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Mapping the consequence of peripheral nerve transection and repair on brain organisation and hand function

Weber, Martin

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Mapping the consequence of peripheral nerve transection and repair on brain organisation and hand function

Martin Weber

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The present author carried out data collection and analysis for both experiments presented in this thesis.

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Declaration

'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.

I confirm that I am submitting this work with the agreement of my Supervisor(s).'

'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.

Rwy'n cadarnhau fy mod yn cyflwyno'r gwaith hwn gyda chytundeb fy Ngoruchwyliwr (Goruchwylwyr)

Abstract

Full recovery is not expected after peripheral nerve repair in the upper limb. Resulting impairments severely limit the patient's ability to use their injured hand in everyday activities and lead to a large financial burden for the individual and society more widely. Evidence suggests that central factors play a major role in limiting recovery. "Faulty touch localisation" is widely recognised as a hallmark of impairment in human patients and animal models reveal dynamic reorganisation of digit maps in primary somatosensory cortex (S1) after nerve repair. Yet, the applicability of map changes to humans and their functional implications remains unknown. In this thesis we study touch localisation and cortical organisation in 21 patients with repair of the median and/or ulnar nerve.

In chapter 2, we employ a novel method to measure touch localisation in which the participants localise touch by indicating the perceived location of a point stimulus on a photograph of their hand. Consistent with previous literature, we find elevated error of localisation in patients that is limited to the territory of the impaired nerve. Additionally, a few patients show an abnormal amount and pattern of misreferrals - errors made across digits or from the digits to the palm.

In chapter 3, we use functional magnetic resonance imaging (fMRI) to reconstruct the organisation of digit maps in S1 to stimulations of the contralateral hand. Consistent with work in animal models, univariate analysis using Dice overlap coefficients revealed a larger overlap of positive-going blood-oxygenation level dependent (BOLD) activity as well as changes to the structure of digit representations. As expected, the increase in overlap was limited to the territory of the injured nerve. Surprisingly, however, both the cortex contralateral and ipsilateral to the injured hand showed structural changes. Additional multivariate analysis using representational distances showed the same structural changes contralateral and ipsilateral to the injury, but we did not observe any changes to the similarity of the multivariate response patterns. Despite clear cortical reorganization and localisation deficits specific to the injured nerve, direct correlations between the two were not found.

Overall, our results confirm previous qualitative observations with rigorous, quantitative methods and indicate that humans exhibit dynamic cortical plasticity in S1 comparable to animal models. At the same time, they highlight the complexity of the interplay between cortical changes and peripheral impairments. Comprehensive quantification of both aspects within a detailed computational model is needed to understand their intricate relationship and improve functional outcomes.

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General Introduction

Full recovery is not expected after peripheral nerve repair. This is especially debilitating if the injury is in the upper limb or hand. Impairments usually severely limit the ability of the patient to use their injured hand in everyday activities and touch sensation never returns to their pre-injury feeling. There is strong evidence to suggest that the recovery is limited to a large degree by central factors. Yet, even though some progress has been made to understand central changes in animal models, their impact on recovery and, indeed, their applicability to human patients, remains unknown. This thesis addresses this gap in the literature. We aim to provide a more precise measure of functional impairment, to evaluate whether findings from animal studies extend to humans and to see whether they can help to predict functional recovery.

Functional impairment after peripheral nerve repair

Peripheral nerve injuries of the upper limb that involve a lesion and subsequent repair to the major hand nerves have poor functional recovery. Even after the acute phase, impairment persists for a long time and full recovery is not expected if the injury occurred in adolescence or adulthood (Rosén and Lundborg, 2001; Lundborg et al., 2004; Lundborg and Rosén, 2007; Vordemvenne et al., 2007). This leads to a reduced quality of life and, often, a forced change of career (Chemnitz et al., 2015). These types of injury are common enough to not only present an appreciable cost to the individual but also to society more broadly (Rosberg et al., 2005; Thorsén et al., 2012). Direct costs of nerve repair, such as surgery and rehabilitation, only make up a comparatively small percentage, while the largest part of the costs (79-87%) are incurred due to lost production as a result of sick leave and forced change of career.

Functional impairments following peripheral nerve injury are multifaceted. They encompass hypersensitivity, cold intolerance, reduced tactile acuity, reduced shape and object recognition and difficulties handling small objects (Chemnitz et al., 2013). One of the hallmarks of impairments, however, is “faulty touch localisation” (Stopford, 1926; Hawkins, 1948). The latter manifests itself in a variety of symptoms. Patients often exhibit substantial localisation errors between the actual stimulus location and their

perceived point of touch, surpassing those observed in healthy controls (Hamburger, 1980; Braune and Schady, 1993). Sensations are frequently misreferred to different parts of the hand (Hamburger, 1980). In some instances, patients report feeling that a diffuse area of the hand has been touched, despite the application of a point stimulus (this is not clearly described in the literature, but has been reported by our patients). This is distinct from merely being uncertain where the stimulation occurred. Finally, patients may experience the perception of a single stimulation in two or more distinct hand regions (Hallin et al., 1981), a phenomenon sometimes referred to as 'ghosting' by certain authors. All of these atypical perceptual experiences remain confined to the territory serviced by the injured nerve (Hawkins, 1948).

Touch localisation can be assessed by stimulating the skin of a participant with a non-noxious point stimulus while they are prevented from seeing where they are touched. The participant then responds by indicating where they felt the stimulation by marking either their skin, a photograph or diagram, or by verbalising the area/location. Touch localisation has been studied scientifically since the second half of the 19th century (see Hamburger (1980) for a review of the early literature). Touch localisation ability differs between different parts of the body. In the upper limbs of humans, localisation accuracy consistently improves from the shoulder to the fingertips where touch localisation is usually accurate within a few millimetres (Hamburger, 1980).

Despite having first been reported at the end of the 19th century (Mitchell, 1895), the majority of studies on "faulty localisation" primarily comprise qualitative case studies. These studies, especially the earlier ones, often lack precise definitions of what counts as "faulty localisation" and a detailed description of their methods, limiting their ability to shed light on the exact nature of the impairment. For instance, Rivers and Head (1908) offer a detailed description of one longitudinal case study in which the radial nerve of one of the authors had been lesioned and repaired. While they do describe their method for measuring touch localisation in detail, their quantification of localisation errors is limited to stimuli that were strong enough to elicit responses from deep receptors (which had not been lesioned). Errors in the localisation of stimuli that only elicit responses from cutaneous receptors are only described in a few general qualitative remarks, such as that the affected territory is likely to refer sensations and

that this tendency is reduced over time as sensation improves generally. Stopford (1926) only remarks that the recovery of "accurate localization of a pressure stimulus" occurs later and less perfectly than touch and pain detection and (Seddon, 1943) remarks on the frequency with which patients refer touch to other digits. Hawkins (1948) highlights the importance of "faulty localization" (by which he means localisation errors of more than 5cm and referrals of touch to another digit) as a diagnostic tool for nerve recovery and shows by way of two case studies that apparently normal localisation ability can be used as a sign that nerve regeneration was not taking place. Yet despite this, he does not provide a detailed characterisation of this phenomenon.

More recently, Hamburger (1980) used a better-documented method to quantify touch localisation in healthy controls in a large amount of detail. Yet, he only presented two case studies of peripheral nerve repair patients. Both of his patients showed impaired touch localisation in their injured hand, but only one of them referred sensations between digits. While the method Hamburger used allows for quantification of localisation error, this was only done for controls but not for patients. Hallin et al. (1981) offered a detailed qualitative description of multiple percepts in the hand elicited by scraping the injured area. Apart from the expected scrapping sensation in the stimulated area, their patients described additional sensations in that area or in other areas of the hand. Some of the additional sensations were strong and could be reproduced when the same skin area was stimulated again while the position of the weaker sensations was more variable between repeated stimulations. But again, they do not provide any quantifications and do not comment on other aspects of localisation impairment.

The first quantitative study of localisation ability after peripheral nerve repair was done by Braune and Schady (1993). They discovered that touch localisation was generally impaired in the injured territory except for the fingertips where localisation error was similar to the uninjured side. This is surprising, not only because nerve regrowth has been shown to advance in proximal to distal direction, but also because they found touch detection (a prerequisite for localisation) was the worst in the fingertips. They did not report any misreferrals of stimulations.

A method that lends itself better to quantitative data analysis is the modified Marsh method, developed by (Jerosch-Herold, 1993; Jerosch-Herold et al., 2006). In this method, rather than identifying the location of the stimulus directly, participants need to identify which of 20 zones on the fingertips has been touched. This method has been shown to have high sensitivity to impairment, high external validity, and excellent test-retest and interrater reliability (Jerosch-Herold et al., 2006; Fonseca et al., 2018), and is especially well suited for the clinic because of its simplicity. Unfortunately, it uses a categorical, rather than continuous, measure of touch localisation which greatly reduces the richness of the data that can be collected.

These studies collectively underscore the importance of "faulty touch localisation" for better understanding impairments due to peripheral nerve injury. But a detailed quantitative assessment of touch localisation is still outstanding.

Hand nerve anatomy

There are four receptors for discriminative touch in the skin: Merkel cells, Ruffini organs, Meissner corpuscles and Pacinian corpuscles (Johansson and Vallbo, 1983). Based on their response properties, these receptors can be subdivided into slow adapting or SA (Merkel cells and Ruffini organs) and rapid adapting or RA (Meissner and Pacinian corpuscles) types. The information encoded by the receptors is transmitted by peripheral axons to the brain. Peripheral axons are enclosed by Schwann cells and an endoneural cell matrix (Brushart, 2011). The endoneural tubes are then bundled into fascicles by a perineural cell matrix which are in turn enclosed by a matrix of epineural cells that defines the actual nerve. There are three major hand nerves. The median nerve services the radial part of the palm as well as D1 through D3 and the radial part of D4. The ulnar nerve services the ulnar part of the palm as well as the ulnar part of D4 and D5. The radial nerve services the dorsal part of the hand (Brushart, 2011). Note that there is some variation between people regarding the exact boundaries of the territories serviced and a sub-set of the population also has communicating branches between the nerves (Unver Dogan et al., 2010).

Radial, median and ulnar nerves form a complicated network that transmits touch information first to the dorsal root ganglia of the spinal cord and then on via the cuneate nucleus and thalamus to the primary somatosensory cortex (S1) (Brushart, 2011). In S1, as well as along the entire transmission chain, the inputs are processed topographically (Hamburger, 1980; Brushart, 2011). That means that inputs from neighbouring receptors in the skin are generally processed in neighbouring subcortical/cortical areas.

In S1, the whole skin is represented in the form of a so-called homunculus. There are at least two independent homunculi within S1: one in BA3b and another one in neighbouring BA1 (Kaas et al., 1979). The size of the area devoted to each segment of the body does not reflect the relative sizes of the represented body parts, but rather their innervation density (Merzenich et al., 1987). Areas with high receptor densities, such as the hands and lips, have a larger area devoted to them; a fact sometimes known as cortical magnification. The subdivision of these areas is, however, much more fine-grained than in areas that represent body parts with lower receptor density. In the hand area of BA 3b digit representation is well structured with digits following a progression from the thumb positioned most laterally to the little finger most medially. Additionally, within each digit representation, receptive fields are ordered from the most distal receptors at the anterior tip of the representation to the most proximal receptors at the posterior end of the representation and this progression then continues through the palm to the wrist.

Nerve injury and cortical reorganisation

Peripheral nerve injuries are measured in five grades (Li et al., 2021). In the lowest two grades, the nerve fibre and myelin sheath or at least the endoneural tube is still intact. This means that there is a high chance of self-recovery from the injury. Chronic functional impairment is usually slight or not detectable. In the highest grade, the entire nerve, including the epineurium, is transected and nerve fibres undergo Wallerian degeneration. Surviving proximal nerve cells will regrow and attempt to again make connection with the receptor cells in the periphery (Brushart, 2011). But the regrowth process is not topographically guided. This means that a part of the nerve fibres will connect to other cells than the ones they had been connected to pre-injury. This

miswiring can result in axons connecting with new receptors that are located at a completely different part of the injured territory, e.g. on a different finger or the palm if the nerve fibre had previously connected to a digital receptor. As a consequence, the spatial structure will differ from the pre-injury state. Additionally, sprouting axons can not only make contact with other similar receptors within the injured territory, but also with receptors of a completely different modality or they can grow into the surrounding tissue developing into neuromas.

This makes it necessary that nerve lesions are repaired surgically to guide the regrowth process (Lundborg and Rosén, 2007). This is usually done by wrapping the nerve or parts of the nerve into some sort of conduit. The level at which the conduit is applied has an important influence on how much miswiring can take place. Conduits which surround the entire nerve fibre might be able to prevent neuromas, but cannot prevent connection errors within the nerve. The finer the organisational unit repaired during surgery, the higher the likelihood that long-range reinnervation errors can be avoided. Even with modern microsurgery techniques, however, the finest level of repair possible is a repair on an intra-fascicular level. That means that nerve fibres will still often regrow to a different receptor than the one they had been connected to pre-injury. So, structural changes in the periphery are currently unavoidable.

Use of the hand and object manipulation critically rely on discriminative touch and the information extracted from it. On this basis alone, it can be assumed that peripheral rewiring will lead to an impaired sense of touch. To make this concrete, let us consider a reinnervation error in which an axon that pre-injury had connected to the index finger now connects to the middle finger. That means that the former territory of the index finger is now activated when the middle finger is touched. In the simplest explanation, this would be the sole reason why touch localisation, and by extension higher level functional tasks, is impaired after nerve repair. That explanation ignores, however, the lifelong capacity of the brain to adapt its organisation. There is evidence for structural, molecular and functional changes following nerve injury and repair in S1 and, in fact, all along the pathway from the periphery to the cortex (Wall et al., 2002).

There is a large corpus of evidence, mainly from animal studies, to suggest that there are two separate cortical reorganisation processes at play. Injury-driven reorganisation needs to be separated from regeneration-driven reorganisation.

Injury-driven reorganisation

Directly after nerve lesion the cortical territory previously responsive to the injured nerve is often unresponsive to any input. We call this territory S1-deprived. Within hours to days after the deafferentation, however, most of the territory starts to become responsive to the same inputs as neighbouring cortical territories (Merzenich et al., 1983). Since the time course of these changes is too short for structural changes, such as sprouting of new axons, to occur this is generally regarded as an unmasking of latent inputs. This is also sometimes interpreted as an invasion or capturing of cortical area by neighbouring receptive fields. Initially, there is no well-defined topography and many parts of the deprived area are responsive to several different skin areas, but eventually, a new topography emerges. Albeit the new topography differs in layout and cortical magnification from the normal topography.

Calford and Tweedale (1988) report that, immediately after the amputation of D1 in flying foxes, cortical areas which had been responsive to D1 or to skin areas that crossed the amputation boundary now had receptive fields that stretched from the amputation boundary to the remaining metacarpals, wing arm or wrists. Within eight days post-amputation, however, the receptive field sizes reduced considerably and only stretched from the amputation boundary to a small part of the remaining hand.

Dynamic map changes are also reported by Merzenich et al. (1983) after lesion and ligation of the median nerve in monkeys. Initially, the part of the cortex previously responsive to stimulations of the injured nerve was unresponsive to any stimulation (a state they call a “black hole”). But within days the territory formerly devoted to the injured nerve became activated by neighbouring receptive fields. For the most part, they were activated by touch to the dorsal side of the digits of their pre-lesion receptive fields. Occasionally other hand territories and some face territory were also represented. Following these immediate changes, there is a prolonged dynamic period of cortical reorganisation that was followed in one monkey up to 144d post-lesion. While the area

unresponsive to any stimulation continuously shrinks, the position of this area changes as well. So that areas that had already been reactivated by neighbouring territory might become unresponsive and vice versa. There was initially a large degree of overlap between the skin regions, but with time boundaries became sharper until the degree of overlap was comparable to the one observed in normal hand maps.

Similar changes to hand maps have been reported after digit amputation in which the deprived territory becomes responsive to stimulations of the neighbouring digits (Merzenich et al., 1984) and after amputation of the complete hand in which the deprived territory became responsive to stimulations of the face and residual arm (Florence and Kaas, 1995; Florence et al., 2000).

It is worth noting that these changes do not necessarily happen continuously but might proceed in discreet phases instead. After deafferenting the sciatic nerve in the hind paw of rats, Cusick et al. (1990) found that there is an initial rapid expansion of the area activated by the saphenous nerve within the first one to three days after which the amount of area activated by that nerve remains constant for several months. It is only after seven to eight months that there is another expansion event after which almost all of the former sciatic territory now is responsive to the saphenous nerve.

The situation in humans is less clear. While there has been a large number of studies in the 1990s that attempted to address this question (see Wall et al. (2002) for an overview), electrophysiological measurements of digit maps are only possible under special circumstances in humans. Research in humans, therefore, generally relies on proxies of reorganisation.

Grüsser et al. (2001) is exemplary of this early research in amputees. They used the localisation of the initial EEG response to stimulation of the left and right lip and digits 1 and 5 on the intact hand to estimate cortical reorganisation. This method does not allow a map to be constructed, but it rather estimates the centre of the cortical response. The logic is that if the area of response shifts, so too should the centre of that response. Since it was not possible to stimulate the missing hand, the loci of digits 1 and 5 of the intact hand were mirrored to S1-deprived under the assumption that they should be located in roughly similar positions in both hemispheres. The measure for

reorganisation was then the Euclidian distance between the lip locus and digit loci in S1-healthy and S1-deprived. Using this method, the authors found that for patients with phantom limb pain, the distance in S1-deprived was substantially shorter than in S1-healthy and that the amount of shift was positively correlated with pain intensity. This was then taken as evidence for cortical reorganisation and that this reorganisation is maladaptive.

More recent studies have used fMRI to assess cortical digit maps more directly and the findings not only are inconsistent with previous studies in humans, but also our understanding from animal models. Kikkert et al. (2016) employed movement of the intact and the phantom hand of amputees to elicit cortical responses of two amputees. They discovered digit maps that qualitatively follow a normal sequence. They also calculated what is known as representational distances between each digit- pair. Representational distances are a multivariate measure of how similar or dissimilar the entire pattern of positive- and negative-going activation between two conditions is in abstract feature space; in this case, each digit is one condition (Ejaz et al., 2015). In controls, the pattern of representational distances closely corresponds to a canonical pattern with only small variations between individuals (Ejaz et al., 2015). The degree of correlation between an individual's pattern and the canonical template is known as typicality. The analysis by Kikkert et al. (2016) showed that although representational distances between the digits were reduced for the phantom hand, the typicality of their pattern was similar to controls. A result that was also reported by Wesselink et al. (2019), who could additionally show that for congenital one-handers, in contrast, both mean representational distances and the typicality of these distances are reduced significantly. These results indicate that in contrast to animals, the hand map is preserved in humans after permanent deafferentation. This would mean that the effect of injury-driven reorganisation is much smaller in humans than in other animals.

Another line of evidence that reorganisation is not as dramatic in humans comes from peripheral or cortical microstimulation studies. Schady et al. (1994) used micro-neurography to stimulate the deprived nerve of five patients with digital amputations. While two of them could only feel the stimulations on their stump, the rest felt it on the stump as well as (partially) up their phantom digit. Strauss et al. (2019) tested four

patients who had undergone an amputation of their entire hand with micro-electrodes implanted into their upper arm. All of the patients were able to feel some sensation in the respective part of their phantom hand when the median and ulnar nerves were stimulated. While the exact sensations elicited were highly variable between participants, only stimulations above the perceptual threshold elicited an EEG response. Finally, Flesher et al. (2016) implanted a micro-electrode array into BA1 of a single tetraplegia patient. They found that all stimulations elicited touch sensation in the proximal phalange of D2 - D3 and adjacent distal palm regions. Most electrodes only elicited responses in a single identifiable skin region, while a smaller part caused the sensation of touch in larger continuous or (in one case) discontinuous areas. Moreover, when the electrodes were coupled to touch sensors in a hand prosthesis that were stimulated by an experimenter, the patient was able to correctly identify approx. 84% of stimuli, even without any training.

These results indicate that different methods of measuring reorganisation can lead to different results. So, it is important to closely match the measures between different studies if inferences are to be drawn across species.

Regeneration-driven reorganisation

The most detailed study of regeneration-driven cortical reorganisation was done by Wall et al. (1986) who studied the time course after surgical transection and immediate repair of the median nerve in four owl monkeys up to 322 days post repair. Before regrowth of the nerve, they observed a black hole in S1 - cortical territory that was completely unresponsive to any peripheral stimulation - that was progressively and dynamically activated by neighbouring territories, similar to Merzenich et al. (1984). As the nerve regrew, patches of the median territory started to be represented in S1-deprived again. First in small, isolated patches that then grew in extent at the expense of the areas that had become responsive to adjacent skin territories until S1-deprived had largely become responsive to only the median nerve again. There were, however, still patches that activated for touch to both the median and adjacent territories. The size of these patches did not vary much with time. Additionally, the pattern of the re-established median map was abnormal. Skin regions were represented in inappropriate

locations, non-adjacent skin regions showed extensive overlap and adjacent skin regions were represented in separate and discontinuous cortical regions. Overall, however, the representation of the skin was still discrete, not diffuse as could be assumed from the fact that nerve regrowth is unguided, and many sites were only responsive to a single receptive field. Additionally, at least some receptive fields were in their appropriate cortical location.

In contrast to nerve injury-driven changes, the number of studies that look at generation-driven changes in humans is much smaller. There are only seven studies we are aware of that have addressed the question using fMRI (see Table 2). The majority of these only look at changes to overall positive activity in S1-deprived, either in terms of activation area, peak voxel or percent blood oxygenation level dependent (BOLD) signal change (%-BSC). They do not measure the location of digit representations within the cortex (also known as digitopy).

Taylor et al. (2009) compared the brain activity of 14 median nerve patients with that of controls and found increased activity within BA3 and 1, but reduced activity in BA2 and S2. Rath et al. (2011) reported a case study of a single participant in which the ratio of the peak voxels of S1-deprived to S1-healthy increased from 0 to 0.72 within the first 12 months post-repair. Rosén et al. (2012) looked at four median patients and found that stimulation of the injured hand led to a larger activation volume contralaterally and ipsilaterally than stimulation of the uninjured hand for both median and ulnar stimulation. This effect was more pronounced for the contralateral side when the median nerve was stimulated, leading to a larger lateralisation, while for stimulation of the ulnar nerve, the lateralisation was reduced. This contrasts with Fornander et al. (2016) who found for another sample of four median patients that lateralisation for the stimulation of the median nerve was reduced. They did agree with Rosén et al. (2012), however, in reporting cortical activity relative to rest was less negative in S1-healthy for stimulations of the injured hand. Increased activity in S1-deprived and S1-healthy was also reported by Chemnitz et al. (2015), Björkman and Weibull (2018) and Nordmark and Johansson (2020) for 15 patients, 18 patients (15 of which were identical to Chemnitz et al. (2015)) and 11 patients respectively.

Similar to injury-driven changes, the percept to peripheral microstimulation has also been studied in peripheral nerve repair. Schady et al. (1994) stimulated eight patients with nerve repair to the median and/or ulnar nerve at the forearm or wrist. They applied the stimulation above the elbow and found that, just as in healthy controls, their stimulations always elicited percepts in the projection territory of a single fascicle or of two adjacent fascicles plus the adjoining interdigit webspace between them. The projection territory was qualitatively similar to that expected from healthy controls. The same stimulation paradigm was also employed in a longitudinal study of ten patients by Moore (2000) with similar results. Moore and Schady additionally commented that there was little overlap between the projection territory of fascicles servicing the injured and the uninjured parts of the hand. What little overlap there was could be explained by localisation errors similar in magnitude to what might be expected in healthy controls. They did find that the projection territory of a fascicle would occasionally break up, that is there were portions within that territory in which the patient did not feel any percept. But these gaps were much smaller than the projection territory and the overall shape of the projection territory still followed the pattern expected from healthy controls. Moore and Schady tested nine of their ten patients on two or three occasions up to 61 weeks post-injury and could not find any qualitative changes to the elicited percepts.

These studies show that there is a strong precedence from animal literature to expect changes to the hand maps to occur after peripheral nerve repair. There are clear predictions about what changes to expect, but the evidence in humans is scant and contradictory.

Functional impact of cortical reorganisation

Despite this, the connection between central changes and functional impairment has been made even before the nature of cortical organisation was known. Stopford (1926) argued the fact that coarse pain, heat and cold sensation return earlier than fine tactile and temperature sensitivity point towards central factors in the recovery process. This is because all types of sensory fibres seem to regrow at similar rates and exposure

to cold at later stages of the recovery can result in a temporary loss of finer sensations, but not of coarse sensations.

Wall et al. (1986) made a strong case that cortical reorganisation in S1 might be the central factor that determines the impairment of touch localisation. Both cortical reorganisation and functional impairment are limited to the territory serviced by the repaired nerve. Re-established cortical digit representations are partially in their own old territory, partially in the former territory of other digits while multiple simultaneous percepts to touch in different parts of the injured hand area are often observed. And both cortical reorganisation and faulty touch localisation are highly idiosyncratic. This might still be the case if cortical reorganisation only reflects peripheral regrowth errors. But the authors showed that the re-established functional structure in areas 3b and 1 are markedly differed from one another, even though they were comparable before the nerve had been sectioned. A fact incompatible with the assumption that organisation is entirely driven by peripheral connections. Despite this, the degree to which cortical reorganisation predicts functional impairment is currently unknown.

In contrast to this are the studies that use intra-neural microstimulations (Schady et al., 1994; Moore, 2000). These studies showed that direct nerve stimulations still elicited a percept that was qualitatively similar to that of healthy controls. This led Moore (2000) to speculate that the cortical changes observed in monkeys are not actually functionally significant, but instead merely reflect peripheral reinnervation errors.

As mentioned above, the majority of studies that report impaired touch localisation do so only in a qualitative way. Those that use quantitative methods do not measure reorganisation. Braune and Schady (1993), for instance, found touch localisation to be impaired on the proximal pad and the palm but not at the fingertips. They speculated that due to the functional importance of the fingertips, the brain reorganises to extract the maximum amount of information from this part of the hand specifically. This would point towards adaptive cortical plasticity, but no similar finding has been reported in any other study. Indeed, Jerosch-Herold et al. (2006) only tested the fingertips using a categorical measure of touch localisation and found a clear

impairment of the digits within the injured territory. And while only qualitative, both Hamburger (1980) and Hallin et al. (1981) show clear impairment of their patients on the fingertips.

There are only a handful of studies that measure functional impairment and structural or functional reorganisation, either in the cortex or in the periphery, in the same patients. Hallin et al. (1981) mapped the occurrence of multiple percepts in peripheral nerve repair patients and also mapped the receptive fields of peripheral afferents. They showed multiple percepts in the territory of the injured nerve and also found that multiple unit recordings of neighbouring nerve fibres displayed a patchy distribution of the combined receptive field. But they do not attempt to explicitly link one to the other. It remains unclear, for instance, whether the area in which the additional percepts can be felt overlaps with the patchy receptive field of the corresponding bundle of nerve fibres.

So far, only three studies have looked at the relationship between cortical reorganisation and functional recovery. Rath et al. (2011) presented a case study of a single individual whose mechanical detection thresholds gradually improved from 0% to 66% of normal performance within 12 months. Simultaneously, the ratio between the peak voxels in S1-deprived and S1-healthy in response to vibrotactile stimulation increased from 0 to 0.72 in the same period. Since they use detection threshold, however, and since they did not reconstruct digit topography, it is likely that their result simply reflects the gradual reactivation of S1-deprived as the sensory afferents regrew. Taylor et al. (2009) tested mechanical detection thresholds with von Frey filaments and vibrotactile stimulators. They found overlapping areas of reduced BOLD activity and cortical thinning in S1 and S2 and noted that cortical thickness was negatively correlated with vibration detection thresholds. But again, the measures of functional impairment were only detection thresholds, and no digit topography was reconstructed. Furthermore, Taylor et al do not report whether there was also a correlation between detection thresholds and BOLD activity.

In contrast to the previous two studies, Chemnitz et al. (2015) used the Rosen score as their measure of functional impairment. The Rosen score is a standardised clinical

tool that measures mechanical thresholds to stimulation with Semmes-Weinstein monofilaments, tactile acuity in the form of the two-point discrimination test as well as shape and texture identification and small object manipulation in the form of a reduced Sollerman hand function test (Rosén and Lundborg, 2000). Chemnitz et al. (2015) found a negative correlation between the volume of activation and functional recovery. Again, digit topography was not reconstructed and, while the measure of functional impairment includes higher level function, touch localisation was not assessed.

While Wall et al. (1986) has made a strong proposal for how cortical reorganisation and impaired touch localisation could be related, this has never been tested directly. Evidence for a connection between reorganisation and touch localisation remains speculative and whether reorganisation even has any functional implications remains uncertain.

Aims and structure of this thesis

The extent and nature of cortical reorganization following peripheral nerve injury in humans remains unclear. While animal studies reveal dynamic map changes in the primary somatosensory cortex after nerve lesions, human data paint a more ambiguous picture. Non-invasive imaging has yielded inconsistent results, with some studies finding evidence of reorganization resembling animal models, while others report preserved somatotopic maps. Studies in peripheral nerve repair patients have so far relied on coarse proxies of reorganisation rather than directly measuring digit topography.

Furthermore, our understanding of the functional consequences of cortical changes is limited and it is unclear whether cortical reorganisation even has functional implications. While impaired touch localisation has been recognised as a hallmark of nerve repair for over a hundred years, most studies only represent case studies with poorly documented methods. Even those studies which report quantitative statistics, only manage to capture a small portion of the multifaceted phenomenon of touch localisation. Moreover, there are currently no studies which directly link touch localisation to cortical reorganisation.

Therefore, this thesis aims to: 1) provide a more comprehensive characterisation of touch localisation impairments after nerve injury using more rigorous and quantitative methods, 2) assess whether there is evidence for changes to the fine-grained digit topography in humans similar to what has been reported by Wall et al. (1986), 3) relate cortical reorganisation to touch localisation impairment within the same patients.

In the second chapter, we introduce a novel instrument to measure touch localisation and use it to characterise the impairments of nerve repair patients compared to controls. This chapter has already been published (Weber et al., 2023). There have been small adjustments to the layout to make it fit the layout of the thesis (this includes the presentation of the statistical results). In addition, the section "Limitations" has been expanded on request by the examiners.

The third chapter reports the results of the fMRI experiment and links reorganisation to touch localisation impairment.

Finally, the fourth chapter synthesises results from the preceding two chapters and discusses their impact in the context of the wider literature.

Touch localisation after nerve repair: Insights from a new measurement tool

Martin Weber[1], Andrew Marshall[2], Ronan Timircan[1], Francis McGlone[2], Simon Watt[1], Obi Onyekwelu[3], Louise Booth[4], Edwin Jesudason[4], Vivien Lees[5,6], and Kenneth F. Valyear[1]

[1] School of Human and Behavioural Sciences, Bangor University, Bangor, UK

[2] University of Liverpool, Liverpool, UK

[3] Portsmouth Hospitals University NHS Trust, Cosham, UK

[4] Betsi Cadwaladr University Health Board, Bangor, UK

[5] University of Manchester, Manchester, UK

[6] Manchester University Foundation Hospitals Trust, Manchester, UK

Introduction

Injuries to the nerves of the hand are common and have significant longstanding consequences. When a nerve is cut in adulthood, complete recovery is not expected. Sensory and motor impairments, and often pain, persist indefinitely (Lundborg and Rosen, 2001, 2007; Chemnitz et al., 2013). A major challenge, thought to limit recovery, is that nerve regeneration following surgical repair is not topographically guided (Lundborg et al., 1994; Puigdellivol-Sanchez et al., 2005; Witzel et al., 2005; Brushart, 2011). Sprouting fibres establish new connections, innervating end receptors at different locations relative to the pre-injury organisation. These rewiring events, known as targeting or reinnervation errors, are difficult to measure directly in humans; yet one accepted proxy is the presence and character of aberrant touch localisation. In this study, we develop an improved method for measuring touch localisation on the hand and evaluate its value for use in nerve injury.

The classic literature on peripheral nerve injury is richly populated with accounts of aberrant touch localisation. At the turn of the 20th century, several independent investigators voluntarily had their own nerves cut and sutured for the purpose of experimentation (Rivers and Head, 1908; Trotter and Davies, 1909; Boring, 1916). Self-observation featured both introspective and objective measures, and aberrant touch localisation was extensively reported. Early clinical observations of aberrant touch localisation were also extensively documented (Stopford, 1926; Seddon, 1943), and in a cogent report featuring selected patient cases, Hawkins (1948) highlights the clinical significance of aberrant touch localisation as a positive marker of nerve regeneration success after nerve repairs. It was said that "[aberrant localisation] can always be elicited when sensory regeneration of a sutured nerve has occurred." Without quantitative group results based on rigorous statistical methods, however, what can be understood from the classic literature is limited.

An elegant method for quantifying touch localisation on the hand was introduced by Noordenbos (1972), and further developed by his student Hamburger (1980). In this approach, which we call the 'red-lens method', participants wear a set of glasses with red lenses. While blocked from the participant's view, the experimenter uses a pen to

mark the hand. The marks serve as targets for touch stimulation, visible to the experimenter yet invisible to the participant when viewed through the red lenses. Following stimulation of a given target, the participant reports where they felt they were touched using a different coloured pen, making their own mark on the hand. Measurement of the distance between stimulated and felt locations can be taken, directly, in continuous units. This measurement is known as the error of localisation.

Hamburger used this method to characterise touch localisation in healthy controls, revealing, for example, a distal-proximal gradient in the error of localisation, with the distal fingertips outperforming the middle and proximal pads of the digits and the palm (Hamburger, 1980). Original clinical applications were limited, however. Four patient case studies were provided—two with hand-nerve injuries and two with brain injuries—and the results were purely descriptive. No quantitative comparisons were made.

The first quantitative applications of the red-lens method to clinical populations were made by Braune & Schady (1993). Eleven patients with complete median/ulnar nerve transection injuries were tested. The findings revealed increased error of localisation for responses within the territory of the injured nerve compared to homologous locations on the uninjured hand. Surprisingly, impairments were restricted to the middle and proximal digit pads; touch localisation at the distal digit pads was no different between injured and uninjured sides. This result conflicts with expectations based on peripheral regrowth, where reinnervation takes longer to complete at more distal sites from the repair, and was attributed to central factors.

A variation of the red-lens method was used to measure touch localisation after major hand reconstruction (Philip et al., 2022). Three patients who had undergone complete hand replantation and two hand transplant recipients were tested. Error of localisation was increased for the repaired hand, and longitudinal tests (taken only in the transplant patients) showed marked improvements over time. Conclusions from this study are limited, however, as statistical comparisons are based on a small sample of patients, heterogeneous along various dimensions known to impact functional recovery.

The red-lens method has significant limitations, however. First, it is difficult to take repeated measures from the same targets. Each new measurement requires clearing the marks from prior responses. Accordingly, much of the original results of Hamburger (1980) are based on single measurements. This makes it necessary to average across targets for statistical analyses, limiting spatial resolution. Second, it can be difficult to acquire accurate and precise measurements without the experimenter touching the participant's skin. Contact with the skin will provide additional cues, and, thus, is to be avoided. Yet, to do so, the measurement instrument (e.g., calliper) must be held away from the skin surface, limiting accuracy and precision, and, possibly, measurement consistency. Otherwise, if measurements are performed after testing is complete, tracking which responses belong to which targets is challenging. With numerous targets and/or multiple responses per target, this would be difficult to achieve. Finally, although not necessarily a limitation, participants touch their skin to record responses. This provides an opportunity to compare felt stimulation against felt (and viewed) responses, which may improve future performance. The method we develop in the current study addresses these limitations.

Other research has used an 'area of localisation' method to evaluate touch localisation in hand-nerve injury. In the modified-Marsh method developed by Christina Jerosch-Herold (Jerosch-Herold, 1993, 2003, 2005; Jerosch-Herold et al., 2006; see also, original work by Marsh, 1990), the distal pads of the digits are divided into quadrants, comprising 20 zones. Touch is applied to each zone, and the participant verbally reports which zone they felt was touched (while viewing a diagram of a hand with the zones labelled). Performance is measured as a score: 2 points for the correct zone; 1 point for an adjacent zone; 1 point for the homologous zone of a neighbouring digit; 0 points for other responses. Applied to patients with hand-nerve injuries, the modified-Marsh method shows high sensitivity to impairment, high external validity, and excellent test-retest and inter-rater reliability (Jerosch-Herold, 1993, 2003, 2005; Jerosch-Herold et al., 2006; Fonseca et al., 2018). The test is standardised and simple to administer, and the materials are affordable and easily portable: test properties of high value for clinical research and assessment.

The modified-Marsh method also has significant limitations, however. The error of localisation is not measured. Performance scores reflect arbitrary units averaged across zones, and spatial resolution is ultimately limited by zone size. Errors that span between digits, which we call misreferrals (see Methods, page 30ff), are scored but not otherwise distinguished. To better understand the nature of localisation deficits in nerve injury, such as their potential relationship with reinnervation errors, we believe it will be necessary to capture more detailed features, including absolute and directional error of localisation and misreferrals. The method developed in the current study enables rigorous quantification of these features.

The purpose of this study was to develop an improved method of measuring touch localisation and evaluate its value for use in nerve injury. Addressing the significant methodological limitations described above, our method enables detailed quantification of the error of localisation, multiple measurements from the same skin locations in a repeatable and efficient manner, and eliminates the need to measure error directly from the participant's hand. Also, participant responses do not involve touching the hand, making our assessment of touch localisation unconfounded by the possible influence of response feedback.

We use our new method to evaluate touch localisation in eighteen individuals with transection injuries to either the ulnar or median nerves, or both. Thirty-three healthy controls are tested for comparison. The method generates a rich profile of information at the level of individual participants, and across different parts of the hand. Our findings provide a more comprehensive evaluation of touch localisation in nerve injury than previously available, revealing significant increases in the error of localisation within the projection territory of the repaired nerve(s).

Methods

Participants

Patients. Eighteen patients completed testing (age range: 21—75 years; mean age: 38.3 years; seven female). Most patients had complete transection injuries: eight ulnar, two median, and five ulnar and median ('both'). The remaining three patients had incomplete transection injuries of the median nerve. All patients underwent surgical repairs within 24 hours of injury. One patient's injury, a partial median transection, was due to self-harm. This patient was deemed mentally stable when tested. All other injuries were of traumatic origin.

All patients had sustained their injuries in adulthood (mean: 34.8 years; median: 33 years; range: 17—68 years). Time-since-repair (and when tested) ranged from 8 to 130 months (mean: 42.3 months; median: 34 months). Two patients were left-handed according to the modified version of the Waterloo Handedness Inventory (Steenhuis and Bryden, 1989; scores range from -30 to +30). Seven patients had injured their dominant hand. See Table 1 for complete demographic details.

Healthy controls. Thirty-three control participants completed testing (age range: 19—63 years; mean age: 31.9 years; 13 female). Two participants were left-handed.

All participants gave informed consent before taking part in the study. Procedures were approved by the Bangor University School of Human and Behavioural Sciences Ethics Board and by the NHS Ethics Committee Wales Rec 5. Patients and 28 healthy controls completed the reported tests as part of a larger study, also involving functional MRI. These data will be reported elsewhere. The tests reported here took approximately 90 minutes to complete. Participants received financial compensation.

Table 1. Patient demographics and standardised test scores.

Subject	*Demographics*						*Standardised Tests*				
	Sex	WS	Age	MSR	Side	Nerve	DASH	McGill	Rosen	Marsh	
										Inj.	Uninj.
P1	F	28	29	19	L	M	29	47	0.15	--	--
P2	M	30	32	10	L	U	21	31	0.23	--	--
P3	M	30	51	60	R	U	66	25	0.51	63	92
P4	F	30	26	37	R	M+U	53	41	0.13	96	63
P5	F	-8	23	62	R	U	4	25	0.90	100	96
P6	F	30	39	26	L	U	10	27	0.58	100	96
P7	M	15	68	75	R	U	33	54	0.90	71	92
P8	M	30	41	82	R	M+U	22	44	0.28	--	--
P9	F	29	37	11	L	M	18	29	0.26	73	68
P10	F	30	24	8	L	M+U	28	52	0.00	--	--
P11	M	30	31	28	L	M+U	26	47	0.18	--	--
P12	M	30	41	18	R	M+U	15	34	0.14	65	98
P13	M	30	45	30	L	M (part.)	21	69	0.60	70	75
P14	M	22	34	31	R	M (part.)	3	25	0.94	96	89
P15	F	27	21	45	R	U	8	28	0.23	83	100
P16	M	30	39	49	L	M (part.)	0	21	0.91	91	88
P17	M	-30	75	130	R	U	9	11	0.25	50	83
P18	M	3	34	40	L	U	23	36	0.29	92	88

F = female, M = male; WS = Waterloo score (-30 to 30; neg. values = left handedness, pos. values = right handedness); MSR = months since repair; L = left, R = right; M = median, U = ulnar, part. = partial injury; Inj. = injured hand, Uninj. = uninjured hand.

Locognosia: Digital Photograph Method

Setup and materials

Participants were seated at a table in a well-lit room. On the table, there was a wooden blinder box with a small hole, through which the participants put their arm through with the palm of the hand facing up (Fig. 1A). Wrist and hand cushions were provided for comfort. The box was open on the other side to allow the experimenter to deliver the stimuli. A Logitech C270 webcam and switchable UV lights were mounted to the ceiling of the box. A monitor and mouse were placed at the side of the participant's body that was currently not being tested—the 'participant monitor'. The monitor displayed a picture of the participant's hand, and the mouse was used to register responses (see 2.2.2 Procedure, below). A second monitor, the 'experimenter monitor', faced the experimenter and was positioned so that participants could not see what was displayed.

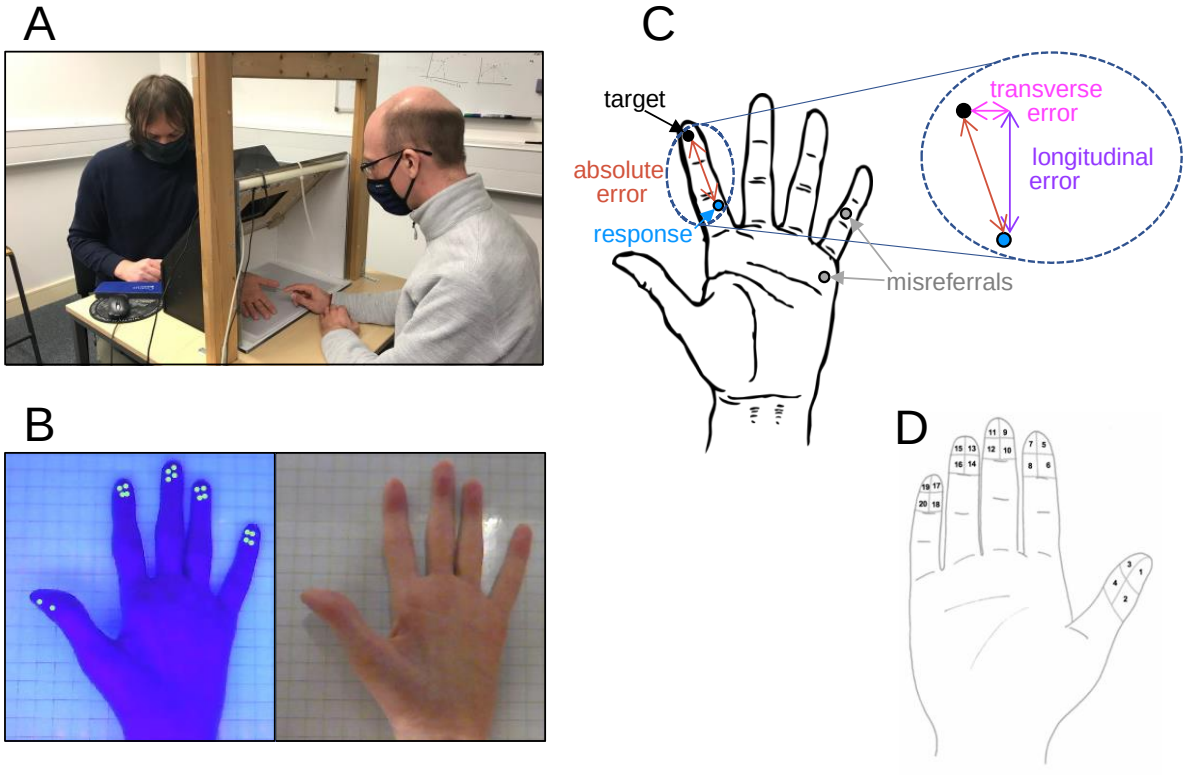

Figure 1. Locognosia methods. A: Position of experimenter (right) and participant (left) during the Digital Photograph method. The blinder box can be seen in the centre. **B:** UV-light image (left) that was used by the experimenter to register the targets and a normal light image (right) on which the participant registered their response. **C:** Target is the location where the experimenter applies the touch stimulus. Response is where the participant indicates where they felt they were touched. The absolute localisation error is computed as the Euclidian distance between target and response. The absolute error can be decomposed into a longitudinal component (along the axis of the finger) and a transverse component (perpendicular to the axis of the finger). Note, the inset does not accurately depict longitudinal/transverse components but is shown for conceptual visualisation purposes only. Responses made to another digit or to the palm are defined as misreferrals. **D:** Right-hand diagram used for the modified Marsh method (image taken from Jerosch-Herold et al., 2006). A corresponding left-hand diagram was provided when the left hand was tested.

Stimuli were delivered manually by the experimenter using a 6.1 Semmes-Weinstein monofilament with a peak force of 100gf. This level of force was suprathreshold for all locations for 17/18 patients and for all healthy controls. The remaining patient reported difficulty feeling the 6.1 filament and was tested using the 6.65 Semmes-Weinstein monofilament with a peak force of 360gf. This patient had a median nerve injury, tested at 19 months since repair.

A custom-written Visual Basic programme was used to control the experiment.

Procedure

The participant placed their hand through the blinder box. The experimenter marked 18 points on the volar surface of the participant's hand using a UV pen. Four points were made on the distal-pad of each finger in an arrangement divided into relative ulnar/radial-distal/proximal positions (Fig. 1B), matching the target 'zones' of the modified Marsh method (Fig. 1D; see page 32). Two points were marked on the radial side of the distal pad of the thumb. The ulnar side of the thumb was untested due to technical challenges (see below). This differs from the modified Marsh method and represents a limitation of the digital photograph method.

After the targets were marked, the participant was asked to open and flatten their hand against the base of the apparatus while two photographs were taken in succession (1 second apart), one with and one without UV lighting (Fig. 1B). It is important to appreciate that during testing participants assumed a relaxed posture, described below. Flattening the hand was only required for the brief few seconds for which the photographs were taken. The experimenter used the photograph with UV lighting to register the x- and y-coordinates of each target. This was done using a mouse to manually indicate the centre of each UV mark. The photograph with UV lighting was displayed on the 'experimenter monitor', visible only to the experimenter.

After target registration was complete, the photograph of the hand with normal lighting (and targets invisible) was displayed to the participant. This image was oriented such that participants would see their hand as it was positioned within the blinder box from their own perspective, with the fingertips pointing upwards, and was made visible to participants throughout the experiment. Each target was then stimulated in turn by the experimenter. To know which target to stimulate on a trial-by-trial basis, a normal-light image of the participant's hand was displayed on the experimenter monitor indicating the location of a target with a dot and its corresponding target number. This image was oriented so to align with the experimenter's view of the participant's real hand, with the fingers pointing downwards.

Stimulation was delivered for approximately one second, and accompanied by a verbal cue "now", from the experimenter. Participants then used a computer mouse to indicate the felt position of each stimulation on the photograph of their hand with normal lighting. After each response was indicated, a pop-up window appeared in the centre of the screen that asked participants to confirm their choice. This allowed participants to correct their choice in case they accidentally missed the location they wanted to click. Confirmed responses registered the x- and y-coordinates of the cursor. Participants were instructed to keep their hand still during stimulation, and to avoid moving between stimulation and choosing their response. Moving the fingers after stimulation can improve localisation performance (Hamburger, 1980). Participants were asked to find a comfortable posture, with the hand open yet relaxed. Supporting cushions were provided, as needed. It was not necessary to flatten the hand against the base of the apparatus during testing, as for the photograph. Sometimes participants had to be asked to reopen the hand during testing, if the fingers were curled inwards such that access to targets with the monofilament was difficult. No feedback regarding performance was given to the participant during the experiment.

Before collecting any responses, the experimenter applied stimulation to two or three different targets so that the participant could experience how a trial felt. After these initial trials, the testing began. The complete test comprised five blocks of 18 trials, per hand. In each block, all 18 possible target locations were stimulated, and target order was randomised within blocks. Participants were not told that all targets would be stimulated once per block. Rest breaks were permitted throughout testing, and encouraged between blocks. Some participants found it fatiguing to keep their hand in an appropriate posture, and thus took more breaks. Participants were allowed to take their hand out of the blinder box during breaks, but were asked not to study their hand closely. For each hand, the test took approximately 20min to complete.

Both hands were tested. For patients, the injured hand was always tested first. This was done to prioritise measurement of the injured hand, in the event that a patient decided to discontinue testing. This did not occur. For healthy controls, hand order was counterbalanced between participants. Among the other tests reported here, see below,

the digital-photograph method was always completed first (aside from the control task, see next).

Control task

A short control task was implemented to begin the experiment. This control task involved participants using a computer mouse to indicate the position of 12 visible dots on a photograph of a lettered six-by-two grid. The dots were labelled with letters A-through-H. The experimenter asked the participant to click the dot corresponding to each letter in succession, presented in a random order. The setup was identical to the main task, using the same monitor and mouse positioning. This control task was done to evaluate whether participants had difficulties controlling the mouse. The task was done for each hand. Error of localisation (as calculated below) was negligible for all participants. Performance on the main task could therefore not be attributable to movement difficulties.

Dependent measures

Absolute error. The differences between x- and y-coordinates of each target-response pair were first computed in pixels, and then converted to millimetres. The conversion from pixels to millimetres was done using conversion factors defined separately for x- and y-dimensions. The conversion factors were derived by measuring known distances in the picture, based on the background grid, using ImageJ version 1.53k. Specifically, the experimenter used a mouse to manually indicate points in the grid, separately for x- and y-dimensions, and the corresponding pixels-to-mm conversions were computed. Absolute error was then calculated as the Euclidian distance between target-response pairs using x- and y-error in millimetres.

$$E_{absolute} = \sqrt{E_x^2 + E_y^2}$$

Absolute error is otherwise known as the error of localisation.

Directional error. We were also interested in examining directional error, preserving the constituent directionality of the error of localisation. This way, we can evaluate evidence of bias—systematic directionality in responses to stimulation of a

given digit. The longitudinal error is defined in the proximal-distal axis along the length of a digit, and the transverse error is defined in the ulnar-radial axis along the width of a digit. To calculate each, an angle per digit was defined in the photograph of each hand, using ImageJ. The angle was measured with reference to the lower edge of the image and an extended line drawn by the experimenter through the midline of the digit being measured. The longitudinal and transverse error were then calculated as follows:

$$E_{longitudinal} = E_x \times \sin(\theta_{digit}) + E_y \times \cos(\theta_{digit})$$

$$E_{transverse} = E_x \times \cos(\theta_{digit}) + E_y \times \sin(\theta_{digit})$$

Misreferrals. Trials where responses were made to an incorrect digit, or to the palm of the hand were defined as misreferrals. To identify misreferrals, responses were displayed on the image of the hand, colour coded according to which digit had been stimulated (using R). The experimenter then visually identified misreferrals as those responses that were made on an incorrect digit, or the palm. Responses made over the permanent crease separating digits and the palm were counted as belonging to the corresponding digit. Those below the crease were defined as misreferrals to the palm.

Absolute and directional error, described above, were computed excluding misreferrals. This was done since interpretation of error in the case of misreferrals is problematic. In the case of misreferrals, it is unclear how error should be defined, using a straight line between targets and responses, or the shortest path along the skin's surface, for example. Further, the magnitude of the error in the case of digit-to-digit misreferrals would depend on relative digit position—i.e., whether the digits were together or apart. As such, misreferrals were analysed separately.

Analyses

Absolute error. To evaluate impairment, target locations on the injured hand of patients were defined as either within or outside the territory of the injured nerve. Targets within the territory of the injured nerve comprised the 'Inj' condition. For isolated median nerve injuries, Inj targets comprised all locations on digits D1-to-D4 (14 targets). For isolated ulnar nerve injuries, Inj targets comprised all locations on digits

D4-to-D5 (8 targets). For patients with injuries to both median and ulnar nerves, all targets on the injured hand were defined as Inj targets.

Canonically, the division between median and ulnar nerve territories runs through the middle of D4, so radial targets on D4 are within the median nerve territory while ulnar targets are within the ulnar nerve territory. There is overlap through communicating branches, however, and the precise anatomy varies between individuals (Sunderland, 1978; Unver Dogan et al., 2010; Di Stefano et al., 2021). Thus, we defined all D4 targets as within the Inj condition for both median and ulnar nerve patients, as noted above. If anything, this may underestimate impairment, since we may be including within the Inj condition target locations that are serviced by an intact median/ulnar nerve, accordingly.

For comparison, the homologous target locations on the uninjured hand were defined as the 'Uninj' condition. All statistical comparisons between Inj and Uninj conditions were made using paired t-tests. In the case of violations of normality, the Wilcoxon matched-pairs-signed-rank test was used. Normality was tested using the Shapiro-Wilk test.

Since the patient group comprised a mixture of isolated median, isolated ulnar, and both ulnar and median nerve injuries, we needed to organise our data from healthy controls so that fair comparisons between patients and controls could be made. Otherwise, group comparisons would involve estimates of error from different combinations of digits. As such, the controls' data were formulated to 'match' the patient group based on the proportions of patients with median/ulnar/both nerve injuries. Specifically, five patients had isolated median nerve injuries (~28% of the group); thus, nine controls were treated as median-nerve-injured (~27% of the control group). This meant that the data from these nine controls comprised responses from all targets on digits D1-to-D4 (14 targets), matching the median nerve patients. In the same fashion, eight patients had isolated ulnar nerve injuries (~44%), and so, 15 controls were assigned to match these patients (~45% of the control group). Their data comprised all targets on D4 and D5 (eight targets), matching the ulnar patients. The remaining proportion of controls were matched against the patients with both median and ulnar

nerve injuries. Their data were taken from all targets. The assignment of controls to patient subgroups was otherwise random. Once this matched control group was defined, a paired-samples t-test was used to evaluate whether there were differences between the dominant and non-dominant hands. If no differences were observed, the controls data were averaged across hands.

All statistical comparisons of the absolute error of localisation between patients and controls were made using unpaired t-tests. If the variances between groups were unbalanced, a Welch's correction was applied. If the residuals of the initial tests were not normally distributed, as measured using Shapiro-Wilk, non-parametric Mann-Whitney tests were used.

Directional error. To evaluate whether the longitudinal or transverse components of the error of localisation showed any systematic biases, one-sample t-tests were performed (against zero). This was done separately for digits two and five, and per patient and control groups, as part of our digit-specific analyses. The critical p-values were corrected for multiple comparisons using Bonferroni corrections.

Misreferrals. Misreferrals were identified as described above. Although typically few misreferrals per individual were observed, and for some participants no misreferrals were made, we nonetheless carried out the following analyses.

First, we wanted to evaluate whether patients showed a greater number of misreferrals due to their nerve injury. To do so, we converted the total number of misreferrals observed per hand to proportions, dividing by the total number of trials (i.e., 90 per hand). For subsequent statistical comparisons, we arcsine transformed these data, calculated as the arcsine square root of the proportions. This makes the resultant distributions more symmetrical and reduces problems with violations of the assumption of normality. This is appropriate to do when numerous scores are near ceiling/floor.

We then compared arcsine transformed proportions of misreferrals for the injured hand of patients against that of controls. To estimate the mean proportion of misreferrals in controls, we first tested whether there was a difference in the mean proportions of misreferrals between hands. If no significant difference was found, the

data were averaged across hands. Comparison of controls against patients was done using an unpaired t-test, unless either the data or the residuals of the original test were non-normally distributed. In this case, a Mann-Whitney test was used.

Second, we wanted to evaluate whether there was any structure to the frequency of occurrence of misreferrals across the hand. Do participants make more misreferrals on some digits than others, for example, and if so, does this pattern differ in nerve injury? To our knowledge, these questions have not been addressed.

To evaluate this, we tested whether the distribution of observed misreferrals was different from the expected distribution if all digits had the same probability of misreferrals. In other words, if participants were equally prone to making misreferrals on all digits. Notably, since the thumb was probed 50% less than all other digits, the expected distribution is 11.11% for the thumb, and 22.22% for digits D2-through-D5. Two chi-squared tests for goodness of fit were performed. One test was used to evaluate whether the distribution of misreferrals in healthy controls, averaged across hands, differed from the expected distribution. The second chi-squared test was used to evaluate whether the distribution of misreferrals for the injured hand of patients differed from the expected distribution (again, based on the null hypothesis that participants are equally likely to make misreferrals on all digits).

Finally, we also wanted to visualise directionality of misreferrals. To do so, we plotted the number of misreferrals that were made from a given digit according to the direction of the misreferral itself—i.e., which digit, or the palm, was the percept misreferred to? The data are expressed as the proportion of total misreferrals for the hand in question. This provides information on both the frequency of occurrence of misreferrals per digit and their directionality—i.e., where the perception of touch was mislocated. For healthy controls the proportions were calculated separately per hand, and then the average was computed.

Tests of validity

In the process of developing a new method, it can be useful to compare its outcome measures against those of established tests designed to assess similar constructs.

Agreement across tests can strengthen confidence in the validity of the measures provided by the new method. We selected two methods for comparison, described next.

Sensory Rosen test

The sensory Rosen test is a standardised test of hand function after median/ulnar nerve repair, with established validity, reliability, and sensitivity (Rosen and Lundborg, 2000, 2001). Subtests include Semmes-Weinstein touch detection, two-point discrimination, shape-texture-identification (Rosen and Lundborg, 1998), and the Sollerman hand function subtests 4, 8, and 10 (Sollerman and Ejeskar, 1995).

We followed the procedures available at https://hakir.se/about-hakir/ (2018). Touch detection thresholds were taken using Semmes-Weinstein monofilaments, and two-point discrimination was taken using The Two-Point Discriminator (Exacta Precision & Performance, 2019 North Coast Medical, Inc.). Our shape-texture-identification and the Sollerman test materials were both produced in-house. The blinder box from the main experiment was used to block the participants view of their hand during the first three components of the Sensory Rosen test (i.e., touch detection, two-point discrimination, and shape-texture-identification).

Modified-Marsh method

As discussed in the Introduction, the modified-Marsh method is a standardised test of touch localisation after median/ulnar nerve repair. The test shows good sensitivity to impairment in nerve injury, with excellent test-retest and interrater reliability and external validity (Jerosch-Herold et al., 2006). Target locations in the main experiment of the current study were modelled after the zones of the modified-Marsh method (Fig. 1D).

The current study followed standardised procedures (available on request at https://www.uea.ac.uk/about/school-of-health-sciences/research/resources-and-tools/the-locognosia-test). Participants were provided with a hand diagram (one each for the left and the right hand) that showed all 20 zones that could be stimulated (Fig. 1D). All zones were numbered and after stimulation, participants reported the number of the zone where they felt the stimulation.

Two trials were taken per zone, randomised for presentation. The number of zones tested depended on the type of injury. Median nerve patients were tested in zones 1 through 14. Ulnar nerve patients were tested in zones 15 through 20. Patients with both nerves injured were tested in all 20 zones. Both hands were tested. The zones tested for the uninjured hand were the homologous locations defined by the type of nerve injury, as described above. The injured hand was tested first.

Performance is measured as a score: 2 points for the correct zone; 1 point for an adjacent zone; 1 point for the homologous zone of a neighbouring digit; 0 points for other responses. The Marsh score is then computed as the sum of points across trials. Since the zones tested differed for different patient types, see above, we converted raw Marsh scores to percentages based on the number of maximum points attainable per patient type.

On the day of testing, the modified-Marsh method was completed last, and four patients could not complete this test due to time constraints. As noted above, patients underwent other tests on the same day, including functional MRI scans. We had run overtime with these four individuals.

Clinical questionnaires

We also administered two additional standardised questionnaires: (1) The Disabilities of the Arm, Shoulder and Hand (DASH) Outcome Measure (Hudak et al., 1996); (2) The short-form McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987).

The DASH questionnaire assesses the impact of injury on activities of daily living. The SF-MPQ assesses the type and level of pain caused by injury. Both questionnaires produce a single score.

Results

Individual level data separates injured from healthy hands

Figure 2 provides a qualitative overview of the information provided by the digital photograph method, at the individual participant level. Data from two patients and one control participant are shown as examples. Responses are overlaid with targets in raw x- and y-coordinates, shown separately per hand. Different coloured responses indicate which digit was stimulated.

A number of observations can be made. First, there is a greater spread of responses for the patient's injured hand, consistent with increased error of localisation. Second, increased error of localisation appears to be restricted to the projection territory of the injured nerve. Patient P2 provides a clear example. In this patient, the ulnar nerve was injured and the spread of responses for digit five is relatively pronounced (Fig. 2B). Localisation performance for the uninjured hand of patients, and for either hand in controls, is comparatively better; responses tend to cluster close to targets. Third, and perhaps less obvious, error of localisation appears to show a proximal bias; off-target responses are generally seen as more proximally located. This proximal shift in response error is apparent in patients and controls. Lastly, both patients and controls make misreferrals, yet some patients show higher numbers of misreferrals (Fig. 2A). These apparent differences are again specific to the injured hand. Below, we offer more detailed analyses of misreferrals (see Results page 42ff, Fig. 5).

To summarise, our method provides information about error of localisation, its potential systematic directionality, and misreferrals. This information separates injured from healthy hands at the individual participant level, as qualitative descriptive observations. Next, we investigate whether these observations hold quantitatively, at the group-level.

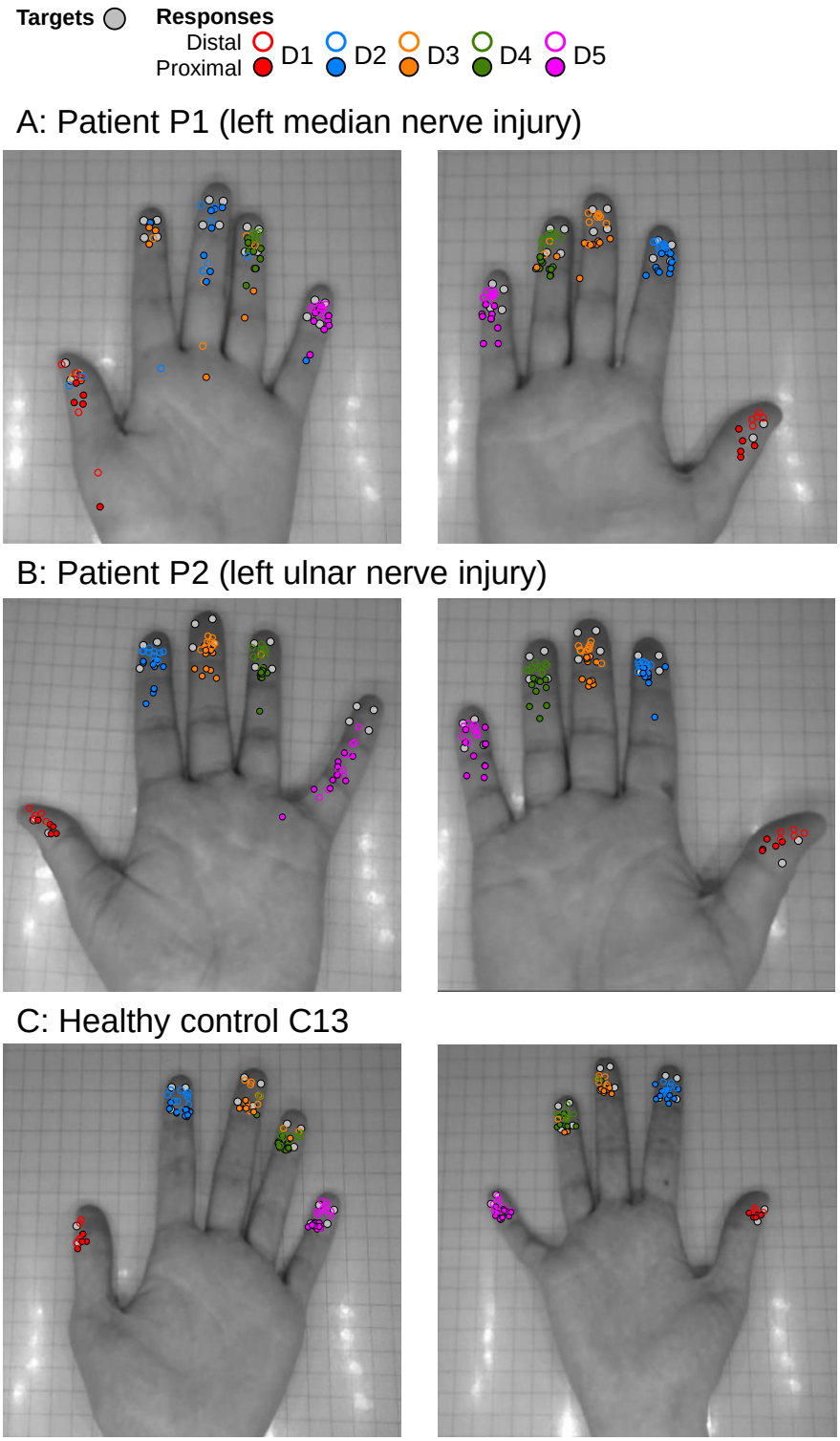

Figure 2. Individual level touch localisation data. Targets (grey circles) and responses (coloured circles) of three sample participants overlaid on the photographs of their hand. The colour of the responses indicates which digit the stimulation had been applied (see colour key inset). **A:** This median nerve patient shows many misreferrals, especially from their injured D2 to D1 and D3. Additionally, the responses show a large spread of error. There are also a few misreferrals from D3 to D4 on their uninjured hand. **B:** This ulnar nerve patient showed a large spread of responses specific to D5 of their injured hand. They make one misreferral to the palm and one misreferral from D3 to D4. **C:** Healthy control participant. Note that even healthy controls can show some misreferrals, especially between D3 and D4 as can be seen in this example participant, for both hands.

Group level data separates injured from healthy hands

Figure 3 plots absolute error of localisation. Patient data are shown for responses to targets within the injured nerve territory of the injured hand, 'Inj', and the homologous targets on the uninjured side, 'Uninj'. These same data are also shown as difference scores—computed as the difference in absolute localisation error between Injured minus Uninjured sides (first inset in Fig. 3). Positive difference scores indicate greater error for the injured side, consistent with impairment due to injury.

The results reveal sensitivity to impairment. Error of localisation is significantly increased for responses to targets within the injured nerve territory relative to the homologous targets on the patient's uninjured side ($t(17) = 4.50$, $p < 0.001$, $\eta_p^2 = 0.54$). In other words, as a group, the patients are significantly worse at localising touch on their injured hand.

Visualising these effects as difference scores also shows that not all patients are impaired. Negligible differences are observed for a subset of patients—all three patients with part-median-nerve repairs, and four patients with ulnar nerve repairs. As described below, an apparent absence of impairment in touch localisation within a given individual tends to agree with other independent measures of functional recovery—namely, sensory Rosen scores. Those patients who show negligible differences in absolute error of localisation between injured and uninjured sides also tend to show high levels of functional return according to their scores on the sensory Rosen test (see Results page 46).

Figure 3 also plots the absolute error of localisation in healthy controls. Controls' data reflect responses to targets matched to those of the patient group based on the proportions of patients across subgroups defined by injured nerve (see Methods 2.2.5 for details). Controls data are averaged across hands since no reliable differences between the dominant and non-dominant hands are observed ($t(32) = 1.11$, $p = 0.277$, $\eta_p^2 = 0.04$).

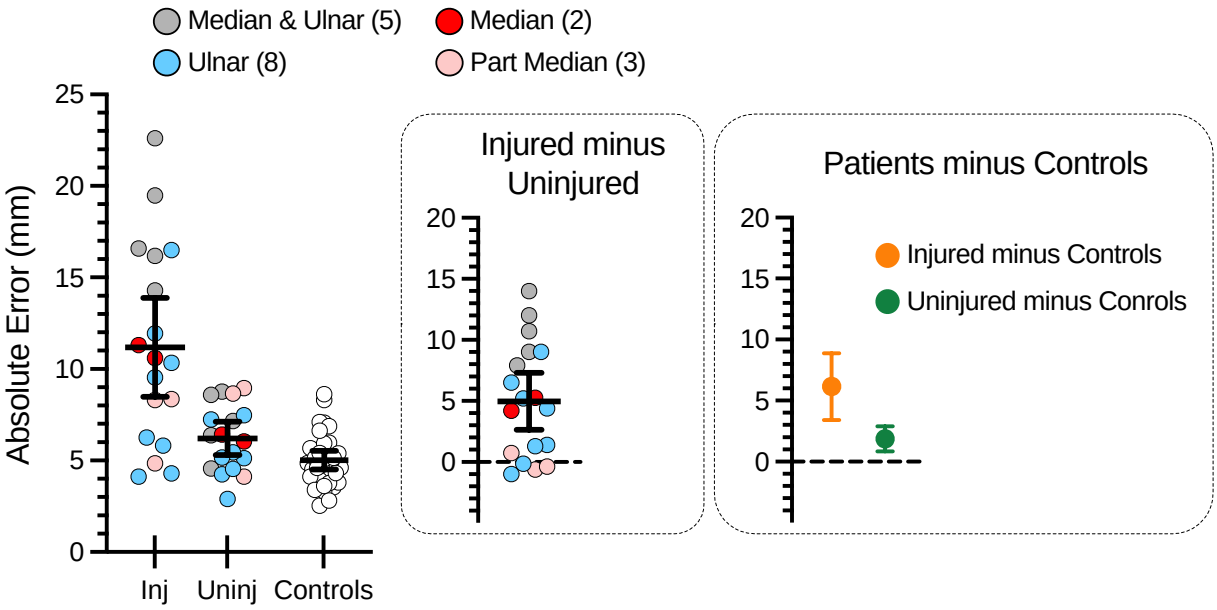

Figure 3. Group level results: Absolute error of localisation. Mean values of absolute error of localisation are shown for patients and controls. Inj = injured territory, Uninj = homologous uninjured territory. Individual datapoints are mean estimates per participant and error bars are 95% confidence intervals around the group means. The same data are shown as difference scores, computed as the difference in absolute localisation error between Inj minus Uninj sides (first inset). The second inset shows the mean differences between groups, with estimated 95% confidence intervals around the differences, respectively.

These results further demonstrate the sensitivity of the digital photograph method to nerve impairment. Absolute error of localisation for the injured hand of patients is significantly increased relative to that of healthy controls (Welch-corrected $t(18.3) = 4.7$, $p < 0.001$, $\eta_p^2 = 0.55$).

Unexpectedly, although much smaller in magnitude, we also find a statistically reliable difference in performance between the uninjured hand of patients and healthy controls (Welch-corrected $t(29) = 2.4$, $p < 0.05$, $\eta_p^2 = 0.16$). Localisation is worse for the uninjured hand of patients. There are several possible interpretations to consider with regards to these unexpected findings, including potential confounding factors.

First, although we include a control task designed to catch motor problems (see above, Methods 2.2.3), it is possible that patients experienced difficulties operating the mouse with their injured hand and that our control task failed to capture this. This could happen, for example, if difficulties were to arise later in time, after the control

task was completed. Even if only minor, these challenges could, in principle, negatively impact performance. Worse localisation for the uninjured hand would arise. This could help explain our unexpected findings. This is a limitation of the digital photograph method. In the extreme, if controlling the mouse to record responses with the injured hand is too problematic (e.g., painful), then testing of the uninjured hand may not be possible.

Second, the current tests were carried out in the context of a broader study involving additional experiments, and not all controls underwent the same tests, or test schedule, as patients. Specifically, all patients underwent functional MRI testing prior to completing the behavioural experiments reported here, and all tests were performed on the same day. This was not the case for all controls. Four control participants did not complete fMRI testing, and ten controls completed fMRI and behavioural tests on separate days. Perhaps patients were generally more fatigued than controls at the time of completing the digital photograph method, and this could help to explain why touch localisation performance with their uninjured hand was worse than controls.

Finally, although similar, the mean age and range of age of our patient group is larger than that of our control group. Perhaps touch localisation performance declines with age, and this could explain why, as a group, patients perform worse with their uninjured hand. Motivated by this possibility, we tested for evidence of a relationship between mean absolute error of localisation and age. No reliable relationship was detected (healthy controls and average hand performance, $r(31) = 0.122$, $p = 0.500$, $r^2 = 0.02$; patients and uninjured hand performance, $r(16) = 0.071$, $p = 0.779$, $r^2 = 0.01$; combined controls and patients, considering only the uninjured hand performance, $r(29) = 0.173$, $p = 0.225$, $r^2 = 0.03$). This suggests that age differences between groups are unlikely to explain why patients performed worse with their uninjured hand relative to controls.

Altogether, it remains unclear why the uninjured hand of patients performed worse than healthy controls. What is clear, however, is that these effects were minimal compared to the effects observed due to nerve injury. The injured hand of patients showed far worse performance compared to both their uninjured hand and to the

healthy hands of controls. Clearly, these effects are due to nerve injury and cannot be explained by the potential confounding factors considered above.

Digit-specific analysis separates patient subgroups

To evaluate whether our method is sensitive enough to distinguish patient subgroups according to which nerve is injured, we performed a separate digit-specific analyses of error of localisation. Focusing on digit 2, patients with median nerve repairs are defined as an 'expected impaired' group, while patients with isolated ulnar nerve injuries are defined as a patient control group. The converse is true for our analyses of digit 5. Patients with ulnar nerve injuries comprise the 'expected impaired' group, while those with isolated median nerve injuries comprise the patient control group. We also include analyses of data from healthy controls, similar to above.

The results reveal sensitivity to impairment at the digit-specific level, depending on which nerve is injured. Absolute error of localisation for responses to stimulation of digit 2 is increased for patients with median nerve injuries, but not for those with isolated ulnar nerve injuries (Fig. 4A). This is confirmed statistically as a significant difference between the injured vs. uninjured hands in the 'expected impaired' group ($t(9) = 3.87$, $p = 0.004$, $\eta_p^2 = 0.67$), and between the injured hand of the 'expected impaired' group and healthy controls (Welch-corrected $t(9.3) = 5.09$, $p < 0.001$, $\eta_p^2 = 0.74$). No reliable differences are observed in the patient control group, with isolated ulnar nerve injuries (injured vs. uninjured hands: $t(7) = 0.467$, $p = 0.655$, $\eta_p^2 = 0.05$; injured vs. healthy controls: Welch-corrected $t(9.1) = 0.342$, $p = 0.740$, $\eta_p^2 = 0.01$).

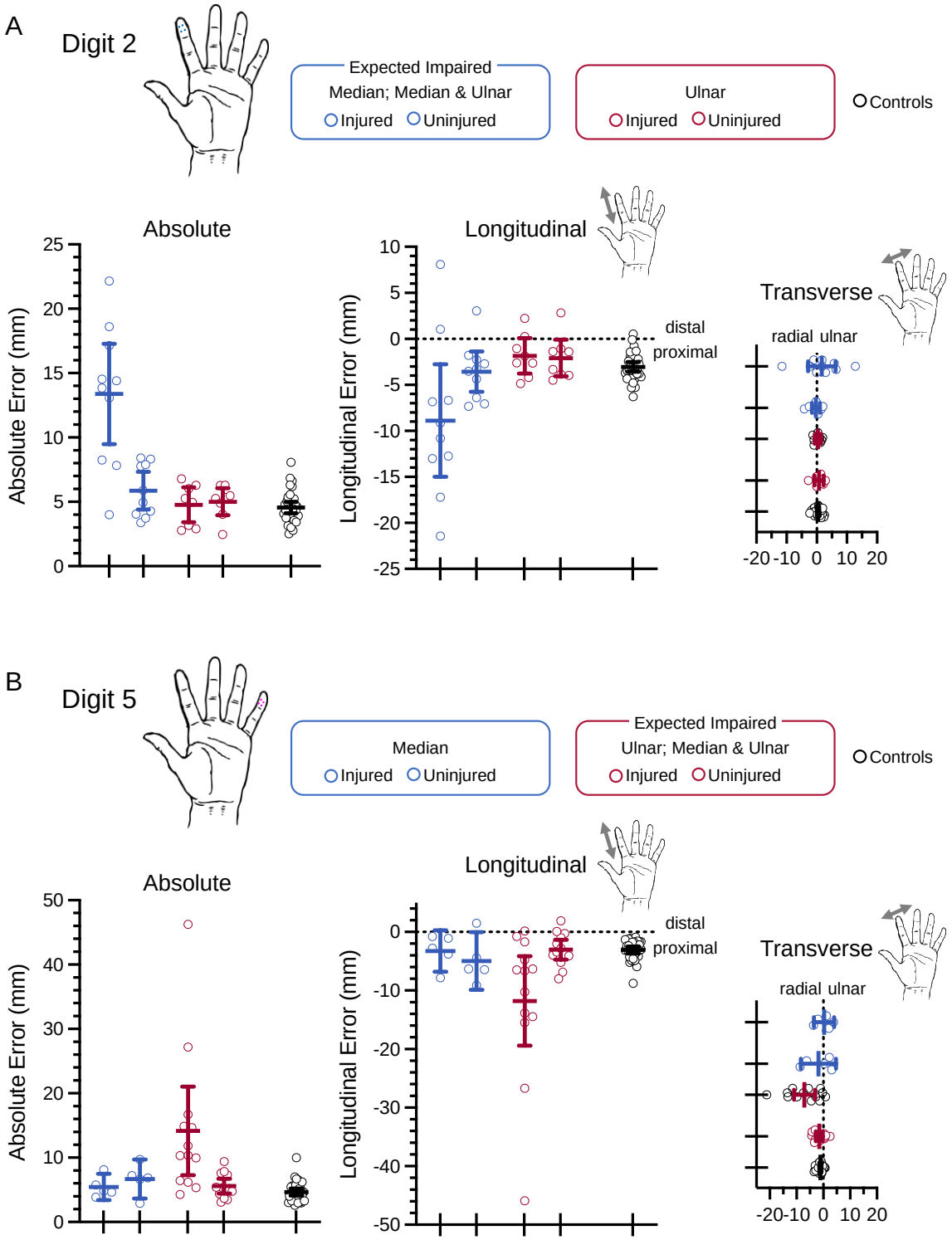

Figure 4. Digit-specific results: Absolute and directional error of localisation. The mean absolute error of localisation and its longitudinal and transverse components are shown for patient subgroups and controls for digit 2 (A) and digit 5 (B). Patient subgroups are defined as 'expected impaired' depending on the nerve injured and digit examined. **A:** Data for digit 2. Patients with median nerve injuries are expected to show impairments. **B:** Data for digit 5. Patients with ulnar nerve injuries are expected to show impairments. Individual datapoints are mean estimates per participant and error bars are 95% confidence intervals around the group means.

The complementary results are observed for analyses of digit 5 (Fig. 4B). Here, impairment is seen for patients with ulnar nerve injuries (injured vs. uninjured hands: $t(12) = 3.07$, $p = 0.0097$, $\eta_p^2 = 0.44$; injured vs. healthy controls: Welch-corrected $t(12.2) = 3.01$, $p = 0.0107$, $\eta_p^2 = 0.43$), but not for those patients with isolated median nerve injuries (injured vs. uninjured hands: $t(4) = 1.21$, $p = 0.293$, $\eta_p^2 = 0.20$; injured vs. healthy controls: Welch-corrected $t(5.1) = 1.02$, $p = 0.355$, $\eta_p^2 = 0.17$). Again, this demonstrates sensitivity to impairments according to which nerve is injured and which digit is examined. Localisation impairments are identified for digits within the territory of the injured nerve; touch localisation for digits outside the territory of the injured nerve appears normal.

As an additional step, we evaluate whether these results depend on including the patients with injuries to both nerves—the 'median & ulnar' group. Since these patients are included within the 'expected impaired' group for both analyses, digit 2 and digit 5, it is possible that the above results are driven entirely by this group. To evaluate this, we repeated analyses of digit 5 using only isolated ulnar nerve patients as the 'expected impaired' group. The results support our conclusions above; again, we find evidence for specificity. Performance is impaired for the injured vs. uninjured sides ($t(7) = 2.59$, $p = 0.0357$, $\eta_p^2 = 0.49$), and for injured vs. healthy controls (Welch-corrected $t(7.1) = 2.42$, $p = 0.0457$, $\eta_p^2 = 0.45$). It was not possible to conduct a similar complementary analysis for digit 2 given too few patients with isolated median nerve injuries. Nonetheless, we are confident from these findings that our new digital photograph method has the potential to identify impaired touch localisation at the level of individual digit responses according to whether the ulnar or median nerve is impaired.

Figure 4A and 4B also show the error of localisation for digit 2 and 5 as longitudinal and transverse components, respectively. These analyses were done to explore the added potential of our method. We wanted to test whether the digital photograph method could identify potential biases in touch localisation responses—evidence for systematic directionality in the error of localisation. Although prior reports suggest a proximal bias in localisation error on the volar surface of the hand in healthy controls

(Hamburger, 1980), we had no a priori predictions regarding a possible change in such biases resulting from nerve injury. These analyses were thus exploratory.

Several inferences can be made from these results. First, most of the localisation error is expressed along the length of the digits. For both patients and controls, localisation error is greater in the longitudinal relative to the transverse direction, and this is true for both digits 2 and 5. This is unsurprising given that there is more 'room' to make errors along the length of the digit relative to its width. Second, in healthy controls the error in the longitudinal direction shows a significant proximal bias (D2: $t(32) = 11.7$, $p < 0.001$, $\eta_p^2 = 0.81$; D5: $t(32) = 10.7$, $p < 0.001$, $\eta_p^2 = 0.77$). This pattern is generally unchanged in the case of the injured hand of the 'expected impaired' group, yet not all tests reach significance following corrections for multiple comparisons. Third, no evidence for a directional bias in localisation error along the transverse component is observed in healthy controls for digit 2 ($t(32) = 2.32$, $p = 0.0270$, $\eta_p^2 = 0.14$), yet a very small (mean ± 95%CI = -1.1 ± 3.6 mm) but statistically reliable bias is observed in the radial direction for digit 5 ($t(32) = 6.27$, $p < 0.001$, $\eta_p^2 = 0.55$). For patients, this radial bias for digit 5 is also observed, and is more pronounced in magnitude (mean ± 95%CI = -7.05 ± 3.9 mm) due to injury of the ulnar nerve ($t(12) = 3.92$, $p = 0.0021$, $\eta_p^2 = 0.56$). This is of potential interest; yet, with no a priori expectation regarding this finding, we provide no further interpretations, here. Future investigations are needed to replicate and further explore the potential significance of these results.

Misreferrals

Overall, misreferrals were made infrequently. This makes quantitative statistical evaluations challenging. Nonetheless, we report the following results for completeness and to demonstrate the potential of the digital photograph method to capture these details.

Figure 5A shows the number of misreferrals expressed as the proportion of the total number of trials for the injured hand of patients and for the average between hands in controls. Statistical comparison of the group median proportions reveals no reliable differences ($t(47) = 1.60$, $p = 0.116$, non-parametric Mann-Whitney test: $U = 203$, $p = 0.192$, $\eta_p^2 = 0.22$). The number of misreferrals is generally very low for both groups. Most

controls make only 1 or 2 misreferrals or none, and only two control participants made misreferrals at a frequency of 0.138 and 0.144 of total trials averaged over both hands. Patients also generally make few misreferrals. However, three patients stand out from the rest of the patient group, and from controls, showing high numbers of misreferrals. P8, P1, and P10 make misreferrals at a frequency of 0.267, 0.400 and 0.500 of total trials on their injured hand, respectively. Thus, tracking the frequency of misreferrals with the digital photograph method identifies individual patients showing strikingly high numbers of misreferrals, yet at the group level, no reliable differences between patients and controls are observed.

Despite the high interparticipant variability and generally low frequency of misreferrals in either group, we decided to follow through with our planned analyses to evaluate the structure of observed misreferrals across the hand. First, we test whether the observed distribution of misreferrals in either group differs from an expected—theoretical—distribution if all digits are equally likely to make misreferrals. Our findings indicate that the distribution of misreferrals in both patients and controls differs from the expected distribution (Figure 5B; controls: χ^2 (4) = 137.1, $p < 0.001$, patients: χ^2 (4) = 60.22, $p < 0.001$, patients without P1 and P10: χ^2 (4) = 51.4, $p < 0.001$). In other words, not all digits are equally prone to misreferrals. In controls, the majority of misreferrals arise following stimulation of either D3 or D4. Patients also depart from the theoretical distribution, yet relative to controls, show more misreferrals for D2 and D5. Patient data are shown with and without P1 and P10 included, since these two individuals showed abnormally high numbers of misreferrals, as described above.

Finally, the directionality of misreferrals is visualised by plotting the number of misreferrals per digit according to the direction of the misreferral itself—i.e., which digit, or the palm, was the experience of touch mislocalised to. This generates a five-by-six matrix, where the five rows indicate 'misreferred from' and the six columns indicate 'misreferred to'. These data are shown separately for controls and for the injured and uninjured hand of patients, expressed as the proportion of total misreferrals per hand (Fig. 5C). Patient data are presented with and without P1 and P10, and individual-level data for these two patients are provided.

Although purely qualitative, some observations can be made. In both healthy controls and for the uninjured hand of patients, the majority of misreferrals involve confusion between D3 and D4, accounting for 74% of all misreferrals. This suggests that D3 and D4 are disproportionately prone to confusion in the healthy hand. This pattern breaks down for the injured hand of patients. The frequency and directionality of misreferrals are more widely distributed, and misreferrals are made to the palm. Examining these data separately for patients P1 and P10 is useful. Here, we see obvious departures from the pattern observed in controls and the uninjured hand of patients. While merely descriptive, this highlights the added potential of the digital photograph method—individual patients showing high numbers and/or atypical patterns of misreferrals can be identified. This information could be of value, for example, to identify individual patients for further study and/or specialised treatment considerations.

Tests of validity

Good practice in the development of a new method is to evaluate its outcome measures against those acquired from established tests thought to capture the same or similar constructs. Agreement across tests can strengthen confidence in the validity of the measures provided by the new method. The sensory Rosen test and the modified-Marsh method were chosen for comparison. Both tests are known to evaluate meaningful hand function following ulnar/median nerve injury. As such, we expected the outcome measures of our new digital photograph method to relate to those of both tests.

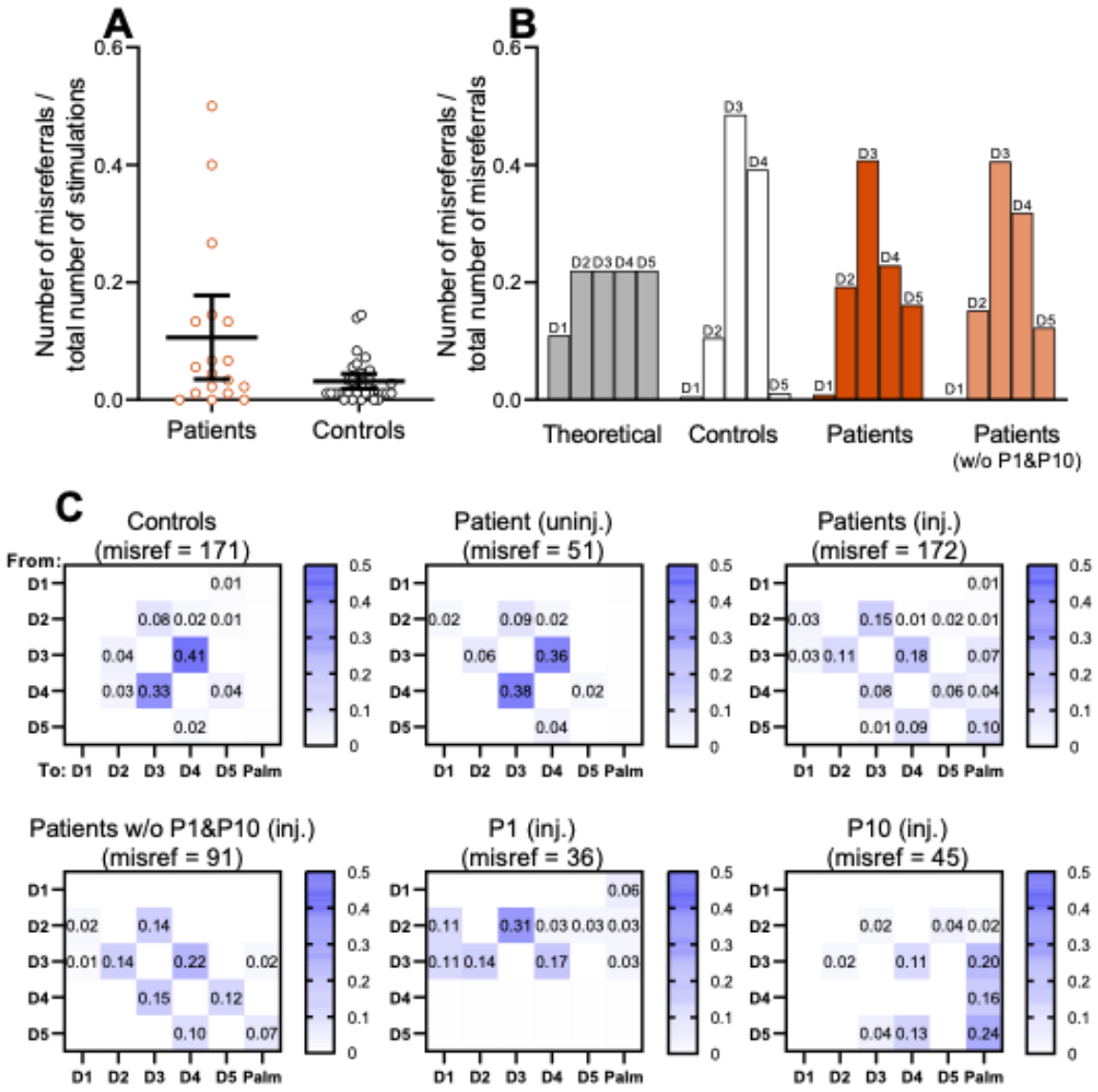

Figure 5. Misreferrals. A: Number of misreferrals per participant expressed as the proportion of total stimulations. Patient data is from the injured hand. Group mean estimates are shown with 95% confidence intervals. Individual datapoints indicate individual participant data. **B**: Number of misreferrals per digit expressed as the proportion of the total number of misreferrals per group. The 'theoretical' distribution is the expected distribution if each digit was equally likely to make misreferrals. Patient data are shown with and without P1 and P10 included. **C:** Confusion matrices showing the number of misreferrals between segments of the hand expressed as the proportion of the total number of misreferrals. The vertical axes indicate where the misperception of touch was 'referred from', and the horizontal axes indicate where the misperception of touch was 'referred to'. Patient data are shown for the uninjured and injured hand. For the injured hand, the data are shown with and without P1 and P10, and the individual data for P1 and P10 are also shown.

To perform these comparisons, the outcome measure examined from the digital photograph method was taken as the mean error of localisation expressed as the difference between Injured and Uninjured hands (see above page 36ff; Fig. 3, first inset). Positive values reflect worse performance—greater localisation error—for the injured side. In other words, these values stand as a measure of touch localisation impairment. Values near zero suggest no impairment.

Comparison with sensory Rosen scores

The sensory Rosen test produces a single composite score, with subtests that evaluate both low- and high-level function (see Methods 2.3.1 for details). Higher sensory Rosen scores indicate better function. The test does not evaluate touch localisation.

Correlational tests reveal a strong significant relationship between our measures of touch localisation from the digital photograph method and sensory Rosen scores ($r(16) = -0.813$, $p < 0.001$, $r^2 = 0.66$) (Fig. 6A). The extent of impairment captured by each test is related. Patients with greater touch localisation impairments also tend to perform poorly on the sensory Rosen test. This suggests that our new digital photograph method and the sensory Rosen test measure related constructs, sensitive to nerve injury.

Comparison with modified-Marsh scores

The modified-Marsh method is a standardised test of touch localisation, producing a single score per hand (see page 32 for details). These scores are expressed as a percentage of best possible performance; values of 100 indicate no errors.

For comparison against the digital photograph method, modified-Marsh scores were expressed as the difference between Injured and Uninjured hands. This makes the outcome measures from the two methods conceptually similar. In the case of the modified-Marsh scores, negative difference values, calculated as Injured minus Uninjured scores, indicate greater impairment.

Our findings reveal a significant correlation between the two outcome measures ($r(11) = -0.652$, $p = 0.016$, $r^2 = 0.43$). Touch localisation performance as evaluated by the digital photograph method relates to touch localisation performance as evaluated by

the modified-Marsh method. This makes sense, and, overall, strengthens confidence in the validity of the measures derived from our new digital photograph method.

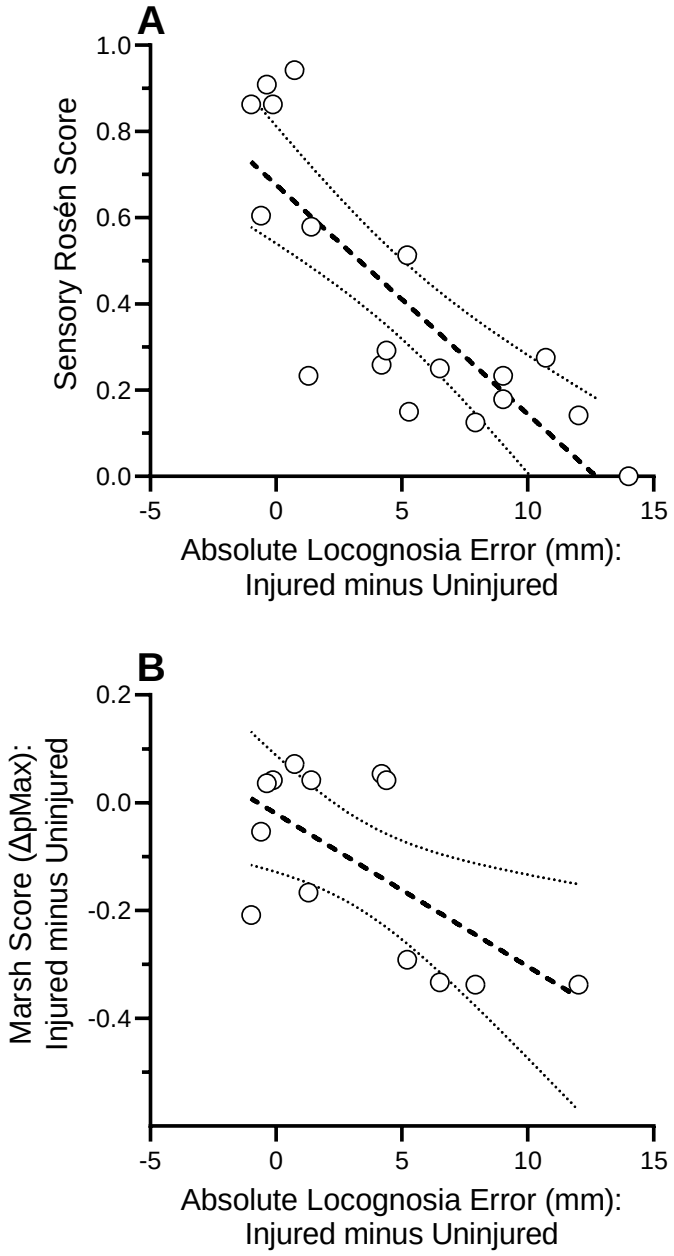

Figure 6. Tests of validity. A: Comparison between sensory Rosen scores and localisation error derived from the Digital Photograph method. Localisation error is expressed as the difference between performance for the injured minus homologous uninjured territories. **B:** Comparison between the Marsh scores and localisation error derived from the Digital Photograph method. Both measures are expressed as the differences between performance for the injured minus homologous uninjured territories. Regression lines are shown with 95% confidence intervals.

Discussion

We develop a new method for measuring touch localisation and evaluate its value for use in nerve injury. Our method enables detailed quantification of the error of localisation and its directional components, separate from misreferrals—errors made across digits, or from a digit to the palm. Our results show that nerve injury increases error of localisation and suggest that these impairments are restricted to the territory of the repaired nerve. A few patients also show abnormally high numbers of misreferrals, and the pattern of misreferrals in patients departs from that observed in healthy controls. We also find close agreement between our new measures of touch localisation and the well-established, validated sensory Rosen scores, commonly used to evaluate hand function after nerve repair. We discuss the significance of our findings, as well as the value and future applications of the digital photograph method.

The characterisation of touch localisation in nerve injury is of key importance. The method we develop in the current study offers far more rigorous and detailed assessment than previous methods provide. Our method makes it possible to acquire multiple measurements from the same skin locations in a repeatable and efficient manner. The error of localisation can be quantitatively examined as absolute and directional components, distinguished from misreferrals, which can also be examined for frequency of occurrence and directionality. This provides a rich profile of information at the level of individual participants, and across different parts of the hand. Below, we argue that such rich detail is necessary to evaluate certain unanswered research questions of great significance, and that the method we develop here is particularly well suited for this purpose. Our current findings also provide new and valuable fundamental insights. We discuss these contributions first.

Fundamental insights

Our findings make numerous new contributions to better understanding the functional consequences of nerve transection injuries. Despite the abundance of single case observations highlighting abnormal touch localisation in nerve injury and its recognised significance in tracking nerve regeneration (Hawkins, 1948), only one previous study provides quantitative data on the error of localisation. Using the red-lens

method, Braune & Schady (1993) evaluate the error of localisation in a group of eleven patients who underwent median/ulnar repairs. Surprisingly, they found normal localisation at the distal pads of the digits, while increased error was found for the middle and proximal pads. The authors suggested that normal performance at the fingertips reflects compensation via central mechanisms, in alignment with their greater significance in active touch. Our results sharply contradict these findings and conclusions. We find that nerve injury leads to significant and lasting impairments in touch localisation at the distal digit pads, challenging the notion that central-level mechanisms can fully compensate for such impairments.

Several inherent limitations of the red-lens method may help to explain these discrepancies. In the red-lens method, participants communicate their responses by touching their skin. With full vision available, they use a pen to mark where they felt they were touched by the experimenter. This provides an opportunity for participants to calibrate differences between the experience of touch caused by the stimulation event and that caused by their response, which is also accompanied by vision. Further, in the red-lens method the marks made by participants are visible and remain visible throughout the test. These features may improve localisation accuracy, and, in the context of evaluating patients with nerve injuries, even obscure impairments.

With the digital photograph method, these concerns do not apply. Participant responses are made on an image of their hand, so no opportunity for calibration via feedback is available. And, once a given response is made, its location is no longer visible, ensuring that the visibility of prior responses does not influence current responses.

With the red-lens method, it is also inherently difficult to repeat measurements from the same skin locations. In Braune & Schady (1993) the estimates of localisation error at the distal digit pads are derived from a single trial. This raises concerns regarding their reliability. In contrast, the digital photograph method enables efficient resampling of measurements at the same locations. This is a major strength. In the current study, numerous repeated measurements were taken to estimate the error of

localisation for each digit. As such, compared to Braune & Schady (1993), our findings are based on significantly more rigorous evaluations.

With these considerations in mind, we are confident about our current findings and conclusions. Nerve injury results in significant impairments in the ability to localise touch at the distal digit pads. Notably, this result is also consistent with findings using an 'area of localisation' method known as the modified-Marsh method (Jerosch-Herold et al., 2006). Although not measuring the error of localisation, this method also targets the distal digit pads, and results from several independent studies reveal impaired touch localisation following median/ulnar nerve repairs (Jerosch-Herold, 1993, 2003, 2005). Taken together, these and the current results firmly challenge the idea that central-level mechanisms can fully correct for such impairments.

Our findings also provide new insights as to the specificity of localisation impairments in nerve injury. Impairment is restricted to digits within the territory of the injured nerve. Localisation is normal for digits outside the injured territory. To our knowledge, this is the first empirical demonstration of this level of specificity, validating prior conclusions drawn from qualitative observations in single patient cases (Hawkins, 1948). This finding also demonstrates the sensitivity of our new method. It seems likely that future studies could use the digital photograph method to evaluate localisation impairments in less severe conditions, such as digital-nerve cuts and chronic nerve compression.

Our findings also reveal evidence of a radial bias in the directionality of localisation errors following ulnar nerve injuries. As this bias was not predicted, we are hesitant to provide further interpretation of its potential significance. Nonetheless, this result highlights additional capacity of the method—it is possible to investigate predictions regarding systematic directionality of localisation errors. By way of example, we are aware of findings from brain injury cases showing systematic biases in touch localisation (Rinderknecht et al., 2019; Ambron et al., 2022). Our digital photograph method could be used to further study these phenomena.

Finally, we also provide new support for the argument that touch localisation is functional. We find a strong significant correlation between the error of localisation and

sensory Rosen scores: better touch localisation is associated with better performance on the sensory Rosen test. The sensory Rosen test includes measures of high-level manual function and fine movement dexterity, as well as haptic object shape and texture recognition. These results reinforce previous findings and conclusions: Touch localisation in nerve injury is a good predictor of performance on high-level functional tests such as the Moberg pickup test (Marsh, 1990) and activities of daily living (Jerosch-Herold, 1993). Taken together, touch localisation is a valid index of meaningful function in nerve injury, and should be considered important for clinical assessment and evaluation of treatment efficacy. In developing our new digital photograph method, we provide a more comprehensive and rigorous means for evaluating touch localisation than previously available.

Applications

One of the driving motivations for the current study was to develop a method that could be applied to the study of reinnervation errors. After a nerve has been cut and surgically repaired, regenerating fibres migrate out to the periphery without topographical guidance (Lundborg et al., 1994; Puigdellivol-Sanchez et al., 2005; Witzel et al., 2005; Brushart, 2011). New connections with end receptors are established at different locations relative to the pre-injury organisation. These rewiring events are known as reinnervation errors, and are thought to significantly limit functional recovery. Despite their considered significance, however, current understanding of reinnervations errors is remarkably limited. Part of the problem is that they are difficult to study.

Microneurography enables direct recording from peripheral nerve in humans, and although impractical for widespread use, may be the most definitive method available for the study of reinnervation errors. Recording from multiple afferents proximal to the site of repair in patients with median nerve injuries, Hallin et al. (1981) document discontinuous sites on the hand where cutaneous stimulation evokes responses. In other words, regenerated afferent nerve fibres were found to exhibit multiple discontinuous receptive fields, in sharp contrast to the unitary receptive fields that characterise healthy nerves. These same patients showed large and numerous touch

localisation errors, including misreferrals. Both discontinuous receptive fields and distorted touch localisation were interpreted as evidence of reinnervation errors.

The digital photograph method could help to significantly advance this line of research, combining touch localisation with microneurography to study nerve injury. Although compelling, the results of Hallin et al. (1981) lack quantitative validation. The neural receptive field properties and touch localisation measures were not directly compared. Application of the digital photograph method in this context would not only enable detailed quantification of touch localisation but also provide a platform for which neural receptive field properties could be defined in comparable units. Neural receptive field properties could be documented in the same 'picture space' as touch localisation data, allowing for comparisons between them. Agreement between measures would help to validate touch localisation as a method for studying reinnervation errors. The digital photograph method enables the rich profiling of touch localisation and means to exchange information between the experimenter and participant suitable to significantly advance this area of research.

The digital photograph method is also well suited to address questions regarding central level changes following nerve injury. The primary somatosensory cortex is organised such that individual digits of the hand are represented separately, in a spatially ordered fashion (Penfield, 1937; Kaas et al., 1979). This topographical organisation is found to change in non-human primates after median nerve transection and repair (Paul et al., 1972a; Wall et al., 1986; Merzenich and Jenkins, 1993; Churchill and Garraghty, 2006). These changes in cortical topography are thought to reflect changes in the periphery, and may relate to aberrant touch localisation and reinnervation errors (Wall et al., 1986). To evaluate whether brain changes relate to abnormal touch localisation in nerve injury, rigorous and detailed characterisation of touch localisation is essential. The digital photograph method enables this level of detail, surpassing the capabilities of previous methods.

Finally, given how well touch localisation stands as a meaningful index of functional recovery following nerve injury, and its putative links to the quality of nerve regeneration, the digital photograph method provides a valuable new tool for evaluating

patient recovery and treatment efficacy. Less rigorous and comprehensive methods may provide an incomplete or even misleading assessment.

Limitations

The digital photograph method has several limitations. The method requires that two photographs of the participant's hand be taken. The hand must be held flat against the base of the apparatus for these photographs, with the palm facing up and the fingers fully opened. Sometimes patients with nerve injuries have difficulties opening their hand. They may have a degree of flexion contracture related to associated tendon injuries and be unable to open their hand fully. The fingers tend to curl inwards, towards the palm. Indeed, not included in the current paper, we have worked with two such patients unable to open their hand sufficiently to complete the digital photograph method. This suggests that a significant proportion of patients with nerve transection injuries may be unable to perform the digital photograph method. A useful future modification would be to validate different ways of completing the test from different hand postures. Also, although a more relaxed hand posture is assumed during testing, some degree of finger opening is necessary when targeting the locations tested in the current study (i.e., the distal digit pads). Otherwise, directing the monofilament with precision and at the appropriate angle for stimulation can be challenging.

With the current method, only the radial side of the thumb could be tested. The ulnar side of the thumb could not be made visible for the photographs, given the hand posture required. This represents a second limitation, and further motivation to explore the viability of implementing different hand configurations in future modifications of the test. Perhaps multiple photos could be taken and used for recording responses, or different hand configurations could be used for different needs and purposes.

Third, in the current study the time between successive photographs was one second. This means that the experimenter must remain vigilant; if the participant's hand moves between photographs, the images must be retaken. This, of course, also requires that participants can keep their hand still while the photographs are taken. Certain clinical populations may find this challenging. Shortening the time delay between successive photographs would be a useful modification.

In this study, all targets are located only on the distal phalange of each digit. In doing so, we followed the pattern of the modified Marsh method (Jerosch-Herold et al 2006). This allowed us to make a direct comparison between localisation error and modified-Marsh scores. This might have led to some overestimation of the difference between patients' injured and uninjured hand or patients and controls if it was if the injury made it more difficult to sense where the targets were being applied. When marking the targets on the uninjured hand, one patient spontaneously commented that he now could feel that we only marked up the fingertips whereas on their uninjured hand he had thought the targets were applied to the whole hand. While this could explain some of the differences between injured and uninjured hands or injured hand and controls, it fails to explain why we also observed a difference between the modified-Marsh score between the injured and uninjured hands. In the Marsh tests, participants are aware that only the fingertips are stimulated and they can see all possible stimulation zones at all times. Furthermore, it fails to explain why there is such a strong correlation between the impairment measured by our method and both the modified-Marsh score and the sensory Rosen score. We are, therefore, confident that this does not invalidate our results.

Another limitation that follows from our choice of target location is that we are unable to collect data from the rest of the hand. Two case studies by Hamburger (1980) show that localisation errors are not limited to the fingertips. Modifying the target configuration so, that it covers the complete hand would allow capturing these errors and to better measure potential reinnervation errors. Additionally, it would allow the pursuit of new research questions. Hawkins (1948) claims that "faulty localisation" is limited to the territory of the injured nerve and in general it is thought that very little cross-sprouting occurs between nerves. Our detailed analysis of D2 and D5 point in the same direction (Fig. 4, see page 39ff) in that it provides evidence that for isolated median nerve patients localisation is impaired on D2 but not D5 and vice versa for isolated ulnar nerve patients. A whole-hand configuration of targets should be able to more clearly delineate the boundary between impaired and unimpaired territory. This would be especially insightful if it would be combined with other measures of nerve territory, such as microneurography.

Our aim in this study was primarily to introduce a new research tool and to validate it. We, therefore, primarily limited our analysis mainly to absolute error. As Fig. 4 (see page 39ff) and Fig. 5 (see page 42ff) indicate, the data allows other types of analysis to be also conducted. It is, for instance, possible to look at error directionality and dispersion of the individual responses around the mean response. Taking that information into account can allow evaluation of different models of body representations in the brain (Medina & Coslett, 2016). In Fig. 2 we code responses according to the digit and position (distal or proximal) of the target. Qualitative inspection of the response patterns shows striking differences even within healthy controls. Some individuals show four distinct clusters of responses on each digit, corresponding to the four targets. Other individuals only show one distal and one proximal cluster. And for some individuals, all responses "bleed together" into a single cluster for the complete digit. These qualitative observations likely hint at interindividual differences caused by differing skin properties and/or different central representations. More sophisticated analysis would allow a better understanding of the fundamentals of touch processing in patients and healthy controls.

One question that cannot be answered by our analysis is what mechanism is responsible for the increased localisation error in the injured territory of patients. While it may be primarily driven by imperfect nerve regrowth, it might also simply reflect the fact that the percept in the patients' injured territory is more noisy. Several of our patients reported abnormal sensations. For example, some reported feeling some point stimuli as area stimuli or feeling some point stimuli in several locations. We did not systematically probe for or record these sensations, but they might have added a layer of noise not present in uninjured nerve territory. Additionally, many of our patients experienced pain, either as a direct result of the stimulation or as a consequence of the hand posture. Attention has been shown to play a crucial part in our ability to localise touch (see Hamburger 1980 for a review). Both abnormal sensations and pain could have diverted attention and might, thus, be the primary driver for the inflated absolute error. To investigate this, future studies should include a measure of regrowth and reinnervation errors (e.g. using microneurography). Using a different target configuration, it might also be possible to compare the observed error with the error

expected from increased noise or other mechanisms; especially, if not only absolute error but also other error measures are used as described above.

Concluding remarks

Our findings significantly enhance our understanding of the functional consequences of nerve injury, providing a far more rigorous and intricate account of touch localisation deficits due to median/ulnar nerve injuries than previously available. Our new method surpasses the capabilities of previous methods and provides a solid platform for which future investigations can build from.

Functional MRI shows evidence for reorganisation of digit maps in area 3b after peripheral nerve repair in human patients

Introduction

Digit representations in the primary somatosensory cortex (S1) are structured in a topographically organised hand map (Penfield and Boldrey, 1937; Paul et al., 1972b; Kaas et al., 1979). The hand representation is adjacent to that of the face and glabrous skin is represented in distinct areas from hairy skin. Even though the exact pattern of representation is idiosyncratic, there are several invariant characteristics that all maps follow. Electrophysiological studies in monkeys showed that each digit forms a continuous area of representation with the thumb most laterally followed by all of the other digits in the order they are arranged on the hand with only small areas of overlapping activation (Paul et al., 1972b, Kaas et al., 1979, Kaas, 1991). Hand maps reconstructed from functional magnetic resonance imaging data in humans show a similar, but slightly different, situation. Rather than forming a continuous area, representations form clusters of multiple yet contiguous activations (Besle et al., 2013, Sanders et al., 2023). Occasionally, individual hand maps show a second, non-contiguous representation of some digits (Besle et al., 2013). Despite this, activation clusters still follow the same general, lateral-to-medial digit organisation as seen in monkeys and neighbouring representations show a higher degree of overlap than non-neighbours (Sanchez-Panchuelo et al., 2010, Besle et al., 2013, Ejaz et al., 2015, Berlot et al 2019, Sanders et al 2023).

Hand maps are known to change after peripheral nerve injury and repair in animals (Kaas, 1991; Merzenich and Jenkins, 1993; Wall et al., 2002). This includes lasting changes to the spatial organisation of digits as well as a fragmentation of representations. Although several studies have used non-invasive brain imaging techniques to investigate brain changes after peripheral nerve repair in humans (see

Table 2), a detailed characterisation of changes to the topography of digit maps is still lacking.

Measuring digitopy

In animals, digit maps are measured with electrophysiology (Merzenich et al., 1978). Animals are anaesthetised deeply and the experimenter then stimulates the skin of the animal while simultaneously recording cortical responses. This makes it possible to clearly outline the area of the cortex responsive to a specific skin patch. With this method two distinct hand representations have been discovered in S1 that differ from one another in details; one in Broadman area 3b and another one in area 1.

Since invasive electrophysiology in humans is only possible in special circumstances two paradigms have been developed recently to measure hand maps with functional magnetic resonance imaging (fMRI). In the travelling wave or phase-encoding paradigm, digits are stimulated in sequence and the hand maps are constructed with a winner-takes-all approach (Sanchez-Panchuelo et al., 2010; Kolasinski et al., 2016). The advantage of this paradigm is that it leads to stable and reproducible digit maps (Kolasinski et al., 2016). But due to the sequential nature of the task and winner-takes-all approach, it is unsuitable to evaluate overlap between digit representations. All digits are always stimulated in sequence. Due to the spatial arrangement of the digit representations and the nature of the hemodynamic response, this would lead to an overestimation of the overlap of neighbouring representations.

To overcome the limitation of the travelling wave paradigm, a block design can be used in which the digits are stimulated in random order (Besle et al., 2013; Berlot et al., 2019). While requiring more data than the travelling wave, the block paradigm has been shown to yield similar digit maps (Besle et al., 2013). But in contrast to the travelling wave paradigm, it is suitable to assess the overlap of representation since the digits are stimulated in random order. This means that results are not biased towards greater overlap.

One important feature of digit maps is that they afford clear confirmatory hypotheses in healthy controls. All hand maps follow certain organisational principles

that can be checked. There is a clear anatomical sequence with the thumb presented most laterally and the little finger most medially (although not every digit representation might reliably activate for all participants (Sanchez Panchuelo et al., 2016; O'Neill et al., 2020)). Also, there is a certain amount of overlap expected between digit representations. This forms a predictable neighbourhood structure where the representations of neighbouring digits display a larger degree of overlap than non-neighbouring representations. In general, the further separated any two digits are on the hand, the smaller the overlap of their representations in S1. This makes it possible to ascertain whether the paradigm succeeded in measuring digit maps.

Cortical plasticity after nerve injury

Both the travelling wave and the block paradigm have been successfully used to study amputees (Kikkert et al., 2016; Wesselink et al., 2019), tetraplegia patients (Kikkert et al., 2021) and patients with musician's dystonia (Sadnicka et al., 2023). But they have not yet been applied to patients with peripheral nerve repair even though animal studies furnish us with clear predictions about the nature of the changes to expect. This is most likely because these paradigms have only been developed recently.

From the animal literature, there is a clear distinction between injury-driven and regeneration-driven reorganisation. Injury-driven reorganisation happens after deafferentation without or before regrowth of the injured nerve. In a classical paper, Merzenich et al. (1983) tracked changes to the hand maps in five squirrel and three owl monkeys that had undergone a median nerve lesion and ligation. They found that while some parts of the cortex deprived of its dominant input (S1-deprived) remained initially unresponsive, other parts started to respond to neighbouring areas innervated by the radial nerve. With time more and more of the territory became responsive to stimulations of radial or ulnar nerve, although the exact pattern of activation and overlap remained highly dynamic for several months. Merzenich et al. (1984) went further and showed that expansion of cortical representation is also observed after amputation of one or two digits. In this case, it is the representation of neighbouring, unaffected digits that come to occupy the former territory of the amputated digit. Similarly, the face representation expands to activate the deafferented area after an

amputation of the complete hand Florence et al. (1998). Recent studies with human amputees (Kikkert et al., 2016; Wesselink et al., 2019) and tetraplegia patients (Kikkert et al., 2021) have, however, revealed that in humans digit maps seem to be maintained even years after the injury.

In contrast to injury-driven changes where communication between receptors and the brain has been permanently interrupted, in regeneration-driven changes nerves are sutured after the lesion allowing them to regrow. Since regrowth is not topographically guided, however, the mapping between the periphery and cortex differs from the pre-injury state.

The most detailed study of regeneration-driven reorganisation has been done by Wall et al. (1986) who studied the sequence of these changes in four owl monkeys that had undergone a transection and immediate repair of their median nerve. Before the nerves had regrown, their findings were similar to Merzenich et al. (1983), but as regrowth proceeded the silenced digits again activated a progressively large territory of S1-deprived until only a small fraction of the territory was still responsive to neighbouring areas. The detailed organisation of the median representation had, however, become less distinct, with more areas of overlap, and in general the spatial arrangement was less typical. It is worth emphasising, though, that the maps were not completely disorganised and diffuse, but still displayed many of the characteristics of maps in healthy animals. These findings are consistent with Paul et al. (1972a).

Table 2. fMRI studies involving patients with peripheral nerve repair

Study	Number of patients	Reorganisation Measure
Taylor et al. (2009)	14[a] (median and/or ulnar nerve)	Amount of activation
Rath et al. (2011)	1 (median nerve)	Ratio of peak-voxel between S1-deprived and S1-healthy
Rosén et al. (2012)	4 (median nerve)	Ratio of volume of activation between S1-deprived and S1-healthy
Chemnity et al. (2015)	28[b] (median and/or ulnar nerve)	Amount of activation
Fornander et al. (2016)	4 (median nerve)	Ratio of volume of activation between S1-deprived and S1-healthy

Björkman and Weibull (2018)	18[c] (median nerve)	Amount of activation
Nordmark and Johansson (2020)	11 (median nerve)	Location of activation of index and little finger, %BOLD signal change

a: Only 11 patients were included in the fMRI part of the study. b: 22 patients sustained the injury during childhood, the rest during adolescence. c: Reanalysis of some of the patients first reported by Chemnitz et al. (2015)

There are only seven studies we are aware of with human nerve repair patients and none of them looks at digitopy (see Table 2 for an overview). Nordmark and Johansson (2020) attempt to look at digit representation. They do this by stimulating the index and little finger with a threshold and oddball detection task and find that irrespective of the task, both fingers are represented in roughly the same location in patients and controls. This is taken as evidence that patients regain their pre-injury digit representation. The method has, however, several shortcomings. It only stimulates D2 and D5. This means it is not able to capture the complete digit map. Yet, doing so is, of crucial importance as there is a clear expectation about both the spatial arrangement and the amount of overlap between digit pairs. They estimated the D2 and D5 territories by calculating the contrast where one of the digits has a higher activation than the other. This is essentially a version of the winner-takes-all approach which, as stated above, is not suitable to evaluate overlap between digits. Furthermore, the authors only do a univariate analysis. While this has some value, it has been shown that positive and negative activation taken together also encodes information which can only be decoded using a multivariate approach like representational similarity analysis. Finally, they used a group analysis to determine the region of interest. This is a common approach in fMRI, but unsuitable for measuring digitopy. While all digit maps in healthy controls follow certain organising principles, the actual structure of these maps varies considerably between individuals (Ejaz et al., 2015). This means that a group-based analysis, which by its nature conflates individual variations, will likely not be able to detect any changes that patients might have undergone.

To accurately measure digitopy, it is necessary to stimulate all digits randomly. Analysis of the sequential order alone is not enough. It is additionally important to characterise the amount of overlap of the representation for any digit pair.

Overlap between digit pairs can be characterised using a univariate approach, such as the Dice overlap coefficient (Dice, 1945; Kolasinski et al., 2016). This approach takes the activation volume of a given digit above a liberal minimum threshold and compares how much of that volume intersects with that of another digit. However, while this yields useful information, it relies on an arbitrary activation threshold. Not all digits of all participants might reliably cross this threshold - especially the little finger shows a larger degree of variability (O'Neill et al., 2020). Furthermore, any information that is contained in the signal below the activation threshold is discarded and lost for analysis purposes.

An alternative approach is the multivariate representational similarity analysis (RSA), also sometimes known as representational dissimilarity analysis. This method compares the entire pattern of positive and negative activation of two conditions within a given area with one another and calculates their similarity. The more alike the two activation patterns are, the smaller the representational distance. Representational distances are influenced not only by spatial distances of the representation alone, but have also been shown to reflect hand use with digits that are more frequently used together having a smaller representational distance (Ejaz et al., 2015).

Crucially, both the Dice overlap coefficient and representational distances have already successfully been employed on an individual level (Kolasinski et al., 2016; Berlot et al., 2019; Kikkert et al., 2021; Sanders et al., 2023). This makes a combination of both approaches ideal for studying map changes after peripheral nerve repair.

To address the fundamental gap in the literature identified, we used 3T fMRI to map cortical responses in S1-deprived of patients with a repaired median and/or ulnar nerve to stimulation of the injured hand using vibrotactile stimulations. This allowed us to measure univariate overlap and multivariate representational distances in the individual patient and assess in which way they differ from the organisation that can be observed in healthy controls. We hypothesised that digit maps in S1-deprived are less distinct and less typical (see Figure 13 D, E, F, H).

Correlation between cortical reorganisation and functional impairment

As we have shown in the last chapter, peripheral nerve repair leads to a striking reduction in the ability to localise touch. It has long been speculated that this phenomenon can be attributed to central factors (Stopford, 1926; Wall et al., 1986; Lundborg and Rosén, 2007). Wall et al. (1986) in particular make a strong argument why this should be directly linked to the reorganisation of the S1 hand maps. Both touch localisation impairment and cortical reorganisation are limited to the territory of the repaired nerve. Reinnervated skin regions are represented in several distinct cortical patches, some of which where the representation had been before injury while others are in the former territory of other digit representations. At the same time, stimuli are often perceived at multiple skin locations at once. Cortical patches vary in size and so do the skin areas with elevated localisation error. Both cortical reorganisation and localisation patterns are highly idiosyncratic after repair. Importantly, the authors point out that in the case of nerve crush pre-injury organisation of hand maps as well as touch localisation are re-established.

While there are strong similarities between cortical reorganisation and touch localisation impairments, it is important to stress that evidence of reorganisation of the hand maps comes from animal models whereas measurements of touch localisation exclusively come from human patients. It has, therefore, not yet been possible to test this hypothesis directly. By combining the touch localisation data presented in the previous chapter with cortical reorganisation measures presented here, we aim to directly validate the hypothesis of Wall et al. (1986). If the connection they make is correct, cortical reorganisation in S1 would be maladaptive. So, we hypothesise that more reorganisation results in reduced touch localisation.

Ipsilateral changes

In addition to the literature that suggests reorganisation of contralateral digit maps after peripheral nerve repair, there is another, separate literature that looked at changes in the activity of S1-deprived after stimulation of the uninjured hand (ipsilateral responses). While in healthy controls, brain activity ipsilateral to the stimulated hand

does not show reliable positive or negative activation relative to rest (Francis et al., 2000; Hlushchuk and Hari, 2006), it was observed that after chronic deafferentation in rat models, ipsilateral responses were less negative or positive (Pelled et al., 2009; Pawela et al., 2010). This is consistent with findings from human amputees (Philip and Frey, 2014; Valyear et al., 2020) and even with findings from otherwise healthy participants whose arm had been immobilised for 72h (Björkman and Weibull, 2018).

Only a few studies in human nerve repair patients have reported similar findings. Chemnitz et al. (2015) found in a study of 28 patients who had been injured in childhood or adolescence, that patients who had been injured in adolescence (n = 6, all median nerve repair) showed less negative activity relative to rest ipsilateral to the stimulated hand than patients injured in childhood or healthy controls. This was true both for stimulation of the injured as well as the uninjured hand. A result confirmed by Björkman and Weibull (2018) in a reanalysis of the same data. In contrast to this, Nordmark and Johansson (2020) in a study involving 11 median nerve patients only found more positive BOLD activity ipsilateral to the uninjured hand, but not ipsilateral to the injured hand.

Based on these prior studies we predicted that patients should show more positive-going activity ipsilateral to the uninjured hand relative to rest. The situation is less clear for stimulations to the injured hand. Additionally, these findings are based only on two data sets with comparatively few patients. Here we test these hypotheses with a larger patient population.

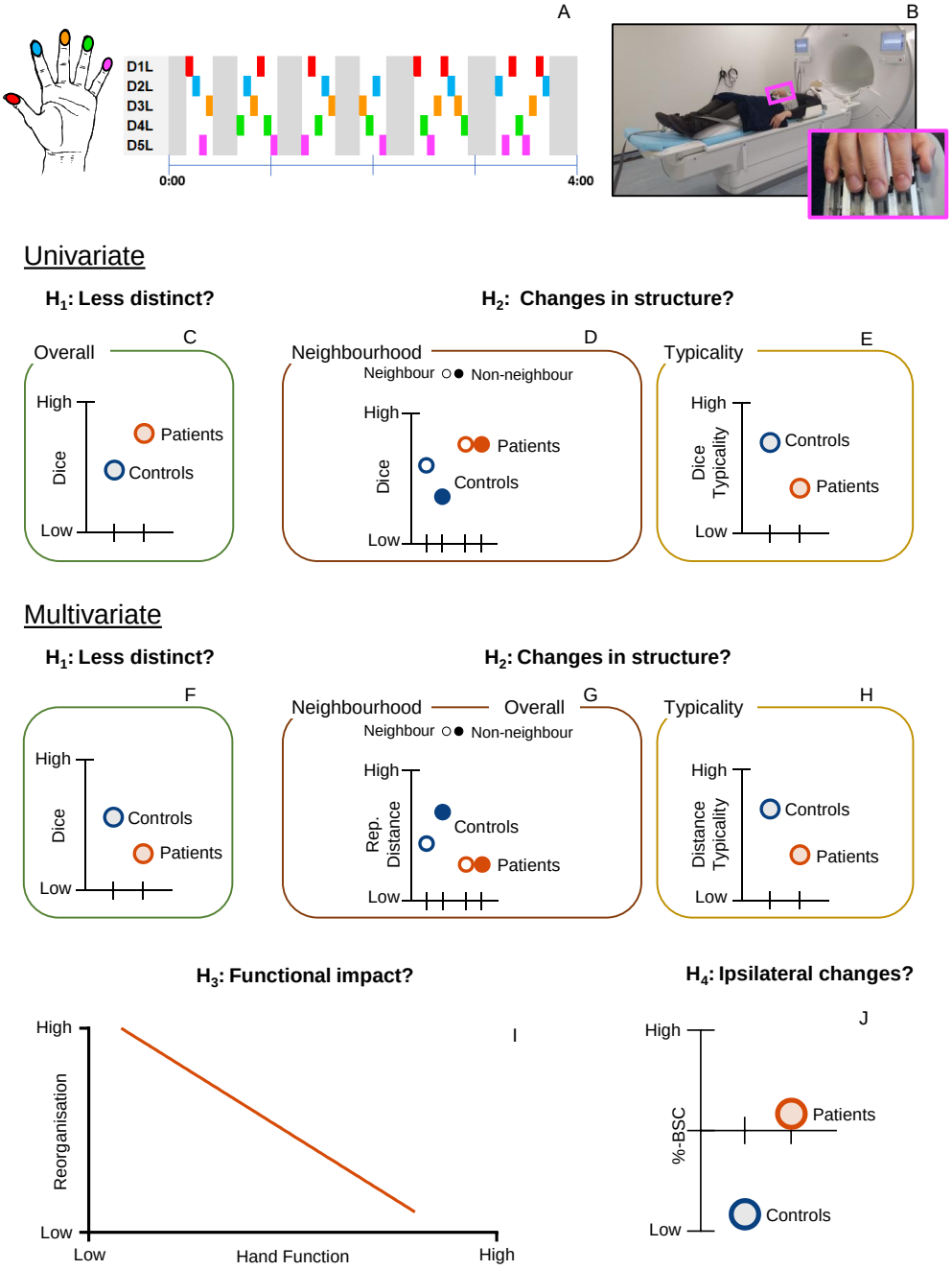

Figure 7. fMRI experiment setup and predictions. A: Example of a run for one participant. Colours represent different digits as indicated in the inset. Grey represents a fixation period. Note that one stimulation block consists of the stimulation of each digit once. Rest periods can occur within a block or at the end of a block. **B:** The stimulators were held by a custom-built gauntlet and digits were aligned to the wafer. The gauntlet was located on the participants lap, stomach or chest as preferred by the participant. **C to E:** Predictions for univariate Dice overlap coefficient. **F to H:** Predictions for multivariate representational distances. **I:** Predicted correlation between cortical reorganisation and hand function. **J:** S1-deprived is predicted to show less suppression for the stimulation of the ipsilateral (healthy) hand. Note that while patients are shown with positive %BSC, this is not necessarily the case.

Methods

Participants

Patients. Twenty-one patients completed testing (age range: 29 - 75 years; mean age: 39.6 years; seven female). In the complete data set, eighteen patients had complete transection injuries: three median, ten ulnar and five median and ulnar. The remaining three patients had incomplete transection injuries of the median nerve.

All patients had sustained their injuries in adulthood (mean: 35.6 years; median: 34 years; range: 17—64 years). Time-since-repair (and when tested) ranged from 7 to 139 months (mean: 47.4 months; median: 37 months). Three patients were left-handed according to the modified version of the Waterloo Handedness Inventory. Ten patients had injured their dominant hand.

Healthy controls. Thirty-two control participants completed testing. Of these, one participant had to be removed due to excessive movement during the fMRI scans (> 3 voxels) and two due to technical problems leaving twenty-nine participants in the data set (age range: 19—63 years; mean age: 31.0 years; 13 female). Two participants were left-handed.

All participants gave informed consent before taking part in the study. Procedures were approved by the Bangor University School of Human and Behavioural Sciences Ethics Board and by the NHS Ethics Committee Wales Rec 5. Patients and 28 healthy controls completed the reported tests as part of a larger study, also involving touch localisation tests. These data have been reported in the previous chapter. The tests reported here took approximately 2.5 hours to complete. Participants received financial compensation.

Somatosensory mapping

Setup and materials

Cutaneous sensory stimulations were administered to the distal pads of the digits using a custom-built 8-channel device that delivered vibrotactile stimulations. Each stimulator consisted of an encased piezoelectric strip with a circular waver at the end that delivered the stimulation to the digit. Since the maximum amplitude was larger for some stimulators than for others (measured mechanically), the stronger stimulators were run at slightly below maximum amplitude. This ensured that the perceived stimulation strength was approximately similar for all stimulators.

The stimulators were held in place by a custom-built gauntlet that followed the curvature of the hand and allowed sliding of the stimulators to accommodate different hand sizes. The gauntlet was placed on the participant's chest, stomach or lap as the participant preferred. Care was taken to align the wafers with the whirl of each finger. If the gauntlet was not enough to ensure that the digits stayed over the wafer, tape was used to help keep the digits in place. In a few cases, patients had difficulties straightening their digits and then only tape was used to fixate the stimulators.

Procedure

The left and right hands of both groups were tested in two separate sessions - one per hand. For patients, the injured hand was always tested first. This was done to prioritise measurement of the injured hand, in the event that a patient decided to discontinue testing. There were five scans per hand. One participant only underwent four scans for their injured and three scans for their uninjured hand due to feelings of anxiety while in the scanner. For healthy controls, hand order (left/right) was counterbalanced between participants.

Before the first scan session, each digit was stimulated outside the scanner. This was done to ensure that participants were able to perceive the stimulation. All participants reported feeling something, even if, for some patients, the sensation was not localised to the tip of the finger.

Each session started with a scout scan followed by four functional runs and ended with a field map scan. An additional anatomical scan was collected during the first session. This was usually done after all functional runs had been completed but could be advanced if the participant felt tired and needed a break.

Each functional run lasted approximately 4 minutes in which each of the 5 digits was stimulated separately. Thus, there were five conditions per run (D1, D2, D3, D4, D5) corresponding to each of the digits on each hand (thumb, index, middle, ring, little). Each condition was repeated seven times within a single run. The order of stimulation within a run was pseudo-randomised, controlled for condition history and counterbalanced between runs participants. Stimulations were delivered in a block design. Each block comprised 4s of stimulation alternating between 500ms of vibrotactile pulses at a frequency of 30Hz and 500ms rest. The on-off pattern of stimulus delivery was done to minimise sensory adaptation. Each functional run started with a 10s fixation period. During each run, there were five fixation baseline periods the length of which were randomly jittered between 13s and 16s and it ended with a rest period that lasted between 6s and 21s depending on the length of intermediate rest periods. In 30 scans, however, the final rest period was only between 2s and 6s long because one or several of the synchronisation signals from the scanner were missed. One run for one participant only included six stimulations for two of the conditions due to technical problems.

Throughout the experiment, participants were instructed to lay still and to passively pay attention to the stimulations. Participants were asked after every functional scan whether they could feel the stimulation at each fingertip. If they could not feel the stimulation on all digits, the run was repeated. This was done both for patients and controls. Patients sometimes reported abnormal feelings or that they perceived some of the stimulations as weaker. In that case, the run was not repeated as long as they could feel the stimulation.

MRI parameters

Scans were performed on a Philips 3T “Ingenia Elition X” using a standard bird-cage radio-frequency coil. Functional MRI scans were performed via T2*-weighted

functional scans with echo-planar imaging sensitive to the blood-oxygen-level-dependent contrast (BOLD-EPI)), with an acceleration factor of 4. These scans used the following parameters: time to repetition (TR) = 2000 ms, time to echo (TE) = 30 ms, flip angle = 90°, matrix size = 112 x 110 x 58 slices, FoV = 224mm x 220mm x 116mm, 58 contiguous axial slices (no gap) with interleaved order, multi-band = 2, thickness = 2.0 mm, in-plane resolution at 2.0mm by 2.0 mm, bandwidth = 1905 Hz/pixel. Each BOLD scan comprised 120 volumes (240 s). The first two volumes in each scan were discarded to allow steady-state magnetization to be approached.

One high-resolution T1-weighted structural image was acquired using a multiplanar rapidly acquired gradient echo (MP-RAGE) pulse with the following parameters: time to repetition (TR) = 1500ms, time to echo (TE) = 3.45ms, flip angle = 8°, matrix size = 224 x 220 x 175 slices, field of view (FoV) = 225mm x 225mm x 175mm, 175 contiguous transverse slices, thickness = 1.0 mm and in-plane resolution = 1.0mm by 1.0mm. The total duration of the T1-weighted structural scan was 5:38 min. The fMRI session concluded with a double gradient echo sequence to acquire a field map used to correct for EPI distortions.

fMRI pre-processing

DICOM images were converted to NIFTI using mcverter version 2.1.0 version 434. Structural and functional fMRI data was pre-processed and analysed using fMRIB's Software Library (FSL v6.0, http://www.fmrib.ox.ac.uk/fsl/) (Smith et al., 2004). Non-brain structures were removed using BET. Head movement was reduced using MCFLIRT motion correction. EPI unwarping was performed to correct for distortions due to magnetic field inhomogeneities using FSL PRELUDE and FUGUE. For this a separate field map was collected following the functional runs; except for the first 6 participants for who no field maps had been collected.

Slice-time correction was applied. Intensity normalization was applied using "grand mean scaling", wherein each volume in the dataset was scaled by the same factor to allow for valid cross-session and cross-subject statistics. High-pass temporal filtering (90s cut-off) was applied to remove low-frequency trends. EPI unwarping was carried out with an effective EPI echo spacing of 0.37ms and a signal loss threshold of 10%.

Functional data were registered with the high-resolution structural image using boundary-based registration (Greve and Fischl, 2009), and resampled to 1mm x 1mm x 1mm resolution using MCFLIRT; these images were then registered to standard images (Montreal Neurological Institute MNI-152) using FNIRT linear registration at 12 degrees of freedom. Time series statistical analysis was carried out in FEAT v.6.00 using FILM with local autocorrelation correction (Woolrich et al., 2001).

fMRI data analysis

The hemodynamic response function was modelled by explanatory (predictor) variables (EVs) locked to the onset and modelling the duration of the vibrotactile stimulation at each site: D1, D2, D3, D4 and D5. Additional covariates of no interest were included based on the mean time series of the whole-brain, and single-point predictors for each time point of high-motion outliers. Outliers were identified within each run as time points with a framewise displacement exceeding 1.5*interquartile range above the third quartile using FSL Motion Outliers.

Using these EVs, first-level contrasts of parameter estimates (COPEs) were calculated for each of the following contrasts: D1 > Rest, D2 > Rest, D3 > Rest, D4 > Rest and D5 > Rest. Second-level analyses were performed for each participant by combining first-level analyses (i.e. all functional runs per hand) using a fixed-effects model.

ROI analysis

Left and right hemisphere S1 regions of interest (ROIs) were defined based on the individual anatomy. We aimed to confine our analysis to the central sulcus as Brodmann area 3b is located here (Penfield and Boldrey, 1937). For this, researchers first used the landmarks of the brain to manually identify the central sulcus of each participant. The course of the central sulcus that was visible on functional scans that were transformed to individual anatomical space was traced manually in fsleyes (v1.3.0). To stay within the central sulcus, the contrast was manually adjusted to provide a clear outline of the sulcus. The extent of the mask was 20 slices (10 above/below the manually identified hand knob). This was done to exclude pre- and post-central gyri. Areas at the intersection of sulci where it was not clear whether they belonged to the central sulcus

or another sulcus were included in the mask as the inclusion of these areas leads to more conservative values for our predictions. Depending on the dependent measure, the mask was then further restricted functionally as described below.

Dependent measures

Distinctness and typicality of contralateral digit maps were measured twice. Once with a more traditional univariate analysis and then again using a multivariate analysis that has been developed more recently. This was done to directly compare and contrast results from these two methods. Ipsilateral activation was measured using univariate analysis only.

Dice overlap coefficient. The pairwise Dice overlap coefficient is a univariate measure of cortical organisation. Digit-specific activation maps within the central sulcus were functionally defined based on the individual response averaged over all functional scans for that hand. For each ROI the defining contrast was: Digit > Rest. The contrasts were minimally thresholded at $z \geq 2.0$ which is lower than what is acceptable in most fMRI studies but is in line with other Dice analysis in the literature (e.g. Kikkert et al 2016). These masks were then anatomically restricted by intersecting them with the contralateral anatomical mask of that participant.

The number of voxels within the digit-specific maps as well as in the intersection of these maps was calculated using the FSL fslstats command. The voxel count of the intersection of the digit-specific maps was then divided by the voxel count of the smaller of the two digit maps (in contrast to the classical definition of the Dice coefficient, but in line with previously published work in digitopy (Sanders et al., 2023). This results in 10 coefficients per hand per participant which were calculated using R.

$$D_{AB} = \frac{A \cap B}{\min(A, B)}$$

Representational distances. The pairwise representational distance is a multivariate measure of cortical organisation (Ejaz et al., 2015). They are estimated by calculating the similarity of the activation pattern of two digits, taking into account the entire range of β-values within all voxels of the anatomical central sulcus ROI.

Representational (cross-validated Mahalanobis) distances between the individual digit representations were calculated using the Matlab library rsatoolbox_matlab (freely available at https://github.com/rsagroup/rsatoolbox_matlab).

Absolute localisation error and misreferrals. Functional impairment was measured using the touch localisation results reported in the previous chapter. Briefly, absolute localisation error is the Euclidian distance (in mm) between the point the participant was stimulated at (target) and the point where they indicated that they felt the touch (response). Misreferrals are responses made on another digit than the one stimulated or on the palm. For every patient, misreferrals were excluded and the mean localisation error within the territory of the hand serviced by the injured nerve(s). Misreferrals in response to stimulation of the injured hand were analysed separately and expressed as a proportion of the maximum number of stimulations.

Ipsilateral %-BOLD signal change. To analyse activation ipsilateral to the stimulated hand, we calculated the mean percent blood-oxygenation-level dependent (BOLD) signal change (%-BSC) within the area of the central sulcus that was activated by stimulation of the contra-lateral hand using the FSL featquerry command. Contra-lateral activation was used to identify the hand area to avoid double-dipping. First, the functional representations of the individual digits were calculated at a conventional threshold of $z \geq 2.3$ and then anatomically restricted, as described above. Then hand area was defined by the union of the digit-specific ROIs.

Analysis

Neighbourhood structure. There are clear predictions that neighbouring digits should have a larger degree of overlap than non-neighbours in healthy controls. This makes it not only suitable for investigating reorganisation in patients, but also as a quality check for our controls data. To test whether control participants showed the expected neighbourhood structure, we calculated the mean value for neighbours and non-neighbours per individual per hand. A two-way repeated measures ANOVA was calculated to test for a main effect of hand (dominant hand, non-dominant hand) a main effect of neighbourhood (neighbour and non-neighbour) and an interaction between the two. If there was no effect of hand and no interaction effect, we collapsed across

hands and calculated a paired-sample t-test to evaluate whether the values differed between neighbours and non-neighbours. Otherwise, we calculated the same paired-sample t-test for each hand individually. Cohen's d was calculated using the R package rstatix which uses standard deviation of differences for paired –sample t-tests and pooled estimates for independent-sample t-tests (Kassambara 2023).

To test whether there was a change to the neighbourhood structure in patients, we first excluded all digit-pairs that did not lie within the injured territory. The expected neighbourhood structure results in larger degree of overlap for neighbours than non-neighbours. After nerve repair, it is expected that this difference becomes less pronounced or even vanishes entirely. At the same time, it is also expected that digit-pairs serviced by the injured nerve also display generally increased overlap for all digit-pairs within the injured territory. So, if we compare values of neighbouring digit-pairs serviced by the injured nerve with values of non-neighbouring digit-pairs serviced by the uninjured nerve, any changes to the neighbourhood structure would likely be masked by changes to the injured territory as a whole. This comparison is, therefore, problematic. That means that for isolated median nerve injuries, we only included six digit-pairs (D1-D2, D1-D3, D1-D4, D2-D3, D2-D4 and D3-D4) while we included all digit-pairs for combined median and ulnar nerve injuries. For isolated ulnar nerve injuries, there is only one digit-pairing that falls within the injured territory: D4-D5. Since there is no non-neighbouring digit-pair within the injured territory to test it against, isolated ulnar nerve patients were excluded from the neighbourhood analysis.

To compare controls against patients, the controls' data were formulated to 'match' the patient group based on the proportions of patients with injuries to their dominant median or combined median and ulnar nerves or injuries to their non-dominant median or combined median and ulnar nerves. Specifically, there are two patients with an isolated median nerve injury to their dominant hand (~18% of the group after exclusion isolated ulnar patients) and four patients with an isolated median nerve injury to their non-dominant hand (~36% of the group after exclusion of isolated ulnar patients). Thus, if there was a difference in the neighbourhood structure between hands, six controls were treated as having an isolated median nerve injury to their dominant hand (~20% of the group) and twelve were treated as having an isolated median nerve

injury to their non-dominant hand (~41% of the group). If there was no difference between hands, we collapsed across hands for a total of eighteen controls treated as having an isolated injury.

Two two-way mixed ANOVAs was calculated to test for a main effect of group (S1-deprived and controls, or S1-healthy and controls) a main effect of neighbourhood (neighbour and non-neighbour) and an interaction between the two. If the controls' data had been collapsed across hands, the same values were entered into both ANOVAs. Otherwise, the data of the 'simulated injured' hand compared against S1-deprived and the data of the 'simulated uninjured hand' against S1-healthy. If there was an interaction between group and neighbourhood, we calculated post-hoc paired-sample t-tests for each group to evaluate for which group the difference between neighbour and non-neighbour was weaker.

An analogous procedure was used for representational distances.

Distinctness. To assess whether digit maps in S1-deprived were less distinct than in S1-healthy and control participants, the mean Dice overlap coefficient per hemisphere per participant was calculated. A paired-sample t-test was calculated to test whether there was a difference in overlap between S1-deprived and S1-healthy.

For healthy controls, a paired-samples t-test was used to evaluate whether there were differences between the hemispheres contralateral to the dominant and non-dominant hand. If no differences were observed, controls were averaged across hands. Then two unpaired t-tests were used to test whether the overlap differed between patients and controls. Otherwise, control's data were again formulated to 'match' the patient group based on the proportions of injured nerve and injured hand. The logic was analogous to the one described for neighbourhood structure above, except that this time isolated ulnar nerve cases were also included.

An analogous procedure was used for representational distances.

Typicality. To assess the typicality of the overlap pattern, we calculated the correlation between the Dice coefficient pattern of a participant with the mean pattern of controls as described by Wesselink et al. (2019). For patients, a paired-sample t-test

was calculated to test whether there was a difference in typicality between S1-deprived and S1-healthy.

For controls, we used a leave-one-subject-out analysis. The correlation between the pattern of one healthy control and the mean pattern of all other controls was calculated. This was first done separately for each hemisphere. A paired-samples t-test between hemispheres of the dominant and non-dominant hand was used to evaluate whether there were differences between the hemispheres contralateral to the dominant and non-dominant hand. If no differences were observed, controls were averaged across hands. Then two unpaired t-tests were used to test whether the typicality differed between patients and controls.

An analogous procedure was used for representational distances.

Functional impact of reorganisation. To test whether there was any relationship between reorganisation of the digit maps and impairment, we calculated a correlation between the difference between the absolute localisation error of the injured territory minus the homologous territory on the other hand and each of our measures for contralateral reorganisation that yielded a significant difference for S1-deprived (mean Dice coefficient, typicality of Dice coefficient pattern, typicality of representational distance pattern) per patient. Note that two patients had been excluded from this analysis as they could not flatten their hand enough to have their injured hand tested.

Ipsilateral BOLD signal change. To assess whether ipsilateral activation was less negative relative to rest in S1-deprived than in S1-healthy, a paired-sample t-test was calculated. For controls, we first tested whether there were differences between the hemispheres contralateral to the dominant and non-dominant hand using a paired-samples t-test. If no differences were observed, controls were averaged across hands. Then two unpaired t-tests were used to test whether the overlap differed between patients and controls.

Additionally, we tested whether the value of ipsilateral activation depended on how much time had passed since the nerve repair. We calculated a correlation between time since repair and the %BOLD signal change per patient.

Results

Figure 8 provides a qualitative overview of the data collected with our paradigm. A digit map from one control (Fig. 8A) is shown as an example. The control participant shows a clear gradient of representation of all digits in order from the thumb most laterally to the little finger most medially. This is especially clear in the right hemisphere. In the left hemisphere, the gradient is weaker but still discernible. While there is some variation between participants and not all digits activate robustly for every participant, qualitatively most control participants conform to the expected topographical organisation of digit representations. This is supported by quantitative analysis (see below).

Figure 8B shows the digit maps of one sample patient. This patient had an injury to their left median nerve, so the right hemisphere is S1-deprived. The map in S1-deprived displays what looks like a big swath of overlap between the individual digit representations. S1-healthy, however, still shows the expected topography, albeit not as clearly as the control participant above. This is a qualitative pattern that can be observed in many patients and is again supported by the quantitative analysis below.

Univariate measures: Dice coefficients

The Dice coefficient is a measure of overlap between two maps. In our case, the overlap between the minimally thresholded, positive-going activation maps of the individual digits within the central sulcus. Due to the graded preferential nature of digit responses and the spatial extent of the hemodynamic response, some overlap between digits is expected. Crucially, the degree of overlap is expected to differ for different pairs of digits. Adjacent digit representations will show a higher degree of overlap and, hence, a larger Dice coefficient. And, generally, this extent of overlap is expected to fall off with increased cortical distance between digit representations. The expected topography of cortical digit representation in healthy control participants starts with the thumb positioned most laterally and then progresses in the medial direction along the sulcus through all digits to the little finger in order.

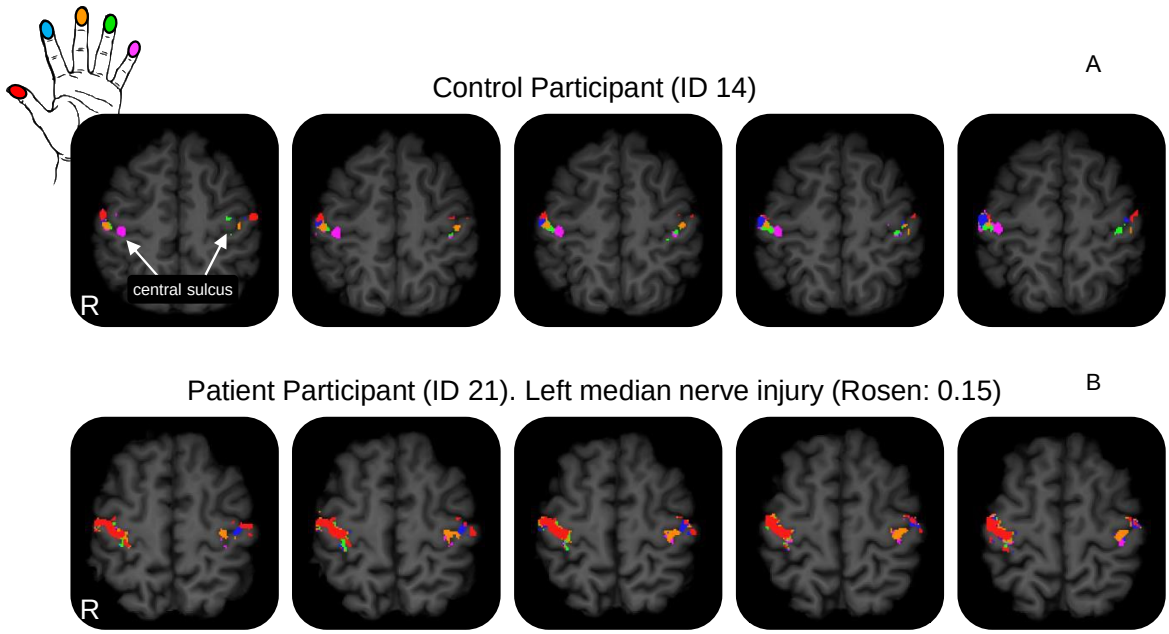

Figure 8. Volumetric digit maps. **A:** Positive activation of a sample control participant in volume space (threshold z ≥ 2.3). Colours represent the digit stimulated (see insert). **B:** Positive activation of a sample patient in volume space (z = 2.3).

Figure 9A shows the expected and actual mean overlap between digit representation averaged across all participants for controls, S1-deprived and S1-healthy. To test whether control participants show the expected difference between neighbouring and non-neighbouring representations, we calculated the mean Dice coefficient of neighbouring and non-neighbouring representations per participant. A two-way repeated measures ANOVA showed a main effect of neighbourhood ($F(1, 28)$ =

110.1, $p < 0.001$), no main effect of hand ($F(1, 28) = 2.56$, $p = 0.121$) and, importantly, no interaction effect (NxH: $F(1, 28) = 0.0006$, $p = 0.981$). Neighbours had a larger Dice coefficient than non-neighbours (mean of differences ± 95%CI: 0.14 ± 0.027), in line with predictions. This shows that our stimulation paradigm is indeed successful in capturing the known topographic arrangement of digit representations.

As reviewed above, peripheral nerve transection and repair leads to characteristic regeneration-driven cortical reorganisation in area 3b. This includes smaller receptive fields, some of which are in abnormal locations, multiple discontinuous cutaneous fields, large Pacinian-like receptive fields and a more extensive overlap between representations than before the injury, as well as larger idiosyncratic differences between individual maps. Translated to Dice coefficients this should result in a loss of distinctness between digit representation and a weakening or even breakdown of the neighbourhood structure.

Loss of distinctness

To evaluate loss of distinctness, we calculated the mean Dice coefficient averaged over all digit representations (Fig. 9B). We predicted that an increase in the overlap of representations should result in an overall increase in Dice coefficients specific to S1-deprived. T-tests showed that the mean Dice coefficient was significantly elevated compared to controls ($t(48) = 2.11$, $p = 0.0405$, Cohen's $d = 0.60$) and also compared to S1-healthy ($t(20) = 2.67$, $p = 0.0148$, Cohen's $d = 0.58$). In contrast, S1-healthy did not significantly differ from controls ($t(48) = 0.568$, $p = 0.573$, non-parametric Mann-Whitney test: $U = 273$, $p = 0.546$, $r = 0.09$). This result reveals an increased overlap between digit representations in S1-deprived.

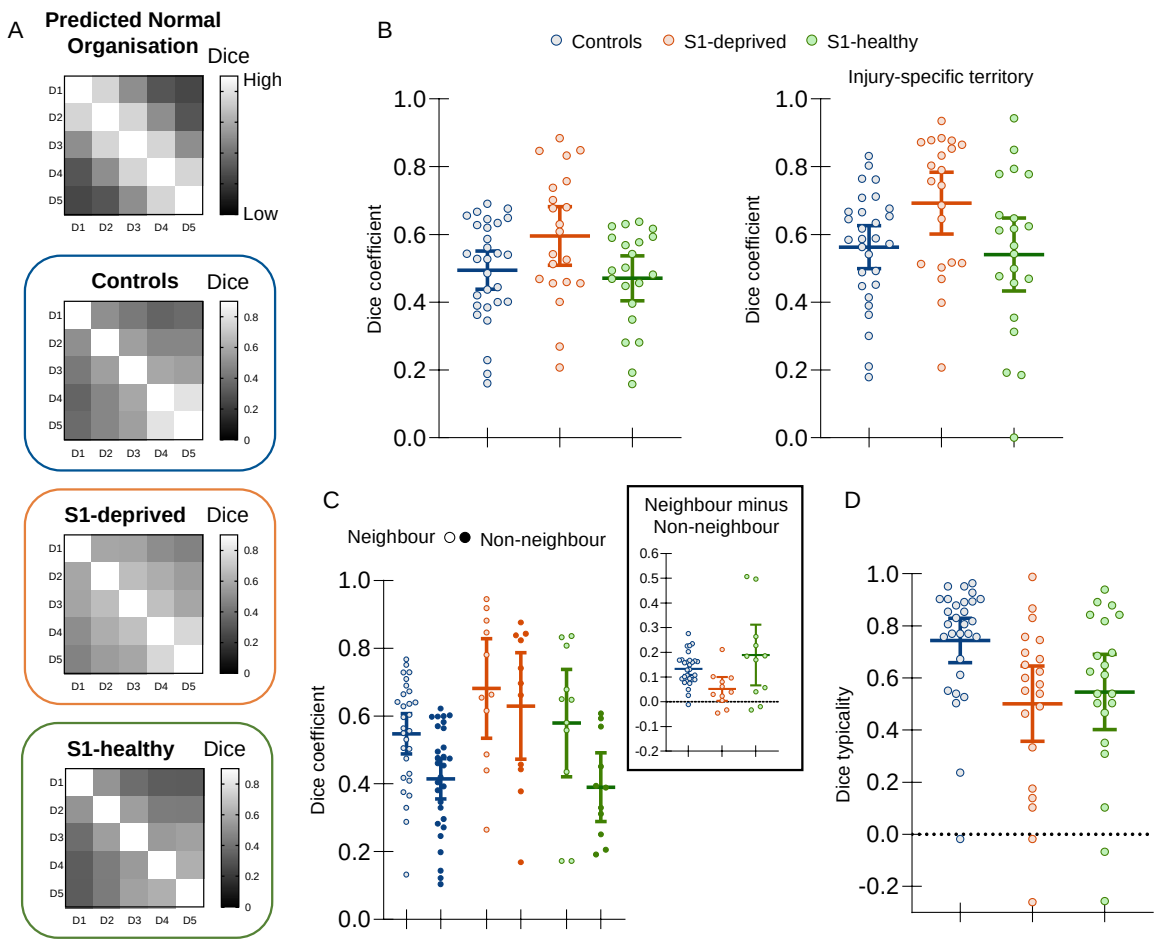

Figure 10. Univariate analysis: Dice coefficients. Error bars represent mean and 95%CI. A: Actual Dice coefficient patterns for control participants, S1-deprived and S1-healthy of patients. Each pattern represents the mean across all participants in this group. B: Mean of Dice coefficients over entire area 3b and over injury specific territory. C: Mean Dice coefficients of neighbouring and non-neighbouring representations only for digit pairings for which both representations are serviced by the injured nerve. The insert shows the same information as difference score between neighbours and non-neighbours. D: Typicality of Dice coefficients. 1 represents total agreement with the mean control pattern, 0 represents no agreement, -1 represents a pattern that is the exact opposite of the mean control pattern. Note that values for controls are the result of a leave-one-subject-out analysis.

Further, based on the animal literature reviewed above, S1 reorganisation after nerve transection and repair is expected to be limited to the zone serviced by the injured nerve. So, focussing on the injured zone should increase the effect observed above. We, therefore, repeated these analyses targeting only those digit pairs serviced by the injured nerve. This leads to an increase in the robustness of the results compared to controls ($t(48) = 2.57$, $p = 0.0132$, non-parametric Mann-Whitney test: $U = 186$, $p = 0.0194$, $r =$

0.27) and S1-healthy (t(20) = 2.8, p = 0.011, Cohen's d = 0.58), while the effect size of the difference between S1-healthy and controls remained similar to the effect size with all representations included (t(48) = 0.345, p = 0.731, Cohen's d = 0.17). These results reveal that nerve repair leads to increased overlap and that this is more pronounced in the digit representations serviced by the injured nerve.

Altogether, this offers evidence for reorganisation resulting in a general loss of distinctness between digit representations. Moreover, the reorganisation is specific to S1-deprived and within S1-deprived to the zone that formerly was preferentially activated by the injured nerve, in line with findings from animal studies.

Changes in the representational structure

It is possible to see an overall increase in Dice coefficients even though the structure of the representation remains unchanged. This would be, for instance, the case if the representational volume of both neighbours and non-neighbours are elevated by a similar amount or if the overall elevation is primarily driven by increased overlap in neighbouring representations. We, therefore, investigated in how far the structure of the representational overlap differs between patients and healthy controls. As above, changes are expected to be specific to the injured zone.

Neighbourhood. We first evaluated whether the difference in the overlap between neighbours and non-neighbours can still be observed in patients. For this, we repeated the analysis we had carried out with controls (Fig. 9C).

It is important to note that this approach has an important limitation. Both digit representations participating in the overlap calculation must be located within the injured territory. But for patients with isolated ulnar nerve injuries, the only digit-pair that is within the injured cortical zone is the D4 and D5 pairing. This means that there are no non-neighbouring pairs within the injury zone for which to compare against. Comparing the overlap between D4 and D5 to that between either of these two representation to a digit outside of the injured zone for isolated ulnar nerve patients would inflate the difference between neighbours and non-neighbours (because overlap is more pronounced for representations serviced by the injured nerve). We are,

therefore, forced to restrict this analysis of neighbourhood structure to patients with isolated median nerve injuries or injuries to both the median and ulnar nerves.

A two-way mixed effects ANOVA between S1-deprived and healthy controls showed a main effect of neighbourhood ($F(1, 38) = 61.0$, $p < 0.001$) and of group ($F(1, 38) = 8.01$, $p = 0.007$) as well as an interaction effect ($F(1, 38) = 11.9$, $p = 0.001$). Similarly, a two-way repeated measures ANOVA between S1-deprived and S1-healthy showed a main effect of neighbourhood ($F(1, 10) = 18.7$, $p = 0.002$) and a significant effect of hemisphere ($F(1, 10) = 5.23$, $p = 0.045$) as well as a non-significant interaction ($F(1, 10) = 4.78$, $p = 0.054$). Post-hoc analysis revealed that the difference between the mean overlap of neighbours and non-neighbours was smaller for S1-deprived than for S1-healthy and controls (S1-deprived: mean of differences ± 95%CI = 0.0518 ± 0.0482, $t(10) = 2.40$, $p = 0.038$, Cohen's $d = 0.72$, S1-healthy: mean of differences ± 95%CI = 0.189 ± 0.123, $t(10) = 3.42$, $p = 0.007$, Cohen's $d = 0.96$, controls: mean of differences ± 95%CI = 0.133 ± 0.0248, $t(28) = 11.0$, $p < 0.001$, Cohen's $d = 2.05$). This result shows that there still is a reliable neighbourhood structure in S1-deprived - yet the magnitude of the difference is reduced. This suggests a weakening of the structure.

In contrast, a two-way mixed ANOVA between S1-healthy and healthy controls only showed a main effect of neighbourhood ($F(1, 38) = 69.3$, $p < 0.001$), but not of group ($F(1, 38) = 0.004$, $p = 0.95$) nor did it show an interaction effect ($F(1, 38) = 2.07$, $p = 0.16$). This demonstrates the specificity of the changes. The neighbourhood structure remains comparable to controls for S1-healthy.

We, therefore, see evidence for, if not a complete breakdown at least a weakening of the neighbourhood structure in the injured zone of patients. The difference in the overlap between neighbours and non-neighbours is reduced in S1-deprived.

Typicality. Typicality measures the correlation of the complete overlap pattern of an individual participant to a canonical pattern. High correlation coefficients indicate good agreement with the canonical pattern and, thus, high typicality. High typicality suggests a pattern of overlap between digit pairs that closely resembles the expected pattern based on the known topographic organisation of 3b. In our study, we took the mean pattern of control participants as an approximation of the canonical pattern

against which we compared patients. To calculate typicality in controls, we used a leave-one-subject-out analysis. This involves calculating the correlation between the overlap pattern of one individual against the mean pattern of all other control participants excluding this individual. Note that not necessarily all individuals will show a high correlation with the mean. The spread of correlation coefficients across all control participants, therefore, is a measure of the inter-subject variability of the sample. It is expected that most individuals will conform closely to the canonical pattern which means that the spread of values should be smaller for controls than for S1-deprived. This gives us another possibility to evaluate expectations based on known organisational principles.

In contrast to neighbourhood structure, typicality offers a more fine-grained assessment of structure that does not require averaging Dice coefficients and can, therefore, take account of the complete relative pattern of overlap. This allows for a more detailed assessment of structure than what is possible with neighbourhood analysis. It is possible that, although neighbours and non-neighbours can still reliably be distinguished in S1-deprived, patients deviate in other ways from the canonical pattern. As described above, there is a well-established topography in humans (and, in fact, many non-human mammals as well) which leads to a characteristic pattern of overlap that most people will closely adhere to. In contrast, reorganisation not only means that patients, in general, diverge from this pattern, but since reorganisation is highly idiosyncratic, it is also expected that the spread of patients should be larger than that of controls. Additionally, it allows including isolated ulnar cases in the analysis.

Figure 9D shows the results of the typicality analysis. As expected from animal models, we found that S1-deprived is significantly less typical than controls (difference between means ± 95%CI: -0.24 ± 0.15, $t(48) = 3.19$, $p = 0.003$, non-parametric Mann-Whitney test: $U = 143$, $p = 0.0012$, $r = 0.45$) and also the range of values was larger for patients (S1-deprived: 1.25, controls: 0.98). Unexpectedly, the changes appeared in both hemispheres. The typicality of S1-healthy, contralateral responses to stimulation of the uninjured hand, was also significantly less than controls (difference between means ± 95%CI: -0.20 ± 0.15, $t(48) = 2.59$, $p = 0.013$, non-parametric Mann-Whitney test: $U = 173$, $p = 0.0090$, $r = 0.45$) with a larger spread of values (S1-healthy: 1.20) and the difference

between S1-deprived and S1-healthy was not significant (difference between means ± 95%CI: -0.04 ± 0.20, t(20) = 0.461, p = 0.650, Cohen's d = -0.10). This suggests that both hemispheres of patients depart from the expected canonical pattern.

Multivariate measures: Representational distances

In contrast to the Dice coefficient, which is a univariate measure of brain activation, the representational (dis)similarity analysis is a multivariate measure that quantifies the relationships between voxels and, thus, the full pattern of activity within a region, including correlations between voxels. Additionally, it is not limited to positive-going activity, but uses the full spectrum of positive and negative activation within the region of interest. Since a decrease of activation from baseline also represents an important component of processing, this allows to salvage more of the information contained within a specific activation pattern. We calculated the representational distance between any two digit representations; that is the distance of these two representations in an abstract feature space that takes into account the entire spectrum of activation. Representational distances are a measure of dissimilarity which means that 0 represents identical patterns and +1/-1 represents patterns that are maximally different.

For healthy control participants, the predicted pattern of representational distances is very similar to the expected Dice pattern. Neighbouring representations should be more similar to each other than non-neighbouring representations. And, in general, non-neighbouring representations are expected to become progressively more dissimilar the further away they are located in cortical space. This method has been used extensively for this purpose (Ejaz et al., 2015; Kolasinski et al., 2016; Berlot et al., 2019; Sanders et al., 2023). This means that there are clear and explicit expectations for controls that can be compared against.

Figure 10A shows the expected and actual representational distances between digit representation averaged across all participants for controls, S1-deprived and S1-healthy. As for the Dice coefficient, to test the difference between neighbouring and non-neighbouring representations apparent in controls quantitatively, we calculated the mean representational distance of neighbouring and non-neighbouring representations

per control participant. A two-way repeated measures ANOVA showed a main effect of neighbourhood ($F(1, 28) = 130.3$, $p < 0.001$) and a main effect of hand ($F(1, 28) = 5.46$, $p = 0.027$) as well as an interaction effect (NxH: $F(1, 28) = 4.57$, $p = 0.041$), indicating that there is a difference between hands. Post-hoc comparisons showed, however, that for either hand the difference between neighbours and non-neighbours is significant (dominant hand: mean of differences ± 95%CI = -0.13 ± 0.31, $t(28) = 9.03$, $p < 0.001$, non-dominant hand: mean of differences ± 95%CI = -0.18 ± 0.04, $t(28) = 9.50$, $p < 0.001$) as expected, even though the difference for the dominant hand was not as robust. This is in agreement with other published studies (Kolasinski et al., 2016; Berlot et al., 2019). Additionally, the difference between neighbours and non-neighbours is robust between individuals. Every one of our controls exhibited this difference. But since there was a difference between hands, we kept hands separate for the subsequent analysis against patients and assigned each control a simulated injured condition as described above.

For patients, predictions are not as straightforward as they are for Dice coefficients. On the one hand, everything that was said about a loss of distinctness and weakening of the neighbourhood structure is still valid. So, it is reasonable to expect that representational distances might parallel Dice coefficients. On the other hand, representational distances are not a direct measure of representational overlap as Dice and electrophysiology are. Instead, they are a measure of the information that can be extracted from two representational patterns.

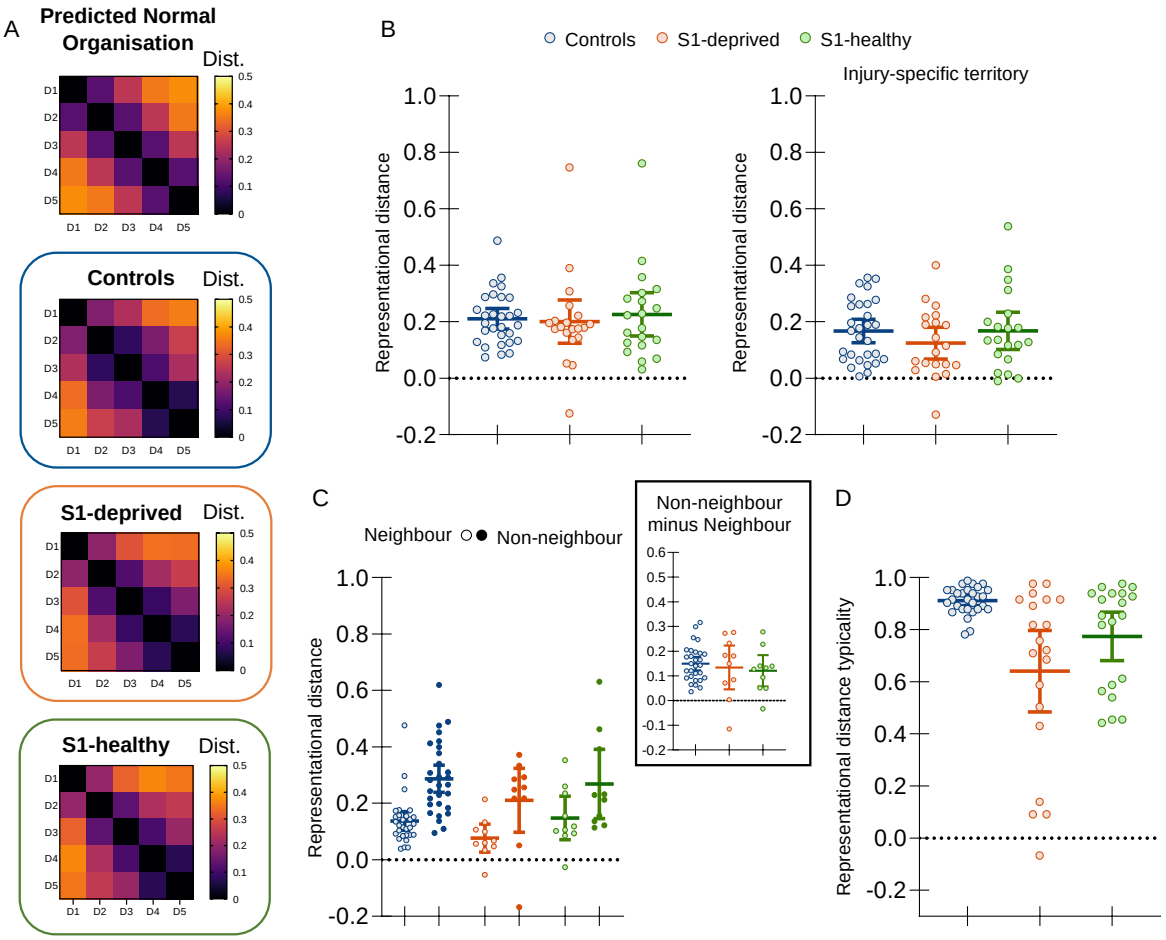

Figure 11. Multivariate analysis: Representational distances. Error bars represent mean and 95%CI. **A:** Actual representational distance patterns for control participants, S1-deprived and S1-healthy of patients. Each pattern represents the mean across all participants in this group. **B:** Mean of representational distance over entire area 3b and over injury specific territory. **C:** Mean representational distance of neighbouring and non-neighbouring representations only for digit pairings for which both representations are serviced by the injured nerve. The insert shows the same information as difference score between neighbours and non-neighbours. **D:** Typicality of representational distances. 1 represents total agreement with the mean control pattern, 0 represents no agreement, -1 represents a pattern that is the exact opposite of the mean control pattern. Note that values for controls are the result of a leave-one-subject-out analysis.

Wall et al. (1986) stress that in each of their monkeys reorganisation did not result in diffuse representations, but that in each case a new, distinctive structure was re-established. This might very well mean that the mean information content is not appreciably lower after reorganisation than it was before. Translated to representational similarity analysis, this means an area that is responsive to several digits should lead to

both an increase in Dice overlap and a reduction in representational distances. But a change in topography where the new representations form a patchwork (yet each representation is still distinct) could lead to a situation where there is a larger degree of overlap of positive-going activation but negative-going activation patterns are still distinct. This would lead to higher Dice overlap with no corresponding reduction in representational distances.

Loss of distinctness

We evaluated the loss of distinctness again by calculating the mean representational distances averaged over all distance representations (Fig. 10B). We predicted that a loss of distinctness between representations should result in an overall decrease of representational distances, specifically in S1-deprived. Contrary to this, differences in the mean representational distance of S1-deprived did not differ significantly from either healthy controls ($t(47) = 0.771$, $p = 0.444$, non-parametric Mann-Whitney test: $U = 267$, $p = 0.650$, $r = 0.06$) or S1-healthy ($t(19) = 0.545$, $p = 0.592$, non-parametric Wilcoxon signed rank test: $W = 4$, $p = 0.956$, $r = 0.05$). S1-healthy also did not differ from controls ($t(47) = 1.12$, $p = 0.269$, non-parametric Mann-Whitney test: $U = 262$, $p = 0.579$, $r = 0.05$). This suggests that nerve repair does not lead to more similar digit representations if both the positive- and negative-going activity are taken into consideration.

Focusing specifically on the injured zone within S1-deprived did not change these results. While the direction of numerical differences is as predicted, S1-deprived was still not significantly different than controls ($t(47) = 1.24$, $p = 0.221$, non-parametric Mann-Whitney test: $U = 243$, $p = 0.348$, $r = 0.15$) or from S1-healthy ($t(19) = 1.30$, $p = 0.209$, non-parametric Wilcoxon signed rank test: $W = 26.0$, $p = 0.648$, $r = 0.11$). S1-healthy and controls did not differ ($t(48) = 0.537$, $p = 594$, non-parametric Mann-Whitney test: $U = 283$, $p = 0.896$, $r = 0.01$).

These results show that when below-threshold activation is included, digit representations remain distinct. This suggests that below-threshold activity carries information that is distinct from the information contained in above-threshold activity alone.

Structural changes

Neighbourhood. Evaluation of neighbourhood structure was carried out analogous to the corresponding Dice analysis. Figure 10C shows the results of the neighbourhood analysis. A two-way mixed effects ANOVA between S1-deprived and healthy controls showed a main effect of neighbourhood ($F(1, 37) = 54.8$, $p < 0.001$) but no main effect of group ($F(1, 37) = 2.54$, $p = 0.120$) and no interaction effect ($F(1, 37) = 1.01$, $p = 0.321$). Similarly, a two-way repeated measures ANOVA between S1-deprived and S1-healthy showed a main effect of neighbourhood ($F(1, 9) = 23.0$, $p < 0.001$), no main effect of hemisphere ($F(1, 9) = 1.35$, $p = 0.275$) and no interaction effect ($F(1, 9) = 0.0966$, $p = 0.763$). A two-way mixed ANOVA between S1-healthy and controls likewise only showed a main effect of neighbourhood ($F(1, 37) = 94.5$, $p < 0.001$), but not of group ($F(1, 37) = 1.08$, $p = 0.307$) and no interaction effect ($F(1, 37) = 0.290$, $p = 0.593$). This again highlights the robustness of the neighbourhood structure and shows that the difference remains robust even after nerve repair. In contrast to Dice overlap, the neighbours are more similar than non-neighbours and the size of the difference in S1-healthy is not different from controls nor S1-healthy.

Typicality. While our analysis of distinctness and neighbourhood structure did not show evidence for divergence from the canonical pattern shown in healthy controls, typicality might still reveal differences due to nerve injury. The reason is that typicality is a more fine-grained measure that utilises the complete pattern whereas the former two analyses rely on aggregate measures that might obscure differences. As noted above, in animal models a new structure emerged that was different from the canonical structure, paralleling reorganisation in the periphery. The new structure was, moreover, a highly idiosyncratic structure. This might lead to a departure from the normal arrangement, affecting the representational distance of different digit pairs differently and, hence, result in reduced typicality. That is, although structure is reconstituted, step-wise relationship between digit pairs may be lost. Although neighbours are clearly differentiated from non-neighbours, the exact neighbourhood relationships and the further systematic relationships that accompany second, third and fourth neighbours may be distorted. Typicality can capture such changes, but neighbourhood analysis may not.

Figure 10D shows the results of the typicality analysis. We found that organisation in S1-deprived is again significantly less typical than in control participants ($t(47) = 4.32$, $p < 0.001$, non-parametric Mann-Whitney test: $U = 127.5$, $p < 0.001$, $r = 0.47$) and that the range was much larger (S1-deprived: 1.0, controls: 0.21). This suggests that the fine-grained pattern of representational distances in S1-deprived departs from the expected canonical pattern. We also found in contrast to expectations, that S1-healthy was less typical than controls ($t(47) = 3.59$, $p < 0.001$, non-parametric Mann-Whitney test: $U = 183$, $p = 0.0286$, $r = 0.47$), but not different from S1-healthy ($t(19) = 1.85$, $p = 0.080$, non-parametric Wilcoxon signed rank test: $W = 79$, $p = 0.145$, $r = 0.33$). The range of values was in between that of controls and S1-deprived (0.53).

The results of the typicality analysis suggest that the pattern of digit representations differs between S1-deprived and controls. This is consistent with expectations from animal models and also agrees with the result of the univariate typicality analysis. Unexpectedly, there is also a departure from the canonical pattern for S1-healthy, the hemisphere contralateral to the uninjured hand, which is again in agreement with the results of the Dice typicality analysis. Wall et al. (1986) did not map changes S1-healthy, but there is some evidence for bilateral changes reported by Calford and Tweedale (1988).

Function

As described above, Wall et al. (1986) made strong arguments for why cortical reorganisation should correspond to distorted touch localisation. We tested this hypothesis by testing for a correlation between brain measures of reorganisation against our measures of touch localisation (Fig. 11). We restricted our measures of brain reorganisation only to those that showed a group effect, specifically mean overall Dice coefficients, Dice typicality and typicality of representational distances.

For touch localisation, we restricted our analysis to the difference between the localisation error in the injured territory minus the localisation error in the homologous uninjured territory. This was done to account for inter-subject variability in touch localisation. We did not test for a relationship with the number of misreferrals as our

analysis in the previous chapter has shown that both the number as well as the pattern of misreferrals are similar to controls for most patients.

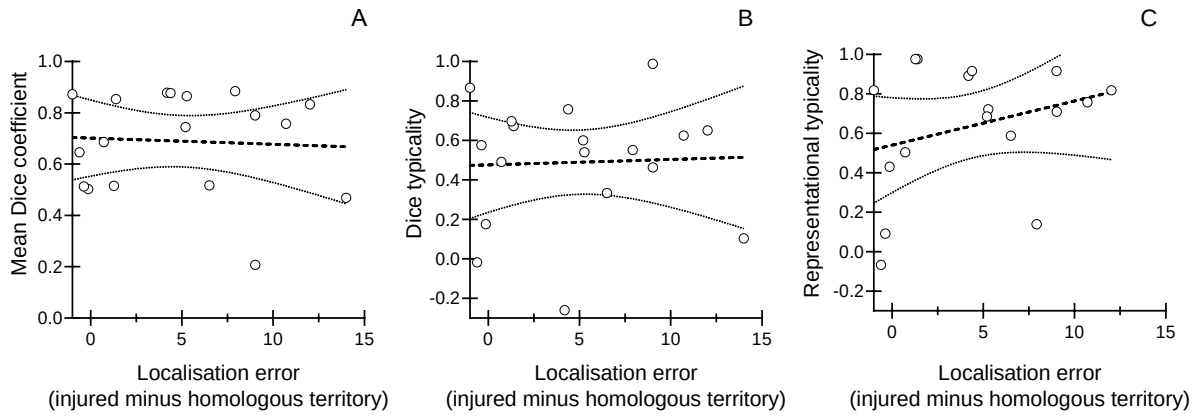

Figure 12. Correlation between brain reorganisation and functional impairment. In all sub-figures the measure for functional impairment is the difference between the mean absolute localisation error within the injured hand territory and homologous uninjured on the uninjured hand. Lines represent trend line and 95%CI boundary lines. **A:** Mean Dice coefficient within the injured cortical territory. **B:** Dice typicality. **C:** Typicality of representational representations.

Wall et al. (1986) suggest that both the size of cortical patches and whether they are re-established in the "correct" territory might influence the spread of localisation on the hand. While we cannot measure patch size and location directly, both factors would be expected to influence overall mean Dice coefficients. Larger patches and a larger degree of intermixing between patches from different digits would result in higher Dice coefficients. A correlation test between our estimates of touch localisation impairments and mean Dice coefficients, however, did not reveal any significant covariance between these two variables ($r(16) = -0.0576$, $p = 0.820$). This suggests that overall separability of positive activation maps does not relate to touch localisation error.

Similarly, Wall et al. (1986) suggest that idiosyncrasies in cortical organisation lead to idiosyncrasies in touch localisation. Cortical idiosyncrasies can be measured by typicality as both the actual mean typicality value as well as the spread signify how closely a group adheres to the canonical organisation. And indeed, whether we look at the typicality of Dice coefficients or representational distances we find that patients are

significantly less typical and have a larger spread of typicality values relative to controls, as described above. This is qualitatively mirrored in the touch localisation data where patients have an elevated localisation error and a larger spread of errors than controls, as described in the previous chapter. Yet, again, correlational tests failed to identify reliable relationships between touch localisation and Dice typicality ($r(16) = 0.0409$, $p = 0.872$) or the typicality of representational distances ($r(15) = 0.296$, $p = 0.248$). The results suggest that departure from typicality is also not related to touch localisation error.

Ipsilateral activation

As described above, nerve transection and repair is expected to result in ipsilateral responses in S1-deprived for stimulations of the uninjured hand that are less negative-going or even positive-going. To test this, we calculated the total %BOLD signal change in the hand area for ipsilateral stimulation (Fig. 12A). Our results showed no difference between either S1-deprived versus S1-healthy ($t(20) = 0.739$, $p = 0.468$, non-parametric Wilcoxon signed rank test: $W = -7$, $p = 0.919$, $r = 0.03$) or S1-deprived versus controls ($t(48) = 0.320$, $p = 0.751$, non-parametric Mann-Whitney test: $U = 278$, $p = 0.612$, $r = 0.08$). Nor was there a difference between S1-healthy and controls ($t(48) = 0.827$, $p = 0.413$, non-parametric Mann-Whitney test: $U = 258$, $p = 0.369$, $r = 0.13$).

Since increased ipsilateral activation can also be seen after hand amputation (Valyear et al., 2020), this may be a sign of injury-driven reorganisation. It is conceivable that regeneration-driven reorganisation results in a progressive reduction of BOLD activity back to pre-injury values. If that is the case, ipsilateral BOLD-activity levels should decrease with time since injury. To test this hypothesis, we calculated a correlation between time since repair and ipsilateral %BOLD signal change ($r(19) = 0.00779$, $p = 0.973$) (Fig, 6B). Therefore, in contrast to (Chemnitz et al., 2015; Björkman and Weibull, 2018; Nordmark and Johansson, 2020) we find no evidence of elevated ipsilateral BOLD activity in our patient population.

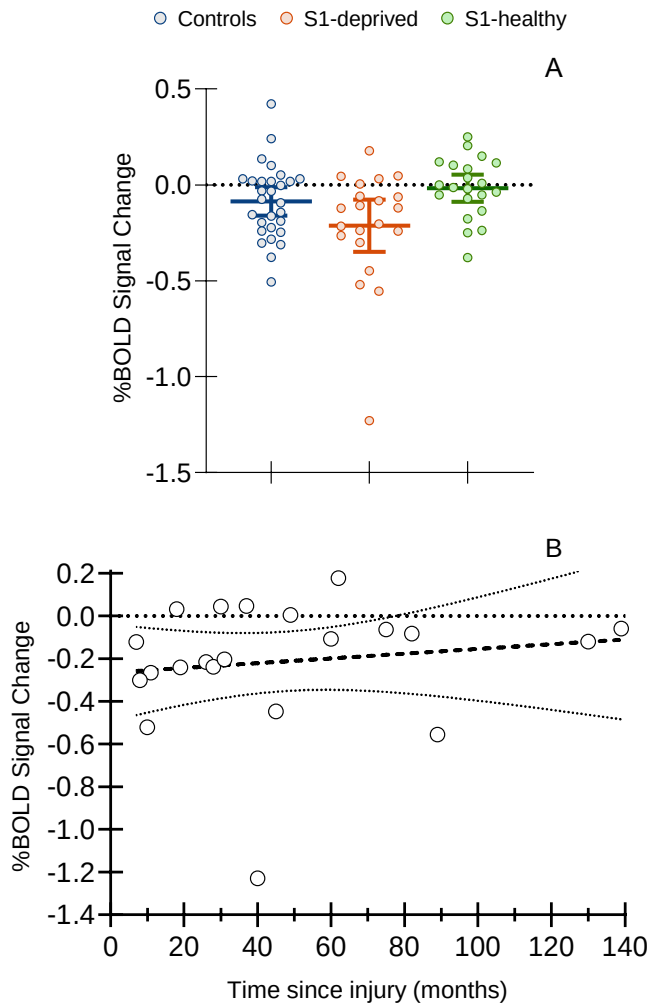

Figure 13. Ipsilateral reorganization. A: % BOLD signal change in S1 ipsilateral to the stimulated hand. Error bars represent mean and 95%CI. B: Correlation between time since repair and % BOLD signal change in S1-deprived. Lines represent trend line and 95%CI boundary lines.

Discussion

In this chapter, we tested whether there is evidence for cortical reorganisation after peripheral nerve repair similar to what has been observed by Wall et al. (1986). Wall et al. (1986) observed that nerve repair in S1 in monkeys leads to smaller receptive fields, large, Pacinian-like receptive fields and fields that are activated by several, discontinuous locations on the skin. Additionally, neighbouring skin locations are often represented in non-adjacent cortical fields and there is in general more overlap between representations. And yet, representations are not diffuse, but a new organisation of distinct receptive fields is re-established - albeit one that does not follow the normal somatotopic layout.

Due to the resolution of MRI as well as constraints in the vascular architecture, it is not possible to observe this level of detail directly. Instead, we focussed on two proxy measures we called “distinctness” and “structure”. In univariate analysis, distinctness measures the mean overlap of positive-going BOLD response. In multivariate analysis, it measures the (dis)similarity of the entire pattern of positive- and negative-going activity. Structure measures how far cortical representations follow the expected somatotopy. Neighbouring representations should show more overlap/similarity than representations that are non-adjacent. At the same time, the complete relative pattern of overlap/similarity closely follows a proto-typical pattern in control. As Figure 13 shows, smaller but scrambled receptive fields, receptive fields activating for multiple, discontinuous skin locations or Pacinian-like receptive fields, as well as larger overlap can all lead to a loss in distinctness, at least for univariate measures. At the same time most, but not all, of these changes would also be visible as a departure from the expected structure. If reorganisation simply leads to more overlap between representations, this will only result in a loss of distinctness, but not in a change of structure.

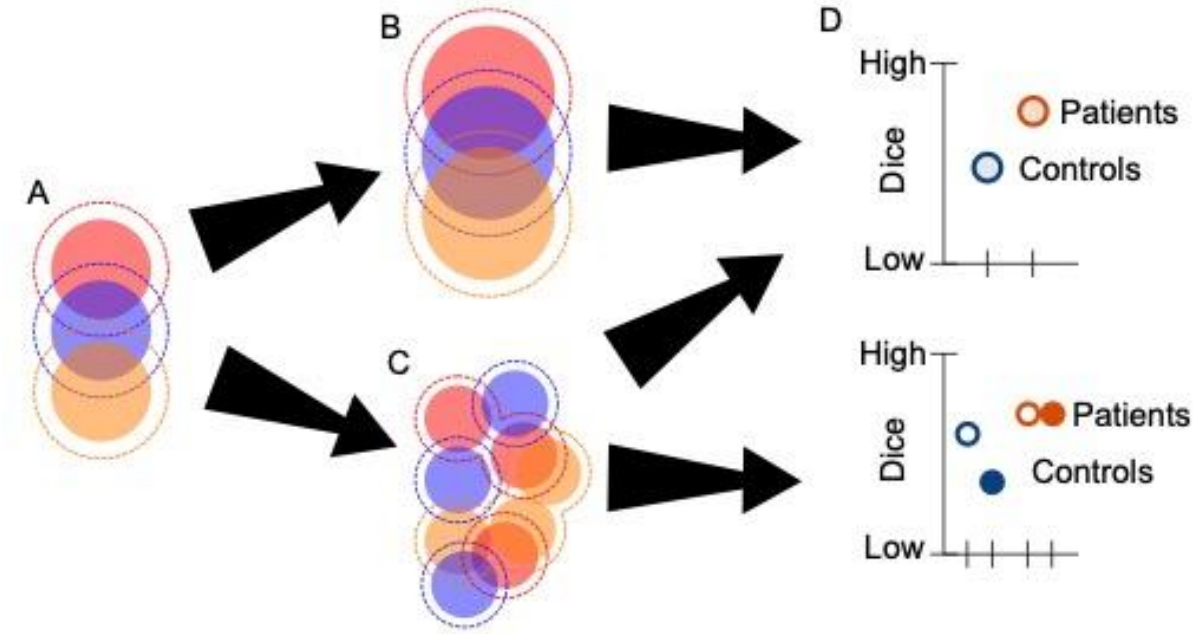

Figure 14. Translation from electrophysiological activation to Dice measures. A: Organisation prior to injury. Filled circles represent the population of cells that shows increased electrophysiological activation, dashed circles show area in which BOLD response is increased. For clarity only three digit representations are shown. **B:** Reorganisation after injury, assuming that reorganisation primarily leads to release from inhibition. **C:** Reorganisation after injury, if reorganisation leads to fragmentation of digit representations some of which are in "normal" others in "abnormal" location. Note that areas of increased BOLD response can bleed into each other resulting in larger activation areas. **D:** Resulting Dice distinctness. If the reorganisation is primarily driven by release from inhibition, we should only expect to see a loss of distinctness. Fragmentation of digit maps leads to both loss of distinctness and weakening of the neighbourhood structure.

Evidence for cortical reorganisation

Our Dice analysis shows a significant elevation of overlap between digit representations which is specific to the representations serviced by the injured nerve. This not only agrees with Wall et al. (1986), but with the animal literature more widely. Nerve lesion, nerve repair, digit amputation, digit fusion and other experimental manipulations always lead to reorganisation that is restricted to the territory of the affected nerve (Kaas, 1991; Wall et al., 2002). It is possible that this increase in overlap could be the result of other factors. It is known that BOLD activity in response to touch can be influenced by attention (Pessoa et al., 2003; Nordmark and Johansson, 2020; Kassraian et al., 2023). Since many of our patients anecdotally commented on the

strangeness of sensation in their injured hand territory, they could have attended more to these stimulations. Alternatively, the increased overlap could be a sign of a general disinhibition. There is evidence for GABA reduction after nerve lesion (Garraghty et al., 1991). Since GABA is linked to inhibition of activity, this could lead to widespread overlap. These explanations are, however, not very likely as they should not lead to a change in structure. But we do see both overall elevated overlap as well as a weakening of the neighbourhood structure and a departure from the canonical pattern of overlap. This makes reorganisation as described by Wall et al. (1986) the much more likely explanation for the observed changes. Additionally, the typicality of Dice overlap and representational patterns were lower for patients than for controls. Not only that, but the variance of the patient data was also much larger than that of controls. This agrees with the observation that re-established cortical patterns are highly idiosyncratic.

In contrast to the Dice analysis, the analysis of representational distances did not show a higher similarity between representational patterns or a weakening of the neighbourhood structure. This could be due to the level of noise in the data. Representational similarity analysis as a multivariate measure can detect effects that cannot be detected by univariate analysis, but it is also more susceptible to noise (Ritchie et al., 2021). The noise ceiling, the inter-subject variability of the data due to sources of no interest, limits the amount of information that can be read from the data. This is especially problematic in our case as patient data is expected to be much more variable than that of controls. Since we did not account for this difference in noise ceiling here, it could be that effects are masked by the noise. A second possibility is that distinct digit representations are re-established that do not follow a somatotopic organisation. In contrast to univariate measures that rely on systematic activation of a larger number of voxels, representational similarity analysis can detect representations even when no or weak somatotopy can be detected (Wiestler et al., 2011; Diedrichsen et al., 2013). Since the complete pattern does show a departure from the canonical pattern in patients also with respect to representational distances, this would agree with the observations by Wall et al. (1986) that re-established digit maps exhibit discreet cortical patches even if their organisation is highly abnormal.

Previous studies have used representational distances as a way to measure hand maps. The logic behind this practice has been described in detail by Ejaz et al. (2015). Due to the variability of individual hand maps, a classical group average leads to maps with a great degree of blurring. Yet despite their inter-subject variability, certain features are invariant across participants, such as that neighbouring representations should be more similar than non-neighbouring representations. Transforming the activation pattern into representational distances offers a way to compare these features across participants. Yet, as we have shown here, transforming subject-specific positive activation maps into Dice coefficients is another suitable way to compare invariant features across individuals. In fact, both patterns are highly correlated. Our patient results suggest, however, that the correlation might break down after nerve repair. If this result can be confirmed in future studies, this would have important implications on how to interpret patient data. Several studies based their evaluation of digit representations after injury primarily on representational distances (Kikkert et al., 2016, 2021; Wesselink et al., 2019; Sadnicka et al., 2023), but comparing changes in representational distances to those in univariate overlap provides a richer picture than either method could provide alone.

Both the analysis of Dice coefficients and of representational distances agreed in that the individual relative patterns were less typical. Surprisingly, this was true not only for S1-deprived but also for S1-healthy. In contrast to that overall overlap was increased and neighbourhood structure was reduced specifically in S1-deprived compared to controls. The majority of animal studies exclusively focus on S1-deprived, setting no precedence on whether to expect changes in S1-healthy. There are a few studies, however, that report expanding receptive fields in both hemispheres after digit anaesthesia and amputation (Calford and Tweedale, 1988, 1990; Calford and Tweedale, 1991). What could explain this apparent change in organisation? It cannot be a result of generally increased activity, widespread fragmentation or a general change in the nature of the receptive fields as observed in S1-deprived, because in that case, we would also expect to see changes in the overall overlap and/or the neighbourhood structure. But it might reflect a rebalancing of the existing cortical field. There is evidence of information sharing between left and right S1 (Ragert et al., 2011, Tamé et al., 2016). This means that

changes in one hemisphere could also result in changes in the opposite hemisphere. In the context of injury-driven reorganisation in S1-deprived, (Merzenich et al., 1983) argue that the observed temporal pattern is best explained by a model of activity-based competition. This model states that neurons that are more active gain a competitive advantage over less active neurons. Peripheral input is transmitted to an area in the cortex that is much larger than its observable representation, but the strength of that input varies between different regions. The result is that the area in which the signal is detectable is much smaller and less well-delimited. Missing or asynchronous inputs after nerve injury then lead to a different equilibrium point of the competition which results in altered hand maps. While this model only takes peripheral input into account, it is conceivable that input from the opposite hemisphere also influences this equilibrium point. Yet, since responses are primarily driven by afferent inputs, the resulting changes are on a much smaller scale than in S1-deprived.

Functional impact of cortical reorganisation

Wall et al. (1986) argue that the cortical changes they observed are directly analogous to touch localisation impairment reported in the literature. In the previous chapter, we presented touch localisation data recorded in the same patients as the ones for which we reported cortical data in this chapter. We showed that impaired touch localisation is indeed specific to the injured hand territory and there was more inter-subject variation in patients than in controls. We also found that most patients are not more likely to make misreferrals than healthy controls and that in general, the pattern of misreferrals is comparable between patients and controls (although patients show occasional misreferrals to the palm that are absent in controls). Here we tested Wall's hypothesis using only those measures that showed a group difference between patients and controls but could not find any correlation between the degree of impairment and the amount of reorganisation.

There are several reasons why this might be the case. For one, while we were able to successfully quantify absolute localisation error the way we measured touch localisation still has several limitations. We only stimulated the fingertips even though reinnervation advances from proximal to distal skin regions. This might have led to an

overestimation of the error, especially for patients early on in recovery, leading to a data set that is generally noisier. This should be addressed in the future by testing localisation in the entire hand area. Furthermore, the absolute localisation error is, by definition, the error for any stimulus that has been referred to the correct digit. Yet, our measures for cortical reorganisation only measure distinctness and structure between digits, meaning that they are more likely to be reflected in misreferrals than in absolute localisation error. As mentioned above, our data did not show any evidence that patients, in general, are more prone to making misreferrals or that the pattern of misreferrals differs significantly from controls. This might, however, be because we used supra-threshold stimuli. Changes to the ability to identify the correct digit stimulated might be more subtle and can potentially only be detected close to the localisation threshold (Schweizer, 2000). Alternatively or additionally, a more detailed characterisation of cortical organisation that is able to measure changes to within-finger maps could be more suitable for a comparison to absolute error than the measures we used in this study. Wall et al. (1986) also makes a case that the establishment of several discontinuous cortical representations of the same skin patch could be responsible for multiple percepts that are sometimes reported by patients. Several of our patients also reported sometimes feeling touch in multiple skin locations at the same time, but we did not try to quantify this phenomenon. This is another area that needs to be addressed in future studies.

In addition to the limitations of our touch localisation method, it is not clear how to best compare cortical reorganisation and touch localisation. We limited ourselves here only to those measures which showed a group difference between patients and controls which we compared individually. We already know, however, that both distinctness and structure are linked, being driven by mostly the same underlying changes in representations. So, it is likely that they would reveal more about the exact nature of reorganisation when taken together. Similarly, absolute localisation error and misreferrals are not fundamentally different phenomena, but are linked. We have argued in the last chapter for why it is important to not conflate the two measures. Some form of model that respects the distinctions as well as the linkage between the two would, undoubtedly, allow for better predictions against brain changes, however.

Ipsilateral BOLD increase

Finally, we also looked at ipsilateral BOLD activation. BOLD activity has been shown to be elevated relative to rest in S1-deprived for activation of the ipsilateral (uninjured) forepaw in rats. Pelled et al. (2007) and Pelled et al. (2009) found that, after lesion of several forepaw and hind paw nerves, electrical stimulation of the intact nerve did lead to significant positive BOLD activation in S1-deprived. A result that was also reported by Pawela et al. (2010) with a similar protocol. Similar findings have been reported in humans for both acquired amputees and nerve repair patients. Philip and Frey (2014) found that when performing a drawing task, amputees showed significantly increased activity in the hand area ipsilateral to the preserved hand compared to controls. Likewise, Valyear et al. (2020) found a significantly increased in BOLD activity relative to rest, after stimulation of the preserved hand of amputees with air puffs. In contrast to that, Makin et al. (2013) did not find any difference between amputees and controls in ipsilateral S1 for movement of the digits of the intact or phantom hand. For peripheral nerve repair, Chemnitz et al. (2015) observed increased ipsilateral activation relative to rest for stimulation of both the injured and uninjured hand with pneumatically controlled membranes. A result confirmed by Björkman and Weibull (2018) who re-analysed the same data. Contrary to that, Nordmark and Johansson (2020), who used oscillating ridges as their stimulus, could only find increased ipsilateral activation for stimulations of the uninjured hand.

In our study, we did not find any difference in ipsilateral BOLD activation between patients and controls either for the injured or the uninjured hand. This might be due to differences in our stimulation protocol. Philip and Frey (2014) used a higher-level motor task in their study. And while Chemnitz et al. (2015), Nordmark and Johansson (2020) and Valyear et al. (2020) all use sensory tasks, the task of Nordmark and Johansson (2020) involves active detection rather than passive observation. The tasks of Chemnitz et al. (2015) and Valyear et al. (2020) are comparable to ours in that they are sensory and passive, but the nature of their stimuli is different. In addition, they (as well as Nordmark and Johansson (2020)) only tested a subset of digits. Furthermore, increased ipsilateral activity has not only been reported for nerve repair patients but also for

patients that suffered a permanent lesion or whose hand had to be amputated. It is, therefore, also possible that it is a sign of injury-driven reorganisation and that BOLD levels drop back to normal as regeneration progresses. We tested for this possibility, but could find no correlation between time since repair and BOLD activity. This is consistent with the literature in so far as the meantime since repair of Nordmark and Johansson (2020) is 8.5 years and of Chemnitz et al. (2015) even 14 years. Both populations were, thus, further out from repair than our population and still showed increased ipsilateral activity.

Limitations

One of the limitations of this study is that it does not properly account for inter-patient variability with respect to the injury. In contrast to previous studies, our measures for reorganisation respect the individual functional anatomy rather than analysing a group mean on a standard volume. Nevertheless, both injury and regrowth of the injured nerve are highly idiosyncratic (Brushart, 2011) and also dependent on the exact surgery technique used. This adds a layer of noise that we are not able to address in our current analysis. Neither can we address the question of how far cortical reorganisation reflects regrowth errors in the periphery and in how far it reflects central mechanisms. Microneurography allows to quantify reinnervation errors (Hallin et al., 1981) and combining it with the methods employed in the present study would allow to address these shortcomings. It would also allow to tailor predictions better to the individual patient and potentially move from group-based effects towards single-case effects.

The same is true for functional recovery. Functional recovery does not only depend on nerve regrowth but also on psychological factors and how much the patient engages with rehabilitation exercises (Lundborg and Rosén, 2007). We did not capture these factors in the present study, resulting in additional noise in our functional data. Measuring these factors would again enable us to make more individualised predictions and promises to detect effects that might be hidden by a group-based analysis.

In this study, we created manual ROIs by tracing the central sulcus for 10 slices above and below the manually identified hand knob. This was done to avoid noise

associated with using traditional, volume-based probabilistic atlases. The quality of masks based on these atlases depends on the quality of alignment of the individual brain with the MNI template. Manually tracing the sulcus eliminates noise from distorted alignment at the cost of adding noise from manually identifying the hand knob. A better approach would have been to have an independent localiser task. We considered adding that to our protocol, but ultimately abandoned the idea to be able to include other important tests into the test battery. More recently, new probabilistic atlases have been developed that promise a better alignment with the individual brain by using surface reconstruction (Berlot et al., 2019, O'Neil et al., 2020). It would be useful to compare the results calculated using these atlases with the results calculated using our hand-drawn maps to evaluate the sensitivity of the results to ROI definition.

Concluding remarks

We found strong evidence that suggests that reorganisation after peripheral nerve repair in humans shows characteristics similar to those reported by Wall net al. (1986) in animal models. Overall Dice overlap is larger and the difference in overlap between neighbours and non-neighbours is smaller in S1-deprived than in S1-healthy or controls Analysis suggests that this loss of distinctness maybe limited specifically to the territory serviced by the injured nerve. Representational structure is abnormal both in S1-deprived and in S1-healthy compared to controls as can be seen from the lower typicality values. These structural changes can be seen both in the univariate and the multivariate analysis. Despite this, the connection to impairment remains uncertain at this point.

General Discussion

We set out to characterise touch localisation after nerve repair, to examine whether there is evidence for reorganisation similar to that found by Wall et al. (1986) and to test whether the two are correlated. We showed that our method of measuring touch localisation is capable of detecting functional impairment and that this impairment is specific to the territory of the injured nerve. This agrees with qualitative observations by Hawkins (1948) who claimed that the area where “faulty localisation”

can be observed is limited to the innervation territory of the injured nerve. This is also the assumption that the modified Marsh method operates under as only the zones that belong to the injured nerve are tested (Jerosch-Herold et al., 2006). But, to the best of our knowledge, our study is the first to demonstrate this quantitatively. Additionally, similar to Jerosch-Herold (1993) we found excellent agreement between the elevation of touch localisation error in the injured territory and impairment of higher-level hand function (measured by the sensory component of the Rosen score in our case). Among the variety of functional impairments, elevated touch localisation error has been recognised as the most striking by early researchers (Stopford, 1926; Hawkins, 1948) and it appears that there is a direct connection between the ability to localise touch and the ability to use our hands.

On the other side of the relation between function and reorganisation, we found evidence for cortical reorganisation as it has been observed in monkeys by Wall et al. (1986). While being qualitative itself, their study allows clear predictions for what effects should be observable after peripheral nerve repair. We translated these into hypotheses that can be tested with fMRI and found evidence that digit maps become less distinct and that the normal pattern of representation is weakened. Crucially, these observations are again specific to the representation territory of the injured nerve similar to what can be seen in animal studies in general (Kaas, 1991; Wall et al., 2002). It is of note that while univariate analysis showed both a loss of distinctness and a divergence from the canonical pattern of overlap, multivariate analysis could only detect a divergence from the canonical structure. As we have argued in chapter two, interpreting these results is not straightforward but they might be an indication that univariate and multivariate analyses can assess complementary features of the topography.

That means we found evidence for elevated touch localisation error and cortical reorganisation in area 3b of S1-deprived. In both cases the observed changes are specific to the territory of the injured nerve and, in general, follow the predictions by Wall et al. (1986). Despite this, we did not find any correlation between the two. Before discussing why this might be the case, it is important to first re-examine why we should expect that there is a correlation between central representation and functional impairment. After all, changes to the peripheral nerves alone might be sufficient to explain functional

impairment and any central representations could simply reflect these changes (although even in that case one might expect that the degree of cortical changes should have some correlation with impairment).

The case for a connection between cortical reorganisation and impaired touch localisation

The connection between central changes and functional impairment has already been made quite early. Stopford (1926) used this as an explanation for why there appears to be a two-stage recovery process that can be observed in many patients. He speculated that difficulties in localising touch might be due to nerve fibres connecting to different end organs than before the injury and that this effect could be reduced by re-education. More recently, Lundborg and Rosén (2007) have put together a case for why cortical plasticity is an important contributor to functional recovery: 1) Children that are injured before roughly the age of 10 - 12 usually show full recovery whereas patients injured in adolescence and adulthood in most cases do not, 2) expected recovery not only depends on age at injury, type and level of injury and so on, but also on cognitive brain capacity, and 3) functional recovery continues for at least five years post repair whereas nerve conduction velocity and amplitude stop improving after approx. two years.

In another study, Rosén and Lundborg (2001) go further and show that the curve of expected recovery (measured in this case by a score that combines two-point discrimination and the shape-texture-identification test) is qualitatively very similar to a curve of mean grammar test scores of immigrants as a function of the age of the immigrant when they entered the US reported by Barinaga (2000). Notably, both curves show a small improvement for patients who had their injury in their mid-twenties / immigrants who came to the US in their mid-twenties as opposed to people in their late teens or later in life. This points to some form of learning effect taking place in the brain. The argument is further strengthened by a study by Chemnitz et al. (2015) who compared nerve conduction characteristics, cortical activity in S1 and functional impairment in patients who had been injured before the age of 10 with patients injured during adolescence. They found that in both groups had reduced sensory amplitudes in their median (injured) nerve. But the extent of cortical activation to stimulation of the

injured hand in the group that had been injured in childhood was comparable to that of controls whereas patients injured during adolescence had a larger volume of activation. Similarly, the recovery in the sensory and pain/discomfort domain was significantly better for the group that had the injury during childhood.

A different argument was advanced by Wall et al. (1986). While it is likely that some of the reorganisation they observed is due to peripheral misalignment during regrowth or cell degeneration and death, the authors maintain that not all features can be explained by peripheral factors. Among them are the re-establishment of discrete receptive fields and local topographical organisation. More important is the fact that they observed reorganisation in areas 3b and 1, yet the actual observed reorganisation pattern differed quite markedly between the two sites. A fact that can only be explained if the organisation is also shaped by central factors.

Wall et al. (1986) then go on to enumerate how cortical reorganisation and the pattern of distorted touch localisation agree with one another. Both the area in which touch localisation is impaired and the area of cortical reorganisation is limited to the territory of the injured nerve. Secondly, reinnervated skin regions are represented in several distinct cortical patches. Some of these are where they would have been pre-injury, and others are located where the representation of other skin patches had been. At the same time, it is quite common that point stimuli are perceived in multiple locations at once (the actual location may or may not be one of them). Thirdly, cortical areas vary in size and so do the skin areas to which "mislocalisations" are referred. Also, both cortical reorganisations and the patterns of "correct localisations" and "mislocalisations" are highly idiosyncratic. Finally, in the case of nerve crush pre-injury organisation is re-established and touch localisation is not impaired. It is important to note, though, that reorganisation here always refers to reorganisation in animal models, as non-invasive imaging techniques were still in their infancy, while all knowledge about touch localisation was derived from human patients.

The contribution of central factors in functional recovery also becomes evident in the technique of sensory re-education (Rosén et al., 2003). It is based on the idea that the adult brain relies on a mapping between percepts encoded in S1 and higher-level

brain areas originally learned in childhood. Reorganisation means that this mapping is no longer correct and that recovery requires the brain to learn a new mapping. In sensory re-education, patients are subject to known sensory stimuli of increasing difficulty to aid the remapping process. There is limited evidence that these programs result in improved recovery (Xia et al., 2021) which is difficult to explain if reorganisation was entirely driven by peripheral changes.

This led to the canonical hypothesis of the role of brain changes after nerve repair (Lundborg and Rosén, 2007). The transection of the peripheral nerve leads to an initial "black hole" when all input from the transected nerve ceases. The cortical territory is first captured by the expansion of adjacent cortical territories of neighbouring nerves. As the nerve re-grows, it can not re-establish the same structure as before the injury. This is partially due to misalignment errors during regrowth and partially because of the expanded nerve representations. As a consequence, higher brain areas need to relearn the mapping between peripheral stimuli and cortical representation resulting in a long and incomplete recovery process. A process that can be improved by sensory re-education.

Another line of evidence comes from Braun and colleagues who in several studies demonstrated that in healthy participants misreferrals are made predominantly to the neighbouring digit (Schweizer, 2000; Schweizer et al., 2001; Braun et al., 2005; Braun et al., 2011). They note how closely the observed pattern of misreferrals corresponds to the structure of cortical digit representations as observed in animals(Schweizer et al., 2001). Interestingly, the misreferral pattern can be altered by repeated co-stimulation of several digits. They subjected their participants to 1h of training per day for 4 weeks in which both D1 and D5 were stimulated simultaneously. This resulted in a reduction of the number of misreferrals to their direct neighbours (D2 and D4 respectively) in favour of the co-stimulated digit. While not examining cortical structure directly, their result is in line with expectations from animal literature that suggest that co-activation of digits results in increased overlap of the digit representations (Jenkins et al., 1990).

As mentioned before, similar to Wall et al. (1986), we found that both cortical reorganisation and touch localisation impairment are specific to the territory of the

injured nerve. It is difficult, however, to connect the two. Wall et al mention the size of the area in which "mislocalisations" occur as one criterion that can be evaluated. But it is not clear what exactly is meant by this. All early researchers conflate localisation error and misreferrals under terms such as "faulty localisation" or "mislocalisation". It would be conceivable that a new representation that is established in the former territory of another digit will result in a digit misreferral. Alternatively, and in line with the hypothesis of Schweizer et al. (2001) a loss of distinctness could lead to increased digit misreferrals. But we do not see any evidence for that. There are only three patients that show an exceptionally high number of misreferrals. For the rest of the patients, both the number and pattern of misreferrals are comparable to controls. We do see misreferrals to the palm in patients, though, something not observed in controls. It is not clear, however, whether these represent the same type of misreferral as localisations to another digit or whether they are merely a sign of a very large localisation error. In general, however, impairment in touch localisation manifests itself as an elevated absolute localisation error in the injured territory while patients seem to be otherwise more similar to controls than might be expected from early case studies.

To test the hypothesis that reorganisation in area 3b is directly linked to impaired touch localisation, we, therefore, opted for a linear correlation between the reorganisation measures that showed significant signs of reorganisation with absolute localisation error and found no relationship. Our approach assumes a linear relationship between reorganisation and impairment which might not be true. It also takes the measures of reorganisation and compares them independently to localisation error, but they might very well be interrelated in which case some form of multivariate test would be more appropriate. This is also true on the side of localisation impairment. While it is important to distinguish between localisation error and misreferrals, we only focussed on localisation error since misreferrals did not show any departure from healthy controls in most patients. But this ignores part of the information contained in the data. Instead, it would be better to integrate these two measures in a way that respects their independent nature. We still opted for this simplified approach in this study as part of the original hypothesis was that there should be a direct correspondence between the

reorganisation and the localisation patterns. Our results show that the relationship, if it exists, is not as simple as previously imagined.

Another fact is worth mentioning. Schweizer et al. (2001) argue that the pattern of misreferrals seen in healthy controls is a direct consequence of the structure of cortical representations. Neighbouring digit representations are less distinct than non-neighbouring digit representation in S1 and therefore more misreferrals are made between neighbouring digits than between non-neighbouring digits. Yet to establish this relationship, they need to balance the number of misreferrals across digits. That means it becomes impossible to see which digits tend to make the most number of misreferrals. In line with this, we also observed that most misreferrals tended to be made towards direct neighbours. But since we did not impose the restriction that all digits need to have the same number of misreferrals, we can ask which digits are most likely to make misreferrals. We found that the likelihood to make misreferrals is not distributed evenly across digits, but that D3 and D4 are exceptionally likely to refer sensation to one another. If misreferral patterns would be a direct consequence of the distinctness of cortical representations, we should expect that D3 and D4 are the least distinct of all digits. But this is not the case. Instead, D4 and D5 are the two digits whose representation is least distinct in controls. This is an observation that is true both for Dice overlap coefficients and representational distances and in line with what has been reported previously (Berlot et al., 2019). Taken together, our results show that the link between organisation in area 3b and localisation ability is less straightforward than previously imagined.

Several other studies point in the same direction. The size of cortical representation areas does not reflect the size of the represented body part, but the number of receptors for that body part - a phenomenon known as cortical magnification (Merzenich et al., 1983). This means that the same distance on the skin results in larger cortical distances in the hand than in the back representation. Yet, while distance judgements on the hand are inflated compared to other body parts, the inflation is not as big as what would be expected based purely on maps in area 3b (Medina and Coslett, 2016). Additionally, touch localisation and tactile acuity not only differ between body parts but are particularly good close to body-part boundaries (Cholewiak and Collins,

2003; Cody et al., 2008), even though this is where one would expect more uncertainty due to overlapping representations.

Furthermore, the ability to localise touch and noxious stimuli is similar in the same body part (Koltzenburg et al., 1993; Moore and Schady, 1995; Mancini et al., 2011, 2013) even though the number of receptors for each modality can be markedly different (Mancini et al., 2013). Cortical representations of noxious stimuli appear to be confined to area 1 (Kenshalo et al., 2000; Ploner et al., 2000; Mancini et al., 2012; Omori et al., 2013) (but see Mancini et al. (2019)) and there are only two types of cortical pain neurons: nociceptive specific and wide dynamic range neurons, the latter are also activated by hair movement and light touch or pressure (Kenshalo et al., 2000).

Apart from misreferrals between different parts of the hand, all of which are represented closely together, it is also possible to elicit misreferrals between hands and feet (Badde et al., 2019) even though their representations are not neighbours in cortical space. There is some evidence that reducing stimulus strength does not uniformly increase localisation error, but localisations are rather biased towards the centre of the body part (Medina and Coslett, 2016).

Finally, Shen et al. (2018) found in an EEG study that the detection of tactile stimuli seems to be accompanied by two types of short-term responses. One after 100 - 200ms which is generated in S1 followed by a second one after 300ms which is connected to the fronto-parietal attention network and accompanied by a shift in attention. The former signal was larger when the cortical representations were closer, the latter was larger when the physical distance on the body was larger.

All of these studies together suggest that activation of area 3b alone is not enough to localise tactile stimuli, but that it is necessary to first combine this information with some form of body schema (Heed et al., 2015; Longo et al., 2015). Recently, Miller et al. (2022) have proposed a neural surveyor model that provides more detail on how this might be done by the brain. According to their model, the brain localises stimuli by multilateration. Multilateration means that an unknown distance is calculated based on several known distances. The brain measures the distance between a stimulus and several known landmarks to calculate the position of that stimulus on a body part.

Tactile inputs are transmitted from the receptors to area 3b where they are encoded. From there they are sent to another brain region (as of yet unidentified) where the signal is transformed to represent a distance from a permanent or artificial landmark. To do so, both tactile and proprioceptive information are necessary. This information is then decoded by yet another brain region which determines the actual localisation. Integrating several noisy signals leads to a more accurate estimate of the real location of a stimulus.

Miller et al demonstrate this with a stimulation of the forearm. The two landmarks that are used to localise the stimulus are the wrist and the elbow. Cutaneous touch receptors detect the stimulus and forward it to S1 where it is encoded in the forearm region. The encoded signal is then sent to the transformation regions and here, they speculate, there are two types of neuron populations. Neurons that activate most strongly if the stimulus is close to the wrist and neurons that activate most strongly if the stimulus is close to the elbow. In both cases the response decreases the further away the stimulus is from the respected landmark of these neurons. That means as stimuli are applied progressively further away from the elbow and closer to the wrist, the strength of the response of "elbow neurons" decreases and at the same time the strength of the response of "wrist neurons" increases. In a noiseless world, the information contained in the response of these two neuron populations would be redundant. But since the entire signal chain is noisy, rather than encoding a definite distance from their respective landmark, each population only encodes a probability of how far the stimulus is from the landmark. Integrating the estimates of both populations yields a more accurate estimate than just relying on one of the populations alone. Because of this, it is necessary to encode distance relative to at least two landmarks per body region for every dimension in which a localisation needs to be made.

Miller et al then go on to test their model empirically. They first tested results from passive and active touch on the forearm. As predicted by their model, the amount of variable error followed an inverted U-shape with the error being lowest close to elbow and wrist and largest in the middle of the forearm. They also applied their model to localisation on the index finger and showed some participants used two landmarks (the metacarpophalangeal joint and the distal tip of the digit) while others used three

landmarks (either of the two interphalangeal joints) as a basis for trilateration of the stimulus.

As we have shown in this thesis, the strength of the study of Wall et al. (1986) is that it allows to make testable predictions for the nature of reorganisation to expect. In addition, they provide a point-by-point comparison of how different features of reorganisation correspond to impaired touch localisation. Due to the nature of their work, however, the predictions necessarily remain qualitative. Miller's model promises to pick up where Wall left off. It makes it possible to embed the reorganisations in S1 in the complete localisation pathway and offers a framework to make direct, quantitative predictions. In addition, it offers fresh ideas on what can influence touch localisation beyond the reorganisation of maps. For instance, Miller et al. (2022) predict that noise correlation (e.g. due to a line rather than a point stimulus or due to movement) should increase the magnitude of the localisation variability. Several studies report increased latency and reduced amplitudes in peripheral afferents after reinnervation (Hallin et al., 1981; Rosén et al., 2012; Chemnitz et al., 2015). It is possible that this can drive up the noise of the signal independent of any map changes.

Limitations of this study

As mentioned in the introduction, there are four main components of impaired touch localisation in nerve repair patients: localisation error, misreferrals, diffuse sensations and simultaneous sensations/ghosting. Of these, we only measured the first two. Since the number of misreferrals is generally low, we were, furthermore, only able to make qualitative observations. This could be overcome, however, by lowering the stimulus intensity to the so-called localisation threshold, the intensity at which a participant is equally likely to make a correct or a misreferral Schweizer (2000). This would be a small change to implement with our current setup.

Intriguingly, while the number of misreferrals of the majority of our patients was comparable to that of controls, three patients showed an unusually large number of misreferrals and two of them also showed an abnormal misreferral pattern. This raises the possibility that touch localisation could be used as a way to phenotype sub-populations of patients or recovery paths. To achieve this, it is necessary to also

quantitatively capture the last two components of impaired touch localisation. Only in this way is it possible to achieve a comprehensive characterisation of touch localisation. This does not require a completely new method, though, but can rather be done with an adaptation of the existing setup. Simultaneous percepts could be captured by allowing the participant to register more than one response and for diffuse sensations they might outline an area rather than indicating point responses. It is also important to assess a larger area of the hand than just the fingertips.

One limitation of our locognosia approach is that we only tested the fingertips. While this allowed us to find an injury-specific increase in localisation error, it is not clear that the division between injured and uninjured territory is equally clear in the palm (as predicted by Hawkins 1948) where there is no natural boundary between the territories. Since reinnervation progresses proximally to distally it could also be assumed that localisation error to proximal targets should improve earlier than to distal targets. With our configuration of targets, we are unable to evaluate these predictions. Testing the whole hand would also yield more data that can be used to weigh different models of the functional impact of reorganisation.

With regard to our fMRI data, it is important to note that we did not assess topography itself quantitatively. Instead, we assessed the invariant features of the underlying organisational principles of the topography in line with similar studies in this field (Diedrichsen et al., 2013; Ejaz et al., 2015; Kikkert et al., 2016, 2021; Kolasinski et al., 2016; Berlot et al., 2019; Wesselink et al., 2019; Sadnicka et al., 2023; Sanders et al., 2023). This is usually done because the differences between individual digit maps are too large which means traditional group analysis leads to a diffuse hand map that is not fine-grained enough to assess the questions of interest (Ejaz et al., 2015). In the past, a winner-takes-all approach has been used to qualitatively assess the preference of specific areas for individual digits (Sanchez-Panchuelo et al., 2010; Kikkert et al., 2016; Kolasinski et al., 2016; Sanchez Panchuelo et al., 2016). Recently, O'Neill et al. (2020) have shown that a surface reconstruction leads to good spatial agreement of the position of individual digit maps in controls. Additionally, their study also delivers predictions of how variable each digit representation can be expected to be. Adding this analysis would allow us to better capture the full extent of digit representations and, thus, allow

a more detailed characterisation of cortical reorganisation. Our results suggest that the close association between the invariant features that can be measured with Dice coefficients and with representational distances may be breaking down in patients. If this is the case, similar dissociations might also be seen between the actual preferential response and either or both of the measures of invariant features. In any case, this would aid understanding of the exact nature of reorganisation.

As for touch localisation, we only mapped digit topography to stimulation of the fingertips. While this makes results from our touch localisation experiment and fMRI experiment more comparable, it also imposes several limitations. In addition to the gradient of digit preferences from lateral to medial, there is a second gradient that progresses distal to proximal in anterior-posterior direction in area 3b (Kaas et al., 1979). Wall et al. (1986) found that this gradient also breaks down in monkeys; a prediction we could not test. In healthy controls, there is also a rough mirror image of the area 3b hand map in area 1. In monkeys, this map also breaks down after peripheral nerve repair, but the re-established topography differs from that in area 3b (Wall et al., 1986). A fact that Wall et al have used to argue that cortical reorganisation cannot exclusively be shaped by peripheral factors, as described above. Observing similar changes in human patients would strengthen our conclusion that human reorganisation is comparable to that of animal models.

Wall et al. (1986) also suggests that touch localisation is "distorted" differently in different parts of the hand and that this distortion might be explainable by distorted cortical maps. Mapping the whole hand, both for touch localisation and for cortical topography would enable us to directly test this claim. Our inability to see any correlation between touch localisation and reorganisation might be because we can currently not map distortions either in the periphery or in the cortex.

Finally, we are currently unable to say how far the observed reorganisation reflects changes to the peripheral organisation and how far it is driven by central factors. This can be addressed by incorporating microneurography in the experimental setup. Microneurography can measure the combined receptive field of a small number of receptive afferents. This enables assessing whether miswiring has taken place and

characterising receptive fields in terms of their cohesion or fragmentation. Additionally, it provides further measures of reinnervation quality, such as signal latency and amplitude which might affect localisation beyond topographical changes.

Conclusion

Considering the long history of research into functional impairment after peripheral nerve repair, it is surprising how little is known about the functional factors that determine recovery. "Faulty touch localisation" has been recognised as a hallmark of nerve repair since the beginning of the 20th century and cortical reorganisation in animal models has been studied since the 1980s. Yet even today it is unclear whether humans show reorganisation similar to animal models and if it has any functional implications. This thesis provides evidence that peripheral nerve injury leads to impaired touch localisation and cortical reorganization in the primary somatosensory cortex in line with predictions from work in monkeys. While both changes were specific to the injured nerve territory, we did not find a direct correlation between the two. This highlights that the relationship between cortical maps and perception is complex. Our study shows that to fully understand the impact of cortical reorganisation on touch localisation, it is necessary to carry out a detailed quantification of both aspects. Future work should map cortical representations and localisation across the whole hand, incorporate microneurography to delineate peripheral and central factors, and test computational models that detail how cortical maps could shape perception. Combining new, data-rich tools for measuring touch localisation and cortical reorganisation, like the ones we have employed in this study, with a detailed quantitative model, based on theory, has the potential to disentangle the intricate relationships that shape functional impairment and recovery. Elucidating these relationships is key to developing better therapies to improve outcomes for nerve injury patients.

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