REVIEW

Understanding central sensitization for advances in management of carpal tunnel syndrome [version 1; peer review: 3 approved]

César Fernández-de-las-peñas ^{1,2}, José L Arias-Buría^{1,2},
Ricardo Ortega-Santiago^{1,2}, Ana I De-la-Llave-Rincón^{1,2}

¹Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Alcorcón, Spain

²Cátedra Institucional en Docencia, Clínica e Investigación en Fisioterapia: Terapia Manual, Punción Seca y Ejercicio Terapéutico, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain

V1 First published: 15 Jun 2020, 9(F1000 Faculty Rev):605
<https://doi.org/10.12688/f1000research.22570.1>

Latest published: 15 Jun 2020, 9(F1000 Faculty Rev):605
<https://doi.org/10.12688/f1000research.22570.1>

Abstract

Carpal tunnel syndrome is the most common nerve compression disorder of the upper extremity, and it is traditionally considered a peripheral neuropathy associated with a localized compression of the median nerve just at the level of the carpal tunnel. Surgery and physiotherapy are treatment approaches commonly used for this condition; however, conflicting clinical outcomes suggest that carpal tunnel syndrome may be more complex. There is evidence supporting the role of peripheral nociception from the median nerve in carpal tunnel syndrome; however, emerging evidence also suggests a potential role of central sensitization. The presence of spreading pain symptoms (e.g. proximal pain), widespread sensory changes, or bilateral motor control impairments in people presenting with strictly unilateral sensory symptoms supports the presence of spinal cord changes. Interestingly, bilateral sensory and motor changes are not directly associated with electrodiagnostic findings. Other studies have also reported that patients presenting with carpal tunnel syndrome exhibit neuroplastic brainstem change supporting central sensitization. Current data would support the presence of a central sensitization process, mediated by the peripheral drive originating in the compression of the median nerve, in people with carpal tunnel syndrome. The presence of altered nociceptive gain processing should be considered in the treatment of carpal tunnel syndrome by integrating therapeutic approaches aiming to modulate long-lasting nociceptive barrage into the central nervous system (peripheral drive) and strategies aiming to activate endogenous pain networks (central drive).

Open Peer Review

Approval Status

	1	2	3
version 1 15 Jun 2020			

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Luca Padua**, Neurosciences and Orthopaedics, Università Cattolica del Sacro Cuore, Rome, Italy
2. **Annina Schmid**, University of Oxford, Oxford, UK
3. **Wolfgang Grisold**, Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria

Keywords

Carpal tunnel, pain, sensitization, nociceptive pain.

Any comments on the article can be found at the end of the article.

Corresponding author: César Fernández-de-las-peñas (cesar.fernandez@urjc.es)

Author roles: **Fernández-de-las-peñas C:** Conceptualization, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Arias-Burúa JL:** Conceptualization, Resources, Supervision, Validation, Visualization, Writing – Review & Editing; **Ortega-Santiago R:** Conceptualization, Supervision, Validation, Visualization, Writing – Review & Editing; **De-la-Llave-Rincón AI:** Conceptualization, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2020 Fernández-de-las-peñas C *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Fernández-de-las-peñas C, Arias-Burúa JL, Ortega-Santiago R and De-la-Llave-Rincón AI. **Understanding central sensitization for advances in management of carpal tunnel syndrome [version 1; peer review: 3 approved]** F1000Research 2020, 9 (F1000 Faculty Rev):605 <https://doi.org/10.12688/f1000research.22570.1>

First published: 15 Jun 2020, 9(F1000 Faculty Rev):605 <https://doi.org/10.12688/f1000research.22570.1>

Introduction

Carpal tunnel syndrome (CTS) is the most prevalent nerve compression disorder of the upper extremity, and it is generally associated with a localized compression of the median nerve in the carpal tunnel area. Although epidemiological data vary depending on the diagnostic criteria used, CTS has an incidence rate of 1.8/1,000¹ and a prevalence rate ranging from 6.3 to 11.7% in the general population². Since people affected by CTS are usually active workers, this condition is associated with substantial healthcare costs and economic burden³. Therefore, a better understanding of the potential underlying mechanisms of CTS could improve therapeutic strategies. This paper discusses current theories combining the presence of peripheral nociceptive barrage with the presence of altered nociceptive central processing and its repercussions for the potential management of CTS. The current paper is an updated version of a previous review on this topic⁴.

This review will try to answer the following questions: 1. is CTS just a localized peripheral entrapment of the median nerve? 2. What are the underlying mechanisms behind the clinical manifestations of CTS? 3. Does the presence of altered nociceptive gain potential have repercussions on treatment approaches in CTS?

Understanding carpal tunnel syndrome

Spreading pain symptoms in carpal tunnel syndrome

The most common symptoms usually experienced by patients with CTS include pain and/or paresthesia in areas innervated by the median nerve, i.e. the thumb, index, and/or middle fingers. Symptoms can be worse during activities involving the hand/wrist but also at night. It seems that paresthesia, but not pain, is the symptom most commonly associated with neurophysiological damage of the median nerve⁵.

It is commonly seen in clinical practice that patients with CTS exhibit symptoms not only in those areas innervated by the median nerve but also in extra-median nerve areas. This was confirmed by Zanette *et al.*, who observed that 35% of patients with CTS exhibit a glove distribution of their symptoms, whereas 5% exhibit an ulnar distribution⁶. The same authors also reported that 45% of CTS sufferers also report pain in proximal areas of the upper extremity including the elbow or the shoulder⁷. A more recent study, using new electronic software for analyzing pain extent, found that 88% of women with CTS showed extra-median pain symptoms⁸. The presence of spreading symptoms is a clinical manifestation of neuropathic but also nociceptive pain involving sensitization mechanisms and plasticity⁹. This hypothesis is confirmed by the fact that extra-median symptoms are not associated with electrical nerve conduction data, suggesting an association between neuropathic and nociceptive pain with expansion of receptive fields of central neurons in CTS¹⁰.

Peripheral and central sensory changes in carpal tunnel syndrome

'Sensitization' is a term describing the changes in nociceptive neurons. It is mainly grouped into peripheral/central sensitization, and it is present in several musculoskeletal and neuropathic

chronic pain conditions^{11,12}. 'Peripheral sensitization' refers to increased responsiveness and reduced threshold of peripheral nociceptors; it is usually associated with the release of endogenous algogenic substances and neurogenic inflammation. 'Central sensitization' is defined by the International Association for the Study of Pain (IASP) as an increased responsiveness of the nociceptive neurons in the central nervous system to their normal or subthreshold afferent input, which may include increased responsiveness due to dysfunction of endogenous pain control systems¹³. The relationship between peripheral and central sensitization is well established. It is accepted that the presence of long-lasting and prolonged nociceptive peripheral inputs induces plastic changes in the central nervous system; therefore, central sensitization seems to be a dynamic process that is dependent on peripheral nociception^{11,12}. In some patients, once central sensitization has been established, minimal peripheral nociception can be required to maintain this process and non-nociceptive inputs might also contribute to the subsequent pain and mechanical allodynia observed in this situation. Nevertheless, central sensitization is mainly driven by peripheral impulses. In such a scenario, in people with CTS, the entrapment of the median nerve at the carpal tunnel represents the peripheral input towards the central nervous system. Gracely *et al.* proposed this model for neuropathic pain in 1992 where peripheral nociception from an entrapped nerve could lead to neuroplastic changes in the central nervous system¹⁴. In CTS, the neurogenic inflammation of the median nerve induced by its entrapment can act as a peripheral driver for the gradual sensitization of nociceptive pathways. In fact, Truini *et al.* found that affectation of both nociceptive and non-nociceptive fibers contributed to the different symptoms experienced in CTS¹⁵.

The peripheral component of entrapment neuropathies such as CTS is supported by current literature¹⁶ and will not be further discussed in this text. In the last decade, different studies have investigated the presence of central sensitization by assessing widespread sensory disorders throughout quantitative sensory testing in CTS. Fernández-de-las-Peñas *et al.* found that women with strictly unilateral CTS symptoms exhibit widespread pressure pain sensitivity over the radial, ulnar, and median nerves, the cervical spine, and the tibialis anterior muscle, suggesting widespread hypersensitivity to pressure pain¹⁷. Widespread pressure hypersensitivity is a manifestation of the sensitization of central pathways; however, pressure pain hypersensitivity has also been found to be heterogeneously distributed in the symptomatic hand, supporting the relevant role of the peripheral input¹⁸. Similar results were also found by Zanette *et al.*, who observed that CTS patients with extra-median symptoms exhibited generalized pressure hyperalgesia and enhanced wind-up¹⁹. Interestingly, widespread pressure pain hyperalgesia was not associated with the electrodiagnostic findings, since women with minimal, moderate, or severe CTS exhibit similar widespread sensory changes²⁰. These results support the notion that widespread hyperalgesia to pressure pain can be a common manifestation of CTS from the beginning of symptom onset. In line with this hypothesis, Tampin, Vollert, and Schmid found that individuals with a peripheral neuropathy such as CTS exhibit similar sensory changes to those with a proximal (cervical) radiculopathy, although pain profiles were different²¹.

Nevertheless, Schmid *et al.* did not observe widespread pressure hyperalgesia in patients with CTS without concomitant neck pain symptoms, suggesting that groups of patients with CTS could exist and that the observed widespread sensory changes can be more related to the presence of extra-median/proximal symptoms²². The hypothesis of different subgroups of patients with CTS has been supported by a study identifying a subgroup of women with CTS with higher bilateral widespread pressure hyperalgesia based on the presence of a cluster of symptoms²³. Therefore, it is possible that CTS can be peripherally mediated in some patients but more centrally mediated in others.

The presence of central sensitization in CTS is also supported by imaging studies.

Tecchio *et al.* found that patients with CTS with symptoms of glove distribution exhibited an enlargement in cortical representation and neuroplastic changes in the somatosensory cortex compared to those individuals with just median nerve distribution symptoms²⁴. Different studies have also shown larger contralateral sensorimotor cortical representation²⁵ and smaller cortical source separation²⁶ of the second/third digits in patients with CTS as compared to controls. All of these studies hypothesized that long-lasting paresthesia/pain symptoms (peripheral drive) can promote blurring of median nerve-innervated digit representations through neural mechanisms (central drive)^{25,26}. There is also current evidence showing the presence of reduced endogenous inhibition and increased pain facilitation in patients with CTS²⁷. In conclusion, long-lasting peripheral nociceptive stimuli originating in the median nerve could lead to neuroplastic changes in the central nervous system at both spinal cord and brainstem levels.

Motor output changes in carpal tunnel syndrome

It is interesting to consider that sensitization mechanisms and sensory loss also have output manifestations. Motor control disturbances may be a perpetuating factor for pain since pain-related fear or avoidance behaviors can also promote negative attitudes. In addition, altered motor control patterns could reflect the reorganization of motor control strategies in the central nervous system, as sensory neuroplastic changes in the somatosensory cortex result in decreased fine motor control²⁸. The presence of bilateral deficits in fine motor control and pinch grip force in women with strictly unilateral CTS supports this hypothesis²⁹. Additionally, these bilateral deficits in fine motor control and pinch grip force were not associated with either median nerve damage or the presence of unilateral or bilateral symptoms³⁰. Data suggest that motor output disorders are present from the onset of symptoms and could be related to neuroplastic changes in the cortex. Nevertheless, it is probable that peripheral and central mechanisms can be involved at the same time in the motor control disturbances observed in CTS.

Implications for clinical practice

Although CTS can be treated with conservative and surgical procedures, surgery continues to be the most common treatment approach proposed for these patients³¹. In fact, both open and endoscopic surgical interventions provide similar clinical

results³². However, although surgery provides positive long-term results, it may not always be entirely successful³³, and the recurrence rate is estimated to be around 30% (from 5 to 57%)³⁴. There is great debate related to which patients with CTS should be treated with conservative or surgical treatment in the first instance³⁵. In fact, no consensus exists on which therapeutic option is the best for CTS. A recent meta-analysis has reported that the differences between surgery and conservative treatment are small³⁶. Interestingly, Jarvik *et al.* observed that 61% of patients with CTS attempted to avoid surgery³⁷. Conservative treatment for CTS could be preferred as the first-line option for patients with minimal or moderate CTS, whereas surgery could be the first-line approach for patients with more severe symptoms or when conservative treatment has failed.

It is important to consider that there is no established algorithm for determining which patients with CTS will benefit from conservative treatment³⁸, i.e. physiotherapy.

In fact, different meta-analyses reported inconclusive evidence for the use of different conservative interventions, such as low-level laser³⁹, ultrasound⁴⁰, or splinting⁴¹. Other conservative techniques, e.g. nerve/tendon (neuro-mobilization) gliding exercises, have shown promising, but also limited, outcomes⁴². Discrepancies in the effects of multiple and different management therapeutic strategies can be attributed to the fact that CTS is a heterogeneous syndrome. In such a scenario, the presence of sensitization mechanisms discussed in this text could provide a physiological explanation for those individuals with CTS who experience persistent symptoms despite apparently successful surgery.

A mechanism-based classification can help clinicians to understand that different signs and symptoms may reflect different underlying nociceptive gain mechanisms. The presence of sensitization mechanisms in people with CTS has potential implications for clinical practice, since it implies that, in some patients, more global, not just localized, interventions should be applied. According to current data, clinicians should identify if symptoms in a patient with CTS are mainly peripherally or centrally mediated. In patients with peripherally mediated symptoms, localized interventions targeting local tissue (i.e. median nerve entrapment at the carpal tunnel) should be provided. There is evidence supporting a peripheral effect of nerve/tendon gliding exercises in patients with CTS, since these exercises affect the biological integrity of the median nerve by increasing fluid dispersion and reducing intraneural edema^{43,44}. In patients with centrally mediated symptoms, clinicians should incorporate therapeutic approaches directed at normalizing peripheral and central nervous system interactions (i.e. soft tissue-based techniques, nerve mobilizations, or pain neuroscience education) and not just localized interventions over the carpal tunnel. It is in this group of patients where medications targeting the central nervous system could be effective⁴⁵.

This clinical reasoning has been applied in a randomized clinical trial comparing the effects of manual therapy including desensitization maneuvers of the central nervous system with

surgery in women with CTS⁴⁶. This promising clinical trial showed that the application of manual therapies following altered nociceptive gain reasoning exhibited better short-term (1- and 3-month) and similar long-term (6- and 12-month) effects on pain and function than surgery in women with CTS⁴⁶. In fact, the cost-effectiveness analysis of this trial also revealed better economic aspects in favor of manual physical therapy⁴⁷.

Nevertheless, the challenge facing clinicians is how to select the most appropriate intervention for each patient, who is likely to be slightly different in their presentation. To determine the most appropriate therapeutic strategy, considerations must be given to interpreting the clinical manifestations of these sensitization processes (peripheral and/or central) and to potential prognostic factors related to clinical outcomes. Nevertheless, although central sensitization has been related to poorer outcome in response to surgical or conservative treatment in musculoskeletal pain, this hypothesis is supported by small and exploratory studies, and no conclusion can be made for this assumption⁴⁸. A recent study has reported that localized, but not widespread, pressure sensitivity was predictive of long-term

clinical outcomes in a sample of women with CTS after the application of manual therapies including desensitization maneuvers of the central nervous system⁴⁹. These preliminary results support the clinical reasoning that not all patients with CTS respond to the same therapeutic approach and subgroups of patients could exist.

Conclusion

This updated review of underlying mechanisms of CTS found that there is evidence supporting the presence of central sensitization mechanisms, potentially mediated by the peripheral nociceptive inputs from the median nerve, in patients presenting with CTS. The presence of central sensitization influences treatment prognosis and the response of patients with CTS to a particular therapeutic strategy. The current paper has proposed the existence of two main subgroups of patients: those with peripherally mediated CTS and those with centrally mediated CTS. Clinicians should apply therapeutic strategies based on current knowledge on pain neuroscience and according to the clinical presentation and predominant identified mechanisms in these patients.

References

- Bongers FJM, Schellevis FG, van den Bosch WJHM, *et al.*: **Carpal tunnel syndrome in general practice (1987 and 2001): Incidence and the role of occupational and non-occupational factors.** *Br J Gen Pract.* 2007; **57**(534): 36–9.
[PubMed Abstract](#) | [Free Full Text](#)
- Thiese MS, Gerr F, Hegmann KT, *et al.*: **Effects of varying case definition on carpal tunnel syndrome prevalence estimates in a pooled cohort.** *Arch Phys Med Rehabil.* 2014; **95**(12): 2320–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Foley M, Silverstein B, Polissar N: **The economic burden of carpal tunnel syndrome: Long-term earnings of CTS claimants in Washington State.** *Am J Ind Med.* 2007; **50**(3): 155–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Fernández-de-las-Peñas C, Plaza-Manzano G: **Carpal tunnel syndrome: Just a peripheral neuropathy?** *Pain Manag.* 2018; **8**(3): 209–16.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Nora DB, Becker J, Ehlers JA, *et al.*: **What symptoms are truly caused by median nerve compression in carpal tunnel syndrome?** *Clin Neurophysiol.* 2005; **116**(2): 275–83.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Zanette G, Marani S, Tamburin S: **Extra-median spread of sensory symptoms in carpal tunnel syndrome suggests the presence of pain-related mechanisms.** *Pain.* 2006; **122**(3): 264–70.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Zanette G, Marani S, Tamburin S: **Proximal pain in patients with carpal tunnel syndrome: A clinical-neurophysiological study.** *J Peripher Nerv Syst.* 2007; **12**(2): 91–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Fernández-de-las-Peñas C, Falla D, Palacios-Ceña M, *et al.*: **Perceived Pain Extent Is Not Associated with Physical, Psychological, or Psychophysical Outcomes in Women with Carpal Tunnel Syndrome.** *Pain Med.* 2019; **20**(6): 1185–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Campbell JN, Meyer R: **Mechanisms of Neuropathic Pain.** *Neuron.* 2006; **52**(1): 77–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Mansiz-Kaplan B, Akdeniz-Leblecicler M, Yagci I: **Are extramedian symptoms associated with peripheral causes in patient with carpal tunnel syndrome?: Electrodiagnostic and ultrasonographic study.** *J Electromyogr Kinesiol.* 2018; **38**: 203–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
- Arendt-Nielsen L, Fernández-de-las-Peñas C, Graven-Nielsen T: **Basic aspects of musculoskeletal pain: From acute to chronic pain.** *J Man Manip Ther.* 2013; **19**(4): 186–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Woolf CJ: **Central sensitization: Implications for the diagnosis and treatment of pain.** *Pain.* 2011; **152**(3 Suppl): S2–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Treede RD, Rief W, Barke A, *et al.*: **Chronic Pain as a Symptom or a Disease: The IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11).** *Pain.* 2019; **160**(1): 19–27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
- Gracely RH, Lynch SA, Bennett GJ: **Painful neuropathy: Altered central processing maintained dynamically by peripheral input.** *Pain.* 1992; **51**(2): 175–94.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Truini A, Padua L, Biasiotta A, *et al.*: **Differential involvement of A-delta and A-beta fibres in neuropathic pain related to carpal tunnel syndrome.** *Pain.* 2009; **145**(1-2): 105–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
- Schmid AB, Hailey L, Tampin B: **Entrapment Neuropathies: Challenging Common Beliefs With Novel Evidence.** *J Orthop Sports Phys Ther.* 2018; **48**(2): 58–62.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
- Fernández-de-las-Peñas C, de La Llave-Rincón AI, Fernández-Camero J, *et al.*: **Bilateral widespread mechanical pain sensitivity in carpal tunnel syndrome: Evidence of central processing in unilateral neuropathy.** *Brain.* 2009; **132**(Pt 6): 1472–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Fernández-de-las-Peñas C, Madeleine P, Martínez-Perez A, *et al.*: **Pressure pain sensitivity topographical maps reveal bilateral hyperalgesia of the hands in patients with unilateral carpal tunnel syndrome.** *Arthritis Care Res (Hoboken).* 2010; **62**(8): 1055–64.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Zanette G, Cacciatori C, Tamburin S: **Central sensitization in carpal tunnel syndrome with extraterritorial spread of sensory symptoms.** *Pain.* 2010; **148**(2): 227–36.
[PubMed Abstract](#) | [Publisher Full Text](#)
- de La Llave-Rincón AI, Fernández-de-las-Peñas C, Laguarda-Val S, *et al.*: **Increased Pain Sensitivity Is Not Associated With Electrodiagnostic Findings in Women With Carpal Tunnel Syndrome.** *Clin J Pain.* 201; **27**(9): 747–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Tampin B, Vollert J, Schmid AB: **Sensory profiles are comparable in patients**

- with distal and proximal entrapment neuropathies, while the pain experience differs. *Curr Med Res Opin.* 2018; **34**(11): 1899–906.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
22. Schmid AB, Soon BT, Wasner G, *et al.*: Can widespread hypersensitivity in carpal tunnel syndrome be substantiated if neck and arm pain are absent? *Eur J Pain.* 2012; **16**(2): 217–28.
[PubMed Abstract](#) | [Publisher Full Text](#)
 23. Fernández-de-las-Peñas C, Fernández-Muñoz JJ, Navarro-Pardo E, *et al.*: Identification of Subgroups of Women with Carpal Tunnel Syndrome with Central Sensitization. *Pain Med.* 2016; **17**(9): 1749–56.
[PubMed Abstract](#) | [Publisher Full Text](#)
 24. Tecchio F, Padua L, Aprile I, *et al.*: Carpal tunnel syndrome modifies sensory hand cortical somatotopy: A MEG study. *Hum Brain Mapp.* 2002; **17**(1): 28–36.
[PubMed Abstract](#) | [Publisher Full Text](#)
 25. Napadow V, Kettner N, Ryan A, *et al.*: Somatosensory cortical plasticity in carpal tunnel syndrome—a cross-sectional fMRI evaluation. *Neuroimage.* 2006; **31**(2): 520–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
 26. Dhond RP, Ruzich E, Witzel T, *et al.*: Spatio-temporal mapping cortical neuroplasticity in carpal tunnel syndrome. *Brain.* 2012; **135**(Pt 10): 3062–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 27. **F** Soon B, Vicenzino B, Schmid AB, *et al.*: Facilitatory and inhibitory pain mechanisms are altered in patients with carpal tunnel syndrome. *PLoS ONE.* 2017; **12**(8): e0183252.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [Faculty Opinions Recommendation](#)
 28. Flor H: Cortical reorganisation and chronic pain: Implications for rehabilitation. *J Rehabil Med.* 2003; **35**(41 Suppl): 66–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
 29. Fernández-de-las-Peñas C, Pérez-de-Heredia-Torres M, Martínez-Piédrola R, *et al.*: Bilateral deficits in fine motor control and pinch grip force in patients with unilateral carpal tunnel syndrome. *Exp Brain Res.* 2009; **194**(1): 29–37.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. de La Llave-Rincón AI, Fernández-de-las-Peñas C, Pérez-de-Heredia-Torres M, *et al.*: Bilateral deficits in fine motor control and pinch grip force are not associated with electrodiagnostic findings in women with carpal tunnel syndrome. *Am J Phys Med Rehabil.* 2011; **90**(6): 443–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. American Academy of Orthopaedic Surgeons: Management of Carpal Tunnel Syndrome Evidence-Based Clinical Practice Guideline. Accessed December 20, 2018.
[Reference Source](#)
 32. **F** Li Y, Luo W, Wu G, *et al.*: Open versus endoscopic carpal tunnel release: A systematic review and meta-analysis of randomized controlled trials. *BMC Musculoskelet Disord.* 2020; **21**(1): 455.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [Faculty Opinions Recommendation](#)
 33. Zieske L, Ebersole GC, Davidge K, *et al.*: Revision carpal tunnel surgery: A 10-year review of intraoperative findings and outcomes. *J Hand Surg Am.* 2013; **38**(8): 1530–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 34. Louie D, Earp B, Blazar P: Long-term outcomes of carpal tunnel release: A critical review of the literature. *Hand (N Y).* 2012; **7**(3): 242–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 35. Huisstede BM, Fridén J, Coert JH, *et al.*: Carpal tunnel syndrome: Hand surgeons, hand therapists, and physical medicine and rehabilitation physicians agree on a multidisciplinary treatment guideline—results from the European HANDGUIDE Study. *Arch Phys Med Rehabil.* 2014; **95**(12): 2253–63.
[PubMed Abstract](#) | [Publisher Full Text](#)
 36. **F** Shi Q, Bobos P, Lalone EA, *et al.*: Comparison of the Short-Term and Long-Term Effects of Surgery and Nonsurgical Intervention in Treating Carpal Tunnel Syndrome: A Systematic Review and Meta-Analysis. *Hand (N Y).* 2020; **15**(1): 13–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [Faculty Opinions Recommendation](#)
 37. Jarvik JG, Comstock BA, Kliot M, *et al.*: Surgery versus non-surgical therapy for carpal tunnel syndrome: A randomised parallel-group trial. *The Lancet.* 2009; **374**(9695): 1074–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
 38. **F** Zarialieva A, Georgiev GP, Karabinov V, *et al.*: Physical Therapy and Rehabilitation Approaches in Patients with Carpal Tunnel Syndrome. *Cureus.* 2020; **12**(3): e7171.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [Faculty Opinions Recommendation](#)
 39. Cheung WKW, Wu IXY, Sit RWS, *et al.*: Low-level laser therapy for carpal tunnel syndrome: Systematic review and network meta-analysis. *Physiotherapy.* 2020; **106**: 24–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
 40. Page MJ, O'Connor D, Pitt V, *et al.*: Therapeutic ultrasound for carpal tunnel syndrome. *Cochrane Database Syst Rev.* 2013; **2013**(3): CD009601.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 41. Page MJ, Massy-Westropp N, O'Connor D, *et al.*: Splinting for carpal tunnel syndrome. *Cochrane Database Syst Rev.* 2012; **7**(7): CD010003.
[PubMed Abstract](#) | [Publisher Full Text](#)
 42. Ballester-Pérez R, Plaza-Manzano G, Urraca-Gesto A, *et al.*: Effectiveness of Nerve Gliding Exercises on Carpal Tunnel Syndrome: A Systematic Review. *J Manipulative and Physiol Ther.* 2017; **40**(1): 50–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 43. Schmid AB, Elliott JM, Strudwick MW, *et al.*: Effect of splinting and exercise on intraneural edema of the median nerve in carpal tunnel syndrome—an MRI study to reveal therapeutic mechanisms. *J Orthop Res.* 2012; **30**(8): 1343–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
 44. **F** Boudier-Revéret M, Gilbert K, Allégue DR, *et al.*: Effect of neurodynamic mobilization on fluid dispersion in median nerve at the level of the carpal tunnel: A cadaveric study. *Musculoskeletal Sci Pract.* 2017; **31**: 45–51.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
 45. **F** Huisstede BM, Randsdorp MS, van den Brink J, *et al.*: Effectiveness of Oral Pain Medication and Corticosteroid Injections for Carpal Tunnel Syndrome: A Systematic Review. *Arch Phys Med Rehabil.* 2018; **99**(8): 1609–1622.e10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
 46. Fernández-de-las-Peñas C, Ortega-Santiago R, de La Llave-Rincón AI, *et al.*: Manual Physical Therapy Versus Surgery for Carpal Tunnel Syndrome: A Randomized Parallel-Group Trial. *J Pain.* 2015; **16**(11): 1087–94.
[PubMed Abstract](#) | [Publisher Full Text](#)
 47. Fernández-de-las-Peñas C, Ortega-Santiago R, Díaz HFS, *et al.*: Cost-Effectiveness Evaluation of Manual Physical Therapy Versus Surgery for Carpal Tunnel Syndrome: Evidence From a Randomized Clinical Trial. *J Orthop Sports Phys Ther.* 2019; **49**(2): 55–63.
[PubMed Abstract](#) | [Publisher Full Text](#)
 48. O'Leary H, Smart KM, Moloney NA, *et al.*: Nervous System Sensitization as a Predictor of Outcome in the Treatment of Peripheral Musculoskeletal Conditions: A Systematic Review. *Pain Pract.* 2017; **17**(2): 249–66.
[PubMed Abstract](#) | [Publisher Full Text](#)
 49. Fernández-de-las-Peñas C, De-la-Llave-Rincón AI, Cescon C, *et al.*: Influence of Clinical, Psychological, and Psychophysical Variables on Long-term Treatment Outcomes in Carpal Tunnel Syndrome: Evidence From a Randomized Clinical Trial. *Pain Pract.* 2019; **19**(6): 644–55.
[PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. **Wolfgang Grisold**

Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria

Competing Interests: No competing interests were disclosed.

2. **Annina Schmid**

Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

Competing Interests: No competing interests were disclosed.

3. **Luca Padua**

Department of Geriatrics, Neurosciences and Orthopaedics, Università Cattolica del Sacro Cuore, Rome, Italy

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research