Phantom limb pain after unilateral arm amputation is associated with decreased heat pain thresholds in the face

Fuchs, Xaver; Diers, Martin; Trojan, Jörg; Kirsch, Pinar; Milde, Christopher; Bekrater-Bodmann, Robin; Rance, Mariela; Foell, Jens; Andoh, Jamila; Becker, Susanne; Flor, Herta

Abstract: BACKGROUND The mechanisms underlying chronic phantom limb pain (PLP) are complex and insufficiently understood. Altered sensory thresholds are often associated with chronic pain but quantitative sensory testing (QST) in PLP has so far been inconclusive due to large methodological variation between studies and small sample sizes. METHODS In this study, we applied QST in 37 unilateral upper-limb amputees (23 with and 14 without PLP) and 19 healthy controls. We assessed heat pain (HPT), pressure pain, warmth detection and two-point discrimination thresholds at the residual limb, a homologous point and the thenar of the intact limb as well as both corners of the mouth. RESULTS We did not find significant differences in any of the thresholds between the groups. However, PLP intensity was negatively associated with HPT at all measured body sites except for the residual limb, indicating lower pain thresholds with higher PLP levels. Correlations between HPT and PLP were strongest in the contralateral face (r = -0.65, p < 0.001). Facial HPT were specifically associated with PLP, independent of residual limb pain (RLP) and various other covariates. HPT at the residual limb, however, were significantly associated with RLP, but not with PLP. CONCLUSION We conclude that the association between PLP and, especially facial, HPT could be related to central mechanisms. SIGNIFICANCE Phantom limb pain (PLP) is still poorly understood. We show that PLP intensity is associated with lower heat pain thresholds, especially in the face. This finding could be related to central nervous changes in PLP.

DOI: https://doi.org/10.1002/ejp.1842

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-212435
Journal Article
Published Version

The following work is licensed under a Creative Commons: Attribution-NonCommercial 4.0 International (CC BY-NC 4.0) License.

Originally published at:
Fuchs, Xaver; Diers, Martin; Trojan, Jörg; Kirsch, Pinar; Milde, Christopher; Bekrater-Bodmann, Robin; Rance, Mariela; Foell, Jens; Andoh, Jamila; Becker, Susanne; Flor, Herta (2022). Phantom limb pain after unilateral arm amputation is associated with decreased heat pain thresholds in the face. European Journal of Pain, 26(1):114-132.
Phantom limb pain after unilateral arm amputation is associated with decreased heat pain thresholds in the face

Xaver Fuchs 1,2 | Martin Diers 1,3 | Jörg Trojan 1 | Pinar Kirsch 1 | Christopher Milde 1,4 | Robin Bekrater-Bodmann 1 | Mariela Rance 1,5 | Jens Foell 1,6 | Jamila Andoh 1,7 | Susanne Becker 1,8 | Herta Flor 1

1Institute of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
2Biopsychology and Cognitive Neuroscience, Faculty of Psychology and Sports Science, Bielefeld University, Bielefeld, Germany
3Department of Psychosomatic Medicine and Psychotherapy, LWL University Hospital, Ruhr University Bochum, Bochum, Germany
4Department of Psychology, University of Koblenz-Landau, Landau, Germany
5Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, Connecticut, USA
6Department of Psychology, Florida State University, Tallahassee, Florida, USA
7Department of Psychiatry and Psychotherapy, Medical Faculty Mannheim, Central Institute of Mental Health, University of Heidelberg, Heidelberg, Germany
8Integrative Spinal Research, Research Chiropractic, Balgrist University Hospital, University of Zurich, Zurich, Switzerland

Abstract

Background: The mechanisms underlying chronic phantom limb pain (PLP) are complex and insufficiently understood. Altered sensory thresholds are often associated with chronic pain but quantitative sensory testing (QST) in PLP has so far been inconclusive due to large methodological variation between studies and small sample sizes.

Methods: In this study, we applied QST in 37 unilateral upper-limb amputees (23 with and 14 without PLP) and 19 healthy controls. We assessed heat pain (HPT), pressure pain, warmth detection and two-point discrimination thresholds at the residual limb, a homologous point and the thenar of the intact limb as well as both corners of the mouth.

Results: We did not find significant differences in any of the thresholds between the groups. However, PLP intensity was negatively associated with HPT at all measured body sites except for the residual limb, indicating lower pain thresholds with higher PLP levels. Correlations between HPT and PLP were strongest in the contralateral face ($r = -0.65, p < 0.001$). Facial HPT were specifically associated with PLP, independent of residual limb pain (RLP) and various other covariates. HPT at the residual limb, however, were significantly associated with RLP, but not with PLP.
FUCHS ET AL.

**Conclusion:** We conclude that the association between PLP and, especially facial, HPT could be related to central mechanisms.

**Significance:** Phantom limb pain (PLP) is still poorly understood. We show that PLP intensity is associated with lower heat pain thresholds, especially in the face. This finding could be related to central nervous changes in PLP.

1 | INTRODUCTION

Phantom limb pain (PLP)—pain perceived in an absent limb or portions of an absent limb—is a common consequence of limb amputation and occurs in about 50%–80% (Nikolajsen, 2013) of all amputees. Both peripheral and central mechanisms are involved in chronic PLP (Flor & Fuchs, 2017; Flor et al., 2006; Ramachandran & Hirstein, 1998). However, their exact roles and impact are under debate. Peripheral factors relate to nociceptive input stemming from the residual limb and can involve peripheral sensitization, spontaneous discharges from the residual limb due to involuntary movement or physiological arousal (Sherman et al., 1989), neuromas (Devor, 1991; Fried et al., 1991; Wiffen et al., 2006), or activity generated in dorsal root ganglia (Vaso et al., 2014). Central sensitization can develop as a consequence of long-term peripheral nociceptive input and is mediated by spinal cord neurons (Latremoliere & Woolf, 2009; Woolf & Salter, 2000) or the brain (Woolf, 2014). In the brain, PLP has been associated with maladaptive reorganization of body maps in the primary somatosensory (S1) (Flor et al., 1995) and primary motor cortex (Lotze et al., 2001) as well as preserved function of the section of S1 that formerly represented the missing limb (Kikkert et al., 2018; Makin, Scholz, et al., 2013).

Increased sensitivity to painful stimuli encompasses both peripheral and central mechanisms (Woolf & Salter, 2000) and is commonly assessed psychophysically by quantitative sensory testing (QST; Magee et al., 2010; Maier et al., 2010; Rolke et al., 2006). Although QST has previously been applied in amputees, the results are mixed and do not support an association with PLP. Some previous studies reported enhanced tactile (Haber, 1955; D. Katz, 1921; Teuber et al., 1949; Wilson et al., 1962), thermal (Engkvist et al., 1985; Wahren, 1990) or pressure pain sensitivity (Cronholm, 1951; Korin et al., 1963; Vase et al., 2011) of the residual limb compared to a homologous site on the intact limb but did not relate these findings to PLP. The studies that examined the relationship of tactile and pain sensitivity to PLP mostly found no significant relationship with tactile sensitivity (Grüsser et al., 2001; Hunter et al., 2005; Katz, 1992; Li et al., 2015), heat pain (Flor et al., 1998; Harden et al., 2010; Hunter et al., 2005; Li et al., 2015) or cold perception (Harden et al., 2010). One study reported hyperalgesia for electrical painful stimulation on the intact limb in amputees with but not without PLP, suggesting central sensitization (Li et al., 2015).

Hence, findings of previous studies do not suggest that there is an association of PLP and thresholds for non-painful stimuli and are inconsistent with respect to the question whether PLP is associated with pain thresholds. However, inconsistencies and negative findings might be partly related to small sample sizes and heterogeneity of the samples (e.g. lower- vs. upper-limb amputations) and large heterogeneity in the applied assessment methods and tested body sites. In particular, comparisons relating the residual to the intact limb might be problematic for various reasons. First, it is difficult to standardize measures taken at the residual limb due to variations in levels of amputation and scar tissue. Second, QST of the residual limb may be related to residual limb pain (RLP) rather than PLP. Third, testing only the residual limb and a homologous contralateral side cannot determine whether altered pain thresholds are also present at remote sites, for instance at the thenar or the mouth. The face and the missing upper limb have adjacent representations in sensory and motor areas of the brain and the mouth might therefore have altered sensitivity related to cortical reorganization.

As central sensitization might also play a role in PLP, the present study tested whether PLP is accompanied by changes in sensitivity to painful and non-painful stimuli applied at several standardized body sites. The aims were (a) to investigate whether there are changes in sensory thresholds, which are associated with the presence and/or the intensity of PLP, (b) to test whether potential changes are restricted to the residual limb, which could involve peripheral mechanisms, and/or whether changes are also present in other areas of the body, which could point to central mechanisms and finally, in order to test the specificity to PLP, we sought to (c) take into account associations with other variables, which are potentially related to sensitization and brain changes, especially RLP (Kern et al., 2009).

2 | METHODS

2.1 | Participants

Thirty-seven unilateral upper-limb amputees and 19 healthy controls (HCs) took part in this study. We employed QST and the assessment of phantom phenomena and chronic pain. The sample was recruited from a nation-wide database on which
we had previously reported (Bekrater-Bodmann, Schredl, et al., 2015). The participants were selected from the database and contacted directly. The criteria for selection were unilateral arm amputation and eligibility for magnetic resonance imaging testing (used in another study). We recruited amputees with and without PLP and attempted to achieve comparable distributions of age, sex and side of amputation between the groups. The study was approved by the Ethics Commission II of the Medical Faculty Mannheim, Heidelberg University. The amputees were divided into two groups—one with PLP (PLP;\( N = 23 \)) and one without PLP (non-PLP;\( N = 14 \)). Grouping was based on the Phantom Pain Severity subscale of the German version of the West Haven-Yale Multidimensional Pain Inventory (MPI; Flor et al., 1990, 1995; Kerns et al., 1985) adapted for separate assessments of PLP and RLP. The MPI is a 22-item questionnaire that uses a 7-point numeric rating scale for each item ranging from 0 to 6. The Pain Severity subscale is calculated as the average value of three items assessing (a) the intensity of momentary pain, (b) the average pain during the last week and (c) the intensity of pain-related suffering. Amputees with a Pain Severity score of 0 were assigned to the non-PLP group and all other amputees to the PLP group. The HC were matched for age, sex and stimulation sites with amputees from both groups. Sample and demographic details are provided in Table 1.

There were no statistically significant differences between the three groups (PLP, non-PLP and HC) in the distribution of sex [ratio male/female: PLP, 20/3; non-PLP, 12/2; HC, 16/3; \( \chi^2(2, N = 56) = 0.06, p = 0.97 \)] and age (mean ± standard deviation [SD, years]: PLP, 51.3 ± 12.3; non-PLP, 53.1 ± 10.6; HC, 51.6 ± 11.7; \( F(2,53) = 0.10, p = 0.90 \)). The PLP group and the non-PLP group did not significantly differ in their level of amputation (mean ± SD [% arm length]: PLP, 32.0 ± 18.8; non-PLP, 40.2 ± 23.9; \( t(22.7) = -1.10, p = 0.28 \)) or side of amputation (\( \chi^2(1, N = 37) = 0.53, p = 0.47 \)). None of the amputees was amputated at an age below 5 years and the groups did not differ significantly with respect to age of amputation (mean ± SD, range [years]: PLP, 27.1 ± 12.5, 13–55; non-PLP, 19.8 ± 11.5, 5–45; \( t(29.5) = 1.80, p = 0.08 \)). All amputees were in a later stage after amputation with at minimum 3 years passing between amputation and sensory testing and the groups did not differ significantly with respect to that (mean ± SD, range [years]: PLP, 24.1 ± 11.4, 9–58; non-PLP, 33.3 ± 15.6, 3–55; \( t(29.5) = 1.84, p = 0.08 \)). All amputees were right-handed before amputation and so were all of the HC, according to the Edinburgh Handedness Inventory (Oldfield, 1971).

2.2 |  Body sites

Sensory testing was performed at five body sites. Amputees were tested at the thenar of their intact hand, both corners of the mouth, the residual limb and at a homologous site on the intact arm. The sites at the corners of the mouth were symmetric and located laterally of the lips on the hairy skin of the cheeks. The test site at the residual limb was located 5 cm from the distal end of the limb (Grüsser et al., 2001; Hunter et al., 2005) and outside of scar tissue. Both sites on the arms were marked using cosmetic colour and a photo was taken for documentation. The sites on the arms used in the HC were anatomically homologous to the ones used in the matched amputees.

Body sites for sensory testing were selected based on the following rationale: the residual limb was tested as the body site directly affected by the amputation with a homologous site on the intact arm as a control site. The corners of the mouth were tested because they are remote from the amputation site and clearly outside the area of potential nerve damage. In addition, the face is a relevant area with regards to central changes, as the hand and the face are represented at adjacent sites within the cortical body map in S1. Previous studies showed that an expansion (in terms of functional S1 reorganization) of the mouth area in the hemisphere contralateral to the amputation into the neighbouring former hand area is positively correlated with PLP (Flor et al., 1995; Lotze et al., 2001; MacIver et al., 2008). It is, however, unclear whether cortical reorganization is reflected in altered sensitivity to stimuli presented at the corners of the mouth. Additionally, we tested the thenar of the existing hand, as sensory changes at the thenar might indicate altered interhemispheric connectivity in the brain as the cortical representation of the existing hand is functionally (van den Heuvel & Hulshoff Pol, 2009) and structurally (Bonzano et al., 2008) coupled to the corresponding area in the contralateral hemisphere. Another reason for including the thenar is that it is a standard site for QST (Rolke et al., 2006).

2.3 |  Sensory testing

Measures were chosen to detect increased or decreased sensitivity to noxious or non-noxious thermal or mechanical stimuli. In total, we assessed four different measures: two pain thresholds—heat pain threshold (HPT) and pressure pain threshold (PPT)—and two detection thresholds—warmth detection threshold (WDT) and tactile two-point discrimination thresholds (2PDT). This allowed us to separate the effects related to the nociceptive system from other somatosensory modalities. The protocol used here adhered to the standards of the German Research Network on Neuropathic Pain (DFNS) but did not use the complete protocol. Thermal QST was selected for comparability with several previous QST studies with amputees (Flor et al., 1998; Harden et al., 2010; Hunter et al., 2005; Li et al., 2015) and because it allows assessment of both detection and pain thresholds using the same stimulus type (temperature). Tactile 2PDT were selected because body sites with larger S1 representation usually have smaller 2PDT and the measure is sensitive to detect changes in S1 representation.
| ID  | Type        | Group | Matching | Sex | Age | EHI score | Lvl. of stim. (%) | Age at amp. | Time since amp. | Side of amp. | Cause of amp. | Phantom limb | Telescope | Prosthesis | PLP intensity | RLP intensity |
|-----|-------------|-------|----------|-----|-----|-----------|------------------|-------------|----------------|-------------|---------------|--------------|------------|------------|--------------|--------------|
| A01 | Amputee     | PLP   | None     | M   | 57  | 100.0     | 15               | 27          | 30             | Right       | Trauma        | Yes         | Yes        | None       | 0.7          | 1.0          |
| A02 | Amputee     | PLP   | HC12     | M   | 48  | 75.0      | 70               | 18          | 30             | Left        | Trauma        | Yes         | Yes        | Cosmetic   | 3.0          | 3.0          |
| A03 | Amputee     | PLP   | HC01     | M   | 69  | 57.1      | 45               | 45          | 24             | Left        | Trauma        | Yes         | Yes        | Myo-el.    | 3.3          | 2.7          |
| A04 | Amputee     | PLP   | HC06     | M   | 42  | 84.6      | 35               | 23          | 19             | Right       | Trauma        | Yes         | Yes        | Myo-el.    | 0.7          | 1.7          |
| A05 | Amputee     | PLP   | HC02     | M   | 50  | 72.7      | 20               | 21          | 29             | Right       | Trauma        | Yes         | Yes        | Cosmetic   | 4.0          | 0.3          |
| A06 | Amputee     | PLP   | HC09     | M   | 52  | 84.6      | 0                | 42          | 10             | Right       | Trauma        | Yes         | No         | Cosmetic   | 2.3          | 0.0          |
| A07 | Amputee     | PLP   | HC08     | M   | 64  | 66.7      | 0                | 55          | 9              | Left        | Tumor         | Yes         | Yes        | None       | 2.0          | 0.0          |
| A08 | Amputee     | PLP   | None     | M   | 62  | 100.0     | 15               | 43          | 19             | Right       | Trauma        | Yes         | Yes        | None       | 2.3          | 2.0          |
| A09 | Amputee     | PLP   | None     | M   | 39  | 80.0      | 35               | 15          | 24             | Left        | Trauma        | Yes         | No         | None       | 0.3          | 0.0          |
| A10 | Amputee     | PLP   | HC15     | M   | 37  | 50.0      | 50               | 13          | 24             | Left        | Trauma        | Yes         | Yes        | Cosmetic   | 0.3          | 0.0          |
| A11 | Amputee     | PLP   | None     | M   | 30  | 75.0      | 25               | 19          | 11             | Right       | Trauma        | Yes         | Yes        | None       | 2.0          | 2.0          |
| A12 | Amputee     | PLP   | None     | M   | 67  | 63.3      | 45               | 38          | 29             | Left        | Trauma        | Yes         | No         | Cosmetic   | 1.7          | 4.7          |
| A13 | Amputee     | PLP   | HC14     | M   | 54  | 84.6      | 21               | 42          | 12             | Right       | Trauma        | Yes         | Yes        | None       | 1.7          | 1.3          |
| A14 | Amputee     | PLP   | None     | M   | 73  | 84.6      | 15               | 15          | 58             | Right       | Trauma        | Yes         | No         | None       | 0.7          | 0.0          |
| A15 | Amputee     | PLP   | HC13     | M   | 26  | 57.1      | 38               | 17          | 9              | Right       | Trauma        | Yes         | Yes        | None       | 2.3          | 2.0          |
| A16 | Amputee     | PLP   | HC04     | M   | 42  | 100.0     | 43               | 19          | 23             | Left        | Trauma        | Yes         | No         | None       | 1.0          | 1.7          |
| A17 | Amputee     | PLP   | None     | M   | 54  | 46.7      | 15               | 14          | 40             | Right       | Trauma        | Yes         | Yes        | None       | 0.7          | 1.0          |
| A18 | Amputee     | PLP   | None     | M   | 63  | 75.0      | 30               | 40          | 23             | Right       | Trauma        | Yes         | Yes        | Myo-el.    | 1.7          | 1.0          |
| A19 | Amputee     | PLP   | None     | M   | 52  | 69.2      | 50               | 16          | 36             | Right       | Trauma        | Yes         | No         | Manual     | 1.3          | 2.0          |
| A20 | Amputee     | PLP   | None     | M   | 48  | 76.5      | 30               | 18          | 30             | Right       | Trauma        | Yes         | Yes        | None       | 4.3          | 3.0          |
| A21 | Amputee     | PLP   | HC19     | F   | 40  | 100.0     | 45               | 25          | 15             | Left        | Other         | Yes         | Yes        | None       | 2.7          | 0.0          |
| A22 | Amputee     | PLP   | HC17     | F   | 58  | 100.0     | 25               | 37          | 21             | Left        | Trauma        | Yes         | Yes        | None       | 2.3          | 0.7          |
| A23 | Amputee     | PLP   | None     | F   | 53  | 66.7      | 70               | 23          | 30             | Right       | Trauma        | Yes         | No         | None       | 3.7          | 2.7          |
| A24 | Amputee     | non-PLP | None    | M   | 59  | 84.6      | 20               | 10          | 49             | Right       | Trauma        | No          | No         | Myo-el.    | 0.0          | 0.0          |
| A25 | Amputee     | non-PLP | HC05     | M   | 67  | 90.0      | 62               | 19          | 48             | Right       | Trauma        | Yes         | Yes        | Myo-el.    | 0.0          | 0.0          |
| A26 | Amputee     | non-PLP | HC07     | M   | 54  | 100.0     | 72               | 23          | 31             | Right       | Trauma        | Yes         | No         | None       | 0.0          | 0.0          |
| A27 | Amputee     | non-PLP | None    | M   | 24  | 83.3      | 45               | 6           | 18             | Left        | Trauma        | No          | No         | Myo-el.    | 0.0          | 0.0          |
| A28 | Amputee     | non-PLP | None    | M   | 60  | 57.1      | 60               | 5           | 55             | Left        | Trauma        | No          | no         | None       | 0.0          | 0.0          |
| A29 | Amputee     | non-PLP | HC11     | M   | 62  | 71.4      | 10               | 10          | 52             | Left        | Trauma        | No          | No         | None       | 0.0          | 0.0          |
| A30 | Amputee     | non-PLP | HC10     | M   | 47  | 60.0      | 0                | 22          | 25             | Left        | Trauma        | Yes         | No         | None       | 0.0          | 0.0          |
| A31 | Amputee     | non-PLP | None    | M   | 48  | 70.0      | 62               | 45          | 3              | Right       | Trauma        | No          | No         | None       | 0.0          | 0.0          |

(Continues)
| ID  | Type        | Group   | Matching | Sex | Age | EHI score | Lvl. of stim. (%) | Age at amp. | Time since amp. | Side of amp. | Cause of amp. | Phantom limb | Telescope | Prosthesis | PLP intensity | RLP intensity |
|-----|-------------|---------|----------|-----|-----|-----------|------------------|------------|----------------|-------------|--------------|-------------|-----------|------------|---------------|---------------|
| A32 | Amputee     | non-PLP | HC03     | M   | 65  | 69.2      | 52               | 15         | 50             | Right       | Trauma       | Yes         | Yes       | Cosmetic   | 0.0           | 0.0           |
| A33 | Amputee     | non-PLP | None     | M   | 51  | 83.3      | 10               | 23         | 28             | Left        | Trauma       | No          | No        | Cosmetic   | 0.0           | 0.0           |
| A34 | Amputee     | non-PLP | HC16     | M   | 56  | 100.0     | 65               | 38         | 18             | Right       | Trauma       | No          | No        | Cosmetic   | 0.0           | 0.0           |
| A35 | Amputee     | non-PLP | None     | M   | 47  | 100.0     | 25               | 15         | 32             | Left        | Trauma       | Yes         | Yes       | Myo-el.    | 0.0           | 0.0           |
| A36 | Amputee     | non-PLP | HC18     | F   | 52  | 100.0     | 50               | 18         | 34             | Left        | Trauma       | No          | No        | Myo-el.    | 0.0           | 3.0           |
| A37 | Amputee     | non-PLP | None     | F   | 51  | 86.7      | 30               | 28         | 23             | Left        | Trauma       | Yes         | Yes       | None       | 0.0           | 0.7           |
| HC01| Control     | HC      | A03      | M   | 71  | 100.0     | 45               | Left       |                |             |              |             |           |            |               |               |
| HC02| Control     | HC      | A05      | M   | 50  | 61.3      | 20               | Right      |                |             |              |             |           |            |               |               |
| HC03| Control     | HC      | A32      | M   | 64  | 100.0     | 52               | Right      |                |             |              |             |           |            |               |               |
| HC04| Control     | HC      | A16      | M   | 41  | 70.4      | 43               | Left       |                |             |              |             |           |            |               |               |
| HC05| Control     | HC      | A25      | M   | 67  | 88.6      | 62               | Right      |                |             |              |             |           |            |               |               |
| HC06| Control     | HC      | A04      | M   | 44  | 75.0      | 35               | Right      |                |             |              |             |           |            |               |               |
| HC07| Control     | HC      | A26      | M   | 54  | 73.9      | 72               | Right      |                |             |              |             |           |            |               |               |
| HC08| Control     | HC      | A07      | M   | 64  | 93.3      | 0                | Left       |                |             |              |             |           |            |               |               |
| HC09| Control     | HC      | A06      | M   | 53  | 88.9      | 0                | Right      |                |             |              |             |           |            |               |               |
| HC10| Control     | HC      | A30      | M   | 47  | 51.7      | 0                | Left       |                |             |              |             |           |            |               |               |
| HC11| Control     | HC      | A29      | M   | 63  | 89.5      | 10               | Left       |                |             |              |             |           |            |               |               |
| HC12| Control     | HC      | A02      | M   | 47  | 63.6      | 70               | Left       |                |             |              |             |           |            |               |               |
| HC13| Control     | HC      | A15      | M   | 25  | 53.8      | 38               | Right      |                |             |              |             |           |            |               |               |
| HC14| Control     | HC      | A13      | M   | 51  | 65.2      | 21               | Right      |                |             |              |             |           |            |               |               |
| HC15| Control     | HC      | A10      | M   | 35  | 89.5      | 50               | Left       |                |             |              |             |           |            |               |               |
| HC16| Control     | HC      | A34      | M   | 55  | 71.4      | 65               | Right      |                |             |              |             |           |            |               |               |
| HC17| Control     | HC      | A22      | F   | 58  | 100.0     | 25               | Left       |                |             |              |             |           |            |               |               |
| HC18| Control     | HC      | A36      | F   | 53  | 31.2      | 50               | Left       |                |             |              |             |           |            |               |               |
| HC19| Control     | HC      | A21      | F   | 39  | 82.9      | 45               | Left       |                |             |              |             |           |            |               |               |

Abbreviations: EHI, Edinburgh handedness inventory; HC, healthy control; myo-el., myoelectric prosthesis; non-PLP, without phantom limb pain; PLP, phantom limb pain; RLP, residual limb pain.

*A value of 100 in the EHI indicates the strongest degree of right-handedness, a value of −100 indicates the strongest degree of left-handedness.

*Level of stimulation was defined as the position of measurements at the arm relative to the length of the (intact) arm, measured from the caput humeri to the tip of the third digit. In the amputees, this position was defined by the length of the residual limb. Homologous sites were measured in the matched HC.

*Side of amputation in the HC (in brackets) refers to the side of amputation of the matched amputee.

*The category ‘other’ causes of amputation subsumes unknown causes not falling into the categories traumatic, injury, dysplasia, infection, tumour or vascular disease.

*Pain severity subscale of the MPI adapted for PLP and RLP, respectively. Values range from 0 (lowest severity) to 6 (highest severity).
2.3.1 Thermal thresholds

Warmth detection thresholds and HPT were measured using a Medoc ATS thermode (3 x 3 cm surface) included in the Medoc Pathway system (PATHWAY Pain & Sensory Evaluation System, Medoc Ltd. Advanced Medical System). Stimuli were applied with a baseline temperature of 32 °C and a rising rate of 1.5 °C/s (ascending method of limits) (Bekrater-Bodmann, Chung, et al., 2015). The maximum temperature of the system was set to 52 °C to avoid skin injuries.

Because amputees, when tested at the thenar, could not respond with button presses, all responses for all body sites and groups, including the ones in the HC, were given verbally to ensure comparability between sites and groups. The assessment of WDT and HPT only differed with respect to the instructions (‘say “stop” as soon as you feel that the temperature is getting warmer’ for WDT and ‘say “stop” when the temperature just becomes painful’ for HPT). When participants said ‘stop’, the experimenter immediately terminated the ascending stimulus and the thermode returned to the baseline temperature at a rate of 8 °C/s. The participants were asked to keep their eyes closed throughout the test.

When assessing WDT and HPT in the face, the thermode was attached to the skin with adhesive tape and the participant was additionally asked to gently press the index finger against the thermode to ensure good contact with the skin. In each series, we conducted five consecutive trials. The first trial of each series was presented to familiarize participants with the test and the remaining four stimuli were averaged to calculate the threshold (Bekrater-Bodmann, Chung, et al., 2015).

2.3.2 Pressure pain thresholds

Pressure pain threshold were measured using a Medoc Algodex (Medoc Ltd. Advanced Medical System) computerized pressure algometer (surface of 1 cm²). Four consecutive stimuli were applied using a rate of 50 kPa/s (ascending method of limits) (Rolke et al., 2006). The participants were instructed to say ‘stop’ when the pressure started to feel painful. Four consecutive stimuli were applied; the first stimulus was excluded and the remaining three were averaged for calculation of the pain threshold. When testing at the corners of the mouth, the participants clenched the teeth to ensure that the tested tissue was pushed against the teeth when applying the pressure algometer. The experimenter gently stabilized the participant’s head using the hand not applying the algometer. This prevented the participant from compensating the pressure using the neck muscles, avoiding discomfort.

2.3.3 Two-point discrimination thresholds

Two-point discrimination threshold were measured using a set of 28 calibrated compasses (Rotring “Centro”; Rotring) ranging in size from 1 to 82 mm in steps of 3 mm. The tips of the compasses were exchanged with blunt rods in order to induce a light touch. Stimuli were applied by placing the compass perpendicularly onto the skin from above. The skin was touched briefly (1–2 s) while the participants kept their eyes closed. We used a simple adaptive staircase (‘up-down’) procedure (Dixon & Mood, 1948; Levitt, 1971), stopping after seven reversals. The first reversal point was excluded and the following six were averaged to calculate the absolute (50%) threshold. To avoid biases in the estimation of the thresholds that can be introduced when the starting point is far away from the threshold, we used different compass sizes as starting points, depending on the body site: 25 mm for the corners of the mouth where the threshold was expected to be lower than on the arms (Mancini et al., 2014; Weinstein, 1968) and 46 mm for the arms. 2PDT at the arms were always measured in proximal-to-distal direction while the participant sat in a chair. 2PDT at the corners of the mouth were measured parallel to the inferior-to-superior axis while the participant was lying on a bench to facilitate applying the stimuli perpendicularly from above. Beforehand, the protocol had been evaluated in a pilot study, testing the dorsal forearms of 10 participants. The procedure showed good within-session reliability (Pearson’s r = 0.81). The data of this pilot are provided in Supplementary Material: (a) use of prostheses (Dietrich et al., 2012; Lotze et al., 1999), (b) telescoping (Flor et al., 2006; Grüsser et al., 2001), (c) compensation in daily

2.4 Specificity for PLP

To test whether associations between PLP and sensory thresholds were specific to PLP and not mediated by other correlates of PLP or related brain plasticity, we performed additional analyses to control their potential influence. Especially, RLP is correlated with PLP (Kern et al., 2009) and can therefore confound interpretations if not statistically controlled. Apart from RLP, we also ruled out confounders and the results of these analyses are reported in detail in Supplementary Material: (a) use of prostheses (Dietrich et al., 2012; Lotze et al., 1999), (b) telescoping (Flor et al., 2006; Grüsser et al., 2001), (c) compensation in daily
activities by the existing hand (Makin, Cramer, et al., 2013), (d) level of the amputation and (e) time since amputation.

2.5 | Statistical analyses

2.5.1 | Data inspection and outliers

Because large variation was observed in the sensory data (see the boxplots in Figure 2 in the Section 3), we performed a systematic analysis for the presence and the influence of outliers which is included in Supplementary Material. Despite the presence of some outliers, the results were not strongly influenced, and the conclusions remain identical for statistical analyses with and without outliers. Therefore, no data were removed for the analyses presented in the article. Supplementary Material includes a reanalysis of the data after removal of outliers.

2.5.2 | Transformation of sensory data

In accordance with the recommendations given by Rolke et al. (2006), we transformed WDT and PPT logarithmically prior to the statistical analyses using a log-transformation. WDT were coded as deviation from the baseline, with the baseline temperature of 32°C subtracted from the thresholds, prior to the log-transformation.

2.5.3 | Statistical models for comparisons between groups and body sites

To compare thresholds between the groups and body sites, we fitted a (repeated measures) linear mixed model (LMM) for each sensory measure using group (PLP, non-PLP and HC) as a between-subject fixed factor and body site (arm ipsilateral, arm contralateral, corner of the mouth ipsilateral, corner of the mouth contralateral and thenar contralateral to the amputation) as a within-subject fixed factor. All models included participants as a random intercept effect. LMMs are a flexible and robust alternative to repeated measures analyses of variance and permit simultaneous analysis of discrete grouping variables, repeated factors and continuous covariates, providing a framework for both factorial and regression-type analyses (Pinheiro & Bates, 2000). To test whether differences between groups depended on the body site (or vice versa), we also included the interaction between group and body site in the models.

The coding of body site (‘ipsilateral’ and ‘contralateral’) in the HC was defined by the side of amputation of the matched (yoked) amputee. For example, if an HC was matched to a right-sided amputee, his or her right corner of the mouth was coded as ipsilateral. Note that in the amputees, ‘ipsilateral arm’ refers to the residual limb. This allowed a balanced mixture of right- and left-side body parts of the HCs within the categories.

Significant effects were followed up by pairwise post-hoc comparisons to test which mean values differed significantly. To avoid alpha error inflation, post-hoc test p-values were corrected using the false discovery rate (Benjamini & Hochberg, 1995).

2.5.4 | Associations between sensory thresholds and PLP

To test the association between the sensory thresholds and PLP intensity, we correlated each sensory threshold in the PLP group with the Phantom Pain Severity score from the MPI using Pearson correlations.

Next, to test whether PLP intensity was associated with a combination of sensory thresholds and to account for the intercorrelation of sensory variables, we performed a stepwise multiple regression analysis. We predicted PLP intensity in the PLP group by a combination of HPT, PPT and WDT at all body sites and determined the best-fitting model using stepwise elimination of regression terms (based on Akaike's information criterion [AIC], as implemented in R’s stepwise function). As missing values are a problem for multiple regression approaches, we imputed missing data with the mean values prior to the analyses (1 value [0.8%] for HPT and PPT, respectively). As 2PDT were only measured in a subset of the participants, this would have resulted in an imputation of 18% of the values. Therefore, we excluded 2PDT from the multiple regression analyses.

2.5.5 | Specificity of associations for PLP versus RLP intensity

To test whether the types of pain (PLP and RLP intensity) are predicted differentially by the sensory thresholds, we performed an LMM that resembled the multiple regression model described in the previous paragraph but included both PLP and RLP intensity as predicted values, coded by a factor ‘pain type’ that was included as a within-subject fixed factor. The model comprised all sensory thresholds as predictors and all two-fold interactions between the pain type and the sensory thresholds. A significant interaction between the pain type and a sensory threshold variable indicates that the prediction is significantly different (and therefore specific) for PLP versus RLP intensity. As for the regression model, we used a stepwise approach to determine the most appropriate model based on AIC. The analysis included all amputees showing either PLP or RLP values above zero. This was the case for the 23 amputees from the PLP group and three cases from the non-PLP group who reported RLP but no PLP; the analysis therefore included 26 participants.
For another regression model aiming at ruling out other confounding variables (described in Section 2.5), see Supplementary Material.

2.5.6 | Software and data resources

All data and code to reproduce all statistical analyses and figures reported in this article are publicly available online in a repository hosted on the website of the Open Science Framework and can be accessed via https://osf.io/v6hjy/

We used the R statistical software (R Core Team, 2014). LMMs were performed using the “lme4” (Bates et al., 2014) and the “lmerTest” (Kuznetsova et al., 2014) packages for R. Degrees of freedom in the LMMs were estimated using Satterthwaite’s approximation as implemented in the lmerTest (Kuznetsova et al., 2014) package. Figures were created using the “ggplot2” package for R (Wickham, 2009).

3 | RESULTS

3.1 | Effects related to the presence of PLP: differences between the groups and body sites

Results from the LMMs for all measures are shown in Figure 1. Table 2 summarizes the coefficients for the full models (including the factor group and body site, and the group × body site interaction). Table 3 summarizes the results from post-hoc comparisons between the body sites.

3.1.1 | Heat pain thresholds

There was no significant main effect of group \([F(2, 53) = 0.1, p = 0.901]\) and no significant interaction between group and body site \([F(8, 211) = 0.65, p = 0.732]\). The main effect of body site was significant \([F(4, 211) = 50.5, p < 0.001]\). Post-hoc comparisons (Table 3) showed that HPT were significantly

![Figure 1](image-url)
lower at the ipsilateral arm compared to the contralateral arm and also at both corners of the mouth compared to both arms and the thenar. The corners of the mouth did not differ significantly from each other, and the thenar did not differ significantly from both arms.

### 3.1.2 Pressure pain thresholds

For PPT, there was no significant effect of group \( F(2, 53) = 0.86, p = 0.430 \) or group \( \times \) body site \( F(8, 211) = 1.91, p = 0.061 \). The factor body site was significant \( F(4, 211) = 4.67, p = 0.001 \).
Post-hoc comparisons between body sites revealed that all body sites differed significantly from each other except for the homologous body parts at the corners of the mouth, which did not differ significantly. At the arms, PPT were significantly lower ipsilateral than contralateral.

3.1.3 | Warmth detection thresholds

No significant effect of group \(F(2, 53) = 2.88, p = 0.065\) and group × body site was found \(F(8, 212) = 0.94, p = 0.485\). The factor body site was significant \(F(4, 204) = 88.91, p < 0.001\). Post-hoc comparisons revealed significant differences between all body sites, except for the comparison between the corners of the mouth and between both arms where the differences were not significant.

3.1.4 | Two-point discrimination thresholds

For 2PDT, there was no significant effect of group \(F(2, 44) = 1.43, p = 0.25\) or group × body site \(F(6, 128) = 0.54, p = 0.775\). Body site was significant \(F(3, 129) = 304.21, p < 0.001\). Post-hoc tests showed that thresholds were lower at both corners of the mouth than at both arms. The homologous parts at the corners of the mouth and at the arms did not differ significantly from each other.

3.2 | Effects related to the intensity of PLP: correlational analyses

3.2.1 | Correlations between PLP intensity and sensory thresholds

All correlations between the sensory thresholds in the PLP group and the reported intensity of PLP are shown in Figure 2. For HPT, the correlations were negative, indicating that more intense PLP was associated with lower HPT, and significant for the ipsilateral corner of the mouth \((r = -0.59, p = 0.003)\), the contralateral corner of the mouth \((r = -0.65, p < 0.001)\), the thenar \((r = -0.64, p < 0.001)\) and the contralateral arm \((r = -0.45, p = 0.031)\). Only at

![FIGURE 2](image-url) Distributions of sensory thresholds and their correlations with the intensity of phantom limb pain (PLP) in the PLP group (orange). The rows represent the thresholds, which were assessed: heat pain thresholds (HPT), pressure pain thresholds (PPT), warmth detection thresholds (WDT) and two-point discrimination thresholds (2PDT). The columns represent the body sites: the arm ipsilateral to the amputation (in amputees the residual limb, in healthy controls a matched site), the contralateral arm, the ipsilateral and the contralateral corner of the mouth, and the contralateral thenar. Within each subplot, the scatter plots (on the left) show the data of the PLP group (orange) and the amputees without PLP (non-PLP; blue) for the respective threshold and PLP intensity. For the PLP group, the result of a linear regression model is shown. The Pearson correlation coefficients together with (two-sided) \(p\)-values are shown within the plots. The right side of each subplot shows the distribution of the sensory thresholds as boxplots for the PLP group, the non-PLP group and healthy controls (HC; grey). The mean values for each group are highlighted as a red point.
the ipsilateral arm (residual limb), the correlation was not significant \( r = -0.33, p = 0.137 \). PPT were significantly negatively correlated with PLP intensity at the contralateral corner of the mouth \( r = -0.48, p = 0.019 \) and at the ipsilateral arm \( r = -0.44, p = 0.036 \). However, the result for the ipsilateral arm was no longer significant when outliers were removed from the data (see Supplementary Material, Table S3). At all other body sites, the correlations were negative but not significant (Figure 2). WDT and 2PDT were not significantly correlated with PLP intensity at any of the body sites (Figure 2).

Intra-individual differences between the homologous areas at the arms and the corners of the mouth were not significantly correlated with PLP intensity for any of the sensory thresholds (all \( r > -0.32 \) and \( <0.37 \), all \( p > 0.07 \)). All correlations are shown Supplementary Material (Figure S1).

### 3.2.2 Association of PLP intensity with a linear combination of all sensory thresholds

The stepwise multiple regression procedure removed 12 out of the 15 sensory thresholds and resulted in a model in which PLP intensity was predicted by a combination of three sensory thresholds, which are listed in Table 4 (Model A). The resulting model was statistically significant \( F(9, 13) = 8.67, p < 0.001; R^2 = 0.57; R^2_{adj} = 0.51 \). Two thresholds in this model significantly predicted higher degrees of PLP intensity: lower HPT \( b = -0.21, t(19) = -4.74, p < 0.001 \) and higher WDT at the contralateral corner of the mouth \( b = 2.96, t(19) = 2.96, p = 0.03 \) Note that HPT received negative and WDT positive weights, indicating that higher PLP intensity was associated with lower HPT and higher WDT, which is shown in Figure 3.

Further multiple regression analyses (reported in Supplementary Material, Table S5) confirmed that the associations of PLP intensity with HPT and WDT at the corner of the mouth were still present when a number of other potentially relevant correlates of PLP were controlled for. This shows that the relationship is robust and not mediated by any of these variables.

### 3.2.3 Specificity of associations of PLP and RLP intensities with sensory thresholds

Only two sensory thresholds remained in the resulting model (Model B): HPT at the contralateral corner of the mouth and HPT at the ipsilateral arm. Importantly, there were significant interactions with type of pain (PLP vs. RLP intensity) for both HPT at the contralateral corner of the mouth \( F(1, 23) = 8.69, p < 0.001 \) and at the ipsilateral arm \( F(1, 23) = 4.41, p = 0.046 \). The interactions are visualized in Figure 4. On the ipsilateral arm, lower HPT was associated with higher levels of RLP but not with PLP \( b = -0.16, t(23) = -2.10, p = 0.047 \). On the contralateral corner of the mouth, however, lower HPT was specifically associated with more PLP \( b = 0.23, t(23) = 2.95, p = 0.007 \). This indicates that the two concurrent types of clinical pain, PLP and RLP were differentially associated with sensory thresholds: PLP was mainly associated with HPT in the face and RLP with HPT at the residual limb.

| Model | Term | \( b \) | \( t \) | \( df \) | \( p \) |
|-------|------|--------|--------|-------|------|
| A     | (Intercept) | 8.99 | 4.84 | 19 | <0.001 |
|       | HPT mouth contra | -0.21 | -4.75 | 19 | <0.001 |
|       | WDT arm ipsi | 1.07 | 1.49 | 19 | 0.152 |
|       | WDT mouth contra | 2.96 | 2.38 | 19 | 0.028 |
| B     | (Intercept) | 9.54 | 3.33 | 42.6 | 0.002 |
|       | Pain type\(^a\) | -2.48 | -0.72 | 23.0 | 0.478 |
|       | HPT arm ipsi | 0.01 | 0.15 | 42.6 | 0.882 |
|       | HPT mouth contra | -0.19 | -3.01 | 42.6 | 0.004 |
|       | Pain type \(\times\) HPT arm ipsi | -0.16 | -2.10 | 23.0 | 0.047 |
|       | Pain type \(\times\) HPT mouth contra | 0.23 | 2.95 | 23.0 | 0.007 |

*Note: The table lists regression terms that remained in the final model after iterative removal of terms not significantly contributing to the model fit. (A) Statistical prediction of PLP by HPT, PPT and WDT measured at all body sites. (B) Statistical prediction of both PLP and RLP by the same combination of thresholds like in model A including the factor ‘pain type’ coding for PLP and RLP, respectively.

Abbreviations: HPT, heat pain thresholds; PLP, phantom limb pain intensity; PPT, pressure pain thresholds; RLP, residual limb pain intensity; WDT, warmth detection thresholds.

\(^a\)The baseline level was PLP, hence the regression coefficient codes the influence of RLP.
4.1 No association between sensory thresholds and the presence of PLP

We tested for associations with the presence of PLP by comparing pain and perception thresholds measured in the PLP group to those measured in the non-PLP group and in HC. Surprisingly, there were no significant differences between HPT and PPT at any of the measured body sites as a function of the absence/presence of PLP. We also did not find any evidence for an association between detection thresholds and the presence of PLP. This negative finding was against our primary hypothesis that the presence of PLP might be associated with pain perception.

4.2 PLP intensity correlates with sensory thresholds

Contrary to the non-significant differences in sensory thresholds between the groups, we found that higher PLP intensity was associated with lower HPT at all body sites except for the residual limb. Similar correlations were also found for PPT although the relationships were numerically weaker and a robust significant correlation was only found at the contralateral corner of the mouth. In contrast to the pain thresholds, detection thresholds for non-painful stimuli were not significantly correlated with PLP intensity. However, when combining pain and detection thresholds of all body sites to statistically predict PLP intensity in multiple regression, we found a differential relationship of PLP intensity with lowered HPT but heightened WDT in the face. At the contralateral corner of the mouth, the combination of HPT and WDT explained a high proportion (of up to 51%) of the variance in PLP intensity. This suggests that when PLP is present, its intensity is strongly associated with decreased pain but increased warmth detection thresholds in the face. Because the face is remote from the residual limb, the observed patterns of sensory thresholds are therefore not likely to have a peripheral origin.

It might strike as a surprise that PLP was differentially associated with, on the one side, lower pain but, on the other side, higher perception thresholds. However, it is well documented that chronic pain is associated with reduced precision in perception of non-painful stimuli (Catley et al., 2014; Moseley, 2008; Moseley et al., 2012). Our results fit well with the ‘imprecision hypothesis’ of chronic pain (Moseley & Vlaeyen, 2015). This hypothesis posits that chronic pain patients learn associations between multisensory events, or bodily states, and painful events (e.g. during an injury). Similar bodily states can later increase the likelihood to perceive pain again due to classical conditioning. This learning mechanism is enhanced when bodily states are less precisely perceived.
4.3 Differences between body sites and their possible relationship to peripheral versus central processes

For all sensory measures, we found significant differences between body sites. Many of the results were expected based on prior research. For example, the corners of the mouth showed lower thresholds than all other body sites in all sensory measures. With respect to processes of PLP, comparisons between the homologous body sites at the corners of the mouth and the arms are of particular interest. The comparison between the arms (i.e., between the residual limb and its contralateral counterpart) can be indicative of peripheral changes. Differences between the corners of the mouth could be indicative of cortical changes in early sensory processing areas such as S1. We found that HPT and PPT were significantly lower at the residual limb compared to the intact limb, which could be viewed as a sign of peripheral hyperalgesia. However, this local hyperalgesia was observed in both the PLP and in the non-PLP group. Moreover, the difference between limbs was not significantly correlated with PLP intensity. These findings do not suggest a close relationship between PLP and pain thresholds at the residual limb. We also revisited the hypothesis of increased tactile acuity of the residual limb. Contrary to early studies (Haber, 1955; D. Katz, 1921; Teuber et al., 1949; Wilson et al., 1962), but in line with more recent ones (Flor et al., 1998; Grüsser et al., 2001; Hunter et al., 2005), we did not find significantly lower 2PDT at the residual limb. There were also no significant differences between the limbs in WDT. Taken together, these results support the conclusion drawn by Hunter et al. (2005) that sensory measures taken at the residual limb do not in any simple way reflect phantom phenomena. Our data further suggest that they are instead more strongly related to RLP.

Because cortical reorganization in S1 is both associated with PLP (Flor et al., 1995) and with sensory changes in the face of healthy subjects (Muret et al., 2016), sensory thresholds might be altered in the mouth region of amputees. We did not find significant differences between the groups at the corners of the mouth and there were no significant intra-individual differences between the corners of the mouth for any of the thresholds. As discussed above, HPT and WDT in the face correlated with PLP intensity in a multivariate analysis. Because the face is remote from the residual limb, this likely represents a centrally mediated effect. The fact that facial pain thresholds were specifically associated with PLP is in line with the notion that preamputation pain leads to the formation of cortical pain memories via growth or broader recruitment of nociceptive neurons in S1, resulting in an increased range of stimuli eliciting pain (Flor, 2002; Vierck et al., 2013; Yi & Zhang, 2011). It is possible that this process also spreads to the neighbouring face area due to PLP-related S1 reorganization. However, this association was present at both sides of the face, whereas PLP-related S1 reorganization of the face was found to be lateralized (Flor et al., 1995), that is mainly affecting S1 contralateral to the amputation. If facial sensitivity closely paralleled cortical reorganization, the sensory changes would be expected to be lateralized as well, with changes primarily in the half of the face that is ipsilateral to the amputation. From this view, it is surprising that we found the strongest associations for the contralateral face. However, associations were also present for the ipsilateral...
face, as evident from the correlations. Due to the high degree of intercorrelations between the thresholds, they are redundant, and the ipsilateral face dropped in multiple regression models. Second, it is possible that different generalization mechanisms overlap and that changes might have affected the ipsilateral face at an earlier and the entire face at a later stage. Further studies are needed to investigate whether there is a relationship between facial cortical reorganization in PLP and changes in the facial thermal thresholds.

Most studies on cortical reorganization processes in amputees used tactile (e.g. Flor et al., 1995) or motor methods (e.g. Lotze et al., 2001) to map the cortical reorganization of the hand and the lips. As a tactile measure, this study assessed 2PDT. There was no significant association between PLP presence or intensity and facial 2PDT. Studies in healthy participants have shown that peripheral input to the hand alters its S1 reorganization and that this effect spreads to the face, leading to altered facial 2PDT (Muret et al., 2016). From this perspective, 2PDT might have been altered in the amputation group. Other studies, however, suggest that 2PDT is not closely related to S1 organization and rather reflects processes outside of S1, for example in the inferior parietal cortex (Akatsuka et al., 2008).

### 4.4 Specificity of associations for PLP versus RLP and other chronic pain

Residual limb pain intensity should be carefully compared with PLP, because as a frequent concomitant in chronic PLP, it might be a driver of plastic changes in the nociceptive system. We therefore compared the statistical association between PLP and RLP intensity with sensory thresholds. This analysis showed that HPT at the contralateral corner of the mouth specifically correlates with PLP whereas HPT at the residual limb is specifically associated with RLP. In fact, the residual limb was the only measured body site where HPT was not significantly correlated with PLP. With respect to the finding that it was mainly PLP, and not RLP, that was associated with pain thresholds at areas of the body that were remote from the residual limb, it can be assumed that it might primarily be PLP that is associated with central factors of pain enhancement, whereas RLP might rather be associated with peripheral factors related to sensitivity of the residual limb.

There are similarities with other types of chronic pain. In fibromyalgia, pain thresholds are lowered in a widespread manner, both at so-called tender points and at other areas, and PPT correlates negatively with clinical pain assessments (Lautenbacher et al., 1994). Other studies reported contralateral transfer of lowered PPT in complex regional pain syndrome (CRPS), but not in arthritis patients (Palmer et al., 2019), or in CRPS but not in a control group with other chronic pain syndromes (Vatine et al., 1998). One study found that transfer of lowered PPT to the forehead in CRPS was more pronounced ipsilateral than contralateral to the affected limb (Drummond & Finch, 2006). This finding is interesting because it is in line with the idea that generalization might be related to S1 reorganization, which is seen both in PLP and CRPS (for a review see Di Pietro et al., 2013). Future research could directly compare sensory processes in PLP, CRPS and other chronic pain to advance the understanding of specific processes in these chronic pain syndromes.

### 4.5 Discrepancy between presence and intensity of PLP

Our results showed that, contrary to our hypothesis, lower pain thresholds were not associated with having PLP. Lower pain thresholds were observed in the PLP as well as in the non-PLP group and were, as such, unspecific. However, for those amputees who reported PLP, pain thresholds correlated with PLP intensity. These two findings seem, at first glance, almost incompatible. However, they might indicate that lowered pain thresholds play a different role depending on whether PLP is present or not. Such differential processing of sensory information depending on the presence or absence of pain is not unusual. In line with this, Davis et al. (2015) suggested that the presence or absence of chronic pain is not merely a quantitatively, but rather a qualitatively different state. When, in their words, the ‘pain switch is turned on’, pain-modulating factors might interact with each other in a different way. As the presence of chronic pain is associated with changes in neural processing of sensory information (Davis & Moayedi, 2013; Latremoliere & Woolf, 2009; Woolf & Salter, 2000), memory, affective learning and emotional processes (Flor & Turk, 2011), we propose that pain thresholds might play a different role when PLP is present compared to absent and influence its perceived intensity.

As another explanation, pain thresholds correlating with PLP intensity, but not its presence per se, could also be the end product of an etiological process. Central sensitization resulting from long-term nociceptive input is a potential explanation for the correlation between PLP intensity and enhanced sensitivity to painful stimuli (Woolf & Salter, 2000) and its generalization to remote areas of the body (Le Bars, 2002) in participants with strong PLP. The strong nociceptive input might decrease both pain thresholds and lead to the formation of pain memories related to PLP, resulting in an association between them. Yet, it is also possible that participants who developed strong PLP already had low pain thresholds before the amputation (Nikolajsen et al., 2000). Low pain thresholds might have been present as a preamputation trait, potentially promoting the emergence of PLP. Preoperation pain sensitivity has been shown to predict...
postoperative pain (Granot, 2009) and PLP early after amputation correlated positively with sensitivity to pain stimuli assessed right before the amputation (Nikolajsen et al., 2000). However, whether later-stage chronic pain is also associated with pain sensitivity before injury is not known yet.

In one way or the other, sensory processes as such do not seem to be able to explain why amputees develop chronic PLP but it is possible that they interact with other factors. Factors determining whether or not amputees develop chronic pain are manifold (Flor, 2002) and altered pain processing might be one among them (Flor et al., 2006; Nikolajsen et al., 1997, 2000). Functional (Apkarian et al., 2013) and structural (Mansour et al., 2013) brain connectivities have been shown to predict the transition from acute to chronic back pain in longitudinal studies. Although PLP patients might differ from chronic back pain patients especially with respect to the role of cognitive and emotional variables (Fuchs et al., 2015, 2018), it should be clarified whether brain connectivity also predicts chronic PLP and how this relates to sensory processing and cortical reorganization. As these relevant questions need to be addressed using a longitudinal design, the present study can, by itself, not contribute to clarify these etiological questions.

Future research should also investigate relationships between the decreased pain thresholds observed in this study and other alterations of sensory processing that have been observed in chronic pain. For example, diffuse noxious inhibitory controls (DNIC) or conditioned pain modulation refer to the fact that the response to a painful stimulus is reduced or inhibited due to another concurrently applied painful stimulus (Le Bars et al., 1979) and this process has been found to be deficient in chronic pain (Lewis et al., 2012). In this study, we only tested single painful stimuli but did not assess pain inhibition as assessed in dual stimulation paradigms testing DNIC. Sensitization and habituation to painful stimuli have been found to be altered in chronic pain (Kleinbölhl et al., 1999). In this study, habituation across HPT trials occurred and reduced habituation correlated with PLP intensity, which did, however, not explain the reduced pain thresholds we have reported (see Supplementary Material, Figure S6).

Future research should use sensitization and habituation paradigms (e.g. Kleinbölhl et al., 1999) to assess the role of these variables in PLP.

4.6 Limitations

There are some limitations for the present study. First, the study is only based on psychophysical thresholds. While the study design invites conclusions about underlying processes, further studies using neuroimaging methods are needed to further investigate whether the mechanisms at play are peripheral or central. Second, the study relied on a cross-sectional design and its findings are only correlational and allow no direct conclusions about the etiology of PLP. Third, the study was restricted to sensory mechanisms related to the amputation and PLP and, in correlational analyses, RLP. This leaves open how specific these findings are to PLP. This could have been investigated by including another clinical group with a pain condition other than PLP (e.g. chronic back pain, CRPS, or fibromyalgia).

Another limitation arises from the choice of tested body sites and used measures. In this study, even the remote sites, such as the thenar of the contralateral limb, are connected to the missing limb via interhemispheric connections. If lowered pain thresholds more strongly generalize to body parts with S1 representations adjacent to the hand than to remote body parts, this suggests that generalization parallels brain reorganization processes. For clarification of the mechanisms of generalization, assessment of another, more remote, site such as the contralateral foot would have been informative. Furthermore, most studies on brain changes in amputees are based on tactile or motor processes and the present study used warmth detection as the primary detection measure. The inclusion of mechanical detection thresholds would have been advantageous but would have prolonged the study protocol, which was not feasible in the context of this study. Unfortunately, 2PDT, which have a close relationship with S1 reorganization, were only available in a subsample of the amputees, resulting in reduced testing power for 2PDT and their exclusion from the multivariate analyses. Hence, this study cannot answer some questions concerning potential changes in tactile spatial acuity and its relationship with PLP. The choice of body sites and the testing protocol also diverged in some respects from the protocol proposed by the DFNS (Rolke et al., 2006), which limits the comparability of the results to other studies and to normative data provided by the network (Magerl et al., 2010). For example, the normative data for the face were assessed on the cheeks for thermal thresholds and over the masseter muscle for PPT, but we assessed them at the corners of the mouth for theoretical reasons related to previous data on reorganization. Further, the DFNS protocol assessed thermal thresholds on the hand dorsum while we used the thenar. While we had theoretical reasons for using the corners of the mouth instead of the cheeks, the thermal thresholds on the hand could instead have been assessed on the dorsum of the hand with the benefit of better comparability with the normative data. Another deviation is that, for the thermal thresholds, we used verbal responses and the experimenter pressed the button as fast as possible. This procedure is not ideal because it creates a bias (overestimation) of the threshold due to the reaction time of the experimenter. Second, the experimenter was not blinded concerning the group assignment of the participants and could have been implicitly biased and reacted slower (or faster) depending on the group assignment of the participants, which could confound the data. The
experimented best to always react as fast as possible and to stay neutral. The finding of some results that were contrary to our hypothesis suggests that this was successful. In future studies, participants could use their feet to press the response buttons, for example. In Supplementary Material, we compared our thresholds with the DFNS normative data, and we found that our WDT were inflated. This difference could be related to the additional delay due to the experimenter’s reaction time but should be interpreted with caution due to the different body sites as mentioned above. Note that these deviations are not problematic for the interpretation of the present results because the protocol was identical for all tested groups, but they limit the possibilities of comparison with the normative data. This could be addressed in future studies. For PPT at the thenar, where the protocols and body site were identical, the thresholds match with the normative studies. For PPT at the residual limb, however, were unrelated to PLP but specifically related to RLP.

**4.7 Conclusions**

In summary, our assessments of pain thresholds at different body sites, remote from the residual limb, suggest that global enhanced sensitivity to painful stimuli is related to the intensity of PLP. The global pattern showed that amputees in the PLP group with low levels of PLP were hypoalgesic and those with strong PLP were hyperalgesic. For facial HPT, for which the association with PLP was strongest, associations were even stronger when WDT was also taken into account. PLP was associated with decreased HPT but increased WDT in the face. This pattern was specific to PLP. Pain thresholds at the residual limb, however, were unrelated to PLP but specifically related to RLP. Surprisingly, any differences in sensory thresholds between the groups were absent and so the mere presence of PLP did not coincide with sensory thresholds at any body site. We suggest that these global sensitivity changes reflect a central aspect of sensory processing rather than peripheral mechanisms, emphasizing the presence of ‘widespread hypersensitivity’ which has already been suggested by Cronholm in 1951 (p. 119). Whether this phenomenon is related to plasticity processes occurring after or to factors already present before amputation cannot be clarified based on the present data.

**AUTHOR CONTRIBUTION**

HF, MD and XF conceptualized and designed the study. XF and PK collected the data. XF analyzed the data and drafted the manuscript. All authors wrote and critically revised the article and approved the final version.

**ACKNOWLEDGEMENTS**

This study was supported by a grant from the Deutsche Forschungsgemeinschaft (SFB1158/B07) to HF and JA and European Research Council Advanced grant ‘Phantom phenomena: A window to the mind and the brain’ (PHANTOMMIND, FP7/2007–2013/230249) to HF. We would also like to thank Astrid Wolf for help with recruitment, Kristina Staudt and student assistants for their help with data acquisition.

**DATA AVAILABILITY STATEMENT**

Data and code of this study are publicly available and can be accessed via the Open Science Framework (https://osf.io/v6hjy/).

**REFERENCES**

Akatsuka, K., Noguchi, Y., Harada, T., Sadato, N., & Kakigi, R. (2008). Neural codes for somatosensory two-point discrimination in inferior parietal lobule: An fMRI study. *NeuroImage, 40*(2), 852–858. https://doi.org/10.1016/j.neuroimage.2007.12.013

Apkarian, A. V., Baliki, M. N., & Farmer, M. A. (2013). Predicting transition to chronic pain. *Current Opinion in Neurology, 26*(4), 360–367. https://doi.org/10.1097/WCO.0b013e328326336ad

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2014). Fitting linear mixed-effects models using lme4. *ArXiv Preprint arXiv:1406.5823.*

Bekrater-Bodmann, R., Chung, B. Y., Richter, L., Wicking, M., Foell, J., Mancke, F., Schmah, C., & Flor, H. (2015). Deficits in pain perception in borderline personality disorder: Results from the thermal grill illusion. *Pain, 156*(10), 2084–2092. https://doi.org/10.1097/j.jp. pain.0000000000002275

Bekrater-Bodmann, R., Schredl, M., Diers, M., Reinhard, I., Foell, J., Trojan, J., Fuchs, X., & Flor, H. (2015). Post-amputation pain is associated with the recall of an impaired body representation in dreams—results from a nation-wide survey on limb amputees. *PLoS One, 10*(3), e0119552. https://doi.org/10.1371/journal.pone.0119552

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society, Series B (Methodological), 57*(1), 289–300. https://doi.org/10.2307/2346101

Bonzano, L., Tacchino, A., Roccagagliata, L., Abbruzzese, G., Mancardi, G. L., & Bove, M. (2008). Callosal contributions to simultaneous bimanual finger movements. *The Journal of Neuroscience, 28*(12), 3227–3233. https://doi.org/10.1523/JNEUROSCI.4076-07.2008

Catley, M. J., O’Connell, N. E., Berryman, C., Ayyan, F. F., & Moseley, G. L. (2014). Is tactile acuity altered in people with chronic pain? A systematic review and meta-analysis. *The Journal of Pain, 15*(10), 985–1000. https://doi.org/10.1016/j.jpain.2014.06.009

Cronholm, B. (1951). Phantom limbs in amputees; a study of changes in the integration of centripetal impulses with special reference to referred sensations. *Acta Psychiatrica Et Neurologica Scandinavica Suplementum, 72*, 1–310.

Davis, K. D., Kucyi, A., & Moayedi, M. (2015). The pain switch: An “ouch” detector. *Pain, 156*(11), 2164–2166. https://doi.org/10.1097/j.pain.0000000000003030

Davis, K. D., & Moayedi, M. (2013). Central mechanisms of pain revealed through functional and structural MRI. *Journal of Neuroimmune Pharmacology, 8*(3), 518–534. https://doi.org/10.1007/s11481-012-9386-8

Devor, M. (1991). Neuropathic pain and injured nerve: Peripheral mechanisms. *British Medical Bulletin, 47*(3), 619–630. https://doi.org/10.1093/oxfordjournals.bmh.a072496
Vase, L., Nikolajsen, L., Christensen, B., Egsgaard, L. L., Arendt-Nielsen, L., Svensson, P., & Staehelin Jensen, T. (2011). Cognitive-emotional sensitization contributes to wind-up-like pain in phantom limb pain patients. *Pain, 152*(1), 157–162. https://doi.org/10.1016/j.pain.2010.10.013

Vaso, A., Adahan, H.-M., Gjika, A., Zahaj, S., Zhurda, T., Vyshka, G., & Devor, M. (2014). Peripheral nervous system origin of phantom limb pain. *Pain, 155*(7), 1384–1391. https://doi.org/10.1016/j.pain.2014.04.018

Vatine, J.-J., Tsenter, J., & Nirel, R. (1998). Experimental pressure pain in patients with complex regional pain syndrome, type I (reflex sympathetic dystrophy). *American Journal of Physical Medicine & Rehabilitation, 77*(5), 382–387.

Vierck, C. J., Whitsel, B. L., Favorov, O. V., Brown, A. W., & Tommerdahl, M. (2013). Role of primary somatosensory cortex in the coding of pain. *Pain, 154*(3), 334–344. https://doi.org/10.1016/j.pain.2012.10.021

Wahren, L. K. (1990). Changes in thermal and mechanical pain thresholds in hand amputees. A clinical and physiological long-term follow-up. *Pain, 42*(3), 269–277. https://doi.org/10.1016/0304-3959(90)91139-A

Weinstein, S. (1968). Intensive and extensive aspects of tactile sensitivity as a function of body part, sex, and laterality. In D. R. Kenshalo (Ed.), *The skin senses: Proceedings of the first International Symposium on the Skin Senses, held at the Florida State University in Tallahassee, Florida* (pp. 195–218). Charles C. Thomas Publishing.

Wickham, H. (2009). ggplot2: Elegant graphics for data analysis. Springer Science & Business Media.

Wiffen, P., Meynadier, J., Dubois, M., Thurel, C., DeSmet, J., & Harden, R. N. (2006). Chapter 4: Diagnostic and treatment issues in postamputation pain after landmine injury. *Pain Medicine, 7*(Suppl 2), S209–S212. https://doi.org/10.1111/j.1526-4637.2006.00234_6.x

Wilson, J. J., Wilson, B. C., & Swinyard, C. A. (1962). Two-point discrimination in congenital amputees. *Journal of Comparative and Physiological Psychology, 55*(4), 482–485. https://doi.org/10.1037/h0042122

Woolf, C. J. (2014). What to call the amplification of nociceptive signals in the central nervous system that contribute to widespread pain? *Pain, 155*(10), 1911–1912. https://doi.org/10.1016/j.pain.2014.07.021

Woolf, C. J., & Salter, M. W. (2000). Neuronal Plasticity: Increasing the Gain in Pain. *Science, 288*(5472), 1765–1768. https://doi.org/10.1126/science.288.5472.1765

Yi, M., & Zhang, H. (2011). Nociceptive memory in the brain: Cortical mechanisms of chronic pain. *The Journal of Neuroscience, 31*(38), 13343–13345. https://doi.org/10.1523/JNEUROSCI.3279-11.2011

**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the Supporting Information section.

**How to cite this article:** Fuchs, X., Diers, M., Trojan, J., Kirsch, P., Milde, C., Bekrater-Bodmann, R., Rance, M., Foell, J., Andoh, J., Becker, S., & Flor, H. (2022). Phantom limb pain after unilateral arm amputation is associated with decreased heat pain thresholds in the face. *European Journal of Pain, 26*, 114–132. [https://doi.org/10.1002/ejp.1842](https://doi.org/10.1002/ejp.1842)