicates the temporal summation of pain which was averaged over the three summation trials. Since the rating of the single pulse was always subtracted from the rating of the 10th pulse of the series, positive summation scores indicate a temporal summation of subjective pain.

2.6. FACS coding

During heat stimulation, the face of the participants was videotaped. The camera was located approximately 2.0 m in front of the participant. In order to enable offline analyzing of the videos and ensuring that the stimulus onset was clearly marked for the FACS coder, a LED visible to the camera, but not to the participant, was lit when either the target temperature was reached (supra-threshold phasic heat stimulus) or alternatively when the temperature deviated from the baseline (summation paradigm). When the stimulus series were presented, only the first of the ten ensuing pulses was marked by the LED.

For the purpose of ensuring that the face always is upright and in a frontal view during stimulation, subjects were asked to look at a neutral picture on the wall in front of them throughout the recording session. Subjects were also instructed not to talk during thermal stimulation. We quantified facial responses using the Facial Action Coding System (FACS, Ekman and Friesen, 1978), a fine-grained anatomically based system that is considered the gold standard when analyzing facial expressions. The FACS distinguishes 44 different Action Units (AUs) produced by a single muscle or a combination of muscles. The intensity (5-point scale) and frequency of the AUs were rated offline. One experimenter (JAP), trained by a certified FACS coder (MK), qualified by passing an examination given by the developers of the system, accomplished the coding (intrarater reliability with MK calculated using the Ekman–Friesen formula was 0.84 which indicates a good accordance of the two coders).

Facial activity during the plateau of the phasic heat stimulus and during the application of the series of stimuli in the summation procedure was coded. Since we aimed to investigate the facial expression of pain in PD patients in response to a wide range of pain stimulus configurations we were not interested in differences between phasic pain and temporal summation. Thus, we combined facial responses across painful stimulation (phasic heat-pain and temporal summation). In order to subject only pain-indicative AUs to further analyses, we selected those AUs that occurred in at least 10% of the painful segments recorded (Table 3) in the control group (Off and On) which is seen as the non-pathological reference. Intensity scores of the pain-indicative AUs were kept for further analyses.

2.7. Neurological examination, questionnaires and self-report of pain

PD patients’ motor symptoms were quantified by experienced neurologists (PR and CM) using the third scale of the Unified Parkinson disease Rating Scale (UPDRS). Additionally, the Mini-Mental Status Examination (MMSE) [16] and the German version of the Non-Motor Symptoms Questionnaire for PD patients (NMSQuest) (self-report) were applied [9,24]. Additionally, PD patients rated their present clinical pain experience and their pain experience during the last weeks.

2.7.1. 3rd scale of the unified Parkinson disease rating scale (UPDRS): motor examination

The 3rd section of the UPDRS is a common tool to quantify motor symptoms in PD patients. Typical motor symptoms like rigidity, hypomimia, abnormalities regarding speech or tremor are rated on a scale between 0 and 108. Higher scores indicate increased symptom load [39].

2.7.2. Non-motor symptoms questionnaire (NMSQuest)

In order ensure the representativeness of our PD sample regarding non-motor symptoms as well, the NMSQuest was completed by the patients. The NMSQuest consists of 30 questions dealing with non-motor symptoms which might occur in PD, like sexual dysfunctions, psychiatric symptoms or sleeping problems. Each question is answered with “yes” or “no”. One point is scored for each positive response (“yes”) resulting in a score ranging from 0 to 30 [9,24].

2.7.3. Self-rating of pain

Participants gave information about their PD related pain. In order to support PD patients to differentiate between PD related pain and pain stemming from further pathologies, they were instructed to consider only those pain symptoms which fit the following two criteria: First, pain symptoms which may be some kind of “unexplainable”, i.e. which cannot be attributed to another known somatic pathology. Second, pain which has been noticed by the patient to improve after dopaminergic medication. PD patients had to rate their highest and lowest pain intensity during the last 4 weeks and their current pain intensity using the already familiar 11 points NRS (0 = “no pain”, 10 = “highest pain imaginable”).

Footnote

1 Since we intended to study the facial responses to summated pain for the first time we were not able to apply the well-established protocol of our lab for selecting the pain-relevant AUs [27]. This protocol was developed for phasic heat stimuli and combines a 5% criterion with an effect size criterion of the difference between AU frequencies in response to non-painful and AU frequencies in response to painful stimulation. Since the effect size criterion cannot be realized in our study, we chose a 10% criterion which also leads to a quite similar sample of AUs in our healthy controls as the ones in earlier studies (see below).
2.8. Statistical analysis

2.8.1. Heat-pain thresholds, rating data and sample characteristics

Since the pain thresholds as well as the rating data were not normally distributed (Kolmogorov–Smirnov-test: all p’s < .01) non-parametric tests (Mann–Whitney-U-tests and Wilcoxon-rank-tests) were used for between-group (PD vs. controls) and within-group (PD Off vs. PD On) comparisons. In addition, between-subject t-tests were used to test potential between-group differences in the sample characteristics.

2.8.2. Facial activity

According to our hypotheses, facial data were analyzed regarding (1) an overall quantitative reduction in the facial expression of pain and (2) more qualitative, changes in the facial expression of pain augmenting or diminishing only certain AUs in PD patients relative to the healthy controls. The latter was investigated via testing differences in the frequencies and the distribution of the single pain-indicative AUs.

(1) Overall (quantitative) changes in the degree of facial expression of pain

For the purpose of generating a measurement for the overall facial expression of pain we formed pain-indicative composite scores. This was done by first multiplying mean intensity and frequency values for each AU reaching the 10% criterion. Then, these product terms were averaged to form a composite score. Composite scores were computed for the controls as well as for the PD patients separately in the Off and On. Since the facial data were not normally distributed (Kolmogorov–Smirnov-test: all p’s < .001) Mann–Whitney-U-tests and a Wilcoxon-rank-test were used for between-group (PD vs. controls) and within-group comparisons (PD Off vs. PD On).

(2) AU specific (qualitative) changes in the facial expression of pain

(a) In order to test if all pain-indicative AUs are equally affected by hypomimia in PD patients, Mann–Whitney-U-tests were computed comparing the frequencies of each AU reaching the 10% criterion between PD patients and controls both in the Off and On.

(b) We further aimed to investigate differences in the makeup of the single facial actions indicating pain between PD patients and controls, i.e. if the percentages of the pain-indicative AUs were comparable in both groups. For this purpose, the frequency distribution of the pain-indicative AUs was compared between groups both in the Off and On. \( \chi^2 \)-tests were computed in which the distribution of AU frequencies in controls in the Off (On) served as expected distribution while the distribution of AU frequencies in PD patients in the Off (On) served as observed distribution. This was done because we considered the distribution of AU frequencies in the controls as “normal, non-pathological”. Since the total frequencies of shown AUs might differ between PD patients and controls due to overall hypomimia, the relative frequencies (see F1 in Fig. 1 for the formula) of the relevant AUs were used in this analysis.

(c) Additionally, we were interested which AUs are dominant (relatively most prevalent) in the facial response to pain in each group and each condition. Therefor \( \chi^2 \)-tests were used which test deviations of the observed AU frequency distribution from the equal distribution of AU frequencies for both groups in each condition (PD Off, PD On, CG Off, CG On).

In the case of a significant \( \chi^2 \)-test which is an omnibus test checking for overall differences in distributions the standardized residuals (see F2 and F3 in Fig. 1 for the formulas) were used for identifying which AUs contribute most to the deviation of the observed from the expected distribution (post-hoc test).

For all tests, significance level was set to \( \alpha = 5\% \). Generally, we used two-tailed tests. If we had directed hypotheses we used one-tailed tests which are clearly denoted. Statistical Package for the Social Sciences version 20 (IBM SPSS, Chicago, IL, USA) was used for all analyses.

3. Results

3.1. Sample characteristics

Table 1 provides an overview over the sample characteristics. Mean age of the 23 PD patients (3 female) was 67.1 years (SD = 9.90), mean age of the 23 controls was 68.2 years (SD = 7.78). The difference regarding age between the groups was not significant (t < 1). Additionally, groups did not differ in height and weight (all t’s < 1). Mean disease...
duration of PD patients was 8.1 years (SD = 5.65) indicating a PD sample in rather earlier disease stages. In the PD patients, the mean UPDRS score was 18.4 (SD = 9.06) and the mean NMSQuest score was 8.82 (SD = 4.47), which both are in line with the assumption of rather weak symptoms [34,9].

Five PD patients took dopaminergic agonists alone, one took levodopa supplements alone and 17 took a combination of both. In addition, 6 patients were treated with dopamine reuptake inhibitors, 3 with MAO inhibitors and 2 with COMT inhibitors, while 5 PD patients were treated with NMDA receptor blockers. Sixteen of the patients reported clinical pain which was related to PD (musculoskeletal or central) while seven did not report pain. The clinical pain occurring in patients was always responsive to dopaminergic treatment.

### 3.2. Heat-pain thresholds, pain ratings and temporal summation score

Table 2 provides an overview over the heat-pain thresholds, the ratings of the two phasic heat stimuli (sub- and supra-threshold) and the summation scores for both groups in the Off and On.

We found heat-pain thresholds to be significantly reduced in PD patients compared to controls only in the Off, \( U = 1.80, p = .036 \) (one-tailed), but not in the On, \( U = 1.46, p = .073 \) (one-tailed) using Mann–Whitney-U-tests. In addition, the Wilcoxon-Rank test revealed a significant increase of the heat-pain threshold in PD patients in the Off relative to the On, \( U = 1.908, p = .028 \) (one-tailed). Fig. 2 illustrates the results of this analysis.

Table 3 provides an overview over the absolute frequencies and percentages of AUs, which were considered for further analyses: AU1_2 (raised eyebrows), AU4 (furrowed brows), AU6_7 (narrowed eyes), AU9_10 (wrinkled nose and raise of the upper lip), AU14 (dimpler), AU17 (chin raiser), AU18 (lip pucker) and AU25_26_27 (opened mouth). All met the inclusion criterion of >10% occurrence frequency in both groups. We have to point out, that AU43 (eye closure) reached the 10% criterion in PD patients while it did not in the control group. Since we consider the AU frequencies of the control group as “normal” reference, AU43 was dropped.

#### 3.3.1. Overall (quantitative) changes in the degree of facial expression of pain

When comparing single AUs between groups, we found reduced frequencies both in the Off and On for AU6_7 (\( U = 1.684, p = .046; \) \( U = 2.084, p = .019 \)), AU17 (\( U = 3.652, p < .001; \) \( U = 2.677, p = .004 \)) and AU18 (\( U = 1.646, p = .05; \) \( U = 2.630, p = .005 \)) in PD patients compared to controls (one-tailed Mann–Whitney-U-tests). In addition, AU9_10 (\( U = 2.097, p = .018 \)) was reduced only in the Off and AU1_2 (\( U = 1.708, p = .044 \)) was reduced only in the On in PD patients compared to controls. Fig. 3 illustrates the results of this analysis.

#### 3.3.2. AU specific (qualitative) changes in the facial expression of pain

When considering single AUs between groups, we found reduced frequencies both in the Off and On for AU6_7 (\( U = 1.684, p = .046; \) \( U = 2.084, p = .019 \)), AU17 (\( U = 3.652, p < .001; \) \( U = 2.677, p = .004 \)) and AU18 (\( U = 1.646, p = .05; \) \( U = 2.630, p = .005 \)) in PD patients compared to controls (one-tailed Mann–Whitney-U-tests). In addition, AU9_10 (\( U = 2.097, p = .018 \)) was reduced only in the Off and AU1_2 (\( U = 1.708, p = .044 \)) was reduced only in the On in PD patients compared to controls. Fig. 3 illustrates the results of this analysis.

The relative frequencies of the relevant AUs were compared between groups by means of \( \chi^2 \)-tests (Table 3) to determine group-specific changes in the AU distribution.

The \( \chi^2 \)-test revealed significant between-group differences in the Off, \( X^2(7) = 62.54; p < .001 \), and On, \( X^2(7) = 40.55, p < .001 \). Table 3 provides an overview over the expected and observed frequencies as well as the standardized residuals. Both in the Off and On, the massively increased relative frequency of AU25_26_27 in PD patients provides the biggest contribution to the between-group deviations, stand. res. (Off) = 7.41 and stand. res. (On) = 5.90. This means that despite of a totally reduced facial expression of pain, the PD patients exhibited relatively much more mouth opening than the healthy control subjects.

The within-group and within-condition \( \chi^2 \)-tests (to investigate which AU is the most dominant facial response in each group and each condition in contrast to the assumption that all AUs occur always with equal frequencies) revealed significant deviations from the equal distributions of the AU frequencies in both groups in each of the 2 conditions, i.e. controls in the Off, \( X^2(7) = 43.22, p < .001 \), controls in the On, \( X^2(7) = 57.91, p < .001 \), PD patients in the Off, \( X^2(7) = 48.93, p < .001 \) and PD patients in the On, \( X^2(7) = 89.93, p < .001 \). In PD patients AU25_26_27 (mouth opening) occurred clearly more frequently than expected both in the Off and On, stand. res. (Off) = 4.85 and stand. res. (On) = 7.55, while AU6_7 (narrowed eyes) was the most outstanding AU in controls in both phases, stand. res. = 3.93 (Off) and stand. res. = 5.74 (On). In contrast, the frequency of AU25_26_27 was significantly lower than expected in controls, stand. res. (Off) = −3.33 and stand. res. (On) = −1.22. Table 3 provides an overview over the standardized residuals. Furthermore, Fig. 4 illustrates the results of the distribution analyses.

### 4. Summary

In summary, PD patients and controls showed the same pain-indicative facial movements in response to pain (except closed eyes
which was pain-indicative only in PD patients) both in the Off and On. Yet, the overall frequency and intensity, with which these facial movements were displayed, was reduced in PD patients (general hypomimia) relative to the controls in the Off, a finding which was less pronounced in the On. Interestingly, the pain-indicative facial movements were not affected by hypomimia to the same extent (qualitative changes). While the occurrence of furrowed brows (AU4) and the movements of the upper lip (AU9_10) was hardly reduced, narrowed eyes (AU6_7) – which was the most prominent facial movement in the controls – occurred substantially less frequently in PD patients both in the Off and On (see Fig. 3). Instead, mouth opening (AU25_26_27), which was the only facial action occurring

Table 3

<table>
<thead>
<tr>
<th>Action Unit (AUs)</th>
<th>CG Off</th>
<th>CG On</th>
<th>PD Off</th>
<th>PD On</th>
<th>Stand. res. between</th>
<th>Stand. res. within</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU1_2 (raised eyebrows)</td>
<td>40</td>
<td>10.13</td>
<td>32</td>
<td>18.88</td>
<td>6.18</td>
<td>-1.36 -0.46</td>
</tr>
<tr>
<td>AU4 (furrowed brows)</td>
<td>36.02</td>
<td>14.68</td>
<td>64</td>
<td>39.75</td>
<td>12.36</td>
<td>1.22 -0.10 -0.54 -0.33</td>
</tr>
<tr>
<td>AU6_7 (narrowed eyes)</td>
<td>77</td>
<td>19.49</td>
<td>111</td>
<td>68.94</td>
<td>21.43</td>
<td>1.91 5.74</td>
</tr>
<tr>
<td>AU8_10 (wrinkled nose and raise of the upperlip)</td>
<td>61</td>
<td>15.44</td>
<td>76</td>
<td>47.20</td>
<td>14.67</td>
<td>1.65 1.39 -0.32 -0.51</td>
</tr>
<tr>
<td>AU14 (dimpler)</td>
<td>36.65</td>
<td>14.94</td>
<td>72</td>
<td>44.72</td>
<td>13.90</td>
<td>1.37 0.89 1.40 0.04</td>
</tr>
<tr>
<td>AU17 (chin raiser)</td>
<td>45</td>
<td>11.39</td>
<td>50</td>
<td>31.06</td>
<td>9.65</td>
<td>-0.63 -1.84 -3.08</td>
</tr>
<tr>
<td>AU18 (lip pucker)</td>
<td>29</td>
<td>7.34</td>
<td>58</td>
<td>36.02</td>
<td>11.20</td>
<td>-2.00 -1.35 -2.90 -0.84 -2.05 -2.71</td>
</tr>
<tr>
<td>AU25_26_27 (opened mouth)</td>
<td>26</td>
<td>16.15</td>
<td>6.8</td>
<td>34.16</td>
<td>10.62</td>
<td>7.41 5.90 -3.33 -1.22 4.85 7.55</td>
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<tr>
<td>AU43 (eye closure)</td>
<td>10</td>
<td>6.21</td>
<td>16</td>
<td>9.94</td>
<td>41 25.47</td>
<td>23.60</td>
</tr>
</tbody>
</table>

Illustration of the absolute frequencies (F) of the pain-specific AUs, percentages of the stimulation segments recorded in which the AUs occurred (%segments) and relative frequencies (%F) of the AUs for the control group (CG) in the Off and On as well as for the PD patients (PD) in the Off and On. The table only contains those AUs that reached the 10% criterion (bold numbers in column “%segments”) in any of the conditions (CG Off, CG On, PD Off, PD On). Since AU43 reached the 10% criterion only in PD patients, it was not considered for further analysis (blackened cells). Furthermore the standardized residuals both for the between-group (stand. res. between) and the within-group (stand. res. within) frequency distribution analyses are illustrated. Shaded numbers label the AUs with the biggest deviation from the expected value.

Fig. 2. Means and standard deviations (SD) of the facial composite scores for PD patients (PD) and the control group (CG) both in the Off and On. As the asterisks mark, we found significant differences between PD patients and controls in the Off but not in the On (tested using the Mann–Whitney-U-test) and significant differences between the Off and On in PD patients but not in controls (tested using the Wilcoxon-rank-test). ** indicates significant differences (p < .05).
(descriptively) more frequently in PD patients compared to the controls, was the dominant facial movement in PD patients in both phases. Fig. 5 gives some examples of photographs of the facial expressions of pain both of PD patients and controls.

5. Discussion

The aim of our study was to investigate alterations in the facial expression of pain in PD. Furthermore, some psychophysical measures were taken. The main findings were: (1a) compared to controls, PD patients showed increased pain sensitivity (indicated by lower pain thresholds) in the Off but not in the On. (1b) Reported pain elicited by the supra-threshold heat stimuli, which were tailored to the individual pain threshold, did neither differ between groups nor between phases. (2) Regarding the facial expression of pain in PD patients we found (a) an overall reduction in the Off which was less prominent in the On, (b) reduced occurrence of narrowed eyes (AU6_7) compared to the controls and (2c) mouth opening (AU25_26_27) as the dominant element of the facial expression of pain in both phases.
5.1. Pain sensitivity in PD

Increased pain sensitivity in PD patients in the Off, which returns to the range of controls in the On, is in accordance to previous findings. Disturbances in the nociceptive basal ganglia loops due to DA deficiencies which diminish after medication intake are considered to account for these findings [7,13,33]. Thus, replicating this well-established effect argues for the representativeness of our sample and conditions regarding nociception in PD.

5.2. Facial expression

5.2.1. General reduction of the facial expression of pain in PD patients

Our data provide evidence that the general hypomimia in PD [23], which has been shown for classical emotions [22,42,43], also affects the facial expression of pain. The overall reduction of facial activity in PD patients in the Off, which attenuates in the On, might be related to disturbances of the basal ganglia loops which normalize slightly after medication intake. Especially the caudate nucleus as an important component of the nigrostriatal DA system might play an important role. In an imaging study with healthy participants Kunz and colleagues (2011) report a negative correlation between facial expression of pain and the frontostriatal activity including the caudate nucleus. In PD the balance of excitatory and inhibitory inputs within the nigrostriatal DA system gets disturbed which includes a reduction of inhibitory inputs from the substantia nigra to the caudate nucleus, which in consequence becomes hyperactive [3]. Again, this structure is negatively correlated with the facial expression of pain.

One might argue that the slightly lower intensity of the noxious stimulation due to its definition relative to the pain threshold in PD patients compared to the controls may account for the reduced facial activity in PD patients. Yet, the pain ratings indicate that the subjective pain elicited was comparable in both groups. Additionally, it seems like a contradiction in itself that the decreased pain thresholds of PD patients in the Off, suggesting increased pain sensitivity, go along with a reduction of facial activity, suggesting rather decreased pain sensitivity. Yet, since the pathophysiological basis of both increased pain sensitivity and reduced facial expression of pain in PD may be located in the nigrostriatal DA system, the findings can be integrated. Dysfunctions in the nigrostriatal DA system may lead (1) to increased pain sensitivity via disturbances in the nociceptive loops [5] and (2) to a reduced facial expression of pain via hyperactivity of the motor-inhibiting frontostriatal connection [27]. However, it is at least conceivable that in addition to dysfunctions in the nigrostriatal motor loops – including the frontostriatal connection – also abnormalities in the activation of the nociceptive system affect the facial expression of pain in PD.

5.2.2. Specific changes in the facial expression of pain in PD

Next to the overall reduction in the facial expressions, our data provide evidence for specific changes in the facial expression of pain in PD. The facial movements that are considered to be highly pain-relevant – narrowed eyes, furrowed brows and movements of the upper lip [29,36] – were affected to different extents. Especially narrowed eyes (AU6_7), which is considered as the most frequent and inter-individually most stable element of the facial expression of pain [29] and which was also the most prominent AU displayed by controls in our study, occurred less frequently in PD patients. In contrast, mouth opening (AU25_26_27) was the dominant facial movement in PD patients in both phases.

It is interesting that the functionality of the lower face (AU25_26_27) seems to be preserved while the upper face (AU6_7) is more affected by hypomimia. On a speculative level, differences in the innervation of facial
muscles in different areas of the face may explain the difference. The muscles of the peri-orbital region (upper face) are innervated bilaterally while the muscles of the mouth area (lower face) are innervated contra-laterally. Contra-laterally innervated muscles are assumed to be more accessible to voluntary control than bilaterally innervated muscles [40,12]. The ability of PD patients to voluntarily pose facial expressions has already been shown [43,42], which suggests better motor control of the lower face. It may well be that if the situation demands to voluntarily form a facial expression of pain, the blockade of hypomimia may be easier overcome than if the facial response is more of a reflex.

It is further interesting that alterations in the facial expression of pain could already be observed in PD study in which motor symptoms are still weak (mean UPDRS = 18.4/108) but lead already to communicative problems.

5.3. Consequences of the altered facial expression of pain in PD

One might argue that we evaluated facial expressions in response to intensive phasic/short-term experimental pain stimuli, which create pain, which differs from rather long-lasting and ongoing pain. Yet, we are convinced that our study simulated common clinical situations in which pain does not occur spontaneously but is evoked also in (chronic) pain patients for example by active or passive movements (see for example [37]).

Since the adequate facial communication of pain is essential for triggering empathy and care behavior [6,8,45] and important to receive sufficient pain treatment [25,38], an altered facial expression of pain is critical in PD patients suffering from pain. Due to these alterations, the adequate recognition of PD patients’ facial expression of pain by observers is challenged. First, the overall reduction in the facial expression of pain in the Off might lead to an underestimation of perceived pain in PD patients. Second, the facial expression of pain has been shown to be a multi-dimensional response system encoding both the sensory (narrowed eyes) and the affective (furrowed brows, movement of the upper lip) dimension of pain [30]. It is interesting that especially the facial movements related to the sensory dimension (narrowed eyes) are reduced in PD, while the affective dimension (especially furrowed brows) is preserved resulting in an imbalanced pain signal, which would let the patients still appear to be suffering but would not allow for expressing pain intensity differences. This imbalance and, additionally, the dominance of the opened mouth in PD patients’ facial expression of pain may also lead to mistakes in identifying the facial expression of pain by relatives or caregivers. It might be misinterpreted as an expression of other emotions. Mouth opening is, for example, a typical element of the facial expression of surprise (rather positive) [14], which not necessarily demands immediate action.

To address these problems appropriately (1) caregivers should be trained to correctly interpret the facial expression of pain in PD patients and (2) PD patients could be shown alternative behavior in order to communicate pain, like moaning.

Furthermore, the altered facial expression of pain in PD might be especially challenging for PD patients who also suffer from dementia which occurs in 30% of PD patients [1]. Since the verbal expression of pain is limited due to cognitive and linguistic impairments in PD patients with dementia, observational diagnostic tools become especially important in this PD subgroup [21,31]. Since the facial expression is obviously compromised in PD patients and the other two behavioral domains of pain indication, i.e. body movements and vocalization may also be affected by PD, pain diagnostics in PD patients with dementia should be carried out with great expertise.

As a further complication of pain diagnosis, PD-related facial asymmetry, which especially occurs in hemi-PD patients (excluded from our study) [11,32], may further enhance the difficulty of the correct recognition of the facial expression of pain in PD patients.

5.4. Limitations

Our study has some limitations. First, our sample covers PD patients with comparably weak symptoms. We selected this sample because we aimed to investigate specific alterations in the facial expression of pain in PD which might be overlain by massive overall hypomimia in PD patients with severe symptoms. Future studies should also target patients with more pronounced symptoms. Second, although the sex ratio of PD prevalence is 1.6 with men predominating [46], only 3 female patients participated in our study. Since sex might affect facial pain communication future studies should include more female patients. Yet, a previous study from our lab showed at least no sex differences regarding the overall facial expression of pain [28]. Third, although the fixed interval of one hour after medication intake should have ensured reaching the On in every PD patient in our study, different amounts of restoration of the function of the nigrostriatal DA system due to different types of medications should be considered by analyzing subgroups with different medication. Fourth, we did not consider the spontaneous blinking rate (AU45) although it might be a biomarker for the central DA tone in PD patients. Since we were interested in the pain-specific facial activity, we went without FACS-coding blinks, also for economic reasons because coding blinks would have increased the expenditure of time for FACS coding substantially. Fifth, one might be critical that assessing the questionnaires in the transition from the Off to the On is disadvantageous. Yet, since the questionnaires deal with fact-orientated trait-like information the results should be independent from the phase. Sixth, we omitted a randomization of the sequence of the phases (all PD patients were first tested in the Off and then in the On), which would have controlled for effects deriving from the order of the conditions instead from the medication intake. However, we spared by that an extra session for the patients. Furthermore, in order to control for possible sequence effects, the control group was also tested two times.

6. Conclusions

The aim of our study was to explore alterations in the facial expression of pain in PD patients. We found a general reduction of the facial activity in the Off (hypomimia) which was less pronounced in the On (compared to controls). In addition, PD patients showed qualitative changes in the facial expression of pain. Especially the movements of the upper face area (narrowed eyes) were affected in PD patients while the functionality of the lower face was rather preserved. The latter manifests itself in the high prevalence of opening the mouth in the facial expression of pain in PD patients in both phases. Making caregivers aware of these changes might help to prevent poor pain recognition in PD patients.

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References


