Peripheral input and phantom limb pain: A somatosensory event-related potential study

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Abstract

Background: Following amputation, nearly all amputees report nonpainful phantom phenomena and many of them suffer from chronic phantom limb pain (PLP) and residual limb pain (RLP). The aetiology of PLP remains elusive and there is an ongoing debate on the role of peripheral and central mechanisms. Few studies have examined the entire somatosensory pathway from the truncated nerves to the cortex in amputees with PLP compared to those without PLP. The relationship among afferent input, somatosensory responses and the change in PLP remains unclear.

Methods: Transcutaneous electrical nerve stimulation was applied on the truncated median nerve, the skin of the residual limb and the contralateral homologous nerve in 22 traumatic upper-limb amputees (12 with and 10 without PLP). Using somatosensory event-related potentials, the ascending volley was monitored from the brachial plexus, the spinal cord, the brainstem and the thalamus to the primary somatosensory cortex.

Results: Peripheral input could evoke PLP in amputees with chronic PLP (7/12), but not in amputees without a history of PLP (0/10). The amplitudes of the somatosensory components were comparable between amputees with and without PLP. In addition, evoked potentials from the periphery through the spinal, subcortical and cortical segments were not significantly associated with PLP.

Conclusions: Peripheral input can modulate PLP but seems insufficient to cause PLP. These findings suggest the multifactorial complexity of PLP and different mechanisms for PLP and RLP.

Significance: Peripheral afferent input plays a role in PLP and has been assumed to be sufficient to generate PLP. In this study we found no significant differences in the electrical potentials generated by peripheral stimulation from the truncated nerve and the skin of the residual limb in amputees with and without PLP. Peripheral input could enhance existing PLP but could not cause it. These findings indicate the multifactorial complexity of PLP and an important role of central processes in PLP.
Peripheral injury and deprivation drive plastic changes in both the peripheral and central nervous system (Draganski et al., 2006; Elbert et al., 1994; Hamzei et al., 2001; Makin et al., 2015; Merzenich et al., 1984; Yang et al., 1994). After amputation, such changes have been related to chronic neuropathic pain (Flor, 1995, 2002; Kuner & Flor, 2016). Residual limb pain (RLP) has mostly been attributed to peripheral pathological alterations and prosthesis use (Guo et al., 2019; Yazicioglu, Tugcu, Yilmaz, Goktepe, & Mohur, 2008). Phantom limb pain (PLP) has been found to be specifically associated with central plastic changes (Flor, Nikolajsen, & Staehelin Jensen, 2006; Kikkert et al., 2017; Lotze, Flor, Grodd, Larbig, & Birbaumer, 2001; Makin et al., 2013; Reilly & Sirigu, 2008). A positive correlation has repeatedly been found between PLP intensity and expansions and/or shifts of neighbouring cortical representations in relation to the deafferented hand area, assumed to be driven by sensory deprivation (Flor et al., 1995). Makin et al. (2013) reported a positive relationship between increased activation by phantom movement in the representation of the amputated limb and PLP (Makin et al., 2013). Another group related cortical reorganization to phantom sensations and showed that pain might be not critical in functional sensorimotor changes (Bramati et al., 2019; Simoes et al., 2012). Therapies that relieve PLP such as mirror therapy, motor imagery or sensory discrimination training showed a correspondence between a reversal of assumed maladaptive cortical reorganization and a reduction in PLP (Flor, Denke, Schaefer, & Grüser, 2001; Foell, Bekrater-Bodmann, Diers, & Flor, 2014; Gagné, Reilly, Hétu, & Mercier, 2009; MacIver, Lloyd, Kelly, Roberts, & Nurmikko, 2008). In addition, PLP has been shown to be generated by thalamic microstimulation (Davis et al., 1998), spinal metastatic pathologies (Cruz & Dangaria, 2013), spinal anaesthesia (Harrison, 1951; Mackenzie, 1983; Murphy & Anandaciva, 1984) and has been connected to alterations in the brainstem. These findings suggest a preponderance of central mechanisms in PLP.

PLP is highly correlated with RLP (Carlen, Wall, Nadvorna, & Steinbach, 1978; Desmond & Maclachlan, 2010; Gallagher, Allen, & Maclachlan, 2001; Kooijman, Dijkstra, Geertzen, Elzinga, & van der Schans, 2000) and both might be maintained by peripheral input and amplified centrally (Ringkamp & Raja, 2014; Vase et al., 2011; Weeks, Anderson-Barnes, & Tsao, 2010). Ectopic generators have been proposed including neuromas, truncated afferent axons and abnormal activity in the dorsal root ganglia (DRG; Devor, 2009). For instance, peripheral discharges triggered by taps on neuromas were recorded from the truncated nerves using microelectrode recordings and were related to PLP (Nyström & Hagbarth, 1981). After anaesthetizing the DRG or the spine by injecting lidocaine in lower-limb amputees, PLP has been observed to be temporarily eliminated (Vaso et al., 2014). However, placebo-controlled and blinded randomized controlled clinical trials are lacking. Recently, Buch et al. (2019) showed that PLP could be significantly reduced after peripheral nerve block using lidocaine, suggesting a role of peripheral input in postamputation pain including PLP (Buch et al., 2019). A few studies have measured the somatosensory neuraxis from the truncated nerve fibres to the cortex in upper-limb amputees using somatosensory-evoked potentials (SEP; Mackert, Sappok, Grüser, Flor, & Curio, 2003; Schwenkreis et al., 2001). Peripheral input from the truncated nerves was found to reach the deafferented cortex in upper-limb amputees without painful phantom sensations, which could provide a possible neural substrate for spontaneous phantom sensations and PLP (Mackert et al., 2003). However, this study did not include amputees with PLP and another study (Schwenkreis et al., 2001) only examined activity at the cortical level. In addition, computational models of central changes in PLP assume that peripheral generators can drive central reorganizational processes (Boström, de Lussanet, Weiss, Putta, & Wagner, 2015; Spitzer, 1997). The role of peripheral input for PLP and how it interacts with central processes is therefore not yet completely understood.

Here, we aimed to compare somatosensory function in upper-limb amputees with and without PLP and sought to determine how peripheral input is associated with evoked responses and PLP. Specifically, we examined the somatosensory pathways through levels of the brachial plexus, the spinal cord, the brainstem and the primary somatosensory cortex (S1) using SEPs. We expected PLP and RLP to be modulated by peripheral input and corresponding changes in SEP amplitudes.
### TABLE 1 Demographic and clinical details

| Subject | Age/ Gender | Age at Amp. | Amp. site | Pros. use | Habitual PLP intensity (MPI) | Habitual RLP intensity (MPI) | Amplitudes of SEP components by the truncated and contralateral intact median nerve stimulation (μV) |
|---------|-------------|-------------|-----------|-----------|-----------------------------|-----------------------------|---------------------------------------------------------------------------------------------------|
| PG01    | 66/F        | 38          | L, 5      | 0         | 2                           | 0                          | abs abs abs abs 0.19 0.79 |
| PG02    | 37/M        | 20          | R, 5      | 0         | 2                           | 1                          | abs 0.96 abs 0.37         |
| PG03    | 48/F        | 24          | L, 3      | 0         | 4                           | 3                          | 0.55 abs 0.70 abs         |
| PG04    | 76/M        | 33          | R, 5      | 0         | 2                           | 2                          | 7.49 1.38 abs 0.79         |
| PG05    | 58/F        | 23          | R, 2      | 2         | 2                           | 4                          | abs abs abs abs abs abs 0.94 |
| PG06    | 61/M        | 23          | R, 2      | 4         | 1                           | 1                          | 1.09 2.77 1.22 1.80       |
| PG07    | 49/F        | 17          | L, 5      | 0         | 2                           | 0                          | abs 1.62 0.17 0.57         |
| PG08    | 55/M        | 53          | R, 5      | 3         | 1                           | 0                          | abs 10.08 1.91 2.12       |
| PG09    | 50/M        | 17          | L, 3      | 6         | 3                           | 2                          | 0.24 abs 0.23 abs         |
| PG10    | 50/M        | 35          | L, 3      | 4         | 2                           | 1                          | 0.84 abs 0.47 0.48        |
| PG11    | 55/M        | 18          | L, 3      | 6         | 3                           | 1                          | 0.85 0.95 0.62 1.33       |
| PG12    | 58/M        | 28          | R, 5      | 1         | 2                           | 1                          | 2.02 1.90 2.40 1.08       |
| Mean ± SD | 55.3 ± 9.9  | 27.4 ± 10.7 | 6R6L      | 3.8 ± 1.3 | 2.2 ± 2.4                   | 2.2 ± 0.8                   | 1.3 ± 1.2 1.87 ± 2.54 2.81 ± 3.27 0.92 ± 0.77 1.04 ± 0.61 |

PLP = phantom limb pain; RLP = residual limb pain; PLP group: amputees with chronic PLP; Non-PLP group: amputees without PLP; F = female; M = male; Amp. = amputation; Amp. site: L = left; R = right; 1 = hand, 2 = wrist, 3 = forearm, 4 = elbow, 5 = upper arm, 6 = shoulder; Pros. = prosthetics; Pros. use: 0 = never, 1 = rarely, 2 = occasionally, 3 = weekly, 4 = daily (less than 4 hr a day), 5 = daily (more than 4 hr a day), 6 = daily (over 8 hr a day).

MPI: German version of the Multidimensional Pain Inventory adjusted to separately measure PLP and RLP, ranging from 0 (‘no pain’) to 6 (‘extreme pain’).

TN: truncated median nerve; SS: skin of the residual limb; CN: contralateral intact median nerve. Cv2/4/6: the 2/4/6th cervical spinous process. abs: absent.

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assessment of painful and nonpainful phantom phenomena, prosthesis use, a psychological evaluation and several pain measures including the German version of the West Haven-Yale Multidimensional Pain Inventory (MPI; Flor, Rudy, Birbaumer, Streit, & Schugens, 1990) modified to separately measure PLP and RLP (Flor et al., 1995; Lotze et al., 1999).

They were asked to keep their eyes open and fixate a black cross in the centre of a computer monitor in front of them.

#### 2.2.1 Peripheral nerve and skin stimulation

We applied transcutaneous electrical nerve stimulation using a standard bridge electrode (spacing 2.5 cm, cathode proximal) connected to a Digitimer stimulator (Digitimer® DS7A) with monophasic square-wave pulses of 0.2 ms at a 3 Hz frequency. Electrical stimuli were applied over three body sites:
the truncated median nerve (TN), the skin of the residual limb (SS) and the contralateral homologous intact median nerve (CN). The order of stimulated body sites was counterbalanced across the participants. To account for differences in distal variables such as different amputation levels, neuromas, scars and sensitive skin in individuals, we set a proximal level at the sulcus bicipitalis medialis in the upper arm for electrical stimulation of each body site (Mackert et al., 2003). To localize the nerve of the CN and TN, we made sure that electrical stimulation elicited thumb movement for the intact hand and ongoing projected paresthesia towards the elbow, forearm and the territory of the median nerve in the distal intact or phantom hand. In contrast, electrical stimulation of skin site (SS), which was not applied over the peripheral nerve trunk, did not elicit any projected paresthesia and the stimuli were perceived only at the stimulation site.

### 2.2.2 Sensory and pain thresholds

We determined sensory and pain thresholds for each participant and each body site (TN, SS, CN). For each threshold, we calculated the average value of the intensity (mA) of three consecutive measurements when the participant reported...
2.3.1 Data acquisition

2.3.1.1 Somatosensory-evoked potentials

Somatosensory-evoked potentials data were acquired using Ag/AgCl electrodes (diameter: 2 mm) and an actiCap following the standard 10–10 system located at the contralateral CP3/4 (the site of maximal potentials on the scalp over the upper-arm area in S1), contralateral F3/4 on the scalp and another six electrodes placed over the ipsilateral Erb’s point (Epi), the contralateral Erb’s point (Epc), the 2/4/6th cervical spinous process (Cv2/4/6) and a noncephalic site (Larynx) over the laryngeal prominence to obtain median-nerve SEPs. The signals were recorded with a wide bandwidth from DC to 2,470 Hz and a sampling rate of 10 kHz by an actiCHamp amplifier (Brain Products GmbH) and BrainVision Recorder software (version 1.21.0102) was employed (Rossini, Cracco, Cracco, & House, 1981). A total of 3,000 continuous stimuli lasting approximately 17 min for each body site were applied and recorded (Cruccu et al., 2008). The ground electrode was located at Fpz and the montage was referenced for peripheral (N9: Epi—Epc, P9: Fz—Epc), cervical (N13: Cv2/4/6—Larynx; Morizot-Koutlidis et al., 2015; Schabrun, Burns, & Hodges, 2015; Sonoo, Kobayashi, Genba-Shimizu, Mannen, & Shimizu, 1996; Stöhr, Buettner, Riffel, & Koletzki, 1982), subcortical (P14: Fz—Epc, N18: ipsilateral CP3/4—Cv2; Sonoo et al., 1992; Sonoo, 2000) and S1 components (N20 and P25: contralateral CP3/4—Fz; Cruccu et al., 2008). Data in the time window from −10 to 20 ms were applied (Cruccu et al., 2008; Desmedt, 1985; Seyal & Gabor, 1987).

2.2.3 Stimulation intensity

We defined the stimulation intensity to be applied on each body site using verbal ratings from 0 (‘just noticeable’ to 10 (‘it starts to hurt’). The intensity of electrical stimulation (3 Hz) was varied randomly until the participant consistently reported perception levels of 8 of 10, described as strong but nonpainful. This procedure was repeated three times for each body site and the mean intensity was used for electrical stimulation ensuring adequate but nonpainful stimulation for the SEPs. Subsequently, ongoing electrical stimulation (3,000 pulses) of the defined strong but nonpainful intensity was applied at each body site for SEP recordings.

Due to time constraints and the risk of fatigue, in one participant (PG03) the SS stimulation and in three participants (PG01, PG02 and PG03) pain thresholds were not obtained.

2.3 Data acquisition

2.3.2 Ratings

For each participant, the intensity of RLP, PLP and nonpainful phantom sensations was assessed before (pre), during (mid) and after (post) the electrical stimulation of each body site, using a computer-based horizontal visual analogue scales (VAS) [25 cm, with the endpoints: “no pain/ no sensation at all” to “extreme pain/the most vivid sensation”]. They were then transformed into a scale ranging from 0 to 100. In addition, immediately after the end of the electrical stimulation, the participants were instructed via the computer monitor to rate the maximum intensity (mid) of painful or nonpainful sensations that they perceived in the residual or phantom limb during the stimulation using 25-cm-long computer-based horizontal VAS with the endpoints “no pain/no sensation at all” to “extreme pain/the most vivid sensation”, which were then transformed into a scale ranging from 0 to 100. Subsequent to the ratings, a detailed questionnaire regarding phantom phenomena perceived during the TN stimulation was carried out, including the temporal pattern of PLP (such as persistent pain with slight or strong variations, persistent pain with pain attacks or pain attacks with pain-free intervals), quality of PLP (such as warm, cold, sharp, burning, aching, cramping, throbbing or stabbing), spatial distribution of PLP (such as the palm and fingers), involuntary phantom movement, and abnormal sensations or pain at the stimulated body site and other body parts (such as face and mouth).
100 ms were epoched and averaged. SEP components were identified according to the standard median-nerve SEPs with specific reproducible waveforms in response to two sets of 1,500 stimuli (total of 3,000 stimuli) and peak directions arising at the appropriate SEP latencies (4–5 ms shorter than standard SEPs; Cruccu et al., 2008). Mean amplitudes of the 3,000 stimuli were calculated from the peak to the prestimulation baseline. The conditions without significant SEP waves (such as in the SS condition for the peripheral and spinal potentials) were considered as absent with no measurable amplitude. Figure 1 shows a representative time course and waveforms of the SEPs in one amputee (PG06) who reported an increase in PLP intensity only during the TN condition (mid) referred to the baseline (pre).

2.5 Statistical analysis

Statistical analysis was carried out using IBM SPSS software (version 25, IBM Company). We compared the amplitudes of the SEP components, electric stimulation intensity, the sensory and pain thresholds using 2 × 3 factorial analyses of variance (ANOVAs) with the between-subjects factor group (PLP, non-PLP) and the within-subjects factor body site (TN, SS, CN). For PLP and RLP ratings, 2 × 3 × 3 mixed-factorial ANOVAs with the between-subjects factor group (PLP, non-PLP) and the within-subjects factors body site (TN, SS, CN) and time point (pre, mid, post) were carried out. For each measure, cases more than 3 SD from the mean were inspected and extreme outliers were not found. The sphericity assumption for repeated measures analyses was tested using the Mauchly’s test and Greenhouse-Geisser correction ($\epsilon < 0.75$) of the degrees of freedom was applied in case of a violation. For all multiple comparisons, $P$ values were adjusted using Bonferroni correction. We also calculated the changes in PLP and RLP intensity from the pre- to the mid-time point by subtracting the ratings between the two time points (mid to pre). Finally, correlation analyses were carried out to examine associations between the amplitudes of SEPs induced at the residual limb and changes in PLP and RLP intensity (mid to pre) as well as the baseline (pre). Correlations were carried out within the amputees with postamputation PLP and the amputees with postamputation RLP, using two-tailed Spearman rank correlations. Because none of the amputees in the non-PLP group or pain-free amputees, who had neither PLP nor RLP, reported a change in PLP intensity (see Figure 1).

**FIGURE 1** Representative recordings of somatosensory-evoked potentials (SEP) and schematic drawing of the somatosensory system. Time courses of SEP recordings in one participant (PG06) who reported a significant increase in phantom limb pain during electrical stimulation (3 Hz) of the truncated median nerve. For each body site, two sets of 1,500 stimuli (a total of 3,000 stimuli) were superimposed for demonstration. BP, brachial plexus; DRG, dorsal root ganglia; DH, spinal dorsal horn; NuCu, cuneate nucleus; VPL, ventral posterolateral nucleus of thalamus; ML, medial lemniscus; ASL, anterolateral system; Contral., contralateral; Epi/Epc, ipsilateral/contralateral Erb’s point; Cv2/6, the 2/6th cervical spinous process; La, laryngeal prominence; CPi/CPC, ipsilateral/contralateral CP3/4 (PLP, non-PLP) and the within-subjects factor body site (TN, SS, CN).
Results), these two groups were not analysed separately. In addition, SEP data in the SS condition were not taken into the correlation analyses separately since the SS stimulation did not evoke significant SEPs in most of the amputees for the peripheral \((n = 4)\) and cervical SEPs \((n = 6)\).

3 | RESULTS

3.1 | Amplitudes of SEP components in amputees with and without PLP

The latency of the somatosensory component was approximately 4–5 ms shorter compared to the standard latency of the median-nerve SEP since the stimulation sites were more proximal at the upper arm compared to the standard site at the wrist. Figure 2 shows the mean amplitudes of each SEP component in all conditions (see Table 1 for more details). There was no significant group difference for either of the SEP amplitudes between amputees with and without PLP.

3.1.1 | Peripheral N9, P9

For the N9 amplitudes, there was no significant effect for body site \((F(2, 23) = 1.705, P = .204, \eta^2 = 0.129)\), group \((F(2, 23) = 1.705, P = .204, \eta^2 = 0.168)\), but no significant group \((F(1, 23) = 0.081, P = .923, \eta^2 = 0.007)\).

For the P9 amplitudes, there was a significant effect for body site \((F(2, 39) = 3.924, P = .028, \eta^2 = 0.168)\), but no significant group \((F(1, 39) = 0.014, P = .907, \eta^2 = 0.000)\) or group \(\times\) body site interaction \((F(2, 39) = 0.050, P = .951, \eta^2 = 0.003)\). The amplitude of the peripheral component in the CN condition was significantly higher compared to the SS condition (adjusted \(P = .035)\) and there was a trend towards significance for a higher TN versus SS condition (adjusted \(P = .070)\), however, there was no significant difference between the CN and TN conditions (adjusted \(P = 1.000)\) in the post hoc tests.

3.1.2 | Cervical N13

For the N13 \((\text{Cv6—Larynx})\) amplitudes, there was no significant effect for body site \((F(2, 34) = 1.890, P = .167, \eta^2 = 0.100)\), group \((F(1, 34) = 1.474, P = .233, \eta^2 = 0.042)\) or group \(\times\) body site \((F(2, 34) = 0.782, P = .466, \eta^2 = 0.044)\).

Likewise, for the N13 \((\text{CV4—Larynx})\) amplitudes, there was no significant effect for body site \((F(2, 34) = 2.031, P = .147, \eta^2 = 0.107)\), group \((F(1, 34) = 1.188, P = .283, \eta^2 = 0.034)\) or group \(\times\) body site \((F(2, 34) = 0.501, P = .610, \eta^2 = 0.029)\).

A similar nonsignificant effect emerged for the N13 \((\text{CV2—Larynx})\) amplitudes: body site \((F(2, 34) = 1.311, P = 0.283, \eta^2 = 0.072)\), group \((F(1, 34) = 0.984, P = .328, \eta^2 = 0.028)\) and group \(\times\) body site \((F(2, 34) = 0.855, P = .434, \eta^2 = 0.048)\).

3.1.3 | Subcortical P14, N18

For the P14 amplitudes, there was a significant effect for body site \((F(2, 38) = 3.584, P = .037, \eta^2 = 0.159)\), but no significant group \((F(1, 38) = 0.106, P = .747, \eta^2 = 0.003)\) or group \(\times\) body site effects \((F(2, 38) = 0.170, P = .845, \eta^2 = 0.009)\). The amplitudes in the TN condition were significantly higher compared to the SS condition (adjusted \(P = .043)\), and we found a trend towards significance for a higher CN versus SS condition (adjusted \(P = .084)\), however, there was no significant difference between the CN and TN conditions (adjusted \(P = 1.000)\) in the post hoc tests.

Similarly, for the N18 amplitudes, there was a significant effect for body site \((F(2, 50) = 6.109, P = .004, \eta^2 = 0.196)\), but no significant group \((F(1, 50) = 1.410, P = .241, \eta^2 = 0.027)\) or group \(\times\) body site effect \((F(2, 50) = 0.004, P = .996, \eta^2 = 0.000)\). The amplitudes in the CN condition were significantly higher compared to the SS condition (adjusted \(P = .003)\), however, there was no significant difference between the CN and TN conditions (adjusted \(P = .367)\), and
between TN and SS conditions (adjusted $P = .148$) in the post hoc tests.

### 3.1.4 Cortical N20, P25

For the N20 amplitudes, there was a significant effect for body site ($F(2, 58) = 7.478, P = .001, \eta^2 = 0.205$), but no significant group ($F(1, 58) = 0.070, P = .792, \eta^2 = 0.001$) or group $\times$ site effect ($F(2, 58) = 0.093, P = .911, \eta^2 = 0.003$). The amplitudes in the CN condition were significantly higher than in the SS condition (adjusted $P = .001$), however, there was no significant difference between the CN and TN conditions (adjusted $P = .062$), and between TN and SS conditions (adjusted $P = .372$) in the post hoc tests.

For the P25 amplitudes, body site ($F(2, 58) = 5.321, P = .008, \eta^2 = 0.155$) was significant, but there was no significant group ($F(1, 58) = 0.070, P = .792, \eta^2 = 0.001$) or group $\times$ site effect ($F(2, 58) = 0.093, P = .911, \eta^2 = 0.003$). The amplitudes in the CN condition were significantly higher than in the SS condition (adjusted $P = .006$), however, there was no significant difference between the CN and TN conditions (adjusted $P = .070$), and between TN and SS conditions (adjusted $P = 1.000$) in the post hoc tests.

### 3.2 Stimulation intensity, sensory and pain thresholds in amputees with and without PLP

For the electrical stimulation intensity, there was neither a significant group ($F(1, 59) = 1.148, P = .288, \eta^2 = 0.019$) nor a significant body site effect ($F(2, 59) = 1.489, P = .234, \eta^2 = 0.048$), nor a significant group $\times$ body site interaction ($F(2, 59) = 0.719, P = .491, \eta^2 = 0.024$). The same was true for the electrical sensory thresholds (group: $F(1, 59) = 3.778, P = .057, \eta^2 = 0.060$; body site: $F(2, 59) = 0.159, P = .853, \eta^2 = 0.005$ and group $\times$ body site: $F(2, 59) = 0.056, P = .945, \eta^2 = 0.002$). For the electrical pain thresholds, there was neither a significant group effect ($F(1, 51) = 0.912, P = .344, \eta^2 = 0.018$) nor body site effect ($F(2, 51) = 1.400, P = .256, \eta^2 = 0.052$), nor a significant group $\times$ body site interaction ($F(2, 51) = 0.975, P = .384, \eta^2 = 0.037$). Table 2 shows means of the stimulation intensities, the sensory and pain thresholds at the three body sites in amputees with and without PLP.

### 3.3 Ratings

#### 3.3.1 Phantom limb pain

Phantom limb pain could be enhanced by peripheral input with an average increase of $5.37 \pm 14.41 (M \pm SD)$, induced from the TN: $14.58 \pm 20.10$, the SS: $4.09 \pm 7.41$ and the

| Stimulation intensity (mA) | Sensory thresholds (mA) | Pain thresholds (mA) |
|---------------------------|------------------------|---------------------|
| **PNP group**             |                        |                     |
| Stimulation intensity     | Sensory thresholds     | Pain thresholds     |
| 14.17 ± 12.26             | 10.90 ± 5.05           | 16.16 ± 16.06       |
| 11.25 ± 5.96              | 3.21 ± 2.13            | 9.68 ± 5.80         |
| 10.02 ± 5.05              | 3.44 ± 1.88            | 11.57 ± 5.34        |
| **PP group**              |                        |                     |
| Stimulation intensity     | Sensory thresholds     | Pain thresholds     |
| 11.00 ± 3.42              | 7.01 ± 2.76            | 11.61 ± 4.36        |
| 12.35 ± 6.39              | 2.60 ± 1.44            | 11.75 ± 6.80        |
| 13.5 ± 6.9                | 2.50 ± 0.92            | 8.10 ± 2.70         |

**Abbreviations**: CN: contralateral intact median nerve; SS: skin of the residual limb; TN: truncated median nerve.
CN: $-2.67 \pm 4.85$, on a scale from 0 to 100 in the amputees in the PLP group; however, PLP could not be elicited at any body site (VAS, 0) in any amputee in the non-PLP group. Table 3 shows changes in PLP and RLP ratings in all conditions. Figure 3 depicts the mean PLP and RLP ratings in all conditions.

There was a significant group effect for PLP intensity ($F(1, 19) = 7.427, \ P = .013, \ \eta^2 = 0.281$), which showed that PLP increased significantly only in the PLP group. There was also a significant time point effect ($F(1.417, 26.919) = 6.118, \ P = .012, \ \eta^2 = 0.244$) and a significant time point \times group interaction ($F(1.417, 26.919) = 6.118, \ P = .012, \ \eta^2 = 0.244$) for PLP intensity. There was neither a significant body site effect ($F(1.371, 26.044) = 3.578, \ P = .058, \ \eta^2 = 0.158$) nor a significant body site \times time point \times group ($F(1.493, 36.918) = 3.091, \ P = .059, \ \eta^2 = 0.140$), body site \times group ($F(1.371, 26.044) = 3.578, \ P = .058, \ \eta^2 = 0.158$) or body site \times time point interaction ($F(1.493, 36.918) = 3.091, \ P = .059, \ \eta^2 = 0.140$).

In the PLP group, PLP intensity was significantly higher at the mid versus the pre- (adjusted $P = .008$) and the post-time point (adjusted $P = .001$), however, there was no significant difference between the pre- and post-time point (adjusted $P = 1.000$). In the non-PLP group, there was neither a significant difference for PLP intensity between the pre- and mid-time point (adjusted $P = 1.000$), nor between the pre- and post-time point (adjusted $P = 1.000$), nor between the mid- and post-time point (adjusted $P = 1.000$). These results indicate that PLP increased significantly during nonpainful electrical stimulation (pre to mid and mid to post) and in amputees with PLP only.

4 | Residual limb pain

For RLP intensity, there was a significant effect for body site ($F(2, 38) = 7.602, \ P = .002, \ \eta^2 = 0.286$), time point ($F(1.161, 22.061) = 10.588, \ P = .003, \ \eta^2 = 0.358$) and time point \times body site ($F(2.085, 39.610) = 4.774, \ P = .013, \ \eta^2 = 0.201$) as well as body site \times group ($F(2, 38) = 3.384, \ P = .044, \ \eta^2 = 0.151$). However, there was neither a significant group effect ($F(1, 19) = 3.819, \ P = .066, \ \eta^2 = 0.167$), nor a significant time point \times body site \times group ($F(2.085, 39.610) = 2.409, \ P = .101, \ \eta^2 = 0.113$), nor time point \times group interaction ($F(1.161, 22.061) = 0.049, \ P = .861, \ \eta^2 = 0.003$).

In the TN condition, RLP intensity at the mid-time point was significantly higher compared to pre (adjusted $P = .010$) and post (adjusted $P = .019$). There was no significant difference between the pre- and post-time point (adjusted $P = 1.000$). In the CN condition, there was neither a significant difference for RLP intensity between the pre- and mid-time point (adjusted $P = 1.000$), between the pre- and post-time point (adjusted $P = 1.000$), nor between the mid and post (adjusted $P = 1.000$). In the SS condition, there was neither a significant difference for RLP intensity between the pre- and mid-time point (adjusted $P = .362$), between the pre- and post-time point (adjusted $P = .693$), nor between the mid- and post-time point (adjusted $P = .551$). At the pre-time point, there was neither a significant difference for RLP intensity between the TN and CN condition (adjusted $P = .521$), between the CN and SS condition (adjusted $P = 1.000$) nor between the TN and SS condition (adjusted $P = .316$). At the mid-time point, RLP intensity was significantly higher in the TN condition versus CN condition (adjusted $P = .008$), but there was neither a significant difference between the TN and SS condition (adjusted $P = .139$) nor between the CN and SS condition (adjusted $P = .312$). At the post-time point, there was neither a significant difference for RLP intensity between the CN and TN condition (adjusted $P = .209$), between the CN and SS condition (adjusted $P = 1.000$) nor between the TN and SS condition (adjusted $P = 1.000$).

In the PLP group, RLP intensity was significantly higher in the TN versus the CN (adjusted $P = .006$) and the SS condition (adjusted $P = .008$), however, there was no significant difference between the CN and SS condition (adjusted $P = 1.000$). In the non-PLP group, there was neither a significant difference between the TN and CN condition (adjusted $P = .831$), nor between the TN and SS condition (adjusted $P = 1.000$), nor between the CN and SS condition (adjusted $P = .332$). In the TN (adjusted $P = .038$) and CN (adjusted $P = .016$) conditions, RLP ratings were significantly higher in the PLP versus non-PLP group. In the SS condition, there was no significant difference between the PLP and non-PLP group (adjusted $P = .825$).

5 | Correlations between SEP amplitudes and pain ratings

During electrical stimulation of the TN, neither the PLP baseline (pre) values nor increases (mid to pre) were significantly correlated with the amplitudes of the SEP components from the periphery to S1, within the amputees with PLP. In the amputees with RLP, neither the RLP baseline (pre) values nor increases (mid to pre) were significantly correlated with the amplitudes of the SEP components from the periphery to S1. Table 4 shows the detailed correlation matrix.

6 | DISCUSSION

Our results show that nonpainful peripheral input could evoke PLP in amputees with chronic PLP, but not in amputees without a history of PLP. Although peripheral stimulation at the residual limb elicited PLP in the PLP group only, we found no significant group differences for the SEP amplitudes from the periphery to the S1 between amputees
| Subject   | PLP intensity | RLP intensity | PLP intensity | RLP intensity | PLP intensity | RLP intensity | PLP intensity | RLP intensity | PLP intensity | RLP intensity | PLP intensity | RLP intensity |
|-----------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| TN stimulation | pre | mid | post | pre | mid | post | pre | mid | post | pre | mid | post | pre | mid | post | pre | mid | post |
| PG01      | 20  | 65  | 20  | 20  | 35  | 20  | 20  | 35  | 20  | 35  | 20  | 35  | 20  | 35  | 20  | 35  | 20  | 35  |
| PG02      | 0   | 11  | 0   | 0   | 0   | 0   | 7   | 0   | 7   | 0   | 7   | 0   | 7   | 0   | 7   | 0   | 7   | 0   |
| PG03      | 17  | 33  | 8   | 8   | 24  | 8   | 8   | 24  | 8   | 8   | 24  | 8   | 8   | 24  | 8   | 8   | 24  | 8   |
| PG04      | 36  | 81  | 73  | 73  | 81  | 73  | 73  | 81  | 73  | 73  | 81  | 73  | 73  | 81  | 73  | 73  | 81  | 73  |
| PG05      | 4   | 9   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| PG06      | 8   | 54  | 4   | 5   | 6   | 11  | 7   | 5   | 6   | 11  | 7   | 5   | 6   | 11  | 7   | 5   | 6   | 11  |
| PG07      | 8   | 54  | 4   | 5   | 6   | 11  | 7   | 5   | 6   | 11  | 7   | 5   | 6   | 11  | 7   | 5   | 6   | 11  |
| PG08      | 8   | 54  | 4   | 5   | 6   | 11  | 7   | 5   | 6   | 11  | 7   | 5   | 6   | 11  | 7   | 5   | 6   | 11  |
| PG09      | 8   | 54  | 4   | 5   | 6   | 11  | 7   | 5   | 6   | 11  | 7   | 5   | 6   | 11  | 7   | 5   | 6   | 11  |
| PG10      | 8   | 54  | 4   | 5   | 6   | 11  | 7   | 5   | 6   | 11  | 7   | 5   | 6   | 11  | 7   | 5   | 6   | 11  |
| PG11      | 8   | 54  | 4   | 5   | 6   | 11  | 7   | 5   | 6   | 11  | 7   | 5   | 6   | 11  | 7   | 5   | 6   | 11  |
| Mean ± SD | PLP group | 10.8 ± 10.1 | 25.4 ± 27.1 | 13.2 ± 20.9 | 11.2 ± 17.2 | 15.3 ± 17.5 | 11.6 ± 14.9 | 8.3 ± 6.5 | 7.4 ± 4.9 | 6.9 ± 4.6 | 11.8 ± 15.6 | 11.8 ± 15.6 | 9.2 ± 7.4 | 6.5 ± 4.6 | 7.4 ± 4.9 | 6.9 ± 4.6 | 11.8 ± 15.6 | 11.8 ± 15.6 |
| Non-PLP group | | | | | | | | | | | | | | | | | | |
| NG01      | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| NG02      | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| NG03      | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| NG04      | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| NG05      | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| NG06      | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| NG07      | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| NG08      | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| NG09      | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| NG10      | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |

Note: Ratings were performed using a visual analog scale (VAS) and converted to a scale from 0 (no pain at all in the residual/phantom limb) to 100 (extreme pain in the residual/phantom limb), NA: not available for the SS stimulation due to time constraints in one participant (PG03). Abbreviations: CN, contralateral intact median nerve; SS, skin of the residual limb; TN, truncated median nerve.
FIGURE 3  Phantom limb pain (PLP) and residual limb pain (RLP) intensity before, during and after electrical stimulation. (a, b) Mean PLP or RLP ratings in all conditions. (c, d) Significant time point x group for PLP but not for RLP ratings. Peripheral input increased PLP significantly in amputees with PLP only, but could not elicit any PLP in amputees without a history of PLP, while RLP could be elicited in both groups. (e, f) Significant time point x site for RLP but not for PLP ratings. RLP intensity increased significantly during the stimulation of the truncated median nerve (TN) only, but not of the skin of the residual limb (SS) or the contralateral median nerve (CN). There was no significant change for PLP during the stimulation of each body site in all amputees. Pre: before electrical stimulation. Mid: during electrical stimulation. Post: after electrical stimulation. Contral.: contralateral. Ratings were measured using visual analogue scales (VAS) and converted into a scale ranging from 0 to 100. Data are presented as mean and standard error of the mean. *P < .05, **P < .01
## TABLE 4 Correlations between SEP amplitudes and phantom and residual limb pain

| Spearman correlation matrix | Amputees with phantom limb pain (PLP) | Amputees with residual limb pain (RLP) |
|-----------------------------|--------------------------------------|---------------------------------------|
|                             | PLP baseline | PLP changes | RLP baseline | RLP changes |
| Amplitudes                  |             |             |             |             |
| N9                          | $\rho = 0.126$ | $P = .788$ | $n = 7$ | $\rho = 0.643$ | $P = .119$ | $n = 7$ | $\rho = -0.085$ | $P = .828$ | $n = 9$ | $\rho = 0.527$ | $P = .145$ | $n = 9$ |
| P9                          | $\rho = -0.399$ | $P = .254$ | $n = 10$ | $\rho = 0.122$ | $P = .738$ | $n = 10$ | $\rho = 0.527$ | $P = .145$ | $n = 9$ | $\rho = 0.527$ | $P = .145$ | $n = 9$ |
| N13 (Cv6)                  | $\rho = 0.009$ | $P = .983$ | $n = 9$ | $\rho = -0.151$ | $P = .699$ | $n = 9$ | $\rho = 0.024$ | $P = .954$ | $n = 8$ | $\rho = 0.275$ | $P = .509$ | $n = 8$ |
| N13 (Cv4)                  | $\rho = -0.026$ | $P = .948$ | $n = 9$ | $\rho = -0.176$ | $P = .651$ | $n = 9$ | $\rho = 0.024$ | $P = .954$ | $n = 8$ | $\rho = 0.275$ | $P = .509$ | $n = 8$ |
| N13 (Cv2)                  | $\rho = 0.062$ | $P = .866$ | $n = 10$ | $\rho = -0.304$ | $P = .393$ | $n = 10$ | $\rho = 0.024$ | $P = .954$ | $n = 8$ | $\rho = 0.275$ | $P = .509$ | $n = 8$ |
| P14                        | $\rho = -0.143$ | $P = .676$ | $n = 11$ | $\rho = 0.014$ | $P = .968$ | $n = 11$ | $\rho = 0.059$ | $P = .117$ | $n = 9$ | $\rho = 0.126$ | $P = .748$ | $n = 9$ |
| N18                        | $\rho = -0.507$ | $P = .112$ | $n = 11$ | $\rho = -0.101$ | $P = .768$ | $n = 11$ | $\rho = -0.077$ | $P = .845$ | $n = 9$ | $\rho = -0.017$ | $P = .966$ | $n = 9$ |
| N20                        | $\rho = -0.019$ | $P = .952$ | $n = 12$ | $\rho = 0.097$ | $P = .765$ | $n = 12$ | $\rho = -0.091$ | $P = .790$ | $n = 11$ | $\rho = 0.114$ | $P = .738$ | $n = 11$ |
| P25                        | $\rho = -0.074$ | $P = .819$ | $n = 12$ | $\rho = -0.025$ | $P = .940$ | $n = 12$ | $\rho = -0.293$ | $P = .382$ | $n = 11$ | $\rho = 0.014$ | $P = .968$ | $n = 11$ |

6.1 | Comparable somatosensory function between amputees with and without PLP

We found no significant difference between amputees with and without PLP for any SEP component from any stimulation paradigm. These data suggest that the increase in PLP during peripheral nerve stimulation is provoked by a central misinterpretation of regular peripheral input rather than by peripheral amplification. Peripheral input can modulate PLP intensity in amputees who already suffer from PLP but may be insufficient to create PLP, implying that sensitized central processing or multifactorial alterations contribute to the generation of PLP.
SS stimulation, which was lower than at the cortical level and has not been reported previously. Across all amputees, TN showed significantly higher activation than SS at the peripheral level (see Figure S1).

### 6.2 PLP and RLP induced by nonpainful peripheral input

In line with a previous study (Andoh et al., 2017), we could evoke phantom sensations and even PLP by nonpainful electrical stimulation at the residual limb in amputees with chronic PLP. PLP has been shown to be temporally reduced after blocking peripheral inputs by injecting lidocaine in amputees with PLP (Buch et al., 2019; Vaso et al., 2014). However, in these studies it was difficult to determine whether the afferent input can create PLP independently and it was impossible to disentangle the later involvement of central processing from the input, which might be important for PLP generation. In this study, we examined the bottom-up processes and used a homogenous sample of amputees, all with traumatic amputations. The amputees with PLP showed a long history of PLP (28 ± 12 years) and the controls consisted of amputees who never experienced PLP and were matched for time since amputation and age. We also used nonverbal ratings (VAS) to monitor changes in PLP and RLP intensities. This permits a better characterization of changes in PLP without the potential bias from the examiner or confounds from other coexisting painful sensory phenomena, such as RLP (Jensen, Krebs, Nielsen, & Rasmussen, 1985).

Although peripheral input from the truncated nerve could increase PLP intensity temporarily in the majority (7 of 12) of the amputees with chronic PLP, it was not sufficient in generating PLP in any amputee without a history of PLP, suggesting that peripheral input itself is not sufficient to induce PLP but can enhance existing PLP. The generation of PLP probably still requires sensitized central processing or relevant functional alterations. The absence of electrically induced PLP in the non-PLP group cannot be explained by significant differences in peripheral stimulation since there was neither a significant difference in sensory or pain thresholds nor in stimulation intensity or SEP magnitude between both groups.

In addition, we found a significant body site effect for RLP but not for PLP, and RLP intensity increased significantly after the application of nonpainful peripheral stimulation at the TN site only and decreased directly after the cessation of the TN stimulation. In line with this, significantly higher SEPs from the periphery through the supraspinal/brainstem segment were induced in the TN condition versus the SS condition. Our results are in accordance with the study by Haroutounian et al. (2014), who reported that a peripheral anaesthetic nerve block with lidocaine-induced complete foot pain relief in seven patients with unilateral peripheral nerve injury and seven patients with bilateral feet pain with distal symmetric polyneuropathy, while intravenous lidocaine infusion had only a small effect on the latter group. Their findings suggest that spontaneous chronic neuropathic pain induced by peripheral nerve injury may be maintained by peripheral afferent input. Our findings support a role of peripheral input in generating and maintaining chronic RLP. These data also support the different aetiologies of PLP and RLP, with peripheral input having a dominant role for RLP, but not PLP. This might also explain the limited efficacy of treating and preventing PLP using peripheral nerve blocks (Borghi, D’Addabbo, & Borghi, 2014; Pinzur, Garla, Pluth, & Vrbos, 1996).

### 6.3 Correlations between SEP amplitudes and phantom and RLP

We did not observe a significant relationship between PLP/RLP baseline or its change and the amplitudes of any SEP component in amputees with PLP/RLP. The nonsignificant results of the correlations between SEP amplitudes and PLP/RLP do not necessarily exclude the contribution of afferent input for PLP and RLP. PLP/RLP may not be time locked to the input, but might rather be related to an averaged central consequence during the recording procedure. Additionally, we remeasured the estimated peak value in the time window of 3 ms with the central time point at the appropriate latency for those without a typical SEP waveform. Our results were in line with the data obtained without estimated peak values and did not show a significant relationship between PLP and any SEP component, except for a significant correlation between the P14 amplitudes and RLP at baseline ($\rho = 0.656$, $P = 0.028$; see Table S1).

Peripheral afferent input can hence modulate PLP, but seems insufficient to create PLP. There might be constant barrages of residual limb muscle spindles, injured touch and warm/cold fibres as well as ectopic spontaneous discharges in A-fibber afferents, which may transmit impulses from the periphery to the ‘deafferented’ cortex and modulate chronic postamputation PLP. However, such normally not painful afferent inputs might need some other prerequisites such as sensitized central processing or relevant functional alterations to generate PLP.

### 6.4 Limitations

This study has several limitations. Although we used 3,000 repetitions at each body, we did not elicit significant and reliable SEPs in all amputees from all stimulated sites (Mackert et al., 2003). We were not able to identify the activity triggered
by the ascending volley using traditional time-frequency analysis methods such as gamma oscillations because of the fast stimulation rate and short time window, which may possibly relate to PLP. Finally, we did not test for neuromas and could thus not examine if these relationships differ in patients with versus without neuroma.

7 CONCLUSION

Primary afferent input can modulate but may not be sufficient to cause PLP, since PLP could be enhanced by peripheral input in amputees with PLP but not in those without a history of PLP. Moreover, there was no significant difference in amplitude of somatosensory input between amputees with and without PLP. Peripheral input is not sufficient for the PLP generation. Longitudinal studies are needed to further disentangle the role of peripheral and central contributions to chronic PLP.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

H.L., J.A. and H.F. designed the study. M.S., G.C., Y.L. and C.M. contributed to the study paradigm. H.L., J.A., Y.L., C.M., S.D. and F.Z. contributed to perform the experiments and collected the data. H.L. analysed the data. H.L., J.A. and H.F. wrote the manuscript. All authors discussed the results and commented on the manuscript.

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SUPPORTING INFORMATION

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

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