PainWeek

How "Central" is Central Post-Stroke Pain?

Michael Bottros, MD

Disclosure

- None

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Learning Objectives

- List the leading causes of pain after stroke.
- Review the diagnostic criteria for central post stroke pain.
- Describe the proposed mechanisms for central post stroke pain.
- Identify a plan for medical and non-medical management for CPSP.

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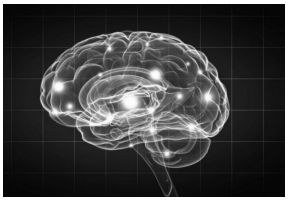
Outline

- Introduction
- Epidemiology
- Clinical Presentation
- Proposed Mechanisms
- Management
- Conclusion



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Central Neuropathic Pain

Common Causes:

- Ischemic/hemorrhagic stroke
- Multiple sclerosis
- Spinal cord injury
- Syringomyelia
- Vascular malformations
- Infections
- Traumatic brain injury
- Parkinson's disease?

Lancet Neurol 2009; 8: 857–68

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Epidemiology

- Annually, 500, 000 people in the US have a first stroke
- 200, 000 have a recurrent stroke
- 80% of strokes are ischemic, either thrombotic or embolic in origin
- 5 million people in the US have had a stroke & are living in the community setting
- Of these, 1.1 million have limitations in their daily functioning or ability to perform activities of daily living
- 100, 000 people have stroke as their primary diagnosis & are receiving in home health care

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Introduction

- Pain is among the most common complications of stroke, with reported prevalence of 39% to 55%.
- The leading types of post-stroke pain are headaches, shoulder pain, spasticity, and central post-stroke pain (CPSP).
- Central post-stroke pain is a neuropathic pain disorder caused by the stroke-related lesion affecting the central somatosensory pathways, and accounts for about 25% of post-stroke pain cases.

PAIN 1995;61:187–93.
PAIN 2011;152:818–24.

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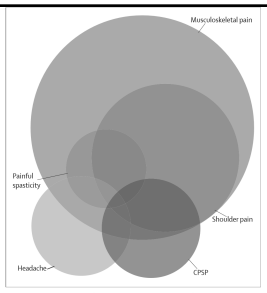

Figure 1: **Common types of chronic pain that can occur after stroke**
Diagram of the complexity of post-stroke pain. Individual patients can have various combinations of one or several pain types (overlapping areas). The sizes of the circles are approximate to relative frequency (spasticity 7%, headache 10%, CPSP 10%, shoulder pain 20%, musculoskeletal pain 40%). CPSP=central post-stroke pain.

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CPSP

- First introduced in 1891 by Edinger.
- In 1906, Déjerine and Roussy provided descriptions of CPSP in 8 pts.
- Further described by Head and Holmes in 1911 describing sensory deficits and pain narratives.
- Riddoch described symptoms of both thalamic and extra-thalamic origin (1938).


L.A.
COUCHE OPTIQUE
LE SYNDROME THALAMIQUE
Le Dr Gustave ROUSSY
PARIS
G. STEINHEIL, ÉDITEUR

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Time Course

- Variable
- Can develop immediately after stroke in some patients and up to years later in others.
- Onset can be delayed, but development of CPSP within the first few months is most common.
- In a prospective study that included 16 patients with CPSP, pain onset occurred within the first month after stroke in ten patients, between 1 and 6 months in three patients, and after 6 months in three patients.
- Any later onset of pain should prompt an examination for other causes, such as a new stroke.
- Gradual onset of pain is most common.

PainWeek Lancet Neurol 2009; 8: 857–68

Diagnostic Criteria

- Mandatory criteria
  - Pain within an area of the body corresponding to the lesion of the CNS.
  - History suggestive of a stroke and onset of pain at or after stroke onset.
  - Confirmation of a CNS lesion by imaging or negative or positive sensory signs confined to the area of the body corresponding to the lesion.
  - Other causes of pain, such as nociceptive or peripheral neuropathic pain, are excluded or considered highly unlikely.
- Supportive criteria
  - No primary relation to movement, inflammation, or other local tissue damage.
  - Descriptors such as burning, painful cold, electric shocks, aching, pressing, stinging, and pins and needles, although all pain descriptors can apply.
  - Allodynia or dysesthesia to touch or cold.

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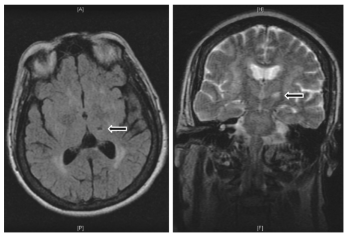

Figure 1. Axial T2 FLAIR MR image (left panel) showing a chronic left thalamic infarction (arrow). A T2 coronal image (right panel) demonstrates the postero-lateral thalamic location of the infarct.

PainWeek Top Stroke Rehabil 2013;20(1):116–123.

Diagnostic Measures

- Pain scales:
  - VAS or NRS are useful in the evaluation of the pain intensity, but there are no scales developed speciifcally for CPSP.
- Quantative Sensory Testing (QST):
  - Have been used to document common or dissociated sensory findings.
  - Enable detailed sensory testing of controlled and graded physiological stimuli, such as thermal, pressure, pinprick, and vibration stimuli.

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Clinical Characteristics

- Pain can be spontaneous or evoked.
- Spontaneous is common and reported in 85% of patients.
- On NRS scale, the mean varies between 3-6/10.
- Symptoms and severity in thalamic versus extrathalamic stroke does not differ.
- Intensity can be increased by internal or external stimuli.

Neurology 1995; 45: S11–S16.

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Spontaneous Pain Descriptions

- Continuous:
  - Burning
  - Aching
  - Pricking
  - Freezing
  - Squeezing
- Intermittent:
  - Lacerating
  - Shooting

- CPSP Can reduce quality of life:
  - Can compromise rehabilitation.
  - Interfere with sleep.
  - Lead to self-mutilation.
  - Even push patients to suicide.

Lancet Neurol 2009; 8: 857–68

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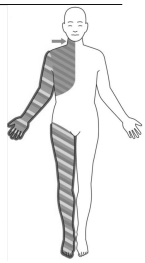
Pain Distribution

- Distribution of pain can range from a small area (eg, the hand) to large areas (eg, to one side of the body).
- Large areas are most commonly affected, with or without involvement of the trunk and face.
- In patients with lateral medullary infarction, the pain can involve one side of the face and the contralateral side of the body or limbs, and periorbital pain is frequently reported.
- Hemibody pain is common in patients with thalamic lesions.



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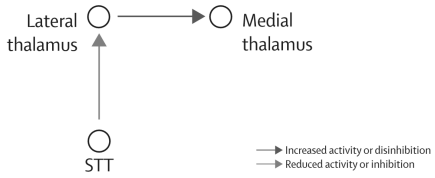
Proposed Mechanisms



Loss of STT input to the posterior lateral part of the thalamus causes disinhibition of the medial thalamus leading to pain.

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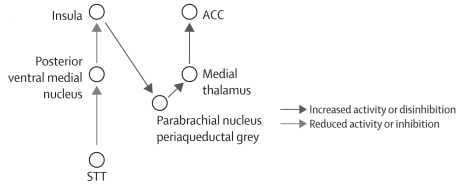
Lancet Neurol 2009; 8: 857–68

Proposed Mechanisms



The thermosensory disinhibition theory. A lesion in the lateral cool-signalling spinothalamocortical projections to the thermosensory area of the insula through the posterior part of the ventral medial nucleus causes disinhibition of a medial limbic network involving the parabrachial nucleus and the periaqueductal grey of the brainstem, the medial thalamus, and the ACC.

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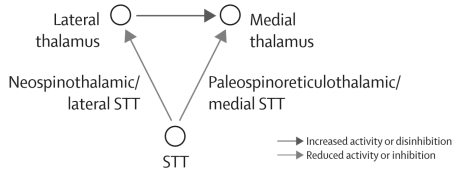
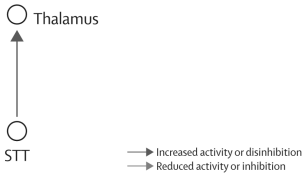
Proposed Mechanisms



A loss of normal inhibition from the rapidly conducting "neospinothalamic" or lateral STT projections causes disinhibition of the slowly conducting polysynaptic paleo spinoreticulothalamic or medial STT projections, resulting in pain.

PainWeek Lancet Neurol 2009; 8: 857–68

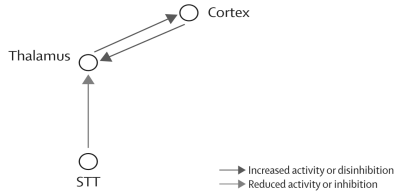
Proposed Mechanisms



Deafferentation of ascending pathways to the thalamus might cause central pain due to hyperactive bursting in the thalamus caused by low-threshold calcium spikes.

PainWeek Lancet Neurol 2009; 8: 857–68

Proposed Mechanisms



The dynamic reverberation theory. A lesion of the STT causes central pain by creating an imbalance in the normal oscillatory "dialogue" between the cortex and the thalamus.

PainWeek Lancet Neurol 2009; 8: 857–68

Treatments for Central Post Stroke Pain

- Antidepressants
- Anticonvulsants
- Antiarrhythmics
- Opioids
- Steroids
- Intrathecal Baclofen
- Rehab Techniques
- Regional Anesthesia
- Electrical Stimulation
- Deep Brain Stimulation
- Neuroablative Procedures
- Transcranial Magnetic Stimulation

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Antidepressants

- TCAs are currently viewed as first-line drugs for CPSP.
- Of these, Amitriptyline (75 mg) is considered drug of choice, with consistent relief reported.
- Mild to moderate side-effects were common, particularly lethargy and dry mouth.
- Other TCAs (nortriptyline, imipramine, desipramine) and serotonin/norepinephrine reuptake inhibitors (venlafaxine, duloxetine, milnacipran) have also been reported to be effective, but efficacies have yet to be established.
- Selective serotonin reuptake inhibitors are mostly ineffective.

Pain Management Nursing 2015; 16(5): 804-818.
Pain 1989; 36: 27–36.

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Anticonvulsants

- Gabapentin and pregabalin have well documented efficacy in central neuropathic pain syndromes.
- In a RCT, pregabalin showed a clinically significant effect of treatment on pain levels in patients with central neuropathic pain.
- Most commonly reported side-effects were dizziness, decreased intellectual performance, somnolence, and nausea.

Pain 2008; 136: 150–57.

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Anticonvulsants

- Lamotrigine monotherapy was found to be moderately effective in amounts up to 200 mg/day in randomized double-blinded placebo-controlled trial of 27 CPSP patients.
- Lamotrigine was well tolerated except for the occurrence of mild rash. However, Stevens-Johnson syndrome and toxic epidermal necrolysis (TENS) are serious potential side effects of lamotrigine, and appropriate patient instruction must be given.

Am J Phys Med Rehabil. 2002;81(9):718–720.

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Anticonvulsants

- In a placebo-controlled, crossover study comparing amitriptyline, carbamazepine, and placebo, carbamazepine was better at 3 weeks only, whereas amitriptyline was signifi cantly better than placebo in relieving pain at 2, 3, and 4 weeks.
- Use of carbamazepine is limited by its side-effect profile and interaction with other medications.
- Clinicians should be aware of possible ataxia, rash, hyponatremia, bone marrow dysfunction, and hepatic dysfunction.
- Overall, the efficacy of carbamazepine is limited.

Pain 1989; 36: 27–36.

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Opioids

- Opioids are generally considered ineffective in CPSP.
- However, morphine has been reported to alter significant aspects of pain perception (allodynia and thermal thresholds).
- In one study, morphine appeared to be effective in reducing CPSP because it reduced concurrent nociceptive pain and psychogenic influence.
- Other investigators have reported a loss or inactivation of opioid receptors in the cerebral hemisphere in CPSP, which would explain the low efficacies of opioids and the need for high doses to treat CPSP.
- Opioid treatment is often discontinued because of significant side effects from the high doses necessary for clinical benefit.

Pain Management Nursing 2015; 16(5): 804-818.

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Intravenous Medications

TABLE 3. Intravenous Drugs Reported to be Effective in the Treatment of CPSP

Drug	Reference	No. of Patients Treated/TPS/PSP	Study Design	Study Level	Dosing Regimen	Outcome Measures	Results	Comments
Lidocaine	Attal et al[13]	16/16/6	Double-blind, placebo-controlled, crossover	A	5mg/kg IV over 30 minutes	1. Spontaneous pain, VAS 1–100 2. Global assessment of pain relief	1. Sig greater relief of pain for up to 45 min with lidocaine 2. 11/16 > 50% pain relief with lidocaine vs 6/16 with placebo	Also sig reduction of brush-induced allodynia and mechanical hyperalgesia
Propofol	Canavero et al[14]	32/16/7	Double-blind, placebo-controlled, crossover	A	Single IV bolus of 0.2mg/kg responders: 0.1mg/kg per h for 6–24 h	VAS 1–10 every 5 min for 30 min	Reduction by > 3 VAS points in 7/7 CPSP patients; 14/16 OT patients; 4/16 with placebo	16 responders alodynia abolished, pain control with prolonged infusion for 6–24 h in 7 patients
Ketamine	Backonja et al[15]	8/3/2	Double-blind, placebo-controlled, crossover	A	250μg/kg IV over 5 min	Pain rating scale 0–10	Pain relief > 50% in 2/3 patients with CPS (with CPSP) lasting 2–3 hours vs 0/5 with placebo	Continous subcutaneous infusion only in 1 patient with neuropathic pain, discontinued because of side-effects
	Yamamoto et al[16]	23/23/23	Uncontrolled trial d1 morphine d2 lidocaine d3 ketamine	B	5mg every 5 min, total dose 25 mg	VAS 1–10	Pain relief > 40% in 11/23 patients, 2/23 patients, duration > 60 min	No long-term application
Thiamylal	Yamamoto et al[16]	39/39/39	Uncontrolled trial, d1 morphine, d2 thiamylal, d3 ketamine	B	80mg every 5 min, total dose 250 mg	VAS 1–10	Pain relief > 40% in 22/39 patients, duration > 60 min	No long-term application
Morphine	Yamamoto et al[16]	39/39/39	Uncontrolled trial, d1 morphine, d2 thiamylal, d3 ketamine	B	5mg every 5 min, total dose 10 mg	VAS 1–10	Pain relief > 40% in 8/39 patients, duration > 60 min	No long-term application
	Attal et al[16]	15/15/6	Placebo-controlled, crossover	A	1. Mean dosage 16 mg IV 2. Mean dosage 97mg oral	VAS 1–100	1. No sig. difference in pain reduction 2. 4 of 10 with long-term efficacy of oral morphine	Sig influence of morphine on allodynia and thermal threshold

A, randomized placebo-controlled trial; B, uncontrolled trial; IV, intravenously; d, day; vs, versus; sig, significant.

ClinJ Pain 2006;22:252–260.

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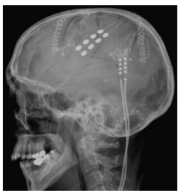
Neurostimulation

- Motor cortex stimulation:
  - Mechanism not completely understood. However, studies have indicated changes in cerebral blood flow in several areas, including the thalamus, after successful motor cortex stimulation.
  - In two recent reviews, the 1-year success rate in patients with CPSP was concluded to be about 45–50%.
  - Severe complications are rare.
  - Most common complications reported are seizures (intra-operatively or during the trial period), infections, and hardware problems.



Lancet Neurol 2009; 8: 857–68

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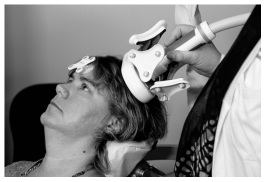
Neurostimulation



- Transcranial magnetic stimulation:
  - Non-invasive method.
  - The effects on pain are often modest and short lasting.
  - Adverse events are rare.
  - Recurring sessions of repetitive transcranial magnetic stimulation of the motor cortex have been shown to extend pain relief.
  - The result of this treatment might be a useful predictor for the efficacy of motor cortex stimulation.

Lancet Neurol 2009; 8: 857–68

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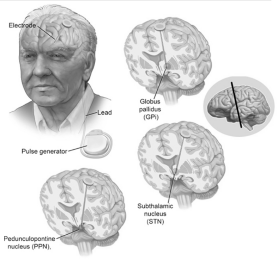
Neurostimulation

- Deep brain stimulation:
  - Main targets are the sensory (ventral posterior) thalamus and the periventricular gray matter.
  - Reported efficacy rates range from 25% to 67%, but with wide ranges of pain relief.



Lancet Neurol 2009; 8: 857–68

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Neurostimulation

- Vestibular caloric stimulation:
  - Effect probably due to activation of the posterior insula and subsequent inhibition of pain generation in the anterior cingulate.
  - Two small studies:
  - In one study (n=2), CPSP was substantially relieved by VCS.
  - In another study of 9 patients, there was a significant immediate treatment effect for cold-water caloric stimulation.

Neurocase 2007; 13(3): 185-188.
Journal of Neurology Neurosurgery and Psychiatry 2008; 79(11): 1298-1301.

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Research Paper

PAIN

How central is central poststroke pain? The role of afferent input in poststroke neuropathic pain: a prospective, open-label pilot study

Simon Harootounian[a,b,*], Andria L. Ford[c], Karen Frey[a], Lone Nikolajsen[d,e], Nanna B. Finnerup[d,f], Alicia Neiner[a], Evan D. Kharasch[b,g], Pall Karlsson[d], Michael M. Bottros[a,b]

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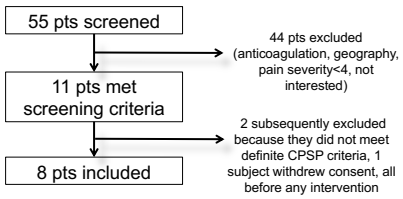
Screening Protocol



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Demographic Data

Table 1

Demographic data and stroke characteristics.

Pt #	Age, sex	Race	BMI	Stroke type	Stroke location	Additional details	Time since stroke	Comorbidities
1	51, F	Black/African heritage	49.2	H	Rt thalamus	Intraventricular extension	6.0 yr	HTN, depression, s/p hysterectomy, dyslipidemia, and DM
2	47, M	Black/African heritage	37.9	H	Rt basal ganglia	Extension into Rt frontal–parietal lobes	6.9 yr	HTN, depression, TIA, CKD, and gout
3	62, M	Caucasian	28.7	H	Lt basal ganglia and thalamus		1.3 yr	HTN, s/p cholecystectomy, and s/p hemorrhoidectomy
4	37, F	Black/African heritage	24.4	H/I	Rt basal ganglia (H) and Rt medial thalamus (I)	Thalamic ischemic stroke occurred 3 months after hemorrhagic stroke	1.7 yr	HTN, depression, DM, and dyslipidemia
5	52, F	Caucasian	28.6	I	Rt thalamus		11 mo	HTN, depression, DM, and dyslipidemia
6	56, M	Black/African heritage	29.0	I	Rt internal capsule		9 mo	HTN and depression
7	60, M	Black/African heritage	28.0	H	Lt basal ganglia	Extension into Lt caudate, thalamus, and lateral ventricle	2.3 yr	Glaucoma, CAD, GERD, CKD, dyslipidemia, and HTN
8	48, F	Caucasian	21	I	Lt basal ganglia, thalamus, and occipital lobe		4.3 yr	Iron deficiency anemia

BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; GERD, gastroesophageal reflux disease; H, hemorrhagic; HTN, hypertension; I, ischemic; IPH, intraparenchymal hemorrhage; Lt, left; NSAID, nonsteroidal anti-inflammatory drug; Rt, right; s/p, status post; TIA, transient ischemic attack.

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Pain Characteristics

Table 2

Central poststroke pain characteristics.

Pt #	Pain onset	Pain duration	BPI—pain severity	BPI—pain interference	NPSI total score	Analgesics	Nerve block site
1	Immediate	>5 yr	6.0	5.4	23	Naprowen and acetaminophen (paracetamol)	Left brachial plexus
2	Immediate	>5 yr	6.8	2.4	37	None	Left leg (tibial and peroneal nerves)
3	3-12 months after stroke	6-12 mo	6.0	3.6	49	Tramadol	Right brachial plexus
4	3-12 months after stroke	6-12 mo	5.8	6.6	26	Gabapentin, NSAIDs, and acetaminophen (paracetamol)	Left brachial plexus
5	3-12 months after stroke	6-12 mo	8.5	8.6	58	Gabapentin	Left brachial plexus
6	0-1 month after stroke	6-12 mo	5.0	5.6	26	None	Left leg (tibial and peroneal nerves)
7	0-1 month after stroke	2-5 yr	7.5	6	60	Gabapentin	Right brachial plexus
8	Immediate	2-5 yr	4.8	2.7	34	Duloxetine	Right elbow (ulnar, radial, and median nerves)

BPI, Brief Pain Inventory; NPSI, Neuropathic Pain Symptom Inventory; NSAIDs, nonsteroidal anti-inflammatory drugs.

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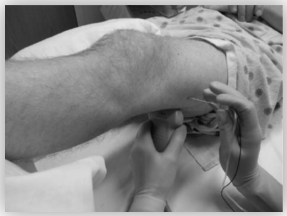
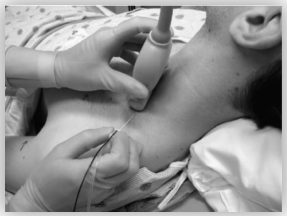
Regional Block Technique





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Pain Distribution

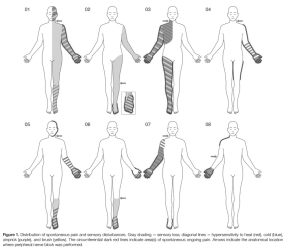

Figure 1. Distribution of spontaneous pain and sensory disturbances. Deep shading = sensory loss; diagonal lines = hypersensitivity to heat (red), cold (blue), pinprick (purple), and brush (yellow). The circumferential dark red lines indicate area(s) of spontaneous ongoing pain. Arrows indicate the anatomical location where peripheral nerve block was performed.

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Primary Outcome of Change in Spontaneous Pain

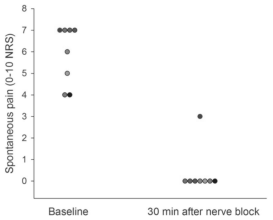

Figure 2. Primary outcome of change in spontaneous pain. Intensity of ongoing pain at baseline (before the block) and 30 minutes after the block (primary outcome). Each subject is coded by a different color. NRS, numerical rating scale.

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Individual Pain Scores

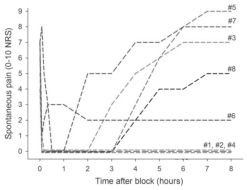

Figure 3. Individual pain score changes after the nerve block. After the peripheral nerve blockade, pain intensity returned to baseline within 4 to 7 hours in 4 patients, consistent with the duration of lidocaine action. In 3 patients, pain scores remained zero for 8 hours after the nerve block, in 1 patient (#4, baseline NRS = 7), pain intensity remained at NRS = 2. NRS, numerical rating scale.

Intensity scores for thermal and mechanical sensation in the painful extremity.

Sensory modality	Baseline	30 minutes after the block	*P*
Cold	7 (4.5-7.8)*	0 (0.0-1.5)*	0.008
Heat	5.9 (±1.4)	0.5 (±1.1)	<0.0001
Brush	4.5 (±1.9)	1.0 (±1.4)	0.004
Pinprick	5.0 (±2.1)	1.1 (±2.2)	0.003

Scores were assessed on a scale from 0 to 10, where 5 is "normal sensation" tested against a contralateral, nonpainful area; lower scores represent hyposensitivity (0 = no sensation), and higher scores represent hypersensitivity (10 = most intense/painful sensation).
* Data were not normally distributed (Shapiro–Wilk test), therefore analyzed by the Wilcoxon signed rank test, and presented as median (interquartile range).

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Plasma Lidocaine Concentrations

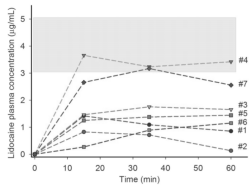

Figure 4. Plasma lidocaine concentrations after the nerve block. Individual plasma concentrations of lidocaine measured at baseline and 15, 35, and 60 minutes after the nerve block. Because of technical reasons, lidocaine concentrations in 1 patient (#8) were not analyzed. The shaded area represents the concentration range (3-5 µg/mL) associated with potential systemic analgesic effect of lidocaine.

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Discussion

- Pain may not be entirely generated and perceived in the CNS.
- Rather, the afferent sensory input from the painful area plays a role in maintaining spontaneous pain in CPSP.
- It is plausible that the sensory neurons in the CNS, which are damaged by the stroke, become sensitized to the afferent stimuli, and generate action potentials secondary to trivial sensory input.
- Supporting the local afferent blockade (rather than the systemic effect) as the cause of pain relief is the finding that no changes in pain intensity occurred after the block in the ipsilateral painful extremity in these patients.

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Conclusion

- CPSP has a variable time to onset after stroke.
- In most cases of CPSP, the stroke lesions are extrathalamic.
- Amitriptyline is the first-line drug of choice.
- If amitriptyline fails or is unavailable, then try lamotrigine.
- In intractable cases, short-term pain relief may be achieved by IV lidocaine, propofol, or ketamine.
- Motor cortex stimulation, DBS, or, rTMS may be tried in resistant CPSP patients.
- Sensory afferent input may play an important role in maintaining pain in CPSP.

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