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The sensory and motor consequences of Carpal Tunnel Syndrome

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The sensory and motor consequences of Carpal Tunnel Syndrome

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This thesis is submitted in partial fulfilment of the requirement for the degree of Doctor in Philosophy, completed in the School of Psychology, Bangor University.

Declarations

Yr wyf drwy hyn yn datgan mai canlyniad fy ymchwil fy hun yw'r thesis hwn, ac eithrio lle nodir yn wahanol. Caiff ffynonellau eraill eu cydnabod gan droednodiadau yn rhoi cyfeiriadau eglur. Nid yw sylwedd y gwaith hwn wedi cael ei dderbyn o'r blaen ar gyfer unrhyw radd, ac nid yw'n cael ei gyflwyno ar yr un pryd mewn ymgeisiaeth am unrhyw radd oni bai ei fod, fel y cytunwyd gan y Brifysgol, am gymwysterau deuol cymeradwy.

I hereby declare that this thesis is the results of my own investigations, except where otherwise stated. All other sources are acknowledged by bibliographic references. This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree unless, as agreed by the University, for approved dual awards.

Signed

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Abstract

Here we examined the sensory and motor consequences of Carpal Tunnel Syndrome (CTS), the most common nerve injury, caused by the entrapment of the median nerve at the wrist level. Patients experience impaired hand function, including diminished tactile sensitivity and impaired fine motor skills, and difficulty manipulating objects. The problematics reported by patients can partially be explained by tactile impairments. However, sensorimotor research underlines the importance of digit proprioception to perform ‘smooth’ and fluid hand movements.

In Chapter 2, we assessed if CTS affects the anticipatory features of grasping movement towards real objects, with and without visual feedback. CTS patients showed preserved grip and speed scaling according to object size and distance, regardless of visual condition, slower movement in the absence of vision, and no increased movement variability.

The results of Chapter 2 can be explained by impaired tactile sensitivity. However, as a consequence of the nerve entrapment caused by CTS, we assumed that digit proprioception is likely to be impaired. Therefore, in Chapter 3 we assessed if digit proprioception is impaired in CTS by asking patients and healthy controls to perform a haptic size-discrimination task to measure the sensitivity of opening of the unseen thumb and index finger. Contrary to our prediction, digit proprioception was not impaired in CTS patients.

Considering the difficulties entitled in the assessment of digit proprioception and the lack of 'good' clinical tests, in Chapter 4 we developed a new tool to assess digit proprioception, the block-difference test.

Overall, our results indicate that CTS preserves the anticipatory features of grasping movement and does not impair digit proprioception. Further, we underlined the importance of creating a better tool to assess digit proprioception and the challenges involved. The implication and limitation of these results are discussed with reference to both theoretical and clinical application.

Chapter 1. Introduction

1.1. Overview of the thesis

Peripheral nerve injuries of the upper extremity are common due to the anatomical location of peripheral nerves that make them vulnerable to injuries (Neal & Fields, 2010). It is estimated that 69% of the upper-limb traumas are related to a nerve injury (Stonner, Mackinnon, & Kaskutas, 2017). Peripheral nerve injuries can result in partial or total loss of motor (i.e., manipulation of objects, generation of force), sensory (i.e., ability to detect touch, pressure, temperature) and autonomic functions in the affected body part (Campbell, 2008; Z.-M. Li, Marquardt, Evans, & Seitz, 2014), which impair the ability of people to perform activities of daily life (Muggleton, Allen, & Chappell, 1999). Considering the long-term consequences of peripheral nerve injury, it is relevant to have tools that facilitate their diagnosis and management (Neal & Fields, 2010).

Here we focused on Carpal Tunnel Syndrome (CTS), the most common nerve injury affecting between 2.7 and 9.2 % of the general population (Atroshi, Johnsson, & Sprinchorn, 1998; Papanicolaou, McCabe, & Firrell, 2001; Prick, Blaauw, Vredeveld, & Oosterloo, 2003). CTS arises from chronic compression of the median nerve at the wrist level, which results in nocturnal pain, tingling and numbness in the distribution of the median nerve in the hand (Aroori & Spence, 2008). Functionally, patients experience difficulties in manipulating small objects and loss of fine motor skills. Tactile impairment caused by CTS can partially explain these problems (Aroori & Spence, 2008). However, sensorimotor research underlines how smooth and ‘fluid’ hand movements, such as reaching and grasping, also depend on feedback from proprioception (Rothwell et al., 1982; van Beers, Sittig, & van Der Gon, 1999), presumably including proprioceptive signals about the posture and movement of the digits. It seems likely that impairment to digit proprioception affects the execution of movements such as reaching to grasp in CTS patients. The median nerve innervates muscles, tendons and skin receptors that provide proprioception information about the hand; however, we do

not know if the nerve entrapment affects these structures. Moreover, digit proprioception is not usually assessed clinically in CTS, and it has arguably been neglected in research on peripheral nerve injuries more generally. One reason for this is the difficulty of isolating proprioception from other sensory signals, like touch (Berryman, Yau, & Hsiao, 2006). Proprioception is not a single sensory modality but is composed of different sub-modalities, served by different receptors, in different organs, and isolating proprioception from tactile sensing, in particular, is challenging. Also, though not uniquely, it is not possible to investigate proprioception directly—the examination has to rely on the participant's subjective answer.

This PhD thesis had three principal aims: i) to characterise functional hand movements in CTS patients, and determine whether and how they differ from movements in healthy controls; ii) to investigate whether digit proprioception *per se* is impaired in CTS patients; iii) to begin the development of a new clinical test to assess digit proprioception that addresses both desired measurement properties, and the practical requirements of use in clinical settings.

Through the dissertation, we examined grasping movements (and grasping-like movements such as holding objects, with the index finger and thumb) because grasping has been extensively investigated in cognitive neuroscience. Therefore, we have a broad knowledge of how grasping movements are performed in the healthy population, and how the system responds to increased noise in sensory control signals, and manipulations such as loss of visual feedback. We explore whether such normative findings can be generalised to clinical populations. In so doing, we hope to increase our understanding of how grasping compensates for impoverished somatosensory information, which may have implications to improve our understanding of peripheral nerve injuries more in general.

1.2. Carpal Tunnel Syndrome

In the following paragraphs, we first briefly review the anatomy of the median nerve. We then provide a description of the clinical presentation of CTS (symptomatology), diagnosis and treatment of CTS, before considering its epidemiological description, and economic impact. This knowledge will help in understanding why we studied CTS, and provide a background to our hypotheses, and for understanding the importance of developing a new tool to assess digit proprioception.

1.2.1 Anatomy of the median nerve and carpal tunnel

To better understand the symptomatology and functional consequences of CTS, it is important to understand how the entrapment of the median nerve happens.

The median nerve paths

The median nerve is a mixed nerve composed of sensory and motor fibres (Demircay, Civelek, Cansever, Kabatas, & Yilmaz, 2011; Wang, 2018). The median nerve arises from the medial and lateral cord of the brachial plexus, proceeds through the arm and reaches the elbow where it innervates different muscles in the forearm (the pronator teres, flexor carpi radialis, palmaris longus and flexor digitorum superficialis) that perform pronation of the forearm, flexion of the wrist and flexion of digits of the hand (Wang, 2018). The palmar cutaneous branch provides skin sensation to the lateral part of the palm (Wang, 2018). The remaining branches enter the hand at the wrist level through the carpal tunnel (Wang, 2018).

The carpal tunnel

The carpal tunnel is a shallow U-shaped canal, on the volar (palmar) side of the hand, near the wrist. Eight irregular carpal bones (Li et al., 2014; Wang, 2018) forms the arch of the carpal tunnel, while the volar side is enclosed by a thick connective tissue (the transfer carpal ligament; Newington, Harris, & Walker-Bone, 2015; Wang, 2018). Through the carpal tunnel,

the median nerve and nine tendons enter the hand (Demircay et al., 2011; Wang, 2018). One tendon is responsible for the thumb flexion (the flexor pollicis longus), while the other eight tendons are responsible for the flexion of the remaining fingers in the hand (four flexor digitorum superficialis and four flexor digitorum profundus; Katz & Simmons, 2002; Wang, 2018). The carpal tunnel is the site where the entrapment of the median nerve happens.

The innervation of the hand

Before leaving the carpal tunnel, the median nerve divides into two branches. The motor branch innervates the thenar muscle, which innervates different muscles associated with movements of the thumb (abductor pollicis brevis, opponens pollicis, superficial head of the flexor pollicis brevis muscles; Chammas, 2014; Demircay et al., 2011; Wang, 2018). The palmar digital branches are responsible for the cutaneous innervation of part of the hand. In detail, the proper palmar cutaneous branches innervate the cutaneous skin of the radial and ulnar aspect of the thumb and the radial aspect of the index finger (Chammas, 2014; Ibrahim, Khan, Goddard, & Smitham, 2012). While, the common palmar digital branches innervate the palmar surface and fingertips of the index, middle and later half of the ring finger (Chammas, 2014; Ibrahim et al., 2012). The areas of the hand—including the other half of the ring finger, and the little finger, are innervated by the ulnar and radial nerve, and so are not directly affected by Carpal Tunnel Syndrome.

Brief discussion of the complex innervation of the hand

As mentioned above, the median nerve is not the only nerve that supplies the hand. Indeed, the ulnar and radial nerve innervates the hand too. The ulnar nerve innervates some muscles in the median nerve territory that are necessary to flex the metacarpophalangeal joints (MP) of the thumb (flexor pollicis brevis), to flex the MCP joint and extension at the interphalangeal (IP) joints of each digit (the third and fourth lumbrical muscles) and to abduct the digits at the MCP joint (the interosseous muscle; Chammas, 2014; Duncan, Saracevic, &

Kakinoki, 2013). The radial nerve innervates the extrinsic extensor muscles in the wrist and in the digits (Ljungquist, Martineau, & Allan, 2015). The radial nerve supplies the muscles that extend the wrist and MP joints and that abducts and extends the thumb (Robson, See, & Ellis, 2008).

1.2.2 Clinical features of CTS

The symptomatology associated with CTS varies depending on the severity of the disease (Aroori & Spence, 2008). In the beginning, symptoms are due to the involvement of the sensory component of the median nerve and only later from the involvement of the motor component (Aroori & Spence, 2008). Common symptoms include tingling, pain, altered sensation, paraesthesia, and weakness in the affected fingers (Aroori & Spence, 2008; Maeda et al., 2014; Middleton & Anakwe, 2014). Usually, the symptoms involve the innervated median nerve territory but, sometimes, patients can report problems in the forearm and elbow, and even in the shoulder (Aroori & Spence, 2008). Symptoms are usually worse at night and awake patients from sleep and can be aggravated following heavy activities (Aroori & Spence, 2008; Middleton & Anakwe, 2014). Patients report problems in manual dexterity, such as impaired fine manipulation skills, dropping objects, and clumsiness (Aroori & Spence, 2008; Middleton & Anakwe, 2014; Zhang et al., 2013). Problems in fine motor control can arise from sensory deficits (tactile impairment) or by the damage created in the muscle innervated by the median nerve (Duncan et al., 2013). Whether proprioception is affected is unknown.

1.2.3 CTS diagnosis

As noted above, CTS is characterized by a complex clinical picture. Currently, diagnosis is based on the combination of clinical symptoms and signs with electro-diagnostic findings (Rempel, Dahlin, & Lundborg, 1999). Here, we briefly review the most common diagnostic tests used, highlighting both strengths and weakness:

1. Nerve conduction studies (NCS): this test measures the sensory and motor conduction velocity of the median nerve at the wrist level (Aroori & Spence, 2008). The NCS compares the latency and amplitude of a median nerve segment with another nerve that does not pass through the carpal tunnel, both stimulated by a transcutaneous pulse of electricity (Ibrahim et al., 2012). CTS is confirmed in the presence of prolonged motor and sensory latencies of the median nerve, and reduced sensory and motor conduction velocities (Bland, 2000). A delay in the sensory nerve conduction velocity is usually observed in the early stages of CTS (Aroori & Spence, 2008). Based on the results of the NCS, CTS can be categorised as very mild, mild, moderately severe, severe, very severe and extremely severe (Bland, 2000). NCS has been considered the gold-standard diagnosis of CTS (Ibrahim et al., 2012). Different limitations have been identified, however, including: i) asymptomatic individuals can have a positive test, ii) the test can give negative results even in the presence of clear symptoms, iii) in severe cases the results of the test might not correlate with clinical findings, due to the varying nature of the impairment in different nerve fibres, iv) the test results are not predictive of the recovery following the release of the carpal tunnel (Aroori & Spence, 2008).
2. Tinel's sign: in this test, the examiner taps lightly with his finger over the site of the median nerve in the wrist area (Aroori & Spence, 2008; Ibrahim et al., 2012). If the subject experiences discomfort or tingling, the test is considered positive (Aroori & Spence, 2008). The test is easy and rapid to administer. However, it is not precise because different factors can affect the outcome (Aroori & Spence, 2008). First, the efficacy of the test is reduced because CTS patients have continuous regeneration of the nerves at the wrist level (Aroori & Spence, 2008). Second, the amount of pressure used to elicit the sign is not constant (Aroori & Spence, 2008). Indeed, different clinicians might use a different amount of pressure that can result in subtle differences

in the performance, which might explain some of the discrepancies in the reported prevalence of the CTS (Aroori & Spence, 2008).

3. Phalen's test: the subject flexes the wrist at 90° and keeps this position for one minute (Ibrahim et al., 2012). The test is considered positive if the subject develops paraesthesia (Aroori & Spence, 2008).

The diagnosis of CTS can still be considered problematic because the clinical value of some tests has been criticised (MacDermid & Wessel, 2004). Therefore, the assessment of CTS should be acknowledged as an important issue for researchers (MacDermid & Wessel, 2004). This is part of our motivation to create a new tool to assess a potential aspect of CTS (impaired proprioception) that is currently typically not assessed routinely in clinical practice.

1.2.4 Epidemiology and risk factors

As noted earlier, CTS affects between 2.7 and 9.2% of the general population (Atroshi et al., 1998; Papanicolaou et al., 2001; Prick et al., 2003), and for this reason, it is considered the most common nerve injury (Aroori & Spence, 2008). CTS affects more women than men (Phalen & Ohio, 1966), and the presentation is often bilateral (Aroori & Spence, 2008). Although CTS is observed in all age groups, peak prevalence occurs in the range 40-60 years old and between 75-84 years (Chammas, 2014; Yunoki et al., 2017). CTS is also common during pregnancy, typically in the third trimester, and usually resolves itself after delivery (Aroori & Spence, 2008; Yunoki et al., 2017). At the moment, it is not possible to identify a unique cause for the entrapment of the median nerve. Therefore, three major risk factors have been identified:

1. Mechanical factors: the risk of CTS is higher in occupations in which the hand is exposed to high pressure, high force, repetitive work, and vibrating tools (Aroori & Spence, 2008).

2. Anatomical factors: narrowing of the carpal tunnel due to trauma or inflammation of the wrist (Solomon, Katz, Bohn, Mogun, & Avorn, 1999), and increased volume of the median nerve due to tumours and tumours-like lesions (Ibrahim et al., 2012).
3. Physiological factors: diabetes, alcoholism, vitamin toxicity or deficit, and exposure to toxins may play a role in CTS (Ibrahim et al., 2012).

1.2.5 Treatment of CTS

CTS treatment procedures can be categorised as surgical and non-surgical (Aroori & Spence, 2008; Ibrahim et al., 2012). The non-surgical treatments are appropriated for patients with mild to moderate CTS and include the use of a hand brace or wrist splint (to keep the wrist at a neutral position; Middleton & Anakwe, 2014), ultrasonic therapy, laser therapy, non-steroid anti-inflammatory drugs, and local injection of corticosteroids (Aroori & Spence, 2008; Chammas, 2014). Surgical treatment is usually recommended for moderate to severe CTS (Aroori & Spence, 2008). The treatment requires to divide the transverse carpal ligament to increase the space in the carpal tunnel, and therefore, to reduce the pressure on the median nerve (Aroori & Spence, 2008; Chammas, 2014; Ibrahim et al., 2012). The surgical procedure can be performed with an open or endoscopic release (Aroori & Spence, 2008; Chammas, 2014). The open release is the most common procedure because it is easy to perform and has a low complication rate (Aroori & Spence, 2008). Some complications include a potentially tender scar, persistent symptoms, wound complications, and reduced grip strength (Middleton & Anakwe, 2014). The endoscopic release is less invasive, facilitates the earlier return to work and reduces post-operative pain (Aroori & Spence, 2008). One stated advantage of this technique is the absence of palmar wound, which can be more comfortable for the patients (Middleton & Anakwe, 2014). However, this procedure has not been shown to provide superior outcomes to the open release (Middleton & Anakwe, 2014).

At present, there is no agreement on how to evaluate the effectiveness of the treatments (Aroori & Spence, 2008). Therefore, the patient undertakes different measures

including self-reported questionnaires, quality of life questionnaires, NCS (Aroori & Spence, 2008). Some questionnaires assess the whole upper body function while others focus on specific body parts (e.g., the wrist), however, only the Boston Carpal Tunnel Questionnaire specifically assesses CTS symptomatology and the functional status of people undergoing carpal tunnel release (Aroori & Spence, 2008; Levine et al., 1993).

1.2.6 Economic implications of CTS

CTS entails relevant individual and societal costs. It has been estimated (based on a study of 181 CTS patients from the United Kingdom) that each individual diagnosed with CTS goes through an economical cost ranging from £65 to £3971 (Lorgelly, Dias, Bradley, & Burke, 2005). Patient costs include transportation expenses, time spends at the clinic for consultation and surgery, time away from work while recovery and delay in returning to normal activities of daily life (Lorgelly et al., 2005). The societal costs refer to the expensive of the National Health Institute (NHS) to treat each patient, which has been estimated between £741 to £1102 (Lorgelly et al., 2005). In particular, endoscopic surgery has been evaluated as more expensive than open surgery (Lorgelly et al., 2005). NHS costs are a combination of resources used at the pre-operative, operative and postoperative stages, and additional expensive arising from complications with surgery or after surgery (Lorgelly et al., 2005).

1.3. Proprioception

Skilful hand function requires knowledge of the spatial location, posture, and movement of one’s hand (Rincon-Gonzalez, Buneo, & Tillery, 2011). In normal situations, this knowledge is available not only from vision, but also from proprioception — the sense of position and movement of the body from sensors in the muscles, tendons, and joints, and skin stretches around joints (see below). Indeed, even when we can see the hand, information from vision and proprioception is integrated to give more precise estimates of

hand position and posture than would be possible from one sense alone (Ernst & Banks, 2002; van Beers, Wolpert, & Haggard, 2002). In the following paragraphs, we outline the structures that provide proprioception information and the role of this sensory modality. Additionally, we detail examples of clinical tests used to assess proprioception. The overall purpose of this section is to understand the importance of proprioception during movement planning and execution and to use this knowledge to understand if the functional problems reported by CTS might arise due to an impoverishment of proprioception. As a secondary aim, we want to present the current tests for the assessment of proprioception and so outline why, in our view, a new clinical tool to assess proprioception is needed.

1.3.1 Overview of proprioception

The term proprioception arises from Latin ‘proprious’, belonging to one’s own, and ‘-ception’, to perceive. Proprioception is the sensation of body position and movement, which is personal, and typically absent from conscious perception (Tuthill & Azim, 2018). Proprioception allows the perception of body position and movement in three-dimensional space (Han, Waddington, Adams, Anson, & Liu, 2016; Sarlegna & Sainburg, 2009). Proprioception contributes to execution of accurate movements (Hoseini, Sexton, Kurtz, Liu, & Block, 2015) and appears to be particularly important for converting a movement plan into the specific motor commands needed to move the hand (Sarlegna & Sainburg, 2009). Proprioception, therefore, plays an important role in manual dexterity and everyday hand movements (Hoseini et al., 2015).

1.3.2 Sensory afferents of proprioception

Proprioception provides information about limb position, movement, and force (Proske & Gandevia, 2012). Here we define proprioception as all of the afferent signals indicating movement and posture/ position of the hand and arm. These afferents are:

1. Muscle spindles are stretch receptors located within the muscle tissues, which primarily detect changes and rate of changes in the length of the muscles (Riemann & Lephart, 2002). Muscle spindles provide information about the position and movement of the body (Proske & Gandevia, 2009, 2012). Evidence regarding the role of these afferents in providing proprioception information came from vibration studies, in which it was shown that the stimulation was predominantly perceived in the muscle spindles endings (Proske & Gandevia, 2009, 2012).
2. Golgi tendon organs provide information about muscle tension (Vallbo, Hagbarth, Torebjork, & Wallin, 1979). These afferents encode the signal for force (i.e., how much I am squeezing) and heaviness (i.e., how much force do I have to exert to hold an object; Proske & Gandevia, 2012).
3. Joint receptors primarily provide information about the movement of the joints (Proske & Gandevia, 2012). The rotation of the joint stretches the joint capsule on one side, as well the overlying skin, while tissue on the other side is unloaded (Proske & Gandevia, 2012). These afferents play an import role as a limit detector, by identifying the limit of the movement (Proske & Gandevia, 2012).
4. Cutaneous receptors are specialised mechanoreceptors in the glabrous skin, which can be dived between rapidly adapting receptors (the Meissner corpuscles and Pacinian corpuscles) and slowly adapting receptors (Merkel endings and Ruffing endings; Proske & Gandevia, 2012). The four cutaneous receptors encode movement sensation (Moberg, 1983; Proske & Gandevia, 2012). These afferents provide important information about the movement of the finger (Proske & Gandevia, 2012). The muscles that move the fingers are located in the forearm and hand, and their tendons have to cross different joint before reaching the fingertips, therefore the signals might be ambiguous (Proske & Gandevia, 2012). The cutaneous receptors in the skin of the fingers provide detailed information about the movement of each finger (Edin & Johansson, 1995).

Considering the complex nature of proprioception, we can suppose that an impairment of proprioception could, in principle, be selective to a particular afferent system. However, if we consider the hand innervation, we know that the afferent systems are innervated by the median, ulnar and radial nerves. Therefore, in this case, it might be difficult to see an impairment of an afferent system if only one nerve is impaired.

1.3.3 Proprioception tests

The complex 'multisensory' nature of proprioception, and the fact that it is used together with vision, and especially tactile sensation, create relevant challenges for the assessment of this sensory modality. To accurately investigate any sensory system, it is necessary to isolate it from the other sensory systems. Vision information is removed easily by preventing vision during the execution of a given task (e.g., by occlusion). Removal of tactile signals is far more challenging, however (Berryman et al., 2006). Indeed, it can be argued that perceiving properties of objects and the environment (as opposed to joint angles etc. per se) may not be possible from proprioception alone. Consider estimating the size of an object. At first, this is encoded by the joint angles of the digits, yielding the width of the grasp opening (Berryman et al., 2006; Perini, Powell, Watt, & Downing, 2020). However, Berryman et al. (2006) point out that hand opening decreases when we squeeze an object hard because the fingers deform. Therefore, understanding object size requires combining force and position information with tactile signals about fingertip deformation. Different tests are currently available to investigate proprioception in clinical settings, which can be categorised in two principal techniques (Hillier, Immink, & Thewlis, 2015):

1. Matching task: in this test, the patient has to match the position of the tested body part moved by the clinician (e.g., the left hand) with the contralateral body part (here the right hand) without visual feedback (Goble, 2010; Hillier et al., 2015; Hoseini et al., 2015). The clinician measures the accuracy of the matching position in different ways

(Goble, 2010; Hillier et al., 2015), ranging from the use of sophisticated equipment to visual inspection (Goble, 2010).

2. Passive motion direction detection threshold: in this test, the clinician moves the hand/joint in a specific direction (up or down), and the patient had to report the direction of motion (Hillier et al., 2015). This test is commonly called the 'up-down test'.

The tests mentioned above have two common features: they are fast and simple to administer — significant benefits in clinical practice, where consulting time is typically short. However, they entail different problems. In the matching test, because the patient has to match the position of the tested body part with the contralateral body part, possible proprioception impairments to the contralateral body might confound the performance. The up-down test can potentially add confounding sensory signals. While touching the finger of the patients, the clinician can apply a different amount of pressure on the side of the finger. This can result in additional tactile signals that can potentially indicate the direction of movement, which can be used to indicate the direction of motion even if proprioception is impaired (Hillier et al., 2015). Further, because the movement generated by the clinician has an unknown magnitude, the test provides a very crude measure of proprioception that can only detect severe impairments. Considering the different weaknesses of the available clinical tests to assess proprioception was the motivation that pushed us to create the prototype of a new clinical-friendly tool (see Chapter 4).

1.4. Grasping

This section aims to present how the visuo-motor control of grasping is achieved in the healthy population and how the system compensates for short-term manipulation of sensory signals, with the purpose of understanding possible long-term consequences of impairments to sensory signals in clinical populations. In our specific case, we predicted CTS affects the execution of grasping for different reasons. First, grasping is programmed to

anticipate consequences of impaired tactile sensation, and disruption to control of digit force could increase difficulties for patients to achieve a stable grasp during the final contact phase with the object (Johansson & Flanagan, 2009; Li & Nimbarte, 2006; Zhang et al., 2011). Second, tactile and proprioception information is essential for calibrating feedforward sensorimotor programmes, over longer timescales (van Beers et al., 2002). Impairments of these sensory signals might therefore result in long-term changes to grasp 'calibration'. Third, impairment to online information about digit posture from proprioception might affect the efficiency of grasping.

1.4.1 The two views on grasping

Grasping is a highly evolved type of motor behaviour that is considered the hallmark of dextrous manipulation (Jeannerod, Arbib, Rizzolatti, & Sakata, 1995) and is fundamental to the performance of many daily activities (Nataraj, Evans, Seitz, & Li, 2014). The function of a grasping movement is to acquire an object with the purpose of manipulation, identification, and use (Jeannerod, 1996). Currently, there is no agreement on how grasping movements are planned and executed, with explanations falling into two domains. The first domain suggests that grasping is composed of two components: reaching (to move the hand to the reach the object) and grasping (closing the hand to enclose the object, so that it can be acquired). In the original view of Jeannerod (Jeannerod, 1999; Jeannerod et al., 1995) , the two components are planned independently but their execution is temporally coupled, while according to the latter view of Goodale & Milner (1992), the two components are planned together. The second domain considers grasping as a combination of two pointing movements, one for the thumb and one for the digits; the movement of the digits is programmed and controlled independently but constrained by the their biomechanical coupling (Smeets & Brenner, 1999).

1.4.2 Key features of grasping

The kinematics analysis of grasping is used to characterise the movement 'velocity profile' of the wrist or thumb, and the 'grip aperture profile' defining the hand aperture. From both profiles it is possible to identify specific landmarks of grasping that occur in-flight, reflecting the anticipatory features of grasping.

The velocity profile is characterised by an asymmetric bell-shaped profile with a single peak (Jeannerod, 1984; Marteniuk, MacKenzie, Jeannerod, Athenes, & Dugas, 1987) An important landmark of the velocity profile is that the maximum velocity reached reliable scales with object distance, such that the hand moves faster for distant objects (Jakobson & Goodale, 1991; Jeannerod, 1984), reflecting anticipatory control of the hand velocity. The analysis of the profile provides additional information about the acceleration and deceleration phases of the movement (Jeannerod, 1996).

The grasping profile shows that the hand gradually opens before closing on the object (Jeannerod, 1996). Here, the landmark is represented by the peak grip aperture (PGA) that represents the moment of maximum opening of the hand, reached in-flight. The PGA scales reliably with object size, such that larger objects are associated with larger PGA (Jakobson & Goodale, 1991; Jeannerod, 1984). Also, distant objects elicit a larger PGA and a longer time to achieve the maximum opening is required (Jakobson & Goodale, 1991). The PGA occurs around 60-70% of the duration of the movement (Jakobson & Goodale, 1991; Jeannerod, 1984), reflecting the anticipatory feature of grasping (Jeannerod, 1984).

Both velocity and grip profiles preserve scaling abilities in-flight even in the absence of visual feedback of the hand and object (i.e., vision is prevented at the movement onset), indicating that the planning of the movement is anticipatory (Jakobson & Goodale, 1991).

Another feature of grasping that is specified partially before the hand contacts the object is grip force (Jeannerod, 1996, 1997). Grip force is necessary to grasp the object and to prevent slipping during object manipulation (Westling & Johansson, 1984). Cutaneous afferents and frictional changes provide useful information to update grip force (Johansson &

Westling, 1984). To correctly grasp an object, the grip force varies in parallel with the load force (to lift the object) until a stable grasping is achieved, demonstrating an anticipatory control of coordination (Jeannerod, 1996, 1997; Johansson & Westling, 1984).

1.4.3 The execution of grasping

The notion that important features of grasping are specified during the pre-contact phase should not mislead one into believing grasping control relies only on anticipatory behaviours. Indeed, the grasping system can rapidly react to unexpected changes in object size or position while the hand is moving (Hesse & Franz, 2009; Paulignan, Jeannerod, MacKenzie, & Marteniuk, 1991). Grasping control relies on a combination of anticipatory and online control from vision and proprioception. The combination of anticipatory features and online control allows the brain to estimate and control the execution of grasping under different conditions and in the presence of delays in the sensory feedback (Jeannerod, 1984; Paulignan, et al., 1991). Therefore, the execution of grasping can be considered as an optimisation problem.

An important assumption of the optimisation framework is that sensory feedback and sensorimotor controls are corrupted by noise, uncertainty (Ernst & Banks, 2002). According to the optimisation framework, the brain receives different noisy signals and combines them to create a final estimate (Ernst & Banks, 2002). During this process, the different sensory signals are weighted depending on their noise level, so that the nosier signals are weighted less (Ernst & Banks, 2002). Therefore, the final estimate is more reliable (i.e., less noisy) than each sensory signal alone. The optimisation framework underlines that the sensory system takes into consideration not only the estimate of object properties and state of the hand/arm, but also the noise (uncertainty) of these estimates to perform a grasping movement efficiently.

It has been shown that increased noise related to increased object size results in appropriated margin-for-error responses, in which the grip aperture increased to reduce the

chances of falling to grasp the object while preserving the scaling of grip aperture to object size (Hesse & Franz, 2009; Keefe, Suray, & Watt, 2019; Schlicht & Schrater, 2007). Calculating the margin-for-error appropriately implies that the brain knows how uncertain its estimate of object properties is, how that will inflate the probability of failure of the movement, and what 'adjustments' to make to compensate for that increased risk (Keefe et al., 2019). This indicates that the brain can manage the increased noise efficiently.

Also, when visual feedback is prevented at the movement onset, grip aperture is wide, and the overall movement is slower (Jakobson & Goodale, 1991; Jeannerod, 1996; Schettino, Adamovich, & Poinzner, 2003; Wing, Turton, & Fraser, 1986), which reflects compensatory strategies used by the sensory system to manage the increased noise. Therefore, even in these situations, the brain can manage increased noise in an efficient way.

1.4.4 The role of vision, tactile and proprioception information in grasping

The efficiency of grasping in a healthy system arises from a combination of visual, cutaneous and proprioception information (van Beers et al., 2002; Witney, Wing, Thonnard, & Smith, 2004). In the following sections, a brief description of the role of the different sensory modalities is presented, and evidence about the compensatory strategies used in the absence of each sensory modality.

The role of visual information

The contribution of vision to grasping movements has received considerable attention. Vision provides information about the target position with respect to the viewer, its spatial relations with other objects and the intrinsic object properties (Jackson, Jones, Newport, & Pritchard, 1997; Jeannerod et al., 1995). To gain insight into the contribution of vision, studies investigated changes in the movement due to different visual conditions. One method consists of comparing the execution of grasping under binocular and monocular

viewing conditions. Removing binocular information (by closing an eye), either before or during the movement, results in larger grip apertures (Keefe, Hibbard, & Watt, 2011; Melmoth & Grant, 2006). In this case, the absence of binocular information increases visual uncertainty, therefore, the margin-for-error response increases the grip aperture to prevent missing the object. As well, in the absence of binocular information, the overall movement and hand velocity are slower (Schettino et al., 2003; Servos, Goodale, & Jakobson, 1992), reflecting a compensatory strategy to manage the increased noise. However, another study reported no effect of removing binocular on hand velocity (Melmoth & Grant, 2006).

Another method used to examine the role of visual feedback is to remove vision at the starting of the movement (Jakobson & Goodale, 1991; Jeannerod, 1984). In this situation, the hand aperture is consistently wider, and scaling is still preserved (Jakobson & Goodale, 1991; Jeannerod, 1984; Rand, Lemay, Squire, Shimansky, & Stelmach, 2007). Again, this can be interpreted as a safety margin strategy, used in the presence of increased uncertainty to reduce the probability of failing to grasp the object (Hesse & Franz, 2009; Keefe et al., 2019; Schlicht & Schrater, 2007). When vision is removed at the movement onset, it is required more time to start the movement, the overall movement is slower with extended deceleration and acceleration phase (Jakobson & Goodale, 1991; Jeannerod, 1996; Schettino et al., 2003; Wing et al., 1986). As before, these changes reflect the ability to manage the increased variability generated by the absence of vision.

Overall, these results indicate that grasping movements in healthy populations are affected by the loss of visual feedback, but the consequences are subtle, and they can interpret as efficient management of the increased noise.

The role of the tactile information

Tactile signals arise from mechanoreceptor's afferents and myelinated fibres (Johnson, Yoshioka, & Vega Bermudez, 2000). As mentioned before, it is possible to identify the rapidly adapting receptors (the Meissner corpuscles and Pacinian corpuscles) and slowly

adapting receptors (Merkel endings and Ruffing endings; Johansson, 1978; Johansson, Landström, & Lundström, 1982; Johansson & Vallbo, 1979; Proske & Gandevia, 2012). Tactile signals provide useful information for dextrous manipulation (Nowak, Glasauer, & Hermsdörfer, 2004). First, the cutaneous deformation of the skin reflects the successfulness of grasping (Johansson, 1991). Second, each tactile stimulus activates different mechanoreceptor populations, which generates a unique pattern of activation (Johansson & Vallbo, 1976; Johansson & Flanagan, 2009). Third, tactile signals provide information about the shape of the contact site, direction and spatial resolution of the fingertip friction between the skin and the object (Flanagan, Bowman, & Johansson, 2006; Johansson & Vallbo, 1983).

Mechanoreceptors concentration is higher in the distal part of the finger, with a higher concentration in the index and middle finger than the thumb and the radial part of the ring finger (Johansson & Vallbo, 1979). The distribution of the mechanoreceptors explains why spatial discrimination is higher at the fingertips and decreases toward the wrist (Johansson & Vallbo, 1983). The high density of mechanoreceptors units in the fingertips seems to match the function of the skin as an exceptional sensory region (Johansson & Vallbo, 1979).

Effects of impoverished tactile information on grasping: the anaesthesia case

To our knowledge effects of chronic tactile impairments (e.g., caused by CTS) on grasping kinematics has not been determined. Experimental studies have, however, examined the effects of temporary digit anaesthesia, offering insight into how the sensorimotor system might compensate for tactile impairment during the execution of grasping. Gentilucci, Toni, Daprati, and Gangitano (1997) showed that the application of anaesthesia causes an increase in the maximum opening of the hand, stretching of the movement duration and the time to reach the maximum opening of the hand, which was more variable (Gentilucci et al., 1997). Anaesthesia did not affect the ability to scale the hand aperture according to object size and to grasp the object (Gentilucci et al., 1997).

Additionally, anaesthesia has been shown to affect digit force. Grasps made with anaesthetised fingertips have been found to result in a higher grip force baseline and increased intensity of grip force modulation in response to load changes, while the ability of the system to anticipate changes in load force is not affected (Nowak et al., 2001). Cutaneous anaesthesia also disrupts the coordination between grip and lifting force, resulting in more object slips (Monzée, Lamarre, & Smith, 2003; Westling & Johansson, 1984). This can be interpreted as an increase of slip force (i.e., the minimum force needed to lift an object) due to the reduced sweating and lower object friction caused by anaesthesia (Johansson & Westling, 1984; Nowak et al., 2001). Therefore, to prevent increasing numbers of object slips, participants increase the grip force to maintain an adequate safety margin (Nowak et al., 2001).

The role of *proprioception information*

As noted previously, isolating the role of proprioception from tactile signals is challenging, and so its role in grasping, specifically, is relatively understudied. We can, however, gain some insights into the effects of impaired proprioception from work that has removed proprioception through surgery, studied rare sensory neuropathy or used vibration methodologies (Sarlegna & Sainburg, 2009).

Impairment of proprioception information: the deafferentation case

Deafferentation is caused by the damage to large sensory fibres resulting in the loss of sense of touch and proprioception (Miall, Rosenthal, Ørstavik, Cole, & Sarlegna, 2019; Sarlegna & Sainburg, 2009). Deafferentation offers a unique opportunity to study how the sensorimotor system works in a situation of profound sensory loss. The study of deafferentation can improve our understanding of how proprioception deficits affect the execution of grasping (both anticipatory and online control) and how the sensorimotor system compensates for it. Research studies have assessed the anticipatory features of grasping by

assessing the kinematics of patients' movement. Gentilucci, Toni, Chieffi, and Pavesi, (1994) found that a deafferented patient showed increased grip aperture in the absence of visual feedback, which reflects an increased reliance on a safety margin strategy during movement. As well, the deafferented patient showed preserved grip aperture and velocity scaling regardless of visual feedback condition (Gentilucci et al., 1994). Independently from visual feedback condition, deafferented patients showed prolonged movement time (Gentilucci et al., 1994; Miall et al., 2019), which is likely to reflect a great task difficulty. Gentilucci et al. (1994) found longer peak velocity and closing time for the deafferented patient. Miall et al. (2019) and Hoellinger et al. (2017) found extended deceleration time for deafferented patients.

Also, different studies assessed the grip force control in deafferented patients. These studies showed that patients use a higher amount of grip force to lift an object in the presence of visual feedback (Hermsdörfer, Elias, Cole, Quaney, & Nowak, 2008; Nowak, Glasauer, & Hermsdörfer, 2003; Nowak et al., 2004), which is likely to reflect a strategy to compensate for the sensory loss (Nowak et al., 2004). These results indicate that the presence of visual feedback can improve the performance of deafferented patients, but, the help provided is still not sufficient to produce a comparable performance to healthy controls (Hermsdörfer et al., 2008). Although quite variable, the patients in the study of Hermsdörfer et al. (2008) showed preserved force scaling. The patient in the study of Nowak et al.(2004) showed inaccurate grip force scaling, while the patients in the study of Nowak et al. (2003) showed preserved force scaling. The difference in the results might be due to the fact that in Nowak et al. (2003),the patient was required to repeatedly lift the same object, while in Nowak et al.(2004) the object to lift varied in each trial.

As we saw previously, another relevant feature of the grasping system in healthy participants is the ability to quickly adapt to online perturbations. This has also been explored in deafferented patients. However, the results of this grasping feature are not straightforward. Gentilucci et al. (1994) applied a spring between the fingers that started to develop force

when the finger aperture reached a pre-determined size. Following this, the patient was not able to correctly adjust the hand aperture and failed to grasp the object (Gentilucci et al., 1994), which might indicate the impossibility to use new feedbacks (i.e., vision to update the online control of the hand). In another experiment by Sarlegna, Malfait, Bringoux, Bourdin, and Vercher (2010), the patient had to move towards the object in a new force field created by a rotating platform, which generated a novel force field that deviated the arm from its intended trajectory. The patient was able to adapt to the new force, however, the performance was more variable and less efficient than the performance of healthy participants (Sarlegna et al., 2010). Interestingly, and in contrast to the results of Gentilucci et al. (1994), the deafferented patient in the study of Sarlegna et al. (2010) showed after-effects when tested after the rotation, indicating that it is possible to update the central representation of the limb just with vision and without proprioception information. A possible explanation of the results mentioned above could lie in the type of perturbation adopted by the two experiments, mechanical in the case of Gentilucci et al. (1994; spring between the fingers) and visuomotor in the case of Sarlegna et al. (2010). It seems that mechanical perturbations rely on proprioception information, while, visuomotor perturbations rely on vision information (Pipereit, Bock, & Vercher, 2006).

Overall these results indicated that in the presence of loss of tactile and proprioception information deafferented patients can manage efficiently the increased noise generated by the loss of sensory information.

1.4.5 Grasping in CTS

The majority of studies of grasping in CTS have examined grip force. Some work has looked at the accuracy of pinching movements (between thumb and index finger), while other work has examined whole-hand grasping, focusing on the challenge of coordinating affected and non-affected digits. To our knowledge, no previous work has examined grasp kinematics in CTS.

Different studies that assessed the whole-hand grip force in CTS showed that patients exhibited higher grip force (Chen et al., 2015; Zhang, Johnston, Ross, Smith, et al., 2011; Zhang et al., 2012). CTS patients showed lower force coordination between the affected (innervated by the median nerve) and non-affected digits (part of the ring finger and little finger; Chen et al., 2015; Zhang et al., 2011). CTS patients showed anticipatory grasp control, indicated by the preserved ability to scale grip force to object weight (Zhang, Johnston, Ross, Smith, et al., 2011). As well, CTS patients showed preserved ability to adapt to change in the position of the object centre of the mass, achieved by adding additional weight on the side of the thumb, the centre of the object or finger side (Zhang et al., 2012). However, CTS patients showed a less accurate force scaling than controls, which underlines the pivotal role of cutaneous mechanoreceptors in tasks that require fine motor control (Zhang, Johnston, Ross, Smith, et al., 2011).

Similarly, Lowe and Freivalds (1999) showed that CTS patients exhibited higher grip force and impoverished abilities to modulate grip force when using the thumb and index finger. The increased grip force might reflect a compensatory strategy to prevent object slips (Lowe & Freivalds, 1999). In contrast, in another pinch force task, Li, Evans, Seitz, and Li (2015) reported a similar amount of force between CTS patients and healthy controls, when visual feedback of the hand was available. Only when vision was removed, patients showed less accurate grip force (Li et al., 2015). Overall, independently from the visual feedback conditions, patients showed increased pinch force variability than healthy participants (Li et al., 2015). In another study, Zhang et al. (2013) showed that CTS patients used the same amount of force as healthy participants when using the median nerve innervated fingers (thumb, index finger and middle). However, CTS patients significantly increased the amount of force used when the ring and little fingers were used. These results suggest that the integration of sensory feedback from affected and non-affected digits might challenge more the sensory system than integrating only signals from the CTS affected digits (Zhang et al., 2013).

Only two studies to our knowledge assessed the accuracy of pinch movement in CTS. In the study by Gehrmann et al. (2008), CTS patients and healthy controls were asked to close the eyes and reproduce a pinch movement between thumb and index finger as if they were picking up a small object, therefore, the tips of the digits did not touch. CTS patients showed increased variability in the position of the joint angles of the tips of the thumb and index finger, and in the distance between the tips of the thumb and index finger compared to controls (Gehrmann et al., 2008). Overall the results indicate impoverished precision of the pinch performance in CTS patients (Gehrmann et al., 2008). As suggested by the authors, the results can be attributed to the impairment of the muscles, and therefore the innervated joints, in the thumb and index finger (Chammas, 2014; Demircay et al., 2011; Duncan et al., 2013; Wang, 2018), and by the impairment of the cutaneous receptors in the skin of those fingers (Chammas, 2014; Ibrahim et al., 2012). The study from Gehrmann et al. (2008), provide relevant information about the pinch variability, however, it does not provide information regarding the execution of the overall movement.

In another study by Nataraj et al. (2014), CTS patients and healthy controls were required to perform a reach-to-pinch movement towards the reflection of a virtual object, which was displayed on a mirror. The hand used to perform the movement was positioned behind the mirror, therefore, visual feedback of the hand was not available (Nataraj et al., 2014). As previously reported by Gehrmann et al. (2008), CTS patients showed increased variability in the distance between thumb and index finger and the joint angles compared to healthy controls (Nataraj et al., 2014). CTS patients showed increased variability in the transport of the hand and a reduction in the accuracy and precision of the pinch position compared to the virtual target (Nataraj et al., 2014). The results might be interpreted as consequence of the impairment of the muscles, joints and cutaneous receptors in the skin of the thumb and index finger (Chammas, 2014; Demircay et al., 2011; Duncan et al., 2013; Ibrahim et al., 2012; Wang, 2018). CTS patients showed increased variability in pinch performance and during reaching movement, therefore, it is likely that CTS affects not only

the hand but also the entire upper extremity (elbow and shoulder; Nataraj et al., 2014). The results from the study of Nataraj et al. (2014) showed that CTS impoverish the ability to perform a reach-to-pinch movement. However, in our opinion is still missing a comprehensive understanding of how CTS affect the execution of grasping towards real objects.

Perhaps the closest study of grasping task in CTS is a study by Glazebrook, Brown, Prime, Passmore, and Marotta (2020). The study compared grasping movements towards real objects, without visual feedback, made with and without temporary paraesthesia, induced by electrically stimulating the median nerve at the forearms (Glazebrook et al., 2020). Paraesthesia induced a manipulation that is somewhat close to a short-term CTS. Paraesthesia extended the time to reach peak velocity, peak deceleration time and peak grip aperture time (Glazebrook et al., 2020). Paraesthesia increased the overall movement variability, in particular the landing position of the index finger (Glazebrook et al., 2020). Even in the presence of paraesthesia the grip scaled with object size (Glazebrook et al., 2020). However, the hand aperture was smaller in the presence of paraesthesia (Glazebrook et al., 2020), indicating that the system did not embedded the margin-for-error. The authors suggested that this might arise from a bias in interpreting the proprioception signals. Therefore, the hand is perceived as larger than it is, and so it is open less (Glazebrook et al., 2020). This interpretation, however, conflicts with the idea that minor impairments can be managed efficiently by the sensory system.

The above discussions highlight that is missing a comprehensive characterisation of grasping movement, towards real objects, in CTS patients. By doing so, we could understand if relative mild impairment can be interpreted as adaptive responses to increased sensory uncertainty.

1.5. Thesis outline

In this thesis, we decided to assess the sensory and motor consequences of CTS. Functionally, patients report problems in manipulating small objects, and impaired fine motor

skill. Tactile impairment caused by CTS can partially explain these problems, however, sensorimotor research underlines the importance of proprioception to perform ‘smooth’ hand movement. It is still unclear if CTS impairs digit proprioception.. As well, we used CTS to assess if relative mild impairment can be interpreted as adaptive responses to increased sensory uncertainty.

Chapter 2 examines if CTS affects the pre-contact events of grasping. We recorded movement trajectories of CTS patients and healthy participants towards objects of different sizes/distances while manipulating the availability of vision to force participants to rely on non-visual signals. To our knowledge, this is the first study that investigates the anticipatory feature of grasping towards real objects in CTS. By doing so, we hope to understand if the current theory of grasping can explain the sensorimotor deficit showed in these patients.

Chapter 3 investigates if digit proprioception is impaired in CTS patients. We used a two-interval forced-choice (2-IFC) haptic size-discrimination judgement task, to measure the sensitivity to the opening of the unseen thumb and index finger. CTS patients, with mild to moderate severity and healthy participants, took part in this experiment.

Chapter 4 develops a new clinical tool to investigate digit proprioception, the *block-difference test*, in which participants have to discriminate the bigger block out of three objects. To assess the validity of our new test we aimed to compare the performance with three experimental-based tests: i) comparing static-proprioception to vision task, aims to investigate if participants can correctly discriminate if a virtually presented object is smaller/larger than the hand aperture, we used a psychophysical approach; ii) manual estimation task, which aims to investigate if participants can correctly reproduce the size of a seen object by separating the unseen thumb and index finger; iii) haptic size-discrimination test, the same test that we used in Chapter 3. We used different techniques to assess the validity of our new clinical test because we want to create a simple and practical tool that can provide results that correlate with more rigorous experimental procedures. However, due to the COVID outbreak, we could only pilot the different tests.

Chapter 5 summarises the findings of the empirical chapters. It presents the broad implications of the work included in the thesis, addressing gaps in our knowledge, and pointing to new directions.

Chapter 2. Does Carpal Tunnel Syndrome affects the anticipatory features of grasping?

2.1 Introduction

Grasping movements are an integral part of human hand function, and impairments to grasp control are disruptive to daily life. Healthy grasping is characterized by predictive movements and relies not only on vision but also proprioception and touch. The hand shapes to approximate target object properties such as size, shape, and orientation ‘in flight’, prior to object contact (Jakobson & Goodale, 1991; Jeannerod, 1984; Marteniuk, Leavitt, MacKenzie, & Athenes, 1990). These anticipatory pre-contact movements are markers of a sophisticated “feedforward” planning process necessary for fluid and efficient control of actions (Hesse & Franz, 2009). In healthy individuals, the control of grasping relies on a combination of feedforward control and online feedback from vision and proprioception. This sophisticated process can be disrupted following both central (Pisella et al., 2009) and peripheral-level (Hermsdörfer, Hagl, & Nowak, 2004) injuries, the study of which has yielded valuable insights as to the fundamental nature of these mechanisms.

The combination of highly refined feedforward and feedback control mechanisms necessary for fluid and efficient grasp control enables the brain to estimate and control the probability of successful action outcomes under varying conditions, and despite inherent delays in sensory feedback (Jeannerod, 1984; Paulignan, et al., 1991). Therefore, we can consider the sensorimotor control of grasping as an optimisation problem. An important premise of this framework is that perception and sensorimotor control are corrupted by noise, or uncertainty (Ernst & Banks, 2002), and that managing this noise appropriately is critical to efficient and effective movement control. This approach highlights how effective reach-to-grasp movements require not only taking into account the magnitude of estimates of object properties, and the state of the hand/arm, but

also the noise (uncertainty) in those estimates. To better understand this framework, we can consider a situation of visual uncertainty (e.g., blurring the vision). Left ‘unmanaged’, this increased uncertainty would presumably propagate into noisier movements, and thus a higher probability of grasping errors. Instead, the sensorimotor system opens the grasping hand systematically wider with increasing uncertainty, increasing the spatial margin-for-error and thereby controlling the (otherwise increased) error rate (Keefe et al., 2019; Schlicht & Schrater, 2007). These findings suggest that the brain is sensitive to both the degree of visual uncertainty and how it affects the probability of errors, enabling movements to be adjusted accordingly, to anticipate end requirements. Generally, the theoretical framework of uncertainty/optimisation highlights how relatively subtle impairments may have substantial effects on the fluidity and efficiency of grasping movements. It also provides a principled approach to understanding these effects, by considering them as (appropriate, compensatory) responses to impaired sensorimotor signals.

Here, we examine how Carpal Tunnel Syndrome (CTS) affects the anticipatory movements that characterise reaching-to-grasp. CTS results from chronic median nerve compression at the wrist (Aroori & Spence, 2008; Middleton & Anakwe, 2014). Well-established consequences of CTS include diminished tactile sensitivity in the affected digits (Aroori & Spence, 2008; Chen et al., 2015; Gehrmann et al., 2008; Wolny, Saulicz, Linek, & Myśliwiec, 2016). Functionally, patients experience difficulty handling objects (Aroori & Spence, 2008; Middleton & Anakwe, 2014), and fine motor skills are diminished (Amirjani, Ashworth, Olson, Morhart, & Chan, 2011). CTS also disrupts digit force control when grasping and manipulating objects (Zhang et al., 2011, 2012), and the spatial alignment of affected digits during non-object directed precision pinch movements (Gehrmann et al., 2008; Nataraj et al., 2014). The portion of the median nerve affected by CTS (i.e., beyond the wrist) mediates both sensory and motor functions that are involved in grasping. This includes some of the thenar and lumbrical muscles of the hand, involved in so-called precision grip, using the thumb and index finger, respectively (Duncan et al., 2013). The median nerve is also

typically described as innervating cutaneous afferents in the palmar surface of the thumb, index, middle, and first half of the ring finger (Chammas, 2014; Duncan et al., 2013). Notably, other structures largely unaffected by CTS are also likely to contribute to reach-to-grasp movements, including forearm muscles used predominantly in executing whole hand 'power grips', and skin-stretch receptors in the back of the fingers, and digit joint receptors, both of which mediate proprioceptive signals (Moberg, 1983) and can potentially signal hand opening (Duncan et al., 2013).

Current theoretical ideas about grasp control, together with empirical data from patients and healthy participants, suggest CTS (and other impairments to the peripheral nervous system of the hand and arm) could affect reach-to-grasp movements for any of several different reasons. First, the finely tuned nature of grasping suggests that movements may be programmed to anticipate the consequences of impaired somatosensory signals. For example, impaired tactile sensation could make it harder to detect when the digits have made contact with a target object (Johansson & Flanagan, 2009), and sense and control digit forces after object contact (Li & Nimbarte, 2006; Zhang et al., 2011). If the sensorimotor system can predict the consequences of these 'post-contact impairments', similar to the visual uncertainty case above, we might expect to see appropriate increased margin-for-error responses. Specifically, the hand may move slower and open wider. Consistent with this hypothesis, anaesthetising the fingers results in slower movements and wider hand opening during grasping (Gentilucci et al., 1997).

Second, CTS may impair the calibration of feedforward sensorimotor programmes used to plan and control efficient movements. 'Forward models' allow the brain to determine differences between predicted and actual sensorimotor consequences of movements, enabling updating of future action plans, and rapid online correction of errors during movements, despite inherent delays in sensory feedback (Shadmehr, Smith, & Krakauer, 2010) . Tactile and proprioceptive signals are essential for calibrating these processes (van Beers et al., 2002). Chronic impairments to these signals caused by

CTS could therefore disrupt this calibration, altering grasp control in a more general way. Assuming that noisier inputs result in greater uncertainty in sensorimotor programmes, the predicted effects are similar to those described above. Movements based on noisier 'internal models' in CTS may be both more variable, and error-prone. Alternatively, if increased uncertainty can be estimated and appropriately taken into account, the sensorimotor system may programme slower movements and/or wider hand opening, to mitigate the risk of errors.

Third, CTS may impair the precise control of hand position in-flight. As noted above, the median nerve innervates some intrinsic hand muscles involved in moving the index finger and thumb. CTS may impair precisely calibrated activation of these muscles, resulting in grasping movements that less reliably anticipate end requirements. CTS may also impair the associated proprioceptive signals that provide moment-by-moment feedback about digit position as movements unfold. An important premise here is that proprioception contributes to movement control even when vision is simultaneously available. The optimisation framework outlined above describes how when input sources convey redundant information, in this case, vision and proprioception provide redundant signals to the state of the hand, the ideal way for the brain to use this information is to integrate across input sources, giving less weight to nosier signals, rather than to rely selectively on one or the other signals (Ernst & Banks, 2002). This allows a more precise estimate of the state of the hand than is possible from either signal alone. Empirical data show close agreement with this principle (Balslev, Miall, & Cole, 2007; Rossetti, Desmurget, & Prablanc, 1995; Sober & Sabes, 2003; van Beers et al., 1999). According to this framework, impaired proprioception due to CTS is expected to result in noisier estimates of the state of the hand during reach-to-grasp movements. Together with noisier motor output, online control of the hand in CTS may therefore be subject to increased noise. If the sensorimotor system has knowledge of this noise and its consequences for movement control, the system may respond adaptively, slowing movements and opening the hand wider, to mitigate against failures. Consistent with this hypothesis and the optimisation framework, loss of hand (and arm) proprioception in

chronic upper-limb deafferented individuals results in broadly this pattern of compensatory changes to grasping kinematics (note that these results cannot be unambiguously attributed to impaired proprioception and/or muscle recruitment since these patients also have diminished or absent tactile sensitivity; Gentilucci et al., 1994; Miall et al., 2019). Alternatively, if the sensorimotor system cannot reliably estimate and manage noisy somatosensory input signals, this noise may propagate and contribute to grasping errors.

In this study, we characterise how mild to moderate CTS affects the controls of reach-to-grasp movement towards real objects. We examined reach-to-grasp movements made both with normal vision throughout, and with vision occluded at movement onset (i.e., without visual feedback). This manipulation is important since the removal of visual feedback of the moving limb will force the system to rely more on non-visual signals, and thus should provide a more sensitive test of the effects of CTS on grasping. Healthy controls show robust compensatory responses to this 'challenge', reliably increasing hand opening during grasping, and also (in some studies) reducing the speed of their movements (Connolly & Goodale, 1999). If CTS patients are able to manage noisy non-visual signals in an optimal way, only subtle differences between CTS and Controls are expected when vision is available because redundant and highly reliable information from vision is available. Also, if noise is accurately estimated and managed in CTS then we expect to see characteristic scaling of grip aperture and hand speed according to object size and distance (Churchill, Hopkins, Rönnqvist, & Vogt, 2000; Connolly & Goodale, 1999; Jakobson & Goodale, 1991), even in the absence of visual feedback. Finally, removing vision may result in more pronounced increased margin-for-error responses — slowing of movements, and/or opening of the hand during grasping — to compensate for less reliable non-visual inputs.

Alternatively, if increased noise is 'unmanaged' in CTS, increased variability in grasping movements is expected, and, in the extreme, increased noise may propagate and raise the probability of grasping errors. Increased variability in the spatial alignment of the index finger and thumb while making non-object directed precision pinch movements has

been documented in CTS (Gehrmann et al., 2008; Nataraj et al., 2014). Similarly, after anaesthetising the digits, Gentilucci et al. (1997) report increased variability in the time taken to reach peak grip apertures (hand opening phase of the movement), and the spatial trajectories of the digits when grasping without visual feedback. Notably, increased movement variability and evidence that CTS patients nonetheless manage increased noise in ways that are consistent with the optimisation framework is also possible.

Another possibility that we had not considered before our study was planned and data collection completed is motivated by new findings from Glazebrook et al.(2020). This study compared reach-to-grasp movements (without visual feedback) made with and without temporary paraesthesia, induced by electrically stimulating the median nerve at the forearm. This manipulation, which is somewhat analogous to short-term CTS, had the primary effect of reducing in-flight hand opening. The authors suggested this effect might result from nerve stimulation causing a bias in the interpretation of proprioceptive signals (i.e., the hand opening felt wider than it was). This account conflicts with the idea that responses to minor impairments can be understood in terms of adaptive management of sensorimotor uncertainty (i.e., that they can be explained by normative theories of sensorimotor control).

2.2 Methods

2.2.1 Participants

Twenty-five CTS patients and 32 healthy controls participated in the study. All participants provided informed consent in accordance with the Declaration of Helsinki. The study was approved by the Bangor University School of Psychology Research Ethics Committee, and the Betsi Cadwaladr University Health Board (IRAS project ID: 195274).

The mean age of the CTS patient group was 52 years (SD = 10.6 years; range: 25-67 years) and included 8 males, 17 females. Patients were diagnosed clinically and confirmed as mild (N = 11), moderate (N = 12), or severe (N = 2) based on electrophysiological measures. Eleven patients had bilateral CTS, six had unilateral left-hand CTS, and eight

patients had unilateral right-hand CTS. Patients had no other comorbidities. All were right-handed according to self-report.

The mean age of the group of healthy controls was 40.5 years (SD = 11.99 years; range: 25-70 years) and included 12 males and 20 females. One participant was left-handed, and the rest were right-handed, according to self-report.

All participants had normal or corrected-to-normal vision, and no participants had a history of neurological or psychiatric illness. Normal depth perception was confirmed using the Randot® Stereotest (Stereo Optical Co., Inc.). The study took approximately 2 hours to complete, and participants received financial compensation. All participants were naïve to the predictions of the study.

2.2.2 Primary measure: the grasping task

Participants were seated at a table, with their eyes ~400mm above the table surface (Figure 2.1). In the starting hand position participants held down a start button positioned 5cm from the table edge. Participants were positioned such that the start button was on the same side of the body as the hand being used, and could be pressed while holding the wrist straight, and with the forearm alongside the body, parallel to the body midline. This posture was intended to minimise wrist extension/flexion when the hand was at rest, and thus reduce the likelihood that CTS patients would experience increased symptoms (e.g., paraesthesia, pain, numbing) as a consequence of performing the task. To make the starting posture easy to maintain, participants rested their arm in an arm support (a foam-lined channel protruding from the table). To control the starting position of the digits, participants pinched their thumb and index finger together to hold a 1 cm diameter sphere attached to the start button. The setup also enabled the start button to be held depressed passively, by just the weight of the digits, again to avoid exacerbating patients' symptoms. The state of the start button was monitored by the experiment computer.

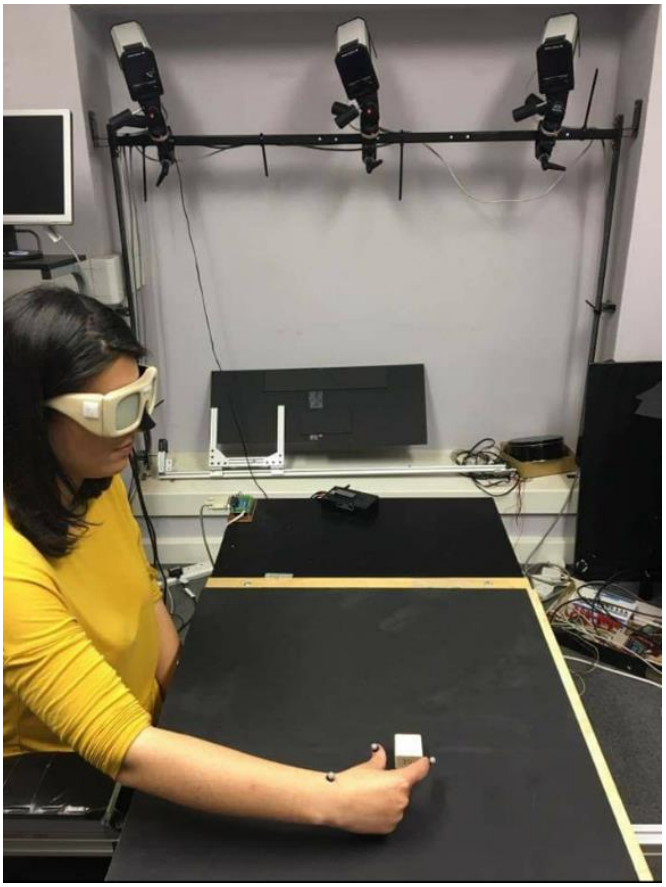


Figure 2.1. Experimental set-up. Photo of a participant performing the task with the right hand, while wearing the PLATO googles. It is possible to observe (on the bottom left) the arm support on which participants rested the arm before the beginning of each trial, and the three markers on the participant's hand.

On each trial, participants reached to grasp objects front-to-back, with their index finger and thumb. Target objects varied in both size and position. There were five different target objects, all rectangular cuboids made from wood. Their sizes, in the grasped direction, were 25, 30, 35, 40, and 45 mm (they were all 35mm wide and 25 mm high). The objects were presented at three different distances — 150, 300, and 450 mm — straight ahead of the starting hand position. To manipulate the availability of visual feedback (and to control vision of the scene between trials) participants wore liquid crystal shutter goggles (PLATO; Translucent Technologies, Toronto, ON, Canada) for which the state of the lenses can change quickly from transparent to opaque, and vice-versa.

Grasping movements were recorded using an infrared motion capture system (ProReflex; Qualisys AB, Sweden). The system captured the instantaneous *x, y, z* positions

of spherical infrared-reflective markers at a sampling rate of 240 Hz. Three markers were used, affixed to the: (1) ulnar tip of the thumb nail, (2) radial tip of the nail of the index finger, and (3) wrist, on the radial side.

Procedure

Each trial began with participants in the starting hand position with the start button held down and the goggles closed, so that vision was unavailable. After the experimenter placed the target object down on the table, the trial was initiated by the goggles changing from opaque to transparent. After a one-second 'object preview' period in which the goggles remained open and participants were instructed not to move, an auditory tone cued participants to initiate their grasping movement. Participants were required to respond within 600 ms after the auditory start cue. These experimental design choices were included to minimise potential differences in object viewing and premovement planning times between patients and controls; differences should instead be expressed in post-movement-onset kinematics. Trials where the start button was lifted before the auditory cue, or >600 ms after, were excluded and repeated at the end of the block to obtain a complete data set, with balanced conditions (i.e., an equal number of trials per object size and distance). Participants were instructed to grasp objects from front-to-back, using the thumb and index finger only (i.e., a 'precision pinch'), and to move at a comfortable speed, lift the object, and place it to the side of the table.

CTS patients and controls performed grasping movements both with and without visual feedback, completed in separate blocks of trials. In the Visual Feedback condition, the goggles remained open throughout the entire movement, so vision of the hand and scene was available from the start of the trial. In the No-Visual Feedback condition, the goggles turned opaque when the start button was released, so that no vision of the moving hand and scene were available during grasping.

Participants performed eight blocks of 45 trials; 360 trials in total. Four blocks were performed with each hand: two with visual feedback and two without. Left- and right-hand grasping alternated after the execution of two blocks of trials (one with Visual Feedback and one with No-visual Feedback), giving each hand rest periods to minimise the likelihood that CTS patients' symptoms would change during the experiment. Block order was counterbalanced across participants. Within each block, each combination of target object size and distance was presented three times, randomly ordered. Thus, with two blocks per condition, participants completed 90 trials with each hand, in each visual feedback condition (with the exception of one CTS patient who discontinued testing halfway through the experiment due to discomfort, after completing 45 trials per visual feedback condition per hand).

Dependent measures

Motion capture data were processed using custom software written in Matlab (Mathworks Inc., Natick, MA, USA). Raw 3-D coordinates from each marker were low-pass filtered using a 2nd order Butterworth filter (12 Hz cut-off) before analysis. For a very small proportion of trials, motion capture data were incomplete due to technical issues with marker registration. This means that we could not compute values for 0.35% trials from CTS patients, and 0.14% trials from controls.

Kinematics data were analyzed using the data acquisition software Qualisys Track Manager (Qualisys AB, Sweden). We identified all the four markers positioned on the thumb, index finger, wrist and object of one trial to generate an Automatic Identification of Markers (AIM) model. After, we applied the AIM model to all the trials performed by the CTS patients and Controls to facilitate the labelling process. Then, we manually checked all the trials to assess that the AIM model correctly identified all the markers and to correct possible mistakes in the labelling procedure. During the manual screening, a gap fill procedure was applied to fill the gap between a maximum of 20 consecutive frames.

Peak Velocity. Peak velocity was defined as the largest point of inflection in the 3-D velocity profile of the wrist marker, and was used to quantify the overall speed of grasping movements.

Movement duration, acceleration and deceleration. Movement duration was defined as the time between the start of the movement (i.e., participants lifting the starting button) and the movement end point (i.e., object grasped). The movement end point was considered to be when the object was picked up, defined as the first frame where the marker attached to the object was raised vertically by > 5 mm. We also checked that the digit and object markers were moving consistently at this point (i.e., that a stable grasp had been achieved) to guard against collisions with the object falsely triggering end-point detection. Movement duration intentionally captures the pre-contact phase of the movement, and any fumbling and final adjustment required to obtain a stable grasp.

Movement duration was also divided into acceleration and deceleration times, defined as the periods before and after the time at which peak velocity occurred, respectively. Previous work has found that removing vision at movement onset increases the duration of grasping movements in healthy controls, and, in particular, the time spent decelerating (Jakobson & Goodale, 1991; Jeannerod, 1996; Schettino et al., 2003; Wing et al., 1986). Other work demonstrates that the manipulation of visual conditions, such as when comparing grasping under monocular vs. binocular ('normal') visual conditions, results in extended deceleration times and movement durations (Schettino et al., 2003; Servos et al., 1992). Similar to our expectations regarding peak velocity, we reasoned that CTS may show increased movement durations disproportionately expressed as increased deceleration times when visual feedback is unavailable, and patients are forced to rely on impoverished somatosensory signals.

Peak grip aperture. Peak grip aperture is defined as the maximum separation between the index finger and thumb during grasping — i.e., pre-contact with the object. The peak grip aperture was calculated as the Euclidean distance between the x, y, and z coordinates of the index finger and thumb markers on each frame, and corrected for the position of the markers on each participant's hand, so the data represent the separation of the thumb and index finger pads, not marker separation per se.

Time to movement onset. Movement onset was defined as the first frame at which either thumb or index finger velocity exceeded 20 mm/s, and continued to do so for twenty-five consecutive frames (to avoid falsely identifying small movements postural adjustments of the hand while still holding down the start button). Time to movement onset was defined as the time elapsed between the auditory 'go' signal and movement onset. It is reasonable to suspect that CTS patients may require more time to plan grasping actions relative to controls, due to comparatively noisy proprioceptive and tactile signals that are used (along with other signals) to specify the sensorimotor parameters of those plans and calibrate them on the basis of feedback from recently performed actions. However, as a consequence of our experimental design, we did not expect to identify such differences. Our design involves a one-second viewing period before the signal to move is given. As such, any potential differences in planning times between CTS and controls, we hypothesised, would be resolved within this time, before the movement cue was given.

Planned analyses

Scaling. To assess the presence of scaling in peak velocity, we performed a mixed ANOVA with Feedback (two levels: Visual Feedback, No-Visual Feedback), Distance (three levels: 150, 300 and 450 mm) as within-subject factors, and Group (two levels: CTS, Controls) as the between-subject factor. To assess the presence of peak grip aperture scaling, we decided to perform mixed ANOVA with Feedback (two levels: Visual Feedback, No-Visual

Feedback), Size (five levels: 25,30, 35, 40 and 45 mm) as within-subject factors, and Group (two levels: CTS, Controls) as the between-subject factors.

Compensatory responses. For peak velocity and peak grip apertures, we tested the presence of increased compensatory responses in CTS using the same mixed ANOVA above, yet focusing on Feedback (two levels: Visual Feedback, No-Visual Feedback) and Group (two levels: CTS, Controls) as within- and between-subject factors, respectively. For all other measures, we used the 2-way Vision x Group mixed ANOVA.

Noise/variability. To assess the presence of increased noise in CTS, we entered standard deviations of peak velocity and peak grip aperture into respective mixed ANOVAs with Feedback (two levels: Visual Feedback, No-Visual Feedback) and Group (two levels: CTS, Controls) as within- and between-subject factors, respectively.

In the case of violation of sphericity, for tests with more than two levels of a within-subject factor, Greenhouse-Geisser corrected p-values will be reported with corrected degrees of freedom. Where significant interaction effects were identified, post-hoc t-tests will be used to evaluate all pairwise comparisons of interest, using Bonferroni correction to control for multiple comparisons, where appropriate.

2.2.3 Standardised clinical tests

We used a small number of standardised clinical assessments to evaluate participants sensorimotor performance, and for patients exclusively, CTS symptomatology to estimate symptom severity. Test outcomes were used to perform exploratory analyses; in particular, to evaluate whether any statistically significant patient-specific grasping effects were related to clinical assessment outcomes of hand function and/or CTS symptom quality/severity.

CTS symptom quality and severity

Patients completed the Boston Carpal Tunnel Questionnaire (BCTQ) to estimate the quality and severity of their CTS symptom (Levine et al., 1993). The standard test comprises eleven 5-point Likert-scale items addressing six areas: pain, paraesthesia, numbness, weakness, nocturnal symptoms and symptom severity when performing activities (Levine et al., 1993).

We added two sets of additional questions to the standard questionnaire (see Appendix A, Figure S1.1 for the standard BCTQ and the additional questions). First, we added four questions that address symptom quality and severity at the time of testing. The standard questionnaire does not explicitly address current symptomology, which can vary over a short timescale, and so a possible better predictor of grasping performance at the time of testing. Second, the standard BCTQ includes only one question addressing symptom severity during the performance of manual activities of daily living. We included four additional questions addressing this, since we reasoned that these aspects, in particular, may relate to grasp performance. Added questions use the same scoring system and similar wording as the standardised questions.

Touch sensitivity

Fingertip touch sensitivity was assessed in CTS patients and Controls using the Semmes-Weinstein Monofilament test (monofilament test) and the Two-Point Discrimination (2PD) test, both commonly used to evaluate nerve injuries (Novak, 2001). The monofilament test estimates touch detection threshold, defined as the minimum force required to reliably detect cutaneous stimulation (Novak, 2001; Raji, Ansari, Naghdi, Forogh, & Hasson, 2014). The 2PD test estimates touch discrimination threshold, defined as the minimum separation between two points at which participants can reliably distinguish stimulation of two points (simultaneously) versus one (Novak, 2001; Wolny & Linek, 2018).

The monofilament and 2PD tests were performed according to the procedures

outlined by Bell-Krotoski and Tomancik (1987) and Moberg (1990), respectively. Only static and not moving 2PD thresholds were evaluated. We assessed touch sensitivity on the distal pad of the volar surface of the thumb, index, and little finger. The testing equipment was unavailable at the start of the study, and we could collect for 20/25 patients, and 28/32 controls. One patient had recently undergone Carpal Tunnel Release surgery on their left wrist, and so did not complete any tasks/testing involving their left hand.

Manual dexterity

Manual dexterity was assessed in CTS patients and Controls using the Purdue Pegboard test, commonly used to assess hand function in healthy participants (Tiffin & Asher, 1948), and functional impairments in CTS (Amirjani et al., 2011). This test involves both large movements of the hands and fine control of the fingertips, and so provides a general assessment of impairment to hand function. The complete test comprises three subtests: unimanual, bimanual, and assembly. In the unimanual test, participants have 30 seconds to pick up small metal pegs and insert them into holes in the pegboard using one hand (each peg inserted is scored as one point). The bimanual test is the same, but both hands are used to insert respective pegs at the same time. The assembly test involves using both hands to ‘assemble’ as many four-element units as possible in 60 seconds, wherein each unit comprises a peg, two washers and a collar. The elements of each unit are assembled in a specific order, using one hand and then the other. Placement of each element is scored as 1 point; a fully assembled unit is worth 4 points. For the CTS patient that had recently undergone surgery of the left hand, we tested only the right (i.e., unimanual subtest).

Grasp-opening comfort test

Hand sizes (and therefore maximum grasp opening) differ across people. Moreover, CTS is known to restrict the range of motion of impaired digits (Marquardt, Nataraj, Evans, Seitz, & Li, 2014) and a wider hand opening may cause greater discomfort and pain. These

factors could potentially confound the interpretation of our grasping data. To better understand whether this was likely to be a concern, we measured each participant's 'maximum comfortable grasp opening' with either hand, respectively. Before completing the grasping experiment, participants gripped an array of objects of increasing size (34 to 98 mm, in 4 mm increments) with their index finger and thumb and reported the largest object they could grasp without discomfort or pain.

2.3 Results

2.3.1 Grasping task

The affected hand of patients with unilateral CTS, and the most affected hand (according to Boston Carpal Tunnel Questionnaire scores) of patients with bilateral CTS were analysed (see Maeda et al. (2014), for a similar approach). The resultant CTS data comprised 11 left and 14 right hands. For comparison, we used the same proportion of left/right-hand data from Controls (i.e., 14/18, left/right hands), otherwise randomly selected. The data of one healthy participant were excluded due to non-compliance with the task. This participant routinely grasped and then rapidly released objects, without lifting and replacing them back on the table. All statistical outcomes are reported in Appendix A, Supplementary Table S1.

Peak velocity

Preserved peak velocity scaling in CTS. Figure 2.2 plots peak velocity for CTS patients and Controls as a function of object distance with and without visual feedback. Results of a 3-way mixed ANOVA of peak velocity with Vision and Distance as within- subject factors and Group as the between-subject factor reveals consistent scaling of peak velocity in CTS, indistinguishable from Controls (Table S1.1). Specifically, these analyses reveal a significant main effect of Distance ($F(1.1, 58.9) = 1670.14$, $p < 0.001$) yet critically, no significant Distance x Group interaction ($F(2, 108) = 1.74$, $p= 0.17$), and no significant 3-way Vision x

Distance x Group interaction (F (2, 108) = 0.16, p = 0.84). Both groups show scaling of peak velocity as a function of object distance, both with and without visual feedback, moving faster for more distant object locations. We also find a significant interaction between Vision and Distance (F (1.4, 74.5) = 5.50, p = 0.01), reflecting greater differences in peak velocity for movements to objects at different distances when vision is available, for both CTS and Controls. These findings are consistent with the hypothesis that CTS patients can accurately estimate object distance and use this information to programme the speed of their grasping movements in a way that is similar to healthy controls, even without visual feedback of the scene and moving limb while grasping.

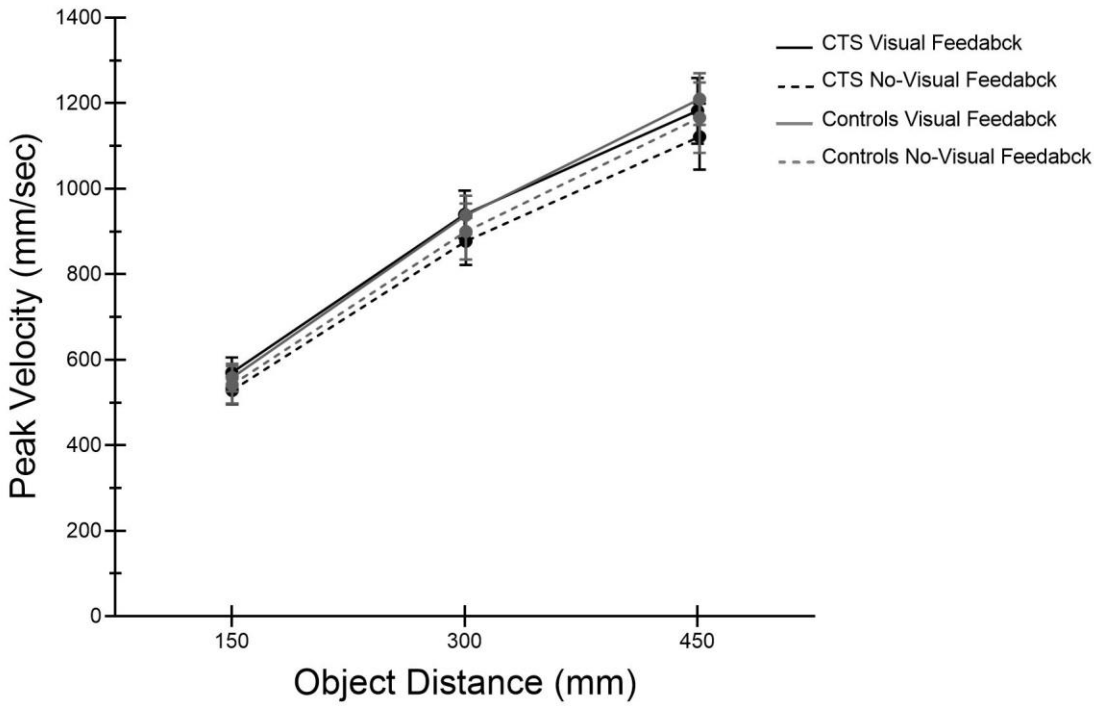


Figure 2.2 Peak Velocity Scaling. In the figure is plotted the peak velocity data (mean with 95% confidence intervals) based on object distance for CTS (black lines) and Controls (grey lines), for Visual feedback (solid line) and No-Visual feedback (dash line). Both CTS patients and Controls scaled peak velocity depending on the object distance.

Slower movements in CTS when visual feedback is unavailable. The results of the same ANOVA introduced above also reveal evidence of more pronounced slowing of movements in CTS (Figure 2.3). A significant Vision x Group interaction ($F(1, 54) = 9.06$, $p = 0.004$) is identified, accompanying a main effect of Vision ($F(1, 54) = 24.41$, $p < 0.001$) and no main effect of Group ($F(1, 54) = 0.44$, $p = 0.50$; Table S1.1). Post-hoc analyses show that these effects reflect significant decreases in peak velocity when vision is unavailable in the CTS group ($t(24) = 5.45$, $p < 0.001$), but not Controls ($t(30) = 1.14$, $p = 0.16$). These data are consistent with CTS patients slowing their movements when vision during grasping is unavailable to compensate for the relatively noisy non-visual input signals caused by their median nerve impairments.

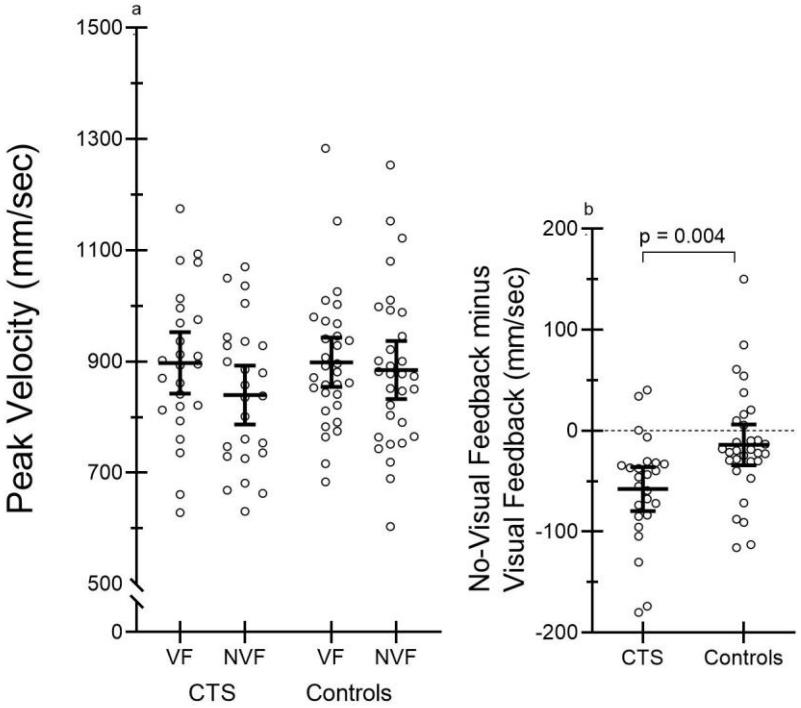


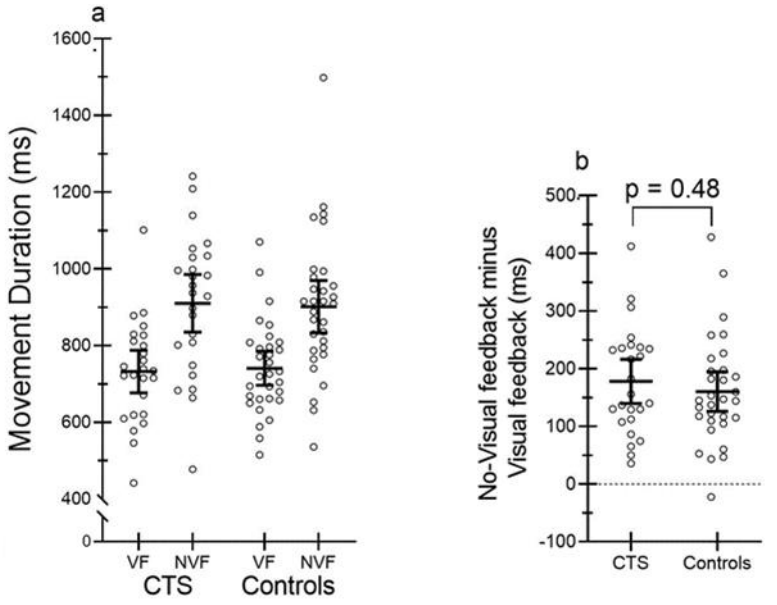
Figure 2.3 Peak Velocity. (a) The plots show the group means and intersubject distribution of mean peak velocity measures for CTS and Controls as a function of Visual Feedback (VF) and No-Visual feedback (NVF). (b) The group mean and intersubject distribution of mean difference scores between No-Vision and Vision (No-vision minus Vision) per CTS and Controls are shown. The error bars in all plots reflect 95% confidence intervals.

No evidence for increased variability of movement speed in CTS. Accepting that CTS does lead to noisy non-visual inputs, if this noise was unreliably estimated or poorly 'managed' then greater variability in movement kinematics may be expected. As a simple probe of this possibility, we tested for evidence of increased variability in peak velocity in CTS when grasping with or without visual feedback. Results of a two-way Vision by Group mixed ANOVA of the standard deviations of peak velocity revealed no significant main effect of Vision ($F(1,54) = 3.54$, $p = 0.065$) nor Group ($F(1,54) = 0.11$, $p = 0.91$), and no significant Vision x Group interaction ($F(1,54) = 0.77$, $p = 78$; Table S1.2). These data indicate similar variability in movement speed between CTS and Controls, independent of visual feedback condition. These findings are at odds with the idea that increased noise in CTS due to faulty somatosensory signals goes 'unmanaged' and manifests as increased movement variability.

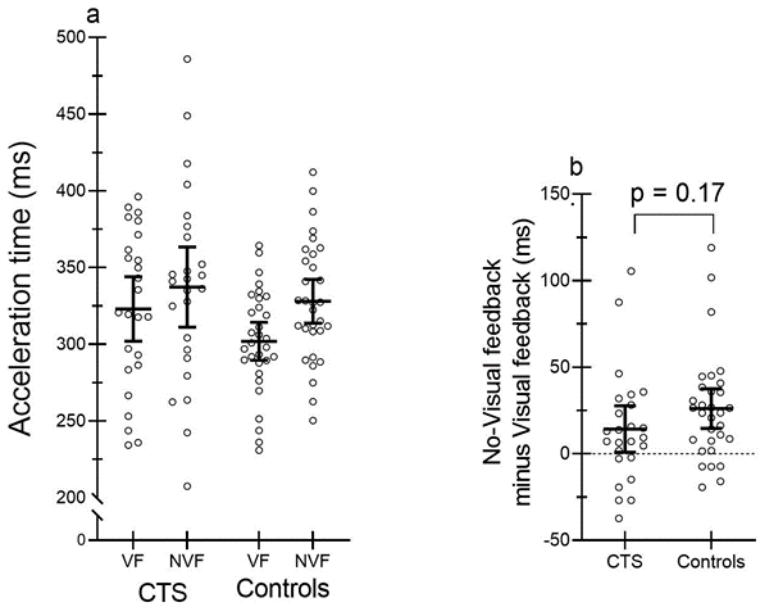
Movement duration, acceleration time, and deceleration time

Figure 2.4 A plots movement duration for CTS patients and Controls with and without visual feedback (Table S1.3). Mixed ANOVA results show that both groups extend the time taken to perform movements when vision is unavailable, qualified as a significant main effect of Vision ($F(1, 54) = 182.44$, $p < 0.001$), yet no evidence for reliable differences between CTS and Controls — no significant main effect of Group ($F(1, 54) = 0.01$, $p = 0.99$) nor Vision x Group interaction ($F(1, 54) = 0.49$, $p = 0.48$).

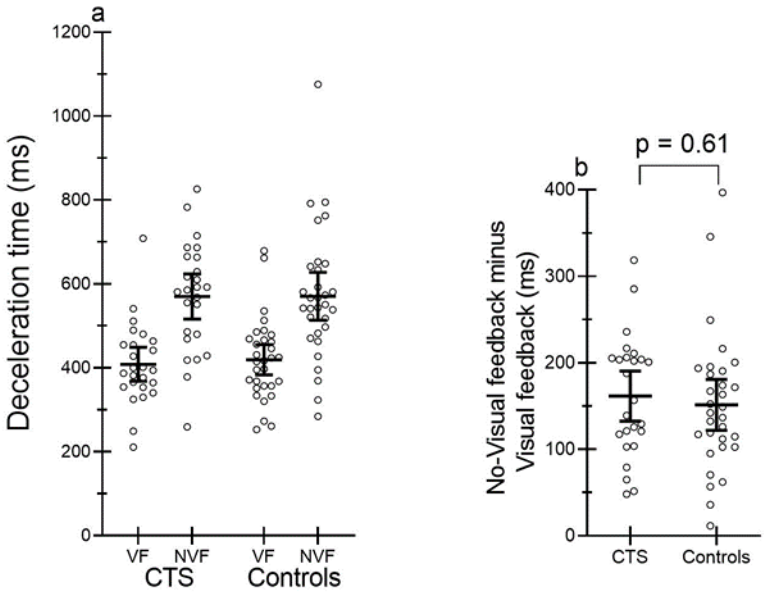
The same pattern of statistical outcomes was observed for the analyses of both acceleration (Figure 2.4 B, Table S1.4) and deceleration times (Figure 2.4 C, Table S1.5)


a
Movement Duration (ms)
1600
1400
1200
1000
800
600
400
0
VF
NVF
VF
NVF
CTS
Controls
b
p = 0.48
No-Visual feedback minus
Visual feedback (ms)
500
400
300
200
100
0
-100
CTS
Controls

A.


a
Acceleration time (ms)
500
450
400
350
300
250
200
0
VF
NVF
VF
NVF
CTS
Controls
b
p = 0.17
No-Visual feedback
minus Visual feedback (ms)
150
100
50
0
-50
CTS
Controls

B.



C.

Figure 2.4 Movement Duration, Acceleration Time, and Deceleration Time. The plots show (A) movement duration, (B) acceleration time and (C) deceleration time. The plots on the right show the distribution of the kinematic parameters as a function of Visual Feedback (VF) and No-Visual feedback (NVF) for CTS and Controls. The plots on the left show the difference scores between No-Vision and Vision (No-vision minus Vision). All the plots show group means and intersubject distribution, while the error bars reflect 95% Confidential Interval.

Peak grip aperture

Preserved peak grip scaling in CTS. Figure 2.5 plots peak grip aperture for CTS patients and Controls as a function of object size with and without visual feedback (Table S1.6). As with peak velocity scaling, 3-way ANOVA results indicate 'normative' scaling of grasp opening according to object size in CTS. We find a significant main effect of Size ($F(1.78, 96.12) = 642.5$, $p < 0.001$) and no significant Size x Group interaction ($F(4, 216) = 0.67$, $p = 0.60$), nor Vision x Size x Group interaction ($F(4,216) = 0.208$, $p = 0.93$). Both groups show scaling of peak grip aperture as a function of object size, both with and without visual feedback, opening their hand ('in-flight'; pre-contact) larger for larger objects. We also find a significant interaction between Vision and Size ($F(2.47, 133.87) = 19.3$, $p < 0.001$), reflecting greater differences in peak grip apertures for movements to different sized objects when vision is available, for both CTS and Controls. These findings are consistent with the

hypothesis that CTS patients can accurately estimate object size and use this information to programme hand opening during grasping in a way that is similar to healthy controls, even without visual feedback of the scene and moving limb while grasping.

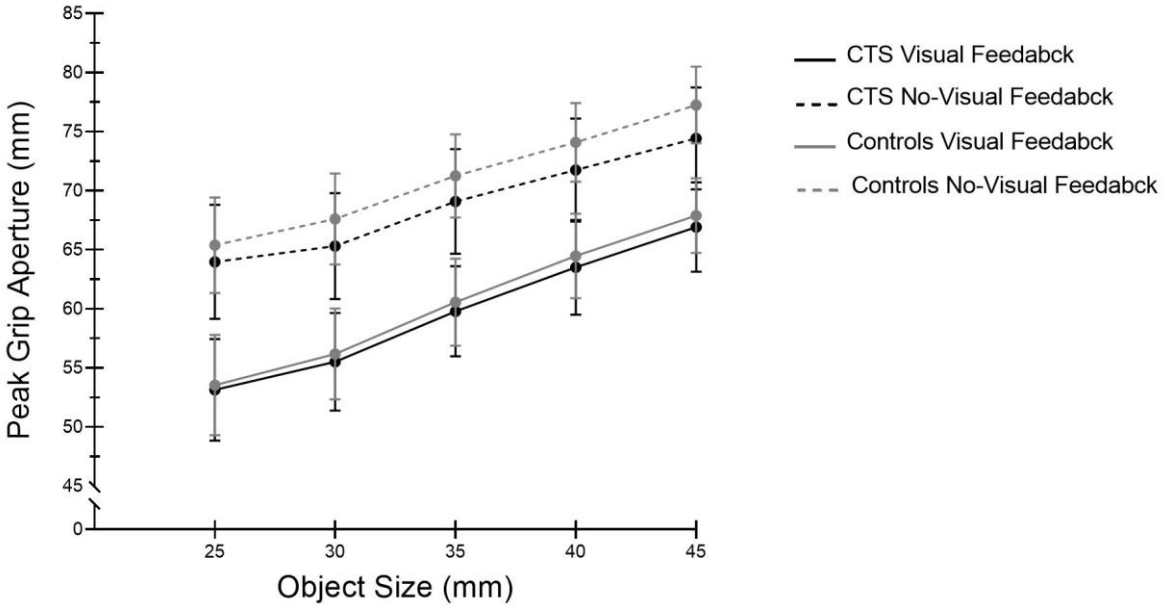


Figure 2.5 Scaling Peak Grip Aperture. The figure shows peak grip aperture data (mean with 95% Confidence Interval) based on object size for CTS patients (black lines) and Controls (grey lines), for Visual feedback (solid line) and No-Visual feedback (dash line). Both CTS patients and Controls scaled the hand aperture depending on the object size.

No evidence of increased hand opening in CTS. Removing vision while grasping, is known to results in increased hand aperture. Further, evidence supports the notion that these changes reflect a compensatory mechanism to increase the margin-for-error in the absence of visual feedback (Keefe et al., 2019). We hypothesised that CTS should show more pronounced increases in peak grip aperture measures than Controls in the No-Visual Feedback condition due to impaired somatosensory signals. This pattern would be considered consistent with a strategy to further increase the margin-for-error in CTS, to compensate for impoverished and noisy non-visual signals about digit sensitivity, position, and kinesthetics.

Figure 2.6 plots peak grip aperture for CTS patients and Controls with and without visual feedback (Table S1.6). The results reveal a significant main effect of Vison ($F(1,54) = 131.8$, $p < 0.001$), indicating wider hand aperture when vision was not available, and no significant main effect of Group ($F(1, 54) = 0.40$, $p = 0.52$), nor Vision x Group interaction ($F(1,54) = 1.05$, $p = 0.31$). The findings are inconsistent with the hypothesis that CTS patients will show increased margin-for-error responses by opening their hand wider when vision is unavailable compared to Controls.

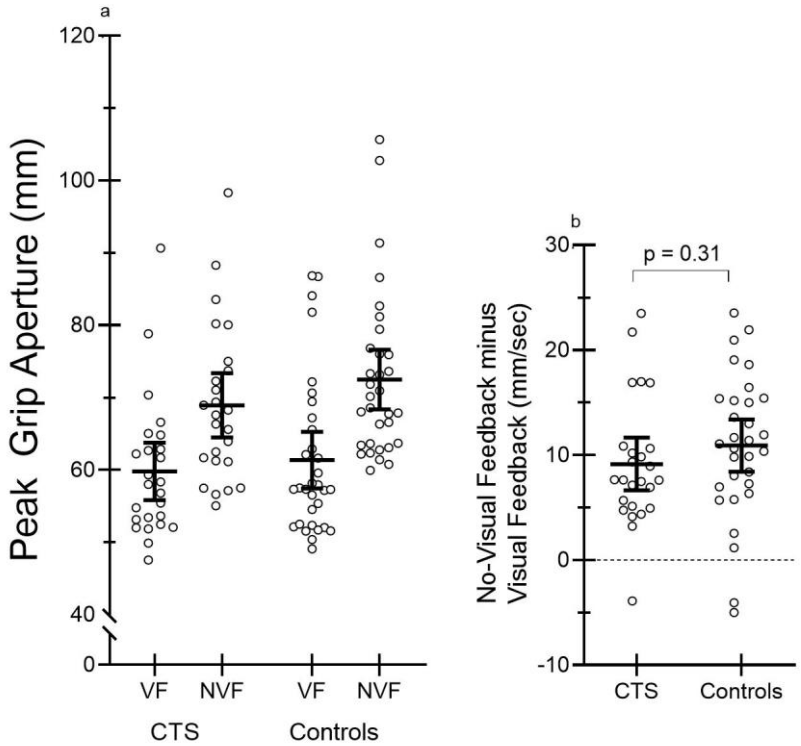


Figure 2.6 Peak Grip Aperture. (a) The plots show the group means and intersubject distribution of mean peak grip aperture measures for CTS and Controls as a function of Visual Feedback (VF) and No-Visual feedback (NVF). (b) The group mean and intersubject distribution of mean difference scores between No-Vision and Vision (No-vision minus Vision) per CTS and Controls are shown. The error bars in all plots reflect 95% confidence intervals.

No evidence for increased variability of peak grip apertures in CTS. Similar to the logic applied to our analyses of standard deviations of peak velocity, if noisier signals in CTS go 'unmanaged', this noise may propagate and lead to higher variability in grasping kinematics, including measures of peak grip apertures, and these effects should be more pronounced

when visual feedback is unavailable. Instead, the mixed ANOVA identified a significant Vision by Group interaction ($F(1, 54) = 5.03$, $p = 0.02$) in the opposite direction (Figure 2.7; Table S.1.7). Post-hoc tests reveal increased variability in peak grip apertures when grasping without visual feedback in Controls ($t(30) = 4.93$, $p < 0.001$), yet not CTS patients ($t(24) = 1.42$, $p = 0.16$). The reason for this pattern of results is unclear. The mixed ANOVA identified no significant main effect of Group ($F(1, 54) = 0.54$, $p = 0.46$), and a significant main effect of Vision ($F(1,54) = 18.96$, $p < 0.001$).

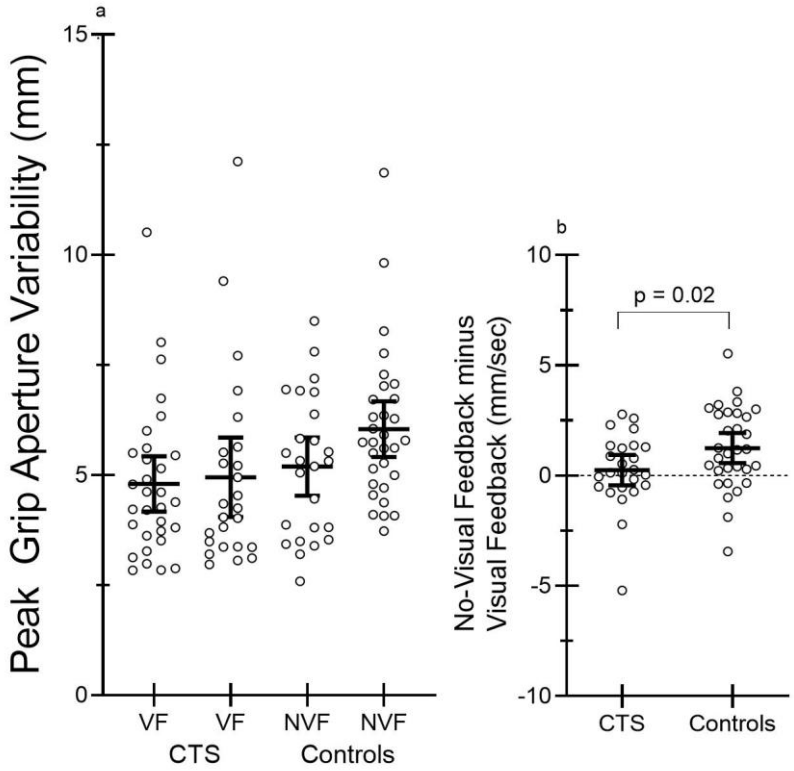


Figure 2.7 Peak Grip Aperture Variability. (a) The plots show the group means and intersubject distribution of mean peak grip aperture variability measures for CTS and Controls as a function of Visual Feedback (VF) and No-Visual feedback (NVF). (b) The group mean and intersubject distribution of mean difference scores between No-Vision and Vision (No-vision minus Vision) per CTS and Controls are shown. The error bars in all plots reflect 95% confidence intervals.

Time to movement onset

Figure 2.8 plots time to movement onset for CTS patients and Controls with and without visual feedback (Table S.1.8). The results reveal a significant Vision by Group interaction ($F(1,54) = 9.00$, $p = 0.004$) that reflects increased movement onset times when (upcoming) grasping was performed without visual feedback compared the full vision condition in CTS ($t(5.41)$, $p < 0.001$) but not Controls ($t(1.06)$, $p = 0.29$). These results were unexpected. As noted above (see Dependent measures), although it is reasonable to suspect that CTS patients may require more time to plan grasping relative to Controls, our experimental design involves a one-second viewing period before the signal to move is given. Any potential differences in planning requirements between CTS and Controls were expected to be effectively resolved by the time the signal to move was given. We share our possible interpretations of these results in our Discussion, below. A mixed ANOVA identified a significant main effect of Vision ($F(1,54) = 20.22$, $p < 0.0001$) and no main effect of Group ($F(1,54) = 0.93$, $p = 0.33$).

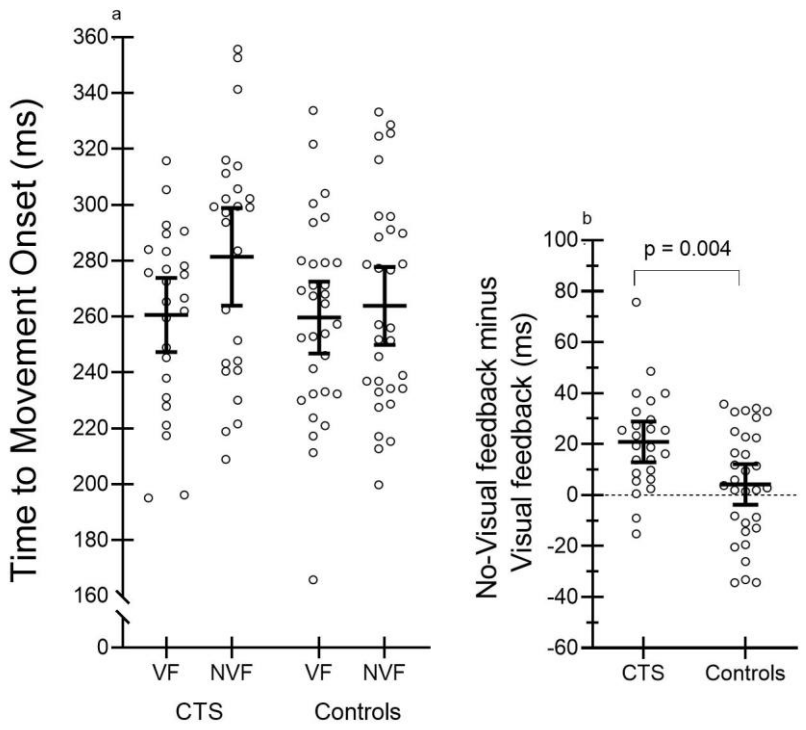


Figure 2.8 Time to movement onset. (a) The plots show the group means and intersubject distribution of time to movement onset measures for CTS and Controls as a function of Visual Feedback (VF) and No-Visual feedback (NVF). (b) The group mean and intersubject distribution of mean difference scores between No-Vision and Vision (No-vision minus Vision) per CTS and Controls are shown. The error bars in all plots reflect 95% confidence intervals.

2.3.2 Standardised clinical tests

CTS symptom quality and severity

Table 2.1 shows the full details of CTS patients' symptom severity, along with key demographic variables, and nerve conductance measurements. The electrodiagnostic studies confirmed the diagnosis of CTS in all the patients (see Table 2.1). Symptom severity according to BCTQ standard scores ranged from "asymptomatic" (N = 3; score between 0 to 11), to "mild" (N =15; score between 12 to 22) to "moderate" (N = 7; score between 23 to 33; group average = 18.6 [15.65, 21.55]). The scores of our additional questions regarding the symptom severity at the test and the symptom severity during daily activities had a score ranging from 0 to 16, with lower values indicating lower severity.

Table 2.1. CTS patient's characteristics.

Nerve Conductive Study. The sensory velocities and latencies are recorded between digit III and wrist; only for the subject with an asterisk (*) these measures have been recorded between digit II and wrist. The motor latency has been recorded between the wrist and the thumb (abductor pollicis brevis, APB).

Boston Carpal Tunnel Questionnaire: a) Standard score = the score of the eleven standardized items; b) Severity = the severity level based on the Standard Score; c) Symptom severity at the test = the score of the additional questions regarding the symptomatology at the moment of testing; d) Symptom severity during daily activities = the score of the questions regarding the symptomatology during daily activity.

Demographic			Nerve Conductive Study (abnormal values in bold)[1]			Boston Carpal Tunnel Questionnaire			
Sex	Age	Affected hand	Median Nerve Study	Velocity (m/s)	Latency (m/s)	Standard score[2]	Severity	Symptom Severity at the test[3]	Symptom Severity during daily activities[4]
F	59	Left	Sensory(µv) Motor (mV)	**38.5**	3.38 **3.83**	0	Asymptomatic	0	0
M	65	Right	Sensory(µv) Motor (mV)	44.4	3.38 **4.63**	8	Asymptomatic	1	3
F	45	Right	Sensory(µv) Motor (mV)	45.6	2.85 **3.70**	11	Asymptomatic	1	2
F	41	Left	Sensory(µv) Motor (mV)	**32.3**	3.50 **4.27**	13	Mild	1	6
F	36	Left	Sensory(µv) Motor (mV)	**37.2**	3.23 **4.67**	13	Mild	0	9
M	45	Left	Sensory(µv) Motor (mV)	**20.7**	6.51 **9.17**	13	Mild	2	3
F	45	Bilateral (right)	Sensory(µv) Motor (mV)	**38.6**	2.85 **4.79**	14.5	Mild	3	6.5
F	65	Bilateral (right)	Sensory(µv) Motor (mV)	**38.0**	3.42 **4.08**	15	Mild	4	10
M	44	Right	Sensory(µv) Motor (mV)	40.2	3.23 **3.94**	16	Mild	0	8
M	51	Left	Sensory(µv) Motor (mV)	**28.4*** 	4.76* **6.06**	17	Mild	1	3
F	67	Bilateral (right)	Sensory(µv) Motor (mV)		Absent Absent	19	Mild	5	6
F	54	Bilateral (right)	Sensory(µv) Motor (mV)	44.6	2.69 **3.17**	19	Mild	0	5
M	60	Bilateral (left)	Sensory(µv) Motor (mV)	**26.5**	4.52 **5.06**	19	Mild	5	13
F	33	Bilateral (right)	Sensory(µv) Motor (mV)	40	3.4 4.7+	19.5	Mild	2.5	3.5
M	53	Left	Sensory(µv) Motor (mV)	**37.2**	3.63 **4.25**	20	Mild	7	5
M	50	Bilateral (left)	Sensory(µv) Motor (mV)	**38*** 	3.9* **5.3**	20	Mild	4	6
F	55	Right	Sensory(µv) Motor (mV)	**38.6**	2.98 **4.65**	20	Mild	4	7
F	57	left	Sensory(µv) Motor (mV)	**34.1**	3.81 **5.02**	22	Mild	2	7
F	56	Right	Sensory(µv) Motor (mV)	40.6	2.88 **3.58**	23	Moderate	1	4
F	25	Bilateral (left)	Sensory(µv) Motor (mV)	**35.2**	3.61 **5.05**	23	Moderate	3	7
F	58	Right	Sensory(µv) Motor (mV)	**34.1**	3.08 **2.79**	24	Moderate	6	6
M	60	Bilateral (left)	Sensory(µv) Motor (mV)	48.7	2.67 **3.63**	25	Moderate	6	11
M	59	Right	Sensory(µv) Motor (mV)	**38.1*** 	3.54* **4.31**	29	Moderate	6	10
F	55	Bilateral (right)	Sensory(µv) Motor (mV)	46.6	2.79 **3.52**	30	Moderate	6	13

Demographic			Nerve Conductive Study (abnormal values in bold)[1]			Boston Carpal Tunnel Questionnaire			
F	63	Right	Sensory(µv)	46.8	2.63	33	Moderate	8	16
			Motor (mV)		**3.21**				

[1] Normative Median Nerve Conduction Values, Canterbury scale. doi.org/10.1002/1097-4598(200008)23:8<1280::
AID-MUS20>3.0.CO;2-Y: i) grade 0, no neurophysiological abnormalities; ii) grade 1- very mild, detected only in two sensitive tests (e.g., inching, palm/wrist median); ii) grade 2- mild CTS, conduction velocity < 40 m/s with motor terminal latency < 4.5 ms; iii) grade 3- moderately severe, motor terminal latency > 4.5 ms and > 6.5 ms with preserved index finger sensory nerve action potential (SNAP); iv) grade 4- severe CTS, motor terminal latency > 4.5 ms and > 6.5 ms with absent SNAP; v) grade 5- very severe, motor terminal latency > 6.5 ms; vi) grade 6- extreme severe, surface motor potential from APB < 0.2 mV, peak to peak.
[2]max score = 44
[3]max score = 16
[4]max score = 16

Touch sensitivity

Table 2.2 shows the results of pairwise comparisons between CTS patients (N=20) and Controls (N=28) in both of our measures of tactile sensitivity — monofilament test and 2PD. Note that fewer patients and controls completed these tests. Both assessment tests identified significantly higher thresholds for the index finger and thumb in CTS compared with Controls. Unexpectedly, CTS patients also showed elevated touch detection and discrimination thresholds for the little finger compared with Controls. These results may suggest that impairments to touch sensitivity are not restricted to the median-nerve innervated digits.

Table 2.2. **Semmes-Weinstein Monofilament and Two-Point Discrimination scores**. Statistical significance with group means and 95% IC indicated in parenthesis.

Digit	Semmes-Weinstein Monofilament (millinewtons)[1]				Two-Point Discrimination (millimetres)[2]			
	CTS	Controls	Mann-Whitney test	p-value	CTS	Controls	Mann-Whitney test	p-value
Thumb	2.7 [2.4]	0.3 [0.06]	U = 117.5	p < 0.001	4.5 [0.5]	3.35 [0.3]	U = 126	p < 0.001
Index	1.6 [1.2]	0.3 [0.04]	U = 96	p < 0.001	4.6 [0.6]	3.32 [0.3]	U = 116	p < 0.001
Little	0.6 [0.3]	0.2 [0.04]	U = 119.5	p < 0.001	5.2 [0.6]	4 [0.4]	U = 144.5	p = 0.003

[1] Normative value to distinguish normal sensitivity is 2.83 (Bell-Krotoski, Fess, Figarola, & Hiltz, 1995; MacDermid, Kramer, & Roth, 1994) or 0.66 millinewtons.

[2] Normative value is < 6 mm (Gelberman, Urbaniak, Bright, & Levin, 1978).

Manual dexterity

Figure 2.9 shows the scores for the Purdue Pegboard for CTS patients (N = 25 for unimanual subtests, N = 24 for the bimanual and assembly subtest) and Controls (N = 32). CTS patients inserted significantly fewer pegs in the unimanual subtest (t (55) = 2.85, p = 0.006) and bimanual subtest (t (54) = 2.38, p = 0.021), and were able to 'assemble' less complete units (of four elements) in the assembly sub-test (t (54) = 2.59, p = 0.012) compared to Controls. Our results are in line with previous research showing impaired manual dexterity in CTS patients based on Purdue Pegboard performance (e.g., Amirjani et al., 2011)

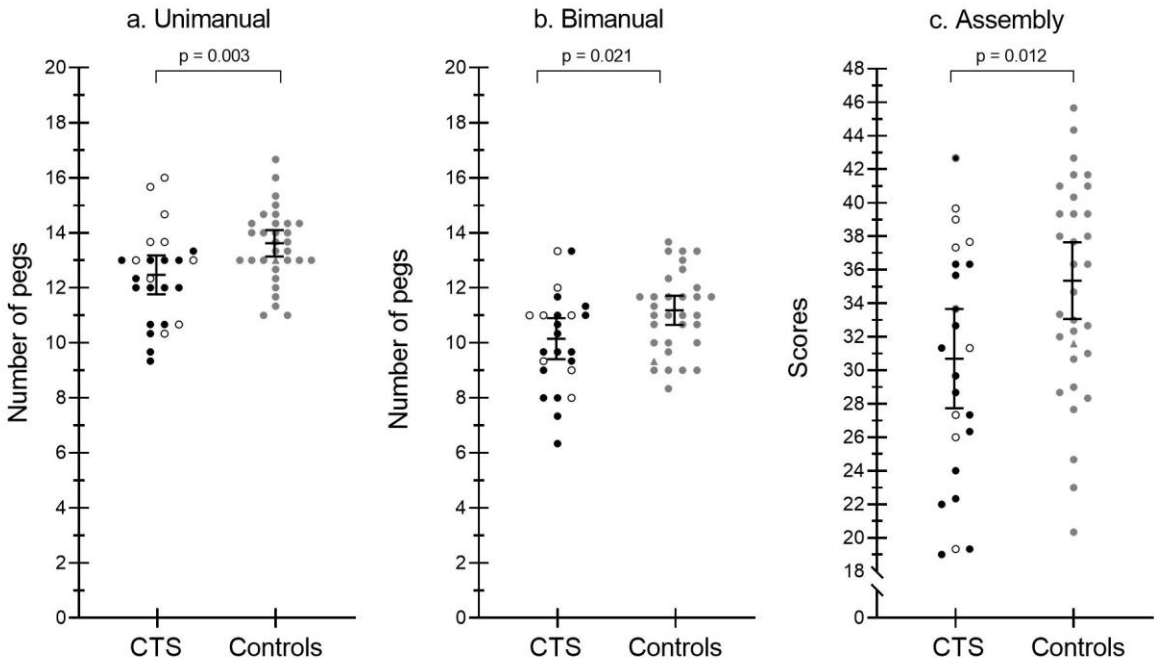


Figure 2.9. Purdue Pegboard scores. Distribution of the Purdue Pegboard scores (mean and 95% Confidence Interval) for CTS patients and Controls for the three subtests. Filled circles represent the unilateral CTS patients, while unfilled circles represent the bilateral CTS patients. The triangle in the Controls group represents the only left-hand subject.

Grasp-opening comfort test

We were concerned that CTS may have restrictions in the range of their 'precision grasp' (index-finger to thumb) opening, either due to their nerve impairments directly (Marquardt et al., 2014), or related to changes in the likelihood of experiencing CTS symptoms — for example, opening the hand wide may add greater risk of experiencing paraesthesia or numbness. To help mitigate these concerns we measured each participant's 'maximum comfortable grasp opening'. Our test found no evidence for group differences between CTS and Controls ($t(55) = 1.04$, $p = 0.37$). This result mitigates concerns regarding restricted grasp opening in CTS that would complicate the interpretation of their peak grip aperture data.

2.3.3 Exploratory analysis of grasp performance and clinical scales

We ran exploratory tests for evidence of reliable relationships between our results showing distinct measures of grasp performance in CTS and their scores from standardised clinical tests. Specifically, we ran a set of (6) correlational tests (using Kendall's τ) to evaluate our two CTS-specific grasp performance measures — the differences between No-Visual Feedback minus Visual Feedback in (1) peak velocity and (2) time to movements — against the clinical scores from the (1) Boston Carpal Tunnel Questionnaire, (2) monofilament test, and (3) Purdue Pegboard unimanual subtest scores. The rationale here is straightforward. If measures of impairment captured using these standard clinical assessment tests contribute to the unique features of grasping identified between CTS and Controls, we might expect to see a reliable correlation between impairment severity on clinical tests and CTS-specific grasp performance. We chose the Purdue Pegboard unimanual subtest rather than the bimanual or assembly test scores since in this way we could match the hand used in both tests.

We applied a conservative Bonferroni correction to control us performing 6 tests; defined as statistically significant at $\alpha < 0.008$. The results revealed no reliable evidence for a relationship in any of the tests (all $p > 0.2$; see Table 2.3 for all statistical outcomes and Figure S1.2 for correlation plots).

Table 2.3 Relationship between CTS features and grasp kinematics. The table shows Kendall's τ correlations between CTS features — symptom severity, touch detection and manual dexterity — and grasp kinematics — peak velocity and movement onset.

	Peak Velocity No-Visual Feedback minus Visual Feedback	Time to movement onset No-Visual Feedback minus Visual Feedback
Boston Carpal Tunnel Questionnaire standard	r (25) = 0.47, p = 0.74	r (25) = 0.44, p = 0.76
Monofilament test (millinewtons)	r (20) = - 0.51, p = 0.76	r (20) = - 0.21, p = 0.21
Purdue Pegboard unimanual score	r (25) = 0.15, p = 0.30	r (25) = - 0.14, p = 0.34

Since we included new additional sub-tests of the Boston Carpal Tunnel Questionnaire, (1) time of test; (2) daily activities, we felt compelled to also test for evidence of a relationship between these scores and our results showing distinct measures of grasp performance in CTS. Here, we applied Bonferroni correction to control for 12 tests; statistical significance was accepted at $\alpha < 0.004$. Again, no reliable evidence for a significant correlation was identified for any of these additional tests (see Table 2.4 for all statistical outcomes and Figure S1.3 for correlation plots). A strange outcome was suggested, however; when the sub-test score "time of test" was compared against the peak velocity measures reflecting the differences between No-Vision minus Vision, the results suggest a relationship ($r(25) = 0.40$, $p = 0.006$) wherein CTS patients with greater severity scores show *less* of a decrease in hand speed when grasping without versus with visual feedback. In other words, the individuals showing greater compensatory slowing (costs due to loss of vision) were not the same individuals who reported high symptom severity levels at the time of testing.

Table 2.4 Relationship between CTS symptom severity and grasp kinematics. The table shows Kendall's τ correlations between CTS symptom severity and grasp kinematics — peak velocity and movement onset.

	Peak Velocity No-Visual Feedback minus Visual Feedback	Time to movement onset No-Visual Feedback minus Visual Feedback
Symptom Severity at the time of test	$r(25) = 0.40$, $p = 0.006$	$r(25) = 0.03$, $p = 0.81$
Symptom Severity during daily activities	$r(25) = 0.08$, $p = 0.55$	$r(25) = 0.13$, $p = 0.37$
Boston Carpal Tunnel Questionnaire standard plus additional questions	$r(25) = 0.23$, $p = 0.10$	$r(25) = 0.04$, $p = 0.70$

2.4 Discussion

Normal grasping is characterised by anticipatory movements of the hand that reflect estimated target object properties (size, shape, orientation, and location) 'in-flight', prior to object contact, and increased compensatory responses, opening the hand wider and moving slower, when vision of the scene and moving hand is unavailable after movements have been initiated. In this study, we test whether these anticipatory signatures of normative grasp control are preserved in patients with mild to moderate CTS, and whether CTS patients show normative compensatory responses when grasping without visual feedback. Consistent with the uncertainty/optimisation framework, if CTS patients are able to estimate and appropriately manage the increased noise in non-visual signals due to their nerve impairment, they should demonstrate preserved anticipatory signatures of normative grasp control, and compensatory increases in margin-for-error responses when grasping without visual feedback. We predicted that these increased compensatory responses will be more pronounced in CTS patients relative to healthy controls, since removing visual cues forces greater reliance on somatosensory signals, which are presumed to be noisier in CTS due to nerve impairment. Greater increases in compensatory responses would be taken to reflect appropriate management of increased uncertainty.

Our findings are consistent with the idea that CTS patients are able to manage the increased noise in non-visual signals due to their nerve impairment, and produce appropriate compensatory responses and normative anticipatory movements during grasping. Without visual feedback of the scene and moving limb, CTS patients reliably slowed their movements down compared to when grasping with full-vision available. Controls tended to show this same pattern, yet the differences were not statistically reliable. Both CTS and Controls widened their hand opening during grasping without visual feedback compared to full vision, with no differences between groups. We also found normative scaling of movement speed and hand opening according to object distance and size, respectively, in CTS, even in the absence of visual feedback. Analyses of the standard deviations of peak velocity and peak

grip aperture measures showed no reliable evidence for increased movement variability in CTS.

We first discuss our findings supporting evidence of impairments in our group of CTS patients according to clinical tests. This is critical to establishing confidence in the idea that CTS patients are required to manage noisier non-visual signals contributing to hand and reach-to-grasp control. We then discuss our results for each of our measures of grasp performance. Lastly, we discuss the results of our exploratory tests for relationships between grasp performance measures and clinical-test scores in our CTS patients.

Evidence of impairment according to clinical tests

At referral, our patients were diagnosed using standard electrophysiological criterion, confirmed as mild (N = 11), moderate (N = 12), or severe (N = 2) CTS. At the time of testing in the lab, we took three measures of hand function using standardised clinical tests, as well as CTS symptom severity using the Boston Carpal Tunnel Questionnaire. Our patients showed impairments in tactile sensitivity. Threshold levels of the distal pads of the index finger and thumb were significantly elevated for both touch detection, measured using the Semmes-Weinstein Monofilament test, and two-point discrimination, measured using the Two-Point Discrimination (2PD) test. Both findings are consistent with previous reports (Chen et al., 2015; Gehrmann et al., 2008; Wolny et al., 2016). Unexpected, we also found impaired tactile sensitivity for the little finger; unexpected since the little finger is not innervated by the median nerve. Similar findings have been reported by Li et al. (2015) and Chen et al. (2015), however, may reflect indirect effects of increased pressure within the carpal tunnel that transfers to also impede ulnar nerve function (Ginanneschi et al., 2008; Tamburin, Cacciatori, Praitano, Marani, & Zanette, 2009).

Our CTS patients also demonstrate impaired manual dexterity as assessed with the Purdue Pegboard test. Patients scored worse than controls in all three subtests, replicating the results of prior work, including a large previous study by Amirjani et al. (2011) involving

190 CTS patients and demonstrating excellent test-retest reliability of the Purdue Pegboard test for use with assessing CTS (see also, Fernández-De-Las-Peñas et al., 2009). Altogether, our results demonstrate impairments in our CTS patients, consistent with previous works, and provide some confidence that our group of CTS patients had impaired non-visual signals important for the control of the hand when we tested their grasp performance. This suggests that those aspects of our results showing statistically equivalent measures of grasping in CTS patients and controls are not attributable to a general absence of significant (somatosensory and/or kinaesthetic) impairments in our group of CTS patients.

Grasping performance: Hand transport

CTS patients showed significantly decreased peak velocity when visual feedback was not available compared to controls. These results are considered consistent with predictions formulated in the introduction, as part of the uncertainty/optimisation framework. Moving slower in the absence of visual feedback of the moving hand is interpreted as a compensatory strategy to make-up for noisy somatosensory signals. Moving slower may limit movement-related variability, for example, in the endpoint position of the digits at the point of object prehension, and make online adjustments easier to complete. These results are consistent with previous work involving grasping after anaesthesia of the digit tips. Following a temporary block of tactile sensitivity with anaesthetic injections to the digit tips of the index finger and thumb, hand movement speed was reduced when vision of the moving limb was removed after movement onset, compared with a no-anaesthesia control condition (Gentilucci et al., 1997). By moving slower, the sensorimotor system may obtain better control of the hand to prevent failures (Schmidt, Zelaznik, Hawkins, Frank, & Quinn, 1979). In the extreme, our results may reflect a strategy to minimise the likelihood of object collision, or fumbling.

We also find normative scaling of peak velocity as a function of object distance in our CTS patients, independent of visual feedback condition. Both CTS and controls also show

sharper scaling, greater differences in peak velocities between distances, when vision is available, and we find no evidence for differences in the standard deviations of peak velocity between CTS and Controls, independent of visual feedback condition. Analyses of movement duration, and its constituent components of acceleration and deceleration times, also provides no reliable evidence for differences between CTS and Controls—both groups extend the time taken to complete grasping when visual feedback is unavailable, and these changes are reflected in both the acceleration and deceleration times.

Altogether, the results of our analyses of hand transport parameters are consistent with the idea that CTS patients are able to appropriately estimate and manage the increased noise in non-visual signals due to their impairments, and produce adaptive compensatory responses and normative anticipatory movements.

The lack of evidence for increased variability in movement speed in CTS appears to conflict with other previous findings, however, and warrants further investigation. Previous studies have measured the kinematics of repetitive non-object directed (intransitive) precision pinch movements in patients with CTS, involving the repeated opening and closing of the index finger and thumb without visual feedback (Gehrmann et al., 2008; Nataraj et al., 2014). The findings suggest that CTS patients are impaired in sensing the position of their affected digits, showing higher variability in the spatial trajectories, endpoint position and orientation of the digit tips as compared to healthy controls. Likewise, precision grasping of a virtual object without visual feedback of the moving hand is characterised by increased variability of the spatial trajectories and endpoints of the affected digits in CTS (Nataraj et al., 2014). A possible explanation for these apparent discrepant findings may relate to the fact that we tested the standard deviations of peak velocity, rather than kinematic indices of spatial (hand path) variability. We believe that future research should quantify the variation of spatial trajectories, such as the alignment of the pinch between thumb and index finger.

Notably, similar increases in movement variability have been reported after anaesthetic nerve block of the digits, including greater variability in the final endpoint

positions of the index finger and thumb when performing repetitive non-object directed precision pinch movements (Li & Nimbarte, 2006), and in the spatial trajectories of the digits when grasping without visual feedback (Gentilucci et al., 1997). Again, this motivates consideration of whether our analyses of the standard deviations of peak velocity are comparable — perhaps we should be testing for differences in the variability of spatial endpoints of the digits after object contact. Another possibility, at least regarding comparison with previous work involving nerve block manipulations, is that the consequences of acute anaesthetic nerve block on hand movement and grasp control may differ from those of CTS due, at least in part, to different timescales of impairment; acute versus chronic, respectively. We pick back up on this possibility in our discussion of the peak grip aperture results, next.

Grasping performance: Hand opening

Counter to our expectations, CTS patients did not show more pronounced hand opening during grasping without visual feedback. Without visual feedback, peak grip apertures increased to a similar extent in CTS and Controls. This conflicts with the hypothesis that CTS patients should generate a more pronounced version of the normal pattern of increased margin-for-error responses, opening their hand wider, to compensate for forced reliance on noisy somatosensory signals in the absence of visual feedback of the scene and moving hand while grasping. The results conflict also with data from Gentilucci et al. (1997) showing more pronounced opening of the hand during grasping without visual feedback following anaesthesia of the index finger and thumb in healthy controls. Both groups showed scaling of peak grip aperture as a function of object size, both with and without visual feedback, opening their hand larger for larger objects. The results suggest that CTS patients can manage the increased noise in non-visual signals due to their nerve impairment, producing normal anticipatory pre-shaping of the hand to reflect target object size, and normal compensatory margin-for-error increases in hand opening when grasping without visual feedback.

We offer a number of possible interpretations for why our CTS patients did not show the expected more pronounced increases in hand opening compared to Controls. First, in formulating our predictions, we may have underestimated how reduced range of motion in CTS may confound interpretation of grip aperture measurements. Restricted range of motion of the index finger and thumb has been documented in CTS (Marquardt et al., 2014), and may reflect impaired muscle recruitment, and/or increased passive-tissue-rigidity brought on by repeated episodes of paraesthesia and pain. Related, it is possible that wider hand opening is associated with increased probability of experiencing CTS symptoms. These factors would drive against the likelihood of opening the hand wider in our CTS patients, therein complicating the interpretation of our peak grip aperture measurements. One surprising finding from our study is that while both CTS and Controls show increased variability in peak grip apertures when grasping without visual feedback versus with visual feedback, these differences were only reliable in Controls. Although speculative, perhaps this finding relates to the possibility that CTS patients limit hand opening as a consequence of either restricted range-of-motion or to protect against raising the likelihood of exacerbating their symptoms. Both accounts might predict a narrower range of variability in hand opening in CTS as compared with Controls, as we observed.

There are two other accounts worth discussing, in particular, with respect to comparing our findings to those of previous working involving grasping after anaesthetic block of the digits (Gentilucci et al., 1997). First, relative to our CTS patients, the anaesthetic manipulation carried out in the study by Gentilucci et al. (1997) may have introduced more extreme tactile deficits. Gentilucci et al. (1997) report “loss of pain, pressure and light touch”. Conversely, tactile sensitivity impairments in our CTS patients were relatively mild. While our CTS group effects revealed significantly elevated detection and discrimination thresholds relative to Controls, there was nonetheless substantial overlap in the distribution of these measures between groups. Indeed, most of our CTS patients scored within the range of scores defined by our Controls. It remains possible, then, that we had tested individuals with

more severe impairments, we may have found a similar pattern of compensatory changes in kinematics as did Gentilucci et al. (1997). Certainly, grasping in patients with severe sensory loss as a result of large-fibre neuropathies is characterised by pronounced increases in peak grip apertures (Gentilucci et al., 1994; Miall et al., 2019). Notably, however, these patients also suffered from dramatic/complete loss of proprioception, while Gentilucci et al. (1997) report that their anaesthetic manipulation did not influence digit proprioception.

Second, since the impairments that accompany CTS are chronic, and develop gradually (Aroori & Spence, 2008), there may be an opportunity for the central nervous system to better 'understand' these impairments, and adapt in ways that are different from the case of acute anaesthesia. That our patients can accurately estimate their sensorimotor impairments and factor these into the formation of appropriate action plans is supported by our data showing preserved grip scaling in CTS in the absence of visual feedback, and indistinguishable in kind from healthy controls. This idea is also supported by previous results showing that CTS patients can accurately update plans for the control of digit forces during object grasping and manipulation on the basis of recent prior sensorimotor experience (Zhang et al., 2011). Nonetheless, how the brain adapts to acute versus chronic impairments, and in particular, differences in the way peripheral nerve injuries may impact sensorimotor control mechanisms over time is poorly understood. Future longitudinal studies of grasp control in patients with conditions that compromise the peripheral nervous system and sensory processes will be of value.

As reported in the introduction, a recent study from Glazebrook et al. (2020) was published after we had specified our predictions and completed data collection. The authors performed a manipulation analogous to short-term CTS by inducing paraesthesia, which resulted in smaller hand aperture in-flight. According to the authors, paraesthesia interfered with the online feedback of the hand (i.e., proprioception). The authors suggested that hand aperture was misperceived as wider than the real hand aperture, and as a result, the hand was opened less wide with stimulation-induced paraesthesia. This interpretation conflicts with

the idea that minor impairments can be managed in an optimal way, as stated in the introduction, and, altogether, at odds with our findings. We again wonder whether the differences in timescales contributes to this difference, acute in the case of the Glazebrook et al. (2020) study, and chronic in the case of CTS and our study. This, however, would not explain why acute anaesthetic knock-out leads to increased peak grip apertures (Gentilucci et al., 1997) while acute stimulation-induced paraesthesia (Glazebrook et al., 2020) has the opposite effect, reducing peak grip apertures. Clearly, further research characterising grasping after different kinds of acute experimental manipulations that disrupt hand-nerve function in different ways, and comparing with chronic conditions like CTS, will be important.

Grasping performance: Time to movement onset

Due to our study design, we did not expect to find any difference between the time to movement onset of CTS patients and Controls. Specifically, our experiment participants were required to wait for a period of one second while the object to be grasped was visible, and begin their movement following the sound of an auditory cue. Further, their response time following this auditory cue, what we define as time to movement onset, needed to take place within 600ms, or the trial was discarded and repeated at the end of a block of trials (with explicit verbal feedback to the participant that this had occurred). These details complicate comparison with previous studies that involved no such constraints, wherein the time to initiate actions has has been compellingly linked to premovement planning requirements (e.g., Klatzky, Fikes, & Pellegrino, 1955; Rosenbaum, Vaughan, Barnes, & Jorgensen, 1982). To say that our measures of time to movement-onset straightforwardly reflect planning requirements is not possible.

With these caveats in mind, our results reveal significant increases in movement onset in CTS patients when visual feedback of the upcoming trial was unavailable. In comparison, Controls were not affected by the prospective unavailability of visual feedback;

time to movement onset was comparable between visual feedback conditions. We offer two speculative interpretations. First, this may reflect some kind of general motor readiness, or attentional-set differences between patients and Controls. Simply put, this interpretation posits that patients are less ready to act, when they know that vision of the moving hand will be unavailable. Why this should be the case, however, is unclear. Second, we speculate that perhaps the brain performs a kind of quick re-plan under these conditions, almost like a re-cap of the plans that should already have been completed during the 1s preview phase. If this were to happen, then perhaps our results do indeed reflect differences in the time taken to plan actions between CTS patients and Controls, when knowledge of the forthcoming absence of visual feedback is present. This, therefore, may in fact reflect an appropriate compensatory strategy, taking more time to plan (or, perhaps 'replan') their actions to account for the increased sensory noise/uncertainty patients experience due to their nerve impairment. Future experiments may help to disentangle these various interpretations, for example, by investigating time-to-movement onsets under both constrained (as in the current experiment) and unconstrained (arguably, more natural) conditions.

Exploratory tests for relationships between measures of grasping and clinical tests

We performed exploratory tests to investigate whether distinct measures of grasp performance in CTS relate to their scores from standardised clinical tests. We limited our search to those measures of grasp performance that yielded statistically reliable differences between CTS patients and Controls, and tested these measures against Boston Carpal Tunnel Questionnaire scores (indexing CTS symptom severity), touch detection thresholds measured using the monofilament test, and performance scores from the unimanual subtest of the Purdue Pegboard test. Our analyses reveal no evidence for any reliable relationships. Although speculative, these null results may be taken to suggest that the unique features of grasping we have identified in CTS — namely lower movements and longer movement-onset

times when grasping without visual feedback — are not explained by impaired tactile sensitivity, nor impaired fine motor control; at least, not as defined by the monofilament and Purdue Pegboard tests, respectively. Our grasping task and clinical tests may capture at least partly non-overlapping behavioural consequences of CTS.

Consideration about the power of our analyses

Our ANOVAs with 25 CTS patients and 32 healthy controls had a statistical power, calculated with G*Power (Faul, F., Erdfelder, E., Lang, A.G., & Buchner, A.,2007) at only 51% to find an effect size of 0.13 for grasp kinematics difference between groups. According to a priori power analysis, with 95% statistical power we would need a sample of at least 180 participants to reliably detect the same effect size. Similarly, our correlations with 25 CTS patients had power, calculated with G*Power (Faul, F., Erdfelder, E., Buchner, A., & Lang, A.G., 2009) at only 61% to find a correlation coefficient of 0.44 for a relationship between CTS features and grasp kinematics. We would need at least 61 participants to detect such a correlation coefficient, as calculated with a priori power analysis with 95% statistical power. Both calculations underline the importance of future follow-up work in this area involving large numbers of CTS patients and healthy controls.

Concluding remarks

Our study is the first to characterise the kinematics of real object grasping in CTS. We saw this as an opportunity to not only better understand the behavioural consequences of CTS, but also probe how relatively minor peripheral somatosensory impairments may affect functional movements, using CTS as a model. By considering CTS as source of sensorimotor noise, we examined whether the effects of minor peripheral neuropathies on reach-to-grasp movements can be understood as adaptive (i.e., appropriate) responses in terms of normative theories of healthy sensorimotor control, which place taking account of noise/uncertainty at their centre. We view our findings as consistent with this framework,

overall, showing that CTS patients are able to manage the increased noise in non-visual signals due to their nerve impairment, and produce appropriate compensatory responses and normative anticipatory movements during grasping.

Precisely which impaired signals drive the increased compensatory responses we identify in CTS, and why reduced movement speed but not increased hand opening characterise these responses, remains unclear. It is likely that diminished touch sensitivity, long established in CTS and confirmed in our patients, plays a role. So too may proprioceptive impairments. However, whether digit proprioception is impaired in CTS is unknown. The next set of experiments in the thesis set out to address this fundamental question.

Chapter 3. Is proprioception impaired in Carpal Tunnel Syndrome?

3.1 Introduction

The sensory consequences of nerve injuries are typically explored in the context of impairments to tactile sensation. Less attention is given to digit proprioception: the sensation of digit position and movement in three-dimensional space (Sarlegna & Sainburg, 2009) that arises from joint receptors, muscle spindles, Golgi tendon organs and skin stretch receptors (Moberg, 1983; Proske & Gandevia, 2009, 2012). Digit proprioception plays a crucial role in everyday life activities because it is essential in the execution of accurate movements and manual dexterity (Hoseini et al., 2015), and in haptic perception per se. Therefore, impairment of this sensory signal can dramatically impair the functional use of the hand.

Digit proprioception is likely to be impaired in various nerve injuries, such as Carpal Tunnel Syndrome (CTS), which is expected to affect some structures that provide this sensory signal to the hand. Different clinical tests are available to investigate digit proprioception. However, they entail different limitations, and it is fundamentally challenging to isolate proprioception from, for example, tactile signals. Here, we investigate if CTS impairs digit proprioception by comparing the precision of the sense of opening of the index finger and thumb in CTS patients relative to healthy controls, by measuring their ability to discriminate the sizes of felt objects.

As discussed previously, CTS arises from chronic compression of the median nerve at the wrist level (Aroori & Spence, 2008; Middleton & Anakwe, 2014). CTS affects the thumb, index, middle finger and lateral part of the ring finger (depending on the particular organisation of the median nerve projection territory, which is known to vary between individuals; Aroori & Spence, 2008; Middleton & Anakwe, 2014). Thus, the nerve entrapment affects different structures of the hand, such as muscles and joints, which are necessary to perform a grasping movement (Chammas, 2014; Duncan et al., 2013). Also, the nerve

entrapment affects the skin stretch receptors in the glabrous area of the innervated fingers (Johansson & Vallbo, 1979). Consistent with this, tactile sensation, which relies on cutaneous mechanoreceptors, is impaired (Chen et al., 2015; Gehrmann et al., 2008; Wolny et al., 2016). And so is force production, which relies on control of muscle output and tactile sensing, and the sense of force (e.g., derived from Golgi tendon organs; Zhang, et al., 2011; 2012). However, patients often report various functional problems (e.g., clumsiness, fine motor control problems; Amirjani et al., 2011; Aroori & Spence, 2008; Middleton & Anakwe, 2014) that might not only be explained by the tactile or force-control problems. Indeed, the median nerve innervates some structures of the hand (e.g., muscle and mechanoreceptors) that also provide digit proprioception signals. Therefore, we hypothesised that chronic entrapment of the median nerve will lead to impaired digit proprioception. Problems in accurately sensing hand position are likely to result in functional problems while performing manual activities, increasing the likelihood of dropping objects, for example. Digit proprioception is also a primary signal by which we sense the shape and size of objects when vision is unavailable, such as when reaching in a bag for our keys (Berryman et al., 2006). It also contributes to such perceptual estimates when vision is available, although to a lesser degree (Ernst & Banks, 2002). So impairments to digit proprioception would be expected to have consequences beyond movement control per se, including how we perceive the world from haptics. To our knowledge, whether CTS affects digit proprioception per se has not been determined. Thus, the purpose of this experiment is to assess if digit proprioception is impaired in CTS.

The common tests used to assess hand/arm proprioception can be categorised into two principal techniques. First, a matching task where the clinician arranges the body part being tested (e.g., the left hand) in a specific position, and the patient has to match (or mirror) this position with the other, intact hand (here, the right hand; Goble, 2010; Hillier et al., 2015; Hoseini et al., 2015). Second, passive motion direction detection — informally referred to as

the ‘up-down test’ — where the clinician moves a finger/joint in a specific direction, up or down, and the patient has to report which direction of motion they perceived (Hillier et al., 2015). These tests are widely used in clinical settings because they are easy and quick to administer.

The clinical tests presented above, however, entail different problems. The up-down test, for instance, adds potentially confounding sensory signals. The clinician touches the fingers, and different patterns of pressure on either side of the finger result from movements up or down. This may provide a tactile cue to the direction of movement, potentially indicating the direction of motion to the patient even when proprioception is impaired (Hillier et al., 2015). Moreover, the up-down test relies on the clinician generating a movement of unknown magnitude, and so it provides only a very crude measure of sensitivity to movement, rather than a precise quantitative measure. As such, it may only detect severe impairments, and does not provide a precise measure of any subtle changes (for example, during recovery). A basic problem with matching tests is that they require a response with another body part, and so potentially confound (possibly undiagnosed) impairments to the body part used to respond with proprioception in the tested body part.

Another shortcoming of the current clinical tests is that they do not isolate proprioception bias and sensitivity (Hoseini et al., 2015). Sensitivity relates to how noisy the signals are about digit position. That is, how precisely is digit position sensed, and therefore how small of a change in this position can the person detect? Proprioception bias reflects systematic errors in the sense of digit position, for example consistently overestimating or underestimating the angle of a finger joint. Sensitivity is arguably the more direct index of the integrity of sensory signals form proprioception. It reflects the basic ability of the proprioception system to convey meaningful signals to the brain, analogous to measuring visual acuity in the eye tests, for example. Proprioception bias and sensitivity are in-principle independent (a participant could in-principle be very sensitive but extremely biased, or vice-versa). The up-down test does not measure bias, but instead only (crudely) measures

sensitivity. Matching tests appear to measure bias (unless sufficient trials are conducted to reliably measure the variability in responses). However, it is also possible that noisy proprioception (poor sensitivity per se) causes biases in response, for example in the direction of the starting position of the responding body part, in which case this type of test conflates bias and sensitivity. Hoseini et al. (2015) note that it would be valuable to consider bias and sensitivity components independently, and conflating them may result in misinterpreting impairments.

Hoseini et al. (2015) proposed a quantitative test of digit/hand proprioception to address some of these issues. They proposed a method based on psychophysical principles, using an adaptive staircase procedure (in which the stimulus is adjusted based on participants' responses) to assess sensitivity and bias of static position sense of the index finger. The hand to be assessed was positioned on a stand, under a table-style computer. Their unseen index finger was then positioned by the experimenter at a certain, fixed angle. During the task, visible lines were displayed on the computer screen, superimposed on the hand, and the participant had to indicate if the line displayed on the screen was rotated more clockwise or anti-clockwise than the angle of the finger. Thus, in psychophysics terminology, the finger position (from proprioception) was the standard stimulus, and the visual line was the comparison stimulus. The value of the (visual) comparison was controlled by a staircase procedure, to allow a psychometric function to be estimated. From this function, sensitivity (visual-proprioceptive discrimination threshold) and bias (the point of subjective equality, or PSE, between sensed finger position and the visual line) could be determined. The test, therefore, allowed the independent investigation of proprioception sensitivity and bias.

The approach of Hoseini et al. (2015) addresses many of the problems with existing tests. It isolates proprioception in a single hand, eliminates confounding tactile signals, and provides independent measures of proprioception bias and sensitivity. One shortcoming of the test, however, is that it requires an estimate of digit position from the 'target sense '— proprioception — to be compared with an estimate of line angle from another sense (vision).

This is potentially problematic for two related reasons. First, the task requires that sensory signals from different senses be transformed into comparable ‘units’. This process itself may induce noise that contributes to the measured performance. Second, and more directly, the task conflates visual sensitivity and proprioception sensitivity. The task requires comparing ‘positions’ specified by proprioception and vision, and so sensitivity in both sensory systems contributes to the measured discrimination threshold. Consider two patients with equivalent proprioception sensitivity, one of whom also has impaired vision. For the latter patient, impaired vision will manifest as poor proprioception. This confound is likely to be particularly problematic for assessing peripheral nerve conditions, because they are more prevalent in older populations. Visual acuity declines with age, and the incidence of visual impairments such as cataracts increases (Horowitz, 2004). Indeed, something as simple as a patient not wearing their glasses for the test could result in an inaccurate assessment of their proprioception.

The above discussion highlights some of the challenges involved in measuring the integrity of digit proprioception in isolation from other signals. All of the approaches involve trade-offs and as such the best test to use may depend on the particular questions of interest in a specific instance. Below, we describe our approach to assessing proprioception in CTS, and the rationale for our choices. In so doing, we highlight the trade-offs that we made, in the context of previous work.

As Hoseini et al. (2015), we considered *sensitivity* in digit proprioception to be a fundamental measure for characterising proprioception impairments (as an analogue to visual acuity in eye tests). The current study also focuses on the scientific question of whether CTS causes impaired digit proprioception, therefore we were not concerned here with developing a method that would be practical in clinical settings (though of course, it was important to consider the specific requirements of patients in developing the procedure; see below). We also wished to obtain an absolute measure of the sensitivity of digit proprioception. As noted above, Hoseini et al. (2015) procedure conflates sensitivity of

proprioception *and* vision. Discrimination thresholds (the index of sensitivity) reflect noise in both sensory systems, and so an absolute estimate of the noise/sensitivity of proprioception alone cannot be recovered. Therefore, we used a task where judgements were independent of vision. To do this, we used a two-interval forced-choice (2-IFC) haptic size-discrimination judgement task. This task has been used previously in studies of how information from vision and haptics is integrated (Ernst & Banks, 2002; Takahashi, Diedrichsen, & Watt, 2009; Takahashi & Watt, 2017), and of the neural underpinnings of haptic size perception (Perini et al., 2020), therefore is thought to produce accurate absolute estimates of haptic size sensitivity. During the task, participants feel two objects (a standard, and a comparison, which varies across trials), one after the other, by squeezing them between the unseen thumb and index finger, and judge which one is largest. The comparison size was controlled using an adaptive staircase procedure, similar to Hoseini et al. (2015).

Our central assumption is that haptic size is primarily encoded by proprioceptive signals specifying the magnitude of the opening of the thumb and index finger (Berryman et al., 2006). Therefore, haptic size-discrimination thresholds should index digit proprioception. One trade-off this incurs is that, unlike the up-down test, and Hoseini et al. 's (2015) method, judging haptic size from proprioception relies on a combination of information from numerous joints, and even across digits (in our case, the thumb and index finger). Our task therefore does not isolate specific joints, but can only assess overall effects. This, potentially, has advantages and disadvantages. If in a particular patient, deficits due to CTS are limited to certain structures (e.g., the thumb only), our test would make this harder to detect than one that examined each digit, or joint, in isolation. On the other hand, the pinch opposition between the thumb and index finger is considered the hallmark of dextrous manipulation (Jeannerod et al., 1995), and by simultaneously assessing effects on the ensemble of structures served by the median nerve , which are used in this task, our measurements may more closely reflect any functional impairments to proprioception.

Another trade-off is that our task does not measure proprioception bias, only sensitivity. Because both standard and comparison stimuli are felt under the same conditions, by the same hand, the two stimuli will feel the same size when they are the same size (and the PSE should always equal the standard size), regardless of any bias in the perceptual experience. As outlined above, the benefit of this method is, however, that we can obtain an absolute measure of haptic size sensitivity, which we considered more valuable for our aims than measuring bias (note that measuring across left and right hands, within the haptic system, also conflates noise in estimates from both hands', and so does not provide a unilateral measure of sensitivity to haptic size — our aim).

Perhaps a more significant trade-off with our task is that it potentially conflates tactile signals with digit proprioception per se. As seen above, this is the case with other tasks/tests, and it reflects fundamental challenges in assessing proprioception in isolation from other sensory and motor signals. Whereas vision and audition, for example, and even tactile sensation, can easily be stimulated in isolation simply by stimulating one sense at a time, this cannot readily be achieved for proprioception due to the closely linked nature of tactile and proprioceptive sensation, and their mutual dependence on motor activity. Indeed, to an extent, this 'problem' reflects the fact that, unlike vision or audition, our sense of hand posture and movement is itself inherently multisensory processing, involving a close interplay of various types of tactile afferents, joint receptors, and sensors in muscles. So understanding impairments at a functional level, as opposed to sensor level, in any case, requires considering all of these systems together. Nonetheless, a specific concern with our task, especially when used with CTS patients, is that impaired tactile sensation—a primary symptom of CTS—may itself cause inflated haptic size-discrimination threshold even when proprioception is unimpaired. One reason for this relates to the interactive, multisensory nature of haptic perception described above. Consider our case of estimating the size of an object by holding it. At first approximation, the object size can be estimated by proprioceptive signals (although including skin-stretch receptors) that signal the separation of the grasping

digits (Lederman & Klatzky, 2009). However, Berryman et al. (2006) highlighted how finger-tip tactile information must also play a role, because digit posture alone does not provide unambiguous information about object size. There are at least two reasons for this. First, when grasping an object, the digit tips are compressed by different amounts depending on the digit force applied, resulting in different digit separation. Berryman et al. (2006) showed that the brain correctly takes this compression into account, on the basis of tactile signals at the fingertips, allowing it to achieve *haptic constancy* — the same perception of size — across different digit separations. A similar situation occurs when feeling compliant objects. The same object, felt with different force, can result in different digit separation. Here, again, tactile signals about force, and the material properties of object surfaces, are used to compensate for the changes in digit separation, leading to reliable estimation of the object size (Berryman et al., 2006). We do not know what effect impairments to tactile sensing *alone* would have on these processes, and so we cannot be sure whether they would lead to inflated size-discrimination thresholds, causing us to falsely conclude that proprioception per se is impaired. As above, however, we take the view that taking this functional approach — does CTS affect haptic size-discrimination judgements — is overall beneficial.

We also considered how, at a more practical level, tactile impairments in CTS might inflate size-discrimination thresholds, and therefore our estimates of impairments to proprioception. These include participants experiencing uncertainty about when they were feeling the stimuli, which would result in increased uncertainty in their judgements. We took several detailed steps in our method to address these issues, which are detailed in the Method.

We hypothesised that the compression of the median nerve should impair digit proprioception. As a consequence of the compression, the sensory noise should increase, and the quality of the sensory signals available should decrease. We, therefore, predicted worse performance (i.e., larger haptic size JNDs) for CTS patients compared to controls.

3.2 Methods

3.2.1 Participants

Twenty CTS patients and 27 healthy controls participated in the study. Thirteen CTS patients and 23 of the controls of this experiment took part in the experiment in Chapter 2. All participants provided written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Research Ethics Committee of the School of Psychology, Bangor University, and by Betsi Cadwaladr University Health Board (IRAS project ID: 195274).

The mean age of CTS patients was 51.5 years (SD = 11.30 years; age range: 25-65 years) and included 7 males, 13 females. As in Chapter 2, patients were diagnosed clinically and confirmed as mild (N = 9), moderate (N = 6), or severe (N = 5) based on electrophysiological measures. Twelve patients had bilateral CTS, two had unilateral left-hand CTS, and six had unilateral right-hand CTS. One patient had recently undergone carpal tunnel release surgery on her left wrist, and so did not complete any tasks/testing involving her left hand. One patient reported an ulnar nerve problem in the right hand, and so did not complete any tasks/testing involving his right hand. Another patient reported additional problems in the right hand, other than CTS, and so we did not complete any tasks/testing involving this hand. Patients had no other comorbidities. All patients were right-hand dominant according to self-report.

The mean age of healthy controls was 41 (SD = 12.57 years; age range: 26-66 years) and included 11 males and 16 females. One participant was left-handed, and the other participants were right-handed, according to self-report.

All participants had no history of neurological or psychiatric illness. All had normal binocular stereopsis (depth perception from binocular vision), according to the Randot Stereotest (Stereo Optical Co., Inc.). The study took approximately 2.5 hours to complete, and participants received financial compensation. All participants were naïve to the predictions of the study.

3.2.2 Primary measures

CTS symptom quality and severity

As in Chapter 2, our patients completed the Boston Carpal Tunnel Questionnaire (BCTQ standard; Levine, et al., 1993) to characterise the quality and severity of their CTS symptoms, as well as our additional four questions addressing symptom quality and severity at the time of testing, and four questions addressing symptom severity while performing manual activities of daily living (see Appendix A, Figure S1.1 for the standard BCTQ and the additional questions).

Haptic size-discrimination test

As described in the Introduction, the task was a two-interval forced-choice (2-IFC) psychophysical size discrimination procedure, to measure just-noticeable differences (JNDs) in haptic size. The JNDs represent the smallest difference in millimetres that participants need to reliably identify the larger object to a given criterion level (see *Procedure*). As mentioned above, there are various artefactual ways in which impairments to tactile sensation could cause inflated haptic size JNDs without impaired proprioception. For instance, patients might experience increased uncertainty about whether and when the digits are touching the objects, and so when they should pay attention to their size percepts, resulting in poorer discrimination performance. Also, increased thresholds might arise from problems in performing the pinch movement required (and even locating the object by touch alone). To mitigate these concerns, the starting points of the digits were set close to the object surfaces (on two *digit-platforms*; see below), so that simply closing the hand guaranteed that the object would always be successfully grasped. We reasoned that this should minimise uncertainty due to any tactile impairments.

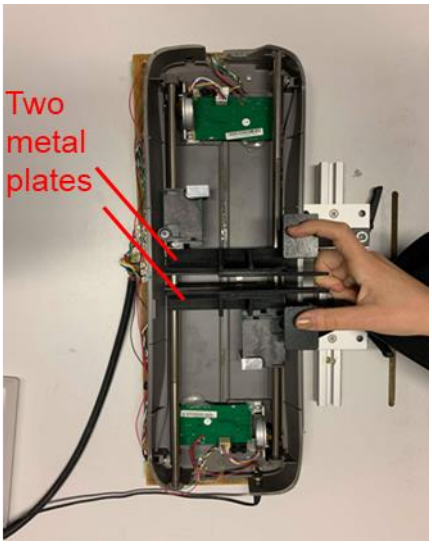
We measured size discrimination JNDs at three different object sizes (see below). Sensitivity to haptic object size is known to vary with size (Takahashi & Watt, 2014), and the qualitative shape of the function relating JNDs to size varies considerably across individuals

(Perini et al., 2020; Stevens & Stone, 1959; Takahashi & Watt, 2014). Measuring JNDs only at one size might therefore miss differences in certain parts of this 'space', and effectively add noise that makes it harder to find differences between patients and controls. By assessing JNDs at different object sizes, we can more fully characterise how hand sensitivity is affected by CTS.

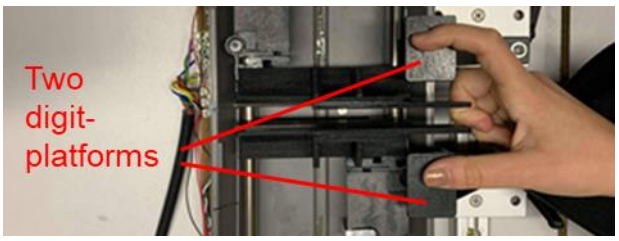
Experimental setup

The object size felt by each participant was created using a custom computer-controlled device, which altered the separation of two rigid metal plates (each 100 mm wide) by moving them along a track using two high-precision stepper motors. The apparatus is shown in Figure 3.1A. The position of each plate was controlled by a separate motor in increments of ~0.1 mm. The minimum possible size was 6.7 mm, and the maximum possible object size exceeded the maximum size of the hand opening. The machine was programmed to make a short series of random movements before stopping at each size, so the sound produced was not informative about changes in size. A short auditory tone indicated when to grasp each stimulus. Size discrimination thresholds were measured at three different standard sizes: 10, 30 and 50 mm.

At the beginning of each trial, the digits of the participant were positioned on two digit-platforms (each 3 x 4 cm; see Figure 3.1B) close to the object, so the closing of the hand guaranteed the grasping of the object (see earlier). The distance of the digit-platforms was adjusted to suit different hand spans. The arm used to perform the task rested comfortably in an adjustable arm support (Figure 3.1C). The arm support was configured to minimise flexion/extension of the wrist (i.e., to help maintain a neutral wrist position) to reduce the possibility of affecting performance due to awkward wrist posture, and to minimise the likelihood of exacerbating CTS patients' symptoms. The machine and the hand/arm of the participant were covered with an occluder to prevent any visual feedback during the execution of the task (Figure 3.1C).



.A.



B.

C.

Figure 3.1. Experimental set-up. (A) The computer-controlled device used for the presentation of different object' sizes. (B) A closer look at the digits positioned on the digit-platforms and the two plates, gripped by participants. (C) Side view of the experimental setup, with the participant's arm in the arm support, the digits on the digit-platforms and the occluder covering the apparatus.

Procedure

The study took approximately 2 hours to complete. Participants first familiarised themselves with the task and timings (see below), by performing a few practice trials with vision available (the occluder was repositioned before the main experiment began). Experimental trials began with the participant's thumb and index finger on the digit-platforms (Figure 3.1A). Each trial consisted of two stimulus intervals: standard (i.e., the size that always stayed the same; 10, 30 or 50 mm in the different conditions) and comparison (i.e., the size that changed according to the participant's performance). Standard and comparison were presented in a random order on each trial. An audible tone indicated when participants should grip each stimulus. Participants were instructed to gently grip the 'object' with their thumb and index finger, and then immediately return their digits to the platforms (so the device could move to the next position unimpeded). After each trial, participants verbally indicated which object was larger, the first or the second interval (responses were entered into the computer by the experimenter).

The stimulus stayed in one position for 2 s, and participants were trained to release it before this time. There was an interval of 1.5 s between the presentation of the first and second stimulus interval. The comparison size was controlled using adaptive staircase procedures. These procedures adjust the size of the comparison stimulus based on the participant's responses, in order to position the majority of the stimuli at the most informative points on the psychometric function for determining the discrimination threshold (JND). We used two different staircase reversal rules. First, a 1-up, 2-down staircase, in which the comparison size was increased following one trial on which the comparison was judged smaller than the standard, and decreased following two consecutive trials on which the comparison was judged as larger. Second, a 2-up, 1-down staircase, in which the comparison size was increased following two consecutive comparison-was-smaller answers, and decreased following one comparison-was-larger answer. The initial staircase 'steps' in size were 8 mm, which was halved at each of the first three reversals (i.e., to 4, 2, then

1 mm). Staircases terminated after 12 reversals, or after 100 trials. For the 30 and 50 mm object sizes, JND measurements were derived from one repetition of each staircase type. For the 10 mm object size it was not possible to use the 2-up, 1-down staircase because it would likely result in comparison sizes smaller than our device could present, or possibly smaller than zero. For this size participants therefore completed two repetitions of the 1-up, 2-down staircase per JND, and the data for one repetition were flipped to allow a comparable analysis (see below). The overall position of the 'object' was jittered by a small random amount (in the range +/- 10 mm; uniform distribution) in order to prevent the task from being completed on the basis of the position of only one digit only across the two intervals (as opposed to hand opening, per se).

We measured size JNDs at each object size, for each hand (except for the small number of participants who could only complete the experiment with one hand; see above). The experiment was completed in a number of blocks, where each block consisted of a single, separate staircase (i.e., one hand, one object size, and one staircase type). We did this (as opposed to interleaving object sizes, for example) in order to keep experiment blocks short, so as to minimise fatigue and the risk of changes in symptoms in CTS patients. For the same reason, the tested hand was alternated on consecutive blocks (or an equivalent rest period was introduced, as appropriate). Otherwise, the order of object sizes, and staircase type, were randomized.

JNDs were fitted to each participant's data, for each object size, and hand. JNDs were defined as the standard deviation of the best-fitting cumulative Gaussian to the psychometric data in each condition, using a maximum-likelihood criterion. This equates to the ~84% point on the psychometric function. In other words, JND is defined as the difference in size required to go from 50% (chance performance) to reliably judge the comparison size to be larger than the standard size (~84% of the time). Figure 3.2 shows an example psychometric function for one participant in one condition, and illustrates a JND.

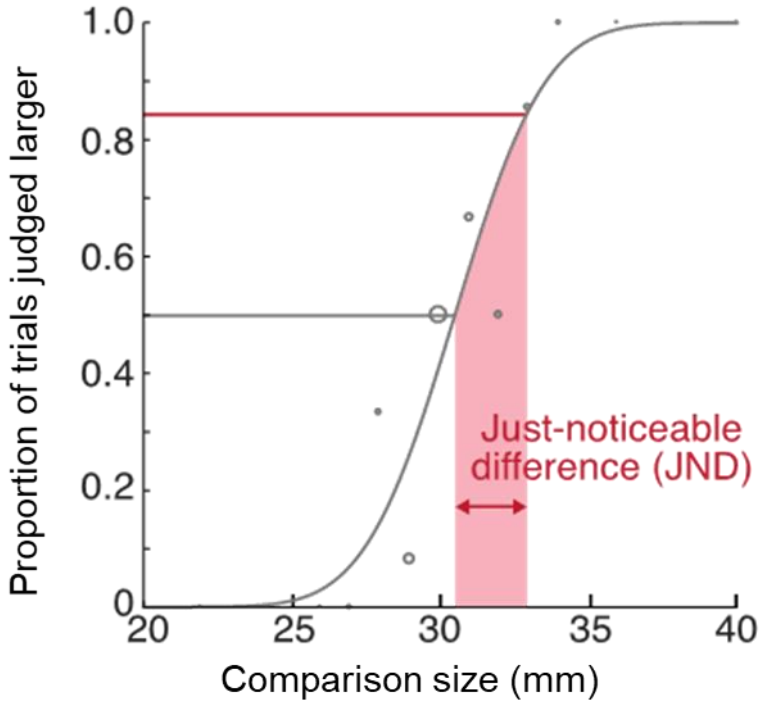


Figure 3.2. **Example of a psychometric function.** The proportion of trials in which the comparison was judged 'larger' than the standard size (30 mm, in this case) plotted as a function of comparison stimulus size. The open black circles show the participant's responses at each comparison size. The curve is the best-fitting psychometric function (see main text). The grey line reflects chance performance (50%) while the red line denotes the criterion value of 84%. The shaded pink area is the JND.

Statistical analyses

Analysis of JNDs across participants and groups was conducted using a mixed ANOVA with Size (three levels: 10, 30 and 50 mm) and Group (two levels: CTS patients and Controls) as within- and between-subject factors, respectively. Where significant interactions were identified, post-hoc t-tests were used to evaluate all pairwise comparisons of interest. Bonferroni correction was used for multiple comparisons. In the case of violations of sphericity, for tests with more than two levels of a within-subjects factor, Greenhouse-Geisser correction was used.

3.2.3 Standardised clinical tests

As in Chapter 2, besides the primary tests, we also characterised participants' sensorimotor performance in other ways, in order to perform exploratory analyses evaluating whether JND is related to standardised clinical test and/or CTS symptom quality/severity.

Touch sensitivity and manual dexterity

As in Chapter 2, fingertip touch sensitivity was assessed in CTS patients and Controls using the Semmes-Weinstein Monofilament (monofilament test) and Two-Point Discrimination (2PD) test. We again assessed touch sensitivity on the distal pulpar surface of the thumb, index, and little finger. The testing equipment was unavailable at the start of the study, and we could only collect touch sensitivity data for 24/27 controls.

Manual dexterity was again assessed in CTS patients and Controls using the Purdue Pegboard test. Both CTS patients and Controls performed the three subtests of the Purdue Pegboard. Because three patients reported additional problems than CTS on one hand, these patients did not complete the bimanual nor assembly subtests (N = 17 for these subtests). However, we used the data for the unimanual subtest for these patients (N = 20 for unimanual subtest).

3.3. Results

The selection of which hand for each participant to enter into the main analysis was carried out in the same way as in Chapter 2 (again following the approach taken by Maeda et al., (2014). For unilateral CTS, data from the affected hand were used for the analyses of all the tests. For patients with bilateral CTS, we analysed data from the most affected hand, based on the scores of the standard BCTQ (see Primary measures 3.3.1). This resulted in 7 left hands and 13 right hands for CTS patients. As before, we used the same proportion of left/right hand data from healthy controls (i.e., 9/18, left/right hands), otherwise randomly selected. Because of the large number of bilateral CTS patients (N = 12), we did not perform

any analyses between the two hands because we could not use one hand as an 'internal control'.

3.3.1 Primary measures

CTS symptom quality and severity

Table 3.1 shows the full details of CTS patients' symptom severity, as assessed by the BCTQ standard and our additional eight questions, along with key demographic variables, and nerve conductance measurements. The electrodiagnostic studies show impaired nerve conductance in all CTS patients (see table 3.1). Symptom severity according to BCTQ standard ranged from "asymptomatic" (N = 3; score between 0 to 11), to "mild "(N=8; score between 12 to 22), to "moderate" (N = 8; score between 23 to 33) and "severe" (N=1; score between 34 to 44; group average = 20.28 [16.12, 24.43]; see Table 3.1). The scores of our additional questions regarding the symptom severity at the test and the symptom severity during daily activities have a score ranging from 0 to 16, with lower values indicating lower severity.

Table 3.1. CTS patient's characteristics.

Nerve Conductive Study. The sensory velocities and latencies are recorded between digit III and wrist; only for the subject with an asterisk (*) these measures have been recorded between digit II and wrist. The motor latency has been recorded between the wrist and the thumb (abductor pollicis brevis, APB).

Boston Carpal Tunnel Questionnaire: a) Standard score = the score of the eleven standardized items; b) Severity = the severity level based on the Standard Score; c) Symptom severity at the test = the score of the additional questions regarding the symptomatology at the moment of testing; d) Symptom severity during daily activities = the score of the questions regarding the symptomatology during daily activity.

Demographic			Nerve Conductive Study (abnormal values in bold)[1]			Boston Carpal Tunnel Questionnaire			
Sex	Age	Affected hand	Median Nerve Study	Velocity (m/s)	Latency (m/s)	Standard score[2]	Severity	Symptom Severity at the test[3]	Symptom Severity during daily activities[4]
M	60	Right	Sensory(µv) Motor (mV)	**35.8**	3.35 **4.58**	7	Asymptomatic	1	3
M	65	Right	Sensory(µv) Motor (mV)	44.4	3.38 **4.63**	8	Asymptomatic	1	3
F	45	Right	Sensory(µv) Motor (mV)	45.6	2.85 3.70	11	Asymptomatic	1	2
F	36	Bilateral (Left)	Sensory(µv) Motor (mV)	**37.2**	3.23 **4.67**	13	Mild	0	9
F	41	Left	Sensory(µv) Motor (mV)	**32.3**	3.50 **4.27**	13	Mild	1	6
F	45	Bilateral (Right)	Sensory(µv) Motor (mV)	**38.0**	3.42 **4.08**	14.5	Mild	3	6.5
F	65	Bilateral (Right)	Sensory(µv) Motor (mV)	**38.6**	2.85 **4.79**	15	Mild	4	10
M	60	Bilateral (Right)	Sensory(µv) Motor (mV)	**39.8**	3.52 **7.04**	17	Mild	2	5
M	62	Bilateral (Left)	Sensory(µv) Motor (mV)		Absent **6.75**	17	Mild	4	5
F	54	Bilateral (Right)	Sensory(µv) Motor (mV)	44.6	2.69 **3.17**	19	Mild	0	5
M	53	Left	Sensory(µv) Motor (mV)	**37.2**	3.63 **4.25**	20	Mild	7	5
F	25	Bilateral (Left)	Sensory(µv) Motor (mV)	**35.2**	3.61 5.05	23	Moderate	3	7
F	56	Bilateral (Right)	Sensory(µv) Motor (mV)		Absent **7.38**	25	Moderate	9	12
M	60	Bilateral (Left)	Sensory(µv) Motor (mV)	48.7	2.67 **3.63**	25	Moderate	6	11
F	34	Bilateral (Left)	Sensory(µv) Motor (mV)		Absent **6.2**	26	Moderate	5	6
F	44	Bilateral (Right)	Sensory(µv) Motor (mV)	41.3	3.03 **4.04**	27	Moderate	10	8
M	59	Right	Sensory(µv) Motor (mV)	**38.1***	3.54* **5.78**	29	Moderate	6	10
F	55	Bilateral (Right)	Sensory(µv) Motor (mV)	**46.6**	2.79 **3.52**	30	Moderate	6	13
F	63	Right	Sensory(µv) Motor (mV)	**46.8**	2.63 **3.40**	33	Moderate	8	16
F	49	Right	Sensory(µv) Motor (mV)		Absent **6.57**	37	Severe	14	16

[1] Normative Median Nerve Conduction Values, Canterbury scale. doi.org/10.1002/1097-4598(200008)23:8<1280::
AID-MUS20>3.0.CO;2-Y: i) grade 0, no neurophysiological abnormalities; ii) grade 1- very mild, detected only in two sensitive tests (e.g., inching, palm/wrist median); ii) grade 2- mild CTS, conduction velocity < 40 m/s with motor terminal latency < 4.5 ms; iii) grade 3- moderately severe, motor terminal latency > 4.5 ms and > 6.5 ms with preserved index finger sensory nerve action potential (SNAP); iv) grade 4- severe CTS, motor

terminal latency > 4.5 ms and > 6.5 ms with absent SNAP; v) grade 5- very severe, motor terminal latency > 6.5 ms; vi) grade 6- extreme severe, surface motor potential from APB < 0.2 mV, peak to peak.
[2]max score = 44
[3]max score = 16
[4]max score = 16

Haptic size-discrimination test

Figure 3.3 shows the JNDs for CTS patients and Controls for the three sizes. A mixed factors ANOVA revealed a significant main effect of Size ($F(1.61, 69.47) = 122.99$, $p < 0.0001$), and no significant main effect of Group ($F(1,43) = 0.13$ $p = 0.71$) or significant interaction ($p > 0.05$; See Appendix B, Table S.2.1 for all statistical outcomes). The main effect of Size indicated that JNDs increased with increasing object size. Similar patterns have previously been reported in the healthy population (e.g., Steven and Stone, 1959; Takahashi and Watt, 2014; Perini et al., 2020). In detail, JNDs at 30 mm ($M = 2.99$) were significantly higher than at 10 mm ($M = 2.24$, $p = 0.001$), and JNDs at 50 mm ($M = 3.91$) were significantly higher than at 30 mm ($p = 0.009$), and 10 mm ($p < 0.0001$). The lack of a significant main effect of Group indicates that CTS patients had similar JNDs to Controls. Overall, the results indicated that digit proprioception is unimpaired in our CTS patients.

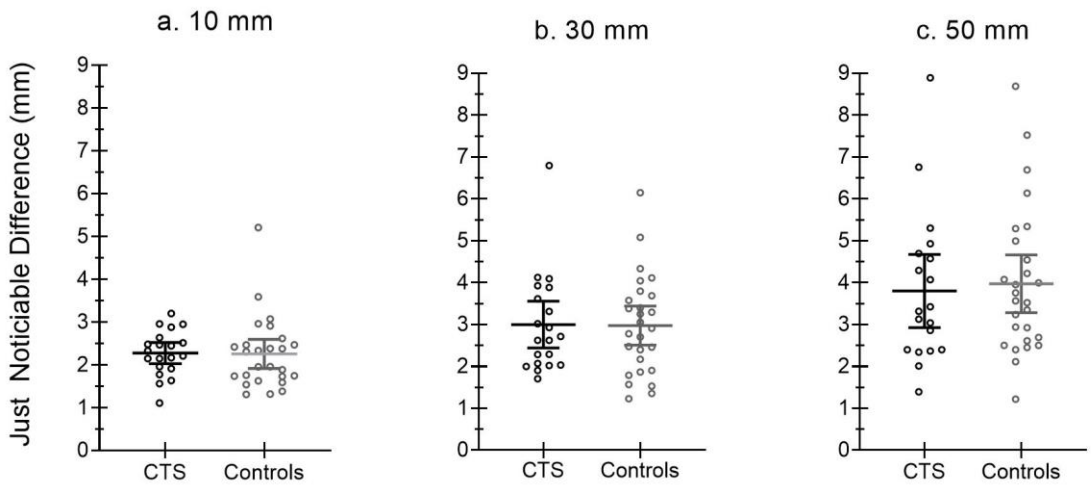


Figure 3.3 Haptic size-discrimination performance. Just noticeable differences (JNDs) for each object size (10, 30 and 50 mm) for CTS patients and controls. The dots represent individual participants. Summary JNDs are presented as means and 95% CIs.

3.3.2 Standardised clinical tests

Table 3.2 shows mean tactile sensitivity for CTS patients and Controls. Both touch detection thresholds (monofilament test) and touch discrimination thresholds (2PD) were significantly higher for the index finger and thumb for CTS patients compared with Controls. As we found in Chapter 2, CTS patients also showed elevated touch detection and discrimination thresholds for the little finger in comparison with Controls. These results suggest that impairments to touch sensitivity are not restricted to the median-nerve innervated digits.

Table 3.2. **Semmes-Weinstein Monofilament and Two-Point Discrimination scores**. Statistical significance with group means and 95% IC indicated in parenthesis.

Digit	Semmes-Weinstein Monofilament (millinewtons)[1]				Two-Point Discrimination (millimetres)[2]			
	CTS	Controls	Mann-Whitney test	p-value	CTS	Controls	Mann-Whitney test	p-value
Thumb	10.2 [11.8]	0.3 [0.06]	U = 79.5	p < 0.0001	4.6 [0.8]	3.2 [0.3]	U = 96	p = 0.006
Index	8.8 [11.8]	0.3 [0.06]	U = 95	p = 0.002	4.5 [0.6]	3.3 [0.3]	U = 93	p = 0.003
Little	1.4 [1.5]	0.3 [0.04]	U = 101	p = 0.0006	5 [0.6]	3.9 [0.4]	U = 115.5	p = 0.007

[1] Normative value to distinguish normal sensitivity is 2.83 (Bell-Krotoski, Fess, Figarola, & Hiltz, 1995; MacDermid, Kramer, & Roth, 1994) or 0.66 millinewtons.

[2] Normative value is < 6 mm (Gelberman et al., 1978).

Figure 3.4 shows the scores for the Purdue Pegboard for CTS patients (N = 20 for the unimanual subtests, N = 17 for the bimanual and assembly subtest) and Controls (N = all). CTS patients inserted significantly fewer pegs in the unimanual subtest compared to Controls (t (44) = 2.65, p = 0.011). The numbers of pegs inserted with both hands (t (42) = 1.855, p = 0.071) and the number of ‘assemble’ element units (t (42) = 1.963, p = 0.056) were lower for CTS patients in comparison with Controls, which is in the direction predicted but not

significant. Overall, our data showed that CTS impairs manual dexterity, as previously reported in other studies where larger sample size was used (e.g., Amirjani et al., 2011).

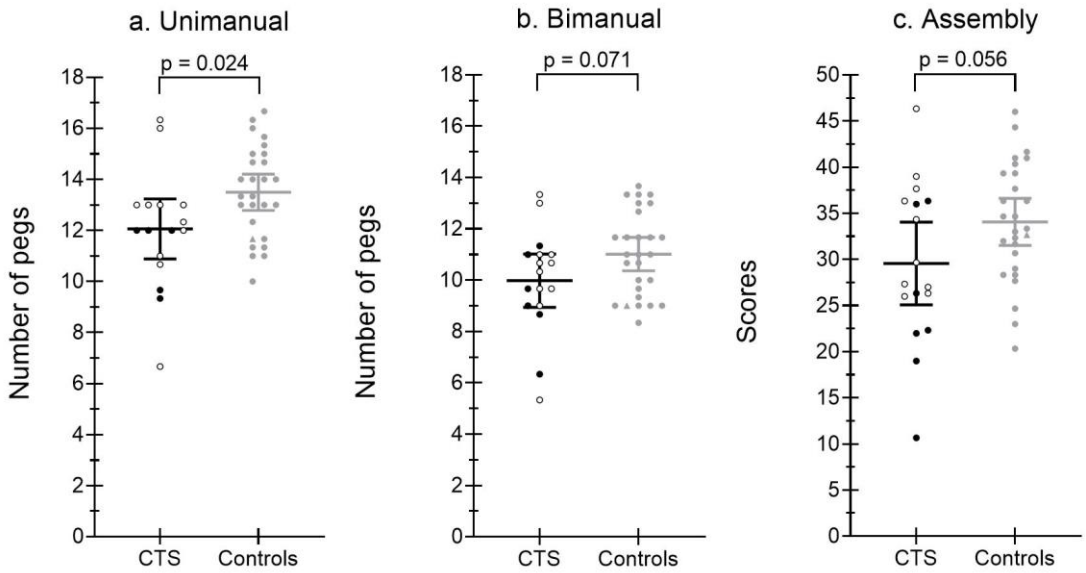


Figure 3.4. Purdue Pegboard scores. Distribution of the Purdue Pegboard scores (mean and 95% Confidence Interval) for CTS patients and Controls for the three subtests. Filled circles represent the unilateral CTS, while unfilled circles represent the bilateral CTS. The triangle in the Controls group represents the only left-hand subject.

3.3.3 Exploratory analyses: relationships between haptic-size discrimination and CTS symptom severity?

Finding a relationship between haptic size-discrimination sensitivity and symptom severity in CTS could be a potential valuable outcome of the current study. We computed correlations between JNDs and CTS symptom severity, using Kendall's τ to assess statistical significance (see Table 3.3 for all the statistical analyses and Appendix B, Figures S.2.1 for the correlation plots).

We might expect a positive relationship between JNDs and BCTQ standard, suggesting that higher symptom severity is associated with poor hand-opening sensitivity. However, we did not find evidence for such a relationship ($p > 0.05$). Further, we tested our additional questions because the BCTQ standard does not explicitly address current

symptomology and includes only one question addressing severity during the performance of manual activities. Therefore, using our additional questions should prevent us from not detecting relevant relationships. However, we did not find evidence of a relationship between JNDs and symptom severity at the time of the test ($p > 0.05$) and symptom severity during daily activities ($p > 0.05$). Overall, even if not significant our results are in the predicted direction (i.e., positive correlations).

Table 3.3. relationships between haptic-size discrimination and CTS symptom severity. The table shows Kendall's τ correlations between JNDs and CTS symptom severity.

	Boston Carpal Tunnel Questionnaire standard	Symptom Severity at the time of the test	Symptom Severity during daily activities
JNDs average (mm)	r (20) = 0.28, p = 0.08	r (20) = 0.17, p = 0.29	r (20) = 0.14, p = 0.39

3.3.4 Exploratory analyses: relationship between haptic size-discrimination and standardised clinical tests in patients and controls?

We performed exploratory analyses to evaluate if haptic size-discrimination sensitivity is related to any clinical assessment tests for both CTS patients and Controls. We ran a set of (3) correlation test using Kendall's τ to evaluate JNDs of (1) CTS patients and (2) Controls against the clinical scores from the (1) monofilament test, (2) 2PD test and (3) Purdue Pegboard unimanual scores. We applied a conservative Bonferroni correction to control us performing 3 tests; defined as statistically significant at $\alpha < 0.016$ for the correlations of CTS patients and Controls (see Table 3.4 for all the statistical analysis and Appendix B, Figure S.2.2 for the correlation plots).

As mentioned above, in a size discrimination task is not possible to eliminate tactile signals. Indeed, as proposed by Berryman and colleagues (2006), this might not even be sensible because both sensory signals provide relevant information when estimating object

size. Therefore, tactile measures and digit proprioception performance may be related. And of course, a relationship between tactile sensitivity and proprioception might exist because both signals are generated from structures in the hand that are innervated by the median nerve (and might therefore be similarly impaired in CTS). However, we found no evidence for a significant relationship between tactile sensitivity and haptic size sensitivity (all p's > 0.016) for both patients and Controls.

Further, we examined if the Purdue Pegboard unimanual subtest was related to JNDs. We did this considering the pivotal role played by digit proprioception in manual dexterity. We chose the scores from the unimanual subtest (and not the bimanual or assembly subtests) because scores from tasks completed only with the same hand are most likely to be correlated. Table 3.4 shows that scores on these tests are not significantly related (all p's > 0.016) for both CTS patients and Controls.

Table 3.4. **Relationship between haptic size-discrimination test and standardised clinical tests.** Correlation analyses between Just Noticeable Difference (JND) and monofilament test, 2PD and Purdue Pegboard for CTS patients and Controls.

Group	Monofilament test (mN)	2PD (mm)	Purdue Pegboard unimanual scores
JNDs CTS patients	r (17) = - 0.32, p = 0.10	r (18) = - 0.85, p = 0.64	r (19) = - 0.15, p = 0.39
JNDs Controls	r (24) = 0.23, p = 0.15	r (24) = 0.18, p = 0.23	r (27) = 0.18, p = 0.18

As final exploratory analyses, we performed multiple linear regressions to determine the predictors of JNDs for patients and Controls. In some ways, this of course duplicates aspects of the individual correlation analyses, above, and so might seem redundant. As a purely exploratory exercise, however, we reasoned it could be valuable to take a 'whole model' approach, seeing whether, collectively, our measures of tactile sensation and dexterity can predict JNDs. We therefore aimed to understand the amount of digit

proprioception variance explained by tactile sensation and/or manual dexterity. Tactile sensitivity might be expected to predict proprioception variance due to the strong link between the two sensory signals. Manual dexterity might be expected to predict proprioception variance because proprioception has a pivotal role in manual dexterity. Further, we wanted to assess if symptom severity can explain digit proprioception variance in the CTS patient group. Indeed, it is logical to assume that worse symptom severity should predict worse proprioception ability.

We first explored whether the monofilament test, 2PD and Purdue Pegboard unimanual scores can predict controls' JNDs. The model was a good predictor for controls JNDs ($F (3, 20) = 4.86$, $p = 0.01$, $R^2 = 0.42$; see Appendix B, Table S.2.2 for all the statistical outcomes). The monofilament test was a significant predictor of the JND values ($\beta = 4.24$, $SE = 1.13$, $t (20) = 3.73$, $p = 0.01$), while all the other factors were not (all $p > 0.05$). The regression model for controls seems to suggest that haptic size-discrimination sensitivity can be predicted by touch detection, indicating that worse JNDs are predicted by higher (i.e., impaired) touch detection sensitivity.

Then, we explored if the monofilament test, 2PD, Purdue Pegboard unimanual and BCTQ standard can predict patients' JND scores. The model could not predict the JNDs for CTS ($F (4, 14) = 0.40$, $p = 0.79$, $R2 = 0.105$; see Appendix B, Table S.2.3 for all the statistical outcomes). Indeed, none of the factors was a significant predictor of JNDs (all $p > 0.05$). The regression model of patients suggested that haptic size-discrimination sensitivity is not predicted by any of the factors used.

3.4 Discussion

In the present study, we investigated whether Carpal Tunnel Syndrome (CTS) impairs digit proprioception. To assess our hypothesis, we used a psychophysical haptic size-discrimination task to assess the sensitivity of opening of the unseen thumb and index finger. Differently from previous studies, we focused our attention on size discrimination because

digit proprioception is relevant for size discrimination. Contrary to our expectation, CTS patients had similar haptic size-discrimination thresholds (JNDs) to healthy controls, suggesting that digit proprioception is not impaired in mild-to-moderate CTS.

At face value, the lack of difference in JNDs between CTS patients and healthy controls seems a surprising result. Below we discuss several possible scenarios that could lead to this finding.

Digit proprioception was affected in our sample, but we failed to detect it?

One possibility is that, for some reason, our haptic size-discrimination procedure failed to work properly, rendering our data insensitive to differences across groups. We reasoned this would most likely manifest as unusually high haptic size-discrimination thresholds. We therefore compared our data to haptic size-discrimination thresholds in previous studies, to see if there was evidence for poor measurement in our study. Haptic size-discrimination thresholds have most commonly been measured not using real stimuli, but using robotic force-feedback devices. This might be expected, if anything, to introduce additional noise—the participant wears thimbles, and tactile signals are not correctly reproduced—resulting in higher thresholds. Consistent with this, JNDs measured in this way are typically comparable, but slightly larger than those in the current study, for similar object sizes. For example, Ernst and Banks (2002) reported JNDs of ~4.9 mm for a 55 mm object (N = 4), and Takahashi et al. (2009) found JNDs of around 4.25 mm for a 50 mm object (N = 7). Perini et al. (2020) measured a larger sample of participants (N = 16), with both left and right hands, and the same object sizes as the current study. Their study used an earlier version of the same electro-mechanical device, without digit platforms, and arm position was not controlled. Participants therefore had to make much larger movements to reach the objects, potentially increasing uncertainty, and felt the objects only for a brief duration (a relatively quick pinch-and-release movement). These factors, too, might be expected to cause larger JND measurements compared to the current study. Table 3.5 shows Perini et

al.'s (2020) data and the data for our healthy controls. It can be seen that our JND measurements were smaller (better sensitivity to haptic size-discrimination) at all object sizes, and particularly at the larger sizes than Perini et al.'s (2020). Berryman et al. (2006) also measured haptic size discrimination, but their thresholds are presented in different units, which cannot be directly compared to ours. Moreover, as described in the Results, we found the systematic increase in JNDs with increasing object size which has not only been found in previous studies (Perini et al., 2020; Stevens & Stone, 1959; Takahashi & Watt, 2014), but is also characteristic of sensitivity in almost all sensory domains. Thus our JNDs do not indicate that our procedure 'malfunctioned' in any obvious way.

Table 3.5. JNDs in Perini et al.'s (2020) study and the current study. The table shows the mean JND values (in mm) for each size. 95% confidence intervals are shown in parentheses.

	Perini et al. (2020)		Our healthy controls	
Object size (mm)	Right hand	Left hand	Right Hand	Left Hand
10	3.63 [0.8]	4.15 [1.5]	2.89 [0.6]	2.49 [0.4]
30	6.41 [1.4]	7.22 [4.1]	3.01 [0.4]	2.67 [0.4]
50	9.60 [2.9]	12.10 [4.7]	3.72 [0.6]	3.37 [0.5]

More generally haptic size-discrimination JNDs have been used in computational models of visual-haptic integration, where they have been found to predict, quantitatively, the weight given to haptics, and sensitivity to size when information from vision and haptics is available simultaneously (Ernst & Banks, 2002; Gepshtein & Banks, 2003; Gepshtein et al., 2005; Takahashi, Diedrichsen, & Watt, 2009; Takahashi & Watt, 2014, 2017). This precise fit between measured and predicted performance provides strong evidence that the JNDs measured closely reflect the underlying sensitivity to haptic size in the brain.

Digit proprioception is impaired, but not enough to be detected, in mild to moderate CTS?

Another possibility for the lack of difference between CTS patients and healthy controls in our study is that our patients were relatively unimpaired. Results from our secondary tests showed that our patients did have measurable impairments to tactile sensation, and manual dexterity, due to median nerve compression, *at the time of testing.* We intentionally tested only mild to moderate cases, however (the majority of our patients scored within the mild to moderate range of severity on the basis of both electrophysiological and the BCTQ measures) and it is possible that more severe cases may show evidence of impaired digit proprioception.

To understand this better, it is helpful to consider why mild to moderate CTS could produce measurable effects on tactile sensation, for example, but not on sensitivity to hand opening (or proprioception of the digits as a whole). Tactile signals from the fingertips of the index finger and thumb are exclusively mediated by the median nerve. This means that there is no redundancy, and any impairment to the nerve must therefore affect tactile sensation. In contrast, hand posture is sensed from a combination of signals from muscles, joint receptors, and skin-stretch receptors, some of which are served by the ulnar and radial nerves, or in the case of forearm muscles, are actually extrinsic to the hand (i.e., more proximal than the carpal tunnel). Indeed, muscles and joints in the thumb and index finger are innervated by both the median and ulnar nerves (Chammas, 2014; Duncan et al., 2013). While the radial nerve innervates the posterior aspect of the of the thumb and index finger (Ljungquist et al., 2015). Further, the radial nerve innervates the kin-stretch receptors on the dorsal aspect of the hand (Ljungquist et al., 2015). This means that digit posture is sensed by combining sensory information from the median and ulnar nerve, with contributions from the skin stretch receptors of the dorsum of the hand, mediated by the radial nerve. As such, our patients had mild to moderate impairment to only a subset of the relevant signals (served by the median

nerve), and so might be expected to have only relatively minor effects, which may not be detectable in our experiment (and indeed they may not be functionally significant).

It is important to note that, by considering sensitivity to opening of the whole index finger and thumb, the logic outlined above (and our task more generally) considers the precision grasp as a whole 'system', which may be relatively unaffected when only part of it (the median-nerve innervated part) is impaired. We would still expect to see impairment due to CTS in proprioception structures that are exclusively innervated by the median nerve, such as afferents in muscles served by the median nerve, if ways could be found to examine these structures in isolation.

Digit proprioception is unaffected (or less affected) by CTS than tactile sensation?

Another possibility is that digit proprioception is unaffected by CTS, and that its effects are limited to other sensory (e.g., tactile) afferents. Although the current study cannot rule out this possibility (because it shows a null result) it seems unlikely, as it implies selective impairment to certain classes of nerve fibres at the carpal tunnel. In our view, it would be valuable, however, to determine at what point median nerve impairment does cause measurable effects on digit proprioception (assuming it does at some point) in order both to demonstrate the principle, and to better understand the functional consequences of CTS.

Following the logic above, if the consequences of mild-to-moderate CTS on the proprioceptive functions of the median innervated structures of the hand are too subtle to detect with our task, a clear prediction is that if we were to test patients with more severe symptomatology in our task, we would expect to identify impairments relative to healthy controls. Our data seems to be in line with this prediction because the relationships between CTS symptom severity and size discrimination are in the expected direction (i.e., positive; see Table 3.3), though not significant. Further investigation with a wider sample size is

needed to substantiate this hypothesis. Moreover, it requires a quicker-to-administer version of our procedure that is suitable for use in patients with more severe CTS. We explore such a possibility in Chapter 4.

Alternatively, insights into the role of the median nerve in digit proprioception might be gained by temporarily disrupting median nerve function in healthy controls. This could be achieved by administering temporary nerve block, with the use of non-invasive electrical or magnetic stimulation, or invasive stimulation. If after temporary disruption of the median nerve size discrimination performance is unaffected this would suggest that the median nerve does not provide necessary proprioceptive information about the posture of thumb and index finger. Conversely, decreased performance following transient median nerve disruption would provide strong evidence that the median nerve conveys position-sense information of the thumb and index finger at least under some circumstances.

Further functional considerations: how might CTS affect haptic perception more generally?

Our study focused on digit proprioception per se and, as such, tactile stimulation was treated primarily as a problem or confound. In the real world, however, and as discussed previously, hand function movement, tactile sensation, and digit proprioception work together to provide haptic perception of object properties (and aid with movement control). Berryman et al. (2006) suggested that it may not be meaningful to dissociate proprioception and tactile information for haptic size perception, for example, because variations in digit separation due to compression if the digit tips, and object compliance, need to taken into account to achieve haptic constancy (see Introduction). Extending this logic, impairments to tactile sensation due to CTS (or other conditions) might affect how digit position signals are interpreted — even if they are themselves intact — resulting in errors in haptic perception. Consider the case of judging the size of a compliant object. If fingertip tactile signals about its material properties, and the force with which it is being squeezed, are impaired, this may cause the digit

separation signals to be misinterpreted, resulting for example in a smaller-than-actual percept of object size, because the fingers are closer than they would be for a rigid object. It could also conceivably result in a noisier estimate of object size because the grip force, and therefore digit separation, may be highly variable, and these changes cannot be accurately compensated for in producing a size estimate. We predict therefore that CTS might result in impaired size perception with non-rigid objects, rather than the rigid ones we used in our study. If so, CTS may affect haptic perception more generally, and in more complex ways than caused by reduced tactile sensation alone, in the real-world situation of feeling objects with a range of different properties, potentially with significant consequences for daily life.

Standardised clinical tests

As mentioned in the Methods section (see 3.2), most of participants that took part in this experiment also performed the grasping task (Chapter 1); here we had seven new patients and four new Controls. We found similar results as in the previous Chapter. CTS showed impaired tactile sensitivity of the median innervated finger (i.e., thumb and index finger) and ulnar innervated finger (i.e., little finger). As before, a possible explanation for the increased threshold of the little finger can be explained as an indirect effect of the increased pressure in the carpal tunnel that is transferred to the ulnar nerve (Ginanneschi et al., 2008; Tamburin et al., 2009). Alternatively, and not mutually exclusively, it is possible that at least some of our CTS patients also have ulnar nerve complications that are undiagnosed.

Our results for the Purdue Pegboard are consistent with previous findings showing impaired manual dexterity in mild-to-moderate CTS compared to Controls (Amirjani et al., 2011; Fernández-De-Las-Peñas et al., 2009) and the results from Chapter 1. Notably, however, these previous studies reveal deficits in all subtests of the Purdue Pegboard test, while our data reveal statistically reliably affects only for the unimanual subtest. This discrepancy, we contest, is likely related to the greater numbers of CTS patients tested in these previous studies.

Further, we performed exploratory correlation analyses to evaluate if the JND values are related to our clinical test. We hypothesised that the measures should be related due to the role played by digit proprioception in manual dexterity and tactile sensitivity. However, we did not found any relationship between the measures. Further, we decided to perform additional exploratory analyses (i.e., multiple regression) to see if the different measures collected can predict haptic size-discrimination JNDs. These analyses should be considered as an exploratory exercise that might be useful for further research. Our results seem to suggest that only for Controls the monofilament test could predict the JND values. Overall, when interpreting these results it is important to acknowledge the type of tests that we used. The variability in the force used during the application of the 2PD (Bell-Krotoski, Weinstein, & Weinstein, 1993), and the coarse spacing of different force stimuli in the monofilament test, might have affected our possibility to detect the 'true' value of tactile sensitivity. Also, the difficulty in interpreting the relationship between the logarithmic scale (Levin, Pearsall, & Ruderman, 1978) might have affected our possibility to detect a relationship with other tests. This should drive the scientific community to develop better clinical tools to assess tactile sensitivity.

Concluding remarks

The results presented in this chapter suggest that digit proprioception is not impaired in mild to moderate CTS patients. We outlined different possible explanations that could explain the lack of difference between patients and controls, which are on the face of it surprising. We also delineated possible future experiments that can help to better understand our data, and the implications of CTS for the sense of digit separation.

Chapter 4. Developing a new clinical tool to assess digit proprioception

Study interruption due to COVID-19 pandemic

We began data collection for the studies covered by this chapter at the beginning of March 2020. Data collection stopped shortly afterwards due to COVID-19, at which point we had performed only very limited pilot-data collection. This chapter therefore provides descriptions of our intended studies, focusing on methodological features, and where possible pilot data indicating the types of results that would be obtained, and how they would be analysed. We also explore the logic of our planned approach to the validation of our proposed clinical tool. In the absence of a substantial data set, the Discussion explores further steps that would need to be taken, and the associated challenges, in developing our prototype measure(s) for actual, practical clinical use.

4.1 Introduction

A ‘good’ clinical assessment method is difficult to develop. It must be a valid and reliable index of the intended capability—here, digit proprioception. But a series of different factors is important for an assessment tool to be effective in clinical practice. Generally, from the clinician’s perspective (the assessor), a test that can be done quickly, and does not require expensive equipment nor extensive training to administer is desirable (Kattenstroth, Kalisch, Kowalewski, Tegenthoff, & Dinse, 2013). From the patient’s perspective, time is again important (Kattenstroth et al., 2013). So too is the complexity of the task, and how this may interact with the symptoms of the patients’ condition, and their particular profile of impairments (Hoseini et al., 2015). When designing a method, these factors can be difficult to manage, and a given assessment method is likely to be inappropriate for testing some types of conditions. Developing a standardized protocol for a new assessment method requires

validity and reliability testing, involving administration of the test following the same ("standard") protocol by different assessors. This can involve the same patients, or more often, a comparable group of patients (e.g., a group of individuals with mild-to-moderate CTS) tested at different clinical centres.

The aim of this final study was to develop a clinic-friendly method of assessing hand proprioception — in particular, the positions of the index finger and thumb — in patients with CTS. As discussed in previous chapters, CTS results from chronic compression of the median nerve, characterized by paraesthesia ('pins and needles'), numbing, pain, loss of sensation, and restricted range of motion preferentially affecting the index and thumb (Aroori & Spence, 2008; Middleton & Anakwe, 2014). It therefore makes sense for a clinical assessment test of hand proprioception in CTS to target the index finger and thumb. The psychophysics procedure in the previous chapter is not suitable, however, due to the time required, specialist knowledge for analysing and interpreting results, and bespoke equipment. We therefore explore different, more practical possibilities here.

We wished to develop an assessment method that can be completed (i) with the wrist at a neutral position without requiring extreme flexion/extension, and (ii) relatively quickly, in order to avoid exacerbating patients' symptoms, and provide a window into impairments under normal conditions. Extreme extension/flexion of the wrist often elicits symptoms in patients with CTS; indeed, a bedside test of CTS (known as Phalen's test) involves holding the hands at extreme wrist flexion, which in people with CTS often elicits feelings of numbness and/or paraesthesia of the hand (Aroori & Spence, 2008; Ibrahim et al., 2012). Such tests may be sensitive to underlying problems, but may also confound test performance with increased symptom severity during testing. Long-duration testing involving repetitive and/or too vigorous manual activities should also be avoided if the aim is to avoid increased symptomatology in CTS. In addition, CTS does affect older individuals (although not preferentially) so some consideration of the cognitive and memory demands of the task must be given. If the task taxes memory and/or cognitive resources too heavily, it may be difficult

to tell whether poor performance in older individuals truly reflects impaired proprioception, or can be explained (at least in part) by healthy age-related cognitive/memory decline.

Established assessment tests of hand proprioception used in the clinic do not target the index finger and thumb. The bedside test of hand/digit proprioception is the up-down test (also called passive motion direction detection threshold; Goble, 2010; Hillier et al., 2015). As described previously in this thesis, the test involves the clinician holding and moving the patient's hand/digits while asking the patient to shut their eyes and make judgements about whether their hand or specific digits, have been moved upwards or downwards relative to a neutral/starting position. The test adds a confounding sensory signal because by touching the finger, the clinician provides additional tactile signals, like pressure, which can potentially indicate the direction of motion (Hillier et al., 2015). Also, because the test relies on the clinician generating a movement of unknown magnitude, it provides only a very crude measure of sensitivity to movement, rather than a precise quantitative measure. As such, it may only detect severe impairments and does not provide a precise measure of any subtle changes. Nevertheless, the test is quick and simple to perform, for both the patient and clinician. Likewise, other existing clinical assessments of hand and/or digit proprioception target a single finger, measuring position about the joint axes (Ferrell, Crighton, & Sturrock, 1992 Mallik, Ferrell, McDonald, & Sturrock, 1994; see Hoseini et al., 2015 and Wycherley, Helliwell, & Bird, 2005, respectively, for the development of potential clinical tests not yet trialled with patients).

Kalisch, Kattenstroth, Kowalewski, Tegenthoff, and Dinse (2012) developed a test for clinical use that measures hand posture in a way that better represents how we use our hands in everyday life. During the test, the participant had to judge, with the hand/palm upward, whether a "test sphere" in the one hand was smaller, equal, or larger than a "reference sphere" in the other hand. Exploring the spheres by repeatedly opening and closing the hands was not permitted. A significant age-related decrease in performance was found in a group of 45 healthy controls, demonstrating sensitivity of the test to identify

differences between individuals. Further, in subacute stroke patients, the test showed sensitivity to changes in performance after a rehabilitation period of two weeks (Kattenstroth et al., 2013). The test is quick and simple to administer and is made using non-expensive materials. However, the use of a bilateral procedure presents challenges. It potentially confounds undiagnosed impairments of the contralateral body part with the tested body part, and makes assessing bilateral injuries difficult because the contribution of each hand to the overall performance cannot be determined. This latter is particularly relevant for a condition like CTS where both hands are often affected. Also, the position of the hand that is required to be maintained during testing may exacerbate the symptomatology of different clinical conditions, including CTS. Furthermore, the test requires the use of the whole hand. This means that performance relies not only on structures likely to be affected by CTS (innervated by the median nerve) but also non-affected structures (innervated by the ulnar nerve). It is reasonable to assume that in this situation size estimates rely on integration of signals from all the digits (previous research assessing digit force control during grasping has shown that CTS patients can integrate sensory information from affected and non-affected structures; e.g., Zhang et al., 2013). Thus, we might expect CTS to have only minor effects on performance (i.e., to be relatively insensitive), because it only affects a subset of the digits used.

Different tests that assess digit proprioception sense of the thumb and index finger have been used in experimental settings, and that reflect goal-oriented tests. Han, Waddington, Anson, and Adams (2011) developed a pinch aperture device to measure the perceived distance between the thumb and index finger opposition (i.e,. pinching) movements. Participants inserted their thumb and index finger into thimble-like-ends of the device, and the distance between digits (thumb-index aperture) was tracked. During a training phase, the participant learned five predefined apertures (from 1.22 cm to 3.32 cm) with visual feedback of their hand and the device. During testing, participants moved their digits without visual feedback until the device stopped at one of the five learned apertures,

and then verbally reported which of the five positions they felt they were in. Each test position was sampled several times, in random order. The test is simple and quick to administer, shows good test-retest reliability, and the device is inexpensive and highly portable. The test has yet to be trialled clinically.

More recently, Yahya, von Behren, Levine, and dos Santos (2018) also developed a method to target thumb and index finger proprioception for clinical use. The authors used a modified goniometer to measure the angular separation between the thumb and index finger during thumb-index opposition, similar to the method developed by Han et al. (2011). During a pre-test phase, the assessor moved the participant's digits from a starting position to a target position, and the participant was asked to remember this position and reproduce it during testing. Specifically, during testing the participant actively moved their digits from a starting position to the pre-learned target position, indicating with a verbal report when they felt they were at this position. The difference between their estimated and the actual target position (i.e., error) provided a measure of thumb-index proprioception. Different from Han et al. (2011), vision of the hand and device was prevented during both pre-test and test phases, and participants were only required to remember a single target position. The test is quick and simple, easy for the assessor to administer and for the participant to understand, and showed high reproducibility when used to assess performance in a group of healthy participants across two consecutive days. Moreover, an additional experiment involving concurrent vibration of the finger and thumb extensors was shown to disrupt performance in healthy participants, and when the test was used to assess two patients with diabetic neuropathies, patients' performance was found to be poor compared with healthy participants, suggesting good sensitivity.

Although these tests perform well, they are both measures of proprioception bias, not sensitivity. In Chapter 3 we argued that there is value in measuring proprioception sensitivity directly (Hoseini et al., 2015). In this study, we set out to develop a new method for assessing sensitivity in hand proprioception with practical potential for use in a clinical

setting. We call this the block-difference test. This test was motivated largely by the methods we developed in Chapter 3. Briefly, participants grip wooden blocks, using the index finger and thumb in opposition, presented in sets of three. Participants cannot see their hand or the blocks. Two blocks (distractors) are the same size, and the other is larger (target). The participant grips each block sequentially, in a random order, and reports which is the largest. The difference in size between the target block and the two distractors is varied across presentations (similar to the two-point discrimination test) to determine the participants' capability to identify the largest shape correctly. The logic of the test is simple. We reasoned that hand proprioception — in particular, the ability to perceive the position of the index finger and thumb — should play a role in correctly identifying differences in size between target and distractor blocks, and so greater proprioception sensitivity should be reflected in the correct identification of the odd-block-out at smaller size differences.

The task is similar to our haptic size-discrimination task used in Chapter 3 and, as such, we faced similar challenges related to isolating the role of proprioception from both tactile and motor sources. As discussed in Chapter 3, when movements are performed in a task like this the brain can use the information related to the movement signals to help solve the task and, conversely, noisy motor signals may disrupt task performance. Notably, in the methods of Han et al. (2011) and Yahya et al. (2018) it is difficult to rule out the possibility that movement was used as an additional source of information to perform the task, and therefore it is difficult to separate the contribution of movement and proprioception during task execution. Likewise, tactile signals related to gripping the objects in this task are likely to serve as important cues. And again, noisy, or impaired tactile signalling may impair task performance. These challenges make it difficult to clearly attribute poor performance on this task to impaired proprioception per se. Further, our new task needed to be done quickly, so lacks the rigorous procedures that define conventional psychophysical methods. This was also a challenge we needed to address.

A common method for determining the validity of a new clinical assessment tool is to compare results on the new test to those from existing, established measures. There is currently no clinical test that assesses the specific aspects of hand proprioception sensitivity we are interested in, however, and so a different approach is required. We planned to use the intersection of findings from three additional “in-lab” tests to evaluate whether our new clinical assessment test, the block-difference test, measures hand proprioception in the manner we intended. We use the term “in-lab” to indicate that these methods are not directly suitable for clinical use (though they could potentially be adapted to clinical settings). In this way, they are distinct from our new clinical assessment test. Two of the tests are new and were developed as part of this study, and selected to have complementary strengths and limitations. The third in-lab test is our haptic size-discrimination task, introduced in Chapter 3. To address the challenge of isolating contributions from proprioceptive versus movement sources we developed one in-lab test that does not require the participant to make movements during the task. Instead, the opening of the index finger and thumb is set by the experimenter before a testing session, and the participant indicates whether subsequently presented visual objects are larger or smaller than the grasp opening (using a psychophysical procedure to control the visual object sizes). We call this the comparing static-proprioception to vision task (Section 4.3). This task is based on the task used by Hoseini et al. (2015) to measure proprioception of the angle of a single digit. In a complementary fashion, to address the challenge of isolating contributions from proprioceptive versus tactile sources we developed a second in-lab test that involves the manual estimation of the size of a seen object without requiring the participant to touch any object surfaces during the task. We call this the manual estimation task (Section 4.4). Finally, to address the challenge of whether the new quick-and-easy clinical assessment method is sufficiently sensitive to variations in proprioception we plan to compare participants’ performance on this new assessment with that on the more rigorous in-lab psychophysical task used in Chapter 3, our haptic size-discrimination task (Section 4.5).

These in-lab tests are complementary in nature in that they control for different concerns. In so doing, however, they also unavoidably introduce their own potential problems or confounds (see later sections on specific tests). We reasoned that by comparing a given participant's performance in all three in-lab tests (i.e., by measuring hand proprioception from different 'angles') and comparing these data with performance on our new clinical assessment method (the block-difference test), we would gain a better sense of whether our block-difference test truly measures hand proprioception as we intended. In other words, we aim to evaluate the "construct validity" of our new clinical assessment test by using triangulation across a range of related tests. We can make the broad prediction that performance on all the tests should be correlated, since to some extent they tap into a common process (proprioception). To the extent that the tests also involve other, non-overlapping systems, however, we may see reduced correlation across the tasks, and relationships may be evident between test performance and other measures, such as tactile acuity.

Summary of participant testing

We collected data from five participants, but no participants performed all the tests. The breakdown of which participants completed which tests is shown in Table 4.1. Only two (participants 1 and 2) took part in the block-difference test and manual estimation test. We were, therefore, unable to draw meaningful conclusions about the relationship between performance on these tests.

We presented the result of the pilot in the section of each test. The study was approved by the Research Ethics Committee of the School of Psychology, Bangor University. Participants did not receive financial compensation.

Table 4.1. Participant allocation to each test. Schematic representation of the test(s) that each participant did. Colour codes in parentheses identify the participant in the results figure for each test.

	Block-difference test	Comparing static-proprioception to vision task	Manual estimation test	Size discrimination test (N = 27 healthy participants, see Chapter 3)
Subject 1	✓ (orange)		✓ (orange)	
Subject 2	✓ (green)		✓ (green)	
Subject 3	✓ (blue)			
Subject 4			✓ (black)	
Subject 5		✓		

4.2 New clinical assessment tool: the block-difference test

4.2.1. Rationale for the test

Our intention was to create an equivalent of the psychophysical measure used in Chapter 3 that is practical to use in clinical settings. As mentioned previously, a critical feature of that measure is that it directly measures sensitivity (rather than bias; Hoseini et al., 2015), which is the basic aspect of proprioception we expect to be impaired in CTS and other peripheral nerve conditions. Therefore, we chose to create an analogue of our Chapter 3 task that could be implemented with simple equipment and conducted over short timescales.

There are many precedents for this type of ‘porting’ of psychophysics-based methods into clinical settings. Many commonly used vision tests use this approach, for example. Consider the classic “Snellen Chart” for measuring visual acuity. Here, patients are asked to read increasingly small letters, in order to determine the minimum size they can reliably read, thereby providing an index of the sensitivity of their visual system to letter-shape information. In the tactile domain, the Semmes-Weinstein Monofilament test and the Two-Point

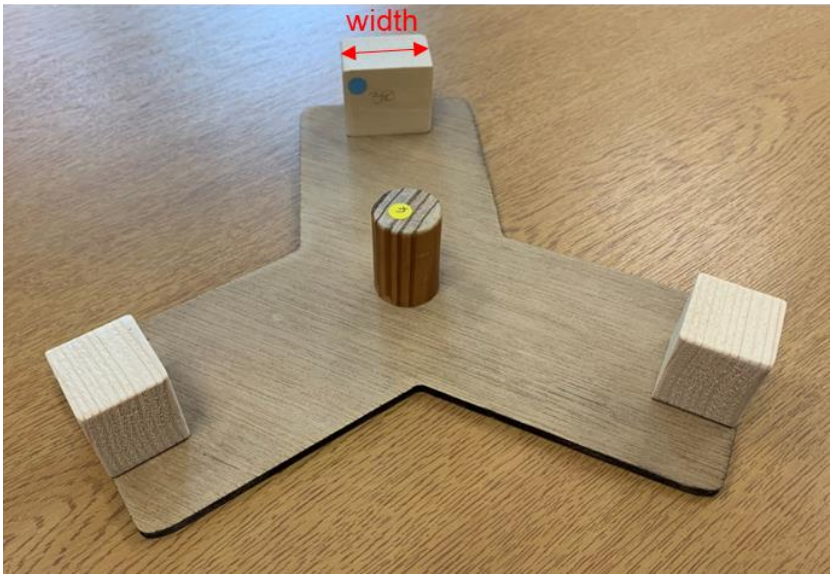
Discrimination test are similar examples of what might be termed ‘bedside’ psychophysics tests. In both cases, a stimulus property of interest is varied to determine sensitivity to tactile contact (Semmes-Weinstein Monofilaments) or sensitivity to the separation of two above-threshold tactile stimuli (Two-Point Discrimination).

Our proposed clinical tool is described in detail in the Method, below. Participants are presented with sets of three objects, two of which are the same size, and one of which is larger (by varying amounts across different sets of objects). Participants feel each object sequentially, with the hand and objects unseen, and report which object they think is larger. Varying the difference between ‘target’ and ‘distractors’ should allow determination of the minimum size difference that can be reliably identified (sensitivity to object size) which as previously we expect to depend primarily on digit proprioception (Berryman et al., 2006).

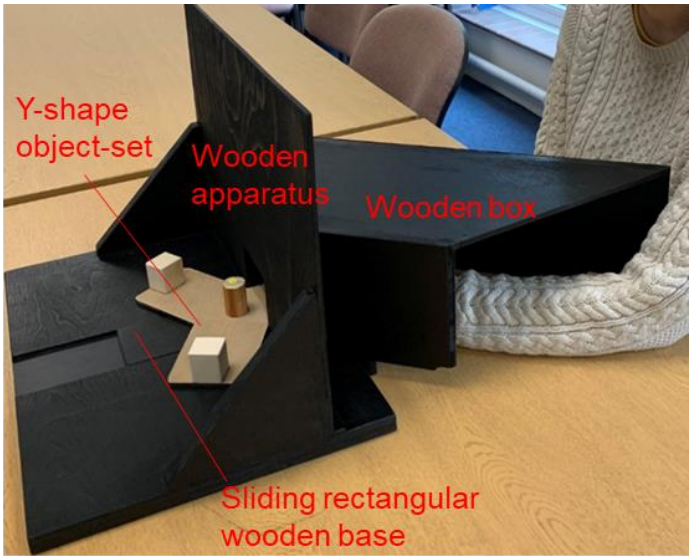
We presented three objects per ‘trial’, because in our view it represents a sensible compromise, or trade-off, between various factors. A benefit of using larger numbers of objects is that it reduces the probability of being correct by chance. This makes it easier and quicker to determine when a threshold level of performance has been reached. Using larger numbers of objects can also be problematic, however. Using more stimulus intervals increases the cognitive demand of comparing between them. This problem is particularly acute for haptic size perception tasks because each stimulus must be felt sequentially, resulting in long trial durations. This renders it increasingly difficult to remember all the stimuli at the point a decision is needed. As such, large numbers of objects per ‘trial’ risks confounding proprioception performance with memory and cognitive ability. This is a particular concern given the potential use of the test with people with central nervous system problems or with an elderly population, given the healthy decrease of memory abilities with age (Stephan, Sutin, Caudroit, & Terracciano, 2016). We chose three objects per trial as a compromise with respect to these factors. Our choice was guided in part by a widely used stereoscopic vision test (Randot Stereotest; Stereo Optical, Chicago) in which participants are asked to judge which one of three circles protrudes from the test surface.

It was also important that the stimulus order (the position in which the larger object is presented) is randomised. There are two main reasons for this. First, establishing a threshold requires moving up and down the stimulus steps, presenting the same stimulus sets multiple times. Without randomisation, participants could therefore potentially learn the sequence. Second, and relatedly, our test may need to be repeated on left and right hands, and knowledge of the pattern of trials experienced with the first hand could influence the results of measurements on the second hand. Indeed, knowledge of the stimulus order obtained by the intact hand could then be used subsequently to artificially improve performance with the impaired hand. In terms of the physical implementation of the test, we could have presented the same ‘standard’ object twice. However, we reasoned that having three physically separate objects (see Figure 4.1A) would make the experimenter/assessor’s task of randomising the order less error-prone (e.g., we could assign an arbitrary code to each interval and then present each object in order).

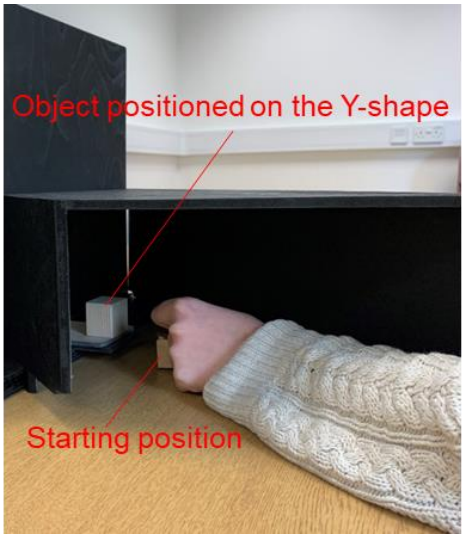
The choice of the difference between target and distractor sizes was based on the results of Chapter 3, though it will of course ultimately need to be determined through testing on a range of clinical populations. The base size of the two distractors is 30 mm for all stimulus sets. The size of the target maps approximately onto the range of size-discrimination thresholds observed in Chapter 3. The smallest increment in size is 2 mm, and the largest is 20 mm. In all, we used seven size increments, with wider spacing towards the upper end (target sizes of: 32, 34, 36, 38, 42, 46 & 50 mm).


width

A.


Y-shape
object-set
Wooden
apparatus
Wooden box
Sliding rectangular
wooden base

B.


Object positioned on the Y-shape
Starting position

C.

Figure 4.1. **Block-difference test apparatus and experimental setup.** (A) Example of a wooden Y-shape object-set. The target object (in this case 36 mm) can be recognised by the presence of a small blue circle on it. This was done to facilitate the recognition of the target object by the experimenter. (B) The figure shows the overall set-up and apparatus. The experimenter can easily rotate and slide forward and backwards the Y-shaped object-set to present one of the three objects of the set to the participant. The participant's view of the object-set is prevented by the upright wooden panel. (C) An image taken from the side, showing the participant in the starting position. The hand is blocked from the view of the participant by the wooden box.

As described previously, a challenge to the development of proprioception tests is neither providing (excessive) additional information from movement cues, nor confounding measured performance with difficulty finding and grasping the object. For instance, patients with tactile impairments might show increased uncertainty about when the object has been grasped, leading to impaired performance for reasons other than impaired proprioception. As in Chapter 3, we took steps to minimise these concerns by keeping the participant's arm/hand in a constant position during the task, and requiring minimal digit movements to grasp the objects (see below).

To test the ability to identify the larger object, we required that the participant could correctly report the same object-size difference on at least 7 of 10 trials. This procedure recalls the one used in other clinical tests where the participant has to provide the same answer a certain number of times (e.g., Semmes-Weinstein Monofilament and Two-Point Discrimination). We adopted the same number of repetitions that are required with the Two-Point Discrimination test (Moberg, 1990), which results in a reasonably quick and easy procedure.

Finally, we considered it advantageous to use a real, physical test rather than an electro-mechanical device, for a range of practical reasons, many of which emerged from discussions with our clinical collaborators (an NHS hand surgeon, and a team of hand therapists). First, our test can in principle be produced inexpensively from materials that are readily available (wood). Second, it is easily transportable. Third, it requires no specialist technical expertise to administer. Fourth, it should be reliable long-term, and (unlike digital

technology) can be repaired easily in the event it breaks. Fifth, it requires no on-going technical support (it does not require software updates) and does not rely on systems that will one day become obsolete (as systems reliant on laptop computers, tablets etc. will). Sixth, our hand therapist collaborators emphasised the simple practical point that in their experience it is problematic to rely on battery-powered devices (computers, tablets). Often a previous user forgets to charge them, and given that patients are seen within a small-time window, this renders tests useless on many occasions. Indeed, technology-based systems in this context are generally prone to failure on the basis that if they do not work straight away they are liable to be dropped from a given assessment session or consultation.

4.2.2 Methods

Participants

Three participants took part in the experiment (24, 32 and 40 years), 2 males and 1 female. All participants were right-handed, according to self-report.

The block-difference test apparatus

Figure 4.1A shows an example of a wooden Y-shape object-set made to present each object (wooden rectangles, affixed on an arm of the Y-shape) to the participant. Two of the three objects were “distractors”, and always had the same 30 mm width. The third “target” object had one of the following widths: 32, 34, 36, 38, 42, 46 or 50 mm, making size differences between distractors and target of 2, 4, 6, 8, 12, 16, and 20 mm. All other object dimensions remained constant. As described in detail below, the task involved the participant gripping each object using the index finger and thumb (pincer grip) and deciding which object was the “target”, the ‘odd-one-out’, larger than the two “distractors”. As such, the seven object sets represent differing levels of task difficulty, starting with a difference of 2 mm between the distractors and the target object, the most difficult object-set, and increasing up to a difference of 20 mm, the easiest set.

A wooden apparatus was created to prevent the participant from seeing the Y-shape during testing (Figure 4.1B). The Y-shape tool was positioned on the bottom of the apparatus on a sliding rectangular wooden base, which allowed the presentation of one object at a time in front of the starting position (Figure 4.1B).

The participant's hand was covered by a wooden box (see Figure 4.1B), which prevented them from seeing their hand and arm during testing. The thumb and index finger were positioned in a pincher shape on a small wooden cube (4 x 4 x 2.5 cm) – the starting position (Figure 4.1C). Their hand and wrist rested on a "Grip Strip" (Firebox ®), a silicon-based material with high frictional properties that facilitated a stable hand position. The apparatus could be configured for testing either the right or left hand by moving the wooden box. Here, the participant's dominant hand was tested.

Procedure

Participants were told that they would grip three objects presented successively and decide which of the three objects gripped — the first, second, or third — was the largest. Experimental trials began with the participant's hand on the starting position. The wrist was kept in a neutral position — no extreme flexion/extension was required. As discussed previously, this is an important part of the methods for any test designed to assess patients with CTS, since prolonged and/or extreme wrist flexion/extension will commonly increase symptom severity in CTS.

The experimenter then positioned one object-set in place, sliding the first object forward for the participant to grip. The participant was asked to grip each object along its width and release, returning to the starting position. The cue to grip each object was provided verbally by the experimenter. After one object was gripped, the experimenter quickly rotated and slid the next object into position, and the participant repeated the task until all three objects were felt. The participant then verbally indicated which of the three objects was the largest. Responses were recorded by the experimenter. The order of presentation of the

three objects of each object-set was randomised, using a custom script written in Matlab (Mathworks Inc., Natick, MA, USA), and printed on a piece of paper for the experimenter to follow.

The easiest object-set, comprising the 50 mm target, was always presented first. After three successive trials on which the target was correctly identified, the experimenter presented the next object-set of increasing difficulty. This was repeated until the participant was unable to correctly identify the target object on three successive trials. At this point, the experimenter moved back to the previous (easier) object-set and tested performance on a total of 10 trials. Discrimination sensitivity was defined as the smallest difference between the target and distractors that could be correctly identified on at least 7 of 10 trials. We called this the participant's discrimination sensitivity score. Best possible performance was a score of 2 mm. The test took approximately ten minutes to complete.

4.2.3 Results

Figure 4.2 shows the sensitivity scores for each of the three participants who completed the test. As can be seen, performance varied across these three individuals. Each person showed a different sensitivity estimate, ranging from 2 mm to 4 mm, to 6 mm in the worst performer. It seems that the test is effective in detecting different performances, but this interpretation is limited by the number of participants that took part in the test and by the fact that we cannot compare the pattern of observer's performance with the other tests.

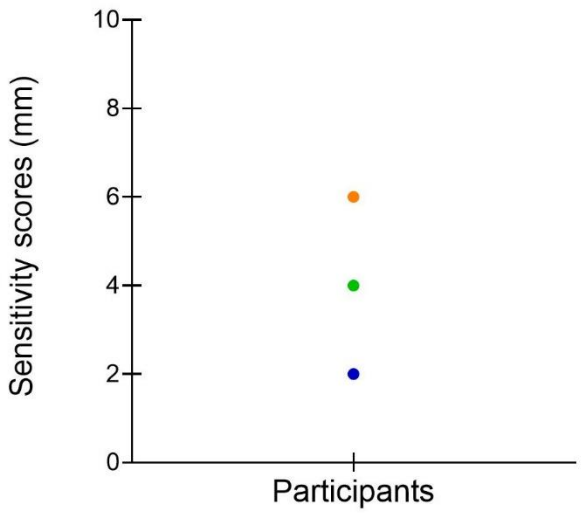


Figure 4.2 Block-difference test results. On the y-axes, we plotted the sensitivity score of each participant, which is the difference in millimetres between the two distractors and the target that each participant could reliably detect.

4.3 Validation test 1: Comparing static-proprioception to vision task

4.3.1 Rationale of the test

This test was designed to assess sensitivity, and any bias, in proprioception in the absence of movement from the participant. The idea was developed from a task used to measure sensitivity and bias of finger proprioception by Hoseini et al. (2015). In that task they assessed static proprioception of the index finger by using a psychophysical approach based on a staircase procedure, which allows a quick examination. During the task, participants had to compare the position of their index finger, which was positioned by the experimenter, to a superimposed visual stimulus.

To make this test more comparable to our other tests, which assess proprioception signals to grasp opening rather than a single digit, we devised a conceptually similar task to Hoseini et al. (2015), but participants compared the opening of their static index finger and thumb — which was adjusted by the experimenter — to the size of a spatially superimposed visual 3D object (see Methods). During the task, the participant had to judge if the size of the visual 3D object was smaller or bigger than the unseen hand aperture. We prevented vision of the hand during the task to ensure that the participant performed the task by only relying

on proprioception. During the task, as Hoseini et al. (2015), we varied the size of the visual 3D object following an adaptive staircase procedure. This is intended to relatively rapidly hone in on stimulus levels close to the discrimination threshold, regardless of where that threshold level is. This is useful for patient testing, where performance may be very different across individuals.

The experimenter passively moved the participant hand to the starting position, removing motor signals. Participants did not feel an actual object but held their grasp opening at a fixed position. This meant that they did not receive any tactile feedback from holding an object in the hand. However, because they had to keep the same hand posture for almost five minutes, participant rested their fingers on the table surface. This was done to prevent additional fatigue and hand movements that could arise by trying to keep the hand in the same position for a long time. Also, keeping the hand still reduced to the minimum degree possible the contribution of movement signals during task execution, which could affect the performance. Keeping the hand of the table surface could, in principle, provide additional tactile signals to hand opening (from sensing the angle the fingertips contacted the surface with). However, we reasoned that this would not have significant effects on performance.

This task requires a comparison of estimates from vision and proprioception, which can generate two different problems. First, the process of transforming between visual and proprioceptive information, in order to compare the two stimuli, might itself be noisy, inflating discrimination thresholds. Second, and perhaps of greater concern, poor visual abilities would manifest as a poor proprioception score on the test.

This test assesses static digit position sense and therefore provides a different but complementary understating of digit proprioception sense than we can get from the block-difference test.

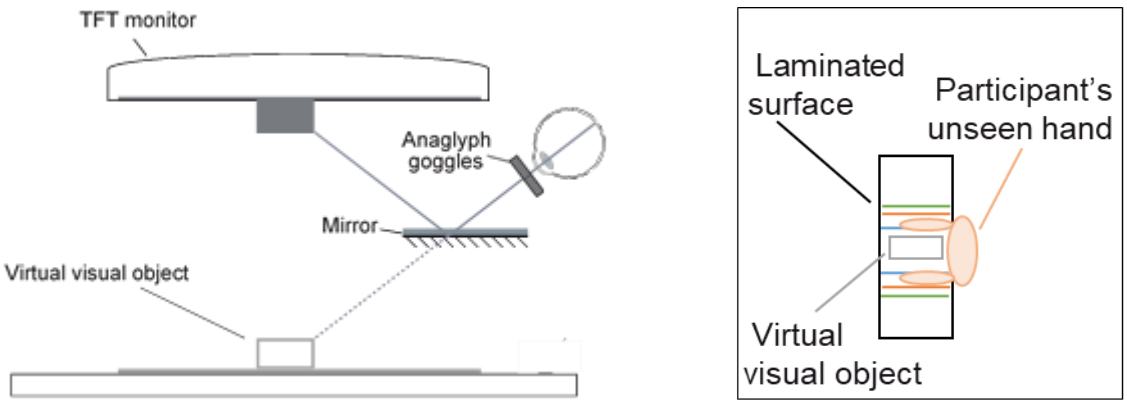
4.3.2 Methods

Participant

Only one participant took part in the experiment (28 years), female, right-handed according to self-report.

Experimental set-up

Figure 4.3A shows the experimental apparatus. Visual 3D objects were displayed on a TFT monitor, placed face down, and viewed via a horizontal first-surface mirror. The monitor surface was optically coincident with the table surface. The position of the mirror prevented vision of the participant's hand. The stereoscopic presentation was achieved using red-cyan anaglyph goggles, attached to the apparatus in a fixed position. This further helped in positioning the head and eyes of each participant at the same height (40 cm above the table surface). The grasp opening (i.e., finger and thumb) were indicated for the experimenter by different lines on a laminated surface, either 10, 30 or 50 mm (Figure 4.3B), depending on the current hand opening being tested.



A B

Figure 4.3 Comparing static-proprioception to vision task. (A) Schematic representation of the lateral view of the experimental set-up. Adaptation from Keefe et al. (2011). (B) Representation of the top view of the set-up. The thumb and index finger of the participant were passively positioned by the experimenter at one of the pre-determined separations indicated on the laminated surface by a different colour. A mirror prevented the participant from seeing their hand during the experiment.

The visual stimuli were 3D renderings of rectangular wooden blocks positioned on a ground plane (230 mm long and 290 mm wide) coincident with the table surface and presented along the mid-sagittal plane. The size of the virtual visual blocks, along the dimension corresponding to the grasp opening, was varied in software as required by the staircase procedure. The width of the objects was always 60 mm. The visual object was spatially superimposed on the location of the participant's hand.

Procedure

Experimental trials began with the participant looking through the goggles and the thumb and index finger of the dominant hand passively moved by the experimenter to one of the three starting separations showed on the laminated surface (see Figure 4.4). Before the presentation of the visual object, a stimulus fixation appeared for one second. Afterwards, the visual object appeared for two seconds. Participants were instructed to report if the visual object was larger or smaller than their hand aperture (responses were entered into the computer by the experimenter).

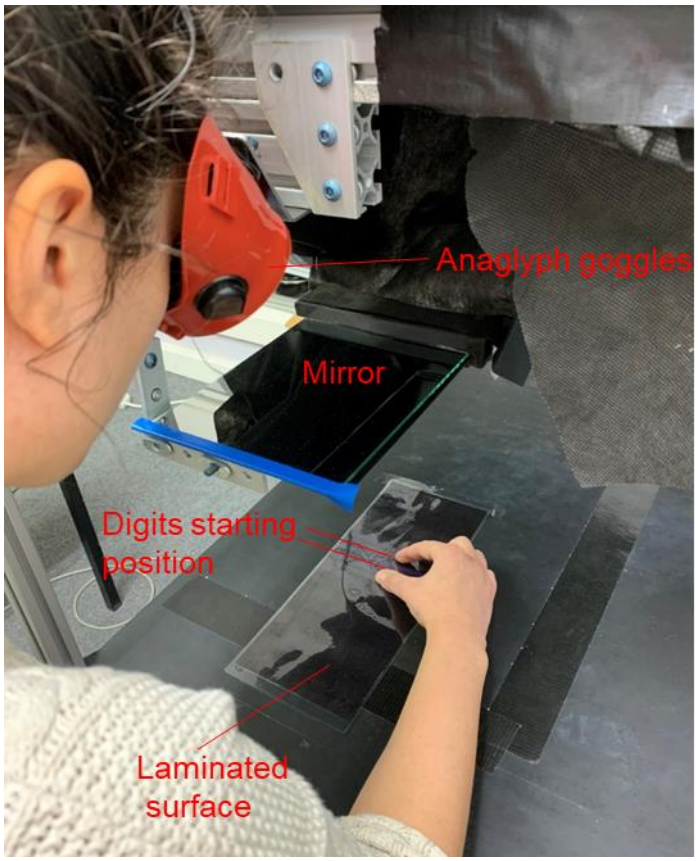


Figure 4.4 Comparing static-proprioception to vision task. Picture showing the participant looking through the anaglyph goggles, with the hand in position on the laminated surface. The digit separation (hand aperture) shown in the picture is 10 mm.

Similar to Chapter 3, the size of the visual object was controlled using adaptive staircase procedures. Here, the digit separation (hand aperture) was the standard and the visual object size was the comparison. These procedures adjusted the size of the visual object based on the participant's responses, in order to position the majority of the stimuli at the most informative points on the psychometric function for determining the discrimination threshold (JND). We used two different staircase reversal rules. First, a 1-up, 2-down staircase, in which the size of the visual object was increased following one trial on which the comparison was judged smaller than the standard, and decreased following two consecutive trials on which the comparison was judged as larger. Second, a 2-up, 1-down staircase, in which the size of the visual object was increased following two consecutive comparison-was-smaller answers, and decreased following one comparison-was-larger answer. The initial staircase 'steps' in size were 8 mm, which was halved at each of the first three reversals (i.e.,

4, 2, then 1 mm). The task was terminated after 12 reversals or after 100 trials. For the 30 mm and 50 mm visual object, JND measurements were derived from one repetition of each staircase type. For the 10 mm visual object, it was not possible to use the 2-up, 1-down staircase because it could result in a visual object that could not possibly be generated (i.e., with size less than zero). For this size the participant, therefore, completed two repetitions of the 1-up, 2-down staircase per JND and the data for one repetition were flipped to allow comparable analyses to the other standard sizes. Each block consisted of a separate staircase (i.e., one hand aperture and one staircase type), presented in random order. The study took approximately 1 hour to complete.

4.3.3 Results

Figure 4.5 shows the data for the 10 mm visual object for the only participant that took part in the pilot experiment so far. As before, we computed the JND by fitting the data of the participant with a cumulative normal-distribution psychometric function. Then, we defined the discrimination threshold as the standard deviation of the fitted function (which equates to the ~84% point on the psychometric function). In other words, JNDs is the difference in visual object size required to go from 50% (chance performance) to reliably (~84% of the time) judging the visual object to be larger than the hand opening. As can be seen, the JND value is small (3.48 mm), indicating a good sensitivity level; in other words, the participant needs the visual object to be 3.48 mm bigger than the hand aperture to reliably indicate it as larger. Also, the proprioception bias is close to the actual size of the object (10 mm) suggesting that, at least for this person, the perceived size from proprioception is correctly calibrated (that is a hand aperture of 10 mm and a visual object of the same size are perceived as the same size).

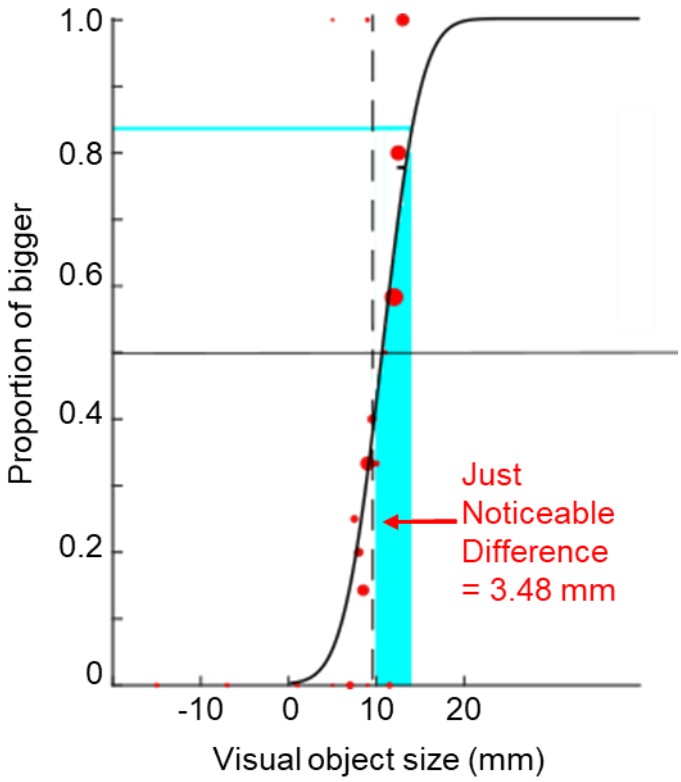


Figure 4.5 Comparing static-proprioception to vision task result. The figure shows the performance of the 10 mm visual object. The figure plots the proportion of trials in which the visual object (comparison) was judged larger than the hand aperture (standard) as a function of visual object (comparison) size. The grey horizontal line/vertical dashed line reflects the 50% or chance point, where the visual object and hand opening were judged the same size (the Point of Subjective Equality, or PSE). The blue line denotes the 84% point, and the shaded blue area denotes the JND value.

4.4 Validation test 2: Manual Estimation test

4.4.1 Rationale for the test

This test was designed to assess bias in proprioception during movement execution, while eliminating all tactile signals. The idea was developed from a task used to measure the bias of finger proprioception by Wycherley et al. (2005), which assessed joint position sense of the index finger by matching the position of the unseen finger to a visible, surface-mounted silhouette.

To make our test more comparable with the other tests that assess proprioception signals of the pinch opening (i.e., thumb and index finger), we devised a conceptually similar

approach to Wycherley et al.'s (2005), but asked participants to 'pantomime' the size of a seen object by adjusting the aperture between the unseen thumb and index finger. We occluded the hand during the task to ensure that the participant could not use vision to perform the task.

As mentioned before in this thesis, a general problem of any assessment that involves touching an object is that the task potentially conflates tactile signals with digit proprioception. Berryman et al. (2006) suggested that it is not sensible to dissociate tactile signals from proprioception during haptic size perception because both signals provide relevant information. Thus, we can postulate that tactile impairments can results in poor performance even if proprioception is not impaired (tactile impairments could cause uncertainty about when the digits are touching the object, or affect interpretation of digit separation with changes in force, or object compliance; Berryman et al., 2006). We cannot eliminate the possibility that performance on our block-difference task would not be affected by tactile impairments. The manual estimation test prevents any influence from tactile signals, because participants do not touch any objects but merely adjust their hand aperture. In addition, we instructed participants to not touch their fingertips together (e.g., between trials) to eliminate the possibility that this could be used as a reference point for determining hand opening. For the same reason, we instructed participants to do not lay their digits on the table surface.

As with the comparing static-proprioception to vision task, the manual estimation task requires comparing visual and proprioceptive signals. Therefore, transforming sensory signals to make them comparable may itself be a source of noise, and therefore poorer test performance. Moreover, the test again confounds visual perception with proprioception: poor visual abilities per se would lead to a noisy visual size estimate, manifesting as a poor proprioception test score. Moreover, because the test involves active movement from the participant, it is not possible to eliminate the possibility that the correct hand aperture is

achieved via sending the appropriate feedforward motor signal, rather than relying on feedback from proprioception.

The manual estimation test allows the investigation of digit position sense after movement, which will add another layer of understanding to the picture provided by the block-difference test, and comparing static-proprioception to vision task.

4.4.2 Methods

Participants

Three participants took part in the experiment (29, 32 and 40 years), 2 males and 1 female. All participants were right-handed, according to self-report.

Experimental set-up

Figure 4.6 shows the experimental set-up. To prevent any visual feedback of the hand during the task, the participant positioned their hand inside a box. A real physical object was positioned on the top of the box, with the surface to be estimated oriented in the fronto-parallel plane. We did this because it should provide the most precise visual estimates of object size (estimates in depth are noisier than estimates in the fronto-parallel plane, Gepshtein & Banks, 2003; Keefe & Watt, 2017), thereby minimising the contribution of visual noise to the measurements. The participant had to pantomime the size of the object by adjusting the distance between the thumb and index finger inside the box. As in Chapter 1, we controlled the availability of vision using PLATO goggles (Translucent Technologies, Toronto, ON, Canada).

Movements were recorded at 240 Hz using the same optical motion capture system as in Chapter 1 (ProReflex, Qualisys). The system tracked the position of two spherical infrared-reflective markers that were affixed to two locations: i) the medial tip of the thumb nail, ii) the lateral tip of the index finger. The objects were the same as those used in Chapter 1, sized 25, 30, 35, 40 and 45 mm. We used these objects instead of recognizable objects

(e.g., a drink can) because in the latter scenario, remembered object properties could provide information to guide the motor system to perform the correct estimation without relying on proprioception signals. Participants performed 45 estimations in total, nine for each object size. This allowed us to evaluate in detail how hand opening varies with changes in object size. For instance, we can determine the slope of the function relating hand opening to object size, and also the 'offset', as well as probe whether size affects variability in responses (we might expect higher variability for larger objects, for example).

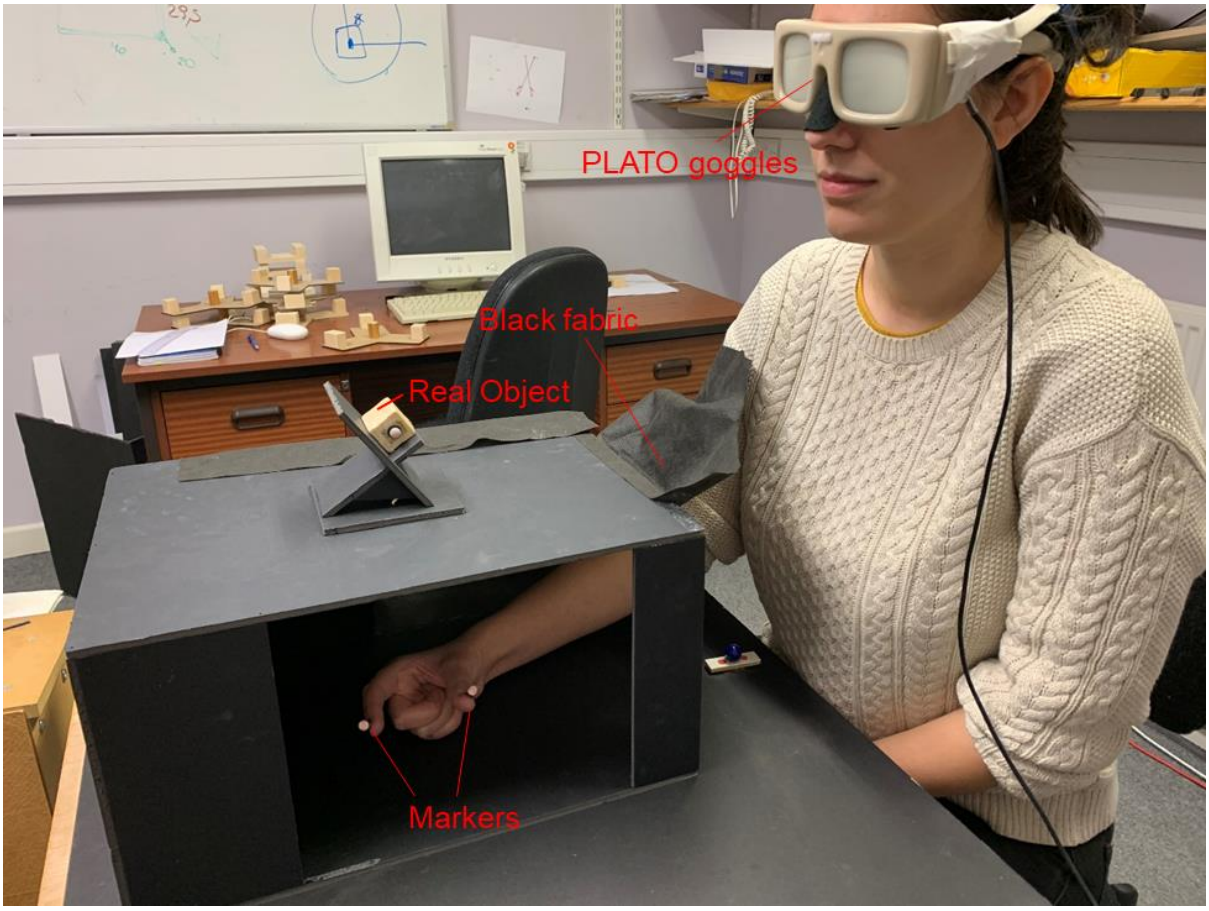


Figure 4.6 Manual estimation task experimental set-up. The picture shows the participant in position to perform the task, with the box and the piece of black fabric preventing vision of the arm. The markers used to record the movement were positioned on the tip of the thumb and index finger.

Procedure

As noted earlier, we instructed participants to not touch the box surface, or the table, and to avoid any contact between their fingertips. Each trial began with the participant's hand inside the box and the PLATO goggles opaque, to avoid participants seeing the object until it was positioned on the top of the box. After the object was in position, the PLATO goggles changed from opaque to transparent, and the trial started. The participant was instructed to view the target object and estimate its size by adjusting the distance between the thumb and index finger as if he/she could grasp the object. The object remained visible throughout the trial. When the participant confirmed their hand was opened the appropriate amount, the experimenter pressed a key on the experiment computer triggering a brief (two seconds) recording of the finger/thumb opening. The order of presentation of object sizes was randomised with a custom script written in Matlab (Mathworks Inc., Natick, MA, USA). The study took approximately ten minutes to complete.

4.4.3 Dependent measure and analysis

As we did in Chapter 1, data processing was done using a customised Matlab program (Mathworks, version R2015b). Raw three-dimensional data from each marker were low-pass filtered using a Butterworth filter (2nd order, 12 Hz cut-off). Manual size estimates were measured as the Euclidean distance between the x, y, and z coordinates of the index finger and thumb markers on each frame, and corrected for the position of the markers on each participant's hand, so the data represent the separation of the thumb and index finger pads, not marker separation per se. We obtained the estimate of each object size by averaging the manual estimation of the nine presentations from the same object.

4.4.4 Results

We plan to analyse the function relating finger/thumb opening and object size. Ordinarily, we would expect all participants to show increased finger/thumb opening with

larger object sizes (a flat slope would indicate an absence of sensitivity to variations in object size). A perfectly calibrated (i.e., accurate) proprioceptive estimate should result in a slope of 1.0, with mean finger/thumb opening matching the physical object size. Departures from this pattern, and differences between patients and controls, will allow us to determine how estimates of finger/thumb opening from proprioception are affected by nerve injury.

We can also analyse the variability in responses (i.e., the standard deviation of individual's responses), which may provide insight into how noisy the estimates of finger/thumb opening from proprioception are. These data can be difficult to interpret, however. In the simplest model, noisy proprioception propagates into noisier (more variable) finger/thumb openings. In practice, however, increased uncertainty per se also often results in changes in *bias* in perceptual responses, such as a reduction in the slope relating perception to changes in the stimulus (this is one reason why psychophysical measures are valuable, as a direct measure of noise/sensitivity). As such, this measure likely confounds changes in accuracy and precision of finger/thumb opening from proprioception. Nonetheless, the different measures can provide a more comprehensive picture, particularly when combined with the other tests.

Figure 4.7 shows the data from the three participants that took part in the pilot experiment. The grey dashed line represents ideal performance (perfect match between the estimate and actual object size). As can be seen, all participants were able to scale the hand according to increases in object size, no flat finger/thumb opening was found. The data seem to suggest that healthy participants perform the task with high accuracy, and reasonably small variability. Therefore, we can speculate that the test will be able to detect deviations from normal performance in situations of impaired proprioception, for example. However, due to the small sample size, we did not perform any analysis of these data.

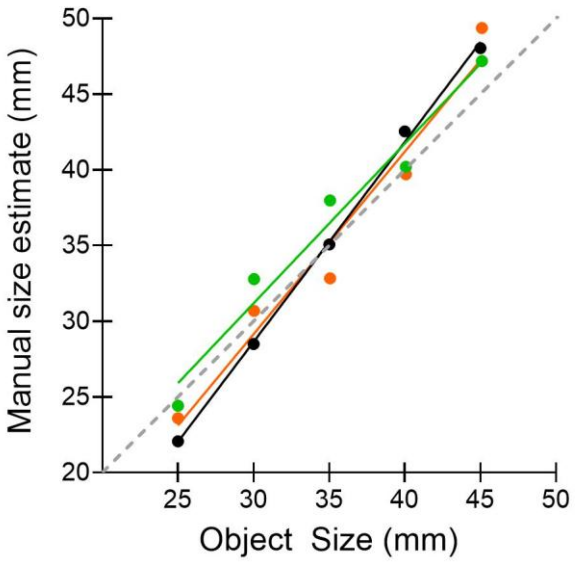


Figure 4.7 Manual size estimate. Manual size estimates plotted as a function of object size. The grey dashed line represents perfect performance, in which the estimation perfectly matches the real object size. The three colours denote the different participants that took part in the pilot.

4.5 Validation test 3: haptic size-discrimination test

We did not test any new participants on this test, but can nonetheless make some informed considerations based on the results presented in Chapter 3. This test produces a precise measure of an individual's sensitivity to object size, based on established psychophysical measures. The data in Chapter 3 provide a detailed picture of the spread of hand sensitivity in different people.

On a practical level, this test is not suitable for clinical use because it is time consuming, requires expensive bespoke equipment, and extensive training of the clinician not only to administer the test but also to analyse the data. However, comparing the results of this test – which has a high sensitivity level – with the block-difference test can provide us with a better understanding of the sensitivity of our clinical test. In this way, we can assess if the block-difference test can track the same variations across people as the size discrimination test. As a part of our long-term plan to compare the performance on each test, we can predict that based on the spread of the hand sensitivity reported in Chapter 3 (see

Figure 3.3), a participant that gets a 2 mm sensitivity score on our new clinical test will have low JND value in the more rigorous size discrimination test.

Further, this can help us understand the type of severity of impairment that our block-difference test can detect. At present we do not know what severity of impairment is associated with different disorders, so further research should be conducted to better clarify this and so understand which levels of impairment the block-difference test can detect. Nevertheless, it is important to test different levels of symptomatology because we ultimately hope to trace the evolution of digit proprioception impairment, for example during recovery.

4.6 Planned analyses to assessing construct validity

As briefly discussed in the Introduction, due to the COVID-19 outbreak we could not collect a sample size sufficient to perform the analyses that we planned. Therefore, we decided to outline the plan to assess the construct validity of our block-difference test. As a first step, we would perform correlation analyses between performance on the different tests. By doing so, we can gain a better sense of whether our new clinical assessment measures hand proprioception as we intended. We can predict that the performances should be positively correlated because the different tests assess digit proprioception from different angles. However, we can assume that the strongest correlation will be between the block-difference test and the haptic size-discrimination test because the clinical test is an evolution of the psychophysical test, and they both assess the same aspects of proprioception. Similarly, we assume that the manual estimation test and the comparing static-proprioception to vision task should be moderately related because they both assess digit position sense in the absence of tactile feedback (and both involve comparisons to visual stimuli).

It is also relevant to recognise the fact that these tests might not show the expected relationships because they do not rely exclusively on proprioception signals. The block-difference test and haptic size-discrimination test conflate proprioception and tactile signals; therefore, poor performance might be caused not only by impoverished proprioception but

also tactile impairments. The tactile impairment could lead to poor performance because participants might have problems finding the object to grasp, and therefore, poor performance at the task may not reflect impaired proprioception per se. The difficulty in finding the object might generate additional movements, which might provide further information that can potentially conflate the 'true' performance. In the case of comparing static-proprioception to vision test and the manual estimation task vision and proprioception are conflated. As mentioned before, this can result in poor performance due to increased noise generated by the cross-modal transformation process, or by visual impairments. Except for the comparing static-proprioception to vision test, all the other tests require an active movement from the participant. Therefore, additional movement signals may be conflated with proprioception, either making it worse (in cases where they add uncertainty) or perhaps better (e.g., motor output in the manual estimation task). The fact that the tests presented conflate different sensory signals (i.e., tactile and/or motor signals) with proprioception might cause additional problems when testing the older population, and/or clinical conditions. It is known that ageing affects the mechanical and physiological properties of the skin, transmission of tactile signals, and is associated with decreased muscle mass (Carmeli, Patish, & Coleman, 2003). Peripheral nerve injuries are known to result in similar impairments (Carmeli et al., 2003). Therefore, poor performance at our tests might arise from impaired tactile and motor signals rather than proprioception per se.

A primary requirement of a clinical test is that it has good test-retest reliability, and so we planned to evaluate this for the block-difference test. Here, test-retest reliability is the consistency of individual’s proprioception sensitivity when measured on different occasions. We should consider as a good outcome a high intraclass correlation coefficient (ICC) between the sensitivity score obtained on different days. Generally, an ICC value less than 0.5 is considered indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability and values greater than 0.90 indicate excellent reliability (Liljequist, Elfving, & Roaldsen, 2019). Previous studies that

assessed the test-retest reliability of new proprioception tools have accepted as a good ICC values scores between 0.62 to 0.96 (Han et al., 2011; Hoseini et al., 2015; Kalisch et al., 2012; Yahya et al., 2018). Therefore, we should aim for an ICC value at least above 0.50 for our block-difference test.

One factor to consider in test-retest reliability is that intense assessment over a short amount of time can induce general learning of the task, unrelated to the underlying factor the test is measuring (Wycherley et al., 2005). This learning can decrease the correlation strength (i.e., reduce the ICC score) because participants get better at the test at every assessment. We would therefore assess the block-difference test over at least two consecutive days, as previously done by Yahya et al. (2018), or preferably after seven days from the initial testing, as Han et al. (2011) did.

Further, a good clinical test requires high inter-rater reliability. That is, similar assessment results should be obtained when the same participants are tested by different examiners. As before, a good outcome would be indicated by a high ICC score across the sensitivity scores from different examiners. As reported above, we should aim for an ICC value at least above 0.50 (Liljequist et al., 2019) to claim moderate inter-rater reliability for our new clinical tool. Indeed, a previous study reported a good ICC value of 0.86 between two different assessors (Hoseini et al., 2015). However, it is important to recognise that we might get low ICC values that can reflect problems in our test. For instance, low ICC scores might arise because there are some subjective components in the administration of the test. One assessor might be faster than the other in administering the test. This could result in a careless administration that can generate noisy scores, and so lead to low inter-rater reliability. Another possibility might be related to the instructions. Even if we developed clear instructions, we might find some assessors change them because they might feel it more appropriate for the testing. This could result in changes to the procedure, resulting in different test scores, and therefore low inter-rater reliability. As well, if the trainings offered to

different examiners are not equal, they may administer the test in different ways, which would decrease the ICC value.

Another potentially valuable approach to validating tests is to take advantage of known (or expected) relationships between observable factors such as demographics, and test scores. Hoseini et al. (2015), for example, examined the effect of age on their digit proprioception scores. We expect age to reduce sensitivity (it results in diminished tactile sensitivity, for instance; Carmeli et al., 2003). And so finding a similar effect for our digit proprioception task (as Hoseini et al., 2015, did) would increase our confidence that the test is sensitive to modest changes. By the same token, not finding an age-effect might indicate some problems with our test, which would require further investigation. Of course, it is important to be cautious when evaluating the effect of age on a new test in case the test also taxes other capabilities than the one of interest, in which case the expected pattern of data might occur for the wrong reasons. Old participants are more likely to have central nervous system problems, for example, and additional challenges are related to the cognitive decline of memory with age (Stephan et al., 2016). A possible way to eliminate the concern of the effects of memory decline is to perform a questionnaire that assesses memory. In the case of performance indicating preserved memory abilities, we could eliminate the possibility that the memory decline played a role during the proprioception assessment.

4.7 Discussion

This study aimed to develop a clinic-friendly method to assess digit proprioception of the thumb and index finger. The block-difference test is a goal-oriented assessment because it resembles an activity of daily living. The test requires to feel three objects, one target and two distractors, and to indicate which was the largest object felt. The test is quick to administer, easy to follow for the participant, and easy to administer for the experimenter.

We outlined a plan to evaluate the clinical test by comparing the performance with three lab-based tests: i) comparing static-proprioception to vision task, ii) manual estimation

test, iii) haptic size-discrimination test. The different tests investigated hand proprioception from different angles and so they can be considered comparable, and together form a comprehensive assessment of proprioception-related measures.

4.7.1 Clinical consideration of the block-difference test

After administering the block-difference test, we can confirm that our assessment has some important features of a ‘good’ clinical test, outlined in the Introduction. The test is simple to administer. In fact, it did not create any confusion in the assessor. The procedure was intuitive for the participant to follow; nobody had problems performing the pinch movement required. The apparatus that we designed was easily moved to a different location in the testing space. Also, it prevented participants from seeing the objects during the testing. Overall, the test requires ten minutes to be performed, and so it is suited to keeping a high concentration level and avoiding fatigue.

The administration process can potentially be made quicker. For instance, we could record the testing so the assessor would not need to write the answers. Also, the assessor could keep a count of the different steps performed by using a counter. Because we only tested three people, we can only speculate on the possibility that we might need to add more levels of task difficulty (i.e., smaller increments between the blocks, larger separations, etc.) to prevent floor and ceiling effects. Another important consideration to make is related to the choice of the base size. By looking at the data of Chapter 3, it might be more sensible to use as a base of 50 mm because participants showed more variation with the larger size. One potential problem with this, however, is that there is an upper limit on hand opening, and this can be smaller than normal in the patient populations. In cases of poor sensitivity, it therefore may not be possible to present a target object large enough to detect, yet small enough to feel. One partial solution to this would be to make the target object *smaller* than the distractors, and ask participants to detect the smallest object.

Clearly, it is necessary to test more participants in order to understand if the base size that we choose is correct or if a change is needed. Further, increasing the sample size can help to define the spread in sensitivity scores across different people. Defining the spread of the sensitivity scores will help to decrease the possibility that higher scores are related to problems in the test instead of reflecting poor proprioception. As outlined before, we should also assess test-retest reliability, inter-rater reliability, and the influence of age.

4.7.2 The future of the validation tests

To evaluate our block-difference test, we developed two in-lab tests besides the haptic size-discrimination test to assess proprioception. Each test has different strengths and weaknesses, but we believe that they can be good candidates to be translated into clinical tests. Here we explore some of the issues around this for each test in turn.

Comparing static-proprioception to vision task

In comparing static-proprioception to vision task, the experimenter passively positions the thumb and index at a predetermined separation distance, and the task of the participant is to report if the size of the visual object shown is bigger or smaller than the distance between the fingers. We believe that the test could be translated into a clinical-friendly tool. The test could be performed by using a tablet, as Hoseini et al. (2015) did for their assessment that we used a starting point to develop our test. Even in this case, the clinician will passively position the digits of the participants under a box. On top of it, the clinician will position the tablet, in a similar manner described by Hoseini et al. (2015).

The use of a box will serve two purposes. The first is to prevent vision of the hand while performing the task. The second is to position the tablet above the participant's hand. On the tablet, it will be shown an object, and as for the in-lab test, the participant will have to judge if the object shown is smaller or larger than the distance between the thumb and index finger.

The manual estimation test

In our manual estimation task, the participant pantomimes the size of real objects by adjusting the distance between the unseen thumb and index finger, while the digits' movements are recorded with a motion capture system. We believe that this task can be translated into the clinical world. The participant would need to position the hand under a box to avoid any visual feedback while performing the task. Instead of the motion capture system, we can use a system such as the Leap motion system — a relatively cheap (~£100), portable optical system for measuring hand movements in real-time. The advantage of the Leap motion system in comparison to other solutions (i.e., asking participants to use a touch screen) is that we can prevent the influence of tactile information, as for the in-lab test.

Therefore, a clinical translation of the test would require participants to position the hand under a box, with the Leap motion system positioned close to the hand. As for the in-lab test, the participant would be required to pantomime the size of the object presented on top of the box, by adjusting the distance between the unseen thumb and index finger. As in our in-lab test, we would present arbitrary objects (wooden blocks etc.), rather than familiar objects. It is possible that remembered object properties, acquired by prior interaction with recognizable objects (e.g., a can of drink) could provide information to guide the motor system to make a correct response, even with impaired proprioception. Thus, we will provide duplicates of the object used in the in-lab test to assess the manual estimation ability of participants.

Future approaches

The clinical versions of our in-lab tests can be used to expand our assessment potential. The clinical tests preserve the complementary properties of each approach, as well as the challenges of measuring hand proprioception from different 'angles'. Also in this way, we could translate into the clinical world some features of more rigorous experimental settings. Further, because the different tests target the pinch opposition of thumb and index

finger, which is usually not assessed clinically, we will have goal-oriented tests that can help in improving our understating of the functional implications of impaired digit proprioception in different clinical populations.

4.7.3 Conclusion

Here, we presented our new clinic-friendly test to assess digit proprioception, the block-difference test. Due to the COVID-19 outbreak, we could not perform the assessment that we planned. Therefore, we outlined the steps needed to assess the validity of the block-difference test that will help in a smooth transition into the clinical world.

Chapter 5. General Discussion

Carpal Tunnel Syndrome (CTS) is the most common nerve injury (Aroori & Spence, 2008), which results in a variety of functional problems (e.g., clumsiness, manual dexterity problems). These problems can potentially be explained by tactile impairments, which might make it harder to detect when the digits have made contact with the object (Johansson & Flanagan, 2009) and to sense and control digit forces after object contact (Li & Nimbarte, 2006; Zhang, et al., 2011). As well, increased passive tissues rigidity associated with paraesthesia and pain, common CTS's symptoms can restrict the range of movement of patients (Marquardt et al., 2014). However, hand/digit proprioception plays a pivotal role in the execution of smooth movements (Rothwell et al., 1982; van Beers & Sittig, 1998) Considering this, we hypothesised that impairments to digits proprioception significantly contributes to the functional problems reported by the patients.

This thesis had three aims: i) assess if the kinematics of hand movements are affected by CTS, ii) assess if digit proprioception is impaired in CTS, iii) and how we can measure digit proprioception deficits in a precise and repeatable way. At the beginning of this section, the findings of the three empirical chapters are summarized. The aim, interpretation and direction of future works are addressed.

5.1. Summary

The optimisation/uncertainty framework postulates that perception and sensorimotor control are corrupted by noise (Ernst & Banks, 2002), and managing this noise is critical to efficiently performing a movement. This framework indicates that the sensory system integrates different sensory information, giving the less noisy signals more weight (Ernst & Banks, 2002). Therefore, this framework makes direct predictions of how sensory noise is managed, which we can use to understand how CTS patients behave. If the increased sensory noise is managed in an optimal way, we expect to see appropriate responses from

CTS, which reflect the ‘normal’ pattern of responses. If the sensory noise is unmanaged, we expect to see noisier movements with a higher probability of errors.

5.1.1 Does CTS affect the kinematics of hand movement?

In Chapter 2, we assessed if CTS affects the kinematics of grasping movements towards real objects. CTS patients showed preserved grip and speed scaling according to object size and distance, regardless of visual condition, slower movement in the absence of vision, and no increased movement variability. These results suggest that our CTS patients can manage the increased noise due to their nerve impairment in an appropriate way, and therefore the optimisation framework can predict the compensatory responses used by the sensory system.

CTS showed longer duration movements when vision was not available, which might reflect a compensatory strategy to minimise the likelihood of object collision, dropping off the object or clumsiness due to impoverished sensory information. This strategy might suggest that patients have to pay additional attention when performing the movement in the absence of vision because it is more expensive for them to correct the movement in-flight. We can speculate that these results indicate an increased reliance on vision for CTS as a consequence of impoverished non-visual information. If this hypothesis is confirmed by further investigations, we could get a deeper understanding of the functional implications of CTS. Indeed, this not only affects the life of the patients because daily activities may be accomplished more slowly (e.g., making a cup of coffee), but also patients may face disadvantages in employment conditions, perhaps in particular, where different steps have to be completed in sequence at a high pace (e.g., in an assembly line).

A possible way to confirm our hypothesis is to investigate the gaze behaviour of CTS patients. Several studies in the healthy population have found that when we aim to interact with an object, we first gain information about its location and shape to plan the movement (Desanghere & Marotta, 2011; Johansson, Westling, Bäckström, & Flanagan, 2001). The

decision about where to look is not casual, the gaze is directed towards environmental features relevant to plan the hand movement (Desanghere & Marotta, 2011; Johansson et al., 2001). The preferred fixation point is the landing position of the index finger (Desanghere & Marotta, 2011; Johansson et al., 2001), instead, the fixation of the moving hand is usually avoided (Johansson et al., 2001). This gaze behaviour probably arises from the fact that the landing position of the index finger is not visible, therefore, precise visual monitoring is required in comparison to the thumb that touches the object first (Cavina-Pratesi & Hesse, 2013). Interestingly, in a study in which the contact points of both thumb and index finger were visible, a preference to fixate the index finger landmark was still observed (Brouwer, Franz, & Gegenfurtner, 2009). Two hypotheses may account for this: i) the landing location of both digits is spatially close, ii) the successfulness of the grasping of the thumb is provided by the tactile information obtained when the thumb contacts the object (Cavina-Pratesi & Hesse, 2013). Whether CTS patients use a similar gaze pattern is unknown. To assess this, we should track gaze movements of CTS and healthy controls while performing a grasping task. We can speculate that CTS will show different gaze behaviour than healthy controls due to impoverished non-visual information. We can assume that CTS should fixate the hand in flight more than healthy controls, as a consequence of (presumed) impoverished proprioception signals. As well, CTS might fixate both the thumb and index finger while the hand is approaching the object, due to impaired tactile sensitivity.

5.1.2 Is proprioception impaired in CTS?

As mentioned in Chapter 2, the grasping results can be explained by impaired tactile sensitivity. However, digit proprioception might be impaired due to the entrapment of the median nerve. The proprioception impairment can affect the calibration between sensory signals and may explain the behaviour showed by CTS patients. However, the results of the grasping experiment cannot confirm this hypothesis. Therefore, in Chapter 3, we assessed if digit proprioception is impaired in CTS. We used a haptic size-discrimination task to measure

the sensitivity of the opening of the unseen thumb and index finger in CTS patients and healthy controls. Inconsistent with our hypothesis, we found no evidence of impaired digit proprioception in our CTS patients. As discussed in Chapter 3, different reasons could explain the lack of differences between CTS and healthy controls. First, the lack of severe symptomatology in our CTS patients might explain our result. Indeed, because digit proprioception arises from a combination of sensory information from affected (i.e., median nerve innervated) and non-affected structures (i.e., innervated by the ulnar and radial nerves; Chammas, 2014; Duncan et al., 2013; Ljungquist et al., 2015), and because our patients had mostly mild to moderate impairments, it is possible that patients had only relatively minor proprioceptive impairments, which may not have been detectable in our experiment. Therefore, it is necessary to assess CTS with more severe symptomatology.

A second possibility that can explain our data is related to the fact that the median nerve impairment affects other sensory (e.g., tactile) afferents than proprioception. However, in our opinion, it seems unlikely that CTS can only affect specific afferents. It will be valuable to determine at what point CTS causes effects on digit proprioception. To assess this hypothesis, we should perform a temporary nerve block of the median nerve in the healthy participants, following a similar approach to Kiernan, Mogyoros, and Burke (1999). The participants will be asked to extend the wrist at 90° for 15 minutes. The extension will lead to a temporary nerve block characterised by a slowing of the nerve responses, mild paraesthesia – pins and needles – and ‘dull discomfort’ during the conduction block (Kiernan et al., 1999). Following this, we will perform our tactile assessment with Two-Point Discriminator and Semmes-Weinstein Monofilament to assess if the temporary nerve block generates a similar tactile impairment as in CTS patients. After, participants will perform our haptic size-discrimination task. If following the nerve block, participants show similar performances to our CTS patients, we could claim that the entrapment of the median nerve does not provide necessary proprioception information about the posture of the thumb and index finger. If following the temporary nerve block participants show worst performances

than our CTS patients (and controls), we would interpret this as evidence that the median nerve provides proprioception information. Therefore, we could speculate that we have not found evidence of impaired proprioception in our patients due to the low level of severity. As we mentioned before in this thesis, finding a decreased performance might suggest that the consequences of acute temporary nerve block might be different than chronic nerve entrapment due to CTS. Indeed, in the case of CTS the central nervous system had an opportunity to better 'understand' the consequences of the nerve entrapment, and adapt in ways that are different from the case of acute nerve block.

Is haptic perception of object size impaired in CTS?

While working on the haptic size-discrimination task, we found a surprising lack of 'good' clinical assessments of hand/digit proprioception. Recognising this, in Chapter 4 we developed a prototype for a new clinical tool to assess proprioception of the pinch between thumb and index finger, the block-difference test. For both our more rigorous haptic size-discrimination test and the block-difference test, we assumed that haptic size estimation relies on proprioceptive signals, therefore, haptic size performance can be interpreted as a functional index of digit proprioception (Berryman et al., 2006). A relevant trade-off of both our task is that they potentially conflate tactile signals with proprioception. As mentioned before, according to Berryman et al. (2006) it is not appropriate to dissociate proprioception from tactile signals because they both provide relevant signals to estimate the size of a felt object. The compliance of the object and variation in forces and compression signals arising across the digits are taken into account to estimate the size of an object (Berryman et al., 2006). Therefore, based on the outcomes of our haptic size-estimation study (Chapter 3), we may be tempted to conclude that the haptic perception of object size is not impaired in CTS.

However, we might not have found impaired haptic perception in CTS because we used rigid objects. A relevant premise of the interpretation proposed by Berryman et al. (2006) is that when estimating the size of an object held in hand, the tactile system provides

local texture information about the compliance of the object. Therefore, one possibility with respect to our study is that patients may not have shown performance impairments because they did not have to compensate for object compliance. In other words, on the basis of Berryman et al. (2006), we hypothesise that patients would show impaired performance in our haptic size estimation task if we asked them to grasp objects with varying compliance, including non-rigid (soft) objects. Due to the impairment of tactile signals, we would expect patients to struggle to accurately estimate and thus compensate for the varying material properties of objects, and so they should show worse size discrimination ability than controls. It would be of value to test this hypothesis.

5.2 Future directions

The work described in this thesis advances our understanding of how the sensorimotor system is affected by impoverished somatosensory information, and which strategies are adopted to compensate for it. Further, our findings suggest that the sensorimotor system can respond efficiently in the face of mild-to-moderate sensory impairments to the nerves of the hand. Finally, our work highlights the need to develop better assessment tools to assess hand/digit proprioception, both experimentally, for the purpose of advancing basic knowledge (i.e., basic science), and clinically

5.2.1 The use of the optimisation framework to understand nerve injuries

We focused our attention on CTS because it is the most common nerve injury (Aroori & Spence, 2008), and it entails relevant economic costs for the individual and the society (Lorgelly et al., 2005). CTS was used as a model to understand the sensory and motor consequences of peripheral nerve injuries to the upper extremities. We believe that the knowledge obtained by studying CTS can improve our understating of how peripheral nerve injuries affect the sensory and motor domains of more complex clinical conditions, such as Dupuytren's contracture or arthritis. By studying a broad continuum of mild to more severe

conditions we can hope to better understand both the consequences and time-course of recovery from hand-nerve injuries, and, most importantly, the underlying mechanisms of impairment (and thus, recovery from impairment).

Findings from Chapter 2 suggest that people suffering from nerve injuries manage the increased sensory noise caused by their injuries in an optimal way when controlling their hand during grasping. Indeed, they should show preserved scaling ability regardless of the visual conditions and slower movement in the absence of vision. Considering this, we can speculate that similar compensatory strategies would be adopted by patients in everyday life task. Therefore, in a work environment, we can assume that CTS patients might have problems with accomplishing a certain number of tasks in a predetermined time; indeed, it might not be possible for a person suffering from a nerve injury to be as quick as a co-worker without a nerve injury. In this case, it might be sensible to adopt modifications in how daily tasks are performed.

Findings from Chapter 3 indicated that people suffering from mild-to-moderate CTS do not have problems estimating the size of rigid objects using haptics alone. As we discussed in Chapter 3, we should assess the size estimation of soft objects because, in this case, the sensory system of CTS should not be able to compensate for object compliance due to tactile impairments. Therefore, this should result in poor performance. We can speculate that other nerve injuries in which tactile signals are impaired should show similar behaviour to CTS. In the case of people suffering from a hand-nerve cut, we might see poor performance even with a rigid object because both sensory signals are impaired. This might be the case because as consequences of the nerve(s) cut the intrinsic hand muscle became atrophic and tactile sensitivity is impaired (Schenker, Burstedt, Wiberg, & Johansson, 2006). In this case, the quality of both sensory signals should be impoverished, and therefore the size estimation of both rigid and soft object will be affected.

5.2.2 The importance of visuo-motor techniques

Through the empirical Chapters, we used different techniques to assess the sensory and motor consequences of CTS, which can help in improving our understanding of nerve injuries more generally.

Movement kinematics

We used a motion capture system in Chapter 2 to assess the anticipatory features of grasping towards real objects. The motion capture system offers the opportunity to characterise with high precision the different components of the movement. Movement kinematics are not assessed in the clinical world because of the expensive hardware, highly technical set-up, extensive training required for data collection and data analyse (Colyer, Evans, Cosker, & Salo, 2018). The kinematics analysis can convey important information about the quality of motor features that is not clear from the clinical evaluation (Bigoni et al., 2016), such as speed and accuracy, smoothness (Mackey, Walt, & Stott, 2006) and repeatability (Sejnowski, 1998). The information obtained by the kinematic analysis can provide useful implications for the effectiveness of a rehabilitation program. Indeed, it is possible to quantify the functional recovery of the movement through kinematic analysis.

Motion kinematics can improve our understanding of the motor consequences of nerve injuries by individuating the kinematic feature that is more affected by the clinical condition. Therefore, the scientific community could use this information to further develop experiments designed to improve our understanding of how this affects movement execution. However, a relevant challenge is represented by how the information gained by rigorous scientific experiments can be translated to the clinical community to improve clinical assessment and rehabilitation. In this thesis, we made small steps towards this by focusing our attention on the grasping movement. In detail, we used goal-oriented tasks by focusing our attention in all empirical chapters on the pinch between the thumb and index finger, which resembles an activity of daily life more closely. In this way, we can get a better insight

into how the person performs daily activities; however, we have to remember that performing a grasping task in an experimental setting is different from doing the same at home. Indeed, different confounding factors that are controlled during an experiment can affect the performance in a less rigorous setting, such as daily life context. For example, when reaching for a can of drink in the refrigerator, the presence of different items in the can's environment can be treated as obstacles and therefore affects the movement kinematics of the hand, by deviating the movement trajectory from the original plan. Another confounding factor might be related to the number of digits used while grasping. In an experimental setting, the participant might be asked to grasp the can of drink only by using the thumb and index finger, while, in a less controlled environment the same person might use the middle finger too to help grasping the can of drink.

Psychophysics

Psychophysics has been used to underline the neural mechanisms relating physical stimuli to perception with rigorous methods (Barack & Gold, 2016; Read, 2015). Psychophysics is a precise measure, which offers the possibility to assess the construct of interest in a detailed way that is not possible with other techniques. For instance, with psychophysics it is possible to isolate bias and sensitivity of proprioception while other tests usually conflate the two components (Hoseini et al., 2015). As mentioned before, sensitivity reflects how noisy the signals of digit proprioception are, while bias reflects the systematic errors in the sense of digit proprioception. The possibility to assess independently bias and sensitivity is particularly relevant in the clinical context because we could assess which component is impaired in a specific clinical condition. Knowing if only bias and/or sensitivity is impaired can improve the rehabilitation and assessment methods. Indeed, a test that measures proprioception bias could miss the impairment of proprioception in a population that has a deficit in proprioception sensitivity. To better understand this, we can consider the case of grasping a can of drink. A patient with proprioception bias might show a systematic

error in the landing position of one finger on the can of drink. Therefore, during rehabilitation, the clinician might suggest adopting compensation strategies to reduce the range of motion of the specific finger, which should help in positioning the finger closer to the can of drink. A different patient might show an impairment of proprioception sensitivity which can result in a more variable landing position of the fingers on the can of drink (i.e., not always the finger will land on the can of drink). During rehabilitation, the clinician can physically guide the execution of the movement of the affected hand to re-educate the patient to achieve a similar level of performance as the non-affected hand. From the discussion above it is evident that it is relevant to know which proprioception component is impaired because in this way it is possible to tailor the rehabilitation program to the specific needs of the patient.

5.3 Conclusion

This dissertation aimed to gain new insights into the sensory and motor consequences of nerve injuries by focusing on Carpal Tunnel Syndrome. Through the dissertation, we used the uncertainty/optimisation framework to predict the consequences of CTS. The theoretical framework of uncertainty/optimisation correctly predicted the behaviour of CTS as appropriate responses to impairments to specific sensorimotor signals. As well, in this work, we outlined the importance of creating better tools to assess proprioception and the challenges involved in doing so. Finally, we discussed the implications of these findings and potential future work.

Appendix A

Figure S1.1. Boston Carpal Questionnaire and additional questions

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Modified Boston Carpal Tunnel Questionnaire

Select the answer that best fits the question.

How severe is the hand or wrist pain that you have at night?

None or Never (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

How often did hand or wrist pain wake you up during a typical night in the past two weeks (times/day)?

Never (0)
1 (1)
2 to 3 (2)
4 to 5 (3)
5 or more (4)

Do you typically have pain in your hand or wrist during the daytime?

None or Never (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

How often do you have hand or wrist pain during the daytime (times/day)?

Never (0)
1 x (1)
2 to 3 x (2)
4 to 5 x (3)
5 or more x (4)

How long on average, does an episode of pain last during the daytime (minutes)?

0 (0)
<10 (1)
10-60 (2)
>60 (3)
Constant (4)

Do you have numbness (loss of sensation) in your hand?

None or Never (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

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Do you have weakness in your hand or wrist?

None or Never (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

Do you have tingling sensations in your hand?

None or Never (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

How severe is numbness (loss of sensation) or tingling at night?

None or Never (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

How often did hand numbness or tingling wake you up during a typical night during the past two week?

0 x (0)
1 x (1)
2-3 x (2)
4-5 x (3)
5+ x (4)

Do you have difficulty with the grasping and use of small objects such as keys or pens?

None or Never (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

Reference: Levine et al. (1993). A Self-Administered Questionnaire for the Assessment of Severity of Symptoms and Functional Status of Carpal Tunnel Syndrome. *The Journal of Bone and Joint Surgery*, 75-A(11): 1585-1592.

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Additional Questions:
A. Sensations experienced during activities of daily living

A-1. How severe is the pain in your hand or wrist that you have experienced during activities?
None (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

A-2. How severe is the numbness (loss of sensation) in your hand or wrist that you have experienced during activities?
None (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

A-3. How severe is the weakness in your hand or wrist that you have experienced during activities?
None (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

A-4. How severe are the tingling sensations in your hand or wrist that you have experienced during activities?
None (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

B. Current sensations

B-1. How severe is the pain in your hand or wrist that you are currently experiencing?
None (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

B-2. How severe is the numbness (loss of sensation) in your hand or wrist that you are currently experiencing?
None (0)
Mild (1)
Moderate (2)

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Severe (3)
Very Severe (4)

B-3. How severe is the weakness in your hand or wrist that you are currently experiencing?
None (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

B-4. How severe are the tingling sensations in your hand or wrist that you are currently experiencing?
None (0)
Mild (1)
Moderate (2)
Severe (3)
Very Severe (4)

Table S1.1 Mean estimates of Peak Velocity (mm/ms)

Preserved peak velocity scaling in CTS

ME Distance F (1.091,58.89) = 1670.14, p < **0.0001**				
150 mm	551.09			
300 mm	916.06			
450 mm	1172.60			
Interaction Vision by Distance F (1.38,74.52) = 5.50, p = **0.01**				
	150 mm	300mm	450mm	
Visual Feedback	562.88	937.10	1193.66	
No-Visual Feedback	539.30	895.02	1151.50	
Interaction Distance by Group (F (2,108) = 1.74, p = 0.17				
	CTS	Controls		
150 mm	548.27	553.91		
300 mm	906.90	925.22		
450 mm	1149.99	1195.20		
Interaction Group by Vision by Distance F (2, 108) = 0.164, p = 0.84				
	CTS		Controls	
	Visual Feedback	No-Visual Feedback	Visual Feedback	No-Visual Feedback
150 mm	570.01	526.53	555.75	552.07
300 mm	939.71	874.09	934.49	915.96
450 mm	1182.17	1117.82	1205.15	1185.25

Slower movements in CTS when visual feedback is unavailable

ME Vision F (1, 54) = 24.41, p < **0.0001**				
Visual Feedback	897.88			
No-Visual Feedback	861.95			
ME Group F (1, 54) = 0.44, p = 0.50				
CTS	868.39			
Controls	891.44			
Interaction Vision by Group (F (1,54) = 9.06, p = **0.004**				
	CTS	Controls		
Visual Feedback	897.30	898.46		
No-Visual Feedback	839.48	884.42		

Bold values indicate significant main effect and/or interaction.

Table S.1.2 Peak Velocity Variability (mm/ms)

ME Vision F (1, 54) = 3.54, p = 0.065		
Visual Feedback	79.14	
No-Visual Feedback	73.46	
ME Group F (1, 54) = 0.01, p = 0.91		
CTS	76.62	
Controls	75.98	
Interaction Vision by Group F (1, 54) = 0.49, p = 0.483		
	CTS	Controls
Visual Feedback	79.05	79.24
No-Visual Feedback	74.71	72.71

Bold values indicate significant main effect and/or interaction.

Table S1.3 Movement Time (ms)

ME Vision F (1, 54) = 182.44, p < **0.001**		
Visual Feedback	736.18	
No-Visual Feedback	905.29	
ME Group F (1, 54) = 0.000003, p = 0.99		
CTS	820.77	
Controls	820.70	
Interaction Vision by Group F (1, 54) = 0.49, p = 0.48		
	CTS	Controls
Visual Feedback	731.80	740.56
No-Visual Feedback	909.75	900.83

Bold values indicate significant main effect and/or interaction.

Table S1.4 Acceleration Time (ms)

ME Vision F (1, 54) = 22.37, p < **0.001**		
Visual Feedback	321.49	
No-Visual Feedback	332.65	
ME Group F (1, 54) = 1.64, p = 0.20		
CTS	330.17	
Controls	314.97	
Interaction Vision by Group F (1, 54) = 1.92, p = 0.17		
	CTS	Controls
Visual Feedback	323.05	301.93
No-Visual Feedback	337.29	328.01

Bold values indicate significant main effect and/or interaction.

Table S1.5 Deceleration Time (ms)

ME Vision F (1, 54) = 235.04, p < **0.001**		
Visual Feedback	413.79	
No-Visual Feedback	570.17	
Me Group F (1, 54) = 0.31, p = 0.86		
CTS	489.18	
Controls	494.78	
Interaction Vision by Group F (1, 54) = 0.25, p = 0.61		
	CTS	Controls
Visual Feedback	408.43	419.15
No-Visual Feedback	569.93	570.41

Bold values indicate significant main effect and/or interaction.

Table S.1.6 Mean estimates of Peak Grip Aperture (mm)

Preserved Grip Scaling in CTS

ME Size (F (1.78, 96.12) = 642.52, p < **0.0001**					
25 mm	59.11				
30 mm	61.21				
35 mm	65.24				
40 mm	68.53				
45 mm	71.68				
Interaction Group by Size F (4,216) = 0.67, p = 0.60					
	CTS	Controls			
25 mm	58.56	59.67			
30 mm	60.41	62.01			
35 mm	64.44	66.05			
40 mm	67.63	69.42			
45 mm	70.68	72.69			
Interaction Vision by Size F (2.47, 133.87) = 19.28, p < **0.0001**					
	25 mm	30mm	35 mm	40 mm	45 mm
Visual Feedback	53.33	55.84	60.17	63.98	67.40
No-Visual Feedback	64.89	66.59	70.32	73.07	75.92
Interaction Group by Vision by Size F (4,216) = 0.208, p = 0.93					
	CTS		Controls		
	Visual Feedback	No-Visual Feedback	Visual Feedback	No-Visual Feedback	
25 mm	53.14	63.98	53.53	65.81	
30 mm	55.51	65.31	56.16	67.86	
35 mm	59.79	69.09	60.55	71.54	
40 mm	63.50	71.75	64.47	74.38	
45 mm	66.92	74.43	67.88	77.50	

Similar peak grip aperture between CTS and Controls

ME Vision F (1,54) = 131.82, p < **0.0001**		
Visual Feedback	60.14	
No-Visual Feedback	70.11	
ME Group (F (1, 54) = 0.40, p = 0.52		
CTS	64.34	
Controls	65.97	
Interaction Vision by Group F (1,54) = 1.05, p = 0.31		
	CTS	Controls
Visual Feedback	59.77	60.52

No-Visual Feedback	68.91	71.42

Bold values indicate significant main effect and/or interaction.

Table S.1.7 Peak Grip Aperture Variability (mm)

ME Vision F (1, 54) = 18.96 < **0.001**		
Visual Feedback	4.59	
No-Visual Feedback	5.61	
ME Group F (1, 54) = 0.54, p = 0.46		
CTS	4.94	
Controls	5.26	
Interaction Vision by Group F (1, 54) = 5.03, p = **0.02**		
	CTS	Controls
Visual Feedback	4.69	4.48
No-Visual Feedback	5.18	6.03

Bold values indicate significant main effect and/or interaction.

Table S1.8 Time to movement onset (ms)

ME Vision (ms) F (1,54) = 20.22, p < **0.0001**		
Visual Feedback	260.08	
No-Visual Feedback	272.59	
ME Group F (1, 54) = 0.93, p = 0.33		
CTS	270.97	
Controls	261.70	
Interaction Vision by Group F (1, 54) = 9.00, p = **0.004**		
	CTS	Controls
Visual Feedback	260.54	259.62
No-Visual Feedback	281.39	263.79

Bold values indicate significant main effect and/or interaction.

Figure S1.2 Correlations plots between CTS features and grasp kinematics

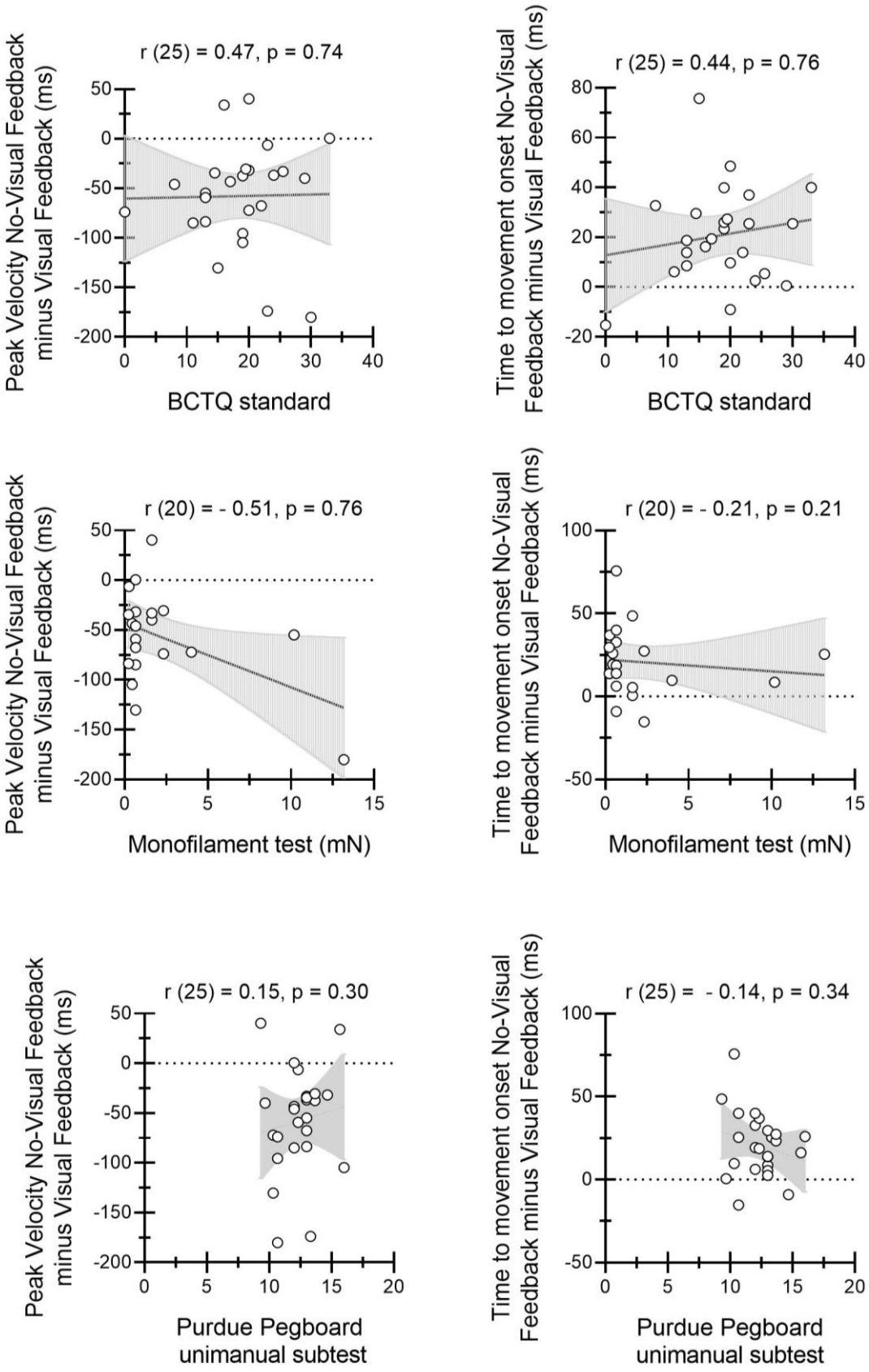


Figure S1.2 Correlations plots between CTS features and grasp kinematics. Plots showing the correlation between CTS-specific grasp kinematics—the differences between No-Visual Feedback minus Visual Feedback in (1) peak velocity and (2) time to movement onset measures— against Boston Carpal Tunnel Questionnaire standard, monofilament test and Purdue Pegboard unimanual subtest.

Figure S1.3 Correlations plots between CTS symptom severity and grasp kinematics

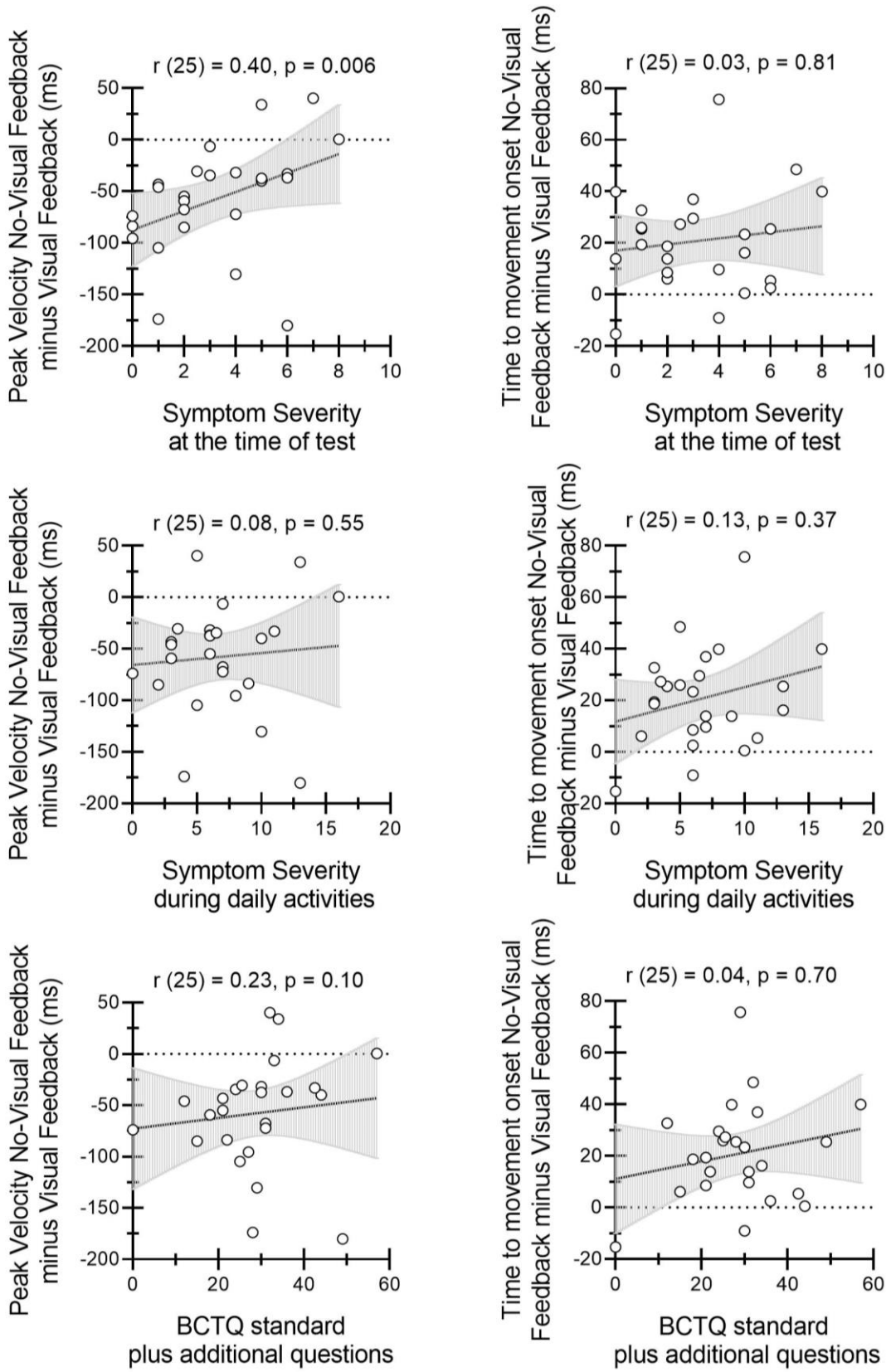


Figure S1.3 Correlations plots between CTS symptom severity and grasp kinematics.

Plots showing the correlation between CTS-specific grasp kinematics—the differences between No-Visual Feedback minus Visual Feedback in (1) peak velocity and (2) time to movement onset measures— against Boston Carpal Tunnel Questionnaire scores.

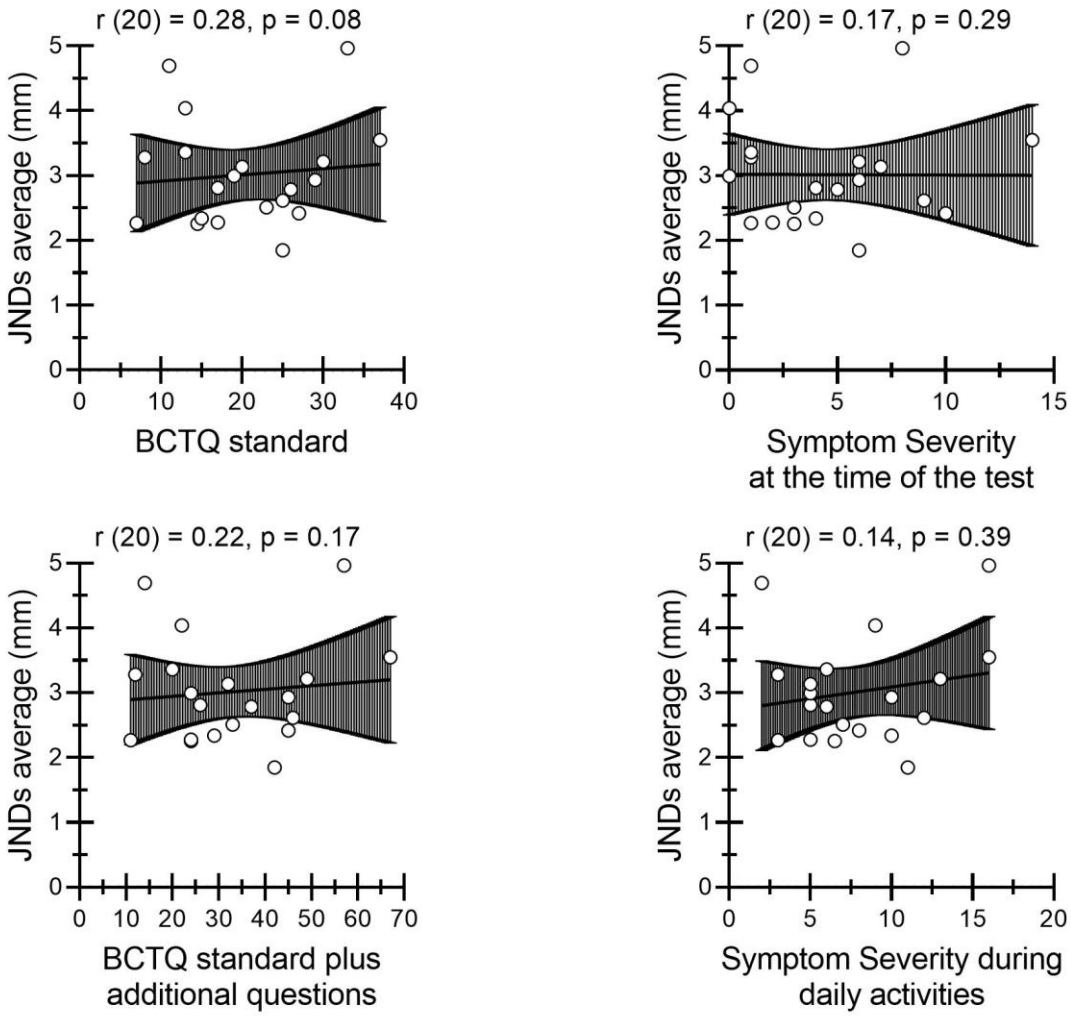
Appendix B

Table S.2.1 Haptic size-discrimination test

ME Size F (1.61, 69.47) = 22.99, p < **0.0001**		
10 mm	2.24	
30 mm	2.99	
50mm	3.91	
ME Group F (1, 43) = 0.13, p = 0.71		
CTS	3	
Controls	3.1	
Interaction Size by Group F (2, 86) = 0.11, p = 0.89		
	CTS	Controls
10mm	2.23	2.25
30mm	2.96	3.01
50 mm	3.79	4.03

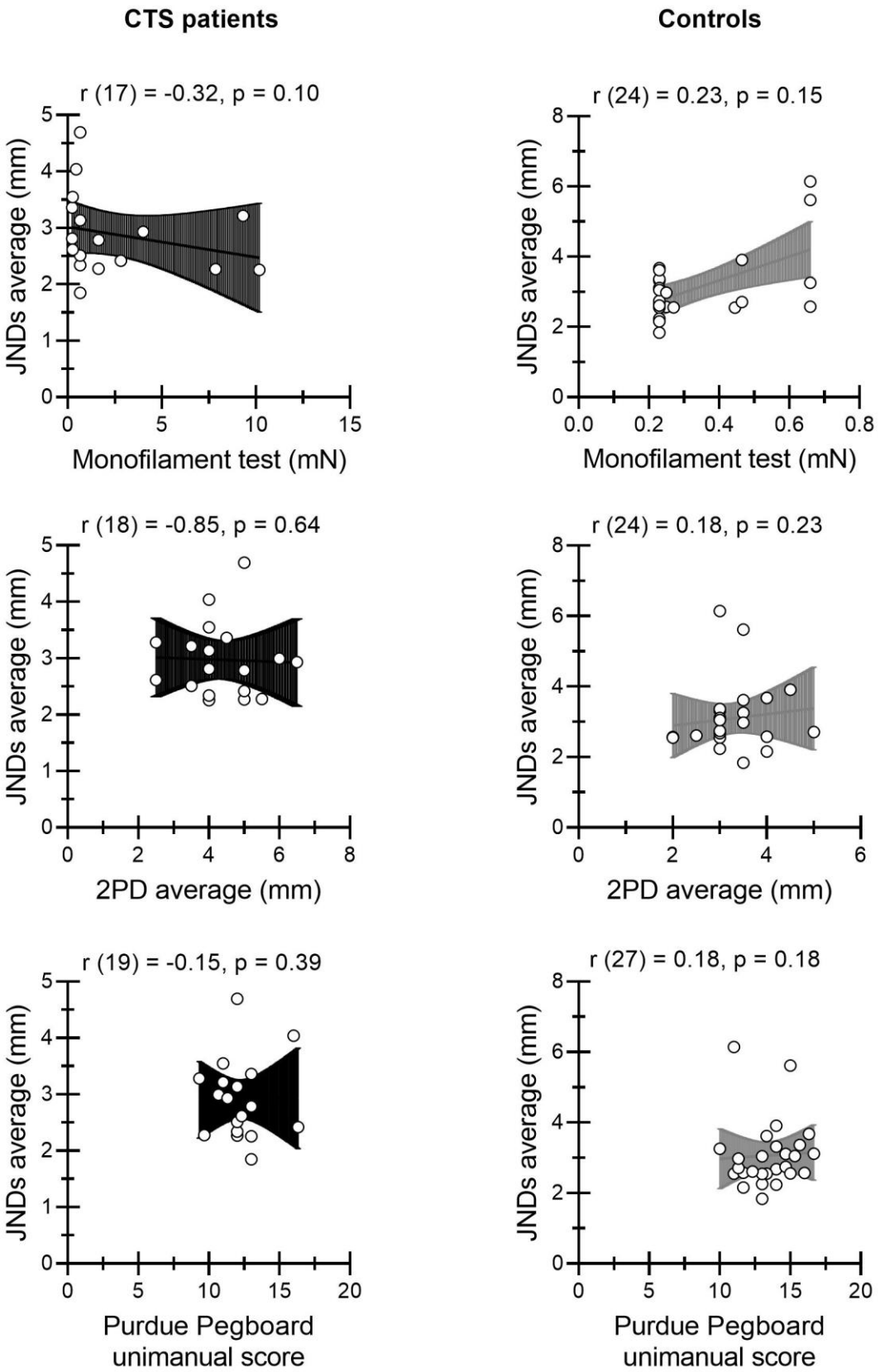
Bold values indicate significant main effect and/or interaction.

Figure S.2.1 Correlation plots between haptic size-discrimination test and CTS symptom severity



Supplementary Figure S.2.1 Correlation plots between haptic size-discrimination test and CTS symptom severity. The plots are showing correlations analysis between patients' performance at the haptic size-discrimination test and CTS symptom severity.

Figure S.2.2 Relationship between haptic size-discrimination test and sensorimotor performance in CTS patients and Controls



Supplementary Figure S.2.2 Correlations between haptic size-discrimination test and sensorimotor performance in CTS patients and Controls. The plots are showing correlations analysis between the performance of CTS patients and Controls at the haptic size-discrimination test and monofilament test, 2PD and Purdue Pegboard unimanual score.

Table S.2.2 Controls multiple regression

	β	SE	t-test	p
Constant	-0.81	1.89	-0.43	0.67
Monofilament test	4.24	1.13	3.73	**0.01**
2PD	-0.005	0.26	-0.01	0.98
Purdue Pegboard unimanual score	0.18	0.10	1.17	0.09

Bold value indicates the significant predictor.

Table S.2.3 CTS patients multiple regression

	β	SE	t-test	p
Constant	3.38	1.65	2.34	0.03
Monofilament test	-0-16	0.03	-0.42	0.67
2PD	-0.13	0.12	-1.13	0.27
Purdue Pegboard unimanual score	-0.007	0.11	-0.063	0.95
BCTQ standard	-0.01	0.02	-0.44	0.66

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