Section 1 Introduction

Those who cannot remember the past are condemned to repeat it.
G. Santayana

Section 1 Introduction

Chapter 1

Introducing central pain

Definition

Ever since Dejerine and Roussy's description of central pain (CP) after thalamic stroke in 1906, *thalamic pain* (itself part of the *thalamic syndrome*) has remained the best-known form of CP and it has often – misleadingly – been used for all kinds of CP. Since CP is due to extrathalamic lesions in the majority of patients, this term should be discarded in favor of the terms central pain of brain–brainstem or cord origin (BCP and CCP). Unacceptable terms include *pseudothalamic pain*, *parainsular pain*, *central deafferentation pain*, *neural injury pain*, *anesthesia dolorosa* (if it refers to central nervous system [CNS] lesions). If a stroke is the cause of CP, the term central post-stroke pain (CPSP) is used. Even though some clinical features are similar, peripheral neuropathic pain (PNP), e.g., brachial plexus avulsion pain, postherpetic neuralgia, and complex regional pain disorder, is not CP, although in some cases the dorsal horn may be involved.

CP is akin to central dysesthesias/paresthesias (CD) and central neurogenic pruritus (CNP): actually, these are facets of the same disturbance of sensory processing following CNS lesions. Dysesthesias and paresthesias differ from pain in being abnormal unpleasant and non-unpleasant sensations with a non-painful quality. Virtually all kinds of slowly or rapidly developing disease processes affecting the spinothalamic and quintothalamic tracts (STT/QTT), i.e., the pathways that are most important for the sensations of pain and temperature, at any level from the dorsal horn/sensory trigeminal nucleus to the parietal cortex, can lead to CP/CD/CNP. These do not depend on continuous receptor activation.

CP/CD/CNP is defined as:

> **Spontaneous and/or evoked, anomalous, painful or non-painful, sensations projected in a body area congruent with a clearly imaged lesion impairing – transitorily or permanently – the function of the spinothalamoparietal thermoalgesic pathway.**

For simplicity, we will refer to CP *tout court* throughout the text. Parkinson's disease (PD), epileptic pains, and perhaps other diseases with a painful CP-like component should be classified as *central pain-allied conditions* (CPAC). In PD there is no impairment of the spinothalamoparietal (STP) path, but an anomalous modulation of the acute pain networks (no thermoalgesic deficit), and in epilepsy there is an over-recruitment of pain-coded neurons.

History

Cases of CP following brain or cord damage have most certainly been observed since antiquity, but never understood as such. We have to wait until the nineteenth century for published descriptions of what we now understand to be CP (Table 1.1) in Western medicine (there appear to be reports of what is most likely CP in ancient Chinese medicine, this being the result of a "deficiency of the Qi and attendant blood stasis, in turn depriving the nourishing of meridians and tendons"; see Kuong 1984). However, the possibility of *centrally arising* pains was simply dismissed by most authorities.

It was not until 1891 that Edinger, a German neurologist, challenging the prevailing opinion of the day, and "*avec une rare sagacité*" (with rare sagacity; Garcin 1937), introduced the concept of *centrally arising pains*. In his landmark paper "Are there centrally arising pains? Description of a case of bleeding in the nucleus externus thalami optici and in the pulvinar, whose essential symptom consisted in hyperesthesia and terrible pains in the contralateral side, besides hemiathetosis and hemianopsia" (Fig. 1.1), he remarked how only a few cases of pains associated with damage of the brain, brainstem, and spinal cord were on record ("*Die Durchsicht der Literatur nach aehnlichen Beobachtungen hat nur wenig ergeben*" – a literature review of similar cases has borne little

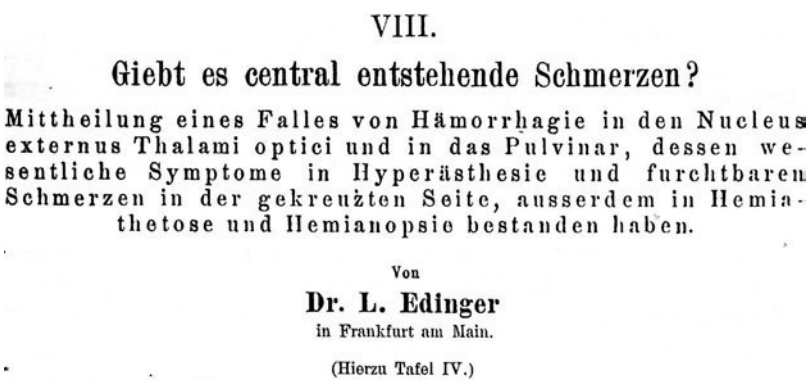
Table 1.1. Historic highlights of central pain (CP), from De Ajuriaguerra (1937), Garcin (1937)

Viesseux (1810)	Presented his own experience of dissociated sensory loss after brainstem stroke
Marcet (1811)	Describes pain after bulbar lesions
Fodera (1822)	Describes pain after spinal hemisection
D'Angers (1824)	First describes syringomyelia
Brown-Séquard (1850)	Describes the syndrome named after him; confirms previous description of hyperesthesia below lesion level on the plegic side
1860–70s	Descriptions of pain after spinal trauma during the US Civil War
Charcot (1872) [pp. 239–40]	Description of multiple sclerosis and the associated pains
Marot (1875)	Further describes pain after bulbar lesions
Nothnagel (1879)	First precise description of constant pain following tumors of the pons (mentioned by other authors) and other sites
Page (1883)	Describes pain in spinal cord injury patients
Edinger (1891)	Birth of the concept of CP
Hardford (1891)	Describes pain of cortical origin
Mann (1892)	Matches CP to infarctions of medulla at nucleus ambiguus level
Gilles de la Tourette (1889)	Describes syringomyelic pain
Wallenberg (1895)	(Re)describes the syndrome named after him; insists on facial pains; ascribes it to PICA embolism (verified autoptically in 1901)
Reichenberg (1897)	Describes CP as resulting from parietal stroke (autopsy confirmed)
Link (1899)	Describes CP as resulting from pontobulbar lesions
Dejerine and Roussy (1906)	Describe the syndrome named after them
Head and Holmes (1911)	First quantitative assessment of sensory deficits in CP
Holmes (1919)	"Typical thalamic pain" observed in spinal cord injured patients (World War I soldiers)
Souques (1910), Guillain and Bertrand, Davison and Schick, Schuster, Wilson, Parker (1920s–30s)	Autoptic confirmation that CP may arise without thalamic involvement
Cassinari and Pagni (1969)	Pinpoint the anatomic basis of CP

Also of note: Elsberg (cordonal pain), Förster (dorsal horn pain), Gerhardt (recognized CP in multiple sclerosis), Anton. See Canavero and Bonicalzi (2007a) for other authors.

fruit), but that other reasons were adduced to explain them (generally peripheral nerve causes or muscle spasms).

One of the few "well investigated" cases was that of Greiff (1883), concerning a 74-year-old woman who developed "*Hyperaesthesie und reissenden Schmerzen im linkem Arm, geringgradiger im linkem Beine*" (hyperesthesia and tearing pains in the left arm and of lesser intensity in the left leg) as a consequence of several strokes, which lasted for two months until death. At autopsy, two areas of thalamic softening were found, one of which was in what appears to be ventrocaudalis (Vc). Greiff commented on vasomotor disturbances as a possible cause of pain. According to Edinger, "*Vielleicht giebt es auch corticale Schmerzen*" (perhaps there are also cortical pains), and he cited as evidence "*schmerzhaften Aura bei epileptischen, abnorme Sensationen bei Rindenherden und*



VIII.

Giebt es central entstehende Schmerzen?

Mittheilung eines Falles von Hämorrhagie in den Nucleus externus Thalami optici und in das Pulvinar, dessen wesentliche Symptome in Hyperästhesie und furchtbaren Schmerzen in der gekreuzten Seite, ausserdem in Hemiathetose und Hemianopsie bestanden haben.

Von

Dr. L. Edinger

in Frankfurt am Main.

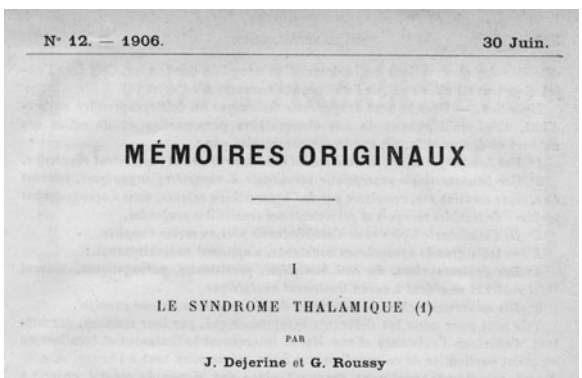
(Hierzu Tafel IV.)

Figure 1.1. Title page of Edinger's 1891 paper marking the birth of the concept of central pain.

Reizerscheinungen im Bereich des Opticus bei Affectionen des Hinterhaupts-lappens" (painful aura in epileptics, abnormal sensations in cortical foci, and signs of excitation in the territory of the opticus following diseases of the occipital lobe). Edinger reported on "*einen Krankheitsfall . . . in dem als Ursache ganz furchtbaren Schmerzen post mortem ein Herd gefunden wurde, der dicht an die sensorische Faserung grenzend im Thalamus lag. Der Fall erscheint dadurch besonders beweiskraftig fuer die Existenz 'centraler Schmerzen', weil die Hyperaesthesie und die Schmerzen sofort nach dem Insulte und monatelang vor einer spaeter auftretenden Hemichorea sich zeigten*" (a patient . . . in whom the origin of truly terrible pains was at autopsy a lesion that impinged on the fibers abutting the thalamus. This case is thus especially convincing evidence for the existence of "central pains," as the hyperesthesia and the pains showed immediately after the insult and months before a later arising hemichorea). The patient was "*Frau R*" (Mrs. R), aged 48, who developed "*heftige Schmerzen und deutliche Hyperaesthesie in den gelaehmten Gliedern*" (violent pains and clear-cut hyperesthesia in the paretic limbs: right arm and leg), "*Wegen der furchtbaren Schmerzen Suicidium 1888*" (due to the terrible pains, suicide 1888). This woman developed an intense tactile allodynia for all stimuli bar minimal, which hindered all home and personal activities (e.g., dressing) and made her cry; also "*Laues Wasser wurde als sehr heiss, kaltes als unertraeglich schmerzend*" (lukewarm water was felt as very hot, and cold water as intolerably painful) in both limbs. Very high doses of "*Morphium*" were basically ineffective. This patient's pain reached intolerable peaks, but sometimes could be tolerated for a few hours or at most half a day before shooting up again. In this patient, "*Vasomotorische Stoerungen, wie sie in dem Lauenstein (D.Arch.f.klin.Med. Bd.XX.u.A.)'schen . . . Falle bestanden haben, sind nicht zur Beobachtung gekommen*" (vasomotor disturbances, as present in Lauenstein's case, were nowhere to be observed). At autopsy, "*Der Herd im Gehirn nimmt also den dorsalen Theil des Nucleus externus thalami und einen Theil des Pulvinar ein, er erstreckt sich lateral vom Pulvinar fuer 1 mm in den hintersten Theil der inneren Kapsel hinein. Der Faserausfall, der dort in Betracht kommt, ist sehr gering*" (the brain lesion involved the dorsal portion of the nucleus externus thalami and a portion of the pulvinar, extending laterally from the pulvinar for 1 mm into the most posterior part of the inner capsule. The loss of fibers, which can be observed at this point, is minimal). Thus, in Greiff's and Edinger's patients, lesions were respectively found at autopsy in right thalamic nucleus internus and ventral thalamus, and in thalamic nucleus externus and pulvinar.

Edinger should be given the credit for introducing the concept of CP to neurology, as he wrote: "*Man kommt zum Schlusse, dass hier wahrscheinlich durch directen Contact der sensorischen Kapselbahn mit erkranktem Gewebe die Hyperaesthesie und die Schmerzen in der gekreuzten Koerperhaelfte erzeugt worden sind*" (one concludes that here both the hyperesthesia and the pains in the crossed half of the body have been likely caused by direct contact of injured tissue with the sensory path coursing in the internal capsule).

One year later, Mann (1892), another German neurologist, concluded, in Edinger's wake, that CP can be also observed outside the thalamus, namely in the medulla oblongata, thus antedating Wallenberg's classic description (autopsy of this patient performed


N° 12. — 1906. 30 Juin.

MÉMOIRES ORIGINAUX

I

LE SYNDROME THALAMIQUE (1)

PAR

J. Dejerine et G. Roussy

Figure 1.2. Title page of Dejerine and Roussy's 1906 paper introducing the "thalamic syndrome."

in 1912 confirmed Mann's clinical diagnosis and the involvement of the spinothalamic tract). Thereafter, an explosion of reports ensued.

In the first decade of the twentieth century, Dejerine and Egger (1903) and Dejerine and Roussy (1906) described six cases of what they called "*syndrome thalamique*," (Fig. 1.2), whose signs and symptoms were defined thus (Roussy 1907):

> *Définition – Sous le nom de syndrome thalamique on doit comprendre aujourd'hui, ainsi qu'il ressort de nos observations personnelles et de celles des auteurs ci-dessus cités, un syndrome caractérisé par*:
> *1° Une hémiplégie légère habituellement sans contracture et rapidement regressive.*
> *2° Une hémianestésie superficielle persistante à caractères organiques, pouvant être, dans certains cas, remplacée par de l'hyperesthésie cutanée, mais s'accompagnant toujours de troubles marqués et persistants des sensibilités profondes.*
> *3° De l'hémiataxie légère et de l'astéréognosie plus ou moins complete.*
> *A ces trois grands symptômes constants, s'ajoutent ordinairement*:
> *4° Des douleurs vives, du côté hèmiplégié, persistantes, paroxystiques, souvent intolérables et ne cédant à aucun traitement analgésique.*
> *5° Des mouvements choréo-athétosiques dans les membres du côté paralysé.*
> [(1) slight hemiparesis usually without contracture and rapidly regressive; (2) persistent superficial hemianesthesia of an organic character which can in some cases be replaced by cutaneous hyperesthesia, but always accompanied by marked and persistent disturbances of deep sensations; (3) mild hemiataxia and more or less complete astereognosis. To these principal and constant symptoms are ordinarily added: (4) severe, persistent, paroxysmal, often intolerable pain on the hemiparetic side unyielding to any analgesic treatment; (5) choreoathetotic movements in the limbs on the paralyzed side.]

Dejerine and Roussy wrote:

> *Les douleurs . . . Nous les retrouvons . . . dans la plupart des cas de syndrome thalamique . . . avec assez de fréquence, pour nous autoriser à admettre que ces douleurs sont sous la dépendence de la lésion thalamique, ou mieux de la destruction et de l'irritation des fibres qui viennent s'arboriser dans sa portion ventrale.*
> [The pains . . . We find them . . . in most cases of the thalamic syndrome . . . with enough frequency to warrant the conclusion that these pains are due to the thalamic lesion, or better to the destruction and irritation of the fibers branching throughout its ventral portion.]

Thereafter, on the basis of an autopsy study of three cases (Joss . . ., Hud . . ., Thal . . .), they concluded that:

> *Une lesion de la couche optique intéressant le noyau externe dans sa partie postéro-externe et prenant en outre une partie des noyeaux médian et interne ainsi que le fragment correspondant de la capsule interne, donne en clinique un tableau symptomatique toujours semblable à lui-meme . . . Ce tableau symptomatique constitue . . . un nouveau syndrome qui doit prendre rang dans la nosologie: le syndrome thalamique.*
> [A lesion of the optic bed involving the postero-exterior side of the external nucleus and also a portion of the median and internal nuclei plus a corresponding fragment of the internal capsule leads to a consistent clinical picture . . . this collection of symptoms adds up to . . . a new, nosologically separate syndrome: the thalamic syndrome.]

A few years later, Head and Holmes (1911), on the basis of personal and literature autoptic evidence, concluded that thalamic pain depends on the destruction of the posterior part of the external thalamic nucleus. In their book-size article, they provided the best and first quantitative description ever of somatosensory alterations in CP patients.

During World War I several observations on "thalamic pains" associated with spinal cord war lesions were published, as had previously been done – but only descriptively – during the American Civil War

in the 1860s. The term *central pain* was first used in the English literature by Behan (1914). In 1933 Hoffman reported a tiny lesion in the most basal part of the Vc, where spinothalamic fibers end (Hassler's Vcpc), the smallest reported lesion causing CP at the time. Interestingly, he commented that *"Der Fall spricht gegen die Schmerztheorie von Head und legt den Gedanken nahe, dass die Spontanschmerzen durch eine funktionwandelung im Bereiche des Schmerzleitungsystem selbst entstehen"* (the report speaks against Head's theory and suggests that the spontaneous pain is self-generated through a functional change of the pain conducting system).

In the 1930s three major reviews on CP were published (De Ajuriaguerra 1937, Garcin 1937, Riddoch 1938). Here, the interested reader will find an unparalleled review of the literature of the nineteenth and early twentieth centuries, plus unsurpassed descriptions of CP, whose ignorant neglect (admittedly also due to language barriers) on the part of modern investigators is responsible for several "rediscoveries." Nothing new has basically been added to the clinical literature since then. Riddoch (1938) gave this definition:

> By central pain is meant spontaneous pain and painful overreaction to objective stimulation resulting from lesions confined to the substance of the central nervous system including dysesthesiae of a disagreeable kind.

It was clear how "thalamic pains" could follow a lesion of the lateral thalamic area, in the territories of the lenticulo-optic, thalamo-geniculate, and thalamo-perforating arteries, but also of the cortex (rarely), internal capsule, medulla oblongata, and less frequently the pons (no mesencephalic lesions were on record) and the spinal cord (not infrequently; particularly following injury and syringomyelia). Thermoalgesic sensory loss and somatotopographical constraints were clearly delineated.

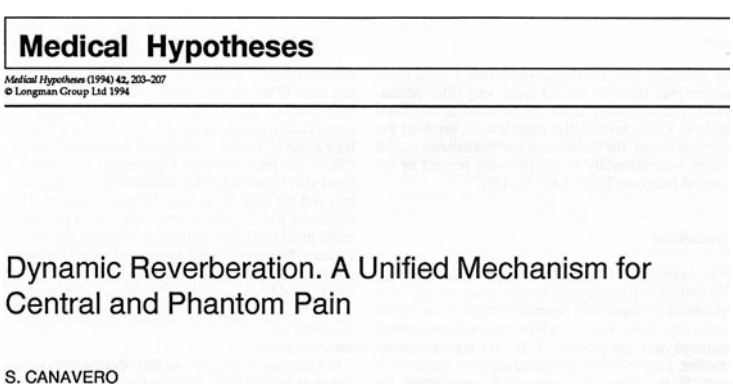
The most frequent cause of CP appeared to be vascular at all levels, except the brainstem, where tumors, tuberculomas, multiple sclerosis, syringobulbia, and hematobulbia contributed. Epileptic pains were also considered CP.

Unfortunately, over the years, despite ample evidence that other lesions can cause CP as well, the term *thalamic syndrome* became synonymous with CP, despite it being clear to many that it was not so.

In 1969 Cassinari and Pagni, in their monograph *Central Pain: a Neurosurgical Survey*, wrote:

> The conclusions of the various workers who have tried . . . to identify the structure in which lesions are responsible for the onset of central pain sometimes conflict. The divergence of opinion is fairly easily explained by the fact that spontaneous lesions are usually extensive, difficult to define, often plurifocal, and affect several systems with different functions.

By studying iatrogenic "pure" lesions (which they equated to "*experimental lesions*") giving rise to CP, they reached the conclusion that the essential lesion was damage to the pain-conveying spinothalamoparietal tract. Also, they observed how operations that interrupt the central pain pathways in order to allay pain may themselves lead to CP (sometimes more severe than the pain that led to the operation), an occurrence practically impossible to foresee. However, the genesis of CP remained an enigma. Thereafter, the subject received little additional attention (the "*hidden disorder*": Schott 1996), with most physicians in practice having little appreciation of the subject. In 1994, Canavero put forth the *dynamic reverberation* theory of central pain (Fig. 1.3), which, as this book will show, is the only one that can explain the genesis of this syndrome and provide what biomedical theories should strive for: a definitive cure.


Medical Hypotheses

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Dynamic Reverberation. A Unified Mechanism for Central and Phantom Pain

S. CANAVERO

Figure 1.3. Title page of Canavero's 1994 paper introducing the dynamic reverberation theory of central pain. Reproduced with permission from Elsevier.

Section 2 Clinical features and diagnosis

Per me si va nella città dolente,
Per me si va nell'eterno dolore,
Per me si va tra la perduta gente.

[Through me you pass into the city of woe,
Through me you pass into eternal pain,
Through me among the people lost for aye]

Written above Hell's Gate
Dante Alighieri, Inferno*, Canto III, 1–3*
(early fourteenth century)