**TOPICAL REVIEW**

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Journal of Neural Engineering

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# Artificial referred sensation in upper and lower limb prosthesis users: a systematic review

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**RECEIVED**
29 April 2022

**REVISED**
19 August 2022

**ACCEPTED FOR PUBLICATION**
23 August 2022

**PUBLISHED**
8 September 2022

**Keywords:** feedback, stimulation, amputation, referred sensation

Supplementary material for this article is available online

## Abstract

*Objective.* Electrical stimulation can induce sensation in the phantom limb of individuals with amputation. It is difficult to generalize existing findings as there are many approaches to delivering stimulation and to assessing the characteristics and benefits of sensation. Therefore, the goal of this systematic review was to explore the stimulation parameters that effectively elicited referred sensation, the qualities of elicited sensation, and how the utility of referred sensation was assessed. *Approach.* We searched PubMed, Web of Science, and Engineering Village through January of 2022 to identify relevant papers. We included papers which electrically induced referred sensation in individuals with limb loss and excluded papers that did not contain stimulation parameters or outcome measures pertaining to stimulation. We extracted information on participant demographics, stimulation approaches, and participant outcomes. *Main results.* After applying exclusion criteria, 49 papers were included covering nine stimulation methods. Amplitude was the most commonly adjusted parameter ($n = 25$), followed by frequency ($n = 22$), and pulse width ($n = 15$). Of the 63 reports of sensation quality, most reported feelings of pressure ($n = 52$), paresthesia ($n = 48$), or vibration ($n = 40$) while less than half ($n = 29$) reported a sense of position or movement. Most papers evaluated the functional benefits of sensation ($n = 33$) using force matching or object identification tasks, while fewer papers quantified subjective measures ($n = 16$) such as pain or embodiment. Only 15 studies (36%) observed percept intensity, quality, or location over multiple sessions. *Significance.* Most studies that measured functional performance demonstrated some benefit to providing participants with sensory feedback. However, few studies could experimentally manipulate sensation location or quality. Direct comparisons between studies were limited by variability in methodologies and outcome measures. As such, we offer recommendations to aid in more standardized reporting for future research.

## 1. Introduction

People who have lost a limb are able to navigate their environment and interact with objects by using a prosthetic device. These individuals can still perform a variety of tasks successfully, however their performance is often limited by the lack of sensory feedback available through their prosthesis. While most commercially available prostheses transmit incidental feedback such as socket normal forces or auditory cues [1], they convey much less sensory feedback than an anatomical limb [2, 3]. This lack of feedback contributes to reduced performance during grasping tasks in upper limb prosthesis users [3–5] and reduced walking speed, symmetry, and balance in lower limb prosthesis users [6], compared to individuals without amputation. Existing methods for providing supplemental feedback to prosthesis users are largely constrained to use in research settings [7], and there is little consensus on how best to translate these methods into everyday use.

### 1.1. Approaches to delivering prosthetic feedback

The most common method for providing a prosthesis user with additional sensory feedback is via sensory substitution [2, 8, 9]. In this approach, prosthetic state variables (e.g. grip force, finger position) are explicitly presented to a prosthesis user through some alternate modality (e.g. vibration, pressure). For example, prosthetic pressure sensor signals from the thumb and index finger can be mapped to the amplitude of a vibro- or mechanotactor on the residual limb [2]. Successful sensory substitution has been shown to reduce upper limb prosthesis users' reliance on visual feedback [8, 10] and improve performance in various functional tasks [8, 10–12]. However, prosthesis users must be trained to make this mapping, which requires conscious effort that may affect functional performance [13].

Researchers have continued to explore different approaches to improve the quality (i.e. naturalness) of sensation provided. Different approaches may provide sensation that matches the location of a stimulus (i.e. *somatotopic sensation*), the modality of a stimulus (i.e. *homologous sensation*), or both in the ideal case of naturalistic sensation [14]. While homologous sensation can be achieved non-invasively through mechanotactors and exoskeletons [2], somatotopic sensation is typically achieved through stimulation of the neural pathways that once innervated a missing limb [10] to refer sensation to the individual's phantom limb.

In some cases, cortical and peripheral nerve reorganization post-amputation can result in phantom projection maps that can be used to elicit referred sensation. These maps are areas of the residual limb (or face, in some cases) that refer sensation to an individual's phantom hand or leg [15, 16]. However, not all individuals who undergo amputation naturally develop phantom projection maps [15]. Artificial phantom projection maps can be created through targeted muscle reinnervation, a procedure in which nerves in the residual limb are redirected to a partially deinnervated muscle [17]. This technique can be further specialized to redirect nerves in the residual limb to specific target cutaneous nerves in a process called targeted sensory reinnervation. This process can restore highly specific phantom hand sensations [18]. In all cases the phantom map is highly specific to the individual. This makes comparing phantom projection maps between participants and studies difficult, and limits the extent to which these findings can be generalized.

Another way to elicit referred sensation is to electrically stimulate the peripheral nervous system. Electrical stimulation approaches vary in terms of their invasiveness and precision [6, 19, 20]. Surface techniques, like transcutaneous electrical nerve stimulation (TENS), activate nerve fibers from the surface of the skin [21]. Other methods require surgery to either implant electrodes that wrap around the nerve trunk [22] (*extraneural*) or penetrate the nerve trunk for direct contact with targeted nerve fibers [23] (*transneural*). Recent literature reviews describing prosthetic sensation have reported that more invasive techniques like transneural stimulation are more 'selective' than extraneural or surface stimulation [6, 19, 24]. In this context, selectivity is used to describe how small of an area a given sensation is, however no specific measures of selectivity were provided.

Regardless of the technology chosen to elicit sensation, electrical stimulation is accomplished by sending pulses defined by a stimulation waveform. Most stimulation waveforms are described by their amplitude, pulse width, and frequency. Modulating these parameters can affect the location, intensity, and modality of sensation [6, 10]. Charge (measured in Coulombs) is a product of amplitude and pulse width, and is primarily associated with the perceived intensity of a referred sensation. Frequency dictates the number of times a waveform (both the negative and positive phases of the waveform in biphasic stimulation) occurs per second, which affects the overall amount of charge delivered per second [19, 25]. Charge per pulse and charge per second are critical factors governing stimulation safety, as excess charge density could result in damage to tissue or to the electrode itself [19, 26]. Other stimulation parameters include interpulse intervals (time between pulse phases) and the overall length of each pulse train (how long stimulation is active for). These parameters are not as frequently reported or experimentally adjusted. While the direct effects of different stimulation parameters on action potential generation has been well established [19], it remains unclear how to modulate these parameters individually and in combination to improve the participants experience of referred sensation, to manipulate stimulation quality, or if different parameters offer distinct functional benefits.

### 1.2. Scope of the review

There are several recent literature reviews and expert reviews describing prosthetic sensation. A comprehensive discussion of the physiology behind sensation in an intact limb can be found in [6, 27, 28], and the role that sensation plays in the human motor control loop can be found in [1, 13]. The technologies that are currently being used to elicit sensation through electrical stimulation are well described and illustrated in [6, 13, 19, 27–29]. Additionally, prior literature reviews have compared perceived sensation locations and qualities [6], described the biocompatibility and physical makeup of different peripheral nerve interfaces [6], and discussed how stimulation parameters may affect participant safety during stimulation [6, 19].

Collectively, prior reviews suggest that electrical stimulation methods are safe and effective at improving performance in a variety of standardized

functional tests and sensory-specific assessments [6, 27, 28] and can improve measures of embodiment [13, 28] for prosthesis users. However, none of these reviews describe the specifics of the stimulation parameters needed to generate these outcomes, nor how these choices may differ between technological approaches. Only one review discussed specific stimulation parameter ranges [19]. This paper focused specifically on the safety of the stimulation in terms of preventing electrode corrosion or tissue damage. As such, they did not discuss any functional outcomes. Furthermore, two reviews specifically noted the lack of common outcome measures and the difficulty in comparing results between different studies [6, 28]. Most prior reviews were also focused exclusively on upper limb prosthesis users [13, 27, 28], though lower limb prosthesis users make up a larger population [30] and could still benefit from sensory feedback [6]. Finally, none of these reviews were systematic, which makes it difficult to generalize findings in a field where the majority of studies are conducted with three or fewer participants.

### 1.3. Statement of purpose

This systematic literature review was performed to complement existing reviews by applying a systematic approach to determining the functional requirements for eliciting referred sensation using electrical stimulation. These requirements included specific parameters used in stimulation (e.g. frequency, amplitude, pulse width), the shape of the stimulation waveform, and encoding parameters for incorporating referred sensation into bi-directional prosthetic control. These parameters have not been systematically analyzed in previous work. Additionally, the focus on referred sensation, rather than any specific category of technology, results in the inclusion of non-invasive stimulation studies (e.g. those using TENS) which have been excluded from previous reviews [6, 19]. This review describes the quantitative and qualitative methods used to characterize the elicited referred sensation, and the functional outcome measures used to evaluate its benefits.

Through this literature review, we hoped to answer the questions: *What current methods can produce and affect characteristics of referred sensation in individuals with amputation? How can electrical stimulation be incorporated into bi-directional prostheses?* and *How is referred sensation currently evaluated in the field?* We believe answering these questions can benefit the field by providing a starting point for parameters needed in future studies, a summary of approaches used for assessment, and a direct comparison of different approaches so that researchers can determine the best technology for their application. In doing so, we hope to help standardize research practices and facilitate better comparisons and collaborations between studies and research groups.

**Table 1.** Inclusion and exclusion criteria used for screening papers.

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Study population | Individuals with limb loss | Non-human studies |
| Stimulation methods | Feedback delivered through electrical signals | Studies that did not provide parameters for stimulation |
| | Studies that induced referred sensation | Studies that did not provide outcome measures related to stimulation |
| | | Studies stimulated a phantom map |
| Publication type | Peer-reviewed journal articles | Literature reviews |
| | Articles in English | Expert reviews |

## 2. Methods

### 2.1. Search strategy

We searched PubMed (1962–2022), Web of Science (1973–2022), and Engineering Village (1962–2022) for journal articles and conference papers in English in March 2021, and again in January 2022. The search terms used were:

$$((\text{feedback OR stimul}^*) \text{ OR } (\text{touch OR sens}^*))\text{AND } (\text{prosthe}^* \text{ AND amput}^*)$$

where * identifies all words with that root. The field tag 'TS' for Topic Search was added to these terms as needed for the Web of Science search. We then used Litmaps, a bibliography analysis tool, to identify papers that were commonly cited but did not appear in our database search.

### 2.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria for each paper fell into three categories: study population, stimulation methodology, and publication type (table 1). All included articles had to discuss sensation that was referred to the phantom limb. Our inclusion criteria also required feedback to be delivered through digital, electrical signals, as we were specifically interested in comparing waveforms and stimulation parameters across papers. Since we were interested in descriptions of sensory percepts coming from a phantom limb we also required studies to have at least one individual with amputation.

We eliminated animal studies due to the inability to acquire subjective responses. We also eliminated papers that did not provide any stimulation parameters or did not evaluate at least one outcome measure based on stimulation parameters. Finally, we excluded studies that stimulated phantom projection maps, whether they were naturally occurring or created through targeted reinnervation. Phantom maps are specific to an individual and do not occur in well

**Table 2.** A list of the data extracted from each paper to include as part of this literature review.

| Category | Data extracted | Description |
|---|---|---|
| Participant details | Number of participants | How many participants with amputation were stimulated in the study, and for which data was recorded |
| | Demographics | The age, sex, and level of amputation for each participant |
| | Study duration | The total time participants spent in a study, typically determined by the time between their first and last session |
| Experimental protocol | Stimulation parameters | The ranges of amplitude, frequency, pulse width, and charge used in referred stimulation |
| | Waveform | The shape of the stimulation waveform, and any particular qualities that define it such as symmetry |
| | Encoding strategy | The way in which parameters like prosthetic grip strength or pose are encoded into stimulation parameters |
| | Independent variables | The variables that were adjusted in order to compare different conditions in an experiment (e.g. stimulation parameters, participants, etc) |
| Outcome measures | Sensory characteristics | The intensity, area, and quality of sensations a participant feels following stimulation |
| | Functional tests | Outcomes intended to demonstrate functional benefits or closed loop control (e.g. object identification, activies of daily living) |
| | Subjective measures | Questionnaires or surveys capturing subjective experience with sensation or with a sensation-enabled prosthesis |

established locations or patterns. As such, sensations felt via the stimulation of phantom maps are difficult to compare between individuals or studies.

### 2.3. Screening and data extraction

After removing duplicates, papers were screened by title and abstract by two independent reviewers (M G and A B) based on eligibility criteria (table 1). Remaining papers were then screened based on their full text. A third reviewer (C L) resolved disagreements in an independent review of the papers.

For each included paper, we extracted information regarding participants, experimental protocol, and stimulation approach (table 2). We first categorized each study by the technology they used for stimulation and noted where stimulation was applied (i.e. nerve, muscle). We then identified individual participant details, including their age, sex, level of amputation, time since amputation, and time enrolled in the study. Importantly, study time does not necessarily equate to implantation time, which was not reported in a majority of studies. Rather, study time refers to the approximate length of time that data in the paper was collected for a particular participant. While many studies also included non-amputee participants, here we only include the data from individuals with amputation. When possible, we also noted instances in which the same participant was included in multiple papers so as not to double count these participants in review totals or averages.

For details regarding the experimental protocol, we documented stimulation parameters, when provided. Pulse amplitude was recorded in units of $\mu$A, pulse frequency was recorded in Hz, pulse width was recorded in $\mu$s, and charge was recorded in nC. Parameter ranges were recorded for each paper's experimental protocol. For papers that provided a range of amplitude or pulse width, but not both, charge ranges were calculated by taking the product of amplitude and pulse width values. Charge could not be confidently calculated in papers that varied both amplitude and pulse width due to uncertainty around how the parameters were co-varied (e.g. it is unlikely that a paper would stimulate using the maximum values of each range).

We recorded which independent variables were varied in each study. Specifically, we identified papers that varied any stimulation parameter (amplitude, frequency, pulse width, charge), whether experiments tested different encoding strategies, and if experiments were run both with and without stimulation.

We also extracted the outcome measures used to study the effect of different stimulation characteristics. These outcomes included characteristics of sensation such as perceived area and quality of evoked sensory percepts. To compare across studies, we converting sensory maps provided in each relevant paper into a more discrete map (see supplemental materials). Due to the lack of formalized surveys for reporting sensation qualities, or the perceived modality of referred sensation, we reported sensation qualities in discrete categories. These included paresthesia (unnatural sensations such as tingling or burning), vibration (pulsing or rhythmic sensations), pressure (including any description of touch), and proprioception (any sense of movement or position of the limb). The naturalness of sensation was not typically reported, however sensations of pressure, proprioception, and vibration are all naturally occurring sensations, while paresthesia is explicitly unnatural. Additionally, we recorded whether studies tracked outcome measures over multiple experimental sessions.

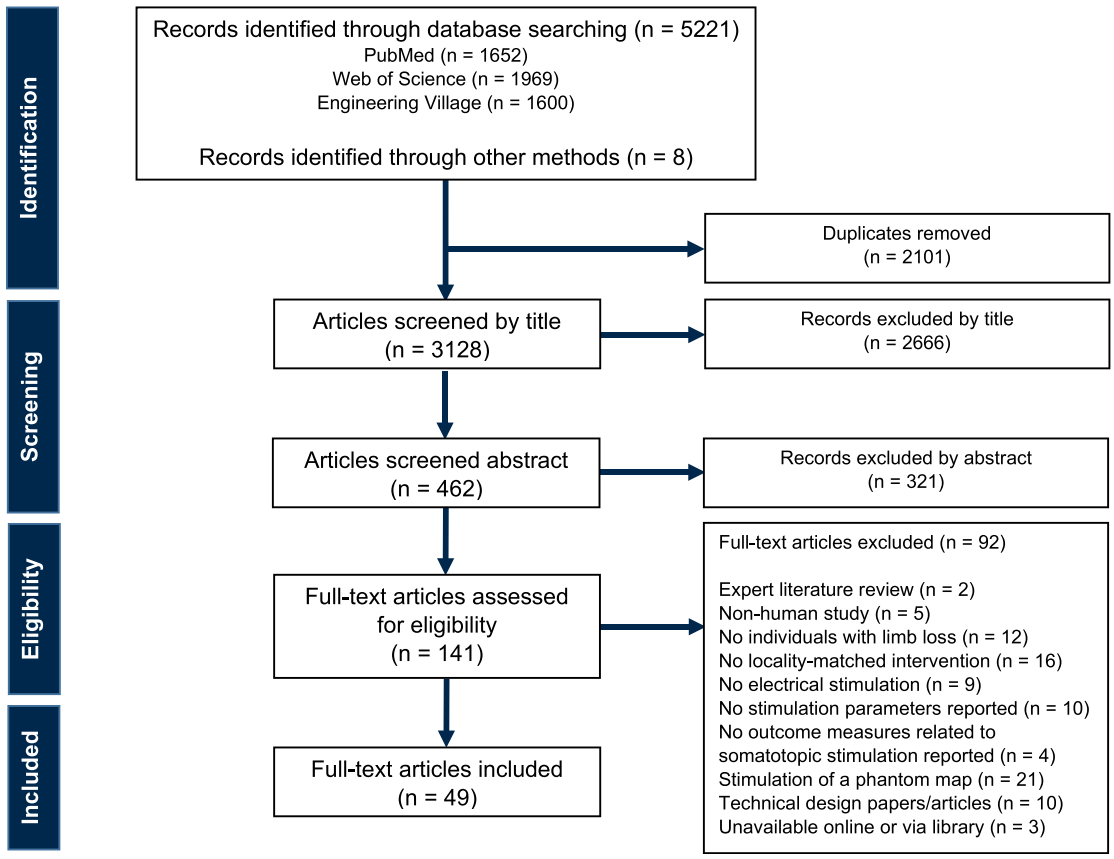


**Figure 1.** PRISMA flowchart of literature review process.

## 3. Results

A total of 5229 papers were identified by our search. After title, abstract, and full-text review, we included 49 papers (figure 1). Papers were then organized by level of amputation and year of publication (table 3).

### 3.1. Stimulation technology

Across included papers, there were nine stimulation methods used to inducing referred sensation. These stimulation methods were categorized by invasiveness ranging from non-invasive methods to maximally invasive methods (figure 2(A)). Importantly, some studies included multiple stimulation methods, and therefore were listed in multiple categories. Of these, only two directly compared the outcomes of the different technologies [31, 32].

TENS and fine wire (purple and blue in figure 2, respectively) were the only two stimulation methods that did not involve surgical intervention. Of these, only TENS was completely non-invasive. TENS involves stimulating muscles or nerves from the surface of the skin. Notably, all reviewed TENS papers used 'low intensity' stimulation designed to stimulate individuals with enough current to evoke a sensory percept. This is typically less than the current used in TENS pain management experiments [33] and in therapeutic contexts [34]. The fine wire approach involved inserting and stimulating fine wire electrodes acutely. In the single fine wire paper we reviewed, fine wires were inserted into an agonist–antagonist myoneural interface (AMI) at each visit and removed once experiments were completed for the session [35].

The remaining technologies required some level of surgical intervention and are discussed in order of their invasiveness. Epidural spinal stimulation (green in figure 2) required a minimally invasive outpatient procedure to implant three leads into the epidural space on the dorsal side of the C5–C8 spinal cord [36]. The leads remained implanted for up to 29 days, and were used to evoke referred sensation in individuals with upper limb amputation.

Extraneural ('*around the nerve*') technologies (yellow in figure 2) required more invasive procedures to identify specific nerves, and are defined by the implantation of electrodes that wrap around the nerve. These technologies included nerve cuffs that conform to the outside of the nerve [37–39] and flat interface nerve electrodes (FINEs) [40–43]. FINEs compress the nerve to reduce its internal volume and provide better electrode coverage. In several papers,

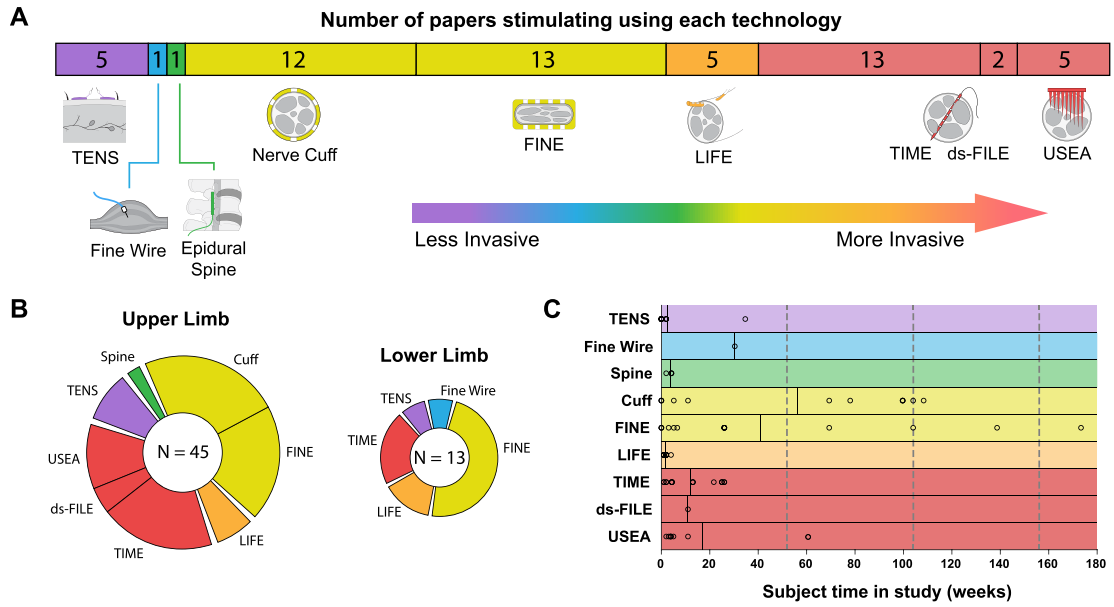


**Figure 2.** Overview of reviewed stimulation technologies. (A) Total number of studies conducted using each stimulation technology. Some studies included multiple technologies, and as such are double counted. Technologies are arranged from least invasive (left) to most invasive (right). (B) The number and distribution of studies conducted using each stimulation technology in individuals with upper and lower limb amputation. (C) The amount of time participants were enrolled in studies conducted using each technology. Each circle represents the enrollment time of one individual. Each solid, vertical line represents the average enrollment time reported across all individuals stimulated with the respective technology. Dashed vertical lines indicate years.

participants were implanted with both cuffs and FINEs [22, 25, 44–47].

Following extraneural technologies are intraneural (‘*within the nerve*’) technologies (orange in figure 2), which we define as any approach that inserts an electrode into the nerve, but does not pierce any nerve fascicles. The only technology in this category was longitudinal intrafascicular electrodes (LIFEs) which are created from Teflon insulated wire in which a small section of insulation is removed to create an active electrode site [48–50]. These flexible wires can then be inserted into a nerve, running parallel to the nerve fascicles. The end of the wire which exits the skin is then sutured in place.

Finally, we defined transneural (‘*through the nerve*’) technologies (red in figure 2) as a subset of intraneural technologies that pierce the nerve in order to stimulate in several locations at various depths across various fascicles. There were three specific transneural technologies used in the literature. The first two are similar in that they contain a series of active sites arranged along the length of a spike that is inserted through the nerve. Transverse intrafascicular multi-channel electrodes (TIMEs) [31, 51, 52] have sites on one side of the spike, while double-sided filament electrodes (ds-FILEs) have active sites on each side of a spike [32, 53]. The third transneural technology was the Utah slanted electrode array (USEA), which consists of a 10 × 10 grid of electrode spikes at depths varying from 0.5 to 1.5 mm [54–56]. The USEA penetrates a nerve and provides active sites at several points along the nerve, as well as at different depths.

### 3.2. Participant details

The papers included were primarily made up of case studies, with 84% of papers having three or fewer participants. The papers were predominantly focused on stimulation of individuals with upper limb amputation (36 papers) compared to lower limb (12 papers) (figure 2(B)). One study included two participants with upper limb amputation and two participants with lower limb amputation [42].

A total of 93 individuals with amputation who underwent sensory stimulation were studied across all papers in this review, 14 of which participated in multiple reviewed studies. Participants were predominantly middle-aged (46.0 ± 11.5 years) and male (68M/19F), with nine participants of unspecified age and six participants of unspecified sex. All participants had acquired amputation of varying levels (i.e. no studies stimulated individuals with congenital limb deficiency). The plurality of individuals across the reviewed papers had transradial amputations (44.1%), followed by transhumeral amputation (20.4%), transtibial amputation (18.3%), wrist disarticulation (6.5%), partial hand amputation (5.4%), transfemoral amputation (4.3%), and a single individual with shoulder disarticulation (1.1%). The majority of participants had an upper limb amputation (77.5%) compared to those with lower limb amputation (22.5%), which roughly matches the

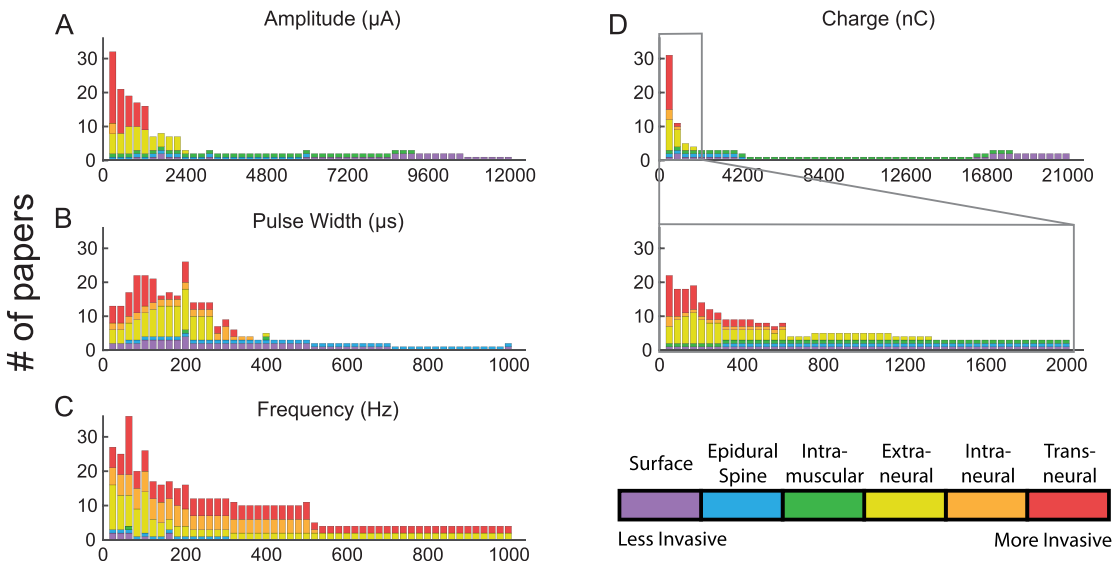


**Figure 3.** Histogram of the stimulation parameters used across all papers in this review. Warmer colors indicate technologies that are more invasive. The charge ranges are presented at two scales (overall range and inset) due to the differences in charge values used in high- and low-invasiveness stimulation technologies.

percentages of papers focused on the upper and lower limb, respectively (figure 2(B)).

The technologies studied in the most participants were FINEs ($n = 19$), TIMEs ($n = 18$), LIFEs ($n = 17$ participants), and TENS ($n = 16$). These were followed by cuffs ($n = 11$) and USEAs ($n = 9$), with only a single paper studying epidural spinal stimulation ($n = 4$). One paper used fine wire intramuscular to stimulate an AMI in a single participant ($n = 1$) [35]. This is a distinctly different approach compared to other stimulation methods, as here the electrical stimulation causes the muscle to contract and pull on the opposing muscle through its tendon connection.

Three papers consisted of only a single session, while the longest study was a longitudinal study lasting 3.3 years. Across all papers the average study length was 28.5 weeks, or approximately 6.5 months (figure 2(C)). Extraneural technologies had the longest average and maximum study times (figure 2(C)). FINEs had an average participant study time of 43 weeks with a maximum study time of 173 weeks. Cuffs had an average participant study time of 63 weeks, and also had a maximum study time of 173 weeks in the same study [45].

### 3.3. Experimental protocol

*3.3.1. Stimulation parameters*

Across all stimulation methods, researchers varied amplitudes from 0 to 12 000 $\mu$A, with the majority of studies in the 0–1200 $\mu$A range (figure 3(A)). The only technology used to stimulate across the full range was TENS. Studies using intramuscular and epidural spinal stimulation stimulated across the majority of the range, while those using transneural methods only stimulated over a range of 0–1200 $\mu$A. Intraneural methods had the smallest range of 0–200 $\mu$A.

Studies varied pulse width from 0 to 1000 $\mu$s across all technologies, with the majority of studies in the 0–250 $\mu$s range (figure 3(B)). Both epidural spinal stimulation and surface methods were used to stimulate across the full range, while transneural and extraneural technologies were used over a much smaller range (0–320 $\mu$s, 0–255 $\mu$s, respectively). Of note, several studies specifically used a pulse width of 200 $\mu$s, and there was also a slight uptick at 400 $\mu$s. Though no specific justification was given, it is notable that 100, 200, and 400 $\mu$s are standard settings on many stimulation devices.

Charge, measured in nC, is an important parameter for stimulation because it is often used to determine safety limitations for stimulation. Some studies specified charge limits citing electrode manufacturer recommendations [57, 58]. Studies using LIFEs [48, 59], TIMEs [31, 58, 60], and FINEs [22, 41] declared safety limits based on the size or materials used in making the electrodes. However, these papers did not specify *how* these limits were determined. Additionally, no human trials were cited in determining electrode limits, and all papers reached pre-set parameter limits or subjective pain/discomfort limits before reaching their charge limitations [31, 44, 61]. The charges used ranged from 0 to 21 000 nC across all technologies, however the majority of studies operated in the 0–400 nC range (figure 3(C)). TENS used the widest range of charges across all methods. All extraneural, intraneural, and transneural methods stimulated at 1300 nC or less, which is less than the maximum charge used by surface stimulation methods by an order of magnitude.

Finally, the range of frequencies studied was 0–1000 Hz, with the majority of studies using a 0–200 Hz range (figure 3(D)). In contrast to amplitude, pulse width, and charge, the widest range of stimulation frequencies was explored in studies using transneural and extraneural technologies rather than surface methods (e.g. TENS). Instead, surface methods used the smallest frequency range of 0–150 Hz, while the single intramuscular study stimulated with a frequency of 50 Hz.

Amplitude and frequency parameter ranges were the same for experiments involving individuals with upper and lower limb amputation. The maximum pulse width used in an upper limb experiment was higher that the maximum used in any lower limb experiment, however the most common pulse width for both upper and lower limb experiments was 200 $\mu$s. Additionally, the one study that included both individuals with upper limb amputation and those with lower limb amputation did not adjust stimulation parameters specifically depending on limb, and did not report any differences in the parameters required to elicit sensation [42].

Current and charge ranges for each technology may also provide expected values for the power consumption of implantable stimulation systems. While TENS clearly requires a greater average amount of current than other technologies (4254 $\mu$A), it also has the benefit of applying stimulation non-invasively, and can depend on external batteries. However, for biologically safe, implantable batteries that have a smaller capacity, efficiency of stimulation may be relevant to how much the stimulation system can be used. Epidural spinal stimulation requires almost as much current as TENS (2150 $\mu$A) which may be restrictive to its use. Intramuscular stimulation of an AMI required, on average, 4500 $\mu$A, however this was only in a single individual and may not be indicative of how AMIs are stimulated in the future. Of the implantable nerve interfaces extraneural methods required the greatest average level of current (672 $\mu$A), followed by transneural stimulation methods (278 $\mu$A). Curiously, intraneural stimulation via TIMEs required less current on average (70 $\mu$A) compared than transneural methods. These values are relevant because stimulation current may not only affect battery draw over a single charge, but also the rate of battery capacity loss over time [62].

### 3.3.2. Waveform

All studies that included waveform details reported using a square, charge-balanced, biphasic, cathodal-first stimulation waveform. Square waves are the simplest waveform to generate, and by charge-balancing the cathodic and anodic waveform phases (maintain equal area under the curve for each phase) charge cannot build up, which could lead to electrode dissolution or tissue deconstruction. The cathodic phase is then presented first as it typically results in lower sensory thresholds for the same amount of overall charge [63]. Charge-balanced waveforms can also be described as either symmetric (equal amplitude and pulse width across both phases) or asymmetric (different amplitudes and pulse widths, but the same product of both values across both phases). Only 21 of the 49 studies reported whether or not waveforms were symmetrical (i.e. identical amplitude and pulse width for the cathodal and anodal phases). Of these, 8 used symmetric waveforms and 13 used asymmetric waveforms.

### 3.3.3. Encoding strategy

While the instantaneous shape of a waveform is defined by a set of stimulation parameters, participants are only able to receive meaningful feedback by varying waveform parameters according to some external input. This typically means encoding prosthetic sensor readings into stimulation parameters. The simplest method of providing feedback is through a binary encoding strategy, in which stimulation defined by static parameters is triggered discretely. Binary encoding is typically triggered in response to a contact event [38, 56].

Most research studies that continuously encoded sensor data into stimulation parameters did so through linear encoding. Linear encoding was typically achieved by mapping a range of sensor values to a range of stimulation parameters. Commonly, stimulation and discomfort thresholds were used for the stimulation parameter ranges. In this way, a sensor value of zero would not result in any stimulation, and a maximum sensor value would have a perceived intensity that is just lower than an individual's discomfort threshold.

A total of 13 studies encoded sensor values linearly with amplitude [31, 35, 38, 51–53, 57, 61, 64–67], which allowed participants with upper limb amputation to prevent object slippage [53] and match target force profiles [51, 66]. Participants with lower limb amputation could also receive some pressure feedback via linear amplitude encoding. Compared to no feedback, feedback enabled users to climb stairs faster and traverse uneven terrain with fewer falls [61], and reduced metabolic cost during walking [52].

Only four studies encoded values linearly with pulse width [14, 25, 68, 69]. In these studies participants with upper limb amputation were able to perceive a continuous sense of intensity [25] and improved ability to match target force profiles [14, 68]. This type of feedback also enabled participants with lower limb amputation to better detect unseen ground features while walking [69].

Seven studies encoded values linearly with frequency [25, 45, 46, 49, 54, 66, 70]. In these studies,

participants could detect when objects were placed in their prosthetic hand [45], and led to increased estimated limb length which indicates greater levels of prosthetic embodiment [46, 54]. Furthermore, in one take-home study that used linearly modulated frequency, sensation led to increased prosthesis wear time compared to a no feedback condition [46]. Object size and stiffness identification could also be performed at better than chance levels when sensor values were encoded into amplitude [31, 66], pulse width [14], or frequency [46, 66, 70].

Two studies explored 'biomimetic' encoding strategies based on simulations in TouchSim (Bensmaia Lab, Chicago, IL, USA) [56, 60]. This strategy was designed to replicate how nerves fire when they encounter a stimulus. In the first study, George *et al* detailed two encoding strategies based on this approach. First, they varied both the amplitude and frequency of stimulation based on absolute sensor value and on the positive rate of change of the sensor [56]. Their second encoding strategy incorporated contact stimulus position, velocity, and acceleration and was developed using the neural recordings of nonhuman primate as they touched objects [71]. In both cases, when the biomimetic encoder was used, the single participant could identify object compliance more quickly and could generate force through a prosthetic hand more consistently compared to linear or binary encoding strategies [56]. In the second study, Valle *et al* [60] took inspiration from neuron firing rate in order to manipulate frequency in conjunction with amplitude, with their second model utilizing non-linear amplitude mapping to highlight state changes associated with contact events. Using these biomimetic encoding strategies, participants demonstrated improved accuracy on a test of manual dexterity (virtual eggs test) and perceived the sensation as more natural than linearly encoded amplitude modulation [60].

While not strictly a sensory encoding strategy, one group experimented with a stimulation waveform that modulated pulse width using a sinusoid [44]. This modulation was designed to mimic natural activation patterns observed in response to constant pressure stimuli. Participants in this study experienced paresthesia when pulse width was not modulated. When pulse width was full-scale modulated (between 0% and 100% of max pulse width), it resolved the paresthesia into a sensation of vibration. Furthermore, small-scale modulation of pulse width (modulation of approximately 5 $\mu$s centered at 90% of max pulse width) resolved into a sensation of constant pressure, specifically when the referred sensation was in an area of glabrous skin (areas where skin would have little to no hair). This pulse width modulation was utilized by two other reviewed studies by the same group, and in both studies participants also reported naturalistic pressure sensations [45, 70]. However, attempts to replicate these findings through pulse width, amplitude, or frequency modulation found no changes in percept quality between the various conditions [39].

#### *3.3.4. Independent variables*

We identified seven independent variables of interest and eight broadly defined outcome measures used across all reviewed papers (table 3). Specifically, we aggregated which independent variables were evaluated using different outcome measures (figure 5). The most common stimulation parameters to experimentally vary or report across the reviewed papers were amplitude ($n = 26$) and frequency ($n = 23$). Less common were papers that experimentally varied or reported pulse width ($n = 16$). There were 13 studies that experimentally varied charge, however charge is varied through a combination of amplitude or pulse width changes, and which parameter was experimentally varied was not always explicitly stated. Seven studies evaluated quantitative and qualitative differences between various encoding strategies. Twenty studies ran experiments both with and without stimulation to evaluate the functional benefits of sensation. Finally, 21 studies tracked at least one outcome measure over time.

### 3.4. Outcome measures

#### *3.4.1. Sensory characteristics*

Perceived sensation locations were reported much more frequently for the median ($n = 39$) and ulnar ($n = 27$) (figure 4(A)) nerves compared to the radial, sciatic, tibial, or common peroneal nerves (figure 4(B)). Percept areas were reported for all five TENS papers [14, 68, 72–74], the only spinal stimulation paper [36], two of the five LIFE papers [59, 75], four of the five USEA papers, and several papers that stimulated participants via FINEs ($n = 6$), cuffs ($n = 4$), and TIMEs ($n = 8$). While several other papers did report areas of perceived location, they were excluded from our summary as they did not specify which nerves were stimulated to evoke specific areas. For example, one upper limb paper did not differentiate areas that were perceived from stimulation of the ulnar or median nerve [56]. More commonly, several lower limb papers did not explicitly differentiate between perceived sensation areas resulting from stimulation of the tibial nerve or stimulation of the sciatic or peroneal nerve branches when presenting maps of perceived sensation [41, 43, 61, 69, 73]. See table 3 for specific papers that reported perceived locations of sensation.

Sensation locations for the median nerve in healthy individuals are typically spread throughout the palmar side of the thumb, the 2nd (index), 3rd (middle), and 4th (ring) digits, and the area of the palm proximal to these digits. Additionally, there are innervation regions on the dorsal side of the thumb, 2nd, and 3rd digits. We generated images using data compiled from 39 studies stimulating

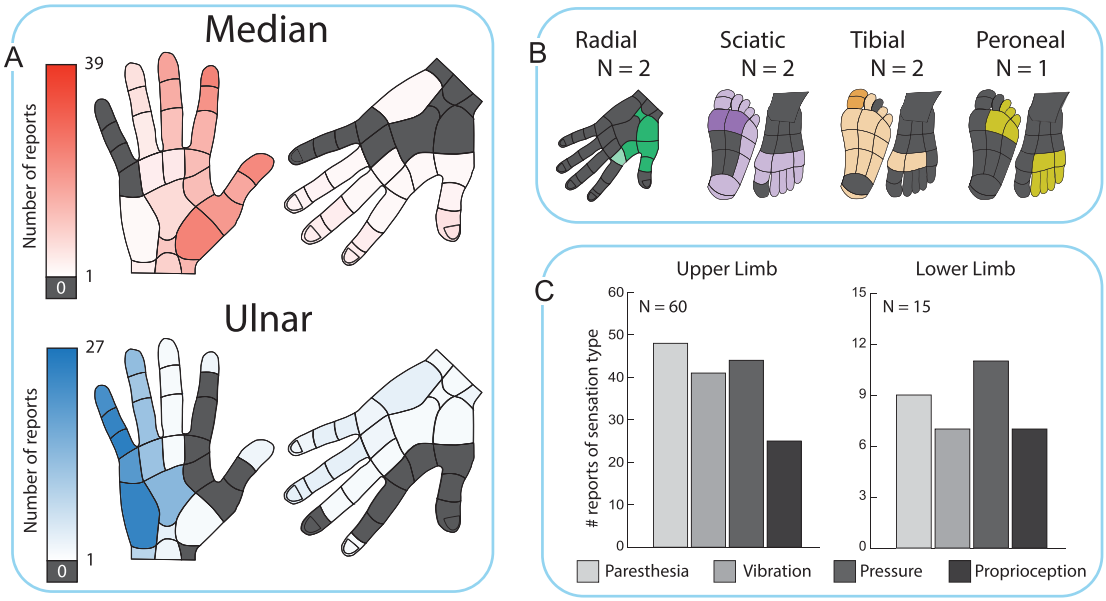


**Figure 4.** Perceived sensations by individuals across all reviewed studies. (A) Heat maps of the location of perceived location for stimulation of the median and ulnar nerve. (B) Heat maps of the location of perceived location for stimulation of the radial, sciatic, tibial, and peroneal nerves. For upper limb hand maps, reported locations for TENS were not included due to their lack of specificity. Reports based on TENS *were* included for lower limb foot maps due to the lack of other reported sensation locations. Dark regions indicate areas where no participants reported sensation. Scale maximums are based on total number of sensation reports across all papers. (C) The number of reports for each broad category of sensation, broken down by participants with upper and lower amputations. Reports were either for individual participants, or for studies that did not differentiate between participants. Proprioception includes perceived movement and position of the phantom hand. Touch includes any description of touch or pressure. Vibration includes pulsing, buzzing, or any unnatural sensation with some rhythmic quality. Paresthesia includes all other general tingling, warmth, or other nondescript sensations.

the median nerve. Data came from individual participants or studies that aggregated sensation locations without disambiguating individuals. The most common regions in which participants reported sensation were the distal phalanx of the index finger (24 reports), the thenar eminence (base of the thumb) (24 reports), and the distal phalanx of the thumb (23 reports). This means that stimulation of any given active site has an approximately 61% chance of stimulating one of those regions.

The innervation regions for the ulnar nerve in healthy individuals are restricted to the 4th and 5th (small) digits, as well as the area of the palm proximal to the 4th and 5th digits. Unlike the median nerve, the dorsal innervation region for the ulnar nerve mirrors the palmar region. We again compiled stimulation studies targeting the ulnar nerve from individual participants or studies that aggregated sensation locations without disambiguating individuals (27 reports). The most common regions in which participants reported sensation were the middle (24 reports) and proximal (25 reports) phalanges of the 5th digit, as well as the hypothenar eminence (the side of the palm proximal to the 5th digit) (20 and 24 reports for the upper and lower sections, respectively). Therefore, the stimulation of any given active site has an approximately 93% chance of stimulating one of these regions.

We also compiled reports of different percept qualities evoked through electrical stimulation. Percept qualities were often reported for the entire cohort of a study (not by individual participant) or for each participant (not by individual nerve). As a result, reported percepts were compiled based only on the sensation modality and whether stimulation was targeting an upper or lower limb (figure 4(C)). Paresthesia and vibration are typically classified as less natural sensations, compared to pressure and proprioception. Together, paresthesia and vibration accounted for the majority of percepts reported by individuals with upper limb amputation when they were stimulated ($n = 44$ and $n = 40$ for paresthesia and vibration, respectively) compared to 43 individuals who reported pressure sensations and 24 individuals who reported some form of proprioception. Only 15 total participants across 10 studies reported perceived sensations for the lower limb. Of these, pressure was the most commonly reported sensation ($n = 11$), followed by paresthesia ($n = 9$), vibration ($n = 7$), and proprioception ($n = 7$).

Of those individuals reporting proprioceptive percepts, 11 reported a sense of joint movement, 6 experienced twitching in their phantom limb, 10 experienced a sense of muscular contraction (even when those muscles no longer existed), and one individual reported a sense of static joint position during

stimulation [75]. Six individuals reported percepts of proprioception without further specification.

*3.4.2. Functional tests*

The most commonly reported outcome measures were focused around the characterization of sensory percepts themselves, while functional outcome measures were less common and measures of prosthetic experience were the least common. The most prevalent outcome measure reported was the area of perceived sensation during stimulation ($n = 33$ papers), though the majority of papers typically reported how percept location changed due to different sites ($n = 20$) or participants ($n = 20$) rather than a manipulation of any given stimulation parameters ($n = 15$). The next most common measures quantified the stimulation threshold required for individuals to detect referred sensation ($n = 25$) and the participants' sensitivity to different levels of sensation ($n = 26$) either through forced choice determination or tracking tasks. A total of 19 studies reported on the quality of percepts that participants felt referred to their phantom limb, though three of these only reported percept quality as brief lists or maps without additional context regarding the parameters used to evoke the sensations [40, 56, 76].

The most common functional measure assessed was object identification ($n = 13$). This included identifying object size [31, 70], shape [57, 65], or stiffness [56, 57]. There were 16 other papers that reported performance on some type of functional task. Upper limb functional tasks included picking the stem off of a cherry [44], moving blocks under various conditions [14, 53, 58, 60], and a standardized clinical assessment of activities of daily living (e.g. activities measure for upper limb amputees (AMULA)) [46]. Lower limb functional tasks involved walking tasks for individuals using a sensorized lower limb prosthesis [35, 52, 61, 69].

Many of the papers in this review measured participant performance in functional tasks with and without any form of stimulation ($n = 20$). Of these, 17 found that stimulation significantly improved performance in functional tasks including manual dexterity tasks [44, 53, 60], object identification [46, 49, 65], prosthetic foot torque control [35, 69], and increased walking speed [52, 61]. In the one take-home study included in this review, sensory feedback led to nominal increases in daily prosthesis wear time for both participants and significantly greater use of the prosthesis (measured by how often the thumb pressure sensor was activated) for one participant during that wear time [46]. One lower limb study also found that stimulation increased the load that individuals were placing on their prosthetic side, thereby decreasing loading asymmetry during standing [43]. Finally, providing participants with stimulation resulted in a perceived increase in the length of an individuals residual lower limb [77] which indicates a greater sense of embodiment.

Of the 25 studies that included some form of physical or virtual bi-directional prosthetic task, the majority of them blinded the participant ($n = 17$), or acoustically isolated the participant ($n = 13$) during the performance of functional tasks to quantify the benefits of induced sensory feedback. Of these studies, 19 found that sensory feedback universally improved participant performance, while three studies found that feedback helped only a subset of participants [49, 69] or only benefit participants in specific tasks [46].

Only eight of these bi-directional control studies contained functional assessments without any visual or acoustic restriction, and were typically studies where participants were performing functional tasks that required grasping and coordination [38, 51, 58, 60, 67], required participants to walk on a prosthesis [52, 61], or the single take-home study [46]. Of the studies without any sensory isolation, six studies still demonstrated the sensory feedback via electrical stimulation improved performance over vision and incidental feedback alone [51, 52, 58, 61, 67, 70], one study demonstrated improvement for two of three participants [38], and one study showed that additional sensory feedback improved performance on most but not all tasks performed across two individuals [46].

Finally, while 21 papers tracked at least one outcome measure over time (acutely over the course of a session, or chronically over the span of weeks and months), these papers were primarily tracking stimulation thresholds ($n = 14$). Very few papers tracked perceived sensation location ($n = 5$) or quality ($n = 1$) over time. Evidence suggests that the perceived locations [36, 75] and qualities of sensation can change over time [37], however it remains unclear if these changes are clinically significant or would present a barrier to long-term home use.

*3.4.3. Subjective measures*

Twelve studies assessed the impact of sensation on prosthetic embodiment. These studies used qualitative surveys [31, 54, 60] and/or quantitative measures, such as perceived limb length [60] and perceived prosthesis weight [64]. Seven studies measured phantom or residual limb pain in prosthesis users, typically via visual analog scales (VASs). This includes one study that purposefully explored 'noxious' sensations in order to allow users to identify sharp objects [74].

Only two papers reported any measures related to cognitive load. An upper limb study found that when their participant completed a cognitive task in addition to the virtual eggs test, the participant's score decreased while they were receiving electrotactile

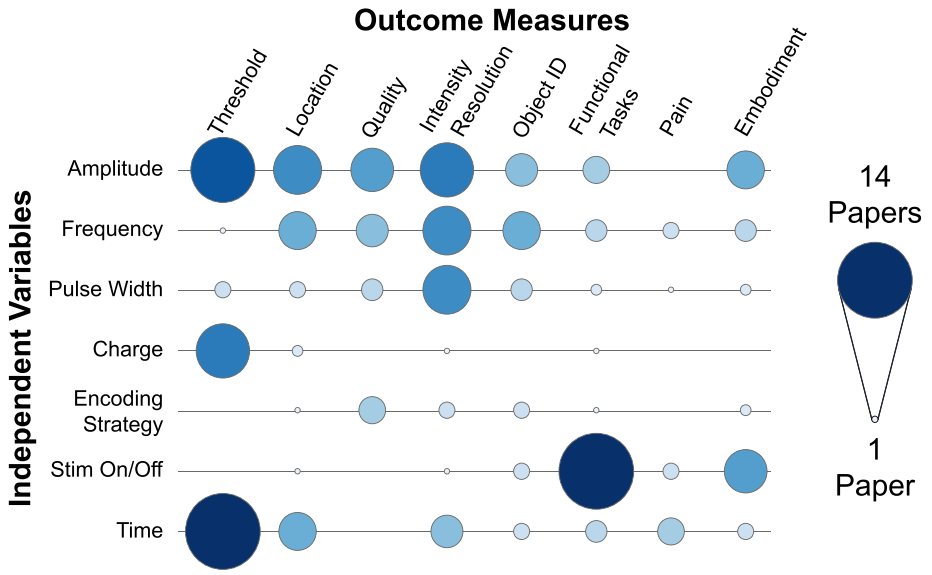


**Figure 5.** A summary of experimental designs. The diameter of each circle indicates the number of studies measuring the relationship between a particular independent variable (along the left side) and a particular outcome measure (along the top). Studies with multiple outcome measures, or which varied multiple independent variables are represented multiple times.

stimulation but remained the same when they were receiving intraneural feedback [67]. Another study found that a participant using a lower limb prosthesis could more accurately complete a cognitive task while walking with referred sensory feedback compared to when no feedback was provided [64]. While these results indicate that referred sensory feedback decreases cognitive demand compared to both no feedback and compared to sensory substitution, these studies were each conducted with a single participant.

## 4. Discussion

We performed a systematic literature review to determine what electrical stimulation methodologies are currently being used to successfully elicit sensations that are referred to the phantom limb, and how their success is being evaluated. Collectively, the literature suggests that referred sensation is possible with a number of different approaches, which vary in their level of invasiveness and mechanism of stimulation, and that most referred sensation has an unnatural quality which prevents it from being homologous. Researchers used a broad range of stimulation parameters (figure 3) and used a variety of methodologies to characterize the results of stimulation, or to assess changes in function with sensation (figure 5). As such, it was difficult to generalize findings across studies. Additionally, studies in this field are typically limited to only a few individuals (table 3), with the largest sample size across all studies being eight participants with amputation. While the results from each individual study are limited, this systematic review highlights areas where there is sufficient evidence for best practices in the field. We also provide recommendations for how the field can standardize assessments and reporting to enhance future comparative studies.

### 4.1. Manipulating characteristics of sensation

Regardless of the technology used for stimulation, all studies delivered electrical stimulation using a square [27], charge-balanced, biphasic, cathodal-first waveform [19]. All 48 reviewed studies used this approach. None used different waveform shapes (e.g. exponential, quasi-trapezoidal), however different waveform shapes have been studied in previous literature [19, 27]. Waveform symmetry was not uniform across reviewed studies, with a mix of symmetrical and asymmetrical waveforms. A previous review stated that asymmetrical waveforms are part of 'traditional safety restriction[s]', along with charge-balancing biphasic waveforms [19], though none of the reviewed studies that used symmetrical waveforms indicated safety concerns. One study reported using both symmetrical and asymmetrical stimulation waveforms, but did not report any comparisons between the two [36]. While no study directly assessed the effect of waveform symmetry on sensation, studies using either option were able to elicit referred sensation. Most studies focused on varying other parameters of the waveform including amplitude, pulse width, and frequency. The next sections will detail the effects of stimulation parameters on various characteristics of sensation as tested in individuals with amputation.

#### *4.1.1. Sensation intensity*

The intensity of a perceived sensation was the most frequently reported characteristic across reviewed studies. This is likely because the intensity of sensation can be communicated by a participant

**Table 3.** Characteristics of studies included in this review.

| Study | Stimulation technology | Amputation level | Number of participants (M/F) | Study length | Independent variables | Outcome measures |
|---|---|---|---|---|---|---|
| | | | Upper limb studies | | | |
| Benvenuto *et al* [48] | LIFE | Upper | 1 (1/0) | 4 w | PF, PW | IR |
| Rossini *et al* [59] | LIFE | Upper | 1 (1/0) | 4 w | PA | ST |
| Horch *et al* [49] | LIFE | Upper | 2 (2/0) | 2 w | PF | ID |
| Tan *et al* [44] | Cuff, FINE | Upper | 2 (2/0) | 24 m | PA, PF, PW, ES | ST, AP, FQ, IR, FT, PN |
| Raspopovic *et al* [57] | TIME | Upper | 3 (1/0) | 1 w | PA | ST, AP, IR, ID |
| Schiefer *et al* [45] | Cuff, FINE | Upper | 2 (2/0) | 40 m | PF, PW | FT, EM |
| Tan *et al* [22] | Cuff, FINE | Upper | 2 (2/0) | 24 m | C | ST, AP |
| Oddo *et al* [81] | TIME | Upper | 1 (1/0) | NS | PF | ID |
| Davis *et al* [55] | USEA | Upper | 2 (NS/NS) | 4 w | PA, PF | ST, AP, FQ |
| Graczyk *et al* [25] | Cuff, FINE | Upper | 2 (2/0) | 8 m | PF, PW, ES | IR |
| D'Anna *et al* [14] | TENS | Upper | 4 (3/1) | 2 w | PF, PW | AP, IR, ID, FT |
| Wendelken *et al* [76] | USEA | Upper | 2 (2/0) | 5 w | NONE | ST, AP |
| Schiefer *et al* [70] | Cuff, FINE | Upper | 2 (2/0) | 14 m | PW | ID |
| Valle *et al* [60] | TIME | Upper | 2 (0/2) | 4 w | PA, PF, ES | AP, FQ, IR, ID, FT, EM |
| Ackerley *et al* [37] | Cuff | Upper | 1 (1/0) | 25 m | PA, PF | ST, AP, FQ, IR |
| Valle *et al* [66] | TIME | Upper | 2 (0/2) | 6 m | PA, PF, ES | AP, FQ, IR, ID |
| Valle *et al* [66] | TIME | Upper | 1 (0/1) | NS | PA | AP, FT |
| D'Alonzo *et al* [72] | TENS | Upper | 5 (3/2) | 1 s | PA, PW | ST, AP, FQ, IR |
| Shin *et al* [68] | TENS | Upper | 1 (0/1) | 1 s | PW | AP, IR |
| Page *et al* [54] | USEA | Upper | 1 (1/0) | 14 m | PF | PN, EM |
| Osborn *et al* [74] | TENS | Upper | 1 (1/0) | 8 m | PS, PW | ST, AP, FQ, ID, PN |
| Graczyk *et al* [46] | Cuff, FINE | Upper | 2 (2/0) | 7 w | PA, PF | ST, AP, ID, FT, PN, EM |
| Graczyk *et al* [47] | Cuff, FINE | Upper | 3 (3/0) | 15 m | PF, PW | ST, IR |
| D'Anna *et al* [31] | TIME | Upper | 2 (0/2) | 6 w | PA | IR, ID, EM |
| Strauss *et al* [80] | TIME | Upper | 4 (2/2) | 4.5 m | C | ST, AP, FQ |
| Clemente *et al* [51] | TIME | Upper | 1 (0/1) | 2 w | PW | ST, ID, FT |
| Zollo *et al* [53] | Cuff, ds-FILE | Upper | 1 (0/1) | 3 m | PA | AP, FT |
| Petrini *et al* [58] | TIME | Upper | 3 (1/2) | 6 m | PA | ST, AP, FQ, IR, FT, PN |
| George *et al* [56] | USEA | Upper | 1 (1/0) | 14 m | PA, PF, ES | ST, IR, ID, FT |
| Ortiz-Catalan *et al* [39] | Cuff | Upper | 3 (NS/NS) | 23 m | PA, PF, PW, ES | FQ |
| Mastinu *et al* [38] | Cuff | Upper | 3 (3/0) | 1 s | PA, ES | ST, AP, FQ, IR, FT |
| Chandrasekaran *et al* [36] | Epidural spine | Upper | 4 (1/3) | 1 w | PA, PF | ST, AP, FQ, IR |
| Page *et al* [79] | USEA | Upper | 3 (3/0) | 3 m | PF | AP, FQ, IR |
| Ranieri *et al* [32] | FINE | Upper | 1 (0/1) | NS | PA, C | ST |
| | | | Lower limb studies | | | |
| Dhillon and Horch [50] | LIFE | Lower | 6 (6/0) | 1 w | PF | AP, IR |
| Dhillon *et al* [75] | LIFE | Lower | 8 (8/0) | 2 w | PA, PF | ST, AP, IR |
| Ortiz-Catalan *et al* [87] | Cuff | Lower | 1 (1/0) | 18 m | PA, PF | ST, AP, FQ |
| Clites *et al* [35] | Fine wire | Lower | 1 (1/0) | 7 m | PA | IR, FT |
| Charkhkar *et al* [77] | FINE | Lower | 2 (2/0) | 7 m | PW | ST, AP, FQ, IR, EM |
| Petrini *et al* [61] | TIME | Lower | 3 (NS/NS) | 3 m | PA | AP, FQ, FT, EM |
| Christie *et al* [41] | FINE | Lower | 2 (2/0) | 6 w | NONE | ST, AP |
| Cheng *et al* [40] | FINE, Cuff | Lower | 1 (1/0) | 3 w | NONE | NONE |
| Petrini *et al* [52] | TIME | Lower | 2 (2/0) | 7 m | PA, PF, PW, C | ST, AP, FQ, IR, PN, EM |
| Pan *et al* [73] | TENS | Lower | 5 (4/1) | 1 s | PA | ST, AP |
| Valle *et al* [65] | TIME | Lower | 2 (0/2) | 5.5 m | PA | AP, ID |
| Christie *et al* [69] | FINE | Lower | 3 (3/0) | 3 s | PW | AP, IR, FT |
| Shell *et al* [43] | FINE | Lower | 3 (3/0) | 1 s | NONE | AP, FT |
| Preatoni *et al* [64] | TIME | Lower | 1 (1/0) | 1 w | PA | AP, IR, EM |
| | | | Upper & lower limb studies | | | |
| Christie *et al* [42] | FINE | Both | 4 (4/0) | 6 m | NONE | AP, FQ, IR, FT |

Length of study—s: sessions, w: weeks, m: months, NS: not specified.

Independent variables—PA: pulse amplitude, PF: pulse frequency, PW: pulse width, C: charge, ES: encoding strategy.

Outcome measures—ST: stimulation threshold, AP: area of percept, FQ: feedback quality, IR: intensity resolution.

ID: object identification, FT: functional tasks, PN: pain or discomfort, EM: embodiment.

independent of the sensation's quality, size, or location. As expected, perceived sensation intensity was found to increase with increases in amplitude [31, 57], pulse width [14, 72], and frequency [25, 37]. Amplitude and pulse width both contribute to the total charge injected into tissue per pulse. The charge per pulse required to elicit sensation was typically dependent on electrode design and placement, with more invasive techniques necessitating less charge (figure 3). Changing frequency affects the charge delivered per second. Perceived intensity seems to scale more slowly with increases in frequency, compared to increases in pulse width [25]. We expect that individuals would similarly be more sensitive to changes in the perceived intensity of sensation due to the modulation of amplitude compared to modulation of frequency, as amplitude and pulse width satisfy similar roles in stimulation, however more comparative analysis is required.

#### *4.1.2. Sensation quality*

The quality of a sensation, or *what* an individual perceives upon being stimulated, is another widely reported measure in the field. A large focus of current literature is how to manipulate the perceived quality of a sensation following stimulation, either for functional tasks or to improve the naturalness of sensation.

In intact skin, frequency plays a key role in the organization and interpretation of neural signals. Different types of nerve fibers (fast adapting I and II, and slow adapting I and II) respond to different types of tactile stimulation, and these differences are largely based on frequency characteristics of the stimulation [78]. It is not clear how well the physiology of healthy skin with naturally arranged nerve endings can translate to the direct electrical stimulation of muscles and nerves. However, prior literature reviews of electrical stimulation have identified frequency as the parameter most appropriate for modifying feedback quality [6, 19]. Similarly, here we identified several papers that have reported changes in sensation quality related to different stimulation frequencies. These studies found that some frequency bands resulted in touch sensations while other bands were felt as paresthesia [39, 44, 45, 54, 55, 66, 74]. One study found that only one of four participants experienced changes in sensation quality due to changes in stimulation frequency, with the remainder of participants experiencing consistent sensation quality regardless of stimulation parameters [36]. Unfortunately these studies used different technologies and frequency ranges (figure 3). Thus, while we can infer that frequency is an important characteristic for quality of sensation, we cannot yet determine what frequency ranges are appropriate for achieving natural sensation, nor how this may vary across technologies or individuals.

In addition to frequency, several studies manipulated sensation quality by patterning stimulation in some way. One research group modulated pulse width using a sinusoid [44, 45, 70], where the amplitude and frequency of the sinusoid affected perceived sensation quality [44]. Notably, a separate research group was unable to use pulse width, amplitude, or frequency modulation to manipulate perceived sensation quality [39]. One study also noted changes in perceived sensation quality based solely on if stimulation was provided discretely, continuously, or via a hybrid model over the course of an experiment [38]. Other research groups experimented with how prosthetic sensors encode touch information into stimulation waveforms, theorizing that 'biomimetic' encoding strategies could facilitate more natural sensation. Participants in studies that attempted to replicate dynamics of natural sensation (found in section 3.3.2) reported that their referred sense of touch felt more natural when using the biomimetic encoding strategies compared to linear encoding strategies or waveforms with invariant parameters [44, 60]. However, these results have yet to be replicated in other participants or research groups. Therefore, more evidence is needed to demonstrate that encoding strategy is a consistent tool for producing more natural sensation quality.

While less frequently reported, there is also some evidence that signal amplitude can affect sensation quality [66, 79]. One study using TIMEs reported that two participants perceived certain sensation qualities (touch for one, pressure for another) only when amplitude was modulated but not when frequency was modulated [66]. A study of USEAs reported differences in quality, but not specifically what those differences were, when amplitude was increased [79]. They hypothesized this was due to the recruitment of additional sensory fiber types that were responsible for the new sensation qualities. This is likely due to an increase in charge which, in general, may excite additional fibers that result in the novel sensations. However, it may be difficult to decouple the affects of amplitude on quality from the affects amplitude has on sensation intensity. Therefore, frequency and encoding strategies may still be more consistent and advantageous methods of manipulating sensation quality.

#### *4.1.3. Sensation size and location*

Naturalistic sensation is not only dependent on the sensation being homologous in sensory modality, but somatotopic in terms of the spatial mapping between a prosthetic sensor and the perceived area of sensation on an individual's phantom limb. Several papers reported that the size of a sensory percept could be increased by increasing the stimulation charge [14, 36, 38, 64]. There were also several papers that reported changes to the size of a percept area based only on the day that stimulation took place [36, 55]. These reports may be due to the relative movement of electrodes within the body, or due to differences

in how the brain is processing the signals it receives. However, these explanations are currently difficult to disambiguate.

Of note, we expected that the limitations of evoked percept size would be dictated largely by how invasive a technology was. More invasive technologies typically have a greater number of active sites within a nerve, and can stimulate areas of a nerve more selectively. This expectation has been echoed in previous literature reviews that placed stimulation technologies on a spectrum that equates invasiveness to selectivity [19]. However, empirical results are mixed. In fact, each of the seven technologies targeting peripheral nerves was capable of evoking small percepts on the phantom limb. Small percepts were reported in FINEs [46] and even TENS [14]. Due to the limited number of studies that reported percept areas there is not enough data to make a strong conclusion.

There have been no reports on effectively manipulating the location of referred sensation for an individual stimulation site. However, the location of perceived sensation for a particular site can still change over time [37, 55], likely for the same reasons that area does. Such changes in location are undesirable for a bi-directional prosthesis as they would require regular adjustments for mapping prosthetic sensors to appropriate stimulation sites. The only consistent method for targeting different regions of the phantom limb is to stimulate a new site entirely, as each site targets a new group of nerve or muscle fibers. Accordingly, technologies like the USEAs provide many opportunities for eliciting sensation at many different locations. One study of USEAs reported over ten different distinct areas of perceived location that participants could differentiate between with high accuracy [79].

For those technologies with fewer stimulation sites, there is limited evidence that it may be possible to manipulate the perceived area of sensation by stimulating multiple sites at once. Only three studies reported perceived locations for simultaneous stimulation [14, 55, 80]. In two of these studies, simultaneous stimulation of two sites resulted in a union of the areas of sensation perceived when both sites were stimulated independently [55, 80]. However, the third paper found that simultaneous stimulation of the median and ulnar nerves resulted in novel areas of sensation closer to the center of the hand [14]. While these results have not been replicated, they demonstrate a new possibility for percept manipulation that should be explored in future research.

### 4.2. Feedback in bi-directional prostheses

The ultimate goal for electrical stimulation is to enable bi-directional prostheses to provide naturalistic sensation for individuals with amputation, just as they would receive with their intact limb. To enable this feedback control loop, sensors on the prosthesis need to be mapped in some way to parameters for electrical stimulation, and must be matched to appropriate stimulation sites. As described in section 3.3.3, the majority of studies used linear mapping of a pressure or position sensor to a stimulation parameter value. To date, the literature does not agree on any specific advantage for linearly encoding one parameter over another. Only one study tested participants' sensitivity to changes in intensity due to frequency or pulse width, finding that they were more sensitive to changes in pulse width compared to frequency [25]. However, this study was not conducted using a physical prosthesis, so more studies are required to extend these results to practical use.

While few studies directly compared different encoding strategies, any encoded stimulation parameter still improved how well a prosthesis user could identify objects [14, 31, 66], and the accuracy with which they could perform manipulation tasks [46, 66, 68]. What does seem to vary between different encoding strategies is the extent of functional improvement, and the naturalness of the perceived sensation. For example, linear encoding strategies are effective at providing functional sensation, but may not provide enough complexity for the body to interpret them as natural sensation. Studies that explored using biomimetic encoding strategies found that they result in improvements to both function [56, 60] *and* the naturalness of sensation [44, 60]. These biomimetic strategies should be tested in more participants, and across several different technologies, to determine if there are general benefits to these more advanced methods of encoding prosthetic sensor data.

Notably, the majority of functional tests performed in the field focus on encoding pressure information at common points of contact like the palm, fingertips, or pads of the feet. More uncommon are studies that encoded information from motor position into a sense of movement or the position of the phantom limb. The prominence of pressure encoding is likely due to the ease with which researchers can map most tactile sensation (touch, vibration, paresthesia) to a pressure sensor, as any somatotopic sensation with variable intensity can easily be interpreted as pressure. Proprioceptive feedback, however, cannot be directly substituted in this way, while preserving homology, and is therefore limited to individuals who specifically experience a change in phantom limb position [50] or movement [70] upon stimulation. Two studies have successfully trained participants to remap tactile sensation generated through stimulation to the pose of a prosthesis [31, 70]. However, in another study a participant was unable to remap tactile sensation to the pose of a prosthesis and, therefore, could not identify between three objects at a level above chance [49]. Thus, the ability for participants to remap tactile to prosthesis position or movement must be studied further. Studies that incorporated the participant's sense of position or movement generated through stimulation

into bi-directional prosthetic control demonstrated that participants could use proprioceptive feedback to identify object size in addition to object stiffness [70] and could track the static position of an artificial arm's elbow joint without any visual cues [50].

### 4.3. Current methods of evaluating referred sensation

It is difficult to advance this field without establishing standard metrics that allow comparison of existing solutions and the evaluation of new approaches. Here, we examined the literature to determine how studies of sensory feedback in individuals with amputation characterized sensation and evaluated any functional improvements. With this approach, we determined if there were enough commonalities between studies to (a) effectively compare stimulation techniques and (b) to suggest appropriate outcomes for future studies.

#### *4.3.1. Sensation characterization*

As described in section 4.1, sensory information can be described by its intensity, quality, size, and location. It is important to establish common methodology to characterize these aspects of sensation in order to directly compare stimulation approaches. Here we describe the methodologies used for characterization and suggest best practices for future studies.

Sensation intensity is difficult to quantify because intensity is subjective, without a true intensity scale. One widely reported metric related to sensation intensity is the perception threshold, which is the set of stimulation parameters at which an individual starts to perceive a sensation. Large deviations in the parameters required to elicit sensation may indicate degradation or movement of the electrode within a participant, or scarring of the tissue around the electrode. For this reason, the perception threshold is often reported as a safety metric in studies with long-term implantation [46, 56, 77]. Fewer papers discuss the discomfort threshold [31, 61], which is the maximum set of stimulation parameters that can be used before the participant reports sensations of pain or discomfort. The discomfort threshold should be reported more regularly in studies that modulate percept intensity, either as part of bi-directional control or to measure sensitivity, as it represents the functional upper limit of sensation. Finally, a two-alternative forced choice protocol can be used to calculate the just noticeable difference of intensity, location, or position given changes in a chosen parameter. This assessment is valuable for characterizing sensation in a way that can be directly compared between participants and research groups. Combined with the perception and discomfort threshold, sensitivity measures can provide researchers with expectations for the granularity in force or position feedback that a prosthesis user could reasonably discern. However, only a small number of studies conducted this kind of assessment [64, 77], likely due to the time and mental energy it requires from participants.

Sensation quality is restricted to participant descriptions, and is largely subjective. Many researchers simply record the descriptions of sensations reported by their participants, typically from a predetermined list with the option to create their own descriptors [38, 52, 76]. Some additionally ask participants about the naturalness of the perceived sensation, in addition to its quality [39, 66]. However, it may be possible to identify patterns in the technologies or parameters that evoke certain sensation modalities with more consistent reporting of important study characteristics and methodologies. Papers that do report sensation quality will often report sensations perceived across the entire cohort rather than how many individual participants perceived sensation of a given quality [43, 73, 76]. Many studies that report sensation quality also do not report the stimulation parameters that were used when sensation was felt [36, 38, 61, 66]. While these details may be difficult to report in some cases, their exclusion makes it difficult to identify any potential relationships between sensation quality and participant demographics, stimulation parameters, or any other variables. More studies that specifically report sensation quality in response to stimulation parameter modulation may help address these concerns.

Similarly to sensation quality, the location and size of sensation has been widely reported but is often reported without sufficient context. Methods for collecting the data itself is straightforward: participants indicate either using a computer interface or tracing on a representation of the hand where they felt a percept. However, some papers either described percept locations rather than providing a specific map [45, 81], reported the perceived area of sensation for several participants on the same figure [14], or displayed an area of perceived sensation without specifying which nerve was stimulated [41, 43, 56, 69]. Due to this inconsistent reporting, the aggregated maps of perceived sensation location data in this review (figure 4(A)) do not represent all technologies equally. By providing information for each participant, and for each individual nerve, location and size information can be more easily compared across individuals and technologies to better inform future stimulation experiments.

#### *4.3.2. Functional outcome measures*

Functional assessments are often used to determine the utility of sensory feedback for prosthetic use. Most functional outcome measures require the use of a bi-directional prosthesis with sensors to trigger electrical stimulation of residual tissue (e.g. skin, nerve,

muscle) [14, 44, 58]. For upper limb experiments, the most common functional tasks were object identification. These tasks were not consistent across studies, but involved either identifying object size [31, 56, 70], stiffness [31, 57, 66], or surface coarseness [81]. Another common assessment was force matching, in which participants were asked to increase or decrease the applied force of a prosthesis to different targets [35, 66] For each of these tasks, improved performance indicates effective integration of sensory feedback.

The remaining functional outcome measures were a mix of grasp-and-lift tasks [53, 54], and standardized clinical assessments (e.g. Box and Blocks, AMULA) [45, 46, 56]. Several studies used a form of modified box and blocks, in which an instrumented object needed to be grasped, lifted, and placed in a different location without the prosthetic grip force exceeding pre-determined values [14, 58, 60]. While clinical assessments and modified box and blocks were able to capture performance improvements when participants were given sensation [45, 46, 58, 60], they also include many confounding factors including training, prosthetic hardware, and the dexterity of participants.

The functional benefit of sensation on lower limb prosthesis users has been studied much less frequently ($n = 6$ studies). One study demonstrated that providing participants with tactile sensations in their phantom foot and proprioception of their knee position, three participants could ambulate up and down stairs faster and fell less when stepping over obstacles [61]. Several studies demonstrated that participants had an accurate internal model of the position of their prosthesis [35, 61] and relative force exerted on it [35], which may be helpful in detecting obstructions or helping navigate uneven terrain. In a study that measured the center of pressure path length of three individuals during standing, stimulation of FINEs was only able to decrease path length in one individual [43]. Interestingly, one study reported that two participants could not only achieve higher outdoor walking speeds, but also showed decreased metabolic consumption in indoor and outdoor walking tests when provided with sensory feedback of their phantom knee angle and foot contact [52]. The small sample sizes and fact that no two studies measured the same outcome provide a low level of evidence that sensation enhances lower limb function and stability. Therefore, there is a need for replication of these findings and more studies of the functional of bidirectional lower limb prostheses in general. As this population is at a greater risk of falls [82], special focus should be given to the studying the effect of sensory feedback on balance and falls in lower limb prosthesis users.

In both upper and lower limb studies there was a mix of validated clinical assessments and functional tasks specifically designed to measure the benefits of sensory feedback. We recommend that future studies try to incorporate both types of outcome measures when possible. Measures that focus on sensory feedback are important for demonstrating the specific functional benefits of feedback. These can include abstract tests such as object identification for upper limb prosthesis users [31, 66, 81] or more clinically-relevant tasks, such as completion time traversing obstacles for lower limb prosthesis users [61]. However, testing the benefits of sensory feedback in validated clinical assessments is also important as these tests often have normative data for healthy individuals and/or other prosthesis users for comparison and are more representative of general prosthetic function. Tests such as the Box and Blocks task [83] for upper limb prosthesis users or the Timed Up and Go [84] for lower limb prosthesis users can help determine if the addition of sensory feedback leads to meaningful differences in user performance and can facilitate comparison across studies and approaches. Unfortunately, the current set of validated clinical assessments are not always sensitive to the addition of sensory feedback, which does limit their usefulness [45, 85]. Therefore it is critical for sensorized versions of these tasks (e.g. the virtual egg test [86], the sensorized clothespin task [12]) to be standardized and validated. Doing so will make these tasks more useful to compare outcomes across research groups.

#### *4.3.3. The user experience*

User experience is an essential component of translating electrical sensation from research labs into commercial devices. As such, it is critical to understand the user experience during sensory experiments. While some components of this experience such as sensation quality are often reported (section 3.4.2), others such as pain and prosthetic embodiment are far less common.

Studies that did quantify pain used variations of a VAS [46, 54, 58, 59, 74], or questionnaires [44, 59, 87]. Both methodologies captured the frequency, length, pain level, and lifestyle interference of episodes of phantom limb pain. A VAS was most often used, likely due to its ease of understanding and convenience, however variations in the styles of each VAS across studies makes it difficult to draw meaningful conclusions. A universal VAS, like one proposed by Reed and van Nostran [88], would eliminate finite descriptors such as 'worst pain ever' and improve our ability to aggregate data. Regardless of approach, all papers that measured pain observed significant decreases in chronic or acute phantom pain after sensory stimulation. Future work in relating stimulation parameters to the reduction in phantom limb and measuring pain with a standardized VAS could facilitate a better understanding of how to reduce pain in the future, and may inform future pain interventions.

Embodiment is another factor of prosthetic experience that has implications for long-term acceptance of the prosthesis, and provides a measure of how integrated a prosthesis is into the body image of a particular individual. While embodiment has no single, established definition, a recent systematic literature review of papers discussing and measuring embodiment found that the term is most often associated with concepts of prosthetic ownership and agency [89]. Ownership describes an individual's feeling that the prosthesis is part of, and moves with, their body. Agency describes an individual's sense that they are in control of their prosthesis, and that its movements are their own. Studies in our literature review reported that individuals felt more self-confidence using their prosthesis when it provided them with sensory feedback [46, 52, 64], and felt they had more control over the prosthesis when using feedback [31, 46, 60]. These measures may indicate increased agency. Additionally, several studies reported that individuals felt that the prosthesis was more a part of them after using sensory feedback [31, 45, 46], or that the movements of the robotic limb were aligned with their phantom limb [31, 54, 60]. Some studies also measured perceived phantom limb length, which tended to approach anatomical limb length after bi-directional prosthesis use [46, 60, 77]. These measures may indicate increased ownership. Based on this evidence, we can confidently conclude that referred, somatotopic sensation does increase an individual's prosthetic embodiment. However, current methods in the field are varied, and standardization of ownership and agency metrics would improve the field's ability to compare results and develop a better understanding of the role embodiment plays in function and prosthetic acceptance [89].

One goal in adding sensory feedback is to reduce the cognitive burden associated with prosthetic use, which is contributed to both by the design of motor controllers [14] and by the reliance of prosthesis users on visual feedback [1, 15]. However, augmenting human ability is constrained by limited cognitive capacity to process information and requires there be minimal delay when processing and acting on sensory feedback [90]. Referred sensation is generally believed to be less cognitively demanding than sensory substitution [2, 28], however only one study included in this review directly compared the two approaches in a single individual [67]. Additional studies are required to validate these findings and better understand the potential cognitive advantages of referred versus substituted sensation.

Ultimately improving prosthetic function, achieving more naturalistic sensation quality, and reducing cognitive load are all factors in improving an individual's quality of life. This is difficult to assess from the current literature as only one study involved taking a sensory prosthesis out of the lab. In that study, two individuals used a sensory prosthesis with and without sensation enabled during daily life [46]. Both participants used their prostheses more, had higher self-efficacy, and reported greater levels of social interaction when sensation was enabled. One of the two participants also reported higher quality of life, as measured used the orthotics and prosthetics user's survey (OPUS) quality of life survey [91]. Given the dearth of studies measuring quality of life and mixed findings of this study, the effect of sensation on quality of life remains uncertain.

#### *4.3.4. Stability of perceived sensations*

An important component of each of the aforementioned outcomes is their stability, or consistency, over time. One reason we may expect outcomes to change is limitations of the hardware itself and how it interacts with the body. For example, one study of USEAs found that only a single participant had a steady number of electrodes that evoked sensory percepts over the course of five weeks, with the remaining participants either experiencing a decreasing number of sensation-evoking electrodes or only experiencing sensation during one or two weeks [76]. Another study tracked the migration of implanted leads for epidural spinal stimulation using intraoperative fluoroscopy [36]. While one participant had extreme migration of the implanted leads (over 70 mm) and was explanted after two weeks in the study, the other three participants still experienced lead migration of up to 38 mm and there were small changes to sensory percept location and charge required to evoke sensation.

Tracking the location of perceived sensation is particularly relevant to transitioning research experiments to home prosthesis use. While many studies that reported sensation location did so for the percepts experienced in a single session, including the majority of TENS studies, stimulation of a given site has been reported to change over the span of days [55], weeks [36, 58], months [22], or years [37]. These reports were given for USEAs [55], TIMEs [58], nerve cuffs [22, 37], and epidural spinal stimulation [36], which means these effects are not specific to a particular technology. As such, it is recommended that future studies report the consistency of stimulation threshold, perceived sensation area and quality, and the number of active sites that evoke sensation over the duration of a study, and preferably over months to years. In doing so, we can better understand which technologies produce more stable sensory percepts, and we can make clinical recommendations for how long individuals can expect to go before device parameters need to be updated.

It is also important to measure how sensory percepts change over short timescales. If sensory

stimulation is maintained at suprathreshold levels, participants may experience adaptation. Here, adaptation is the progressive desensitization to prolonged stimulation on the scale of a single study session. Adaptation can affect measures of stimulation threshold and perceived sensation intensity, though adaptation to artificial stimuli seems to behave much like adaptation to natural touch stimuli [47]. Still, adaptation is not often reported, and is relevant for prolonged home use of a sensory-enabled prosthesis. Therefore, more experimentation and reporting of adaptation is required.

### 4.4. Implications in other technologies

There are several other methods of inducing referred sensation that were not included in this review. While outside of our scope, they are relevant to the broader field and may be able to benefit from the information described herein. For example, natural reinnervation of severed nerves after amputation [15, 92] and targeted sensory reinnervation [93] both result in regions of skin that, when stimulated, refer sensation to the phantom limb. Stimulating maps formed from either method can leverage healthy neural pathways, producing naturalistic sensation. However, it is unclear how stable these phantom projection maps are over time, or what their functional benefits are. While these types of maps typically utilize mechanical stimulation rather than electrical, they could benefit from utilizing the same sensory characterization approaches and functional outcome measures as those recommended by this review.

There are also methods of peripheral nerve and brain stimulation that have demonstrated functional benefits in animal studies [94], or have been used for prosthetic control [95], but have not yet been published on in the context of sensory feedback for humans with amputation. Regenerative peripheral nerve interfaces are one such technology [95]. Originally developed to treat neuroma pains in the residual limb of individuals with acquired amputation, they can be used for both sensation and control. Cortical stimulation may also provide a means to directly stimulate the brain in order to evoke referred sensation to missing extremities. While studies have demonstrated these methods being used to evoke sensation in animal models [94], the work in humans is still limited. We hope that the resources and recommendations laid out in this systematic review can facilitate studies of existing and novel stimulation technologies by providing clear measures for comparison and a foundation to base their experiments on.

## 5. Conclusion

This systematic literature review found that several technologies can be used to effectively evoke referred sensation in individuals with amputation. While all studies used similar waveform shapes and studied similar parameters, we found that studies investigating different encoding strategies demonstrated the most potential for electrical stimulation to improve prosthetic function and experience. While promising, there is a significant lack of replication of methodologies within the literature, which limits the extent to which study results can be generalized. The limited studies which have attempted replication have not been successful [39]. By establishing better reporting guidelines for sensory characterization and outcome measures, we can gain a greater understanding for how the brain processes sensory feedback and more quickly develop technologies that can truly replace a lost limb.

To that end, we proposed the following checklist of items to include in future referred sensation studies. With this standard, we may better be able to compare across studies to determine relative benefits of different approaches and define more precise ranges for stimulation parameters that could induce referred sensation.

### 5.1. Checklist of items to include in future referred sensation studies

Items in **bold** we consider **needs**, while the remaining items are conditional and may not always be appropriate.

(a) Participant details:
- ☐ **Demographics (Age, sex, level of amputation) for each participant**
- ☐ Study duration (Implantation timeline, timeline of data collections) for each participant

(b) Experimental protocol:
- ☐ **Waveform details (Shape, symmetry)**
- ☐ **Stimulation parameters (Range of amplitude, frequency, pulse width, and charge, as well as specific values associated with each given result)**
- ☐ **Encoding strategy (For bi-directional experiments)**
- ☐ Parameter restrictions (Due to safety or hardware limitations)

(c) Sensory characteristics:
- ☐ **Functional stimulation thresholds (Perception, Discomfort), including how they were obtained for each participant, and each stimulation site**
- ☐ **Sensation quality at thresholds for each participant, and each stimulation site**
- ☐ **Sensation location at thresholds for each participant, and each stimulation site**
- ☐ Just noticeable difference to changes in stimulation intensity

(d) Functional tests:
- ☐ At least one standardized functional assessment (e.g. Box and blocks, Timed Up and Go)

- ☐ At least one sensory-specific assessment (e.g. Stiffness ID, Walking over uneven terrain)

(e) Subjective measures (For longitudinal studies):
- ☐ Measures of embodiment
- ☐ Measures of pain
- ☐ Measures of quality of life

For any longitudinal study, sensory characteristics and associated stimulation parameters should be reported at several intervals.

## Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

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