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Electro-cutaneous stimulation on the palm elicits referred sensations on intact but not on amputated digits

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Abstract

Objective Grasping and manipulation control critically depends on tactile feedback. Without this feedback, the ability for fine control of a prosthesis is limited in upper limb amputees. Early studies have shown that non-invasive electro-cutaneous stimulation (ES) can induce *referred sensations* that are spread to a wider and/or more distant area, with respect to the electrodes. Building on this, we sought to exploit this effect to provide somatotopically matched sensory feedback to people with partial hand (digital) amputations.

Approach For the first time, this work investigated the possibility of inducing referred sensations in the digits by activating the palmar nerves. Specifically, we electrically stimulated 18 sites on the palm of non-amputees to evaluate the effects of sites and stimulation parameters on modality, magnitude, and location of the evoked sensations. We performed similar tests with partial hand amputees by testing those sites that had most consistently elicited referred sensations in non-amputees.

Main Results We demonstrated referred sensations in non-amputees from all stimulation sites in one form or another. Specifically, the stimulation of 16 of the 18 sites gave rise to reliable referred sensations. Amputees experienced referred sensations to unimpaired digits, just like non-amputees, but we were unable to evoke referred sensations in their missing digits: none of them reported sensations that extended beyond the tip of the stump.

Significance The possibility of eliciting referred sensations on the digits may be exploited in haptic systems for providing touch sensations without obstructing the fingertips or their movements. The study also suggests that the phenomenon of referred sensations through ES may not be exploited for partial hand prostheses, and it invites researchers to explore alternative approaches. Finally, the results seem to confirm previous studies suggesting that the stumps in partial hand amputees partially acquire the role of the missing fingertips, physiologically and cognitively.

1. Introduction

Tactile sensory feedback plays a pivotal role in the motor control of grasping and manipulation (Edin *et al*

1992, Edin and Johansson 1995). The tactile receptors in the palmar areas of the hand inform us about hand-object interactions and thus provide crucial information about the physical properties of the object and the contact between object and hand. People with impaired or no tactile sensibility experience difficulties with many daily life activities because the brain lacks the information required to properly plan and execute motor tasks, in particular manipulation (Johansson and Flanagan 2009).

Losing a hand deprives individuals of their tactile sensibility. While an acceptable level of grasping function is often (re-)gained through motorized prostheses, the restoration of tactile sensibility remains one of the open challenges in this field. Such artificial sensory feedback can be provided invasively or non-invasively (for a review, see Antfolk *et al* 2013b). Invasive feedback can be provided using surgically implanted electrodes, targeting afferent nerve fibers within the residual limb (Ortiz-Catalan *et al* 2014, Raspopovic *et al* 2014, Tan *et al* 2014, Davis *et al* 2016), and holds the potential of eliciting close-to-natural tactile sensations (Graczyk *et al* 2016). In contrast, non-invasive stimulation generally relies on the ability of the individual to learn and interpret artificial sensory stimuli provided on the skin, although modality (e.g., pressure to pressure) and somatotopical matching (e.g., utilizing phantom sensations) can shorten the learning process (Antfolk *et al* 2013a). However, non-invasive feedback has the clear advantage of avoiding surgery. Among the non-invasive methods, vibro- or electro-tactile feedback have been widely investigated in the past because of their high acceptance by the users, low power consumption, small dimensions, and compatibility with the EMG signal (Solomonow *et al* 1978, Kaczmarek *et al* 1991, Cipriani *et al* 2008, Antfolk *et al* 2013b, Dosen *et al* 2014). Notably, the studies conducted so far have focused on complete hand amputation and, hence, have investigated ways to provide tactile feedback of a missing hand – no study focused on partial hand amputations and providing feedback from partial hand prostheses (see Uellendahl and Uellendahl 2012, Imbinto *et al* 2016 for reviews of partial hand prostheses).

In this work, we used non-invasive electro-tactile or electro-cutaneous stimulation (ES), which involves the flow of an electrical current between two electrodes (anode and cathode) placed on the skin. Typically, this current travels locally and through the surface layers of the skin, thus activating cutaneous afferents close to the electrodes (Anani *et al* 1977, Kaczmarek *et al* 1991). However, when the electrode is placed on a skin area close to a nerve, the current can reach the sensory afferents deeper in the tissue, thus inducing sensations that are spread to a wider and/or more distant area, the so called *referred sensations* (Geng *et al* 2012, D'Alonzo *et al* 2014). Referred sensations are usually perceived more distally with respect to the electrode site. This phenomenon was described both for hand amputees and non-amputees (Geng *et al* 2012, Mulvey *et al* 2012, Chai *et al* 2013, 2015, Forst *et al* 2015, Germany *et al* 2016). Non-amputee participants reported referred sensations in the area of the digits/palm, particularly when the electrodes were placed on the ventral side of the forearm, close to the ulnar or medial nerves (Geng *et al* 2012, Mulvey *et al* 2012, Forst *et al* 2015, Germany *et al* 2016). The aforementioned studies agree that non-invasive ES could be a feasible way to provoke close-to-natural, referred sensations (Geng *et al* 2012, Mulvey *et al* 2012, Forst *et al* 2015, Germany *et al* 2016). In addition, it has been hypothesized that, with the use of multiple surface electrodes, the location of evoked sensations could be controlled by varying the stimulation site. A given electrode or electrode pair could be used as a channel to convey sensory information from one specific digit, and the user could perceive different digits from different channels (Geng *et al* 2012).

Building on these findings, we sought to exploit the effects of referred sensations to provide somatotopically matched sensory feedback to users of partial hand prostheses. Such a system could be capable of evoking referred sensations in the missing digits by stimulating branches of nerves that physiologically innervated them through electrodes placed on the proximal part of the hand (i.e., the palm). Hence, in this work, at first we stimulated different sites on the palm of non-amputee participants to evaluate the effects of sites and stimulation parameters on modality, magnitude, and location of the evoked sensation. This study allowed to identify a number of stimulation sites that could induce clearly perceivable and consistent referred sensations on the digits. These promising findings prompted us to perform similar tests with partial hand amputees. Specifically, we tested those sites that had most consistently elicited referred sensations in non-amputee participants. Unfortunately, though, we were unable to evoke referred sensations in the missing digits in partial hand amputees through ES: none of the amputees reported sensations that extended beyond the tip of the stump. Hence, this study suggests that the phenomenon of referred sensations through ES may not be exploited for partial hand prostheses and it invites researchers to explore alternative approaches.

2 Materials and Methods

2.1. Equipment

To deliver ES to our study participants, we used disposable, self-adhesive, pre-gelled Ag/AgCl electrodes (diameter = 10 mm) (GS26, Bio-medical Instruments, Clinton Township, MI) connected to a custom electro-tactile stimulator, which was controlled by a host PC (Figure 1). The electrodes were fixed on the palm of the participants. The stimulator produced bursts of current-controlled rectangular monophasic pulses. The amplitude of the current was controlled by hardware. Pulse widths (PWs), frequency of the rectangular pulses, and the duration of the pulse bursts were adjusted by a custom application running on the PC. The device could provide PWs ranging between 0.1 and 2.8 ms and frequencies from 1 up to 250 Hz.

Figure 1 Experimental setup. (a) Electro-tactile stimulator connected to a subset of stimulation electrodes. The inset shows the detailed placement of the stimulation electrodes on the palm of one non-amputee participant. (b) Representative placement of the electrodes on one amputee participant.

2.2 Participants

A group of ten non-amputee participants [participants *P1 - P10*. 5 males; age 28 ± 4 years (mean ± standard deviation), one left-handed (*P2*)] and five individuals with partial hand amputation (participants *A1 - A5*, Table 1) volunteered in the experiments. Informed consent in accordance with the Declaration of Helsinki was obtained from each participant before conducting the experiments. This study was approved by the local ethics committee of the Scuola Superiore Sant'Anna, Pisa, Italy (approval no. 1 of February 24th 2016). The experiments were carried out in accordance with the approved guidelines.

The partial hand amputees were recruited by phone from a list of upper limb amputees available at Scuola

Superiore Sant'Anna. Inclusion criteria were: partial hand amputation, not taking any medication, and being otherwise physically and mentally healthy. Due to these broad criteria, the group of amputees was relatively unselected: the time after amputation, occurrence of phantom digits, and use of a prosthesis varied greatly in the group. Before the experiments started, we interviewed participants to establish whether they experienced any phantom sensations or displayed a phantom map[1]. Participants A3 and A4 reported rare phantom sensations in the year preceding the experiment. The other participants had never experienced phantom sensations. None of the participants displayed a phantom map.

Table 1 Details of Participants With Partial Hand Amputation.

Participant ID (gender, age)	Dominant hand	Time since amputation	Cause	Prosthesis used	Missing phalanges	Phantom sensations/map
A1 (f, 26)	Left-handed	9 months	Bacteria	Cosmetic	L: 1-D, 2-I, 3-D	No/No
A2 (m,35)	Left-handed	21 years	Trauma	None	L: 2-I	No/No
A3 (f, 40)	Left-handed	10 years	Trauma	Cosmetic	L: 2-D, 3-D	Rare/No
A4 (m, 46)	Right-handed	2 years	Trauma	Cosmetic	R: 3-I	Rare/No
A5 (m, 48)	Right-handed	42 years	Trauma	None	R: 5-I	No/No

Legend. L/R: Left or Right amputation. 1-5: Digits (from thumb, to little finger). D/I/P: Phalanges (Distal, Intermediate, Proximal).

2.3. Pilot study with non-amputees

Prior to testing partial hand amputees, we evaluated 18 different stimulation sites on the palm of the left hand with non-amputee volunteers. The selection of the sites was guided by the anatomic configuration of the nerves and the space available on the hand with respect to the dimension of the electrodes. Specifically, the sites were placed on the skin areas directly above the path of the branches of the medial and ulnar nerves (Figure 2, Table 2). For our tests, we selected a fixed distance between the stimulation sites along the digit axes, because the dimensions of the palms of our participants were comparable (length 9.8-10.7 cm, width 7.5-8.2 cm [min-max]).

[1] Many amputees experience tactile phantom sensations when their residual limb is touched. The sites on the stump that elicit such sensations are called phantom map (Ramachandran and Hirstein 1998).

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We presumed that stimulating the nerve branches that lead to each digit would elicit referred sensations in that digit. Consequently, to stimulate the four fingers, the electrodes were placed 6, 20 and 34 mm below the palmar digital creases, along the axis of the corresponding finger (Figure 2(a)). For the thumb, further sites were evaluated in the area of the thenar eminence, between the palmar digital crease of the thumb and the thenar crease. Three sites were centered at 6, 20 and 34 mm below the palmar thumb crease and along the axis of thumb, and another three were parallel to the axis of the thumb, 15 mm medially. We asked the participants to keep their hand relaxed while we marked the stimulation sites with a pen and throughout the experiment to prevent movement of the skin over the deeper tissue.

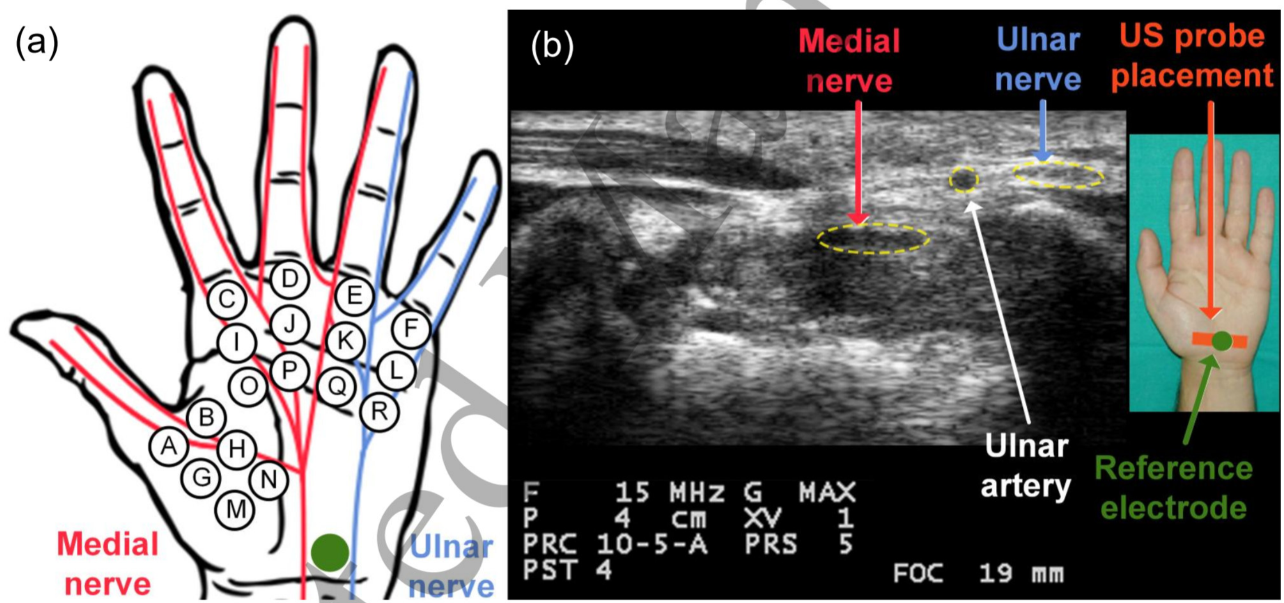

Figure 2 Stimulation sites and reference electrode. (a) Illustration depicting the placement of the stimulation (black circles) and reference (solid green circle) electrodes on the hand with respect to the major nerve branches. (b) Hand section at the level of the reference electrode (ultrasound imaging). Ultrasound imaging was used to guide the placement of the reference electrode, midway between the medial and ulnar nerves.

An additional electrode was placed medially between the pisiform and the tubercle of the scaphoid and approximately 1 cm further distal (towards the palm; on the base of the third metacarpal). This electrode was used as reference (anode) for assessing the 18 stimulation sites (cathodes). We placed the reference electrode midway between the medial and ulnar nerve to minimize any potential anodal block. We checked the validity of the placement of the reference electrode in this position by ultrasound inspection (MyLabFive, Esaote SpA, Italy) (Figure 2(b)).

Table 2 Summary of stimulation sites and presumed target areas for referred stimulation.

Stimulation sites	Target area for the referred sensation
A, B, G, H, M, N	Thumb
C, I, O	Index digit
D, J, P	Middle digit
E, K, Q	Ring digit
F, L, R	Little digit

Throughout the experiment, the participants sat comfortably on a chair in front of a table, with their left arm in a supine position on an ergonomic padded armrest (Figure 1(a)). We began the experiment by placing the electrodes on the selected sites (Figure 1). Then, for each site, we used an adaptive psychophysical procedure (a stair case procedure with adaptive step size[2]) to approximate the rheobase, and we assessed the perceived sensations using twice that value. We chose a stimulation frequency of 100 Hz as in previous studies (Chai *et al* 2013, 2015, 2017, Wang *et al* 2013, D'Alonzo *et al* 2014, Zhang *et al* 2015, Štrbac *et al* 2016, Xu *et al* 2016). This frequency has been reported to lead to a well-localized, more continuous sensation resembling constant pressure compared to lower ones. Frequencies above 100 Hz were not taken into consideration because they produce a continuous, stable sensation exclusively described as "tingling" (Saunders 1977).

The assessment of the perceived sensations was performed on the stimulation sites using a fixed current intensity (amplitude = 2 x rheobase) to provide a stimulation that was easily perceived but not painful. For each site, we evaluated the qualities of the stimulation at different PW, starting at 100 μs and increasing to a maximum of 700 μs in steps of 100 μs. Immediately after a stimulus was applied, each participant verbally reported the perceived sensation regarding location, type, and magnitude. The participants were asked to identify the place where they felt the stimulation as precisely as possible. Similar to Geng and colleagues (2012), we

[2] The rheobase was approximated using a frequency of 100 Hz and a PW of 1.5 ms following the guidelines by Forst et al (2015). Starting from a subthreshold current amplitude (0.5 mA), the intensity was increased by 1 mA until the subject reported a sensation. Then, the current was decreased, with a reduction in step-size of 50% at each reversal until it was within a specified tolerance (0.25 mA). After that point, the procedure was stopped after four reversals and the last value was considered the approximate rheobase.

provided a list of terms to describe the type of induced sensation. The list included "tingling", "vibration", "pricking", "itching", "pressure", "movement", "cold", "warmth", "pain", "touch", "pinching" and "tickling"; participants could use more than one term to describe any given stimulation. The magnitude of a sensation was rated on an 11-point scale (0 - "no sensation", 10 - "upper limit of a sensation or pain") (Geng *et al* 2012). For each stimulation site, the evaluation was concluded if the intensity reached 10, or if a hand muscle contracted; the corresponding PW values were recorded (PW_{max}). If a participant showed a contraction at a certain PW (e.g. 700 µs), the previous PW was considered the PW_{max} (e.g. 600 µs).

The stimulation sites were assessed in a random order across participants. Each stimulus was repeated as often as demanded by the participants to rate each quality. Moreover, the participant could rest as long as desired between each stimulation. We used Min-Max scaling to normalize the scores of each participant for inter-participant comparison.

2.4. Study with amputees

The procedure to evaluate the evoked sensations in partial hand amputees was identical to the one for non-amputees. However, to focus our analysis on sensations referred onto the amputated digits, we exclusively explored those sites that had provided a sensation in the target areas in non-amputee participants. Hence, we assessed those sites of the stimulation matrix that were on the same axis as the amputated digits, as well as other close sites that had elicited sensations on the target digit in the first experiment (Table 3). As the dimensions of the amputees' hands were similar to those of the non-amputees, we did not change the distances between stimulation sites.

Table 3 Summary of stimulation sites for amputee participants.

Participant	Tested hand	Stimulation sites
A1	Left	A, B, C, D, E, G, H, I, J, K, O, P, and Q
A2	Left	B, C, D, H, I, J, O, and P
A3	Left	B, C, D, E, H, I, J, K, O, P, and Q
A4	Right	C, D, E, I, J, K, O, P, and Q
A5	Right	E, F, K, L, Q, and R

2.5. Analysis

The outcomes were analyzed as follows. First, a one-way repeated measures ANOVA, followed by pair-wise comparisons using Bonferroni adjustment, was used to assess differences regarding rheobase and PW_{max} across the stimulation sites in the group of non-amputee participants (after normality check using the Kolmogorov-Smirnov test). Then, the data on the perceived sites of sensation were grouped according to whether the sensation was felt at the level of the stimulation sites (usually under or around the stimulation electrode, but also on larger areas of the palm), or on the digit(s), and, in the latter case, on which phalanx or phalanges (i.e., proximal, intermediate, or distal). Furthermore, the relationship between normalized subjective intensity and PW was identified on each site. Eventual significant differences in the normalized perceived intensities across stimulation sites were assessed by means of a two-way ANOVA (factors: stimulation sites, PW values). Finally, a repeated measures ANOVA (factors: sites of stimulation, group) was used to compare rheobase, PW_{max}, and normalized perceived intensity between amputees and non-amputees. An unpaired t-test was employed to compare the percentage of occurrence of each term used to describe the sensation between amputees and non-amputees. For all statistical tests, a p-value of 0.05 was used as the threshold for significance.

3. Results

3.1. Findings on non-amputee participants

3.1.1. Rheobase and PW_{max}. The rheobase values ranged from 1 to 2.75 mA with a mean of 1.47 ± 0.26 (standard deviation) mA (Figure S1(a) and Table S1 in the Supplementary Materials). These values were significantly different among electrode sites (one-way repeated measures ANOVA – $F(17,153) = 3.04$, $p < 0.001$), with generally lower thresholds for locations closer to the reference electrode compared to those further away. The PW_{max} ranged between 0 and 700 µs, with a significant difference among the stimulation sites (one-way repeated measures ANOVA – $F(17,153) = 5.53$, $p < 0.001$) (Figure S1(a) and Table S1 in Supplementary Materials). Notably, some participants already demonstrated contractions in the hand at 100 µs PW at sites M, N and H (5, 4, and 2 participants, respectively), resulting in a PW_{max} of 0 for those sites.

3.1.2. Sites of referred sensation. The stimulation sites closer to the long fingers (i.e., sites C, D, E, and F) could more easily elicit sensations restricted to the target finger than the more proximal sites (Figures 3 and 4). On the sites 20 and 34 mm proximal from the palmar creases (i.e., sites I, J, K, L, O, P, Q and R), sensations occurred more frequently at the level of the stimulation sites (Figure 3). Stimulation on the most proximal sites usually evoked sensations that involved the site of stimulation, the presumed target finger, and other adjacent fingers. The sites on the thenar eminence fared worse at providing sensations to the target (thumb), but it was still possible for sites A, B, G, and H. On the contrary, sites M and N never elicited sensations restricted solely to the thumb.

In general, an increase in PW (and thus in injected current) increased the perceived area of the sensation, albeit in several different ways (Figure 3). For instance, an increasing PW moved the sensation from the target digit alone, to the target digit and the stimulation site (e.g. site D), or to the target digit and adjacent sites (e.g., site C). In other circumstances, the sensation moved from the stimulation site alone to the target digit and adjacent sites (e.g., G). Similarly, in ~30% of the trials where more than one PW value was tested for the same site, the location of the referred sensation on a single digit grew from a smaller to a larger area (e.g., from one phalanx to all three phalanges) with increasing PWs (most frequently in the index) (Figure 5).

In more detail, the analysis of the perceived location of the stimulus showed that almost every participant had stable referred sensations in each digit from at least one site. In other words, it was possible to identify at least one site, for each digit, that elicited a referred sensation on that digit consistently (i.e., in the whole range of tested PW values) (Figure 4(a)). The only exceptions were the thumb for P7, the ring finger for P4, and the little finger for P6 and P9. Sites M and N were the only ones that did not provide a stable sensation on a digit in any participant. Conversely, the stimulation sites that provoked stable digit sensations in a larger sample of participants were: sites A and H for the thumb (7 and 6 participants, respectively); C and O for the index finger (10 and 9, respectively); D and P for the middle finger (7 and 8, respectively); E and Q for the ring finger (5 and 6, respectively); and R for the little finger (8). Some sites (A, B, Q, and K) elicited stable referred sensations not in their presumed target but in adjacent digits in some participants. The stimulation sites and PWs that optimally elicited referred sensations on each digit (across non-amputee participants) were: H for the thumb (PW 100 μs), C for the index (PW 200 μs), D for the middle (PW 300 μs), E for the ring (PW 400 μs), and F for the little finger (PW 400 μs) (Figure 4(b)).

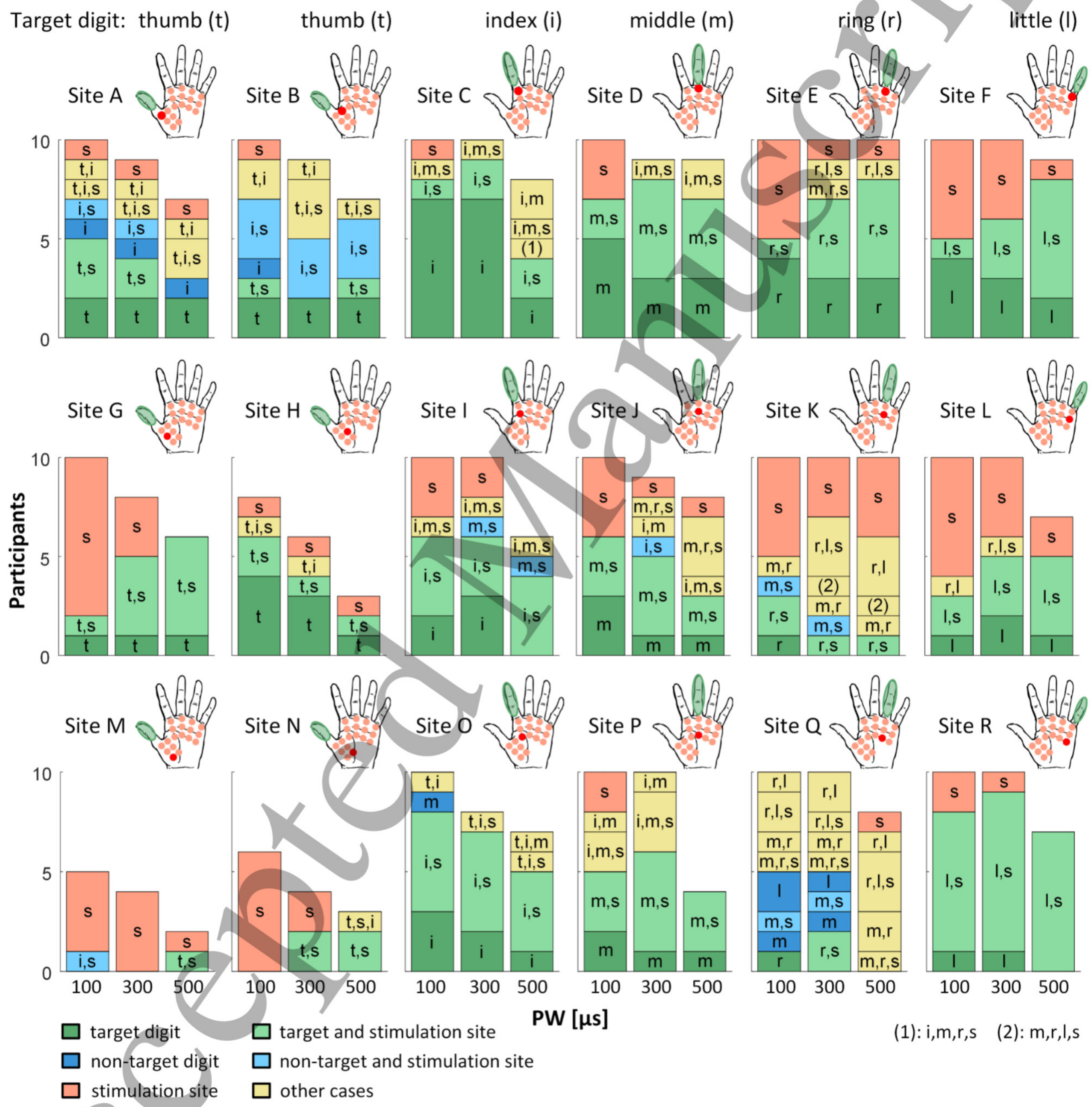

Figure 3 Distribution of the perceived location of sensation with varying PW. The sensations were perceived on the thumb (t) and fingers (index (i), middle (m), ring (r), and little (l)) and at the level of the stimulation sites on the palm (s). Green bars indicate sensations localized only on the presumed target digits, light green represents sensations on the presumed target and at the level of the stimulation sites, blue shows sensations localized on a finger that is not the presumed target, light blue indicates sensations on a non-target digit and at

the stimulation site, red bars indicate sensations localized only on the stimulation areas, and yellow indicates all other cases. For the sake of simplicity and brevity, only results for 100, 300 and 500 µs PW are shown to provide an overview of the distribution of the sensation location with increasing PWs. The y-axis denotes how many participants reported a given location of sensation for each of the three PWs. Each participant reported a location once per PW per site. Some participants experienced muscle contractions or pain, so the bars do not always reach '10' (the total number of participants).

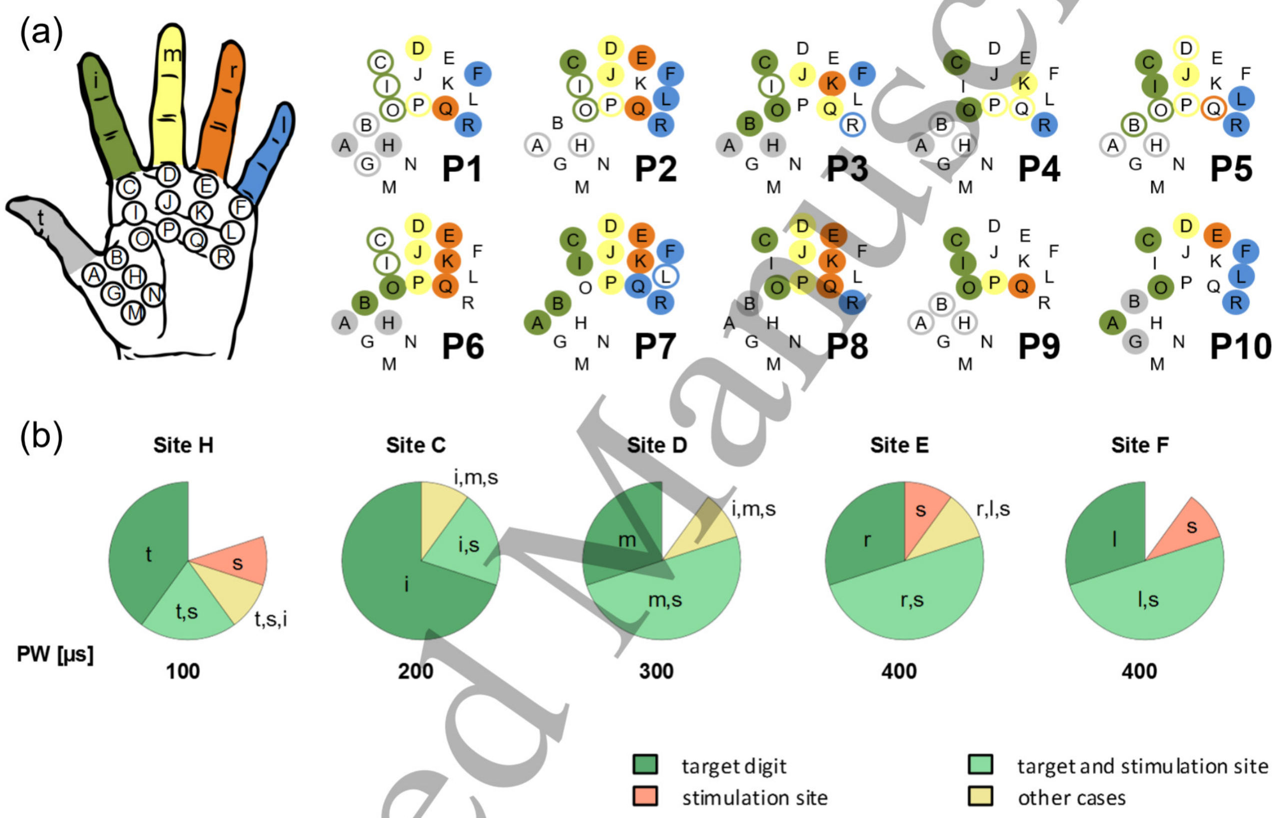

Figure 4 Stimulation sites that elicited a referred sensation on the digits in non-amputee participants. (a) Each hand represents one participant. Each color indicates a different stimulated digit, filled circles indicate sites in which a large range of PWs elicited referred sensations (100 µs to ≥500 µs); empty circles denote sites, which elicited sensations for a lower range of PWs (100 µs to <500 µs). (b) Stimulation sites that showed the best ability to evoke sensations in the target alone and in the target and the stimulation site, at the optimal PW noted below each pie chart. It further shows the other sites that the sensation was referred to.

Electro-cutaneous stimulation on the palm elicits referred sensations on intact but not on amputated digits

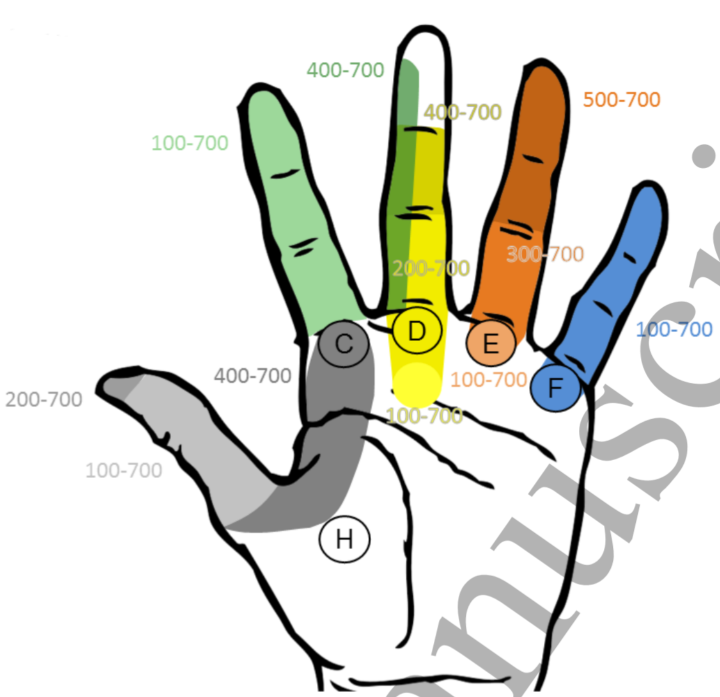

Figure 5 Spread of the sensation With increasing PW. The figure shows an example of how the reported area of sensation grew with increasing PW in one participant. The presented electrode sites were chosen because they proved to generally fare best at providing referred sensations to the target digits. H: gray, C: green, D: yellow, E: orange, F: blue; the numbers denote the PWs in µs at which the stimulation was felt in the indicated areas.

3.1.3. Types and intensity of sensations. The participants most frequently described the sensations as “tingling” (63 ± 29%), “vibration” (48 ± 30%), “tickling” (17 ± 27%), “pricking” (16 ± 13%), and “pressure” (6 ± 13%). These terms describe the vast majority (> 96%) of all reported sensations; “warmth”, “pinching”, and “movement” were each reported in around 1% of the trials, while “itching” and “touch” only occurred in 0.5% of all trials (6 times and once, respectively). “Pain” and “cold” were never used to describe the sensations (Figure 6(a) and Figure S3 in Supplementary Materials).

The relationship between the PW and the normalized subjective intensity proved positive (monotonically increasing) for all sites (Figure S2(a) in Supplementary Materials). The statistical analysis (two-way ANOVA) demonstrated that the normalized subjective intensities were significantly different across the stimulation sites ($F(17,863) = 12.46$, $p < 0.001$) and PWs ($F(6,863) = 379.24$, $p < 0.001$).

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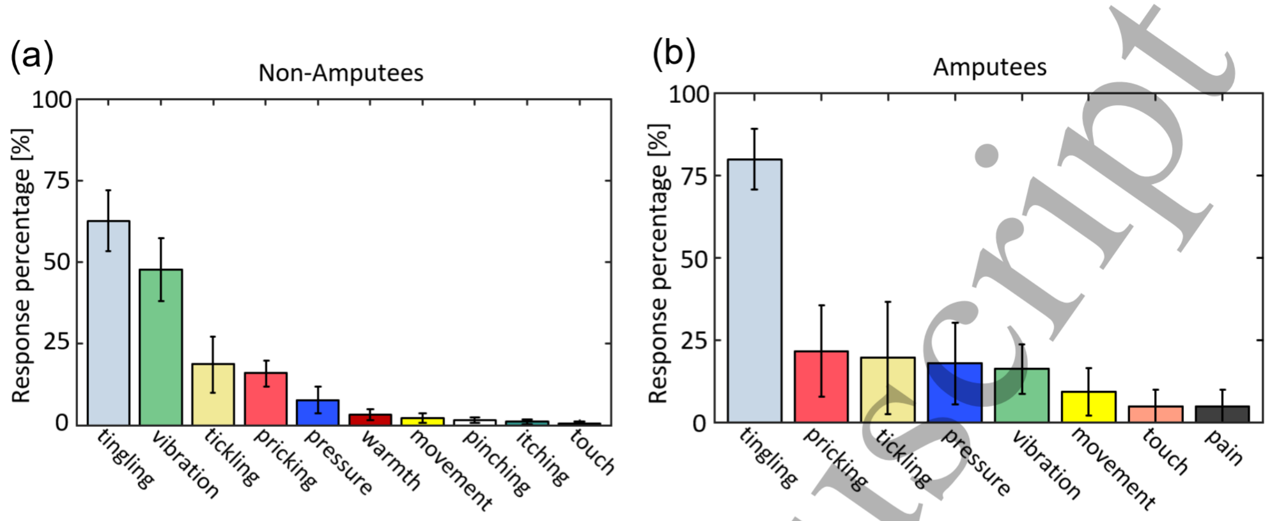

Figure 6 Distribution of the percentage of described sensations (mean ± standard error). (a) Non-amputee participants. (b) Amputee participants. Since the participants could describe each sensation with more than one term, the percentages do not add up to 100.

3.2 Findings on amputee participants

The rheobase values of the amputee participants ranged from 1.25 to 2.00 mA. The PW_{max} values of participants A2 and A3 ranged between 100 and 500 µs, whereas for the other three participants, these values were, on average, higher, ranging between 400 and 700 µs (see Figure S1(b) and Table S1 in Supplementary Materials).

All amputee participants reported, for some sites and a limited range of PWs, that the evoked sensation spread up to the tip of the stump of the amputated digit (Figure 7). However, sites that elicited such referred sensations in the whole range of tested PW values could only be identified for participants A1, A3, and A5 (Figure 8). Remarkably, when stimulating the sites targeting the missing digits, the referred sensation **never extended beyond the residuum** in any of the participants.

The relationship between the PW and the normalized subjective intensity proved positive (monotonically increasing) for all sites, as in non-amputee participants (Figure S2(b) in Supplementary Materials). However, these outcomes are highly variable due to the small sample size. Akin to the non-amputees, the statistical analysis of the normalized subjective intensity showed a significant difference among PW values ($F(6,166) = 49.6$, $p < 0.001$) and stimulation sites ($F(12,166) = 8.82$, $p < 0.001$). With regards to the elicited sensations, the occurrence of "tingling" was by far the most common (75 ± 20 %) in amputee participants. Other frequently evoked sensations were: “tickling” (20 ± 38 %), “pricking” (22 ± 31 %), “pressure” (18 ± 31 %), and “vibration” (16 ± 17 %) (Figure 6(b)). These results are similar to those of the non-amputee group, except that “vibration” occurred less frequently in amputees. A significant difference in the perceived sensations between amputees and non-amputees could, however, not be shown. More generally, the statistical analysis did not highlight a significant difference between amputees and non–amputees for any of the stimulation parameters. The sensations for each amputee participant are detailed as follows.

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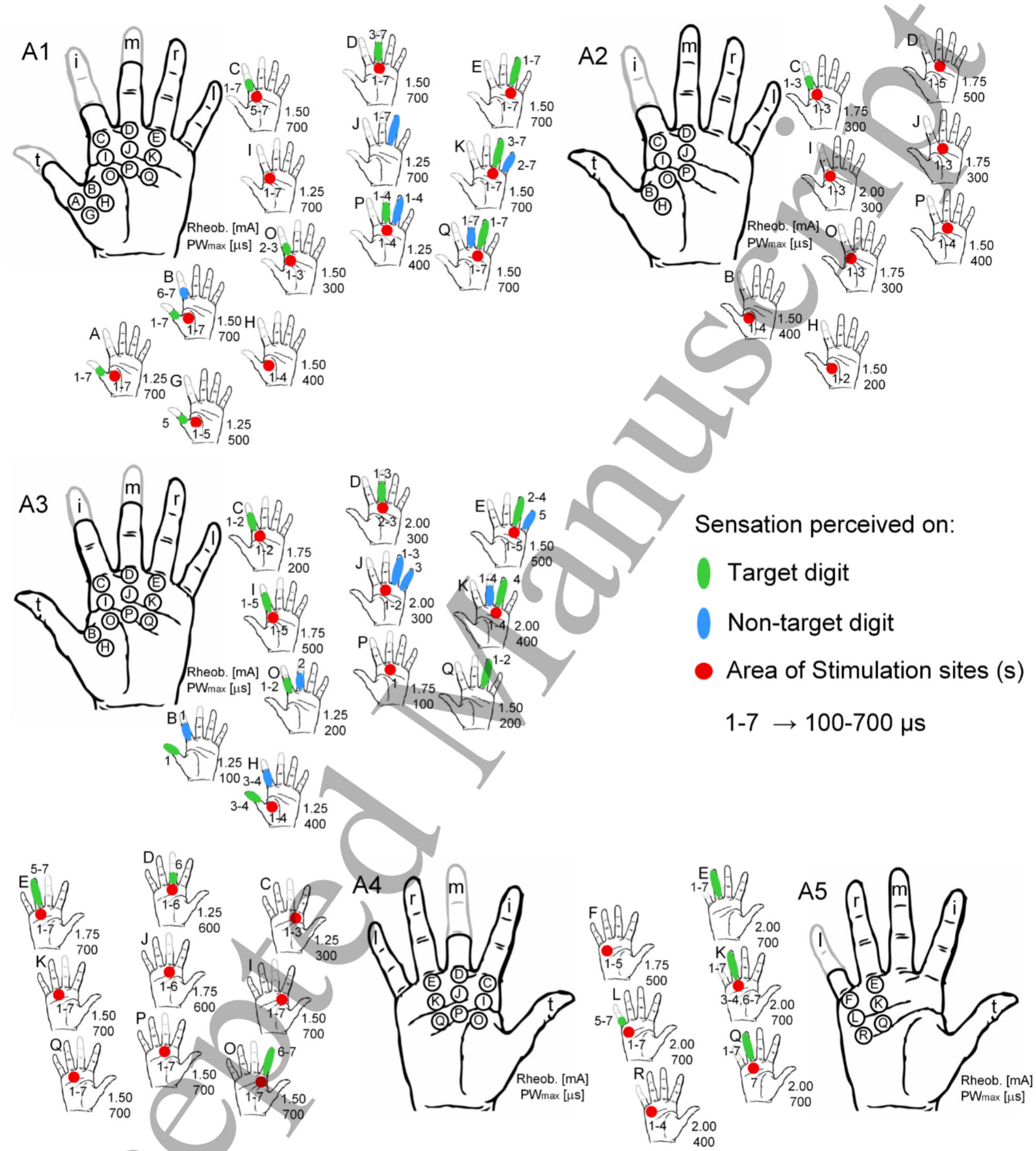

Figure 7 Distribution of the perceived sensation locations for each electrode site for the amputee participants. Red circles denote the location of perceived stimulation on the stimulation area, green ellipses on the target digit, and blue ellipses on other digits. The range of PWs for each site is indicated by the numbers next to it (1-7 → 100-700 μs). The rheobase and PW_{max} for each site is also shown.

Participant A1 (three amputations): the sensation was felt on the residual thumb for stimulation of sites A, B, and G. In all cases, the sensation on the residual thumb coincided with a sensation on the stimulation site and on other sites (for site B, it was referred to the residual index finger) (Figure 7). Only sites A and B consistently elicited sensations on the residual thumb in a large range of PWs (100 – 700 µs) (Figure 8). For sites B, C, and O, the evoked sensation was felt on the residual index finger, but again, in all cases, the sensation was accompanied by a sensation on the stimulation areas (Figure 7). Site C was the only one which provided a consistent sensation on the residual index finger in a large range of PWs (100 – 700 µs) (Figure 8). Sensations on the residual middle finger were reported for stimulations of sites D, J, P, and Q, yet, only for J, the sensation was restricted to the residual finger (PW range: 100 – 700 µs) (Figures 7 and 8). The main sensation elicited was "tingling" (all 13 stimulation sites), but also sensations of "pricking" (2) and "vibration" (2) were evoked. Notably, sites P, E, K, and Q provided referred sensations on the (unimpaired) ring finger in large ranges of PWs (Figures 7 and 8), similar to the non-amputee participants.

Participant A2 (one amputation): only site C evoked sensations localized on the residual index finger (Figure 7). The other sites elicited sensations limited to the stimulation areas. The prevalent elicited sensations were "tickling" (7 sites out of 8), "pricking" (6), "tingling" (5), "pressure" (5), and "movement" (3).

Participant A3 (two amputations) reported sensations on the residual index finger when sites B, C, H, I, O, and P were stimulated. For these sites, the sensation was paired with sensations in at least one other site: for sites B, H, and O the sensation occurred on other digits, and for sites C, H, I, and P it occurred on the stimulation sites (Figure 7). However, only site I elicited a stable sensation on the residual index finger for a large range of PWs (100 – 500 µs) (Figure 8). For sites D, J, and O, the evoked sensation was perceived on the stump of the middle finger. Again, in all three cases, the sensation on the residual middle finger was coupled with a sensation in other sites: other digits in the case of sites J and O, and the stimulation areas in the case of sites D and J (Figure 7). The elicited sensations were "tingling" (9 sites out of 11), "pressure" (3), "pricking" (2), "movement" (1), and "vibration" (1). Sites E, K, and Q provided referred sensations on the (unimpaired) ring and little (E and K) fingers (Figure 7).

Participant A4 (one amputation) reported a sensation localized on the residual middle finger for site D. This sensation was, however, concurrent with a sensation on the stimulation site and only occurred for one PW value

(600 µs) (Figure 7). Overall, the elicited sensations were “tingling” (5 sites out of 9), “vibration” (4) and “tickling” (1). Sites E and O provided referred sensations to the (unimpaired) ring and index fingers.

Participant A5 (one amputation): only site L elicited sensations on the residual little finger and only for PW values higher than 400 µs (Figure 7). The elicited sensation coincided with a sensation in the stimulation area and was described as “tingling” for all tested stimulation sites (6 sites). Notably, sites E, K, and Q provided consistent referred sensations on the (unimpaired) ring finger in a large range of PWs (100 – 700 µs) (Figures 7 and 8), similar to our non-amputee participants.

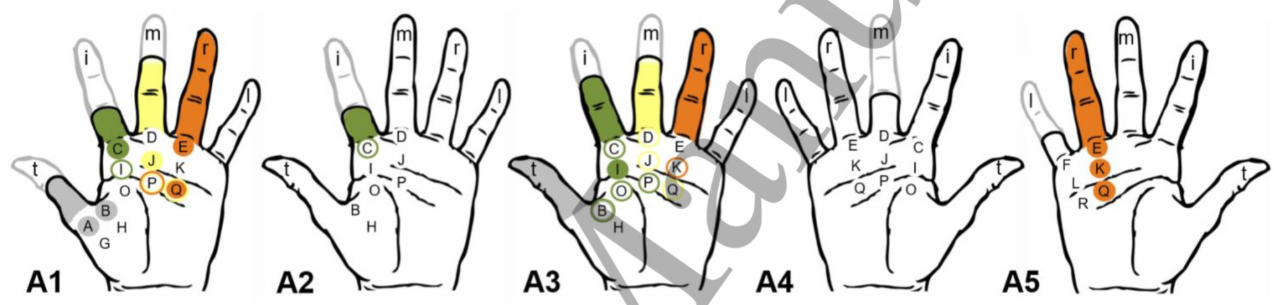

Figure 8 Stimulation sites that elicited consistent referred sensations across PWs in amputee participants. Each hand represents one participant. Each color indicates a different stimulated digit, double colored circles indicate referred sensation on two digits (sites P, Q for A1 and site B for A3), filled circles indicate a large range of PW that elicited referred sensations (100 to ≥500 µs). Empty circles denote sites, which elicited sensations in a lower range of PW (100 µs to <500 µs) or only for 100 µs. Notably, none of the sites could elicit sensations that projected beyond the amputation stump.

4 Discussion

In this work, we sought to investigate the possibility of eliciting referred sensations in the digits by electrically stimulating afferent nerve fibers through surface electrodes on the palm. While we could clearly demonstrate referred sensations in non-amputee participants, we were unable to demonstrate similar effects on the amputated digits of individuals with partial hand amputation. The reported sensations never extended beyond the tip of the stump. Hence, this work suggests that ES on the palm cannot elicit sensation referred to the missing digits in partial hand amputees.

Building on previous findings (Anani *et al* 1977, Kaczmarek *et al* 1991, Geng *et al* 2012, D’Alonzo *et al* 2014), this work demonstrated, for the first time, referred sensations from multiple sites on the palm in non-amputee participants. Stimulation sites closer to the long fingers more easily evoked (referred) sensations restricted to the target fingers, while stimulating intermediate and proximal sites usually elicited sensations also on the palmar areas. However, proximal sites evoked sensations on the fingers more often than intermediate ones (Figure 3). These outcomes seem explained by the anatomy of the hand and its variability across participants. The nerves that innervate the fingers branch off just proximal to the metacarpophalangeal joints, and accordingly, the most distal sites have a higher chance of stimulating each finger individually. Likewise, higher PWs increase the current density and thus the spread of the current (Forrester and Petrofsky 2004), which in turn increases the probability of sensations on more than one location. Furthermore, as the intermediate sites were localized above the ligaments of the metacarpophalangeal joints, and thus on a tissue layer thicker than that under the proximal sites, the injected current less likely reached the nerves beneath. While stimulation of the targeted fingers is an important goal, activating broader sensation sites through higher PWs, as shown in ~30% of our trials, can also be useful (viz. in the prospect of prosthesis feedback). Similar correlations between PW and the number of stimulated nerve fascicles have also been reported in previous studies with implanted electrodes (Ortiz-Catalan *et al* 2014, Graczyk *et al* 2016).

Studies with invasive nerve stimulation also report monotonically increasing subjective intensity ratings with increasing PW (Tan *et al* 2014, Graczyk *et al* 2016). However, due to the different stimulation methods, we tested a much larger range of PWs (100 to 700 µs vs. 80/100-170/180 µs) with much larger step size (100 µs vs. 14-20 µs). Consequently, while agreeing with the trend reported in these papers, a direct comparison to the results of intraneural stimulation experiments should be very carefully assessed.

Stimulating the thumb, in contrast, proved difficult, as contractions of the thenar muscles frequently thwarted the analysis of referred sensations, even at low PWs. The reason why site H fared best at eliciting referred sensations restricted to the thumb is probably anatomical, viz. that site H was located directly over the nerve branches innervating the thumb. Site M, however, was the furthest away from the nerve branches and consequently almost never elicited sensations in the thumb.

The referred sensations elicited in non-amputee participants, unexpectedly, could not be replicated in the missing digits of partial hand amputees, as the sensations never projected beyond the tip of the stump. In the unimpaired digits, however, referred sensations could be elicited, just as in the non-amputee group. This outcome is surprising because it diverges, to the best of our knowledge, from all studies conducted so far on this topic.

In their studies, albeit methodologically different from ours, Chai et al. and Liu et al. demonstrated sensations referred to the fingers in amputees (Chai *et al* 2013, 2015, Liu *et al* 2015). However, in their works, the ES was provided to the forearm of transradial amputees, hence both stimulation site and level of amputation were different compared to our study. Chai *et al* (2015), and Mulvey *et al* (2013), stimulated the phantom map directly, which make their studies even less comparable with ours. In fact, none of our participants presented phantom maps, so we could not assess them. Our results also contrast previous findings where transradial amputees were stimulated using peripheral nerve electrodes, and specific tactile sensations (e.g., “touch” and “pressure”) could be evoked in the fingertips (Ortiz-Catalan *et al* 2014, Raspopovic *et al* 2014, Tan *et al* 2014, Davis *et al* 2016). These results suggest that all central nervous connections, the “core topography”, for interpreting sensations from the fingers of the amputated hand remain intact (Makin and Bensmaia 2017). This is further supported by the finding that phantom sensations of the missing limb could be (re-)elicited even decades after amputation (Ramachandran and Hirstein 1998). Our study, carried out with substantially differing methods (direct neural vs. surface stimulation, transradial vs. digit amputation) indicate that these findings may not be transferred to partial hand amputees when using surface ES.

It is difficult to compare digit and hand amputation, as the difference in scale and impact on the individual is very large: cortical reorganization and peripheral nerve re-growth are substantially different in the two cases (e.g., Florence and Kaas 1995, Manger *et al* 1996, Oelschläger *et al* 2014). Regarding this physiological aspect, Merzenich *et al* (1984) demonstrated cortical reorganization after digit amputation in adult owl monkeys. They found that if a finger stump remains, its representation can expand to the size of the intact digit. It should be mentioned, though, that the residual nerves of the amputated digit were tied with sutures to prevent regeneration, whereas in digital amputations in humans, the nerve is allowed to regenerate proximal to the amputation (after traction neurectomy) (Word Health Organization 2003, Brunicardi *et al* 2014, Ovadia and Askari 2015). Although suturing the nerves presumably alters the cortical representation of the stump due to prevention of re-growth of the damaged peripheral nerves (Inbal *et al* 1987, Braune and Schady 1993, Manger *et al* 1996, Björkman *et al* 2012), the expansion of the representation of the stump in the cortex was indeed later confirmed. Manger, Woods and Jones (1996) showed that in macaque monkeys the cortical receptive fields of digit stumps approached in size those normally seen at an intact fingertip, and additionally reported that the innervation of the skin in the stump was only slightly lower than that of an intact distal phalanx (the peripheral nerves had not been sutured). Also, the ramification of the nerves at the tip of the stump resembled in form that of the adjacent intact fingertips. Hence, these findings suggest that the stump partially acquires the role of the missing fingertip physiologically. In their recent opinion paper, Makin and Bensmaia (2017) argued that cortical reorganization does not necessarily correlate with novel functional representation, and that cortical plasticity in the adult brain is not strong enough to result in functional changes after extreme deafferentiation, such as hand amputation. Our hypothesis does not oppose this interpretation and rather argues that the loss of a (part of a) digit may in fact be small enough to bring about functional changes. Cortical plasticity would not have to connect entirely diverse regions (such as face and hand) but rather enable a small shift of functional representation from the fingertip to the tip of the stump.

The cognitive aspect of digit amputation is consistent with this hypothesis. Behavioral studies by Ramachandran and colleagues showed that the individual's (innate) body image is transitory and profoundly malleable by different stimuli (Ramachandran and Hirstein 1998, Ramachandran and Rogers-Ramachandran 2000, McGeoch and Ramachandran 2012). Accordingly, a small amputation, such as that of a part of a finger, may be much easier to reconcile with one's body image than the loss of a hand. The occurrence of phantom sensation after digit amputation may be an indicator for this hypothesis but, regrettably, limited and conflicting information is available on the matter. Chu (2000) reported that the majority of finger amputees involved in his study (~60%) experienced (occasional) phantom sensations, with larger prevalence in those with proximal amputations compared to distal amputations (~70% vs. ~50%). Notably, phantom sensations were generally present in subjects with recent amputations (on average ~7 months) and generally absent in those with older amputations (~4 years). Similar correlations were reported by others (Henderson and Smyth 1948, Schley *et al* 2008); nonetheless, there is no consensus on this topic. In fact, Karle and colleagues (2002) reported lower prevalence of phantom pain in digit amputees (19%) compared to individuals with more proximal amputations (50-80%, Oelschläger *et al* 2014) – a finding later confirmed by Lotze (2016). If pain is correlated with sensation, as hypothesized by several investigators (Kooijman *et al* 2000, Makin *et al* 2013), the prevalence of digit amputees with sensations would be much lower in the study by Karle and colleagues (2002) than that reported by Chu (2000). None of the participants in our study had frequent or vivid phantom sensations; whether this had to do with time since amputation is unknown. Hence, our results remain to be validated in digit amputees with phantom sensations; if a stable phantom does exist, it might be possible to evoke a referred sensation on it. In short, the inconclusive account shows clearly that there is need to investigate phantom phenomena (pain and sensations) in digit amputees on a larger scale.

Additionally, the literature on the differing impact of hand and digit amputation on the central nervous system is scarce, sometimes contradictory, and its results are often based on experiments with non-human primates and may thus not be applicable to humans (e.g., Rasmusson 1988, Calford and Tweedale 1991, Florence and Kaas 1995, Florence *et al* 1998, Weiss *et al* 2000, Kambi *et al* 2014, Li *et al* 2014). All that seems to be known so far is that digit amputation leads to significantly smaller deafferented areas in S1 compared to amputations of the whole hand (Oelschläger *et al* 2014). Besides this, there are no brain imaging studies comparing human partial hand and transradial amputees that would shed light on the exact differences in cortical representation of the stumps. If indeed a peripheral and/or central difference between digit and hand amputees is responsible for our divergent findings, it would be interesting to determine the exact borders of the two phenomena, i.e., at which level of stimulation/amputation of the limb (e.g., digit vs. transcarpal vs. wrist disarticulation) the sensation can be referred to the phantom digits. It would further be valuable to see whether direct stimulation of the nerves can refer sensation to the phantom fingers in digit amputees, e.g., through microstimulation experiments.

As regards the employed current limits, the rheobase values proved consistent with the previous work of Forst *et al* (2015). Lower threshold values were obtained for locations closer to the reference electrode compared to those further away, as previously reported (Forrester and Petrofsky 2004). Unlike Chai and colleagues (Chai *et al* 2013, 2015) we did not find a statistically different stimulation threshold between amputees and non-amputees. However, this difference may again be attributed to a different methodological approach: we stimulated sites on healthy skin, while Chai and colleagues stimulated sites on the stump. It is known that stump skins may have atypical innervation and atypical amounts or distribution of soft tissue due to the trauma, the surgery, and/or as the result of stump coning, which likely affected the stimulation thresholds.

In accordance with other publications, the provoked sensations were most frequently described as "tingling" or "vibration" by our participants (Vallbo *et al* 1984, Geng *et al* 2012, Tan *et al* 2014, 2015, Forst *et al* 2015, Graczyk *et al* 2016). Furthermore, thermoreception ("warmth" and "cold") may occur so rarely because Aδ and C fibers (pain, thermoreception) are smaller and have a higher stimulation threshold compared to Aα and Aβ fibers (proprioception and tactile perception) (Micera and Navarro 2009) and might, thus, be less likely to become sufficiently activated.

As mentioned above, our group of amputees was not homogenous in terms of the level of amputation, the time since amputation, and the amputation etiology (Table 1). The number of amputees was also lower than the non-amputee control group since it was difficult to find individuals with this level of amputation that were willing to participate in our experiments. Furthermore, hydration of the participants was not controlled and could have affected skin conductance, though we believe this would not affect our results significantly, as the stimulation thresholds were determined for each stimulation site individually. Also, pre-gelled electrodes are usually less affected by this issue than dry electrodes.

To conclude, our results suggest that it may not be possible to elicit sensations referred to the missing phalanges of partial hand amputees through ES. Hence, we invite studies in which the sample size is increased to verify our findings and which include partial-hand amputees with strong phantom sensations. As mentioned above, further experiments with transmetacarpal and wrist disarticulated amputees will shed light on the exact level at which the sensations may stop being referred to the amputated digit. Based on our findings, we invite researchers working in the area of partial hand prostheses to explore and focus on alternative sensory feedback approaches. Nonetheless, we could clearly demonstrate that it is possible to evoke sensations in the fingertips of non-amputees by stimulating the palm of the hand. If this effect can be shown to be stable even during hand and arm movements, it could be used for haptic systems (in virtual or augmented reality, teleoperation, or rehabilitation), to provide sensation on the digits without obstructing the contact area of the fingertips or limiting

Electro-cutaneous stimulation on the palm elicits referred sensations on intact but not on amputated digits

their movement.

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