ABSTRACT

Introduction: After amputation, altered sensory input leads to cortical reorganization that partly explains phantom limb pain (PLP). However, many factors impact the PLP phenomenon, and modern conceptualizations of chronic pain including PLP integrate both peripheral inputs and central interpretation. Clinicians without functional MRI could benefit from clinical measures related to PLP to assess clinical presentations. The purpose of this pilot study was to identify peripheral sensation and cognition measures related to PLP to inform outcome measure selection in future PLP research.

Methods: This cross-sectional analysis included people with PLP of any age, sex, and amputation cause or level. Assessments included patient-reported residual limb pain and PLP using the Prosthesis Evaluation Questionnaire, peripheral sensation measures (light touch, temperature, vibration, two-point discrimination), and cognition measures (latency recognition, trail making, clock drawing). Unadjusted Spearman $\rho$ coefficients were reported.

Results: Eleven volunteers (48.5 ± 13.2 years) with lower-limb amputations (seven transtibial) of various causes (nine medical) participated. More severe PLP symptoms were associated with impaired peripheral sensation (light touch, $\rho = 0.514$; temperature, $\rho = 0.756$) and poorer cognition (latency recognition, $\rho = 0.524$; trail making, $\rho = 0.565$). Residual limb pain was not correlated with cognition measures ($\rho < 0.4$).

Conclusions: This pilot study identified clinical measures assessing cognition and peripheral sensation impairments associated with worse PLP symptoms. Phantom limb pain was related to temperature and light touch sensation measures, but two-point discrimination was not associated with PLP consistent with past research. Latency recognition was associated with PLP prior research, and the association of PLP with the Trail Making Test in this pilot study suggests that the Trail Making Test may be an additional cognition measure potentially useful in future clinical research to document the PLP experience.

KEY INDEXING TERMS: amputation, phantom limb, pain, impaired sensation, cognition, prosthetics, laterality

People with limb loss often experience lasting pain after amputation, with 35% to 68% reporting residual limb pain and 49% to 80% reporting phantom limb pain (PLP) in large American epidemiology studies. Pain after amputation increases the likelihood of depression, interferes with daily life, and has been associated with reduced quality of life. Although many people with lower-limb loss report that PLP had minimal impact on physical function, assessing the impact of PLP on function can be difficult because of its episodic nature. Whether described as phantom sensation or pain and rated as severe or bothersome, PLP can last for years after surgery: over 60% have reported phantom pain at an average 22 years after amputation.

A wide range of invasive and noninvasive treatments for PLP have shown potential for success in reducing PLP, but well-controlled evidence for broad treatment efficacy remains sparse. One surgical intervention that has shown promise for upper-limb amputation, but has not been attempted in the lower limb, has been prophylactic targeted muscle reinnervation. Medical approaches for perioperative phantom and residual limb pain have shown mixed short-term success with antiepileptics, NMDA receptor antagonists, and opioids with or without sodium channel blockers, but long-term efficacy remains elusive. In recent systematic reviews, evidence for invasive spinal stimulation remains limited to uncontrolled studies, and the modest short-term pain relief after noninvasive transcranial magnetic stimulation from small studies has not been maintained long term. Study quality is low for conservative care as well, with only five moderate quality studies identified using electromagnetic liners, graded motor imagery or mirror therapy, and hypnosis. One factor that may contribute to the lack of a well-supported standard of care may be the incomplete understanding of the PLP phenomena.

Among the aspects of PLP that continue to be investigated are the roles of the central nervous system processes and...
Peripheral sensory impairments are infrequently assessed, leaving any potential relationships among sensory impairment, limb pain, and PLP largely unexplored. For people with upper limb loss, two-point discrimination that requires stimulation detection and interpretation has been used to try assess brain adaptations. For people with lower-limb loss, however, sensation testing has rarely been reported. One study of 11 subjects 1 to 3 years after amputation found no clear relationship between PLP and sensory function assessed using tactile touch and two-point discrimination. Overall, few researchers exist exploring sensation impairment after amputation and PLP, although current conceptualization suggests that PLP is affected by both central and peripheral nervous system changes.

Central nervous system adaptation marked by cortical reorganization has been shown to be associated with PLP, but associations between cognition and PLP remain largely unexplored. Subjectively, people with limb loss do note cognitive difficulties with memory, attention, and decision making. Cognition impairments, particularly in executive functions related to the attention and processing speed domains, have been found to impact both upper-limb prosthesis use and lower-limb prosthetic mobility. An activity that requires both attention and processing speed—the ability to recognize left or right limbs in pictures presented for limited time, referred to as laterality recognition ability—has been associated with PLP symptoms in one study of people with lower-limb loss. Graded motor imagery treatment for chronic pain often includes laterality recognition training together with mirror therapy and may help reduce PLP in both the short term and after 6 months.

Relationships between PLP and peripheral sensory sensations and cognitive functions have been studied separately but not concurrently, and the most relevant measures of peripheral sensation and cognition for use in studies of PLP remain unclear. The purpose of this pilot study was to assess whether peripheral sensation and cognition measures were related to residual limb pain and PLP to inform outcome measure selection for clinical research in people with lower-limb loss.

**METHODS**

This pilot study focused on future outcome measure selection. The study included cross-sectional analysis of initial assessment data from a prospective longitudinal study approved by the Columbia University Irving Medical Center Institutional Review Board and conducted in an outpatient research setting.

**SUBJECTS**

Volunteers referred by local clinicians included adults of any age, sex, and race, with major unilateral lower-limb loss of any cause and surgical level. People who reported no PLP in the past year or who were unable to understand the procedures for any reason including English language or cognitive ability were excluded. The sample size was modeled after previous research that also studied sensation in people with limb loss that reported PLP.

**PROCEDURES**

After providing written informed consent, subjects attended one in-person assessment including an intake interview and clinical assessment. Interview data included age, sex, race, amputation cause, surgical level, and years since amputation. The patient-reported Prosthesis Evaluation Questionnaire Bodily Sensations subscale was used during the interview to obtain PLP (defined as pain or sensation perceived in the missing limb), sensation pain descriptors, intensity, and frequency, as well as data regarding residual limb pain (defined as pain in the nonamputated limb).

Clinical assessment included peripheral sensation and cognition tests. Sensation testing common for diabetic patients was assessed 1 cm above the surgical incision line, positioned similarly to another study. Sensations carried by the spinothalamic tract included light touch and temperature. Light touch sensation was tested using a 10-g monofilament (see Figure 1), which has good intertester and intratester reliability in people with diabetes as used to assess light touch with greater than 0.9 specificity for detecting diabetic neuropathy. Temperature was tested using cold temperature discrimination at the standard 3.9°C (39°F), with the presence of hyperalgesia or paradoxical cold reactions that have been found to indicate small fiber diabetic neuropathies noted. Sensations carried by the dorsal column spinal tract included vibration and two-point discrimination. Vibration sense, which has substantial interrater reliability, was tested with a 128-Hz tuning fork. Time to end of vibration perception was documented, which has been useful in identifying those at risk to develop diabetic ulcers. An aesthesiometer was used to test discrimination of two-point distance, a reliable and valid test for sensation testing in people with diabetes. Cognitive function tests associated with limited physical activity used in people with diabetes included three tests: 1) the clock drawing test that has been associated with diabetes in older adults; 2) the Trail Making Test—scored by adding short-A and long-B forms—which is commonly used to test for executive function; and 3) limb laterality recognition score obtained with the Recognise app, using 20 images at 2 seconds per image, with score reported as the accuracy/speed quotient. Test order was consistent for all subjects (Figure 1).

Statistics was analyzed using SPSS, Mac version 25 (IBM Corporation). Unadjusted nonparametric Spearman ρ coefficients were
calculated, with correlations 0.5 to 0.75 defined as moderate to good.

RESULTS

Of the 11 adults recruited, there was a mean age of 48.5 ± 13.2 years; lower-limb loss due to vascular disease (n = 6), trauma (n = 2), and other medical causes (n = 3); and a mean 4.2 ± 3.7 years since amputation (Table 1). Of the 11 subjects, 10 (91%) subjects reported both PLP and sensations. The most commonly reported PLP descriptors, with some subjects using multiple descriptors, were shooting (n = 5), tingling and itching (n = 3), aching and cramping (n = 2), and piercing, spasms, and burning (n = 1). Five reported taking pain medications including aspirin, Tylenol, Lyrica, gabapentin, and oxycodone. The mean PLP intensity was 44.8 ± 34.2 with limb pain 27.9 ± 28.4, as measured on the 100-mm visual analog scale (Table 1).

Most peripheral sensation and cognition measures were insignificantly correlated to PLP and residual limb pain symptoms (Table 2). One peripheral sensation with a significant unadjusted association (p = 0.756) with more intense PLP symptoms was impaired temperature sensation, marked by paradoxic sensation of cold stimuli as hot. In addition, more frequent PLP was associated with slower Trail Making Test A + B performance (p = 0.565). Clock drawing had weak or negligible associations with PLP (Table 2). No cognition measures demonstrated a moderate correlation with any residual limb pain symptoms (p < 0.5).

DISCUSSION

The results of this pilot study were that the frequency and intensity of PLP symptoms were associated with both peripheral sensations (light touch and temperature) and cognition measures (laterality recognition and the Trail Making Test). Unadjusted associations were moderate to good with only the relationship between paradoxical temperature sensation and PLP intensity reaching significance. Sample size was insufficient to reach significance at the moderate correlation levels observed for other variables. However, the direction of the relationship suggested that, in this group of people, less frequent or intense PLP symptoms were associated with better peripheral light touch and temperature sensation and better cognition measured using laterality recognition and the Trail Making Test. The relationships between residual limb pain and both peripheral sensations and cognition measures were generally weak to negligible.

Pilot studies can contribute to health research by assisting the informed selection of reasonable measures for future research. Selecting appropriate peripheral sensation and cognition measures was especially appropriate for clinical research into PLP given the incomplete understanding of the phenomenon. It is generally accepted that cortical reorganization representing brain neuroplasticity in the sensory and motor cortices occurs after amputation as the person adapts to altered sensory input from the residual limb. Some evidence from functional

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>9 men, 2 women</td>
</tr>
<tr>
<td>Amputation cause</td>
<td>4 peripheral artery disease</td>
</tr>
<tr>
<td></td>
<td>2 diabetes</td>
</tr>
<tr>
<td></td>
<td>2 trauma</td>
</tr>
<tr>
<td></td>
<td>3 other medical</td>
</tr>
<tr>
<td>Surgical level</td>
<td>7 transtibial, 4 transfemoral</td>
</tr>
<tr>
<td>Age ± SD, y</td>
<td>48.5 ± 13.2</td>
</tr>
<tr>
<td>Years since amputation</td>
<td>4.2 ± 3.7</td>
</tr>
<tr>
<td>PLP intensity, mm</td>
<td>44.8 ± 34.2</td>
</tr>
<tr>
<td>Residual limb pain intensity, mm</td>
<td>27.9 ± 28.4</td>
</tr>
<tr>
<td>Low back pain intensity, mm</td>
<td>22.3 ± 28.3</td>
</tr>
</tbody>
</table>

PLP, phantom limb pain.
MRI findings even suggest that PLP may be related to the cortical reorganization process, which slows down as the individual learns to make sense of the sensations from the residual limb.\textsuperscript{13} However, many factors may impact the PLP phenomenon, and rehabilitation clinicians without access to functional MRI equipment could benefit from clinical measures related to PLP that could be used to assess and monitor change.\textsuperscript{12,15} Although a number of studies found no relationship between laterality recognition and Trail Making Test measures,\textsuperscript{22} perhaps because the episodic nature of PLP makes it difficult to assess in PLP has been limited. The contribution of this pilot study may be the narrowing in the range of sensation and cognition measures that may be associated with PLP.

Study results documenting a moderate association between PLP frequency and cognition (\(r = 0.524\)) assessed with the limb laterality recognition score were consistent with findings from a separate study that introduced using the accuracy/speed quotient to score laterality recognition performance.\textsuperscript{22} Both studies found no relationship between laterality recognition and PLP duration,\textsuperscript{22} perhaps because the episodic nature of PLP makes accurate recall difficult.\textsuperscript{13} Impaired limb laterality recognition observed in this pilot was similar to the slower recognition speeds found in chronic pain conditions including PLP.\textsuperscript{35} Slower Trail Making Test performance was moderately associated with more PLP intensity in this study (\(r = 0.565\)). This finding has no precedent, although in studies that did not include pain measures, the Trail Making Test performance has contributed significantly to explanatory models for mobility performance that combine multiple movement tasks in people with limb loss,\textsuperscript{36} and could be related to the prevalence of diabetes.\textsuperscript{21} The association between better cognition, measured with both the laterality recognition and Trail Making Test measures, and lower PLP symptom levels suggests that the use of these cognition measures may be warranted in larger clinical research studies of PLP.

Few studies have assessed peripheral sensations in people with lower-limb loss. The results of this study were that there was no clear relationship between PLP and two-point discrimination (Table 2), which confirmed the finding of the other study that used two-point discrimination in people with limb loss.\textsuperscript{17} The peripheral sensation measures found at least moderately associated with PLP were light touch (\(r = 0.514\)) and temperature sense (\(r = 0.756\)), both carried by the spinothalamic tract. That PLP frequency and intensity were associated with light touch, and temperature sense impairments may also be related to diabetes and/or peripheral artery disease, as most subjects had one or both. However, diabetes is known to also affect vibration and two-point discrimination sense carried in the dorsal column tract.\textsuperscript{29} Association of PLP with light touch and paradoxical temperature sense, marked by identification of cold stimuli as hot versus room temperature or cold, has been previously observed in people with diabetes.\textsuperscript{28} The findings that light touch and temperature sense impairment were associated with more PLP symptoms were novel findings and may make these measures useful measures in future clinical studies of people with lower-limb loss.

The results of this study documenting the relationships between sensation and cognition testing and PLP may provide the rationale for using clinical peripheral sensation and cognition measures in PLP-related research. Notably, desensitization of peripheral sensations for decreasing pain in people with limb loss has been recommended by multiple textbooks, although surprisingly without primary evidence. Use of peripheral sensation measures in future research may provide insight into usefulness of desensitization treatments. Study conclusions, however, were limited by the small sample and mixed population and cannot be generalized beyond the subjects included in this pilot study. Other limitations include the fact that most unadjusted associations had \(P > 0.05\) and would not be significant if adjusted for multiple comparisons (Table 2). For correlations greater than 0.50 on two-tailed tests, 13 subjects would be required to reach significance.\textsuperscript{34} All peripheral sensation measures were common clinical assessments, but not tested for reliability and validity in the current study, although the Trail

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|}
\hline
\textbf{Clinical Test} & \textbf{Sensation} & & & \textbf{Cognition} & \\
& \textbf{Light Touch} & \textbf{Temperature} & \textbf{Vibration} & \textbf{2-Point Discrimination} & \\
& \textbf{Frequency} & & & & \textbf{Laterality Recognition} & \textbf{Trail Making Test A + B} & \textbf{Clock Drawing Test} \\
\hline
\textbf{Phantom limb pain} & 0.514 & 0.401 & 0.284 & 0.251 & 0.524 & 0.168 & 0.034 \\
& \(P = 0.105\) & \(P = 0.221\) & \(P = 0.397\) & \(P = 0.457\) & \(P = 0.120\) & \(P = 0.620\) & \(P = 0.922\) \\
\textbf{Residual limb pain} & \(P = 0.788\) & \(P = 0.007\)* & \(P = 0.884\) & \(P = 0.831\) & 0.448 & 0.565 & 0.172 \\
& \(P = 0.0774\) & \(P = 0.387\) & \(P = 0.099\) & \(P = 0.659\) & \(P = 0.194\) & \(P = 0.070\) & \(P = 0.614\) \\
& \(P = 0.931\) & \(P = 0.766\) & \(P = 0.343\) & \(P = 0.866\) & \(P = 0.940\) & \(P = 0.951\) & \(P = 0.312\) \\
\hline
\end{tabular}
\caption{Unadjusted relationships among phantom limb pain, peripheral sensation, and cognition measures (Spearman \(\rho\))}
\end{table}

*Significant at \(P < 0.05\).
Making Test and clock drawing test have been found to require executive function, brain activity during laterality recognition has not been tested. Finally, the Prosthesis Evaluation Questionnaire does not include residual limb pain duration, which was thus not assessed.

In conclusion, this study found that cognition and sensory impairments assessed with laterality recognition, the Trail Making Test, light touch, and temperature were associated with more severe PLP symptoms. No cognition assessments were associated with residual limb pain. Understanding the relationships among PLP, cognition, and sensory function may help clinicians and researchers determine changes related to the PLP experience in people with lower-limb loss.

REFERENCES


