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Protective and Risk Factors for Phantom Limb Pain and Residual Limb Pain Severity

Marionna Münger[1,2], **Camila B. Pinto**[1], **Kevin Pacheco-Barrios**[1,3], **Dante Duarte**[1], **Muhamed Enes Gunduz**[1], **Marcel Simis**[4], **Linamara R. Battistella**[4], **Felipe Fregni**[1]

[1]Neuromodulation Center and Center for Clinical Research Learning, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Boston, Massachusetts, USA. [2]Department of Neuropsychology, Institute of Psychology, University of Zurich, 8050 Zurich, Switzerland. [3]Universidad San Ignacio de Loyola, Vicerrectorado de Investigación, Unidad de Investigación para la Generación y Síntesis de Evidencias en Salud. Lima, Peru. [4]Department of Physical Medicine and Rehabilitation, Instituto de Reabilitação Lucy Montoro.

Abstract

Introduction: The exact mechanisms underlying the development and maintenance of phantom limb pain are still unclear. This study aimed to identify the factors affecting pain intensity in chronic, lower limb, traumatic phantom limb pain patients.

Methods: This is a cross-sectional analysis of patients with phantom limb pain. We assessed amputation-related, pain-related clinical and demographic variables. We performed univariate and multivariate models to evaluate the associated factors modulating phantom limb pain and residual limb pain intensity.

Results: We included 71 unilateral traumatic lower limb amputees. Results showed that (i) amputation related perceptions were experienced by a large majority of the chronic phantom limb pain patients (sensations: 90.1%, N=64; residual pain: 81.7%, N=58); (ii) phantom limb pain intensity has two significant protective factors: *phantom limb movement and having effective treatment for phantom limb pain previously* and two significant risk factors: *phantom limb sensation intensity and age*; (iii) on the other hand, for residual limb pain, risk factors are different: *presence of pain before amputation and level of amputation* (in addition to the same protective factors).

Conclusion: These results suggest different neurobiological mechanisms to explain phantom limb and residual limb pain intensity. While phantom limb pain risk factors seem to be related to maladaptive plasticity as phantom sensation and older age are associated with more pain, residual limb pain risk factors seem to have factors leading to neuropathic pain such as the amount of

Corresponding author: Felipe Fregni, Neuromodulation Center and Center for Clinical Research Learning, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Boston, Massachusetts, USA. Address: 96 13th Street, Charlestown, Boston, MA, United States, Phone: 1 617 952 6153, Fax: 1 617 952 6150, Fregni.Felipe@mgh.harvard.edu.

Declaration of interest

The authors report no conflict of interest.

neural lesion and previous history of chronic pain. Interestingly, the phantom movement appears to be protective for both phenomena.

Keywords

amputation; phantom limb pain; associated factors

Introduction

Phantom limb pain (PLP) and residual limb pain (RLP) are common and disabling painful sensations following limb amputation. Despite high incidence; since up to 85% of the amputees suffer from PLP at one point and about 50 % will still experience it five years after surgery[1, 2] the exact mechanisms underlying the development and maintenance of PLP and RLP are still unclear.

Among multiple findings, it has been suggested that maladaptive cortical reorganization over the brain area of the amputated limb plays a fundamental role in the development and neuronal pathophysiology of PLP[3]. Next, further alterations in the somatosensory system along the neural axis[4] contribute to PLP and RLP (deafferentation pain, peripheral and central sensitization), where central sensitization and lack of inhibition contribute to the development and maintenance of pain. All those physiological alterations are challenging to assess and classify. Demographical and symptom-related characteristics can also provide significant insights. They allow approaching the complex etiology of PLP and can provide insights that contribute to the development, maintenance, and intensity of PLP and RLP.

Several cross-sectional studies in the past evaluated risk factors; amputation related and demographic characteristics that affect PLP and RLP incidence and prevalence[5–7]. While the heritability[8] might have a role in controlling pain severity as well, demographic and psychological factors are influencing symptoms. Previous cross-sectional studies showed that gender[9, 10], side of amputation[9, 11], pre-amputation pain[10, 11], anxiety and depression level[12] can be considered as predictors for PLP. Furthermore, amputation related pain is affected by factors like coping strategies, stress or social support that have been shown to be risk, or protective factors - in PLP, RLP[13] and other chronic pain conditions[14, 15].

Whereas one of those large cross-sectional studies assessed the association of PLP intensity and individual characteristics ([5], N=255), many trials focused on in PLP incidence and prevalence ([7], N=526,[6], N=914,[16], N=139). The understanding of what triggers severe PLP and RLP and correlates with pain intensity might increase the understanding of the underlying mechanism and guide the development of effective pain treatment strategies.

A further challenge in this field of research is the heterogeneity of the population, especially related to the symptoms, but also the site (upper and lower limbs) and the etiology of amputation (vascular disease, cancer or traumatic events). Most clinical and mechanistic studies are considering specific subgroups, which limits the generalizability of the results. For example, mechanistic fMRI studies are almost exclusively performed in upper limb[17–20], as opposed to lower limb amputees[21].

All included participants in this trial suffered a traumatic incidence that terminated in limb loss – this second distinctive property of the study sample is often marginalized. Recent mechanistic studies in upper limb amputees consist of subjects with traumatic cause for amputation[17–20], although this is useful to describe a general burden of PLP and RLP in the community it might cloud pain modulators in the different amputation etiologies. Risk factors emerged from such mixed samples are might valid only for a subgroup of the sample.

Therefore, this study aimed to analyze the protective and risk factors for PLP and RLP, to identify the factors affecting pain intensity in chronic, lower limb, traumatic PLP patients as also to associate them with potential neural mechanisms underlying pain.

Methods

Study Design and Settings

This is a cross-sectional analysis of baseline characteristics of participants enrolled in an ongoing full-factorial, double-blinded randomized clinical trial investigating the effects of tDCS in combination with mirror therapy to treat PLP after a lower limb traumatic amputation (NCT02487966)[22].

Subjects are recruited in two neurorehabilitation study centers: at the Neuromodulation Center of the Spaulding Rehabilitation Hospital (US) and at the University Hospital of Sao Paulo, IMREA (Brazil). All participants signed the approved consent form before trial procedures following requirements and overseen by Partners Healthcare and the University of Sao Paulo Institutional Review Board. The study PI and/or a co-investigator obtained informed consent.

Participants

This cross-sectional study collected and analyzed baseline data from 71 unilateral traumatic lower limb amputees of an ongoing clinical trial[22]. Considered have been all participants that attended the baseline visit before July 2019. The main trial has a target population of 132 subjects.

All participants were pre-screened and passed the following inclusion and exclusion criteria: Inclusion criteria: individuals older than 18 years old and able to provide informed consent, with unilateral traumatic lower limb amputation after complete recovery experiencing chronic PLP for more than three months with an average of 4 or above on a visual analogue scale (VAS) from 0 to 10. If the subject is taking any medications, dosages must be stable for at since least two weeks before the enrollment of into the study. Exclusion criteria: pregnancy or trying to become pregnant in the next 2 months; history of alcohol or drug abuse within the past 6 months as self-reported; presence of the following contraindication to transcranial direct current stimulation and transcranial magnetic stimulation (e.g., plates or pins, bullets, shrapnel, cochlear implants, vagus nerve stimulator); head injury resulting in permanent neurological deficits, such as cognitive or motor deficits, as self-reported (permanent neurological deficit that may interfere with the assessments); unstable medical conditions (e.g. uncontrolled diabetes, uncompensated cardiac issues, heart failure or chronic obstructive pulmonary disease); uncontrolled epilepsy or prior seizures within the

last 1 year; history of unexplained fainting spells or loss of consciousness as self-reported during the last 2 years; history of neurosurgery, as self-reported; mirror therapy within 3 months prior to enrollment.

Sample characteristics

Seventy-one subjects were included: 43 subjects from Sao Paulo and 28 from Boston. The sample was 64.8% male and the mean age of the participants was 43.9 ±15.5 years. The median time since amputation at study enrollment was 17 months (IQR: −2.5 to 36.5). The median BDI and BAI were 5 (IQR: 0.1 to 9.9) and 7 (IQR: 0.5 to 13.5), respectively. Further clinical data related to the amputation are provided in Table 1.

Quantitative and Qualitative Variables

Amputation-related variables: This information was collected using an adapted version of Groningen Questionnaire after Arm Amputation. This questionnaire was adapted for lower limb amputation and included data on PLP, RLP, and Phantom limb sensation (PLS)[10]. For the present study, we extracted data on the side of amputation, level of amputation, time since amputation (in months), pain before to the amputation opioid use, previous treatments and whether it has been effective, PLP/RLP/PLS frequency and PLS qualities.

Beck Depression Index (BDI) and Beck Anxiety Index (BAI): these questionnaires assesses the psychological well-being encompassing diverse symptoms of anxiety and depression as well as their severity.

Visual Analogue Scale: measure the intensity of PLS with a length of 10 cm (no pain to worst imaginable pain). This scale is also colored, from green (at 0 cm) to red (at 10 cm), as a visual indicator of pain. Participants are asked to rate their average pain (during an acute episode) over the last four weeks. Before the participant fills each scale, an experienced researcher explains what PLP, RLP, and PLS means and the differences among them.

Further demographics and medical history were assessed during the consent visit and included in the present study.

Statistical analysis

For this cross-sectional analyses no sample size calculation was performed and data from all 71 participants of an ongoing clinical trial was included. Complete case analysis was used to handle missing data and median and interquartile range to deal with outliers when the data was not normally distributed.

The statistical analyses were performed with Stata version 15.1. To evaluate normality Shapiro-Wilkś test, skewness, kurtosis was applied. Baseline characteristics were reported using descriptive statistics (e.g., mean and standard deviation for continuous variables, frequency tabulations for categorical variables). For group comparisons Mann-Whitney-U-Tests and for correlations Spearman Rank and Pearson’s Correlation Tests were used.

Regression models

We used the Visual Analogue Scale (VAS) as the main outcome for our models. Linear regression models were built to test our main hypothesis, and Q-Q plots and residuals analysis were performed to review the assumptions of the model.

Baseline demographics and clinical characteristics associated with PLP and RLP were tested to investigate the predictors and factors associated with the intensity of pain in these two pain manifestations. The hypothesis is that baseline demographics and clinical characteristics are correlated with the intensity of PLP and RLP and that they have different contributing factors. Firstly, univariate linear regression analysis was performed. Variables with $P<0.05$ were further introduced into two different multiple regression models with backward stepwise selection: one using PLP and the other using RLP as dependent variables. To finalize the models, the removal of single variables was tested, considering their mechanism and/or biological reasoning for PLP and RLP as well as considering the variance in R^2 and Beta coefficient of the models. We also conducted an exploratory regression analysis to understand if interaction terms e.g. pls*movement; response to the previous treatment*opioid affect the models. However, they were all excluded as they did not alter the final model significantly.

Results

Amputation Related Perceptions

The amputation related perceptions, RLP and PLS were experienced by a large majority of the sample (PLS: 90.1%, N=64; RLP: 81.7%, N=58; PLS and RLP: 76.1%, N=54; only PLS: 14.1%, N=10; and only RLP: 5.63%, N=4; from the total sample, N=71). The intensities of these perceptions are summarized in Table 2. The electric sensation (71.9%), itching (59.4%), and movement sensation (54.7%) were the most commonly reported PLS varieties (Table 3).

PLP intensity is weakly correlated with RLP (Spearman's rho=0.30, P=0.01). No significant correlation was obtained for PLP and PLS intensity, age, time since amputation, BDI or BAI scores.

PLP intensity is significantly lower in subjects taking opioids (4.9±0.4 vs 6.2±0.2, P=0.02). The same was observed in subjects having frequent PLP (at least once daily) (5.5±0.30 vs. 6.2±0.3, P<0.001) and with refractory pain (non-responsive to previous treatment) (4.8±0.4 vs. 6.30±0.2, P=0.001). Comparing subgroups according to their gender, level or side of amputation, whether they have PLS or RLP, PLS varieties, whether they had pain prior to the amputation or their BDI or BAI score did not show any statistically significant difference.

Predictors of Phantom Limb Pain (PLP)

In the multivariate analysis, we found that age (P=0.04), the intensity of PLS (P=0.01), and enrollment at the Brazilian study site (P=0.04) were positive predictors of PLP intensity (higher pain levels), whereas the presence of movement sensation (P=0.03) and response to previous treatment (P<0.001), were negative predictors (lower pain levels). The multivariate

regression line (n=67) denoting the relationship between phantom limb pain intensity and associate clinical and demographic variables can be defined by: *PLP (VAS) = 5.38 + 0.03*age + 0.17*PLS - 0.86*movement sensation + 0.89*site - 1.46*response to previous treatment* (see table 4). The model accounts for 31% (P<0.001) of the variance in PLP intensity. The categorical variables are coded as; clinical trial center (0=US, 1=Brazil), movement sensation (0=no, 1=yes), and response to previous treatment (0=no, 1=yes).

Predictors of Residual Limb Pain (RLP)

In the multivariate analysis, we found that high level of amputation (P=0.03) and pain before amputation (P<0.001) were positive predictors of RLP intensity, and the presence of movement sensation (P<0.001) and response to previous treatment (P<0.001), were negative predictors. The multivariate regression line (n=67) can be defined by: *RLP (VAS) = 2.93 + 1.28*above knee amputation + 2.71*pain before amputation – 2.01*presence of movement sensations – 2.13*response to previous treatment* (see table 5). The model accounts for 35% (P<0.001) of the variance in RLP intensity. In addition to the categorical variables of the PLP model, we used pain before the amputation (0=no, 1=yes).

Summary - factors affecting PLP and RLP

Factors included in both models are the presence or absence of phantom limb movement and whether the patient experienced effective treatment before participating in the study. The PLP model further includes age, PLS intensity, and clinical trial center, whereas the RLP model includes the level of amputation and considering if the subject experienced pain in the affected limb prior to the surgery.

Discussion

The present study provide evidence for two common protective predictors for PLP and RLP intensity: phantom limb movement and previous effective treatment. Both conditions present different risk factors for high pain intensity: PLP - phantom limb sensation intensity and age, and RLP – the presence of pain before amputation and level of amputation.

The models, deriving from a population with chronic phantom limb pain patients after traumatic lower limb amputation, describe approximately one-third of the variance in PLP (31%) and RLP (35%). After the univariate regression, the assessed psychological descriptors (BDI, BAI) and general demographics (age, gender, opioid intake) have been dropped.

Our models show how PLP and RLP are affected by common protective factors, as well as distinct risk factors affecting the intensity of these two types of chronic pain. We here discuss first the protective factors: (1) presence of movements in the phantom limb and (2) effectiveness of previous pain treatments. The second part covers the risk factors; that were specific for PLP: (3) clinical trial center; (4) intensity of phantom limb sensation (5) age, and the ones specific to RLP: (6) level of amputation and (7) pain before amputation.

PLP and RLP

(1) Presence of Movements in the Phantom Limb: the motor corticospinal system circuit as a protective circuit

More than half of the enrolled subjects (54%) have spontaneous movements in their missing limb. Like in the study of Koojiman et al.[10] movement was the second most reported PLS after itching.

The multivariate models for RLP and PLP showed a negative correlation between the presence of phantom limb pain movements and pain; indicating that phantom limb movement was a protective factor. Movement in its variety of - imagined, mirrored or executed phantom limb mobility – is an important research topic in phantom pain and other chronic pain conditions, such as stroke or complex regional pain syndrome[23]. First; our data shows that phantom movement is present in the majority of the PLP patients (54%), second; recent fMRI research suggests that poor motor control of the missing limb is associated with increased pain in amputees[18] and third, the ability to move the phantom limb and the associated cortical activity and reorganization is the neurophysiological rationale for current rehabilitation approaches such as mirror therapy and visual illusion. It seems that phantom sensation and movement have a contrary effect on PLP. PLS is associated with increased PLP as opposed to movement sensation that showed to be a protective factor in PLP.

Here it is conceivable that the presence of movement may have a similar effect as some behavioral techniques using movement to treat PLP and not the other qualities of PLS[22]. Studies have shown that movements protect against pain in, pain associated with spinal cord injury - another type of neuropathic pain[24].

Several authors previously described the effects of phantom limb movements on cortical activity assessed with fMRI and its relationship with the presence and intensity of PLP[18, 20, 25–27]. For both – PLP and RLP - our models suggests lower levels of pain for patients that have spontaneous movement in their phantom limb. This supports approaches like mirror therapy which promote the representation of the missing limb in the cortex[23, 28] and aim to strengthen the impaired hemisphere – targeting downstream connection, as for example the thalamocortical pain-modulating pathway[23, 28]. Mirror therapy has been shown effective in reducing pain in upper and lower amputees, as well other chronic pain patients[23, 29–31]. Interestingly, therapies targeted the motor cortex (such as transcranial direct current stimulation) have shown significant effects in decreasing pain[32].

However, it is still unclear what is the best method to activate the motor corticospinal system to induce analgesic effects. Kikkert and colleagues[27] recently demonstrated that phantom pain had a positive correlation with movement execution of the phantom hand through a finger-tapping task. Unlike in their study, our variable describes the presence of spontaneous movement, which might be etiologically different. Also, those neuroimaging studies have been performed in upper limb amputees and need to be further studied in lower limb amputees.

(2) Effectiveness of Previous Pain Treatments: previous neural circuit responsiveness

The effectiveness of previous pain treatment (yes or no) was evaluated using the Groninger questionnaire. It is important to mention that all patients included in this study have a pain rating of at least four on average on the VAS, meaning that all have moderately intensive pain at study enrollment. That said, even participants that considered a previous treatment as adequate, still suffered from substantial phantom pain. The previous pain treatments included medications, other therapies, and non-pharmacological treatments. The most common therapeutic interventions were pregabalin, gabapentin, opioids (in the Boston clinical trial center), and surgeries to remove neuromas.

For both PLP and RLP, success of past treatment was associated with lower pain intensity showing that patients refractory to treatment present a higher intensity of pain at baseline. Yet this association was not influenced by depressive or anxiety symptoms - this indicates general refractoriness.

Chronic pain after an amputation is difficult to treat; this data supports the idea that further understanding of the resistant nature of neural circuits in PLP is critical to improve therapeutic strategies. Previous research in neuropathic pain has shown that many individuals are unsuccessfully treated and keep having pain despite numerous attempts with at pharmacologic treatment and high use of health services. In this context, the need for non-pharmacological alternatives that can be combined with behavioral or pharmacological interventions seems a promising alternative for multidisciplinary and effective treatment for long-lasting pain relief.

The fact that both models include two common factors with the same direction of impact to pain intensity shows in a more discriminative way which was indicated by the slight correlation of PLP and RLP intensity (Spearman’s rho=0.296, P=0.012). It corroborates the hypothesis that both amputation related forms of pain are likely driven by common, as well distinct factors – described here – and general neuropathic pain mechanisms[4].

We did not find any other significant correlation between PLP and assessed demographical or amputation related data. The study included only patients with relatively high PLP (VAS >4), and as it is known low variation in the outcome variable does reduce the sensitivity to find significant correlations[33].

PLP

Publications investigating the prevalence of PLP report mean pain intensities between 5 and 5.5 on a VAS from 0 to 10[5–7]. Interestingly interventional studies, like the one this dataset derives from, do not necessarily report higher pain levels, despite inclusion criteria restricting the sample to amputees with PLP with certain minimal pain intensity. With a mean intensity of 5.9, our sample is between previously reported numbers; 4.4 to 6.5[30, 31, 34].

Besides, the two protective factors shared (movement and efficient pain treatment), there are three detrimental variables to PLP – age, PLS intensity and being enrolled in the Brazilian study center.

(3) Clinical Trial Center

In the PLP model, clinical trial center is the second-largest coefficient and represents whether the subject was enrolled in Brazil (Sao Paulo) or US (Boston). According to the regression model, Brazilian participants reported higher pain levels. This should be interpreted with caution as the clinical trial center is a multilayer variable to which many differences at the study sites might contribute – as for example; the way to report pain, differences in the health care system and variance related specifically to the trial – as for example minor deviances in recruitment strategies. The fact, that study site is a significant factor in modulating PLP intensity in our trial emphasizes the importance to conduct multicenter studies, including different cultures and ethnicity to increase the generalizability of the trial outcomes to the whole PLP population. Importantly, this supports our approach to control for the study site.

(4) Intensity of Phantom Limb Sensation: a potential marker of sensorimotor system maladaptive plasticity

A further variable included in the PLP model is the reported intensity of phantom limb sensation, often specified in the literature as *non-painful*. In our study, we showed that most PLP patients (90%) experience at least one phantom sensation; electric sensations, itching, and movement were reported most often. These findings corroborated previous studies that showed that many amputees do experience both PLP and PLS[1, 5, 10]. The multivariate regression supports the co-occurrence and positive correlation between PLP and PLS intensity; higher PLS intensity is associated with higher PLP intensity.

It is likely that those two forms of amputation related sensations share pathophysiological mechanisms. As a limitation of ours, as well most other trials investigating PLP we did not assess PLP quality – although it is known from early studies that pain is experienced in different varieties[7, 11]. It is puzzling that this aspect is often neglected, especially by looking closer to reported PLS descriptors – in our data as well others[5] – revealing that items like itching and electric sensation sound unpleasant, if not rather painful. Taking itching as an example, a very specific fMRI experiment in healthy subjects, revealed that pain and itching do in part activate the same cortical areas, which show that those two sensations are interlinked on a neurophysiological level[35]. For tingling, a large epidemiological study showed that this term was used by patients to describe their PLP, PLS and RLP. Although the association between PLP and PLS is not fully supported elsewhere as topographical phantom sensations do not occurs in all PLP subjects[36].

(5) ge: a factor that can worsen maladaptive plasticity

Old age can reduce the neuroplasticity potential[37] and neural adaptability; ultimately reducing coping to chronic pain[38]. Age was an important covariate in our PLP modeling, changing the proportion of the variance in the PLP intensity. Several studies have shown that age is associated with changes in compensatory mechanisms, due to age-related atrophy in

brain areas and to age-related decline on cognitive function. This lack in compensatory activity may be related to differences in the sensorimotor cortex reorganization in subjects with amputation leading to PLP[39]. Recently the literature has pointed out that alterations in the brain which are associated with chronic pain can be modified and are reversible. In this scenario, age can delaying this process independently of PLP specific mechanism[40, 41]. Interestingly, age was a significant predictor only in PLP. Other study designs exploring the impact of age on chronic pain longitudinally and associated coping strategies[42], would clarify the underpinnings of age-related pain processing.

Residual Limb Pain (RLP)

Previous studies showed that RLP is, after PLP, the most common form of pain[5] in amputees, which is more prevalent in traumatic and lower limb amputees[6], compared to other causes of limb loss and upper extremities. This form of pain is more prevalent in the early phases after amputation[43]. In our sample, 82% (N=58) of the participants experienced RLP; however, the mean intensity of RLP seemed to be lower (4 ± 5.25; N= 58) compared to other studies reporting 5.1 to 6.2 on a VAS[5–7]. Next to the two protective factors shared with PLP (movement and efficacy of previous treatments), there are two variables that seem detrimental to RLP intensity: level of amputation and pain before amputation.

(6) Level of Amputation

We evaluated the level of amputation of our sample by categorizing participants into below-knee (low) and above-knee amputees (high) and showed that a high level of amputation is associated with higher RLP intensity. Larger surgical operation areas at the thigh result in larger neuromas which are associated with neuropathic pain[4]. Further, increased demands to a prosthesis, with its potential difficulties fitting it to the residual limb can increase pain in the stump. In addition, a larger amputation also represents a large neural injury contributing to additional risk of neuropathic pain[44].

(7) Pain Before Amputation: evidence of central sensitization leading to chronic pain

Pain before amputation is often discussed in the phantom limb pain research field, mainly because of studies showing how pain memory might contribute to pain after amputation. The pain memory model refers rather to an implicit interpretation of the term memory, addressing the neurophysiological changes in the central nervous system[45, 46]. Those alterations are deriving from long-lasting noxious stimuli before the surgery[4, 47], which are supposed to alter the cortical excitability in the sensory cortex and further affecting inhibitory processes at spinal and supraspinal levels[4]. Therefore, pain before amputation leads to central sensitization processes like the ones observed in neuropathic pain, contributing to long-lasting residual limb pain.

Moreover, pain before amputation was not a factor influencing the intensity of phantom limb pain in our sample. The association of pre-amputation pain and PLP was first described in a longitudinal study showing that the incidence of PLP three months after the amputation was higher in patients with pre-amputation pain[11]. However, in our cohort, the median time since amputation is over a year. This suggests, whilst pain prior to amputation can be a predictor

for the incidence of acute PLP, its role in for pain intensity in chronic PLP is not yet elucidated.

One limitation of retrospective pain assessments from before the amputation is the recall issue; chronic patients may have difficulties to rate their pre-amputation pain accurately when the surgery lays back several months or years[9, 48]. Interestingly, Nikolajsen et al.[11] showed that patients significantly overestimated their pre-amputation pain intensity after six months. This recall bias makes it difficult to draw a clear conclusion from analysis with retrospective pain assessment[49, 50].

Strengths and Limitations

To be included in this study, participants had to experience PLP on average with an intensity of at least a four on a VAS from 0–10. This reduces the present overall variance in the dataset and excludes amputees without or only low PLP. The models account for PLP variability of pain intensity, incidence or prevalence.

The data was analyzed in an exploratory manner by comparing the fit of the basic model (all variables with p-value<0.05 in the univariate regression) to model variations where coefficients have been dropped. However, by limiting the number of coefficients and the prerequisite of a p-value of P<0.05 in the univariate regression, we limited the risk of an overfitted model.

For both RLP and PLP the literature shows that amputation site (upper or lower limb) as well etiology (traumatic or non-traumatic) can affect PLP prevalence and intensity[5, 6, 13]. This can limit the comparability of the results among studies and emphasizes the need for addressing specific subgroups of the PLP community, as pathophysiological mechanisms might differ. We here investigated a specific and clearly defined patient group of lower limb amputees with traumatic causes for the amputation.

The analyses have shown evidence for common, as well as distinct factors affecting postamputation pain levels. Both PLP and RLP are forms neuropathic pain, whereas different processes are contributing to varying degrees; in PLP the main emphasis is central sensitization and reorganization, whereas in RLP peripheral processes add and might dominate (neuroma formation, hyperalgesia and allodynia[4]).

This is one of the largest study population investigating traumatic, lower limb amputees with chronic PLP discussing amputation related symptoms assessed from trained research stuff. Most publications investigating pre- and postamputation factors to PLP are questionnaire-based[5, 6, 12] and suffer the well-known response bias and risk of misunderstanding of listed items.

Multicenter studies can provide results representing a more diverse fraction, and hence more relevant representation of the population; here, patients from two countries (US and Brazil). Nevertheless, this complex variable might hide underlying factors like differences in culture, education, or the health care system.

Conclusion

The analysis of predictors for PLP and RLP suggests different neurobiological mechanisms and associated factors, which suggest divergent main emphasis in therapy depending on the main burden of the subject. Notwithstanding, movement sensation seems to be a common protective factor for both pain syndromes highlighting the beneficial outcome of some behavioral therapies for PLP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Nikolajsen L, Jensen TS. Phantom limb pain. British Journal of Anaesthesia. 2001;87:107–116. [PubMed: 11460799]
2. Richardson C, Glenn S, Nurmikko T, Horgan M. Incidence of phantom phenomena including phantom limb pain 6 months after major lower limb amputation in patients with peripheral vascular disease. Clinical Journal of Pain. 2006;22:353–358. [PubMed: 16691088]
3. Jutzeler CR, Curt A, Kramer JL. Relationship between chronic pain and brain reorganization after deafferentation: A systematic review of functional MRI findings. Neuroimage Clin. 2015;9:599–606. [PubMed: 26740913]
4. Cohen SP, Mao J. Neuropathic pain: Mechanisms and their clinical implications. BMJ (Online). 2014;348:1–12.
5. Ehde DM, Czerniecki JM, Smith DG, Campbell KM, Edwards WT, Jensen MP, et al. Chronic phantom sensations, phantom pain, residual limb pain, and other regional pain after lower limb amputation. Archives of Physical Medicine and Rehabilitation. 2000;81:1039–1044. [PubMed: 10943752]
6. Ephraim PL, Wegener ST, Mackenzie EJ, Dillingham TR, Pezzin LE. Phantom Pain, Residual Limb Pain, and Back Pain in Amputees : Results of a National Survey. Archives of Physical Medicine and Rehabilitation. 2005;86:1910–1919. [PubMed: 16213230]
7. Wartan SW, Hamann W, Wedley JR, McColl I. Phantom pain and sensation among British veteran amputees. British Journal of Anaesthesia. 1997;78:652–659. [PubMed: 9215014]
8. Kato K, Sullivan PF, Evengård B, Pedersen NL. Importance of Genetic Influences on Chronic Widespread Pain. ARTHRITIS & RHEUMATISM. 2006;54:1682–1686. [PubMed: 16646040]
9. Bosmans JC, Geertzen JHB, Post WJ, Van Der Schans CP, Dijkstra PU. Factors associated with phantom limb pain: A 3 1/2-year prospective study. Clinical Rehabilitation. 2010;24:444–453. [PubMed: 20442256]
10. Kooijman CM, Dijkstra PU, Geertzen JHB, van der Schans CP, Elzinga A. Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. Pain. 2002;87:33–41.
11. Nikolajsen L, Ilkjaer S, Kroner K, Christensen JH, Jensen TS. The influence of preamputation pain on postamputation stump and phantom pain. Pain. 1997;72:393–405. [PubMed: 9313280]
12. Richardson C, Glenn S, Horgan M, Nurmikko T. A Prospective Study of Factors Associated With the Presence of Phantom Limb Pain Six Months After Major Lower Limb Amputation in Patients With Peripheral Vascular Disease. Journal of Pain. 2007;8:793–801. [PubMed: 17631056]
13. Hanley MA, Jensen MP, Ehde DM, Hoffman AJ, David R, Robinson LR, et al. Psychosocial predictors of long-term adjustment to lower-limb amputation and phantom limb pain Psychosocial

predictors of long-term adjustment to lower-limb amputation and phantom limb pain. Disability and Rehabilitation. 2009:882–893.

14. Fuchs X, Flor H, Bekrater-bodmann R. Psychological Factors Associated with Phantom Limb Pain : A Review of Recent Findings. Pain Research and Management Volume. 2018.
15. Jensen MP, Moore MR, Bockow TB, Ehde DM, Engel JM, Otr L. NIH Public Access. Archives of Physical Medicine and Rehabilitation. 2011;92:146–160. [PubMed: 21187217]
16. Desmond DM, Maclachlan M. Prevalence and characteristics of phantom limb pain and residual limb pain in the long term after upper limb amputation. International Journal of Rehabilitation Research. 2010;33:279–282. [PubMed: 20101187]
17. Foell J, Bekrater-Bodmann R, Diers M, Flor H. Mirror therapy for phantom limb pain: Brain changes and the role of body representation J. European Journal of Pain. 2014;18:729–739. [PubMed: 24327313]
18. Kikkert S, Johansen-berg H, Tracey I, Makin TR. Reaffirming the link between chronic phantom limb pain and maintained missing hand representation. Cortex. 2018;106:174–184. [PubMed: 30005369]
19. Makin TR, Scholz J, Filippini N, Henderson Slater D, Tracey I, Johansen-Berg H. Phantom pain is associated with preserved structure and function in the former hand area. Nature Communications. 2013;4.
20. Raffin E, Richard N, Giraux P, Reilly KT. Primary motor cortex changes after amputation correlate with phantom limb pain and the ability to move the phantom limb. NeuroImage. 2016;130:134–144. [PubMed: 26854561]
21. Simoes EL, Bramati I, Rodrigues E, Franzoi A, Moll J, Lent R. Functional Expansion of Sensorimotor Representation and Structural Reorganization of Callosal Connections in Lower Limb Amputees. The Journal of Neuroscience. 2012;32:3211–3220. [PubMed: 22378892]
22. Pinto CB, Saleh Velez FG, Bolognini N, Crandell D, Merabet LB, Fregni F. Optimizing Rehabilitation for Phantom Limb Pain Using Mirror Therapy and Transcranial Direct Current Stimulation: A Randomized, Double-Blind Clinical Trial Study Protocol. JMIR research protocols. 2016;5:e138. [PubMed: 27383993]
23. Thieme H, Morkisch N, Rietz C, Dohle C, Borgetto B. The Efficacy of Movement Representation Techniques for Treatment of Limb Pain-A Systematic Review and Meta-Analysis. The Journal of Pain. 2016;17:167–180. [PubMed: 26552501]
24. Marcondes BF, Sreepathi S, Markowski J, Nguyen D, Stock SR, Carvalho S, et al. Pain severity and mobility one year after spinal cord injury: a multicenter, cross-sectional study. European journal of physical rehabilitation medicine. 2016;52:630–636. [PubMed: 26616359]
25. Dettmers C, Adler T, Rzanny R, Van Schayck R, Gaser C, Weiss T, et al. Increased excitability in the primary motor cortex and supplementary motor area in patients with phantom limb pain after upper limb amputation. Neuroscience Letters. 2001;307:109–112. [PubMed: 11427312]
26. Diers M, Christmann C, Koeppe C, Ruf M, Flor H. Mirrored, imagined and executed movements differentially activate sensorimotor cortex in amputees with and without phantom limb pain. Pain. 2010;149:296–304. [PubMed: 20359825]
27. Kikkert S, Mezue M, Henderson DS, Johansen-Berg H, Tracey I, Makin TR. Motor correlates of phantom limb pain. Cortex 95 2017:29–36. [PubMed: 28822914]
28. Rothgangel AS, Braun SM, Beurskens AJ, Seitz RJ, Wade DT. The clinical aspects of mirror therapy in rehabilitation: A systematic review of the literature. International Journal of Rehabilitation Research. 2011;34:1–13. [PubMed: 21326041]
29. Bhasin A, Bhatia R, Kumaran S, Mohanty S, Padma Srivastava MV. Neural interface of mirror therapy in chronic stroke patients: A functional magnetic resonance imaging study. Neurology India. 2012;60:570. [PubMed: 23287316]
30. Finn SB, Perry BN, Clasing JE, Walters LS, Jarzombek SL, Tsao JW. A Randomized, Controlled Trial of Mirror Therapy for Upper Extremity Phantom Limb Pain in Male Amputees. Frontiers in Neurology. 2017;8:1–7. [PubMed: 28138322]
31. Seidel S, Kasprian G, Furtner J, Schöpf V, Essmeister M, Sycha T, et al. Mirror therapy in lower limb amputees - Alookbeyondprimary motor cortex reorganization. Fortschritte auf dem Gebiet der Röntgenstrahlen und bildgebenden Verfahren. 2011:1051–1057.

32. Pinto CB, Teixeira BC, Duarte D, Fregni F. Transcranial Direct Current Stimulation as a Therapeutic Tool for Chronic Pain. The journal of ECT. 2018;34:e36–e50. [PubMed: 29952860]
33. Bland JM, Altman DG. Correlation in restricted ranges of data. BMJ. 2011;342.
34. Bocci T, Carolis DG, Ferrucci R, Paroli M, Mansani F, Priori A, et al. Cerebellar Transcranial Direct Current Stimulation (ctDCS) Ameliorates Phantom Limb Pain and Non-painful Phantom Limb Sensations. The Cerebellum. 2019.
35. Mochizuki H, Sadato N, Saito DN, Toyoda H, Tashiro M, Okamura N, et al. Neural correlates of perceptual difference between itching and pain : A human fMRI study ☆. Human Brain Mapping Journal. 2007;36:706–717.
36. Grüsser SM, Winter C, Mühlnickel W, Denke C, Karl A, Villringer K, et al. The relationship of percetual phenomena and coritcal reorganization in upper extremity amputees. Neuroscience. 2001;102:263–272. [PubMed: 11166112]
37. Voss P, Thomas ME, Cisneros-Franco JM, de Villers-Sidani É. Dynamic brains and the changing rules of neuroplasticity: implications for learning and recovery. Frontiers in psychology. 2017;8:1657. [PubMed: 29085312]
38. Cruz-Almeida Y, Fillingim RB, Riley III JL, Woods AJ, Porges E, Cohen R, et al. Chronic pain is associated with a brain aging biomarker in community-dwelling older adults. Pain. 2019;160:1119–1130. [PubMed: 31009418]
39. Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, et al. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. Neuroscience & Biobehavioral Reviews. 2010;34:721–733. [PubMed: 19850077]
40. Apkarian AV, Hashmi JA, Baliki MN. Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. Pain. 2011;152:S49. [PubMed: 21146929]
41. Davis KD, Moayedi M. Central mechanisms of pain revealed through functional and structural MRI. Journal of Neuroimmune Pharmacology. 2013;8:518–534. [PubMed: 22825710]
42. Keefe FJ, Williams DA. A comparison of coping strategies in chronic pain patients in different age groups. Journal of gerontology. 1990;45:P161–P165. [PubMed: 2365972]
43. Ahmed A, Bhatnagar S, Mishra S, Khurana D, Joshi S, Ahmad SM. Prevalence of phantom limb pain, stump pain, and phantom limb sensation among the amputated cancer patients in India : A prospective, observational study. Indian Journal of Palliative Care. 2017;23:24–35. [PubMed: 28216859]
44. Hsu E, Cohen SP. Postamputation pain: epidemiology, mechanisms, and treatment. Journal of pain research. 2013;6:121. [PubMed: 23426608]
45. Flor H Phantom-limb pain: characteristics, causes, and treatment. The Lancet Neurology. 2002;1:182–189. [PubMed: 12849487]
46. Flor H, Nikolajsen L, Jensen TS. Phantom limb pain: A case of maladaptive CNS plasticity? Nature Reviews Neuroscience. 2006;7:873–881. [PubMed: 17053811]
47. Noguchi S, Saito J, Nakai K, Kitayama M, Hirota K. Factors affecting phantom limb pain in patients undergoing amputation : retrospective study. Journal of Anesthesia. 2019;33:216–220. [PubMed: 30603827]
48. Dijkstra PU, Geertzen JHB, Stewart R. Phantom Pain and Risk Factors : A Multivariate Analysis. Journal of Pain and Symptom Management. 2002;24:578–585. [PubMed: 12551807]
49. Nikolajsen L, Ilkjaer S, Christensen JH, Krøner K, Jensen TS. Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. The Lancet. 1997;350:1353–1357.
50. Roullet S, Nouette-Gaulain K, Biais M, Bernard N, Bénard A, Revel P, et al. Preoperative opioid consumption increases morphine requirement after leg amputation. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2009;56:908.

Table 1:

Clinical data related to the amputation, number of participants N (%). Percentages are calculated based on the sample of N=71

Side of amputation	
Left	39 (54.9%)
Right	31 (43.7%)
Level of amputation	
Above the knee	37 (52.1%)
Below the knee	34 (47.9%)
Pain prior to the amputation	
Yes	45 (63.4%)
No	26 (36.6%)
Opioid intake	
Yes	15 (21.1%)
No	56 (78.9%)

Table 2:

Intensity (mean±SD) on a visual analog scale (from 0–10) of amputation related perceptions and frequency of episodes N (%), percentages are calculated on available data of participants N_{part}.

Amputation related perception	N_{part}	Intensity, mean±SD	Frequency, N_{freq} (%)		
			At least once daily	Weekly or less	Never
Phantom limb pain	69	5.9±1.7	38 (55.0%)	31 (44.9%)	NA
Residual limb pain	70	3.8±3.0	26 (37.1%)	32 (45.7%)	12 (17.4%)
Phantom limb sensation	71	5.7±3.3	39 (55.0%)	27 (38.0%)	5 (7.0%)

Table 3:

The percentages of PLS varieties are calculated based on data from all subjects experiencing at least one PLS quality (N=64), multiple answers were possible.

PLS (total N=64)	N	%
Itching	38	59.4
Movement	35	54.7
Abnormal shape	13	20.3
Abnormal position	10	15.6
Something touching	12	18.8
Warmth	14	21.9
Cold	15	23.4
Electric sensation	46	71.9

Table 4:

Model for phantom limb pain (PLP) intensity on a VAS from 0 to 10; PLS (0: absent, 1: present), movement (0: absent, 1: present), clinical trial center (0: US, 1: Brazil), PLP treatment effectiveness of prior to study enrollment (0: not effective, 1: effective).

Phantom limb pain (PLP) 67 observations, adjusted R^2 = 31%			
Factor	**coefficient**	**p-value**	**95% CI**
Age	0.028	0.04	[0.002; 0.054]
PLS	0.168	0.01	[0.047; 0.289]
Movement	−0.860	0.03	[−1.611; −0.110]
Clinical trial center	0.887	0.04	[0.051; 1.724]
PLP treatment effectiveness	−1.464	<0.001	[−2.267; −0.661]
Constant	5.379	<0.001	[3.401; 7.357]

Table 5:

Model for residual limb pain (RLP) intensity on a VAS from 0 to 10; Level of amputation (0: below knee, 1: above knee), treatment effectiveness of prior to study enrollment (0: not effective, 1: effective), movement (0: absent, 1: present), pain prior to the amputation (0: no, 1: yes).

Residual limb pain (RLP) 67 observations, adjusted R^2=35%			
Factor	**coefficient**	**p-value**	**95% CI**
Level of amputation	1.283	0.03	[0.104; 2.462]
PLP treatment effectiveness	−2.126	<0.001	[−3.503; −0.750]
Movement	−2.008	<0.001	[−3.197; −0.820]
Pain prior to amputation	2.705	<0.001	[1.433; 3.976]
Constant	2.932	<0.001	[1.646; 4.218]