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Estimating Risk for Future Intracranial, Fully Implanted, Modular Neuroprosthetic Systems: A Systematic Review of Hardware Complications in Clinical Deep Brain Stimulation and Experimental Human Intracortical Arrays

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Objective: A new age of neuromodulation is emerging: one of restorative neuroengineering and neuroprosthetics. As novel device systems move toward regulatory evaluation and clinical trials, a critical need arises for evidence-based identification of potential sources of hardware-related complications to assist in clinical trial design and mitigation of potential risk.

Materials and Methods: The objective of this systematic review is to provide a detailed safety analysis for future intracranial, fully implanted, modular neuroprosthetic systems. To achieve this aim, we conducted an evidence-based analysis of hardware complications for the most established clinical intracranial modular system, deep brain stimulation (DBS), as well as the most widely used intracranial human experimental system, the silicon-based (Utah) array.

Results: Of 2328 publications identified, 240 articles met the inclusion criteria and were reviewed for DBS hardware complications. The most reported adverse events were infection (4.57%), internal pulse generator malfunction (3.25%), hemorrhage (2.86%), lead migration (2.58%), lead fracture (2.56%), skin erosion (2.22%), and extension cable malfunction (1.63%). Of 433 publications identified, 76 articles met the inclusion criteria and were reviewed for Utah array complications. Of 48 human subjects implanted with the Utah array, 18 have chronic implants. Few specific complications are described in the literature; hence, implant duration served as a lower bound for complication-free operation. The longest reported duration of a person with a Utah array implant is 1975 days (~5.4 years).

Conclusions: Through systematic review of the clinical and human-trial literature, our study provides the most comprehensive safety review to date of DBS hardware and human neuroprosthetic research using the Utah array. The evidence-based analysis serves as an important reference for investigators seeking to identify hardware-related safety data, a necessity to meet regulatory requirements and to design clinical trials for future intracranial, fully implanted, modular neuroprosthetic systems.

Keywords: Adverse events, brain machine interface, deep brain stimulation, hardware, Utah array

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

A new age of neuromodulation is emerging. Established open-loop neuromodulation systems treat a broad range of neurologic network disorders, including Parkinson disease, tremor, dystonia, obsessive–compulsive disorder, epilepsy, and pain. A newly approved closed-loop device provides responsive neural control of epilepsy. A growing body of the literature suggests promise for neuromodulation to treat intractable depression and enhance recovery from spinal-cord injury. Experimental neuroprosthetic systems incorporate intracortical silicon-based arrays and networked sensing and stimulation modules to allow real-time neuroprosthetic control. As technology advances and the number of modular systems grow, a need arises to anticipate the potential safety features and shortcomings of future neuroprosthetic systems. Such analysis, based upon all available

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evidence, may be of value in satisfying prerequisites of regulatory requirements, formulating clinical-trial design and oversight, and fully informing patient consent.

The primary aim of this systematic review is to provide a detailed safety analysis to inform future intracranial, fully implanted, and modular neuroprosthetic systems. To accomplish this aim, we examine the safety profiles of the most widespread intracranial clinical system, deep brain stimulation (DBS), as well as the most widespread intracranial human experimental system, the silicon-based (Utah) array, to identify safety considerations inherent to emerging modular neuroprosthetic systems and to derive the most reliable safety estimates possible for likely future neuroprosthetic systems. Our comprehensive and systematic review of the safety literature for DBS and human trials of the Utah array provides greater detail and scope than many earlier reviews by encompassing all indications for DBS and focusing upon the structural components of the DBS system. Detailed safety evaluation of experimental systems, such as the Utah array, has been difficult due to the dearth of complications reported in the literature, which focuses upon scientific and technological advances. However, indirect indicators exist. For example, we can estimate the duration of complication-free Utah array operation from reported periods of implant longevity in the literature. As a result, in addition to evaluating the potential safety of future modular intracranial device systems, this review also achieves an additional secondary goal of providing the most comprehensive safety and longevity review to date of human neuroprosthetic research using the Utah array.

Currently, U.S. Food and Drug Administration (FDA)-approved chronically implanted intracranial neuromodulation systems include DBS and responsive neurostimulation (RNS). DBS has been used for decades to treat movement disorders (1–3) and, more recently, to treat neuropsychiatric disorders and epilepsy (4–6). DBS systems are modular, consisting of a multicontact lead, an internal pulse generator (IPG), and an extension cable. The multicontact lead is a depth electrode, typically 28 or 40 cm long, inserted into an intracranial target structure through a burr hole in the skull. The lead is secured at the skull entry point via a burr hole cover. The IPG is typically placed subcutaneously in the chest region. The extension cable connects the two via subcutaneous tunneling along the neck. As a related example, however, relatively new and not as widely used, the RNS system for epilepsy (NeuroPace, Inc., Mountain View, CA) is similarly modular, consisting of cortical strip or depth leads connected to a cranially implantable neurostimulator unit (7).

To monitor and record brain electrical activity for neuroprosthetic applications, the commercially available Utah array (NeuroPort, Blackrock Microsystems, Inc., Salt Lake, UT) is FDA approved for human implantation up to 30 days, or longer with an investigational device exemption. The NeuroPort Array consists of a 4.0 mm × 4.0 mm silicon-based microelectrode (Utah) array with 96 electrodes, extending 1.0–1.5 mm, and a wire bundle

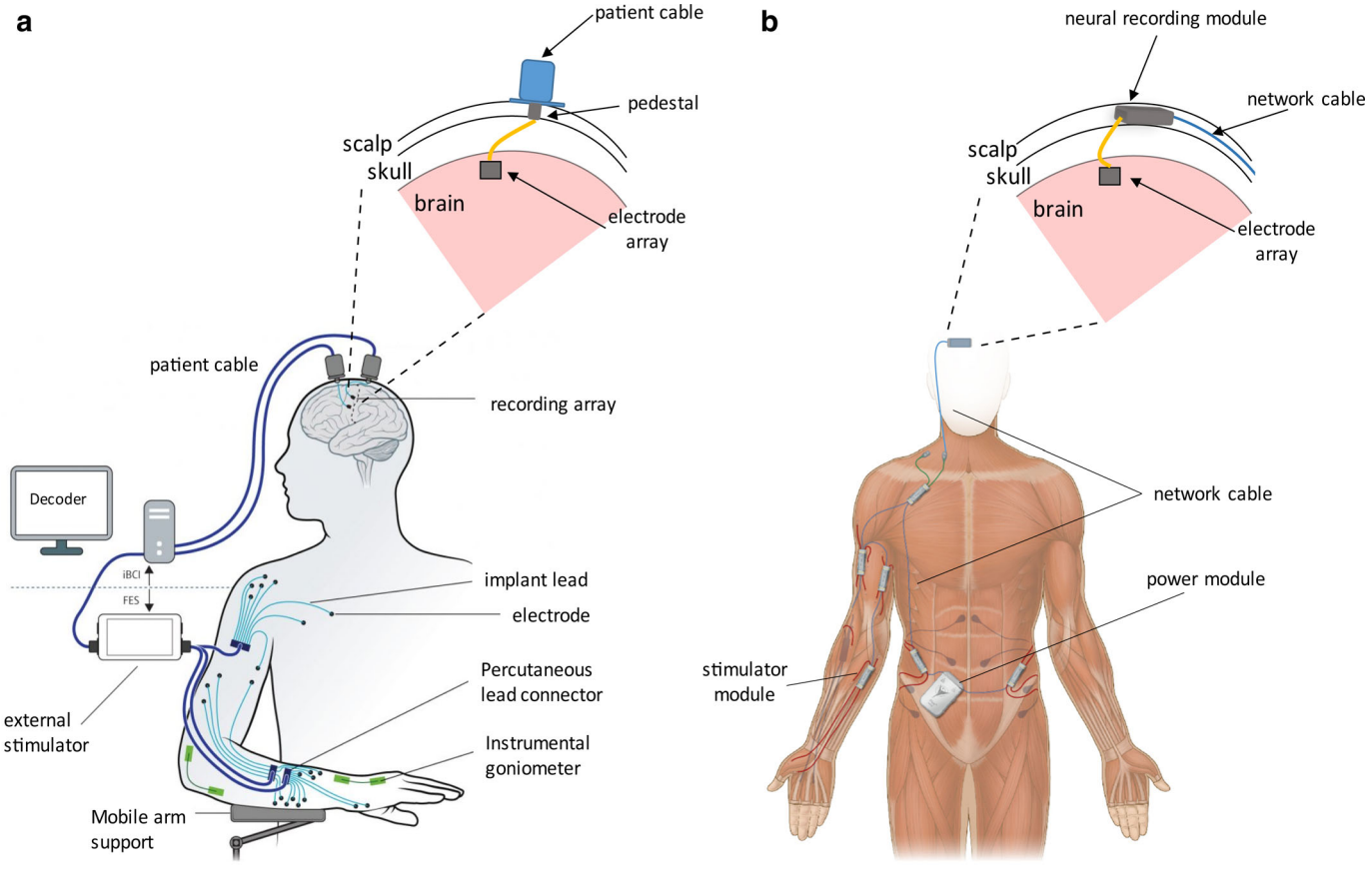

Figure 1. Intracranial neuroprosthetic systems. a. An overview of the standard brain machine interfaces set up. An electrode is implanted in the brain and percutaneous connections are made between the patient and a series of computers. This particular example is of brain-controlled functional electrical stimulation (FES) (252). b. An example of a potential future brain–machine interface set up using a modular network. An electrode is implanted in the brain and connected to an implantable module for processing instead of a series of computers. This portrays the potential for a fully implantable brain-controlled FES system using the networked neural prosthesis. [Color figure can be viewed at wileyonlinelibrary.com]

Table 1. Keywords and Search Structure for Hardware Complications in DBS.

DBS synonyms	Risk synonyms
Deep brain stimulation, thalamic stimulation	Hematoma, bleed*, "short circuit," fracture, breakage, migration, infection, erosion, revision, risk, safety, adverse event*, "adverse effects," complication*, hardware failure

[DBS **OR** DBS synonym…] **AND** [risk **OR** risk synonym…].
* symbol at the end of a word to include other terms that begin with the root word (i.e., -ing, -s).

connecting the array to a pedestal (Fig. 1). The pedestal penetrates the skin to provide electrical connectivity. A cable carries signals from the pedestal to front-end amplifiers and, ultimately, to a computer-based signal acquisition system for recording and decoding (8,9). Currently, the major limitation of the NeuroPort system is that tethering the pedestal to external hardware impedes mobility, constraining array use to laboratory settings. In addition, the transcutaneous pedestal violates the barrier integrity of the skin, potentially raising the risk of infection. Any clinically adopted neuroprosthetic system will require the Utah array to be connected to a fully implanted modular actuator system with the ability to record and respond to stimuli, similar to closed-loop DBS or RNS.

An example of such a system is the networked neural prosthesis (NNP). The NNP is a fully implantable, modular functional electrical stimulation (FES) system, which in conjunction with implanted Utah arrays, could form a fully implanted future neuroprosthetic system. The current NNP consists of multiple interconnected modules each with their own functionality responsible for recording myoelectric activity, providing intramuscular stimulation, and power. Combinations of these modules can be distributed around the body to assist in a variety of functions lost by individuals due to spinal cord injury (10,11). The current-version NNP only records residual myoelectric activity, but it may be possible to add a neural recording module to record directly from the brain and facilitate cortical-controlled FES. Hence, a combined Utah Array-NNP system becomes a useful exemplar system for safety analysis. An overview of the exemplar, prototypical fully implantable, modular, neuromodulation system is shown in Fig. 1b.

To understand potential hardware complications for such emerging systems, we have performed a systematic review focused on the hardware mechanisms of DBS failure as well as longevity or safety of the Utah array in humans. DBS is a well-established, fully implantable system that is similarly modular to our exemplar prototypical neuroprosthetic system. However, the electrode lead used in DBS is not directly comparable. Hence, major safety concerns and potential failure modes of the Utah Array-NNP system are hypothesized to be similar to those documented in both DBS systems and the Utah Array.

MATERIALS AND METHODS

Search Strategy

A systematic review was conducted to identify the relevant literature on hardware complications of DBS, by searching the electronic data bases: PubMed, Embase, ClincalTrials.gov, Scopus, and Cochrane's Library. The search was broken down into two concepts; device and risks. A comprehensive list of keywords was generated to capture all synonyms of DBS and risks, including both general terms and potential risks specific to DBS. This list was then optimized by removing additional keywords that resulted in search results captured by the larger umbrella of another keyword. All device-related keywords were grouped together by an OR operator and the same was done for the risk keywords. The device and risk groups were then merged with the AND operator to identify all articles with mention of DBS and some form of risk or complication in the title or abstract (Table 1).

A similar approach was taken to identify all articles including the use of the Utah array in humans in the title or abstract. The search was again separated into two concepts: device and patient, where a comprehensive list of all synonyms describing Utah arrays and humans was generated. Each separate concept group was combined through the OR operator and then together with the AND operator. In addition, a list of known principal investigators who have conducted experiments with humans implanted with Utah arrays were identified. This was incorporated at the end with the AND operator to help refine the search results (Table 2).

Study Selection

The search results were critiqued through a two-reviewer process. Each reviewer independently read the title and abstract of articles to screen for relevance. They were classified as either possibly relevant or clearly irrelevant. Articles deemed as clearly irrelevant by both reviewers were immediately excluded, and articles classified as possibly relevant by both reviewers were immediately included. The articles where the reviewers disagreed were reviewed again, discussed, and then resolved.

Predefined inclusion and exclusion criteria were created to further refine our search results to include only the papers within the scope of the review, shown in Fig. 2. Selected articles were required to have clinical data from a primary study, report on bleeding, infection, or hardware complications related to DBS, and include a quantification of risk. Articles not reporting data on hardware complications, and articles reporting data solely on revision procedures were excluded, as well as case studies, review

Table 2. Keywords and Search Structure for Utah Arrays in Humans.

Utah array synonyms	Human synonyms	Senior authors
96 channel microelectrode array*, 96 channels electrode array*, microelectrode array*, intracortical microelectrode array*, intracortical brain computerinterface*, Neuroport array*	Human, subject*, patient*, tetraplegic*, quadriplegic*, person, people	Donoghue, Hochberg, Kirsh, Henderson, Shenoy, Greger, Normann, House, Cash, Jang, Zaghloul, Salas, Andersen, Schwartz, Rezai, Collinger, Scheon, Truccolo

[Utah array **OR** Utah array synonym…] **AND** [human **OR** human synonyms…] **AND** [senior author **OR** senior author…]. * symbol at the end of a word to include other terms that begin with the root word (i.e., -ing, -s).

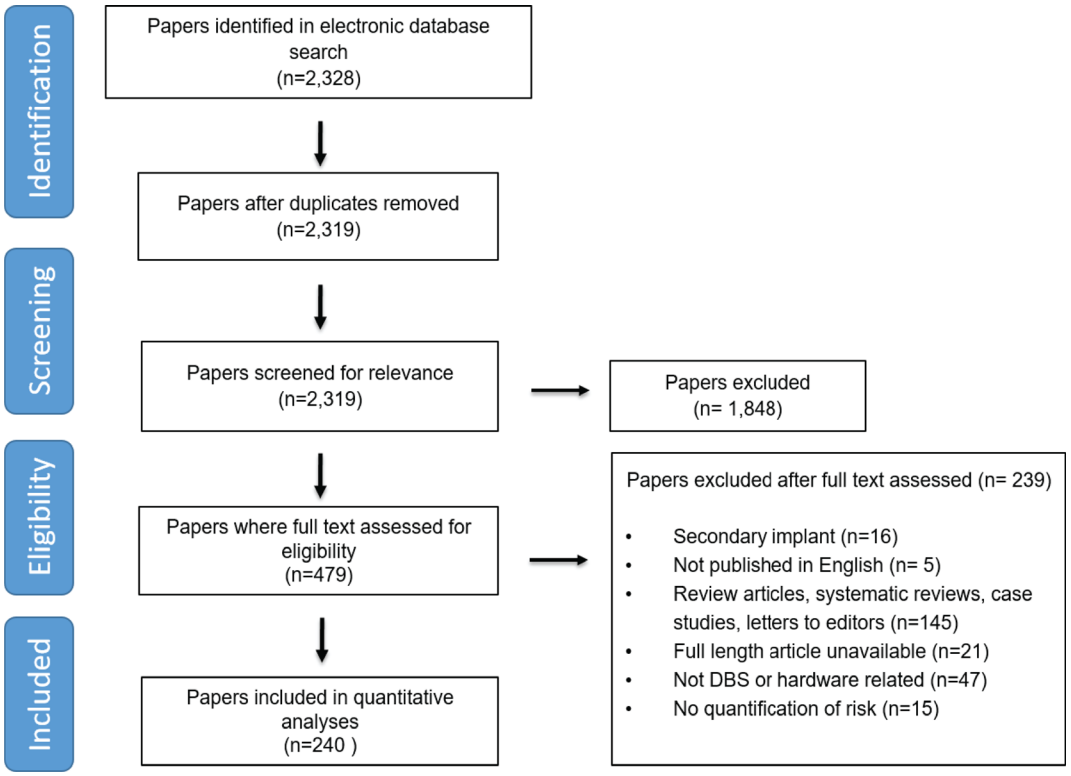

Figure 2. Flow diagram of the study selection for deep brain stimulation hardware complications based on inclusion and exclusion criteria. [Color figure can be viewed at wileyonlinelibrary.com]

articles, and editorial letters. Only full-length articles available in English or easily translatable that met all criteria were eligible for inclusion. Two reviewers (A.B. and J.L.) independently read the full-length articles and assessed against the inclusion criteria. Articles that met all criteria according to both reviewers were included in this review. Articles that both reviewers agreed did not meet one or more of the criteria were excluded. The remaining articles where the reviewers disagreed were reviewed again, discussed, and then resolved.

Data Extraction

To avoid extraction errors, two reviewers independently extracted data from the eligible articles and any discrepancies were discussed and resolved. Infection, hemorrhage, skin erosion, and hardware failures related to malfunctions of the extension cable and IPG, and fracture or migration of the DBS electrode were the primary complications focused on in this review. For each eligible article the following data were extracted about the adverse event: incidence rate, location, the time of occurrence postinitial surgery, if additional surgery was required, and if it resulted in a total explant of the system. Because there are relatively few centers hosting these clinical trials, publications often have studies with overlapping patients and multiple complications occurring in the same patient. Articles with overlapping patients were identified and these patients were only counted once. Per patient data were extracted for each complication, therefore if one patient experienced more than one complication (i.e., infection and hemorrhage) both were accounted for. However, we did not use multiple occurrences of the same complication in one patient (i.e., reoccurring infections).

RESULTS

DBS Search Results and Study Characteristics

Our initial data base search yielded 2328 DBS publications that contained our keywords and MeSH terms in either the title or abstract. After screening titles and abstracts, 479 potentially relevant articles were identified, and the full text was assessed against the inclusion criteria. Finally, 240 articles were chosen to be included in this meta-analysis (12–249) (Fig. 2). The remaining 239 articles were excluded for the following reasons: not DBS or related (N = 47), no quantification of risk (N = 15), secondary revision procedures (N = 16), case studies, review articles, or editorial letters (N = 145), not published in English (N = 5), full-length article unavailable (N = 21). A total of 34,089 patients across articles were included in this analysis. Notably, only seven hardware-related deaths occurred within these patients. The per patient incidence rates of all complications and subgroups of their locations are reported in Table 3. Unfortunately, due to the lack of a comprehensive or standardized reporting system for complications there is missing information within the literature. All papers that reported complications did not also report details on the location. In addition, complications experienced at multiple locations per patient have been accounted for. The results presented in Table 3 are a reflection of thus mentioned.

Hemorrhage

Bleeding is always a major concern when implanting electrodes into the brain. Hemorrhage during and after surgery can lead to neurologic damage and even death in severe cases. Of all the articles included in the study, 133 consisting of 19,389 patients reported on hemorrhage. The overall incidence rate was 2.86%.

Table 3. DBS Hardware-Related Adverse Events.

Complication	Incidence (%)	No. of patients reported
Infection	3.79	1028 (27,072)
IPG	44.2	265 (599)
Scalp/burr hole	17.8	107 (599)
Extension cable	13.6	82 (599)
Lead	11.1	67 (599)
Lead migration	3.49	139 (3977)
Lead fracture or failure	2.53	208 (8214)
Hemorrhage	2.49	483 (19,389)
Intracerebral (ICH)	86.9	374 (430)
IPG	8.13	35 (430)
Extension cable	1.62	7 (430)
Skin erosion	2.46	206 (8347)
IPG malfunction	2.33	101 (4320)
Tethering of extension cable	1.95	103 (5279)
Total overall complication	7.68	2098 (27,299)

Out of all the papers in the literature that reported information on the location of hemorrhages, 86.9% of those were intracerebral hemorrhages (ICH), the most common during the duration of the implanted system. Although hemorrhage is most likely to occur in the brain for these procedures, it also occurred in other areas throughout the body as well: at the site of the IPG (8.13%) and along the extension cable (1.62%). When a bleed occurs, it is usually reported to happen intraoperatively or within a few days of the surgery. Bleeding should always be taken seriously, however the risk posed by the reported hemorrhage ranged in severity and the action taken to resolve it. Some hemorrhages resolve on their own without any external intervention, while others are more serious and may require additional surgeries or other procedures. For the purpose of this review, any adverse events that required an additional surgery were deemed as serious adverse events. In serious cases, the device is normally explanted. Usually bleeds that occur outside of the brain can be resolved and then hardware can be re-implanted. In all the studies, there were only six reported deaths due to ICH (0.02%).

Infection

Second to bleeding, infection is often considered the next most dangerous adverse event to be cautious of in any surgical procedure, especially when there are foreign objects introduced inside the body, particularly the brain. With future modular systems expected to incorporate multiple implantable devices around the body, this is of major concern. There were 174 articles consisting of 27,072 patients that reported data on infection. It was the most frequently occurring adverse event, with an incidence rate 3.79% and was the main reason for ultimate device explanation. This is on par with other implantable devices such as the heart pacemaker. According to a systematic review by Persson et al., infections of cardiac implanted electrical devices range from 0.2 to 3.7% (250). However, this incidence rate varies largely across studies making the true incidence rate hard to establish due to the lack of standard methods for reporting incidences. Additionally, there was only one reported death related to an untreated infection. The infections observed varied widely in their location, time of incidence relative to the initial surgery, and severity. Of the 104 papers that reported the location of where infections occurred, 44.2% were located at the site of the IPG, followed by the scalp or burr hole (17.8%), the connector and extension cable (13.6%), and in the brain along the electrode lead (11.1%). Of the 49 studies who reported time, infections are observed within the first 30 days of surgery (10.2%); however, it can also occur months thereafter. Most cases of infections in the brain were reported early, within days, whereas infections that occurred around hardware outside of the brain took longer to appear. The majority of the reported infections were classified as severe, meaning they resulted in the patient having additional surgery. However, although additional surgery was required, in 35.9% of cases, the infection was resolved and the hardware was ultimately re-implanted allowing DBS therapy to continue. Depending on the location of the infection only a subset of the system would be explanted and re-implanted. It was rare that the entire system had to be explanted and then re-implanted. However, if the infection was extremely severe and widespread the entire system would be permanently explanted (20.7%). This was typically seen in instances of infection that had tracked along the DBS electrode.

Skin Erosion

Skin erosion is defined here as any place where there was a breakage of the skin due to implanted hardware nearby. Erosion of the skin is most commonly seen over the IPG and on the scalp at the site of the burr hole or the connector where the extension cable and electrode meet. This was reported in a total of 2.46% of cases and was very commonly associated with infection. In 62.6% of cases where skin erosion was reported there was also a case of infection reported near the site of erosion. An additional surgery or procedure was required in 25% of cases with skin erosion. Typically, wound debridement or surgical closure was used to repair skin erosion, however some instances required revisions and re-implantation of hardware. The more severe cases stemmed from erosion around the burr hole or the connector site and, where the electrode lead or extension cable was replaced. There were only 18 cases of skin erosion (9%) that led to the permanent explant of the entire system.

Other Hardware Failures

In addition to the previously mentioned hardware failures, there were also malfunctions of the extension cable and IPG, and fracture or migration of the DBS electrode. This includes most of the complications due to DBS hardware that are potentially relevant to future chronic tethered devices. Overall, IPG malfunction occurred 2.33% of the time, extension cable malfunction occurred 1.95% of the time, lead fracture occurred 2.53% of the time, and lead migration occurred 3.49% of the time. These are typically not dangerous in and of themselves, though in a single case, a patient was electrically shocked due to the malfunction of the IPG (123). In most cases, however, these are complications that usually require additional routine surgeries, which do have their own associated risks. In 22.6% of reported cases (including the electrical shock incident), they were able to revise and fix. In only two cases was a complete explantation necessary.

Utah Array Search Results and Study Characteristics

Our initial search identified 433 articles, which resulted in 76 articles after screening where humans had been implanted with the Utah array (Fig. 3). The Utah array, a 96-channel microelectrode array (Blackrock Microsystems), has been implanted intracortically in a total of 48 subjects as of September 2018. This

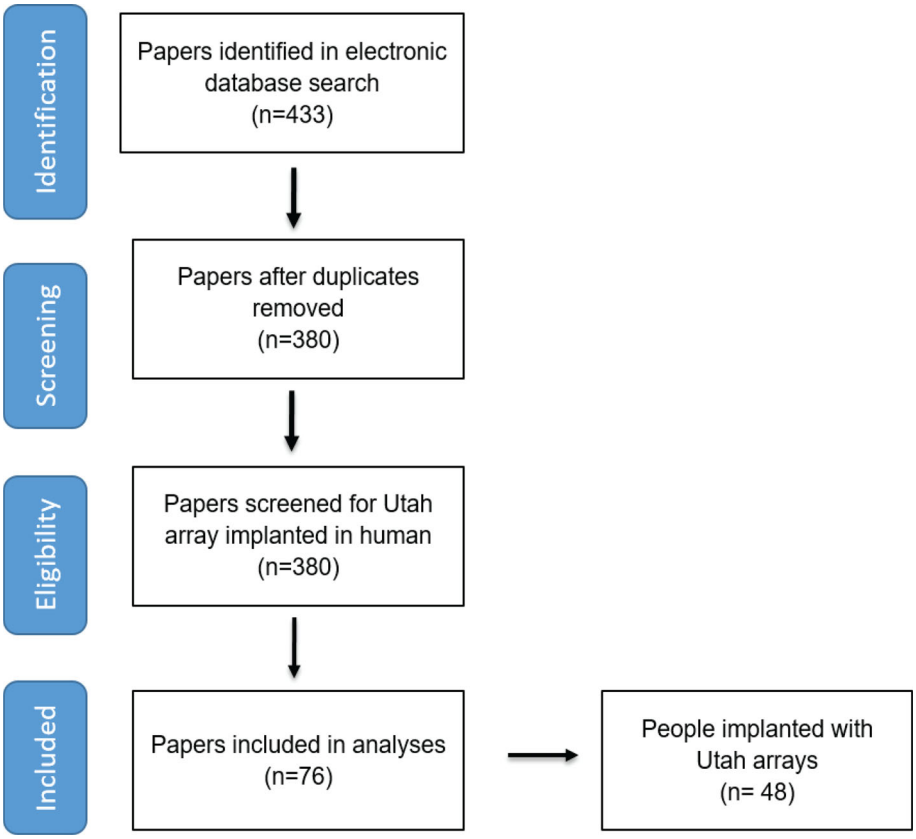

Figure 3. Flow diagram of the study selection for Utah arrays based on inclusion and exclusion criteria. [Color figure can be viewed at wileyonlinelibrary.com]

Table 4. Human Utah Array Implantation Sites and Senior Author Involvement.

Chronic/ acute	Site	Senior authors	No. of implants
Chronic	University of Pittsburgh	Collinger JL Schwartz AB Gaunt RA	2
	California Institute of Technology, Rancho Los Amigos National Rehabilitation Hospital (RLA)	Andersen RA	3
	Brown University, Massachusetts General Hospital	Donoghue JP Hochberg LR	12
	Stanford University	Henderson JM Shenoy KV	
	Case Western Reserve University	Kirsch RF Ajiboye AB	
	Ohio State University	Rezai AR Sharma G	1
	Total Chronic Implants		18
Acute	University of Utah Health Sciences Center	House PA Greger B	2
		Normann RA	6
	Columbia University Medical Center	Schevon CA	6
	Massachusetts General Hospital	Cash SS	3
		Truccolo W	7
	National Institute of Health	Zaghloul KA	6
	Total Acute Implants		30
Total Human Utah Array Implants			48

consists of patients implanted for epilepsy and other intraoperative opportunities where tissue would have been ablated, and patients with paralysis. The demographic of Utah array implants is dominated by acute cases, usually to study epilepsy, anesthesia, or cognition, memory, or language. A smaller subset of the cases is chronic implants, used to study brain machine interfaces for motor control of prosthesis and stimulation for sensory mapping. Of the 48 people implanted with the Utah array, 30 were implanted for less than 30 days and 18 people were implanted chronically for more than 30 days (8,9,251–295). We have identified all the senior authors and the sites, to our knowledge, involved in studies with human implants in Table 4.

The longest reported duration of a person with a Utah array implant is at least 1975 days (~5.4 years), shown in Fig. 4 and Table 5. S3, a participant in the BrainGate2 pilot clinical trial, was first implanted November 30, 2005, and while it has not been reported that her array has actually been explanted, it was documented that she completed her enrollment in the BrainGate2 clinical trial (259). Of the chronic cases, there was only one report of an explanted Utah array in the literature. Participant S1 at the University of Pittsburgh was implanted for 987 days and then explanted due to skin retraction around the pedestals. However, it was reported that there was no sign of infection. The only other mention of the safety of the Utah array implant was with participant EGS at California Institute of Technology. They reported that there was no device-related adverse events to occur throughout their study (278,296). Table 5 shows the breakdown of chronic patients across different studies and the lengths of reported implantation. The end of the reported duration of the implant does not mean that the Utah array has failed, however, just the

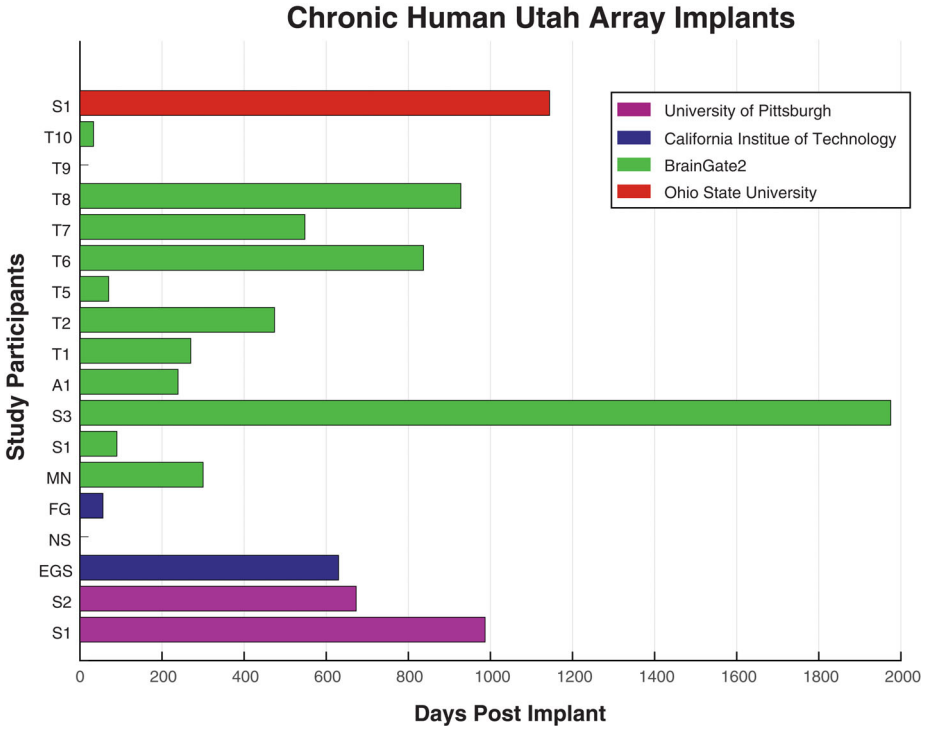

Figure 4. Length of chronic human implants reported in the literature across clinical study sites. [Color figure can be viewed at wileyonlinelibrary.com]

Table 5. Reported Duration of Chronic Human Implanted Utah Arrays.

Location	Participant	Implantation date	Reported duration*	Adverse events
University of Pittsburgh	S1	Feb 10, 2012	987	S1 explanted due to skin retraction around the pedestals, no sign of infection
	S2	–	673	
California Institute of Technology	EGS	–	630	
	NS	–	–	
	FG	–	56	
	S1	–	90	
	S3	Nov 30, 2005	1975	
	A1	Feb 2006	239	
	T1	–	270	
BrainGate2	T2	Jun 2011	474	
	T5	Aug 2016	70	T7 death unrelated to research
	T6	Dec 7, 2012	837	
	T7	Jul 30, 2013	548	
	T8	Dec 1, 2014	928	
	T9	–	–	
	T10	–	33	
	MN	Jun 2004	300	
Ohio State University	S1	–	1144	

*Reported duration is not equivalent to Utah array failure.

last reported published date for that participant. There have been a reported 9254 of total published implant days.

DISCUSSION

The safety surrounding neuromodulation technology is a critical question for both established and emerging systems. Hardware-related complications can result in potential injury to the patient, repeated surgical procedures, and reduced clinical efficacy. In this comprehensive, systematic review, we found that DBS had an incidence rate of 19.04% for total hardware-related complications. The most common adverse events were infection, followed by lead migration, lead fracture or failure, hemorrhage, skin erosion, IPG malfunction, and malfunction of the extension cable. The rates of complications reported here are similar to those found in prior studies and other notable systematic reviews (290,297–301). The most recent and closely related DBS review of hardware

complications by Jitkritsadakul et al., investigated the differences in incidence rates across indications for DBS. They used this information to identify patients more at risk based on their indication in order to inform them prior to surgery (290). While we have similar rates of complications, our review did not focus on specific indications. As a result, our search structure consisted of different keywords and more data bases. Therefore, we were able to include many more papers in our analyses, which offered more data points for a more comprehensive review. Another recent review of DBS complications done by the Neurostimulation Appropriateness Consensus Committee, developed recommendations to improve patient safety and reduce the risk of injury associated with neuromodulation devices (297). This review focused on DBS as a subset of many other neurostimulation therapies. Although we experienced slightly higher incidence rates than reported here, according to this review we are still within accepted rates of invasive brain procedures. It is also unclear how many patients were included in this review.

Using the information about DBS hardware complications, we are able to infer potential safety challenges that future intracranial, fully implanted and modular neuroprosthetic systems may face and begin the discussion on how to plan for and mitigate these risks when developing a clinical trial. We have identified the following adverse events to be potentially most salient to emerging systems: hemorrhage, infections, skin erosions, and malfunctions of the extension cable.

Hemorrhage

Based on this review, bleeding in the brain during or immediately after the surgery is the most critical adverse event that can risk the safety of the patient. In the DBS cases reporting ICH, the clot most often tracked along the lead and extended into the brain. Bleeding was not typically seen on the surface of the brain. The biggest difference between DBS and future neural implants is the type of electrode used. Since the Utah array is currently the only device used chronically in humans, and one of the arrays most likely to be incorporated into future modular devices, we will focus on this array. Although a DBS lead extends several centimeters into the brain, the Utah array is much shallower, inserting only 1.5 mm into the brain. Therefore, if most of the bleeds that occur in DBS are not on the surface, it is likely that the DBS lead is perturbing blood vessels deeper in the brain that the Utah array would miss (302). It is possible that the incidence rate of ICH experienced in DBS could be an overestimate of what we would see in future intracranial, modular neuroprosthetic systems. In the case of both DBS and the Utah array for future devices, additional action can be taken to help possibly reduce the incidence rate. Studies that experienced lower ICH rates attributed it to physicians' cautious and proper use of the equipment and insertion of electrodes, avoiding major vasculature on the brains' surface. Imaging can also be performed postsurgery as a means of proactive monitoring to detect any small or asymptomatic ICHs (303). Although bleeds can be very serious, they are expected, and protocols have been established to manage them.

Infection

Infections pose the highest risk for terminal explantation of the DBS entire system (20.7%). Reported infections were predominantly found at the site of the IPG, followed by the burr hole, and then the extension cable. Although in DBS there is only one IPG, in the case of the NNP and other future modular systems, there will be many more "IPGs" and extension cables routed throughout the body. This has the potential to increase the rate at which infections arise and possibly affect their ability to spread throughout the body. Infections in DBS are typically managed with antibiotics, or portions of the system may be explanted while antibiotics is administered and then successfully re-implanted. Re-implantation is the main treatment for infection in such systems. While they are categorized as serious adverse events, they are very common. Future modular systems may have the potential for increased incidence of infection due to the rise in the amount of modular devices that can be implanted in a single system. However, while some infections may be inevitable, it is important to note that this does not necessarily have to be a failure of the system. As seen in DBS, revision procedures occur frequently without ultimately ending the therapy. Understanding where the infections are most likely to occur and a potential time frame in which they occur more frequently relative to the initial surgery allows for management protocols to be developed within a clinical trial. Physicians can anticipate these complications and monitor patients more closely in areas more predisposed to infection as well as search for symptoms more deliberately time periods where infections typically spike. While this may not necessarily reduce the overall infections rate, being proactive may reduce the rate at which infection leads to system explant or a more sever complication. Studies have also been performed to investigate different antibiotics and the administration of them at different time points throughout the lifetime of the implant to reduce the infection rate (304–306).

Skin Erosion

Skin erosion, while occurring less frequently, commonly occurs with infection. When there is erosion or breakage of the skin the area becomes susceptible and leads to infection of the area. Since skin erosion was most likely to occur over the IPG, a modular system with multiple IPGs, as proposed with the NNP and potential future devices, may experience an increased incidence rate than reported in DBS. Knowing this we can begin to investigate surgical procedures for the best placement of these IPGs or modular devices throughout the body and how to implant them deeper as to reduce the risk of erosion. Similar to infection, cases of skin erosion are also categorized as serious, requiring a surgical revision. This may be treated with wound debridement but is most likely to lead to explantation of a portion or the whole system.

Extension Cable Malfunctions

Although there was a low incidence rate of extension cable malfunctions in comparison to the other adverse events in DBS, this is vital information. The addition of a wire to connect the Utah array to an implantable module is where most of the uncertainty lies with the safety of future intracranial, modular devices. Malfunctions of the extension cable usually involve Twiddler's syndrome or bowstringing, which can lead to fracture of the cable or displacement of the electrode. One of the biggest risks with future Utah array tethered devices is that tension on the extension cable has the potential to dislodge the implanted array. However, of all the reported extension cable malfunctions, none led to the displacement of a DBS electrode, likely due to anchoring at the burr hole. All complications were due to breakage of the cable, which were then replaced. Most of the complications with

the extension cable occur in the neck, however, with future Utah array tethered devices the module directly connected to the Utah array will be secured to the skull. This smaller device may decrease the risk for potential electrode array dislodgement.

Utah Array Safety and Longevity

Utah arrays have been implanted in substantially fewer individuals, for shorter duration, and the literature does not contain much about the safety of these implants as compared to DBS, which has a sufficiently large population to reveal rare safety events. Since there has been no publication to date that explicitly discusses the risks or adverse events that occur in chronic human implants, we systematically reviewed all the published literature to address this topic. We identified 48 individuals implanted with a Utah array and determined the duration of implantation at the time of the study. This represents a starting point for a safety dataset of all FDA monitored studies. Acute studies are more common and have been the dominant contributor to the population of subjects with Utah arrays. Although long-term effects are not observed in these subjects, observations from short-term studies help to estimate intracerebral hemorrhage, although not explicitly mentioned or discussed in any papers we reviewed. Infection typically prompts explantation of the array, so array longevity provides a lower bound on the period of time without serious infection or other adverse event. The mean number of days of Utah array implantation across all participants was 578. This underestimates implant time. With the exception of one paper, no study reported array explantation. In the absence of complication, participants typically remain implanted following the conclusion of the study.

Because DBS systems are clinically available and have been implanted in many patients, incidence rates of DBS adverse events serve as a risk profile benchmark for future Utah array modular systems. Understanding the potential risks and failure modes of a device and how many people must be observed to witness such risks could be useful information when designing a clinical trial. For example, we conducted a power analysis to estimate the number of patients implanted with the Utah array needed to see similar incidence rates as DBS. We found that it would take a very large amount of people within a clinical trial before we would begin to see complications with similar incidence rates as DBS systems. By contrast, if Utah array tethered devices introduced 5× the risk of DBS we would be able to see it much earlier and with fewer people (Table 6). Given the low incidence rate of infection in DBS, we would not have expected to see any complications in cases with as few as 18 chronically implanted Utah arrays. It is also notable that these Utah arrays were all percutaneous and would likely have a higher infection rate than a fully implanted system.

The large number of people needed to do a true safety study is far off. However, few individuals are required to demonstrate the efficacy of neuroprosthetic systems. Efficacy may therefore have to be established before safety studies can begin. Early feasibility human trials would be beneficial in not only moving the needle in technology surrounding the future of implantable intracortical devices, but also helping to increase the population of people with these devices for a comprehensive understanding of safety over time.

Study Limitations

This review focused primarily on the Utah array, using the existing intracranial DBS system as a benchmark for safety data of future implantable neuroprostheses systems that will employ the Utah array for brain-machine interface (BMI) applications. However, reviews of other existing intracranial neuromodulation devices such as the RNS system may add value as well. In addition, there is currently no standardized method for reporting adverse events related to DBS hardware or Utah array safety, thus this review is incomplete. There were some DBS articles that contained data on hardware-related complications that were excluded because either the information was too general (i.e., grouping infections and skin erosions and other skin complications together) or the data were per electrode lead and not per patient. Papers also generally lacked the time in which adverse events took place. In addition, papers discussing human research with the Utah array did not disclose any adverse events and some lacked important details such as the implantation date. Due to the lack of data reported in literature discussing human research using the Utah array, we determined in order to continue to establish a data base of safety data for future and emerging neuromodulation technologies we need to be gathering detailed information about the implantations during experiments such as implant and explant dates, detailed per patient adverse events, the time frame in which adverse events occurred, as well as the responsive action. Access to a detailed data base of adverse events involving intracranial, modular systems will not only influence the design of future devices, but also serve as a reliable reference for investigators seeking to successfully advance their device through the regulatory process toward a clinical trial.

As a result of the poor structure and overall lack of reported complications across the field, we focused on the hardware-related complications that could provide the most data in order to produce a reliable review and serve as a benchmark to infer the most about future intracranial, modular devices. We identified hemorrhage, infection, skin erosion, and other malfunctions; however, these are certainly not the only safety risks future devices have the potential to face. Safety of future devices cannot be fully assessed by looking at the incidence rate of these categories alone, yet this is a quantifiable starting point.

When implanting electrodes in the brain there is always a risk of neurologic damage or neurobehavioral effects experienced by the patient. Neurobehaviroal effects reported with DBS are most often linked to the stimulation, therefore not directly comparable

Table 6. Example Power Analysis.

Complication	Sample size needed to reject null			Power (1-β)	α
	1.5×	2×	5×		
Infection	602	167	15	0.80	0.05
Skin erosion	692	193	18	0.80	0.05
Hemorrhage	956	267	25	0.80	0.05
Extension cable malfunctions	1555	435	41	0.80	0.05

to the Utah array, which would be used for recording. However, these risks persist with the Utah array as well. Implanted Utah arrays are known to result in reactive tissue responses including inflammation, glial scarring, and neuronal death or migration near the site of the electrode, seen in the histological data (307–312). It is possible that this histological response could potentially result in functional deficits, however, because current chronic studies with these arrays include patients already with severe loss of motor functions, we are unable to measure any unintended damage to physiologic functions in these patients. There has been very little research done to investigate the potential motor deficits caused by the implantation of chronic intracortical electrodes in motor cortex. In a study done by Goss-Varley et al., it was shown that healthy rats implanted with chronic microelectrodes in the motor cortex resulted in deficits effecting fine motor function (313). Implanted animals performed the ladder task significantly slower with an increased number of paw slips than the non-implanted control animals. It was reported that while graphically significant, visually watching the animals yielded less conclusive results. Contrarily, many able-bodied rhesus macaques have been implanted for research and shown no signs of any motor deficits. This behavioral response has also been shown in studies investigating neuronal death from moderate traumatic brain injury and resection in rats and similarly in humans, where moderate motor deficits recovered over time or were unnoticeable (314–316). There are considerable complexities of the brain, therefore ultimately, safety questions will be best addressed in a sufficiently powered, prospective clinical trial. In the meantime, pilot studies will continue to contribute valuable data points over time by including implant and explant dates, the time frame of experiments as well as any physiologic and neurobehavioral effects.

CONCLUSION

We identify and quantitatively summarize the hardware-related complications of DBS that can be used to estimate potential safety risks of future modular, implantable neuroprosthetic systems. In addition, we collect longevity data for human Utah array implants. The evidence-based analysis serves as an important benchmark for investigators seeking safety data on intracranial, modular systems. As new devices are developed this information can be used to identify and assess potential hardware failures in advance. These complications can ultimately compromise the safety of the patient, therefore anticipating future risks allows physicians and engineers to develop specific surgical and risk mitigation protocols within their clinical trials. In addition, these safety data are essential to the FDA and should be included to develop a strong portfolio to the meet regulatory requirements and help progress toward clinical trials.

Authorship Statements

Autumn. J. Bullard, Cynthia A. Chestek, Parag G. Patil were responsible for creating the protocol for the literature search and inclusion criteria, analyzing and interpreting the data, and drafting the manuscript. Autumn. J. Bullard, Brianna C. Hutchison, and Jiseon Lee were responsible for reviewing abstracts and full-length papers for inclusion and data extraction. Autumn. J. Bullard, Brianna C. Hutchison, Jiseon Lee, Cynthia A. Chestek, Parag G. Patil were responsible for reviewing and approving the final manuscript. All authors approved the final version.

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COMMENTS

In the manuscript entitled: "Estimating Risk for Future Intracranial, Fully Implanted, Modular Neuroprosthetic Systems: A systematic review of hardware complications in clinical deep brain stimulation and experimental human intracortical arrays," the authors provide a detailed safety analysis of implantable devices. They conducted an evidence-based analysis of hardware complications for the most established clinical intracranial modular system, deep brain stimulation (DBS), as well as the most widely used intracranial human experimental system, the silicon-based (Utah) array. Overall, this is an important contribution to the field of neuromodulation and is of interest to readers of Neuromodulation: Technology at the Neural Interface. It is well researched and well written.

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In this work by Bullard et al., the critical role of hardware failure is examined for electrodes chronically implanted in the brain. The comprehensive literature review provides valuable insight for future device design, clinical and regulatory strategies.

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Comments not included in the Early View version of this paper.

