Visuotactile synchrony of stimulation-induced sensation and natural somatosensation

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Abstract

Objective. Previous studies suggest that somatosensory feedback has the potential to improve the functional performance of prostheses, reduce phantom pain, and enhance embodiment of sensory-enabled prosthetic devices. To maximize such benefits for amputees, the temporal properties of the sensory feedback must resemble those of natural somatosensation in an intact limb. Approach. To better understand temporal perception of artificial sensation, we characterized the perception of visuotactile synchrony for tactile perception restored via peripheral nerve stimulation. We electrically activated nerves in the residual limbs of two trans-tibial amputees and two trans-radial amputees via non-penetrating nerve cuff electrodes, which elicited sensations referred to the missing limbs. Main results. Our findings suggest that with respect to vision, stimulation-induced sensation has a point of subjective simultaneity (PSS; processing time) and just noticeable difference (JND; temporal sensitivity) that are similar to natural touch. The JND was not significantly different between the participants with upper- and lower-limb amputations. However, the PSS indicated that sensations evoked in the missing leg must occur significantly earlier than those in the hand to be perceived as maximally synchronous with vision. Furthermore, we examined visuotactile synchrony in the context of a functional task during which stimulation was triggered by pressure applied to the prosthesis. Stimulation-induced sensation could be delayed up to 111 ± 62 ms without the delay being reliably detected. Significance. The quantitative temporal properties of stimulation-induced perception were previously unknown and will contribute to design specifications for future sensory neuroprostheses.

Keywords: peripheral nerve stimulation, somatosensation, delay, visuotactile, simultaneity, neuroprosthesis, amputees

Supplementary material for this article is available online

(Some figures may appear in colour only in the online journal)
**Introduction**

Over two million people are living with limb loss in the United States [1]. Although there are many different commercially available prostheses, only 59% of upper-limb amputees and 88% of lower-limb amputees report using them routinely in activities of daily living [2]. One contributing factor is that feedback provided by a prostheses is limited: users primarily rely on visual and auditory cues, as well as pressure exerted by the prosthesis onto the residual limb [3–5]. While such feedback mechanisms help users to operate their prostheses, current devices are often not sufficient for navigating in challenging environments or performing intricate movements.

Prior work has shown that the addition of sensory feedback into a prosthesis can improve functional ability [6–15], reduce phantom pain [7, 16], and enhance prosthesis embodiment (the incorporation of a prosthesis into one’s body schema) [8, 17–20]. Until recently, sensory feedback was primarily restricted to ‘sensory substitution’ techniques involving vibration or electrical stimulation applied to the skin of the residuum [4, 14, 16, 21–27]. Neither method directly isolates and activates afferent sensory fibers that refer to the missing limb.

Peripheral nerve stimulation (PNS) takes advantage of the existing neural pathways that carry sensory information from the amputated limb to the brain. Though PNS activates the same afferent fibers as mechanical tactile stimuli, it does not activate these fibers in the same way. Afferent activation in response to mechanical stimuli involves complex firing patterns of populations of neurons, where the particular fibers activated and patterns of firing depend on the spatial and temporal properties of the tactile stimulus [28, 29]. Current neural stimulation paradigms do not achieve the same neural activation patterns as mechanical stimuli. Despite these differences, direct activation of the peripheral sensory nerves in an amputee’s residual limb via chronically implanted neural interfaces successfully evoked somatosensory perceptions referred to and co-located with the missing limb [7, 10, 11, 13, 30, 31].

To maximize the benefits of sensory feedback incorporated into a prosthesis and to more closely mimic an intact limb, sensations from PNS must emulate the temporal characteristics of the intact limb’s tactile sensation. If cognitive perception of a tactile stimulus is delayed by even 200ms, it can significantly compromise the integration of a prosthesis into the body schema of a user [32]. Because of the differences in fiber activation between stimulation-induced sensation and natural tactile sensation, it is possible that their temporal integration with multisensory inputs to promote embodiment could be different, too. Yet, temporal properties of sensations elicited by PNS have not been well characterized.

We previously demonstrated somatosensory restoration using implanted non-penetrating nerve cuff electrodes around the residual peripheral nerves of trans-radial [7] and trans-tibial amputees [31]. Because the elicited sensations were perceived to be natural in terms of location and intensity, we hypothesized that they may also mimic the temporal properties of natural sensation. In this work, we used a visuotactile simultaneity judgment (SJ) task to compare the temporal processing of PNS-induced sensation (‘artificial’ touch) to intact tactile perception (‘natural’ touch). We hypothesized that natural touch and sensation elicited by PNS would be indistinguishable with respect to the point of subjective simultaneity (PSS) and just noticeable difference (JND). To determine the functional implications of visuotactile synchrony, participants also performed a ‘functional delay (FD) task’ in which pressure applied to the prosthesis triggered stimulation-induced sensation after a set delay. Validation of the functional implications of perceived synchrony is unique in the psychometric literature, because it is normally not possible to delay tactile stimuli in this manner in the intact somatosensory system.

**Methods**

**Research participants**

Two people with unilateral trans-tibial amputations (LL01 & LL02) and two people with unilateral trans-radial amputations (UL01 & UL02) due to trauma were enrolled in this study. At the time of device implantation, LL01 was 67 years old, LL02 was 54 years old, and both UL01 and UL02 were 46 years old. All four participants were male, regular prosthesis users, and did not have peripheral neuropathy or uncontrolled diabetes. The Louis Stokes Cleveland Veterans Affairs Medical Center Institutional Review Board and Department of the Navy Human Research Protection Program approved all procedures. This study was conducted under an Investigational Device Exemption obtained from the United States Food and Drug Administration. All participants gave their written informed consent to participate in this study that was designed in accordance with relevant guidelines and regulations.

**Implanted technology**

The two participants with upper-limb amputations (ULA) received surgically-implanted 8-contact flat interface nerve electrodes (FINEs) that wrapped around the nerves [33]. FINEs were installed on the median and ulnar nerves of participant UL01 in 2012, and median and radial nerves of participant UL02 in 2013 (figure 1(a)) [7]. All electrode contacts were connected to open-helix percutaneous leads via spring- and-pin connectors (Ardiem Medical, Inc.). The percutaneous leads exited the skin on the upper anterior arm.

The two participants with lower-limb amputations (LLA) had 16-contact composite flat interface nerve electrodes (C-FINEs) [34] installed around their sciatic, tibial and/or common peroneal nerves (figure 1(b)) [31]. C-FINEs are an updated version of the FINE; they have the same electrode size and mechanism of nerve excitation, but they are more compliant and have less volume while maintaining equivalent performance [34]. The additional compliance of the C-FINEs makes them more suitable for implant locations close to joints, such as in the popliteal fossa near the knee for trans-tibial amputees. Both participants were implanted in 2016. All C-FINE contacts connected to percutaneous leads via industry-standard 8-contact in-line connectors (Medtronic Inc.). The percutaneous leads exited the skin on the upper anterior thigh.
For all participants, percutaneous leads connected to a custom-designed external stimulator [35, 36] that had 24 current-controlled output channels, a maximum stimulation amplitude of 5.6 mA, a maximum stimulation pulse width of 255 µs, and a compliance voltage of 50 V. Stimulation waveforms were monopolar, asymmetric biphasic, charge-balanced, cathodic-first pulses with return to a common anode placed on the skin of the hip or elbow for the ULA and ULA participants, respectively. Stimulation parameters were set in MATLAB (MathWorks Inc.) and then sent to a single board computer running xPC Target (MathWorks Inc.), which controlled the stimulator in real time. An isolator between the xPC target computer and the stimulator ensured optical isolation between the participant and line-powered instruments. Stimulation was limited to a charge density of 0.5 µC mm⁻² in order to minimize the risk of tissue and/or electrode damage [37].

**Visuotactile SJ task**

To evaluate visuotactile synchrony, participants performed a SJ task [38]. During this task, a visual stimulus was paired with either (1) natural tactile sensation on the intact contralateral limb, or (2) stimulation-induced sensation via nerve cuff electrodes.

The visual stimulus was a 10mm blue light-emitting diode (LED, luminance = 7000 mcd) positioned in front of the observer at a distance of ~3 ft. Natural tactile stimuli were administered by a G10 tactor [39] (Kinea Design LLC, Evanston, IL, USA) placed on top of the contralateral intact ankle for the ULA participants (figure 2(b)) and on the anterior surface of the palm of the intact hand for the ULA participants. The tactor was secured to the body with Velcro straps but was not pre-indented on the skin. The tactor was programmed to move in a set direction to exert a pre-defined force of approximately 6N. This force level was selected to be easily detectable and comfortable for each participant. At the start of the trial, the tactor protruded to apply pressure (not vibration) to the skin (inset of figure 2). Stimulation-induced sensation was produced by delivering 2s pulse trains to individual contacts of the cuff electrodes at suprathreshold stimulation levels. Sensory detection thresholds were first found through a forced-choice two-alternative tracking paradigm [40].

Two versions of the SJ task were administered: (1) temporal comparison of natural tactile sensation in the contralateral intact limb versus a visual stimulus (figure 2(b)), (2) temporal comparison of stimulation-induced sensation referred to the amputated limb versus a visual stimulus (figure 2(a)). The visual and tactile stimuli were sequentially presented, separated by a stimulus onset asynchrony (SOA) value between −500 ms (tactile stimuli first) to +500 ms in 50 ms steps. Order of application of the 21 SOA values was randomized and each SOA was tested ten times per electrode contact. The participants used a touch screen graphical interface to select one of three response categories: the stimuli were ‘synchronous’, ‘asynchronous—Stimulus X first’, or ‘asynchronous—Stimulus Y first’. For the ‘tactor versus vision’ condition, Stimulus X was the sensation from the tactor and Stimulus Y was the LED. For the ‘stimulation versus vision’ condition, Stimulus X was the stimulation-elicited sensation and Stimulus Y was the LED. Each trial began with an auditory cue followed by a fixed 2s delay to allow the participant to concentrate on the task. This fixed 2s delay and the randomized SOA values minimized the effects of learning or anticipation of timing. The electrical stimulation, tactor, and LED were all activated and controlled via xPC Target, which enabled syncing capabilities, real-time control, and data conversion at one millisecond precision. The raw tactor data were adjusted by 22 ms (N = 3), which was the measured delay between trial initiation and when the pre-defined maximum force was reached. This delay was measured by using displacement signals produced by an output channel of the tactor.

In the ‘stimulation versus vision’ condition, stimulus levels were selected such that they were far enough above the charge...
threshold to be easily and reliably detected by the participant, but not uncomfortable. Participants verbally rated perceived intensity on a self-selected scale. If the stimulus was imperceptible, the participants assigned an intensity value equal to zero. If an evoked sensation felt twice as strong as a previous sensation, they would assign an intensity value twice as large as the previously reported value. The parameters for each experiment were selected such that the sensation intensity was approximately matched across contacts within each participant. The electrical stimulation in each trial was turned on with a single set of parameter values, and the stimulation parameters did not vary during the stimulus ‘on’ period. Thus, the electrical stimulation was a step function, not a ramp. Table 1 contains the location and quality of evoked sensations.

Table 1. The participants’ most recent descriptions of the location and quality of the stimulation-induced sensation. In the second column, ‘S’, ‘DS’, ‘T’, ‘P’, ‘M’, and ‘R’ stand for sciatic, distal sciatic, tibial, common peroneal, median, and radial nerve cuff electrodes. The numbers indicate the contact number within the cuff.

| Electrode contact | Location of evoked sensation | Quality of evoked sensation |
|-------------------|------------------------------|----------------------------|
| UL01 M2           | Tip of index and middle fingers | Tingling                   |
| M3                | Thumb; webbing of the thumb   | Poking; tingling           |
| M4                | Thenar eminence               | Vibration; light pressure  |
| UL02 M4           | Index finger                  | Fast tapping               |
| M6                | Dorsal surface of thumb       | Tapping                    |
| M7                | Thenar eminence               | Vibration                  |
| M8                | Index finger                  | Vibration, contraction     |
| R8                | Dorsal surface of thumb       | Vibration, contraction     |
| LL01 S2           | Big toe                       | ‘Like I’m trying to push the big toe down’ |
| S13               | Big toe                       | ‘Like someone put a finger on it and was pushing down’ |
| S14               | Big toe                       | ‘Pushing down’             |
| P2                | Medial side of residual calf  | Poking                     |
| LL02 DS1          | Top surface of the foot       | Pressure                   |
| DS3               | Posterior lateral side of the foot | Tingling                |
| T1                | Lateral ankle; residual calf  | Tingling; tightening       |
| T13               | Medial side of the foot       | Tingling                   |

For the LLA participants, a total of eight C-FINE contacts were tested for the ‘stimulation versus vision’ condition. Pulse frequency varied between C-FINE contacts from 20–100 Hz, pulse width varied between 130–250 µs, and pulse amplitude varied between 0.7–2.4 mA. Prior work suggests that stimulus intensity could impact temporal synchrony [41–45]. To examine this effect, we selected two C-FINE contacts per LLA participant for which PSS and JND values were furthest from the ‘tactor versus vision’ results. Subsequently, we re-tested these four contacts with stronger stimulation parameters. We raised the magnitude of an evoked sensation by increasing pulse width, pulse amplitude, and/or pulse frequency [46]. New stimulus parameters were selected based on verbal ratings that participants gave to the perceived intensity of the evoked sensation.
sensation. To identify new stimulus parameters, the reported intensity of sensation had to increase by at least 25%.

For the ULA participants, a total of eight FINE contacts were tested for the ‘stimulation versus vision’ condition. During the first set of experiments in 2014, stimulation pulse frequency was 125 Hz and pulse amplitude and pulse width were selected to be suprathreshold and comfortable, as described above. In addition, the pulse width of each stimulus varied sinusoidally over a 5–10 µs range about this selected pulse width with a 1 Hz envelope. The sinusoidal pulse width modulation was intended to improve the quality of the sensations, following earlier work on this approach described in Tan et al [7]. The stimulus pulse width range was selected per contact to ensure that stimuli were perceptible, comfortable, and had optimal perceived quality throughout the duration of the stimulus. To study the effects of long-term exposure to sensory stimulation on perceived synchrony, the experiments were repeated 3.5–4 years later in 2017–2018. The testing protocol was the same across both sets of experiments. We selected stimulation parameters that best approximated the reported intensities of the previously evoked sensations. Pulse frequency varied between 20–100 Hz, pulse width varied between 120–250 µs, and pulse amplitude varied between 0.5–1.3 mA.

For each electrode contact, 210 trials were required to generate one PSS value and one JND value. We collected trial sets to generate four PSS and JND values for LL01 with low intensity stimulation, two values for LL01 with high intensity stimulation, four values for LL02 with low intensity stimulation, two values for LL02 with high intensity stimulation, two values with UL01 in 2014 (three contacts were tested, though the results from one contact were discarded due to poor curve fitting results, as described in the ‘Outcome measures’ section), three values with UL01 in 2017–2018, five values with UL02 in 2014, and five values with UL02 in 2017–2018. One PSS and JND value were collected for each participant for the ‘tactor versus vision’ condition. Experiments occurred between post-implant months 9–15 and 4–10 for participants LL01 and LL02, respectively. For participant UL01, the 2014 experiments occurred in post-implant month 23 and the 2017–2018 experiments occurred between post-implant months 64–70. For participant UL02, the 2014 experiments occurred in post-implant month 15 and the 2017–2018 experiments occurred between post-implant months 57–60. Each experimental session lasted approximately three hours, including time for breaks. Trials were randomized between different electrode contacts in each session in order to minimize any effects of learning or adaptation [47]. On average, it took 2–3 sessions to collect an entire dataset for each contact per participant.

Identification of noticeable tactile delays in a ‘FD task’

To determine the functional translation of SJ task results, participants LL02 and UL01 performed a task using closed-loop stimulation incorporated into the prosthesis. Pressure applied to a force-sensitive resistor (FSR; IEE, Luxembourg) triggered stimulation. The sensor had an actuation force as low as 3.6 psi, and readings were acquired every millisecond via a Data Acquisition Board (PCI 6071E, NI, TX). The FSR was affixed externally to avoid any confounding factors due to the placement of the sensor inside a prosthesis. For LL02, the FSR was underneath the third metatarsal region of the prosthetic foot. The participant stood with his prosthesis elevated and then placed it onto the ground after an auditory cue signaled the start of the trial. Participant UL01 applied pressure to an FSR with his prosthetic hand. Neural stimulation, delayed by a pre-determined SOA, was triggered by pressure applied to the FSR. Stimulation parameters did not vary as a function of pressure: they were simply on or off. The SOAs varied from 0–500 ms in 50 ms steps, and were applied in random order. Participants reported whether the perceived stimulation-induced sensation was synchronous with the physical contact applied to the prosthesis or asynchronous. Two electrode contacts were tested per participant; all four contacts were previously tested in the SJ tasks.

Outcome measures

Following the method detailed in Stone et al [48], the psychometric curve describing SJ was defined by a Gaussian curve. The percentage of ‘synchronous’ responses was plotted as a function of SOA, and fit to a Gaussian curve limited to 100% (figure 3). Because temporal synchrony results are affected by stimulus intensity [41–45], the raw data from multiple contacts were not combined and fit to one curve. Though stimulus parameters for each electrode contact were selected such that the participant assigned similar ratings to the perceived intensity of the evoked sensation, we did not assume that they were identical.

Gaussian curve fitting was acceptable only if the goodness of fit ($R^2$) was above 0.5. Only one contact fell below this $R^2$ threshold and was discarded: contact UL01 M2 in the early 2014 experiments.

Since the FD tasks were volitional, it was not possible to predict the initiation of pressure on the FSR, and therefore not possible to have a negative delay (defined as stimulation preceding the pressure on the FSR). While SOA values for the SJ task were negative and positive, they were only positive for the FD task (pressure on the FSR preceded stimulation).
Two measures were extracted from the psychometric curve: the PSS and the JND (figure 3). The PSS is the SOA value at which the two stimuli are perceived as maximally simultaneous [48], and represents the processing time of tactile stimuli relative to visual stimuli. Processing time consists of both the physical and neural transmission time in addition to the time it takes for stimuli to be consciously perceived. The JND is the time difference between the PSS and the SOA that corresponds to 75% simultaneity. The JND is the smallest temporal interval that observers can reliably discriminate and represents temporal sensitivity [38].

Statistical analyses

We performed a 2-way ANOVA analysis with fixed factors of amputation level (upper-limb, lower-limb) and stimulus condition (stimulation versus vision, tactor versus vision). Separate analyses were performed for dependent variables PSS and JND. In all analyses, significance levels of $\alpha = 0.05$ defined a statistically significant result. There were no outliers in the data and the assumption of normality was not violated (as assessed by Shapiro–Wilk’s test of normality).

We also performed one-sample t-tests to compare the high intensity values ($N = 4$ contacts, two from LL01 and two from LL02) to the tactor (the average from LL01 and LL02), and the 2014 ‘stimulation versus vision’ results ($N = 7$ contacts, two from UL01 and five from UL02) to the tactor (the average from UL01 and UL02). Paired t-tests were used to compare low intensity against high intensity ‘stimulation versus vision’ results ($N = 4$ contacts, two from LL01 and two from UL02), and 2014 against 2017–2018 ‘stimulation versus vision’ results ($N = 7$ contacts, two from UL01 and five from UL02). A paired t-test also compared the delay values that corresponded to 75% synchronous responses from ‘stimulation versus vision’ experiments and FD experiments ($N = 4$ contacts, two from UL01 and two from LL02).

Results

Perception of visuotactile synchrony

For participants with ULA, the PSS was $-24 \pm 23$ ms for natural tactile sensation and $0 \pm 26$ ms for stimulation-induced sensation, with respect to vision (figure 4, table 2). In figure 4(a), there is a shaded grey region from $-20$ ms to $+20$ ms that depicts the PSS range found in previous studies when comparing vision to finger tapping in able-bodied individuals [49, 50]. The JND was $79 \pm 11$ ms for natural tactile sensation and $91 \pm 19$ ms for stimulation-induced sensation. PSS and JND values for individual electrode contacts are listed in supplemental table 1. For lower-limb amputees, the PSS was $-59 \pm 3$ ms for natural tactile sensation and $-85 \pm 44$ ms for stimulation-induced sensation, with respect to vision (figure 4, table 2). The JND was $83 \pm 16$ ms for natural tactile sensation and $105 \pm 24$ ms for stimulation-induced sensation.

Effect of stimulus intensity on visuotactile synchrony

For lower-limb amputees, when stimulation parameters were increased, the PSS became significantly closer to zero ($p = 0.04$) and the JND decreased ($p = 0.04$). The high intensity PSS was $-38 \pm 30$ ms and the JND was $73 \pm 32$ ms (figure 5). Neither the low intensity stimulation nor the high intensity stimulation results were significantly different from the natural touch delivered by the tactor. Participants reported that the evoked sensations felt noticeably stronger no matter which stimulation parameter was changed (pulse width, amplitude, and/or frequency).
Changes in visuotactile synchrony over time

For upper-limb amputees, the PSS values collected in the ‘stimulation versus vision’ experiments in 2014 were not significantly different than the PSS values collected in 2017–2018 (figure 6, table 2), implying long-term consistency of perceived simultaneity. There was a significant decrease in JND over time \( (p < 0.0001) \): the previous JND was 247 ± 79 ms in 2014, whereas the JND in 2017–2018 was 91 ± 19 ms.

Comparing natural tactile sensation versus stimulation-induced sensation

The PSS and JND values of natural tactile sensation and stimulation-induced sensation were not significantly different (figure 4). The two-way ANOVA analysis did not determine a statistically significant two-way interaction between stimulation condition and amputation level for PSS or JND. There were also no significant main effects for stimulus condition.

Comparing visuotactile synchrony in ULA versus LLA participants

The PSS was significantly different between upper-limb amputees and lower-limb amputees, but the JND was not (figure 4). There was a statistically significant main effect for amputation level with respect to PSS \( (p = 0.001) \) but not to JND. The PSS difference between ULA participants \( (N = 8 \) contacts from 2017–2018 data collection) and LLA participants was 85 ms for the low intensity ‘stimulation versus vision’ \( (N = 8) \) and 38 ms for high intensity ‘stimulation versus vision’ \( (N = 4) \).

Acceptable stimulation delays

For the FD task, we defined simultaneity to be the delay at which the sensation was perceived as synchronous with the prosthesis touching an object at least 75% of the time. Stimulation had to occur within 66 ± 8 ms for participant LL02 and within 156 ± 57 ms for participant UL01 in order to be perceived as synchronous.
On average (across all electrode contacts in both participants), the acceptable delay range was 111 ± 62 ms. For all four contacts, the SOA values that corresponded to 75% simultaneity were not significantly different between the FD task and the SJ task.

Discussion

We performed a visuotactile SJ task with four amputees using tactile stimuli that originated either from a mechanical press on the intact limb or from extraneural stimulation applied to the somatosensory nerves in the residual limb. Two of these participants also performed a FD task that decoupled visual and tactile stimuli: pressure applied to the prosthesis triggered stimulation-induced sensation after a set delay. In the SJ task, participants were able to perceive the electrical stimulation as touch input and compare the timing between tactile stimuli and visual stimuli. We found that the PSS (which represents processing time) and the JND (which represents temporal sensitivity) for electrically-elicited sensation were simultaneous with the prosthesis touch (figure 7). On average (across all electrode contacts in both participants), the acceptable delay range was 111 ± 62 ms. For all four contacts, the SOA values that corresponded to 75% simultaneity were not significantly different between the FD task and the SJ task.

Figure 6. Changes in temporal synchrony over time. For both ULA participants, we performed two sets of experiments that occurred 3.5–4 years apart. (a) The results from the 2014 ‘stimulation versus vision’ experiments are represented with dashed purple lines (each electrode contact has a separate line), the 2017–2018 ‘stimulation versus vision’ results are shown with solid teal lines, and ‘tactor versus vision’ results are in dashed orange lines. Because 2014 data for participant UL01 contact M2 was discarded, the 2017–2018 data for contact M2 was not included in the paired t-tests or in this figure. (b) The mean and standard deviation of PSS for the 2014 and 2017–2018 ‘stimulation versus vision’ conditions. There were no statistically significant differences. (c) The mean and standard deviation of JND for the 2014 and 2017–2018 ‘stimulation versus vision’ conditions. The JND was significantly different between 2014 and 2017–2018 (paired t-test, \( p < 0.0001 \)) and between 2014 ‘stimulation versus vision’ and ‘tactor versus vision’ (one sample t-test, \( p = 0.001 \)).

Figure 7. Validation of the functional implications of perceived synchrony. The results of the FD task (dashed, purple) and ‘stimulation versus vision’ results of the SJ task (solid, teal) are depicted. In each subplot, a horizontal gray line marks the delay at which stimuli were perceived as synchronous at least 75% of the time.

on the intact limb or from extraneural stimulation applied to the somatosensory nerves in the residual limb.
not significantly different than natural tactile sensation. The similarity in visuotactile temporal synchrony provides further evidence that extraneural stimulation-induced sensation is processed in broadly the same way as natural touch [46, 47]. The SJ experiment and FD task did not yield different results, mitigating the need to verify temporal synchrony using a closed-loop sensory neuroprosthesis.

Our findings indicate that the type of tactile stimulus (extraneural stimulation-induced sensation or physical touch) does not affect JND. Such an observation is consistent with prior work evaluating different types of tactile stimuli with able-bodied individuals [50–52]. Previous visuotactile SJ task studies with able-bodied individuals found JND values of ~55 ms [50] and ~94 ms [51] with touch applied to the hand. Similarly, we measured a JND of 80 ± 11 ms when tapping the intact palm of the two ULA participants. We also measured a comparable JND of 91 ± 19 ms when stimulation-induced sensation evoked a sensation in the phantom hand of the two ULA participants. Similar observations were also noted in a forced-choice ‘temporal order judgment (TOJ)’ task where able-bodied participants had to answer which came first: the flash of an LED or a tactile stimulus applied to the foot [51]. The measured JND was ~70 ms. In our study, ULA participants had a JND of 83 ± 16 ms when a tactor touched the contralateral intact foot, and a JND of 73 ± 32 ms with stimulation-induced sensation. The JNDS determined for all four participants for both natural touch and stimulation-induced sensation match with values in prior literature.

Our results also demonstrate that the type of tactile stimulus does not impact PSS. The PSS of stimulation-induced sensation was not significantly different than natural tactile sensation. The results of both the stimulation-induced sensation and tactor experiments in the ULA participants match the PSS values in able-bodied individuals [49, 50]. A similar comparison cannot be made for the LLA participants because, to our knowledge, no previous studies have performed visuotactile SJ tasks on the feet of able-bodied individuals. In agreement with previous temporal synchrony studies [41–45], stronger stimulated intensities caused the PSS to significantly decrease. Such differences support the theory that more intense stimuli are brought to consciousness more quickly [41–45]. Though previous studies with natural touch have not identified a definitive impact of stimulus intensity on JND [44], we found that the JND decreased with increased intensity of PNS.

This is the first characterization of temporal judgments of electrically-evoked sensations for upper- and lower-limb amputees. The location of touch, i.e. lower-body versus upper-body, did not impact JND. The PSS for stimulation-induced perception was significantly farther from zero for LLA participants than for ULA participants. This difference was likely influenced by conduction distances. Despite minor differences in electrode technology (C-FINE versus FINE) among the participants, electrode sizes and the mechanism of nerve excitation remained the same, minimizing the likelihood that the neural interface caused this difference. Afferent sensory information from the foot and hand is carried by \( A_\alpha \) and \( A_\beta \) fibers of similar diameters, which are expected to have similar conduction velocities, and hence, similar information transfer rate to the brain [53]. However, the leg is farther from the brain than the arm, resulting in a delay of ~30 ms [51]. The difference in PSS for stimulation-induced sensation between the ULA participants (from experiments in 2017–2018) and the LLA participants (from the high intensity stimulation versus vision experiments) was ~38 ms, which matches the difference predicted due to transmission delays.

Stimulation-induced sensation could be delayed by up to 111 ± 62 ms after physical contact without being perceived as incongruent with applied pressure. This delay measure represents an important design consideration when developing sensory neuroprostheses. The rubber hand illusion, which is a strong indicator of potential prosthesis embodiment [18], deteriorates when there is perceived temporal asynchrony between visual and tactile stimuli [32]. Therefore, delays larger than this range may disrupt the perception of embodiment and interfere with effective functional prosthesis use. Possible sources of system delay in a sensory neuroprosthesis include signal transmission time and computation time. Neuroprosthesis design specifications should ensure that the total of these system delays does not exceed 111 ms in order to maximize prosthesis embodiment and function.

Additional experience with sensory stimulation and functional context may strengthen the ‘assumption of unity’ between visual stimuli and stimulation-induced sensation. An assumption of unity is thought to govern synchrony perception, and states that the more properties that two stimuli share, the more likely they are to be treated as originating from the same source [38]. The acceptable delay range was larger for participant UL01 than for LL02, though we do not anticipate that this was a result of the level of amputation (below-elbow versus below-knee). Rather, participant UL01 had two additional years of experience with sensory stimulation and had used a closed-loop sensory neuroprosthesis in functional contexts at home [19]. It is also possible that participant UL01 established a stronger assumption of unity because he could clearly see his prosthetic hand touch the FSR; participant LL02’s view of his foot was partially obstructed by his own body. Additionally, pressure on the stump due to foot-floor contact may have affected participant LL02’s responses. Though these were limitations, this experiment represented the real-world use of a lower-limb prosthesis.

The results of the FD task also provide supporting evidence for a common viewpoint that the brain maintains multisensory synchrony by having a window of temporal integration (meaning that it is insensitive to small time lags) [38]. The way that the brain processes multisensory delays is not yet known, partly because tactile sensation and visual information cannot ordinarily be decoupled. Previous studies have identified frontal, parietal, and subcortical regions that integrate visual and tactile information during the perception of one’s own hand [54]. The insula in particular appears to play a strong role in multisensory synchrony [55].

Although we demonstrated that artificial touch has similar temporal perceptual characteristics to natural touch, our study had certain limitations. Our findings could be more generalizable if they are repeated in a larger group of amputees with more diverse demographics in age, sex, and amputation...
etiolologies. The SJ task was used to evaluate perception, but does not quantify how a stimulus is interpreted as closed-loop sensory feedback. Therefore this SJ task cannot evaluate if an additional cognitive load is required once an individual is asked to associate a tactile stimulus with an event. The ‘synchronous’ option in the SJ task may have led participants to assume that the stimuli should belong together, which could have influenced temporal sensitivity [38]. Another constraint was that natural tactile sensation was ramped while stimulation-induced sensation was discrete. To make the natural tactile stimuli as close to discrete as possible, the tactic did not touch the skin before the trial started, and the final position was reached just 22 ms after trial initiation. Because skin compliance varies between people, it is possible that each participant perceived the intensity of the tactic differently. Additionally, although we wished to make comparisons between all stimulus conditions and amputations levels, this comparison may have been limited for upper-limb amputees due to the ~4 year separation between the ‘tactor versus vision’ and the 2014 ‘stimulation versus vision’ experiments. Furthermore, though we did not instruct the participants to focus on one stimulus more than the other and we limited trial blocks to less than 15 min, the results of visuotactile synchrony tasks can be affected by attention [44, 56–60]. Future tests are also needed to determine how the perception of visuotactile synchrony is modified by more complex functional tasks, such as grasping or walking.

Conclusion

This is the first study to compare the temporal perceptual properties of stimulation-induced sensation to natural tactile sensation, and is also the first to compare upper- and lower-limb amputees with respect to somatosensation evoked in missing limbs. Using PNS to evoke somatosensation, we were able to decouple tactile and visual stimuli in a way that is not ordinarily possible, and could therefore evaluate subjective simultaneity in a functional context. Our findings provide important input requirements for prosthetics design and define characteristics of artificial stimulation needed to mimic naturalistic perception.

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Author contributions

BC wrote the original manuscript. BC and EG conducted experiments and analyzed data. BC, EG, and HC conceived the experiments, developed the computer codes, and curated the data. DT and RT guided the development of the scientific questions, analysis and interpretation of the data, and provided overall supervision of the work. All authors reviewed the manuscript.

Competing interests

The authors declare that they have no competing interests.

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