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Peripheral nervous system origin of phantom limb pain

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ABSTRACT

Nearly all amputees continue to feel their missing limb as if it still existed, and many experience chronic phantom limb pain (PLP). What is the origin of these sensations? There is currently a broad consensus among investigators that PLP is a top-down phenomenon, triggered by loss of sensory input and caused by maladaptive cortical plasticity. We tested the alternative hypothesis that PLP is primarily a bottom-up process, due not to the loss of input but rather to exaggerated input, generated ectopically in axotomized primary afferent neurons in the dorsal root ganglia (DRGs) that used to innervate the limb. In 31 amputees, the local anesthetic lidocaine was applied intrathecally and/or to the DRG surface (intraforaminal epidural block). This rapidly and reversibly extinguished PLP and also nonpainful phantom limb sensation (npPLS). Control injections were ineffective. For intraforaminal block, the effect was topographically appropriate. The suppression of PLP and npPLS could also be demonstrated using dilute lidocaine concentrations that are sufficient to suppress DRG ectopia but not to block the propagation of impulses generated further distally in the nerve. PLP is driven primarily by activity generated within the DRG. We recommend the DRG as a target for treatment of PLP and perhaps also other types of regional neuropathic pain.

1. Introduction

The origin of phantom limb pain (PLP) remains uncertain. Religious and psychiatric interpretations once predominated [54,58], but these have since been supplanted by neurobiological and cognitive theories. The fact that pressure on amputation stump neuromas provokes PLP (Tinel sign), and the discovery that neuromas generate ectopic impulse discharge (ectopia), favored the stump as the pain generator [5,14,29,49,50,55,56,63]. However, PLP frequently persists despite neuroma infiltration and nerve/plexus block [4,27,46]. For this reason most investigators have abandoned peripheral nervous system (PNS) explanations in favor of the hypothesis that PLP is a consequence of maladaptive cortical plasticity induced by loss of input from the limb [1,23,28,39,46,48].

The cortical origin of PLP has considerable empirical support. For example, limb amputation or corresponding nerve injury leads to conspicuous neuroplastic remapping of somatotopic representations in the primary somatosensory cortex (S1) [16,21,24,25,31,32,53,66], with the extent of remapping proportional to the intensity of the pain [22]. Likewise, distortions in body schema perception occur when conflict is induced experimentally between the appearance of an individual's limb and proprioceptive feedback. In the rubber hand illusion, for example, the perceptual integration of the rubber hand is so striking that threatening it with injury evokes anxiety and pain affect–related cortical activations [18]. Some subjects report unpleasant sensations, perhaps even pain, due to such sensory–sensory mismatch [28]. Resolving this mismatch, as implemented in mirror box therapy, can relieve PLP, at least temporarily [48,53].

However, a second PNS source, outside of the stump, has never been adequately considered. For decades there has been direct electrophysiological evidence that afferent somata in the dorsal root ganglia (DRGs) also generate ectopia [33,37,52,62]. Indeed, in head-to-head comparisons, the DRG has proved to be a more robust source of spontaneous firing than neuromas [2,42]. Evidence, if indirect, is even available in humans [38,40,49,50]. For example, Nystrom and Hagbarth [50] showed that blocking

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stump neuromas eliminated the percussion-evoked Tinel sign and associated spike activity, but not the ongoing discharge recorded in the nerve. This likely originated in the DRG. DRG electrogenesis could account for the therapeutic failure of neuroma, nerve, and plexus infiltration because these distal blocks do not affect the DRG.

Because DRGs share the same cerebrospinal fluid compartment as the spinal cord, spinal blocks and intraforaminal blocks both have the potential to arrest all PNS ectopia: stump and DRG. We are unaware of any systematic reports on effects of either type of block on PLP. However, spinal block is frequently used in stump revision surgery, and practitioners we have consulted attest that this indeed transiently stops PLP (R. Boas and A. Stav, personal communications). Paradoxically, case studies have reported transient rekindling of quiescent PLP after spinal block, but this is rare [60]. A likely explanation is that the injectate used transiently excited DRG neurons, or the spinal neurons they drive, by a mechanical, thermal, or chemical mechanism (rapid injection of large volumes in a restricted space, cold solution, inaccurate pH/osmolarity, or preservatives). Here we used diagnostic spinal and intraforaminal blocks in human amputees to determine whether preventing central nervous system (CNS) access of ectopic signals generated in the DRG might affect PLP and/or nonpainful phantom limb sensations (npPLS).

2. Methods

2.1. Subjects, experimental design, and rationale

We report results of 4 related procedures intended to block the access of nerve impulse discharge originating in the PNS from reaching the brain. These are represented in 4 experimental groups. In group 1, our primary focus, we tested effects of blocking abnormal afferent input by epidural intraforaminal injection. In group 2, for comparison, we also examined spinal (intrathecal) block. In a few cases (group 3), local infiltration of stump neuromas or peripheral nerve block was performed. Procedures were carried out in 2 centers located in regions that have known recent military conflict and that serve relevant patient populations; staff at such facilities are acutely aware of the limits of current treatment and encouraged the introduction of better therapeutic options. At the Trauma University Hospital and the associated Galenus Clinic (Tirana, Albania), we treated 16 lower limb amputees with ongoing PLP (11 men, 5 women). These participated in experimental groups 1 to 3, where some of the amputees participated, on separate occasions, in 2 or 3 of the groups. Each of the 16 individuals is identified by a unique number to facilitate tracking who underwent which procedure. Finally, group 4 comprised an additional 15 amputees (14 men and 1 woman) who were treated with a modified protocol of intraforaminal injection at the Pain Rehabilitation Unit, Chaim Sheba Medical Center (Tel Hashomer [Tel Aviv], Israel).

Inclusion criteria were age >18 years, good general health, ability to communicate and understand instructions, and presence of significant PLP with a frequency and intensity that interfered with daily life. Subjects were excluded if they had significant sensory deficits, major pain complaints other than PLP (including severe stump pain, which might have distracted from their ability to report on their PLP), major CNS or PNS neurological disorders other than diabetic polyneuropathy and trauma associated with the cause of amputation, major cognitive or psychiatric disorders, or contraindication to the injection of lidocaine, corticosteroids, or contrast agents.

Subject background and demographic information is provided in Tables 1 and 2. Experimental protocols were approved by authorities on human experimentation (Helsinki committees) at both institutions.

Most subjects had experienced traumatic amputation; in Tirana, it was frequently from stepping on a land mine. Some amputations, however, were due to vascular insufficiency or other causes. PLP tends to be similar regardless of the precipitating pathology [7]. The objectives and risks of the blocks were explained to the subjects in their language, including the fact that treatment results may have no effect on PLP, may produce partial and reversible analgesia, or may yield more prolonged pain relief. Informed consent was obtained. We then initiated a protocol that was standardized but subject to minor variations depending on the individual patient. First, a history was taken, and the present quality and location of PLP and npPLS was documented by text, photos, body charts, and sketches. Information on the circumstances of amputation, frequency and duration of PLP, changes over time, and exacerbating and relieving factors was also noted. Special care was taken to ensure that subjects fully understood the difference between sensations experienced in the phantom limb (PLP and npPLS) and those experienced in the stump.

The amputation stump was then systematically examined, and tender points and points at which a Tinel sign could be evoked by palpation or percussion were marked on the skin. Finally, subjects were prepared for injections. No sedation was used so that subjects

Table 1
Subject demographics, baseline pain, and results of spinal (intrathecal) block.

Patient no.	Sex/ age, y	Amputation, cause, interval since amputation	Baseline phantom, effect of percussion over stump neuromas (Tinel →), (notes)	Level	Effect of spinal block on phantom and Tinel
1	M/61	R AKA, diabetes, 30 y	PLP lateral foot (severe), npPLS leg below knee, Tinel → PLP	L3–4	PLP, npPLS and Tinel lost, recovery after >3 h
2	F/40	AKA bilateral, trauma, 11 mo	bilateral PLP, bilateral npPLS (numbness, sensation of movement), Tinel → stump pain (“electric”)	L3–4	PLP lost, npPLS and Tinel persists, all bilaterally
3	F/65	BKA, scleroderma, 7 days	PLP, npPLS, Tinel → stump pain	L3–4	PLP, npPLS and Tinel lost
4	M/52	L AKA, trauma, 3 y, R AKA, vascular, 1 y	L PLP (modest “shooting”), R PLP (severe, “pulsing”), npPLS bilaterally, Tinel → stump pain	L3–4	PLP, npPLS and Tinel lost bilaterally
5	F/24	R hip disarticulation, trauma, 2 y	PLP (severe), npPLS (knee to foot), Tinel → PLP	L3–4	PLP, npPLS and Tinel lost
6	M/61	R AKA, vascular, 5 d	PLP (“electric”), npPLS, Tinel → PLP	L2–3	PLP, npPLS and Tinel lost
7	M/48	R AKA, trauma, 10 y	PLP, npPLS, stump (itch + burning), Tinel → PLP (lateral toes)	L4–5	PLP, npPLS and Tinel lost. Stump pain lost
8	M/22	R lateral foot (toes 2–5), trauma, 9 y	PLP (toe 5), npPLS, Tinel → stump pain, scar “cold”	L4–5	PLP, npPLS and Tinel lost
9	M/24	R BKA, trauma, 10 y	PLP (toes 4, 5), npPLS, Tinel → PLP, ongoing stump pain	L4–5	PLP↓, npPLP and Tinel lost
10	M/39	R BKA, trauma, 10 y	PLP, Tinel → PLP + stump pain, ongoing stump pain (cold)	L4–5	PLP, Tinel and stump pain lost
11	M/51	L foot, trauma, 10 y	PLP (sole), npPLS (foot) Tinel → stump pain	L4–5	PLP, npPLS and Tinel lost

R, right; AKA, above knee amputation; PLP, phantom limb pain; npPLS, nonpainful phantom limb sensation; Tinel, evoked Tinel sign; BKA, below knee amputation; L, left.

Table 2
Subject demographics, baseline pain, and results of intraforaminal block.

Patient no.	Sex/ age, y	Amputation, cause, interval since amputation	Baseline phantom, effect of percussion over stump neuromas (Tinel →), notes	Level	Effect of foraminal block on...			Notes
					PLP	npPLS	Tinel →	
1	M/61	R AKA, diabetes, 30 y	PLP lateral foot (severe), npPLS leg below knee, Tinel → PLP	L3	Lost	Lost	Lost	↑ PLP provoked during insertion; result maintained during 5 d infusion
4	M/52	L AKA, trauma, 3 y, R AKA, vascular, 1 y	L PLP (modest "shooting"), R PLP (severe, "pulsing"), npPLS bilaterally, Tinel → stump pain	R–L5	Lost	Lost	Lost	↑ PLP and npPLS provoked during insertion
			7 days later	L–L5	Lost	Lost	Not certain	
5	F/24	R hip disarticulation, trauma, 2 y	PLP, npPLS knee to foot, Tinel → PLP	L4	↓90%	↓90%	Lost	"Shadow" of phantom remains
7	M/48	R AKA, trauma,10 y	PLP, npPLS, stump (itch + burning), Tinel → PLP (lateral toes)	L4	Lost	No change	Lost	
8	M/22	R lateral foot (toes 2–5), trauma, 9 y	PLP (severe in toe 5), npPLS, Tinel → stump pain, scar "cold"	L5	Lost	Lost	Lost	
9	M/24	R BKA, trauma, 10 y	PLP (toes 4, 5), npPLS, ongoing stump pain	L4	Lost	Lost	Lost	
10	M/39	R BKA, trauma, 10 y	PLP ("pinching, like a very tight sock"), npPLS, Tinel → PLP + stump pain, ongoing stump pain (cold)	L5	Lost	Quality changed	Lost	PLP replaced with "pleasant" npPLS
11	M/51	L foot, trauma, 10	PLP (sole), npPLS (foot), Tinel → stump pain	L5	Lost	No change	Not certain	
12	F/55	R BKA, trauma, 17 y	PLP (foot only), npPLS (foot only), Tinel → stump pain	L4	Lost (→ "numb")	↓60%	No change	Foot telescoped to stump, can be moved
			Next day	L5	Not certain	↓, not certain	Lost	
13	M/55	L BKA, trauma, 11 y	PLP, npPLS ("tingling"), Tinel → PLP (in toe 1)	L5	↓60%	Lost	↓50%	Foot telescoped to stump, toes can be moved.
14	M/57	R foot, trauma, 11 y	PLP (toe 1 "bound"), npPLS (toes 2–5), Tinel → PLP (all toes, "electric")	L5	Lost	Only movement lost	To medial toes lost	Foot telescoped to stump, can be moved
			Soon after L5	L4	Still absent	Lost	To lateral toes ↓ 80%	
15	M/52	L at knee, diabetes, 45 d	PLP (toe 1 and ankle), npPLS (whole leg), Tinel → stump pain	L4	Lost	Lost	Lost	Result maintained during 12 d infusion
16	F/77	L medial toe (toe 1), diabetes, 17 d	PLP ("sharp"), npPLS, Tinel → stump pain	L5	Lost	Not certain	Lost	Result maintained during 10 d infusion

R, right; AKA, above knee amputation; PLP, phantom limb pain; npPLS, nonpainful phantom limb sensation; Tinel, evoked Tinel sign; BKA, below knee amputation; L, left.

would remain fully alert and responsive. Just before beginning the procedure, we asked the subjects to rate the intensity of their PLP on a 10-point scale. They were told that this value would serve as a baseline for assessing changes associated with subsequent injections. The rating used a numerical or a visual analog scale (VAS), where 0 indicates no pain and 10 the worst pain imaginable. "Loss of PLP" indicates a drop from the preinjection value to 0 (Tables 1 and 2). When loss of pain was incomplete, subjects were asked to gauge the percentage reduction from the baseline value. In all spinal and intraforaminal procedures, subjects were unaware of the order of injections; they were blinded to the specific material injected on each occasion; and in most instances, they were unaware of when exactly the injections were made. After completion of the spinal or intraforaminal procedure, subjects rested for 1 to 3 h, during which time the status of their phantom and stump sensations was periodically noted. They were then released. Because of the inaccessibility of many of the subjects, the study focused on the short-term effects of the blocks. We did not attempt systematic long-term follow-up, although sporadic feedback was obtained from some subjects.

2.2. Spinal block (group 2)

Spinal block was carried out (in Tirana only) in 11 subjects. In 8 of them, it was followed up with an intraforaminal block within a few days. The procedure, based on a routine protocol described by Lund [44], involved intrathecal midline delivery of 2 mL lidocaine (1% or 2%, Propharma, Tirana, Albania) within the spinal canal via interspace L2–3, L3–4, or L4–5 (medial approach).

2.3. Intraforaminal block (groups 1 and 4)

The leg is innervated largely by DRG L4, L5, and S1, with lesser L3 and S2 contributions. When PLP was uniform across the phantom foot, we began by targeting the L5 or S1 DRG. However, if pain predominated in 1 part of the phantom foot and/or percussing neuromas evoked pain that was easily localized, we began with the corresponding segment. Because of the substantial overlap between adjacent spinal dermatomes [26,35], we anticipated that it would be necessary to block several adjacent segments. However, this proved necessary only occasionally. Changes in the response to tapping stump neuromas (Tinel sign) also provided information on the completeness of blocks. These checks tend to be painful, however, and thus we used them with discretion.

There were minor differences in procedures at the 2 venues (ie, between groups 1 and 4). In Tirana (group 1), injections were made under radiographic guidance using a Somatom ARC CT (Siemens AG, Munich, Germany). Subjects were placed in the prone position and prepared as for spinal epidural injection. The intended segmental level was identified using anatomic landmarks, and a trajectory for targeting the intervertebral foramen on the side of

the amputation was chosen and infiltrated with lidocaine (Propharma). An 18-gauge Tuohy epidural needle with plastic obturator (Portex, Smiths Medical International, Ashford, UK) was inserted and guided into the foramen. The obturator was then removed and an injection syringe was attached to the needle. During needle insertion, subjects were encouraged to report on sensations felt in the phantom limb or the stump. We took advantage of the fact that 3 of the patients (patients 1, 15, and 16), 2 with recent amputations, were hospitalized for severe pain and stump issues. In these, a polyethylene catheter was inserted to the tip of the needle, and the needle was then withdrawn. This permitted repeated lidocaine injections over subsequent days. Once tip placement was satisfactory, we slowly injected 2 mL saline followed by 0.5 mL contrast medium (Ultravist300 diluted 1:2 with saline; Iopromide, preservative-free, Bayer Schering Pharma, Berlin, Germany). This was followed by lidocaine (2 mL, 1% or 2%). The saline was used to open the intraforaminal space so as to reduce central spread of lidocaine, and the contrast was used to monitor lidocaine coverage of the DRG and its spread beyond.

In lieu of carrying out full nontherapeutic dummy procedures, we controlled for potential effects of the patients' anticipation, solicitousness, and placebo response as follows. Just before each injection, one of a set of messages, varied randomly, was delivered to the subject. For example, the subject might be told that a solution (without specifying which) was about to be injected. Alternatively, the subject was explicitly told that the impending injection was expected to relieve PLP, and then the bolus was either injected or withheld. Most often the injection was covert; the subject was not informed of the actual timing or type of the injection [8]. To minimize potential experimenter bias, subjects were encouraged to report, on their own initiative, changes in phantom sensation. However, if more than about 10 min passed without a self-initiated report, a prompt was given, especially if the time for an injection was approaching. We avoided prompting subjects for a report on sensory changes in the first few minutes after injections. If a subject expressed uncertainty as to whether a change had occurred, he or she was encouraged to decide, but was not pressed.

We made special note of changes, if any, reported within 2 to 5 min after the delivery of a message without actual injection and after injections of saline, contrast, and lidocaine. The observation time was extended to at least 10 min when lidocaine was delivered. In early trials, many subjects reported a transient cold sensation in the lower back after administration of verum injections. This alerted us to prewarm all solutions to 37°C, which eliminated such reports. Finally, a bolus of dexamethasone (4 mg, 1.0 mL; Propharma) was injected in order to enhance the patient's chances of obtaining extended pain relief. The needle was then withdrawn. When a second intraforaminal block was carried out at another level, we proceeded immediately using the identical protocol. The procedure typically took between 30 and 60 min.

In the Tel Hashomer (group 4), the technique differed somewhat, as follows. Imaging for intraforaminal needle insertion used fluoroscopy rather than computed tomography (OEC 9900 Elite C-arm fluoroscope; GE Healthcare, Hatfield, UK). Tip location was confirmed using 1 to 2 mL contrast (Iopamiro 370 without preservative; Dexon Pharma, Or-Akiva, Israel). To enhance the therapeutic effect, in most cases, both the L5 and S1 ganglia were injected, with the initial block usually directed to S1. The injectates were mixed rather than being provided in separate boluses. Specifically, at each level, we injected 3 mL of a mixture containing lidocaine 1% (Esracaine 1 mL; Rafa Laboratories, Jerusalem, Israel), Iopamiro 370 (1 mL), and methylprednisolone acetate (Depo-Medrol 40 mg, 1 mL, without preservative, Pfizer, New York, NY, USA). Results are presented as a case series.

2.4. Nerve block (experimental group 3)

In 3 amputees in Tirana (patients 1, 12, and 13), we evaluated the effects of infiltrating stump neuromas by administering lidocaine and/or by carrying out femoral or sciatic nerve blocks. Effects were followed for at least 30 min. Although these trials were not systematic, we report results briefly.

2.5. Statistical analysis

The proportion of subjects who reported criterion reduction in PLP and/or npPLS was evaluated by the χ^2 or Fisher exact probabilities tests (SigmaStat v3.1). Means ± SD are given. $P \leqslant .05$ was considered significant.

3. Results

3.1. Case description, intraforaminal block (amputee 14 in group 1)

The procedures and key outcomes, which were fairly uniform across subjects, are illustrated by patient 14. Patient 14, an intelligent and articulate 57-year-old man from Kosovo, experienced traumatic amputation of the right foot above the ankle 11 years previously when he stepped on a land mine. He had severe stump pain for the first few weeks after the injury and became aware of his phantom foot only after about 5 weeks. When we saw him, he described his usual sensation: the feeling of phantom toes emerging from the end of the stump (''foreshortening,'' ''telescoping'' [54]). Their position was natural but in forced pronation. The big toe (toe 1) dominated the phantom and felt tightly constricted (''bound''), with PLP rated as 5 to 6 on a scale of 0 to 10. The remaining toes (toes 2 to 5) were also felt, but they were not painful (npPLS, pain score = 0) and could be voluntarily moved laterally, separating them from toe 1. Two sensitive stump neuromas were identified. Pressing on the medial one evoked an electric shock–like pain in the phantom toes, especially toe 1, and a noticeable flinch. Pressing on the lateral one evoked a local stabbing sensation in the stump (stump pain). There was no obvious tactile allodynia, but the subject reported that the stump felt cold (it was not objectively cold).

An injection needle was placed in the L5–S1 intervertebral foramen under computed tomographic guidance, targeting the L5 DRG. Then the subject was told, ''We are about to make an injection'' and that he should report any changes felt. No injection was actually delivered (sham injection), and he reported that he felt no change in the phantom or stump. After 2 to 3 min, 2 mL saline at 37°C was injected with no alert given, and this was followed by 0.5 mL contrast. No sensory change was reported, and both the medial and lateral Tinel signs produced the usual responses. After an additional 5 min, 2 mL 1% lidocaine at 37°C was covertly injected, and within 2 min, he volunteered that the painful constriction of the big toe was gone except for the edge closest to the small toes, which still felt pinched. The npPLS of toes 2 to 5 remained, but the forced pronation relaxed, and he lost the feeling that he could move the toes. Over the next few minutes all feeling of toe 1 was lost, and both Tinel signs weakened markedly. The npPLS of toes 2 to 5 remained. At this point, 1.0 mL dexamethasone was injected. There were no further sensory changes, and the needle was removed. A second needle was then placed in the L4–5 intervertebral foramen near the L4 DRG.

About 30 min after the L5 DRG lidocaine injection, we were prepared to proceed. At this point, the phantom remained as it was after the L5 procedure (ie, residual npPLS of toes 2 to 5). The first step, a sham injection, evoked no change, nor did subsequent covert injection of 2 mL saline. Minor adjustment of the needle position provoked brief pain in toes 2 to 5 (not in toe 1). Contrast

and lidocaine were then injected. This rapidly caused loss of the toes 2 to 5 npPLS. Sensation on the stump was grossly normal, presumably because of incomplete block. Both Tinel signs were suppressed (patient 14 estimated by >80%), and even strong percussion of the medial neuroma no longer caused flinching. Dexamethasone was then administered, and the needle was withdrawn. When the subject was released about 90 min later, his PLP and npPLS were still absent. This remained the case when he was contacted the next day.

3.2. Spinal (intrathecal) block (group 2 results)

Observations were made of 11 amputees in Tirana who were given spinal blocks. Two were bilateral amputees (patients 2 and 4). Eight of the subjects, including subject 4, went on to have an intraforaminal block as well. All 11 experienced PLP at the time of the procedure (baseline pain ratings 7.1 ± 2.1; Table 1), mostly in the phantom foot or a part of it. Common pain descriptors were "electric shock–like," "shooting," "constricting," and "pulsating." The remainder of the phantom leg was felt and could sometimes be moved, but it was not painful. "Telescoped" phantoms were felt by at least 3 of the subjects, all of whom had undergone amputation many years previously. One or more obvious stump neuromas were present in all subjects, and percussion usually evoked pain in the phantom (or a part of it) and/or in the stump. The sensation evoked was most often likened to a stab or an electric shock. A few subjects reported ongoing stump pain, usually burning or cold in quality, and some had tenderness on stump scars. We did not track these stump sensations systematically.

The technical adequacy of spinal block was verified by numbness and paresis of both legs, and in most subjects, loss or major attenuation of pain was evident upon percussion of stump neuromas. Spinal block drastically obtunded ongoing PLP in all 11 amputees, usually within 5 to 10 min, to the point that it was no longer felt ($P < .001$ compared to preblock; Table 1, Fig. 1). In subjects 2 and 4, PLP was lost bilaterally. Interestingly, npPLS, which was present in all of the amputees, was also reported to have vanished shortly after the block in all but one. The exception was patient 2, in whom the Tinel sign also persisted, suggesting incomplete spinal block. Ongoing stump pain, when present, was also suppressed. PLP and npPLS usually began to return by 2 to 3 h after injection, roughly in parallel with recovery of motor control of the legs. Two subjects reported that PLP was still mostly absent 24 h after injection. We are uncertain whether this reflects a persistent effect of the block or spontaneous remission.

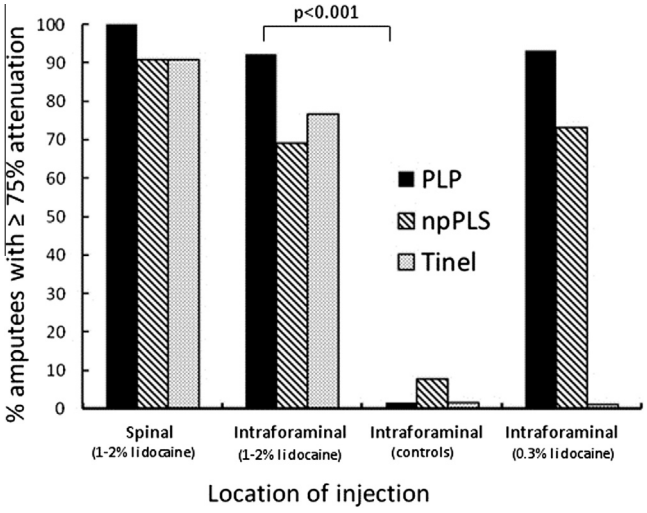

Fig. 1. Covert intraforaminal block using high and low concentrations of lidocaine, and similar covert spinal (intrathecal) block, consistently suppressed phantom limb pain (PLP) and nonpainful phantom limb sensation (npPLS). Control procedures (sham, saline, contrast injections) did not. Group sizes were as follows: spinal block ($n = 11$); intraforaminal block with 1% to 2% lidocaine ($n = 13$); controls ($n = 13$); dilute intraforaminal lidocaine ($n = 15$).

3.3. Intraforaminal block (group 1)

Intraforaminal blocks were provided to 13 amputees in Tirana and 15 in Tel Hashomer. Considering the 13 amputees (baseline pain ratings = 7.3 ± 2.2; Table 2), PLP was eliminated in 11 and reduced by an estimated 60 and 90% in 2 (patients 5 and 13). Surprisingly, major pain relief was usually achieved after blocking a single segment. In patient 4, a double amputee, intraforaminal block on the right eliminated PLP on the right side, with no effect on PLP on the left side. One week later, a left-sided block was carried out, with the opposite result. PLP on the left side was lost, with no effect on PLP on the right side. Overall, compared to preinjection pain, these blocks significantly reduced PLP ($P < .001$, Fisher test, Fig. 1).

Complete loss or near-complete attenuation of npPLS occurred in parallel with the loss of the PLP in the majority of subjects ($P = .005$ compared to preinjection; Table 2). This included loss of npPLS on the right side, and subsequently on the left, in patient 4, who had undergone bilateral amputation. There were 6 exceptions, however. In patients 7, 10, 11, 12, and 16, attenuation of npPLS was modest or uncertain, or no loss was reported at all. Subject 10 volunteered that his painful phantom was replaced by a pleasant nonpainful sensation. We conjecture that in these cases, the afferent drive of the residual npPLS originated in an adjacent DRG. Because PLP had already been eliminated, we usually did not inject additional levels to test this possibility. However, in patient 14 (described above), after a L5 DRG block had eliminated the PLP but not the npPLS, we administered a subsequent block to the L4 DRG. This eliminated the npPLS, supporting our conjecture.

Attenuation of the Tinel sign was variable. In cases where both PLP and npPLS were lost, the Tinel sign also tended to vanish. In others, the Tinel sign was partly attenuated or largely unaffected (Table 2). In some subjects, the Tinel sign from one stump neuroma was attenuated, but not from a second.

During the final phase of needle insertion, or during needle repositioning which was required occasionally, a brief intensification of the PLP was frequently provoked. This sensation faded within seconds or within a minute or two. Deceptive statements by the physician that an impending (sham) injection would suppress phantom sensation, and at least 2 injections per subject of nonblocking solutions (saline and contrast), were almost never followed by a report that PLP or npPLS had changed. An exception was a subject who reported "80% reduction" of her npPLS after the saline injection. PLP remained unchanged until lidocaine was injected, at which time it rapidly disappeared. Overall, lidocaine significantly obtunded both PLP and npPLS compared to nonblocking solutions ($P < .001$, Fig. 1). Finally, in patients 1, 4, and 15, the injection needle was replaced with a catheter that was left in place, permitting repeated bolus injections of lidocaine (1%, 3 mL every 3 to 4 h) for periods of 5, 10, and 12 days. This produced sustained absence of PLP at least for the full duration of the block.

3.4. Intraforaminal block using dilute lidocaine (group 4)

Intraforaminal block was carried out on a therapeutic basis at Tel Hashomer in an additional 15 unilateral lower limb amputees. All had baseline VAS pain scores of 7 to 10. Ten underwent traumatic amputation, and 5 were amputated for other reasons (3 vascular, 1 septic, 1 malignancy). Ten had below-the-knee amputation (BKA; 9 transtibial, 1 Symes [foot]) and 5 had above-the-knee

amputation (AKA; all transfemoral). Two segmental levels, L5 + S1, were injected in all but 4 cases. In these, we injected only S1 ($n = 3$) or only L5 ($n = 1$). When queried after the completion of the intraforaminal blocks, 14 subjects (93%) reported complete ($n = 10$, including 2 single-level cases) or substantial (75–95%, $n = 4$) elimination of their preinjection PLP. The remaining amputee (BKA) estimated 50% reduction in PLP. Attenuation of npPLS was similar: 9 reported complete loss of npPLS, 3 reported major attenuation (70–90%), 2 reported no effect, and 1 was uncertain. Compared to preinjection, the intensity of both PLP and npPLS was significantly reduced ($P < .001$).

3.5. Nerve block (group 3)

Dense femoral or sciatic nerve block using perineurial lidocaine 2% was carried out in Tirana in 2 patients (patients 1 and 13; baseline pain ratings: 10, 7.5). Spinal and/or intraforaminal block had eliminated or obtunded PLP in both of them. Background PLP and npPLS were unaffected by the nerve blocks, although in the amputee in whom the femoral nerve was blocked, pain felt in the phantom limb after neuroma percussion was lost. Lidocaine infiltration of stump neuromas in 2 patients (patients 12 and 13; baseline pain ratings: 10, 7.5) eliminated the Tinel sign from the injected neuromas without markedly affecting phantom sensation. Intraforaminal block was effective in both. Patient 12 volunteered that her sensation of being able to move phantom toes was noticeably weakened after neuroma infiltration.

4. Discussion

Spinal and intraforaminal block consistently attenuated, and often completely eliminated, both PLP and npPLS in lower-limb amputees. Control injections did not. This was documented in 31 amputees at 2 independent centers. The effect came on rapidly because ganglionic sheaths are permeant [6]. Sham injections and intraforaminal injections of nonblocking solutions never blocked PLP, even when patient were intentionally told to anticipate a pain-relieving injection. Blocking solutions, even when injected covertly, consistently did. Nonetheless, we acknowledge that our observations fall short of accepted criteria for randomized blinded placebo controlled trials. For practical reasons, we did not include an experimental arm randomized to placebo injections exclusively, and although patients were blinded to the type and timing of the injections, the medical staff was not. After spinal block, the effect faded within hours, although after intraforaminal block it lingered, probably as a result of the anti-inflammatory and membrane-stabilizing (ectopia-silencing) effects of the coinjected corticosteroids [15,36,41]. Systematic documentation of the duration of effect awaits further research. The abolition of PLP occurred in both recent and veteran amputees, and irrespective of telescoping, with no obvious "pain memory," "centralization," or "transition to chronicity" [13,34]. Although conscious perception is undoubtedly a high CNS function, our data suggest that the raw feel of a phantom limb is driven by activity originating in the PNS, which feeds the CNS in a bottom-up manner.

4.1. PNS location of the ectopic generator

Amputation-induced neuroplastic changes occur in the spinal cord as well as in the PNS. These include somatotopic remapping much like that featured in cortical theories of PLP [16,20] and spontaneous bursting discharge [10,12,43] (although this is mostly driven from the periphery [13,52]). Central sensitization also develops, a phenomenon that both amplifies normal and ectopic nociceptive input and renders low-threshold Aβ input painful [65]. However, the possibility that spinal neuroplasticity drives PLP can be ruled out for 2 reasons. First, intrathecal injections at L4–5/L3–4 vertebral interspaces mostly act on primary afferent axons ("cauda equina"). Because the spinal gray (lumbar enlargement) lies within the T10–12 vertebrae, >12 cm further rostrally, our injections would have blocked spinal access of PNS ectopia with minimal effect on the spinal cord per se.

Results of intraforaminal block further reinforce the conclusion that neither the dorsal horn nor the brain are primary generators of PLP. In 22 amputees, the S1 and/or L5 foramen were injected >16 cm caudal to the lumbar enlargement. Fluoroscopy, which permitted real-time tracking of the lidocaine–contrast mixture, showed that spread was largely limited to the vertebral level or levels injected (Fig. 2). Even if some had reached the lumbar enlargement, it would have been highly diluted in the cerebrospinal fluid. Finally, attenuation of PLP (and npPLS) was topographically appropriate. Most notably, in patient 4, a double amputee, left-sided L5 injection eliminated PLP on the left with no effect on PLP on the right, and vice versa. Had the intraforaminal lidocaine acted at the lumbar enlargement (T10–12) or even the cauda equina (L5), PLP should have ceased bilaterally on both trials. This observation also rules out a systemic action of the lidocaine.

4.2. DRG vs neuroma as the principal generator of PLP

When applied to nerves or dorsal root axons, pain relief reflects block of spike propagation. This requires a high drug concentration; 2% lidocaine (~100 mM) is typical [11]. In contrast, for suppression of spike electrogenesis (initiation) in the DRG, much lower concentrations are sufficient (~10 μM [14,17,59,64]). Thus, impulses generated in both stump neuromas and the DRG would have been blocked by 1% to 2% lidocaine administered intraforaminally, but lower concentrations would selectively block DRG ectopia, sparing through-propagation of impulses generated further distally in the stump. The therapeutic protocol used at Tel Hashomer incorporated this factor by injecting lidocaine intraforaminally at a subanesthetic concentration (0.3%). Selectivity (electrogenesis vs spike propagation) was achieved because even when both L5 and S1 levels were injected (11 amputees), the stump did not become numb, and amputees were fully mobile on their prosthetic limbs moments after the block. The fact that nonblocking 0.3%

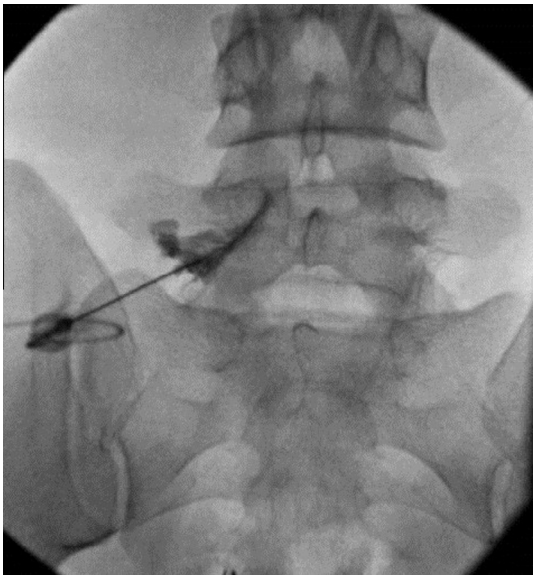

Fig. 2. Fluoroscopic image illustrating limited degree of spread typical of that observed in patients injected intraforaminally with 3 mL lidocaine–steroid solution containing contrast medium (left L5 DRG injection).

lidocaine was as effective as 1% to 2% lidocaine suggests that ectopia originating in the DRG is the primary generator of spontaneous PLP. We suspect that electrogenesis in stump neuromas becomes a more prominent generator of PLP when mechanical forces are applied to neuromas during weight bearing and walking. This accounts for the disappointing clinical experience with nerve blocks and neuroma infiltration, including our own observations.

It is noteworthy that intraforaminal block at a single level usually provided total or near-total relief of PLP despite the fact that at least 3 DRGs contribute to leg innervation. There are several likely explanations. First, PLP is generally located in the foot (primarily L5 and S1) rather than the calf or thigh, and often in only part of the missing foot. Choice of the first segment to block was guided by the location of symptoms; it was not random. Second, even if drivers of PLP originate in 2 or 3 DRG, pain may not become a complaint until the sum of the activity crosses some threshold. Thus, in patients relieved of PLP after L5 block, S1 block might also have worked had it been tried first. Finally, we cannot exclude lidocaine spreading from the injected to DRG to an adjacent one.

4.3. PLP and maladaptive cortical plasticity

Our data are inconsistent with maladaptive cortical plasticity being the primary driver of PLP and npPLS. However, some of the secondary peculiarities of phantom limb sensation (eg, telescoping and reference) may well reflect plasticity of cortical processing. Had the impulses interpreted by a conscious brain as PLP originated in the cortex, spinal and intraforaminal blocks would have been ineffective and certainly not topographically appropriate. Beyond that, the very foundations upon which the cortical plasticity hypotheses rest are equivocal. For example, correlation between the extent of somatotopic remapping and the degree of PLP [22] does not prove causation. This correlation equally supports a CNS effect of a PNS cause. It is known that PNS activity can drive CNS remapping [19,30,57,61]. Thus, discharge originating ectopically in the DRG could well be the cause of both PLP and of remapping. Indeed, brachial plexus block sometimes reverses both [4]. This result might be obtained in all amputees using intraforaminal rather than plexus block.

PLP models based on multisensory mismatch also fall short. Perceptual conflict is usually attributed to loss of afferent input from the limb after amputation. However, this ignores abundant evidence of ectopic electrogenesis in the PNS after nerve section [14]. Amputation may cause the slow dying back of some of the axotomized leg afferents, but most survive for decades and remain capable of signaling pain—thus the Tinel sign. Noninvasive functional recording also challenges the idea of afferent silence. The cortical representation of adjacent skin "invades" that of the amputated limb [20,23], a phenomenon that is thought to account for the frequent reference of sensation from stump and nearby skin into the phantom limb [9,51]. However, this should not evoke (phantom) pain because even direct electrical stimulation of the primary somatosensory cortex is not painful [51]. Importantly, the "invasion" does not displace input originating in the severed afferents that used to serve the (amputated) limb. In fact, the cortical representation of the (phantom) limb actually increases, as one might predict given the ectopia coming off stump neuromas and the DRG [45]. Moreover, the increase is proportional to the intensity of the PLP. These are the observations expected if PLP is driven by a bottom-up process.

We propose that ectopic PNS discharge, primarily that originating in DRG serving the amputated limb, drives CNS somatic representations to generate a conscious percept of the phantom limb. The quality of the sensation, PLP or npPLS, presumably depends largely on the types of primary afferent neurons that contribute to the ectopic barrage [14]. The fact that stimulating adjacent skin sometimes evokes sensation felt in the phantom [9,53] probably is due to CNS plasticity and likewise the sense of limb ownership and distortions of the phantom limb with respect to body schema, including telescoping, movement, and unnatural orientations of phantom limbs [47,54]. In this regard, it is noteworthy that several of our subjects indicated that walking on their prosthesis in the absence of their usual phantom limb sensation was disconcerting. One patient stated, "It feels as if I am on a wooden leg, not on my own leg."

4.4. Therapeutic implications

Our study, together with earlier work, highlights the DRG as a critical source of ectopic impulse discharge in amputees with PLP. The therapeutic potential of targeting the DRG is documented by our 3 amputees in whom PLP was suppressed for up to 12 continuous days with sustained intraforaminal lidocaine given through an indwelling catheter. Because a low concentration of lidocaine (and other membrane stabilizers) is sufficient [14], and undoubtedly less toxic than 1% to 2% lidocaine, current implantable pump systems might provide extended pain relief using a single reservoir charge and a slow pumping rate. Novel anesthetic modalities that are selective to small-diameter afferents [3] might be a way to attenuate PLP while preserving the benefits of nonpainful phantom limb sensation in the maintenance of body image. Furthermore, these approaches might well be applicable to other neuropathic pain conditions in which DRG ectopia is a root cause [14].

Conflict of interest

The authors report no conflict of interest.

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