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Review

Cutaneous silent periods – Part 2: Update on pathophysiology and clinical utility

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HIGHLIGHTS

- Review of pathophysiology and clinical utility of cutaneous silent periods (CSPs).
- CSP testing may aid in the evaluation of small-diameter fibers.
- Most useful in intramedullary spinal cord dysfunctions and small fiber neuropathies.

ABSTRACT

Testing of exteroceptive electromyographic modulation of ongoing voluntary muscle activity is of increasing interest as a diagnostic tool in clinical neurophysiology. The cutaneous silent period (CSP) is a robust and reproducible nociceptive EMG suppression, mediated at the spinal level by small-diameter A-delta afferents. The techniques and physiological principles of CSP testing, which are a fundamental prerequisite for a valid and thoughtful clinical application, are reviewed separately in part 1 (Kofler et al., 2019). This comprehensive review surveys the literature on pathophysiological conditions in which CSPs have been reported, and aims at a critical overview on the clinical utility of CSP testing. The most useful clinical applications seem to be the functional diagnostics of intramedullary, in particular centromedullary, dysfunctions, and the assessment of small fiber neuropathies, in particular those affecting A-delta fibers. CSPs have in addition been studied in a variety of movement disorders and in neuropathic pain and other painful conditions, including fibromyalgia.

Contents

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1. Introduction

Electrical stimulation of peripheral nerves is commonly used as a routine electrodiagnostic technique for the assessment of nerve conduction and elicitation of reflex responses. A special kind of reflex responses are short- and long-latency reflexes, which may have both excitatory and inhibitory components. A particularly strong inhibition of EMG activity is caused by noxious electrical stimuli to cutaneous fibers at the fingers, eliciting the cutaneous silent period (CSP). Physiological aspects of the CSP have been discussed in detail in part 1 (Kofler et al., 2019), while this part 2 deals with its pathophysiological mechanisms and clinical utility. Clinical interest in the CSP stems from its potential usefulness for evaluating segments and components of sensory nerves that are not well assessed by standard electrodiagnostic methods. This pertains mainly to thinly myelinated, slowly conducting, small-diameter A-delta fibers, and their spinal oligosegmental neuronal interconnections with efferent motor pathways. Currently, the most useful clinical applications seem to be the functional diagnostics of intramedullary, in particular centromedullary, dysfunctions, and the assessment of small fiber neuropathies, in particular those affecting A-delta fibers. In selected patients, CSPs may serve to document residual nerve continuity across lesion sites, when routine techniques fail. Table 1 lists publications on CSPs in various pathological conditions, detailing the number of patients and control subjects, as well as stimulus location and muscles recorded from, if reported. These publications were consecutively collected over the last 25 years by one of the authors (MK), with the addition of those found after database search (Medline, Web of Science) and screening abstract books on the topic, published after conferences and meetings. Publications were included if the authors used the CSP in their study in humans. Experimental studies in animals were only included if they were judged relevant for understanding findings in humans.

2. Pathophysiology of cutaneous silent periods

2.1. Peripheral nervous system

2.1.1. CSPs in polyneuropathy

Around the last decade of the last century, several authors described a variety of CSP findings in various forms of polyneuropathies: In small case series up to three patients, CSPs were reportedly normal in *Friedreich's ataxia* (Uncini et al., 1991), *idiopathic sensory neuronopathy* (Uncini et al., 1991; Leis et al., 1992), and *abetalipoproteinemia* (Sandbrink et al., 1999). Serrao et al. (2001) later confirmed normal CSPs in *Friedreich's ataxia*, but noted a higher threshold to induce EMG suppression by activation of preserved A-delta fibers. Absent CSPs were reported in *carcinomatous neuropathy* and in *alcoholic polyneuropathy* (Inghilleri et al., 1995), while one patient with *hereditary sensory and autonomic neuropathy* was found to have absent CSPs when stimulating one finger, and delayed, short-duration CSPs when stimulating two fingers simultaneously (Corsi et al., 2002). CSPs were reportedly delayed in patients with *large fiber neuropathy*, presumably detecting unsuspected small-diameter fiber involvement (Leis, 1994; Francia et al., 1999).

Since the beginning of the current century, larger case series and comparative studies were published, again with varying results. CSPs were either normal, shortened and/or incomplete in the lower limbs, while they were entirely normal in the upper limbs in *Fabry disease* (Syed et al., 2000). Delayed CSPs were reported in *HIV-associated polyneuropathy* (Osio et al., 2004).

Studies in patients with *diabetic polyneuropathy* revealed delayed and shortened lower limb CSPs (Onal et al., 2010; Koytak et al., 2011; Yücel et al., 2015; Khuraibet et al., 2015; Kamel et al., 2015), while concomitantly recorded upper limb CSPs were either within normal limits (Onal et al., 2010; Koytak et al., 2011; Kamel et al., 2015) or delayed with normal duration (Yücel et al., 2015). Two studies investigating only upper limbs reported delayed CSPs, being in one study also shortened (22/35) or absent (2/35) in patients with clinical symptoms of small fiber neuropathy (Yaman et al., 2007b), while in the other study CSP duration did not differ significantly among asymptomatic patients and those with large- or small fiber neuropathy (Kim et al., 2010).

In *uremic polyneuropathy*, upper limb CSPs were delayed and shortened (Kayacan et al., 2011; Denišlič et al., 2015), being reportedly also shortened but not delayed in the lower limbs (Kayacan et al., 2011).

Morkavuk and Leventoglu (2014) reported short-duration CSPs, which were also delayed in upper but not in lower limbs, in *hyperlipidemic small fiber neuropathy* and described a negative correlation of lower limb CSP duration with LDL and total cholesterol levels.

Szmulewicz et al. (2015) found abnormal CSPs in at least 1 upper or lower limb in 7/14 patients with *cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome* (CANVAS), indicating involvement of small-diameter fibers in addition to electrodiagnostic evidence of large-diameter fiber sensory neuronopathy.

Other reports of CSP abnormalities in polyneuropathies published only in abstract form indicated: delayed CSPs in both upper and lower extremities in *psoriasis vulgaris* (Ipekdal et al., 2014); delayed and shortened CSPs in both upper and lower limbs in *systemic lupus erythematosus* (Pamuk et al., 2014); long-duration CSPs in upper and short-duration CSPs in lower limbs, both with normal onset latencies, in *chronic pain and/or dysesthesia due to chemotherapy* (Isak et al., 2017); and increased onset latencies and durations of both CMRs and CSPs in upper limbs in *familial dysautonomia* (Gutierrez et al., 2015).

The largest study so far related to CSPs in polyneuropathy was published by Lopergolo et al. (2015), who reported delayed CSPs in *chronic inflammatory demyelinating polyneuropathy (CIDP)* (n = 84), and shortened CSPs in *axonal polyneuropathy*, which was either due to *diabetes mellitus* (n = 137) or *chronic idiopathic axonal polyneuropathy* (n = 41). No patient with demyelinating neuropathy had an absent CSP, while 26 patients with axonal neuropathy had no measurable CSP. Lopergolo et al. (2015) were the first in a clinical context to emphasize the importance of extracting from CSP onset latency both afferent conduction time in A-delta fibers and efferent conduction time in alpha-motoneurons, in order to

Table 1
List of 67 original and 18 "abstract only" publications on CSPs in various diseases.

	N (+controls)	Diagnosis	Combination
Weinberg et al., 1988	1	Astrocytoma C3-C6	D2-APB, Median-APB
Uncini et al., 1991	2 + 1 (+8)	Friedreich's ataxia + idiopathic ataxic neuropathy	D2-OP
Leis et al., 1992	1 (+5)	Pure sensory neuronopathy	D2-APB, D5-APB
Nakashima and Takahashi, 1992	14 (+8)	Idiopathic Parkinson's disease	D2-APB, Median-APB
Leis, 1994	2 (+5)	Pure sensory neuronopathy	D2-APB, D5-APB
Inghilleri et al., 1995	3 + 2	Carcinomatous polyneuropathy + alcoholic pure sensory neuropathy	(D4 + D5)-FDI
Pullman et al., 1996	11 + 7 (+16)	Dystonia + idiopathic Parkinson's disease	D2-APB
Scruggs and Wertsch, 1996 [abstract]	3	Unspecified ulnar nerve lesion	D5-APB
Kaneko et al., 1997	5 (+15)	Syringomyelia	D2-APB
Aurora et al., 1998	19 (+20)	Carpal tunnel syndrome	D2-APB, D5-APB
Kaneko et al., 1998	4 + 4 (+6)	Syringomyelia + thoracic myelopathy	D2-APB
Francia et al., 1999	2	Paresthetic-dysesthetic burning polyneuropathy	No data
Logigian et al., 1999	5 (+5)	Spinal cord injury	Sural-SOL-
Sandbrink et al., 1999 [abstract]	3 + 1 (+12)	Abetalipoproteinemia + hypobetalipoproteinemia	D5-APB
Syed et al., 2000	24 (+12)	M. Fabry	D5-APB, Sural-TA
Štětkářová et al., 2001	4 (+9)	Syringomyelia	D2-APB
Serrao et al., 2001	4	Friedreich's ataxia	D2-APB
Serrao et al., 2002	14 + 13	Idiopathic Parkinson's disease + atypical parkinsonism	D2-APB
Corsi et al., 2002	1 (+5)	Hereditary sensory and autonomic neuropathy	D2-APB, (D2 + D3)-APB, (D2 + D5)-APB, (D4 + D5)-APB
Štětkářová and Chrobok, 2002	10	Syringomyelia	No data available
Kofler et al., 2003b	9	Intramedullary spinal cord lesion	D2-APB, D5-APB
Kofler et al., 2003a	2 + 2 (+20)	Carpal tunnel syndrome + ulnar nerve entrapment at elbow	D2-FDI, D2-APB, D5-APB
Osio et al., 2004	26 (+12)	Human immunodeficiency virus-associated neuropathy	(D4 + D5)-FDI
Tataroglu et al., 2005	21 (+27)	Meralgia paresthetica	lfc-VM
Svilpauskaite et al., 2006	40 (+40)	Carpal tunnel syndrome	D2-APB, D5-APB, D2-ADM, D5-ADM, Radial-EDC
Espay et al., 2006	10 + 8 (+12)	Definite dystonia + psychogenic dystonia	D2-APB
Yaman et al., 2007b	35 (+29)	Diabetes mellitus (22 with clinical signs of small fiber neuropathy)	D2-APB
Han et al., 2007	157 (+60)	Restless legs syndrome	D1-EDB
Lo et al., 2007a	26 (+30)	Cervical myelopathy	D2-APB, D5-APB, D2-ADM, D5-ADM
Lo et al., 2007b	20 (+30)	Chronic whiplash syndrome	D2-APB, D5-APB, D2-ADM, D5-ADM
Yaman et al., 2007a	58 (+19)	Carpal tunnel syndrome (56 hands w/NCS findings, 45 hands w/o NCS findings)	D2-APB, D5-APB
Nascimbene et al., 2007 [abstract]	8	neuropathic sensory symptoms but normal sensory and motor conduction	Sural-SOL
Gilio et al., 2008	13 + 21 (+25)	Stroke + amyotrophic lateral sclerosis	(D2 + D3)-ADM
Roser et al., 2008	37 (+28)	Syringomyelia	D2-APB
Sollberger and Fuhr, 2008	1 (+1)	Syringomyelia	D2-APB
Jung et al., 2008 [abstract]	10	Stroke	D2-APB
Lee et al., 2008 [abstract]		Diabetes mellitus with putative neuropathy	No data
Truini et al., 2009a	40	Polyneuropathy (19 with neuropathic pain)	D5-ADM
Štětkářová and Kofler, 2009	21	Compressive cervical spondylotic myelopathy	D2-APB
Truini et al., 2009b	70	Carpal tunnel syndrome (117 hands, 76 with, 41 without neuropathic pain)	D3-ADM, D5-ADM
Onal et al., 2010	43 (+41)	Diabetes mellitus, with [n = 23] and without [n = 20] neuropathic pain	D2-APB, Sural-TA
Koo et al., 2010	135 (+30)	Carpal tunnel syndrome (135 hands)	D2-APB
Kim et al., 2010	110 (+30)	Diabetes mellitus (LFN [n = 34], SFN [n = 36], asymptomatic [n = 40])	D2-APB
Kim and Kwak, 2010 [abstract]	5 (+13)	Amyotrophic lateral sclerosis	?-APB
Isak et al., 2011	24 (+31)	Primary restless legs syndrome	D2-APB, Sural-TA
Leis et al., 2011	23	Radiculopathy C6/C7/C8	D1-APB, D3-APB, D5-APB
Koytak et al., 2011	31 (+30)	Diabetes mellitus and small fiber neuropathy	D2-APB, Sural-TA
Sahin et al., 2011	28 (+18)	Fibromyalgia	D5-APB
Kayacan et al., 2011	20 (+20)	Hemodialysis patients (8: small fiber neuropathy)	D3-APB, Sural-TA
Öz et al., 2011 [abstract]	18 (+15)	Obstructive sleep apnoea	?-APB
Öz et al., 2012	25 (+25)	Restless legs syndrome	D2-APB, Sural-TA
Isoardo et al., 2012	13 + 9 + 28 (+52)	post-burn pathologic scars with pain + without pain + carpal tunnel syndrome	D2-APB
Štětkářová and Kofler, 2013	10	Spinal cord injury (chronic, spasticity)	D2-APB
Souayah et al., 2013	1	Stroke	D2-APB, D5-ADM, Median-APB, Ulnar-ADM
Umay et al., 2013	32 (+32)	Fibromyalgia	D2-APB, Sural-TA
Baklaci, 2013 [abstract]	48 (+40)	Fibromyalgia	D3-APB, Sural-TA
Tekatas et al., 2014	36	Idiopathic pruritus	D2-APB, Sural-TA
Tirić-Čampara et al., 2014a	1 (+61)	Carpal tunnel syndrome	D2-APB
Morkavuk and Leventoglu, 2014	48 (+23)	Hyperlipidemia	D2-APB, Sural-TA
Boček et al., 2014 [abstract]	6 (+9)	Idiopathic scoliosis	D2-APB
Akgün et al., 2014 [abstract]	20 (+20)	Essential tremor	"Upper and lower extremities"
Ipekdal et al., 2014 [abstract]	15 (+15)	Psoriasis	"Upper and lower extremities"

Table 1 (*continued*)

	N (+controls)	Diagnosis	Combination
Ipekdal and Karadas, 2014 [abstract]	17 (+15)	Essential tremor	D2-APB
Pamuk et al., 2014 [abstract]	51 (+46)	Systemic lupus erythematosus	"Upper and lower extremities"
Ustun et al., 2014 [abstract]	30 (+30)	Fibromyalgia	?-APB, ?-TA
Štětkářová et al., 2015	15 (+16)	Multiple system atrophy	D2-APB
Yücel et al., 2015	17 (+23)	Diabetes mellitus	D2-APB, Sural-TA
Tekatas and Pamuk, 2015	133	Ankylosing spondylitis with or without restless legs syndrome	D2-APB, Sural-TA
Szmulewicz et al., 2015	14	Cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome (CANVAS)	"Upper and lower limbs bilaterally"
Kamel et al., 2015	26 (+26)	Glycemic dysregulation and suspected painful small fiber neuropathy	D2-APB, Sural-TA
Lopergolo et al., 2015	262 (+265)	Polyneuropathy, 84: demyelinating, 178: axonal	(D2 + D3)-ADM
Vasko et al., 2015	19	Brachial plexus lesion	D1-APB, D3-APB, D5-APB
Denišlič et al., 2015	38 (+38)	Hemodialysis	D2-APB
Sonkaya et al., 2016	30	Essential tremor	D2-APB
Gutierrez et al., 2015 [abstract]	20 (+24)	Familial dysautonomia	D5-FDI
Khuraibet et al., 2015 [abstract]	20 (+47)	Diabetes mellitus	Sural-TA
Baek et al., 2016	24 (+24)	Fibromyalgia	D2-APB
Cogez et al., 2016	2	Symptomatic paroxysmal kinesigenic dyskinesia	D2-APB, Median-APB
Duarte et al., 2016	47	Carpal tunnel syndrome (69 hands)	D2-OP
Boček et al., 2016b	16	Dystonia ON and OFF deep brain stimulation	D2-APB
Vasko et al., 2016	23	Brachial plexus lesion	D1-APB, D3-APB, D5-APB
Boček et al., 2016a [abstract]	1	Stiff person syndrome	No data
Congiu et al., 2017	15 (+17)	Restless legs syndrome	D2-APB, Sural-TA
Isak et al., 2017 [abstract]	30 (+27)	Chronic pain and/or dysesthesia due to chemotherapy	D2-APB, Sural-TA
Kilinc et al., 2018	29 (+30)	Myofascial pain syndrome	D2-APB, Sural-TA

ADM = abductor digiti minimi.
APB = abductor pollicis brevis.
EDB = extensor digitorum brevis.
EDC = extensor digitorum communis.
FDI = first dorsal interosseous.
OP = opponens pollicis.
SOL = soleus.
TA = tibialis anterior.
VM = vastus medialis.
D1 = digit I.
D2 = digit II.
D3 = digit III.
D4 = digit IV.
D5 = digit V.
lfc = lateral femoral cutaneous nerve.
NCS = nerve conduction study.
LFN = large fiber neuropathy.
SFN = small fiber neuropathy.

assess the contribution of small-diameter afferents to an eventual delay in CSP onset. They were also the first to document evidence of demyelination in small-diameter fibers of CIDP patients, as up to then only axonal damage to small-diameter fibers had been reported in the literature. It has to be pointed out, though, that Lopergolo et al. (2015) used simultaneous stimulation of D2 + D3, and differing levels of voluntary contraction in patients and healthy controls.

The seemingly varying results in different studies can actually be clustered as follows:

- In *axonal polyneuropathies only affecting large-diameter fibers* (Fig. 1, broken thick blue line), e.g. pure sensory neuronopathy or Friedreich's ataxia, both CSP onset and CSP duration are normal, even in the complete absence of large-diameter afferents (Uncini et al., 1991; Leis et al., 1992; Leis, 1994). The same is true in combined sensorimotor neuropathies, as long as motor nerve conduction velocity is normal (Sandbrink et al., 1999; Serrao et al., 2001; Truini et al., 2009a). If, however, motor nerve conduction velocity is reduced (Fig. 1, solid thick green line), e.g. due to loss of the fastest thick-myelinated fibers, then obviously CSP onset is delayed, even if small-diameter fiber function is entirely normal.
- In *mixed polyneuropathies predominantly affecting large-diameter fibers* (Fig. 1, broken thick blue line and solid thick green line), CSP onset may be delayed, as soon as motor nerve conduction velocity is slowed (Fig. 1, solid thick green line). This may have been a predominant factor in diabetic patients with vs. those without signs of small-diameter fiber polyneuropathy, who presented with similarly delayed CSP onset latencies, which correlated with prolonged distal motor latencies and slowed motor nerve conduction (Yaman et al., 2007b; Kim et al., 2010).
- In *axonal polyneuropathies purely or predominantly affecting small-diameter fibers* (Fig. 1, solid thin red line), CSP onset is of normal latency as long as CSPs are present at all (Syed et al., 2000; Truini et al., 2009a). With decreasing number of A-delta axons, CSPs progressively become shortened, incomplete, and eventually absent, irrespective of presence and function of large-diameter fibers (Syed et al., 2000). Similar findings were observed in mixed axonal polyneuropathies with few remaining small-diameter fibers (Inghilleri et al., 1995; Corsi et al., 2002; Yaman et al., 2007b; Onal et al., 2010; Koytak et al., 2011; Lopergolo et al., 2015). In polyneuropathies with severe small-diameter fibers involvement, spatial summation by simultaneously stimulating more than one finger may serve to elicit otherwise unobtainable CSPs (Corsi et al., 2002).

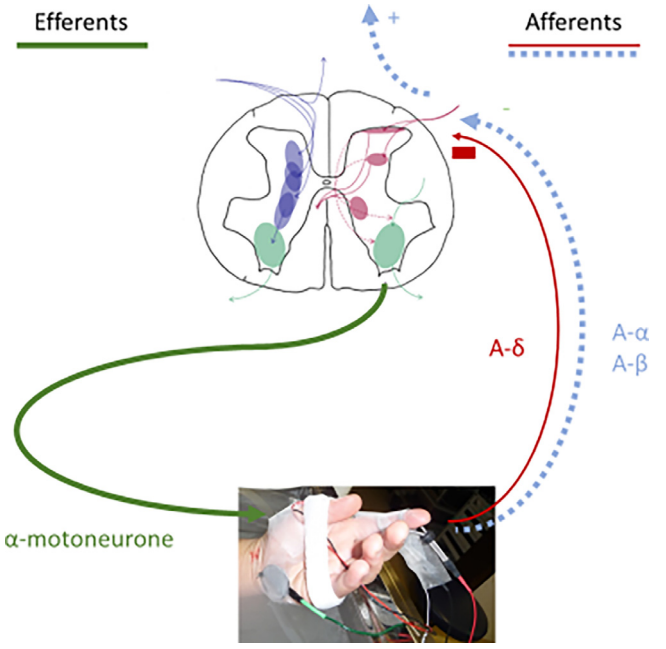

Fig. 1. Schematic illustration of fiber types involved in cutaneous silent period generation, and their spinal circuitry: electrical fingertip stimulation will activate low-threshold thick-myelinated A-alpha and A-beta fibers (dotted thick blue line), and with increasing intensity in addition also high-threshold thin-myelinated A-delta fibers (solid thin red line). Dorsal horn layers in which A-delta fibers end (laminae I and V), and those from where crossing spinothalamic afferents originate (laminae I, V, VII, and VIII), are depicted in red. Putative nerve fibers connecting dorsal horn cells (A-delta endings) with anterior horn cells (corticospinal or alpha-motoneurons) pass close to the central canal (broken thin red lines). Dorsal horn layers in which A-alpha and A-beta fibers end (laminae III to VII and IX) to form mono- and polysynaptic connections with alpha-motoneurons (and hence also the N13 component of median nerve somatosensory evoked potentials) are depicted in blue (shown only on the contralateral side for easier differentiation). Alpha motoneurons and their descending connections from the corticospinal tract are shown in green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In diabetic patients with clinical evidence of small fiber neuropathy, several groups reported normal CSP onset latencies in upper limbs, and delayed and shortened CSPs in lower limbs (Onal et al., 2010; Koytak et al., 2011; Yücel et al., 2015). None of these patients had evidence of motor nerve conduction abnormalities, thus their CSP delay was in fact only due to small-diameter fiber dysfunction.

Kamel et al. (2015) compared CSPs in upper and lower limbs with quantitative sudomotor axon reflex testing, sympathetic skin responses, and autonomic function testing in 26 patients with clinical evidence of small fiber neuropathy due to diabetes mellitus type 1 or type 2, or pre-diabetes based on abnormal oral glucose tolerance testing. CSP abnormalities (delayed onset and shortened duration) did not correlate with results of the other tests. When combining all tests, 81% of patients were identified to have evidence of small fiber neuropathy in the absence of large-diameter fiber involvement (Kamel et al., 2015).

Histopathological evidence of a reduced number of axons in skin biopsies supports the existence and nature of axonal degeneration in small fiber neuropathies (England et al., 2009; Lauria et al., 2010). Only two studies are available comparing CSP latencies with intra-epidermal nerve fiber density, one in patients with type 2 diabetes mellitus, showing no correlation (Lee et al., 2008), the other one in patients with neuropathic sensory symptoms and normal sensory and motor conduction studies, which found a correlation (Nascimbene et al., 2007). CSP duration was associated with cold detection threshold abnormalities in patients with Fabry disease (Syed et al., 2000) and in patients with pathological postburn scars (Isoardo et al., 2012), when damage to A-delta fibers was moderate to severe.

- In *demyelinating large-diameter fiber polyneuropathies*, CSP onset is delayed as soon as motor nerve conduction velocity is slowed (Fig. 1, solid thick green line). CSP duration remains normal though (Lopergolo et al., 2015). Notably, such a delay in CSP onset latency could occur even when small-diameter nerve fiber function is entirely normal.
- Finally, *demyelinating small-diameter fiber polyneuropathy* (Fig. 1, solid thin red line) is characterized by delayed CSP onset and normal CSP duration (Lopergolo et al., 2015), irrespective of large-diameter fiber affection. Notably, CSP onset needs to be delayed either in the complete absence of slowed motor nerve conduction, or the delay must exceed that explained by slowed motor nerve conduction, in order to be unequivocally attributed to abnormal conduction in small-diameter nerves only (Lopergolo et al., 2015).

In summary, delayed CSP onset latencies may be explained by several mechanisms, which need to be considered: (1) decreased conduction velocity of A-delta fibers in demyelinating small fiber neuropathies (Lopergolo et al., 2015) or low limb temperature (Kofler et al., 2014); (2) partial loss of conduction with axonal degeneration of faster and preservation of slower A-delta fibers, similar to axonal large-diameter fiber polyneuropathies (Svilpauskaite et al., 2006); (3) longer time needed to reach the relevant threshold for inhibiting motoneurons at the spinal level in case of only few preserved small-diameter fibers (Koytak et al., 2011; Corsi et al., 2002; Tirić-Čampara et al., 2014b; Lopergolo et al., 2015); (4) and slowed motor nerve conduction in alpha-motoneurons, irrespective of axonal or demyelinating pathology in small-diameter fibers. The latter needs to be taken into account when interpreting delays of CSP onset latencies, in order not to attribute them erroneously to small-diameter fiber dysfunction.

In contrast, shortened CSP duration may depend on involvement of small-diameter fibers. The mere presence of a CSP depends on the presence and intact function of A-delta afferents. CSP duration, hence also CSP end latency, depend on the function and number of A-delta afferents, and not on the function of large-diameter fiber afferents or efferents.

2.1.2. CSPs in entrapment neuropathies

CSPs have been investigated in various forms of entrapment syndromes, yielding partially contradictory results. The principal pathophysiological mechanism of entrapment neuropathies is focal demyelination of larger-diameter fibers, which produces weakness and numbness. Furthermore, nerve ischemia seems to be the main cause of paresthesias and pain (Fullerton, 1963; Werner and Andary, 2002). Both mechanisms may occur to a variable degree in different individuals.

In *carpal tunnel syndrome*, CSPs onset latencies in hand muscles following index finger (D2) stimulation are often normal (Aurora et al., 1998; Svilpauskaite et al., 2006; Yaman et al., 2007a; Duarte et al., 2016), or only slightly delayed (Koo et al., 2010), and CSP duration either within normal limits (Yaman et al., 2007a; Koo et al., 2010), or slightly prolonged (Aurora et al., 1998; Svilpauskaite et al., 2006), suggesting that small-diameter fiber dysfunction occurs late in the course of compressive neuropathy (Aurora et al., 1998; Leis and Kofler, 2014). In a study of 28 patients with carpal tunnel syndrome (bilateral in 16 patients, unilateral in 12, comprising a total of 44 hands, graded as minimal in 4, mild in 5, moderate in 27, severe in 5, and extreme in 3 hands), thenar CSPs were significantly prolonged in the group as a whole (Isoardo et al., 2012).

With increasing severity, CSP latencies progressively increased in thenar muscles following D2 stimulation (Svilpauskaite et al., 2006; Yaman et al., 2007a; Koo et al., 2010; Tirić-Čampara et al., 2014a; Duarte et al., 2016). In the study by Yaman et al. (2007a) a highly significant correlation of CSP onset latency with median distal motor latency suggests that the delay in CSP onset was merely due to impaired conduction in alpha motoneurons. An alternative mechanism put forward by Koo et al. (2010) is partial loss of conduction of faster and relative preservation of slower A-delta fibers, as thicker myelinated fibers are more prone to injury in compressive neuropathies. CSP duration either remained within normal limits (Koo et al., 2010), or grew significantly longer (Svilpauskaite et al., 2006). In very severe forms of carpal tunnel syndrome, CSP latencies returned to normal values (Koo et al., 2010), while CSP duration declined to normal values or below (Svilpauskaite et al., 2006; Yaman et al., 2007a; Tirić-Čampara et al., 2014a), or eventually to complete absence (Aurora et al., 1998; Svilpauskaite et al., 2006; Yaman et al., 2007a; Duarte et al., 2016).

Prolongation of CSP duration in mild to moderate entrapment syndromes was explained by a sort of gating mechanism due to a decreased input from large demyelinated fibers, thereby increasing the relative input of A-delta fibers on spinal interneurons (Aurora et al., 1998). Contributory mechanisms are reduced force exerted against resistance due to impaired perception and partial loss of efferent fibers caused by axonotmesis or conduction block (Svilpauskaite et al., 2006). In contrast, shortening of CSP duration in severe entrapment syndromes may be due to loss of A-delta fibers as a consequence of repeated ischemia due to severe and long-lasting compression.

CSPs in hand muscles did not differ between patients with or without pain (Yaman et al., 2007a; Truini et al., 2009b), concurring with preserved protective reflexes even in chronic pain conditions.

A different approach was used in four patients with very severe entrapment of the median nerve at the wrist, or *ulnar neuropathy at the elbow* (Kofler et al., 2003a), as well as in patients with unspecified ulnar neuropathy (Scruggs and Wertsch, 1996): in cases of median nerve entrapment, ulnar nerve-supplied muscles were used for recording CSPs following stimulation to median-nerve supplied digits (Kofler et al., 2003a), and conversely, in cases of ulnar nerve lesions, median nerve-supplied muscles were used for recording CSPs following stimulation to ulnar nerve-supplied digits (Kofler et al., 2003a; Scruggs and Wertsch, 1996), in order to document residual nerve continuity across the lesion site.

Root compression may also be regarded as a form of entrapment syndrome. Like in other forms of compressive neuropathies in the distal periphery, small-diameter A-delta fibers tend to be preserved to a large degree also in root lesions (Leis et al., 2011). This feature is in contrast to the high sensitivity of CSPs in (centro-) medullary lesions (Kofler et al., 2003b; Lo et al., 2007a; Štětkářová and Kofler, 2009; Roser et al., 2008), which makes them valuable in the differential diagnosis of radiculopathy versus myelopathy (Leis et al., 2011).

CSPs may also serve to differentiate severe radiculopathy from complete *root avulsion*, as in the latter case CSPs are absent from the respective dermatomal level (Leis, 2000; Leis and Kofler, 2014). The usefulness of CSP testing in traumatic plexus lesions has recently been challenged by Vasko et al. (2015, 2016), who reported preserved thenar CSPs following D1, D3, and D5 fingertip stimulation even in some patients with completely avulsed C6 to C8 roots based on CT myelography, a finding which is difficult to interpret, even acknowledging a wide variation of overlapping dermatomes (Rainville et al., 2016).

Only one study has been published to date about CSPs in an entrapment syndrome of the lower extremities: Tataroglu et al. (2005) reported delayed, shortened, and incomplete CSPs in vastus medialis following stimulation to the lateral femoral cutaneous nerve in *meralgia paresthetica*.

2.2. Central nervous system

2.2.1. CSPs in centromedullary spinal cord lesions

To our knowledge, the first paper on CSPs in a spinal lesion was published in 1988 (Weinberg et al., 1988), reporting a patient with *cervical astrocytoma*, who had abnormal silent periods, which was interpreted to be due to loss of spinal inhibitory interneuronal input. Later, CSPs have been studied in a variety of intramedullary spinal cord affections (for putative circuitry see Fig. 1). The prototypic pathology is *syringomyelia*, which may abolish CSPs unilaterally on the side of an asymmetric syrinx, while leaving the contralateral CSP entirely unaffected (Kaneko et al., 1997; Štětkářová et al., 2001, 2002; Floeter, 2003; Roser et al., 2008), even despite normal upper and lower limb SEPs and MEPs (Štětkářová et al., 2001; Roser et al., 2008). Kaneko et al. (1998) showed that also nociceptive MEP modulation was absent on the side of a cervical syrinx while remaining unaffected in patients with thoracic myelopathy. Štětkářová et al. (2001) could demonstrate that the mixed nerve silent period (MNSP) showed the same pattern of absence on one affected side with preservation on the other non-affected side as did the CSP. *Cervical myelopathies* of various other etiologies showed various degrees of abnormal CSPs with or without accompanying abnormalities in SEPs and/or MEPs, in contrast to a patient with widespread thoracic myelopathy who had entirely normal upper limb CSPs (Kofler et al., 2003b). Abnormal CSPs following D2 or D5 stimulation were also reported with intramedullary lesions affecting more rostral lesions within the cervical spinal cord, even up to C1-C2 (Singer et al., 2002; Lo et al., 2007b). *Compressive cervical spondylotic myelopathy* has been reported to be associated with a remarkably high percentage of CSP abnormalities, comprising of either delay, shortening or absence (Lo et al., 2007a; Štětkářová and Kofler, 2009). Štětkářová and Kofler (2009) reported CSP onset latencies in upper limbs being positively correlated with central motor conduction time to abductor digiti minimi, and CSP duration being inversely correlated with central motor conduction time to tibialis anterior muscle, concurring with a facilitatory influence of corticospinal neurons on CSPs (Gilio et al., 2008). At any rate, CSP abnormalities were associated with a remarkably high sensitivity for intramedullary spinal cord pathologies, irrespective of etiology, particularly when affecting spinothalamic pathways (Kofler et al., 2003b; Lo et al., 2007a; Roser et al., 2008; Štětkářová and Kofler, 2009). CSP abnormalities in abductor pollicis brevis and abductor digiti minimi following either D2 or D5 stimulation were significantly correlated to a clinical grading scale of severity of *whiplash syndrome* – unlike to a grading scale based on magnetic resonance imaging findings – supporting the validity of CSPs as an adjunctive evaluation parameter to clinical grading (Lo et al., 2007b).

Few other anecdotal observations on spinal pathologies have been published so far, e.g. a patient with a history of drug dependence, who three years after a complete spinal cord injury developed a purely pain-sensitive segmental myoclonus of the right arm, occurring at random and evolving over time to a more dystonic movement disorder. Due to the intermittent nature of the jerks and fluctuating sensory symptoms a psychogenic disorder or a relapse of drug-dependent behavior was first suspected. Median nerve SEPs were unremarkable, but CSPs in thenar muscles were delayed and attenuated; further diagnostic work-up revealed a posttraumatic cervico-thoracic syringomyelia. After syringoperitoneal drainage, pain and involuntary movements improved persistently (Sollberger and Fuhr, 2008). Another patient with stiff-limb syndrome presented with absent CSPs in the affected tibialis anterior muscle following sural nerve stimulation (Thaler

et al., 1998); yet another patient with slightly asymmetrical stiff-person syndrome had shortened CSPs in thenar bilaterally, predominantly on the more affected side (Boček et al., 2016a,b).

2.2.2. CSPs in corticospinal tract lesions

Gilio et al. (2008) reported delayed upper limb CSP onset in *stroke*. The authors suggested that polysynaptic circuits, which are activated by low-threshold afferents and influenced by supraspinal pathways, may normally facilitate inhibitory effects exerted by A-delta fibers on alpha motoneurons. Hence corticospinal tract dysfunction would alter this integrated mechanism and delay CSP onset by increasing synaptic time. Others reported longer CSP duration on the affected side (Jung et al., 2008), perhaps due to stroke-related reduced recruitment of motoneurons in the paretic limb.

A delayed CSP onset compared to healthy controls was also reported in *amyotrophic lateral sclerosis* (Gilio et al., 2008; Kim and Kwak, 2010). Recently, Truini et al. (2015) reported abnormal thermal-pain thresholds and reduced distal intraepidermal nerve fiber density in patients with spinal-onset *amyotrophic lateral sclerosis*, but not those with bulbar-onset, suggesting that sensory nervous system involvement including distal small-fiber neuropathy may differ according to disease onset. These findings would rather suggest CSP shortening, however, while Gilio et al. (2008) reported delayed CSPs of normal duration. Notably, Shefner and Logigian (1998), who studied MNSPs in amyotrophic lateral sclerosis, reported prolonged EMG suppression, however, being less complete in its middle phase. They interpreted the prolongation to be due to an abnormality of sensorimotor processing, and the incomplete inhibition possibly reflecting abnormalities in Renshaw cell function (Shefner and Logigian, 1998). It should be kept in mind, however, that experimental evidence suggests lack of Renshaw inhibition in distal extensor muscles of the cat (Illert and Wietelmann, 1989; Hörner et al., 1991).

Logigian et al. (1999) observed in patients with complete spinal cord injury a reduced H reflex suppression by conditioning noxious sural nerve stimulation at interstimulus intervals corresponding to the CSP, which they attributed to diminished suprasegmental influence on spinal inhibitory circuitry.

Delayed CSPs have been observed in both mild and severe forms of *cervical compressive myelopathy* (Lo et al., 2007a; Štětkářová and Kofler, 2009) and in multiple system atrophy (Štětkářová et al., 2015), all possibly related to corticospinal tract dysfunction.

Uninterrupted fibrillations and positive sharp waves during the CSP time window in the paretic limb of a stroke patient suggested an origin of denervation activity distal to the upper motoneuron (Souayah et al., 2013).

2.2.3. CSPs in movement disorders

Patients with *idiopathic Parkinson's disease* have CSPs of normal onset latency in abductor pollicis brevis following D2 stimulation (Nakashima and Takahashi, 1992; Pullman et al., 1996; Serrao et al., 2002). Nakashima and Takahashi (1992) reported also normal duration, but less profound inhibition based on the index of suppression, whereas delayed CSP end latency (reported as prolonged CSP duration) was observed in two other studies, perhaps due to a higher stimulus intensity (Pullman et al., 1996; Serrao et al., 2002). This delay was more pronounced on the more affected side (Serrao et al., 2002). Delayed CSP end latency was normalized by levodopa in patients with idiopathic Parkinson's disease, but not those with *atypical parkinsonism*, comprising multiple system atrophy (n = 4), progressive supranuclear paralysis (n = 1), corticobasal ganglionic degeneration (n = 1), and vascular parkinsonism (n = 7) (Serrao et al., 2002). In this line, Štětkářová et al. (2015) reported delayed and prolonged CSPs in abductor pollicis brevis following D2 stimulation in multiple system atrophy, with no difference between patients who received levodopa (n = 9) and those who did not (n = 6). While prolonged CSP duration may be due to altered basal ganglia input to spinal circuitry via reticulospinal neurons, the delay in CSP onset may reflect corticospinal tract dysfunction, as often seen in these patients (Eusebio et al., 2007), or may derive from large-diameter efferent fiber polyneuropathy, an often under-recognized feature of multiple system atrophy (Gawel et al., 2012).

Patients with various forms of *focal dystonia* also showed delayed CSP end latencies (reported as prolonged CSP duration) in abductor pollicis brevis following D2 stimulation on the affected and the contralateral side (Pullman et al., 1996; Espay et al., 2006). Notably, both organic and *psychogenic dystonia* showed the same CSP alteration (among other similar findings), thus nourishing the discussion whether findings of abnormal cortical and spinal excitability in organic dystonia may, in part, be consequence rather than cause of dystonia, or whether these findings may represent endophenotypic abnormalities that predispose to both organic and psychogenic types of dystonia (Espay et al., 2006). CSPs remained constant over 1 year in two dystonia patients, before and during relief from a sensory trick in one patient, and before and after botulinum toxin treatment in the same patient (Pullman et al., 1996). In patients with *cervical* (n = 7) or *generalized* (n = 9) *dystonia,* treated with bilateral deep brain stimulation of the globus pallidus internus, Boček et al. (2016b) found a trend towards shorter CSP duration due to later CSP onset, which was not modified by switching the neurostimulator ON or OFF. This is particularly remarkable, not only because the finding contrasts with reports from other authors (Pullman et al., 1996; Espay et al., 2006), but also because medication in some of Boček et al.'s patients included, among other drugs, escitalopram and tramadol, known to lengthen CSP duration in healthy subjects (Pujia et al., 2012, 2014).

Cogez et al. (2016) reported slightly prolonged CSP duration in abductor pollicis brevis following D2 stimulation in two patients with symptomatic *paroxysmal kinesigenic dyskinesia*. One patient had a transverse myelitis at the C2-C6 segmental level, the other patient suffered from multiple sclerosis and had a lesion at the C6/C7 level.

To our knowledge, CSPs have not been studied so far in *Huntington's disease*. Shortened MNSPs (=shortened MNSP end latency), however, have indeed been reported (Sandyk, 1982; Sandyk et al., 1988; Eisen et al., 1989). Likewise, no CSP studies are available in spasticity, while MNSP abnormalities have been reported in the past (Dietrichson, 1971).

Abnormal sensorimotor integration is thought to play a role in the development of *idiopathic scoliosis*. CSPs as one form of sensorimotor integration, however, did not show significant interside differences in thenar recordings, even when pooled according to the concavity of the scoliotic curve (Boček et al., 2014).

In *restless legs syndrome*, disparate findings have been reported depending on stimulation and recording sites. In the lower limbs, CSPs had normal latencies but were prolonged in extensor digitorum brevis following big toe stimulation (Han et al., 2007), but were delayed and shortened in tibialis anterior following sural nerve stimulation (Öz et al., 2012; Isak et al., 2011). Yet another study reported normal CSP duration in tibialis anterior following sural nerve stimulation (Congiu et al., 2017). Dopaminergic treatment served to (partially) correct for the abnormal CSP duration (Han et al., 2007; Öz et al., 2012). Tekatas and Pamuk (2015) studied the prevalence of restless legs syndrome in patients with ankylosing spondylitis. CSP latencies were delayed and CSP durations shortened in both tibialis anterior following sural nerve stimulation and abductor pollicis brevis following D2 stimulation of 40 of these patients with associated restless legs symptoms as compared to 90 patients without. Isak et al. (2011) also reported

delayed upper limb CSPs, but with normal duration, in abductor pollicis brevis following D2 stimulation. According to the latter authors the ratio of CSP duration in upper versus lower limbs was significantly decreased, being abnormal in 91.7% of patients with restless legs syndrome, thus being proposed as a very sensitive parameter for this disease (Isak et al., 2011). They suggested that dysfunctional spinal interneurons (Renshaw cells, Ib-interneurons) mediating presynaptic inhibition of alpha-motoneurons are responsible for delayed and shortened CSPs in restless legs syndrome, and that this dysfunction may be a consequence of a dysfunctional supraspinal control exerted by abnormal diencephalic A11 dopaminergic projection (Isak et al., 2011). Two other studies reported entirely normal upper limb CSPs (Öz et al., 2012; Congiu et al., 2017). MNSP duration in abductor pollicis brevis following median nerve stimulation, and in tibialis anterior following common peroneal nerve stimulation, were also reportedly normal (Entezari-Taher et al., 1999).

In *essential tremor*, CSPs were reported to have normal onset and end latencies, but prolonged duration in abductor pollicis brevis following D2 stimulation, which was normalized by 4-weeks intake of propranolol (Sonkaya et al., 2016). In a similar study, normal CSP onset latency and prolonged CSP duration was attributed to either insufficient inhibition within the spinal inhibitory circuitry, cortical hypersensitivity, or abnormal cortical inhibitory mechanisms (Ipekdal and Karadas, 2014). In another study in essential tremor, CSPs had reportedly normal latencies and durations in the upper limbs, but were prolonged in the lower limbs (Akgün et al., 2014). In contrast, a study of MNSP in abductor pollicis brevis following median nerve stimulation revealed shortened exteroceptive EMG suppression (Shukla et al., 2002).

2.2.4. CSPs and pain

As CSPs represent nociceptive exteroceptive EMG suppression, they were expected to play an important role in clinical neurophysiological pain assessment. Therefore, they have been studied in neuropathic pain and other painful conditions, including fibromyalgia. Furthermore, they have been used as probes for the effect of pain-relieving treatments, including conditioning heterotopic painful stimuli.

Truini et al. (2009a) studied CSPs inpatients with polyneuropathies of various etiologies (chemotherapy-induced neuropathy [n = 16], diabetic neuropathy [n = 12], peripheral neuropathy of unknown origin [n = 8], and alcohol-induced neuropathy [n = 4], of whom 19 patients had *neuropathic pain*. Upper limb CSP onset latencies and durations did not differ between patients with and without pain, whereas amplitudes of cortical laser evoked potentials were lower in patients with pain than in those without. Unlike LEP amplitudes, CSP parameters did not correlate with pain intensity. The authors concluded that, despite being a spinal reflex response mediated by A-delta afferents, the CSP is not useful for assessing patients with neuropathic pain (Truini et al., 2009a). Somehow it makes sense, however, that CSPs remain intact in neuropathic pain conditions. The CSP is an acute nocifensive protective reflex, whereas neuropathic pain is a chronic disease. A patient suffering from chronic neuropathic pain may still have an acute protective reflex response on top of the chronic pain condition (Wallwork et al., 2017). In this line, CSP onset latency, CSP duration, and afferent conduction time did not differ between patients with and without neuropathic pain in axonal or demyelinating polyneuropathy (Lopergolo et al., 2015).

Similarly, neuropathic pain in diabetic small-diameter fiber polyneuropathy did not influence CSP latency and duration in upper limbs, and CSP duration in lower limbs compared to patients without pain (Onal et al., 2010), albeit lower limb CSP onset latency was found longer in patients with pain compared to those without pain (Onal et al., 2010) or to healthy controls (Kamel et al., 2015).

Neuropathic pain due to carpal tunnel syndrome did not affect CSPs either (Yaman et al., 2007a; Truini et al., 2009b). Yaman et al. (2007a) studied CSPs in abductor pollicis brevis following D2 and D5 stimulation in 58 patients with clinical symptoms suggestive of carpal tunnel syndrome, but neither CSP latencies nor duration differed between hands with and without pain. Truini et al. (2009b) studied 70 patients with a diagnosis of carpal tunnel syndrome. CSPs were obtained from abductor digiti minimi following D3 and D5 stimulation. Again, CSP duration did not differ between hands with and without neuropathic pain.

Similarly, in systemic lupus erythematosus, delayed CSP latencies and prolonged CSP duration in upper and lower extremities did not correlate with neuropathic pain scores (Pamuk et al., 2014).

Notably, Isoardo et al. (2012) studied patients with hypertrophic postburn pathologic scars. Upper limb CSP duration was significantly shorter in 17 hands with neuropathic pain, as compared to 22 hands without pain. CSP duration also correlated to cold detection threshold, both considered to reflect A-delta fiber function. These findings concur with histological evidence of small-diameter fiber loss in skin lesions after burns and with a prominent role of small-diameter fiber damage in the genesis of neuropathic pain in postburn scars (Isoardo et al., 2012).

CSPs in patients with chronic pain and/or dysesthesia due to chemotherapy were of normal latency in both upper and lower limbs. Notably, CSP duration was prolonged in upper and shortened in lower limbs, hence silent period ratio was lower in patients than controls (Isak et al., 2017).

Myofascial pain syndrome is characterized by an increased response to painful stimuli without spontaneous pain, suggesting a pathogenetic role of central sensitization. CSPs in abductor pollicis brevis following D2 stimulation, and in tibialis anterior following sural nerve stimulation, were significantly delayed and shortened within the 95% confidence interval compared to healthy subjects, concurring with a reduction in the activity of central inhibitory mechanisms (Kilinc et al., 2018).

Fibromyalgia syndrome is a clinically well-characterized disabling condition that includes chronic widespread pain, often accompanied by other symptoms suggestive of neuropathic pain. Studies have demonstrated that central nervous system hyperexcitability may play a fundamental role in the poorly understood pathogenesis, leading to abnormally increased temporal summation, alteration of the pain modulating system, abnormal somatosensory and event related potentials, reduced prepulse inhibition at the brainstem level, peripheral C-fiber sensitization, and spinal cord hypersensitivity (Gibson et al., 1994; Lorenz et al., 1996; Lautenbacher and Rollman, 1997; Banic et al., 2004; Staud et al., 2008; Kofler and Halder, 2014). Central hypersensitivity is associated with enhanced excitability of spinal dorsal horn neurons, receiving input from both large- and small-diameter primary afferents. Small-diameter fiber pathology seems to be a contributing factor to pain in a subset of patients with fibromyalgia, based on increased scores in neuropathic pain questionnaires, increased cold and warm detection thresholds in quantitative sensory testing, reduced amplitudes of pain-related evoked potentials, reduced total and regenerating intraepidermal nerve fibers in skin punch biopsies, and impaired autonomic function testing, all concurring with small-diameter fiber pathology (Üceyler et al., 2013; Oaklander et al., 2013). In contrast, routine electrodiagnostic studies assessing large-diameter fibers are usually normal in fibromyalgia (Sahin et al., 2011; Giannoccaro et al., 2014).

The first study addressing CSPs in fibromyalgia indeed described delayed upper limb CSPs, but normal CSP duration, which, however, the authors attributed to abnormal central processing in circuits of sensorimotor integration at spinal and supraspinal levels rather than to afferent or efferent conduction slowing (Sahin et al., 2011). Similarly, Umay et al. (2013) observed

significantly prolonged CSP latencies, but normal CSP duration, in both upper and lower extremities of patients with fibromyalgia. Lower limb CSP latency correlated to disease severity and functional disability based on Fibromyalgia Impact Questionnaire (FIQ) and Short Form-36 (SF-36) (Umay et al., 2013). These authors attributed the observed delay rather to small-diameter fiber conduction dysfunction than to altered central processing, concurring with reported delays in sympathetic skin responses and reduced RR interval variation during deep breathing (Ulas et al., 2006). Baklaci (2013) also attributed delayed and shortened CSPs in upper limbs, and significantly shortened CSPs in lower limbs, to small-diameter fiber dysfunction in fibromyalgia. Another study reported normal CSP latencies and durations in fibromyalgia patients, who differed from healthy controls only in heart rate variability, suggesting autonomic system dysfunction despite normal sympathetic skin responses (Ustun et al., 2014).

In contrast, normal CSP latencies, but prolonged CSP duration was noted by Baek et al. (2016) in their patients with fibromyalgia, which did not correlate to any clinical variables. The different findings in this compared to the previous studies were likely due to different patient selection, as Baek et al. (2016) excluded all patients with indications of small fiber neuropathy based on clinical features and quantitative sudomotor axonal reflex testing. Yet these authors also concluded that central dysregulation at spinal and supraspinal levels, rather than peripheral small-diameter fiber dysfunction, served to explain their findings (Baek et al., 2016). This may indeed be true, given the fact that small fiber neuropathy was excluded in their patients, while it seems more likely that slowed afferent conduction in A-delta fibers might have contributed to the CSP delay in the former two studies.

Obviously, varying CSP abnormalities can be observed in fibromyalgia syndrome, pointing to either peripheral or central dysfunctions, depending on patient selection, and suggesting different pathologies contributing to an "umbrella diagnosis" of fibromyalgia.

Although still poorly understood, itching seems, on a neuronal basis, closely related to the nociceptive afferent system. In fact, there is evidence suggesting that A-delta fibers play an important role in certain types of itch sensation, in particular as selective conduction block in small-diameter myelinated fibers substantially reduces itch (Ringkamp et al., 2011). Indeed, CSPs were delayed and shortened in upper and lower extremities in *chronic idiopathic generalized pruritus* (Tekatas et al., 2014). The abnormalities did not correlate with disease duration or severity of pruritus. The authors attributed the delayed CSP onset to nerve conduction abnormality in A-delta fibers, and the shortened CSP duration to lack of inhibition of spinal inhibitory neurons generating the CSP, or cortical hypersensitivity, or an abnormality of cortical inhibitory mechanisms (Tekatas et al., 2014).

Several procedures that are known to modulate pain sensation have been investigated in the context of CSPs. Painful stimuli applied to remote areas of the body strongly depress nociceptive reflexes and pain sensation in the rest of the body via activation of *diffuse noxious inhibitory control* possibly by acting through a spino-bulbo-spinal loop (Villanueva and Le Bars, 1995). Rossi et al. (2003) studied the effect of such heterotopic painful stimulation on both CSPs and cutaneous withdrawal reflexes in the upper limbs. Applying a cold pressor test to the contralateral hand, they observed an increase in CSP latency in thenar following D2 stimulation by 10%, a reduction in CSP duration by approximately 23%, and a reduction in R III area in biceps brachii by approximately 40%. Notably, H/M ratios in flexor carpi radialis and CMRs in thenar remained unaffected by the cold pressure test. The authors concluded that the effect of heterotopic painful stimulation was similar on both CSPs and cutaneous withdrawal reflexes, thereby providing evidence for their functional and anatomical relationship and their common nocifensive role (Rossi et al., 2003).

High-frequency transcutaneous electrical nerve stimulation (TENS), which has an antinociceptive effect, shortened upper limb CSP duration, and suppressed transcortical LLRs (Kofler, 2004). TENS exerted its inhibitory influence likely at the spinal segmental level via presynaptic inhibition of nociceptive A-delta fibers. These findings concur with a known opiate-insensitive spinal mechanism of TENS.

Finally, pharmacological influence of *antinociceptive or pain-modulating drugs* on CSPs was investigated in healthy volunteers: Fentanyl did not modify CSPs (Inghilleri et al., 2002), and neither did (−)-trans-Δ9-tetrahydrocannabinol (THC) (Fionda et al., 2016). Tramadol, a serotonin and noradrenaline reuptake inhibitor, and escitalopram, a selective serotonin reuptake inhibitor, increased upper limb CSP duration inversely related to subjective pain perception (Pujia et al., 2012, 2014).

3. Clinical utility of CSPs, limitations, outlook to the future

Clinical interest in the CSP stems from its potential usefulness for evaluating segments and components of sensory nerves that are not well assessed by standard electrodiagnostic methods. This is the case with disorders affecting thinly myelinated, slowly conducting, small-diameter A-delta fibers, as in small-diameter fiber polyneuropathies, or their spinal oligosegmental neuronal interconnections with efferent motor pathways, as in centromedullary lesions. In selected patients, CSPs may serve to document residual nerve continuity across lesion sites, when routine techniques fail.

Although a number of studies have described the CSP in patients with a variety of diseases affecting the motor system, one should be cautious in interpreting reports that attempt to explain complex motor phenomena such as posture, control of normal movement, and certain pathological movement disorders (e.g., spasticity, rigidity, tremor, dystonia) on the basis of studies of silent periods.

Other limitations pertain to the fact that, so far with only few exceptions, most studies on CSPs in patients have been based on single case observations or rather small case series. Also, test-retest reliability has so far been tested on few healthy subjects only. Comparisons with other techniques aiming at evaluating small-diameter fiber function are scarce. Finally, no uniformly accepted technique has been applied in patients, and neither have different techniques been compared in the same subjects in a systematic way. Hence, there are still many open questions to be addressed in future research.

E.g., there is only a poor correlation of CSP and LEP findings and clinical pain conditions. Possibly, CSP as a nocifensive reflex is closely related to acute pain states and their disorders, whereas LEPs reflect abnormalities related to chronic neuropathic pain states. A clear understanding of the physiology underlying "acute" and "chronic pain", however, is still lacking. It is also important to keep in mind that CSPs do not assess C-fiber function, which is often compromised in small-fiber neuropathy.

Furthermore, CSPs seem to be correlated with thermesthesia (Syed et al., 2000; Isoardo et al., 2012), but this has not been studied in detail so far. CSPs were reportedly normal in three patients with abetalipoproteinemia, who had severe large fiber neuropathy, but normal temperature perception (Sandbrink et al., 1999). In contrast, personal unpublished observation suggests that CSP abnormalities may correlate with cold perception in quantitative sensory testing, but not vice versa; obviously, quantitative sensory testing, like LEPs, also assesses pathways upstream of the peripheral nerve and spinal circuitry, whereas CSPs test all kinds of A-delta afferents, not only those related to cold perception.

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Conflict of interest

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