nature neuroscience

Supplementary information

https://doi.org/10.1038/s41593-025-01905-6

A streaming brain-to-voice neuroprosthesis to restore naturalistic communication

In the format provided by the authors and unedited

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Supplementary Information

Contents

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Supplementary notes

Note S1. The participant's residual articulatory capacity

While joining the clinical trial, the participant was evaluated by a speech-language pathologist (SLP), as outlined in the Methods (Participant) section. The SLP found that the participant's speech impairment results from weak articulatory muscles and an inability to maintain the necessary airflow. This difficulty in maintaining airflow stems from respiratory weakness and a lack of control over airflow regulation through her vocal cords, lips, and tongue. Additionally, the participant struggles to generate the pressure to produce sounds such as plosives, fricatives, and affricates. In a vocal assessment, she demonstrated limited control over her larynx, producing effortful, monotonous sounds and pitched higher than usual. These challenges lead to speech that is uncoordinated and unintelligible. From the resulting audio and video transcriptions of her speech attempts, the SLP measured her intelligibility to be 5% for the prompted words, 0% for the prompted sentences, and 0% for the open-ended responses.

Note S2. The participant's assistive-communication device

The participant uses a Tobii Dynavox, a commercially available assistive-communication tool, as her primary communication method. This system includes a computer, a monitor, a camera mounted on a mobile stand, and specialized glasses. The glasses feature a reflective marker that allows the camera to track head movements, enabling the user to navigate a cursor across a digital keyboard. Selecting items is achieved by "dwelling" on them, i.e., holding the cursor steady over the selection for about a second. This setup facilitates spelling out messages. An enhanced mode offers predictive text to improve typing speed, suggesting likely follow-up text based on the initial input. For instance, typing "Hel" might prompt a "Hello" suggestion. This mode also includes a text-to-speech feature, allowing users to communicate audibly using a chosen voice. To evaluate the typing speed of this system, a task was designed where the participant would type sentences spoken by a researcher, both with and without autocomplete. Eight sentences were chosen for this purpose. The typing speed was measured in words and characters per minute, excluding the time taken for capitalization or adding final punctuation. Results showed that without autocomplete, the participant's typing speed was 8.61 words per minute and 34.1 characters per minute. With autocomplete enabled, the speed increased to 14.2 words per minute and 56.4 characters per minute [1]. This resulted in speech synthesis latency of 23.2 ± 3.66 seconds. The participant primarily uses this mode in her daily life.

Supplementary methods

Method S1. Modeling

RNN-T loss

The recurrent neural network transducer (RNN-T) framework is a streamable sequence-to-sequence modeling framework designed to predict a target sequence from an input sequence where the target and the input are not temporally aligned [2]. The RNN-T is trained by maximizing the likelihood of target ($Y \subseteq \mathbb{R}^{U \times d}$) given input ($X \subseteq \mathbb{R}^{T \times D}$) while jointly finding the alignment (d and D are the sizes of input data and target data, respectively; At the same time the RNN-T can operate on arbitrary lengths of both input and target sequences, we set T and U to denote the lengths of input and target for simplicity.). The RNN-T consists of three main modules: a transcriber, a predictor, and a joiner. The transcriber and the predictor extract features from the input sequence $\mathbf{x} = (x_1, x_2, \ldots, x_T) \in X$, and the one-time-point shifted target sequence $\mathbf{y} = (\emptyset, y_1, y_2, \ldots, y_{U-1}) \in Y$, respectively, where $\emptyset$ is a blank token. Note that the predictor model is supposed to have a causal architecture that only allows information to flow forward in time (e.g., unidirectional RNN), while there is no architectural limitation on the transcriber.

Let $f_t \in f_1, f_2, \ldots, f_T$ be the t-th time-point of the transcriber output, and $g_u \in g_1, g_2, \ldots, g_U$ be the u-th time-point of the predictor output. Given the causal architecture of the predictor, g_u represents $\mathbf{y}_{1:u-1}$, and f_t represents $\mathbf{x}$ that can be further prescribed to be $\mathbf{x}_{1:t}$ by forcing the transcriber to be causal. The causal transcriber is a requirement for the streaming capability of RNN-T,

which enables inference without the need for future context. The joiner then combines f_t and g_u to represent $P(Y = y|f_t, g_u)$, which is denoted as $h_{t,u}[y]$. The inference (or emission) is made by choosing y that maximizes $h_{t,u}[y]$ at each input time point, t, where a beam search is commonly utilized to reduce the search space (see RNN-T beam search section).

As the input and target sequence are not aligned, multiple emissions (or alignments) patterns should be considered. For example, when predicting (y_1, y_2) from (x_1, x_2, x_3), both $(y_1, \emptyset, y_2)$ and $(\emptyset, y_1 y_2)$ mean the same output. The output of the joiner forms a $T \times U$ grid, on which the probability of alignment between $\mathbf{x}$ and $\mathbf{y}$ can be efficiently calculated. Let α be a possible alignment between $\mathbf{x}$ and $\mathbf{y}$, and $\mathcal{A}$ be the set of all possible alignments, $\alpha \in \mathcal{A}$. The probability of $\mathbf{y}$ given $\mathbf{x}$ is

$$P(\mathbf{y}|\mathbf{x}) = \sum_{\alpha \in \mathcal{A}} P(\alpha|\mathbf{x}, \mathbf{y}) P(\mathbf{y}|\mathbf{x}, \alpha) \tag{S1}$$

For simplicity, let $\alpha := P(\alpha|\mathbf{x}, \mathbf{y})$, and $\alpha_{t,u}$ represents alignments by the t and u time-points on the grid. To efficiently compute the summation, we compute $\alpha_{t,u}$ for every possible pair of t and u using

$$\alpha_{t,u} = \alpha_{t-1,u} h_{t-1,u}[\emptyset] + \alpha_{t,u-1} h_{t,u-1}[y_{u-1}]. \tag{S2}$$

Then, the $P(\mathbf{y}|\mathbf{x})$ can be simplified as $\alpha_{T,U} h_{T,U}[\emptyset]$. The loss function for training RNN-T is defined as the negative log of $P(\mathbf{y}|\mathbf{x})$, which is averaged in a batch sampled from the training dataset. We utilized PyTorch's RNNTLoss function to calculate the RNN-T loss efficiently.

RNN-T beam search

The beam search algorithm was used to predict output units from the RNN-T's joiner emissions. We adopted the algorithm from [2] as

Algorithm 1. The beam search algorithm searches for the optimal sequence of tokens by extending each of the hypotheses in the beam, B, while keeping the search space at each time point limited to the top K hypotheses. Since multiple emissions are allowed per time step, hypotheses per time step is flexible but must be less than or equal to M. At the end of the iterations within each time point; the beam is further truncated to the top J hypotheses that are carried over to the next time point. K is set as 5 for speech and 20 for text. J is set as 1 for speech (given that we cannot correct for speech that has already been synthesized) and 10 for text. M is set as 20 for both modalities. The argsort operation in Algorithm 1 denotes sorting the elements for the given term in descending order.

Algorithm 1 Beam Search Decoding

Parameter: K:= Beam width; J:= # of carry-over hypotheses; $\mathcal{Y}$:= vocab; M:= max tokens per time
Initialize: $B = \{\emptyset\}$; $P(\emptyset) = 1$
for $t = 1$ to T **do**
    $A = B$
    $B = \{\}$
    while $\max_{Y \in A} P(Y) >$ K-th highest hypothesis in B **do**
        $Y^* = \text{argmax}_{Y \in A} P(Y)$
        $A = A \setminus \{Y^*\}$
        $P(Y^*) = P(Y^*)P(\emptyset|Y, t)$
        $B = B \cup \{Y^*\}$
        $\mathcal{Y}^* = \text{argsort}_{w \in \mathcal{Y}} P(w|Y^*, t)$
        for i in $[0, M-1]$ **do**
            $P(Y^* + \mathcal{Y}^*_i) = P(Y^*)P(\mathcal{Y}^*_i|Y^*, t)$
            $A = A \cup \{Y^* + \mathcal{Y}^*_i\}$
        end for
    end while
    $B = B$ elements with top-J $P(Y)/|Y|$
end for

Bimodal pretraining

The predictors and joiners of the brain decoder were pre-trained with a large speech dataset, LibriSpeech, that has 960 hours of speech derived from English audiobooks [3]. As these modules cannot be trained independently, we trained the whole RNN-T with RNN-T loss on automatic speech recognition (ASR) tasks. The input was speech audio for both speech and text; the target was either subword BPE text tokens or discrete-speech units extracted from HuBERT. For speech, we trained a transducer model to predict the discrete-speech units from speech and used the RNN-T loss to optimize the parameters. The architecture of the transcriber consisted of two convolutional layers with 512 hidden units, kernel size of 3, and stride of 2, followed by a unidirectional LSTM with three layers of 512 hidden units. The joiner and predictor have the same architecture as described in the Methods section in the main text. Before being fed to the transducer, the Mel spectrogram with 80 dimensions is extracted from a 16 kHz waveform with a hop length of 160, resulting in a spectrogram sampled at 100 Hz. The transducer is trained with Adam optimizer [4] with a learning rate of 1e$-$3, $\beta_1 = 0.9$, and $\beta_2 = 0.999$, updated for 200K steps using a batch size of 20. For text, we retrieved the checkpoint provided by PyTorch[1], which implemented the RNN-T approach for ASR proposed by [5]. For both modalities, the predictors were employed in the streaming decoding and frozen while training the neural transducer. Also, the trained joiner weights were used to initialize the joiner weights in the ECoG transducer.

[1] https://pytorch.org/audio/main/tutorials/online_asr_tutorial.html

Neural-decoder training details

For the 1024-word-General model, initial training used data from sessions collected up to two days before the real-time experiments. Subsequently, we included all sessions, including those from one day before the final experiments. The training utilized the Adam optimizer, with settings at a learning rate of 1e$-$4, $\beta_1 = 0.9$, $\beta_2 = 0.999$, and a batch size of 64. Initially, the model underwent 745 epochs of training, and after adding additional data, it was updated for an additional 265 epochs. The training was performed on three NVIDIA RTX A6000 GPUs, and real-time inference was performed on a single NVIDIA Tesla V100 GPU.

Data augmentation was applied to enhance model robustness and generalization. Following the methodology described by [1], we implemented a random channel drop, applying it with a 0.75 probability to each training sample. Each channel (HGA and LFS) might be dropped within this framework, with chances uniformly drawn from the range [0.3, 0.6]. Additionally, a temporal window was selected from each training sample, with its size uniformly chosen between 70% and 90% of the sample's original length.

For the 50-phrase-AAC model, the CNN has one convolutional layer with 512 hidden units, a kernel size of 4, and a stride of 4. A unidirectional LSTM replaces the GRU for the RNN component and is comprised of 3 layers with 512 hidden units, each with a dropout rate of 0.4. The modality-specific linear layers used before combining language model outputs were not included. The channel drop probability was set at 0.5, with a fixed drop rate of 0.2 per channel. The temporal jitter window for this model was set between 90% and 100% of the sample length. We used a batch size of 32 and trained the model for 100 epochs on a single NVIDIA RTX A6000 GPU.

The speech synthesizer did not employ duration prediction. For all brain-decoding models, we synthesized training audio from the text prompts using VITS [6].[2] We used a single speaker model trained on LJSpeech dataset [7]. The synthesized audio was then used to extract discrete speech units using HuBERT [8]. For acoustic-speech units, we used 100 units extracted from the sixth layer of the HuBERT transformer encoder 38. We removed adjacent acoustic-speech units repeats in a given sequence (e.g., acoustic-speech unit sequence [71, 14, 14, 76, 76, 62, . . .] would become [71, 14, 76, 62, . . .]), resulting in an effective acoustic-speech unit sampling rate of 39 Hz during training. This decouples the durations of the acoustic-speech units from their contents and allows for learning a better acoustic-speech unit language model. The acoustic-speech unit durations are restored to 50 Hz by a acoustic-speech unit duration predictor in our speech synthesis pipeline.

Synthesizer training

We trained and designed a speech synthesizer to generate personalized, intelligible speech from the predicted discrete-speech units. The speech synthesizer consists of a duration predictor and a discrete-speech-unit vocoder. The duration predictor was trained to predict the duration of de-duplicated units to restore the original speech-unit sampling rate (50 Hz). The discrete-speech-unit vocoder was implemented as HiFi-CAR, a generative adversarial network model that generates a high-fidelity speech waveform from articulatory or acoustic speech features [9]. For training the speech synthesizer, we used a sizeable single-speaker speech corpus

[2]We used the out-of-box model provided in https://github.com/jaywalnut310/vits

(LJSpeech [7]; 20.3 hours for training). We converted every clip in LJSpeech to the participant's voice to make a personalized vocoder that generates speech in the participant's pre-injury voice. We used a short 3-second far-field voice clip provided by the participant, which was recorded before her loss of speech ability. The participant's voice clip was first denoised and enhanced by Adobe Enhancer and then prompted YourTTS to convert every clip in the LJSpeech corpus into personalized audio [10].

The HiFi-CAR is an autoregressive extension of HiFi-GAN [9, 11, 12]. The HiFi-GAN generator was implemented as 1-dimensional (1D) convolutional neural networks (CNNs) that consisted of an input 1D convolution followed by four upsampling modules and an output layer. Each upsampling module contains a Leaky ReLU (0.1 negative slope), a ConvTranspose1D for upsampling, and a Multi-Receptive Field Fusion (MRF)[11]. The MRF was implemented with residual convolutional layers, each consisting of a Leaky ReLU and a Conv1D with various sizes of the receptive field that was configured by kernel size of [3, 7, 11] and dilation of [1, 3, 5] resulting nine combinations in total. The upsampling modules had [8, 5, 4, 2] upsampling factors times respectively. The number of hidden unit channels was halved by each upsampling module, implemented in the ConvTranspose1d layer within the module, which had kernel size of [16, 10, 8, 4], respectively, for four modules. For the input convolution, we used kernel size 7, output channel of 255, with a padding of 255. For the output convolution, we used kernel size 7, out channel of 1, with a padding of 255. The final output was fed into another Leaky ReLU (0.1 negative slope) and an output convolution. Before feeding into the input layer, the discrete-speech units were converted to 768-dim learnable embedding using an embedding lookup dictionary.

The HiFi-CAR extension added conditioning inputs from previously generated wave samples, which was demonstrated to improve the quality of synthesis [9, 12]. This assumes a streaming generation scenario, where the waveform is generated chunk-by-chunk progressively. The previous 512 predicted audio samples were fed into an audio encoder (32 ms, given the 16K audio sampling rate). The audio encoder consisted of four fully connected layers with 512 hidden units and leaky ReLU (0.1 negative slope) activation, followed by an output linear layer with 512 output channels. The output of the audio encoder was concatenated to the discrete-speech-unit embedding before passing this to the input layer of the HiFi-GAN. The vocoder was trained with the generative adversarial neural networks (GAN) paradigm, a generative modeling framework where the generator is trained to fool a jointly trained discriminator that detects real/fake data [13]. To achieve high-fidelity waveform synthesis, the HiFi-GAN utilized two types of discriminators: a multi-period discriminator (MPD) and a multi-scale discriminator (MSD) [9, 11]. The MPD was designed to discriminate between real/fake waveforms chunked with different periods, which consisted of CNN discriminators. For each discriminator, the input waveform with length T was reshaped to (P, T/P), where P is the period specified in each model in the MPD. The discriminator was implemented with 2D CNN with five residual blocks with downsampling factors of [3, 3, 3, 3, 1], respectively, where the kernel size was set as (5, 3) for all layers except the final output convolution that had a kernel size of (2,1). The final output was summed to represent an indicator of the genuinity of the input sample. We used five different periods of [2, 3, 5, 7, 11], and the discriminator for each period operated independently. On the other hand, the MSD was designed to operate on the multiple scales of the input waveform,

which was packaged with multiple CNN discriminators with different scale configurations. Each CNN discriminator with a specified scale, S, processed a waveform downsampled by the factor of S by averaging every S time-point chunk. Each discriminator in the MSD was implemented with 1D CNN with an input layer with output channels of 128 and kernel size of 15; 5 convolutional layers with channels of 128, kernel size of 41, groups of 4, and a stride of [2, 2, 4, 4, 1] respectively; and an output layer with two convolutional layers with output channels of 256, kernel size of [5, 3] for each layer, and stride of 1. Then, the final output was summed up as an indicator of real/fake. We used three different scales of [1, 2, 4], and the discriminator for each scale operated independently. The weights in the MPD and MSD were normalized to have a unit norm.

The adversarial loss was defined as a min-max game between the generator and the discriminator [13]. The discriminator, D, was trained to discern generated audio from the ground truth y, and the generator, G, was trained to fool the discriminator (x is the corresponding input feature of y, sg means stop-gradient and thus no weight update).

$$L_A = -E[-D(G_{sg}(x) + D(y)] + E[D_{sg}(G(x))]$$

Here, we used Mean Squared Error between the discriminator outputs and 1 for D, following [11].

For accurate synthesis, a reconstruction loss, L_M, was calculated between ground truth and generated waveform on an acoustic space represented by Mel spectrogram, minimizing the L1 distance. To enhance fidelity, a feature matching loss, L_F, was also adopted, which was designed to minimize the L1 distance of penultimate features in the discriminators between the ground truth and the

synthesized waveform. This loss was calculated and summed up in all layers of the MPD and MSD. The final loss, L_G, is a weighted sum of discriminator loss and feature matching loss.

$$L_G = L_M + 45 * (2 * L_F + L_A)$$

Following [14]; the duration predictor was implemented as two 1D CNN layers with 384 hidden units, kernel size of 3, followed by ReLU function, layer normalization, and dropout of 0.5. The outputs of CNNs are then passed to a final linear projection layer to infer the duration of each unit in the inputs. For the duration output of the generator, which is in log space, we first convert the ground truth duration into log space and then compute the MSE loss between the two.

During inference, the duration predictor predicted the duration of each input discrete speech unit. Then, each unit was de-duplicated by the predicted duration to restore the 50 Hz sampling rate. The output of the duration was then multiplied by a constant factor of 7 to simulate the participant's slow rate of attempted speech and minimize WER. Finally, the HiFi-CAR generator synthesized audio from the expanded units. The duration predictor was independently trained from the HiFi-CAR.

We used Adam as the optimizer for the generator with $\beta = (0.5, 0.9)$ and no weight decay. We used MultiStepLR as the learning rate scheduler, decreasing by a factor of 2 for every milestone of 80k, 160k, 320k, and 400k iterations. We used a batch size of 32 for each iteration, and a sample in the batch had 260 ms audio (8.32 s per batch). The best model is selected based on the lowest L_M evaluated on held-out validation data (1.23 hours of data). When tested on held-out 2.41 hours of test data, the synthesized speech was highly intelligible, and Whisper ASR ("openai/whisper_large_v2") was

applied to the audio result. To enhance the robustness of the model, the CNN weights were initialized with a pretrained HiFi-GAN trained on 550 hours of audiobook data (LibriTTS)[15].

Incremental text-to-speech

For the design of the incremental text-to-speech (TTS) pipeline, we used the VITS TTS model trained on the single-speaker LJSpeech dataset [7]. Ideally, one would synthesize a single word at a time. However, most TTS models are trained on sentence-level corpora, and thus, single-word generations can often sound degraded or unintelligible. To work around this, we passed the current, complete predicted phrase into VITS for each word-level text generation during streaming text decoding. Since VITS explicitly models the expected duration of each word in the output sentence, we use their duration predictor to identify and segment only the new part of the phrase if at least one new word has been generated. For example, within a trial, if the previous decoded phrase was "How are,". The new update corresponds to "How are you," or "How are you today,", we synthesize these complete phrases and then segment and playback "you," or "you today," respectively.

To match the output TTS with the preferred speaking rate of the participant, we adjusted the VITS length scaling factor to 1.61. This factor scales the modeled duration predictors by a constant value and hence can be used to adjust the speed of the waveform naturally. We asked the participant to listen to 10 VITS TTS-generated waveforms with even-spaced length scaling factors from 0.50 to 3.00 to find this parameter. We asked her to select which waveform most represents her preferred speaking rate during silently attempted speech (miming) with pauses. The scaling factor chosen (1.61) was

then used during inference.

Method S2. Evaluation

Perceptual assessment

We conducted perceptual evaluations through crowdsourcing on Amazon Mechanical Turk, with each experiment from the real-time 1024-word General and 50-phrase AAC test sets reviewed by 12 participants, except for 26 trials reviewed by only 11 workers and five trials reviewed by only ten workers. Each review involved listening to the decoded audio waveform, after which participants were asked to transcribe what they heard. To prevent the workers' time from being spent listening to pre-speech silence, we identified the onsets and offsets of the waveform (see Methods). We then segmented the waveform to include only the active portions before uploading it for perceptual evaluations. The detailed instructions, identical to those in our previous work [1], were as follows:

> Please listen to the audio and write down what you hear. Many of the clips may be difficult to hear. If this is the case, write whatever words you are able to make out, even if it does not form a complete expression. If you are not sure about a word, please only include your guess in your transcription if you feel that you are over 50% confident that your guess is correct. Otherwise, exclude the guess from your transcription. If you cannot make out any words, leave the entry blank. You may listen as many times as needed.

We used the transcript corresponding to the median worker character error rate as the predicted transcript for that trial. Before computing metrics, we removed punctuation, lowercased the transcripts, and removed the terms "N/A" or "Inaudible".

Automatic speech recognition assessment

We use a state-of-the-art large automatic speech recognition (ASR) model known as Whisper [16] to transcribe speech-synthesis results in the manuscript. We downloaded the "openai/whisper-large-v2" checkpoint from Hugging Face and passed the decoded audio waveforms at 16 kHz into the model to obtain a transcript. We observed that for a tiny percentage of the transcripts, typically from the chance distributions, Whisper outputs an excessively long transcript either in terms of the number of words or the number of characters, with a (truncated) example being:

theyressssssssssssssssssssssssssssssssssssssssssssssssssssssssssssss

For this reason, we implemented a rule-based modification of the output transcripts. Specifically, we truncated all transcripts to be a maximum of 9 words and each word to have a maximum of two repeated characters. In this example, the output transcript would be truncated to "theyress". This allows for a better assessment of the transcript quality as decoded from neural data as opposed to artifactual generations from the ASR model. For analyses aimed at generalization across modalities, this 9-word constraint was removed because the target sentences were much longer than nine words for these analyses.

Method S3. Multimodality

Dataset processing

The electrocorticography (ECoG) data for the multimodal generalization analysis was obtained from our published dataset from our current participant [1]. The neural signal processing in [1] was identical to the neural signal processing used in this work. We used their speech-synthesis test set, which tested on 200 unseen 1024-word-General trials. [1] used a model which, at the time, required several days to converge, so they only used 6,449 1024-word-General trials during training of the speech-synthesizer models (approximately $\frac{2}{3}$ of the total data collected in the study). For this work, we used all available unseen 1024-word-General sentences they provided (excluding sentences from the same session as the test session), using 9,368 training sentences. We randomly selected 100 sentences from these training sentences and held them for use as a validation set.

The microelectrode array (MEA) data was obtained from the competition dataset introduced in [17] and released at [18]. It contains data collected in both (attempted) vocalized and silent speech modes from a person with paralysis. This dataset consists of a total of 9680 samples and has a provided split of 8800 training samples and 880 test samples. The utterances in this dataset were from the open-vocabulary Switchboard and OpenWebText corpora and a fixed 50-phrase set that was only used for training. To evaluate generalization on the silent speech task, we only used the silent speech subset of the provided test set for evaluation, and all the other samples were moved to the training dataset. We also removed randomly selected 100 silent speech samples from the training set to form a validation set. This resulted in 9420 training

samples (7560 vocalized and 1860 silent), 100 validation samples (all silent), and 160 test samples (all silent). The training features used for this task were the spike band power and threshold crossing counts, with a threshold of -3.5 x RMS, from 128 electrodes placed in the ventral premotor cortex (area 6v) as computed and filtered in [17]. These features were then z-scored within blocks to account for drifts in feature means across blocks.

The electromyography (EMG) data was obtained from [19] that proposed an EMG-based "voicing silent speech" paradigm. The EMG captured surface articulatory information collected from a participant in two different tasks: voiced and silent [20]. This dataset contains 8653 open-vocabulary samples from public domain books. All of the silent samples were parallel voiced samples collected on the same utterances; there were also additional voiced samples that did not have parallel silent recordings. Unlike [19, 21, 22], we did not attempt to time-warp the voiced and silent sequences or use the voiced audio as the ground truth when training the model. Instead, we generated ground truth audio from the text transcripts provided in the dataset; this procedure was consistent with the ECoG and MEA modalities and ensured that the model did not rely on any aligned ground truth speech. Additional filtering and processing were required to ensure the quality of this generated audio. We removed 19 samples because the utterances had no alphanumeric characters (e.g., "* * * * *" or ".") and removed an additional 246 samples which contained ambiguous words that began or ended with apostrophes (e.g., 'eat or ha'). The utterance texts were cleaned up for the remaining samples without changing their content. For instance, numbers and Roman numerals were converted into word form, and currency amounts were reformatted (e.g., $12 would

become "twelve dollars"). To split the data into training, validation, and test sets, we began with the data splits provided in [19], which had 200 validation samples and 100 test samples. After applying the utterance filtering described above and removing duplicated samples, our validation set had 196 validation samples and 98 test samples, all containing silent speech. We removed the parallel voiced samples from the remaining data corresponding to the samples in the validation and test sets, leaving 7800 training samples (6529 voiced, 1271 silent). The features, which consisted of eight electrodes sampled at 1000 Hz, had the following signal processing steps applied: band-stop filters at harmonics of 60 Hz, a third-order high-pass Butterworth filter at 2 Hz, a subsampling from 1000 Hz to 689.06 Hz, a rescaling to unit values of 20 µV, and a soft de-spiking with a scaled hyperbolic tangent function by [22]. We removed all training and validation utterances with input EMG lengths over 20000 during training due to memory constraints. We did not apply this length limit to filter the test set.

RNN-T training procedure

For the ECoG transcriber, all training and model hyper-parameters were the same as those used for real-time streaming. For other modalities, we designed modality-specific transcribers and used the joiners and predictors in the same way as for real-time streaming. For the streaming MEA transcriber, we used the same Gaussian smoothing unfold operation as in [17]. We chose a size six kernel and a stride of 2 to unfold the input neural features that increased the input dimensionality from 256 to 1536. Note that the session layer proposed in [17] was not included for streaming as we found the session layer harmed streaming performance. After the unfolding, we

used a linear projection followed by a dropout of 0.2 to project from 1536 to 512 dimensions, which was the input dimensionality for an RNN. For this, we chose a 3-layer unidirectional GRU followed by a 1D CNN with 512 input channels, 512 output channels, kernel size of 3, and stride of 2. We followed this with a linear layer followed by a dropout of 0.2 and a second linear layer with 512 units to output the final encoding outputs with 1024 units. We chose 0.7 and 0.3 as the weights of the discrete-speech-unit RNN-T loss and text-encoding RNN-T loss, respectively.

For the full-context MEA transcriber, we added back the same session layer as in [17] and changed the GRU to be bidirectional. We also adjusted the 1D CNN after the BiGRU to have 1024 input channels, 1024 output channels, a kernel size of 3, and a stride of 2. For all linear layers after the 1D CNN, we used an input and output unit dimensionality of 1024. Everything else was kept the same as the streaming MEA transcriber.

For the streaming EMG transcriber, we used four ResBlocks following the implementation in [22], with a hidden dimension 1024 for all of them and kernel size parameter of [1, 2, 2, 2]. This is followed by a linear projection and a dropout of 0.2 to project from 1024 to 768 dimensions. The output is fed into a 4-layer unidirectional GRU with 768 hidden dimensions. The GRU is then followed by a 1D CNN with 768 input channels, 768 output channels, a kernel size of 12, and a stride of 8. We followed this with a linear layer, a dropout of 0.2, and a second linear layer with 768 units. The second linear layer has an output unit of 1024. We chose 0.7 and 0.3 as the weights of the discrete-speech-unit RNN-T loss and text-encoding RNN-T loss, respectively.

We found that unidirectional GRUs perform better than BiGRUs offline for the full-context EMG transcriber. We used 3 Resblocks,

each consisting of a 1D CNN and batchnorm1D with residual connection. We used ReLU as the activation function after the residual connection. For the three 1D CNN modules, we chose kernel sizes of [7, 7, 2], strides of [4, 4, 2], and output channels of [512, 512, 512], respectively. The first 1D CNN has an input channel equal to the number of channels in EMG, which is 8. The 1D CNN modules were followed by a linear projection and a dropout of 0.2 to project from 512 to 512 dimensions. The output is fed into a 3-layer unidirectional GRU with a hidden dimension of 512. We followed this with a linear layer followed by a dropout of 0.2 and a second linear layer with 512 units. The second linear layer has an output units of 1024. We chose an equal weight of 1.0 and 1.0 for the discrete-speech-unit RNN-T loss and text-encoding RNN-T loss, respectively.

For all three models, we used identical beam search parameters that we used for real-time 1024-word-General beam search. For the RNN-T full-context experiments, the streaming buffer was disabled, and for ECoG and MEA, the neural encoder was changed to be bidirectional.

CTC Training procedure

Given an input sequence $X_n = (x_1, x_2, \ldots, x_T) \in X$ and an output sequence $Y_n = (y_1, y_2, \ldots, y_U) \in Y$, the Connectionist Temporal Classification (CTC) loss assumes a monotonic alignment between the two sequences. It requires $U \leq T$ where U is the length of the output sequence and T is the length of the input sequences. Denote α_t as one possible alignment between X_n and Y_n at time step t, and let A be the set of all possible alignments between X_n and Y_n. The standard CTC loss, as defined in [23], is the negative log-likelihood of

the sum of the probabilities of all possible alignments between X_n and Y_n, marginalized over the set of valid alignments:

$$L_{CTC} = -\log P(Y_n|X_n)$$
$$= -\log \sum_{\alpha \in A} \prod_{t=1}^{T} P(\alpha_t|X_n)$$

The CTC loss assumes conditional independence, where each output y_u is conditionally independent of the other outputs given the input sequence X_n. For text decoding, this assumption necessitates a language model to provide contexts for decoding sensible texts, such as "he ate an apple" instead of "ee eight an app."

Using the CTC loss, we trained a CNN-Transformer with two output heads for silent speech synthesis and text-decoding from electrocorticography (ECoG), microelectrode arrays (MEAs), and electromyography (EMG) input features. For all three datatypes – ECoG, MEA, and EMG – the core processing architecture involves initial signal modification followed by the application of a transformer model. We used Adam as the optimizer for all models with beta (0.5, 0.9), the learning rate as 0.0001, and 0.0 weight decay. We used MultiStepLR as the scheduler with gamma as 0.5. A CTC beam search was used to find the most likely hypotheses from the CTC emissions matrix, but no external language model was applied.

For ECoG, we first passed the input through a 1D CNN with an input channel of 506, an output channel of 1024, a kernel size 6, and a stride of 6. This convolution is followed by a linear layer that projects the channel dimension from 1024 to 1024 units. After the linear layer, we used a 6-layer, 8-head Transformer with a 1024 hidden dimension, a 3072 feedforward dimension, 0.2 dropout rate, and a relative-positional embedding that utilizes a relative positional distance of 100. The transformer's output was divided into two

heads, one for speech and the other for text. The speech head consisted of a ConvTranspose1D with an input channel of 1024, an output channel of 1024, a kernel size 6, and a stride of 6. This was followed by a linear projection layer that reduced the channel from 1024 dimensions to 101 dimensions and a final LogSoftmax layer for converting the output at each time step into a log probability distribution. The text head consisted of a linear projection layer that reduced the channel from 1024 dimensions to 41, followed by a LogSoftmax layer. We used the CTC loss function implemented by PyTorch, setting the "zero_infinity" parameter to "true." The blank token index for the speech output was 100, while the text output was 0. The final loss was a weighted sum of the CTC losses for speech and text outputs, with weights of [0.8, 0.2], respectively. For this model, we set the milestones for the multi-step learning rate scheduler to [8000, 15000], where the learning rate was halved every milestone, and trained for a maximum of 20000 steps, where each step represents one forward pass and back-propagation of one batch of data with a batch size of 16. We evaluated the validation set every 100 steps and selected the final model based on the lowest validation loss.

For the MEA processing, we initially subjected the input to the same Gaussian smoothing, session layer, and unfold operation as in [17]. This output was passed through another linear projection layer, reducing the channel dimension from 1536 to 1024. Following this, a 6-layer 8-head Transformer architecture was utilized, featuring a 1024 hidden dimension, a 3072 feedforward dimension, a dropout rate of 0.2, and relative-positional embedding utilizing a distance 100. The transformer's output then diverged into two distinct pathways: one for speech and another for text. The speech pathway utilized a ConvTranspose1D operation (input and output channels of 1024,

kernel size of 6, and stride of 2), followed by a linear projection layer that reduces the dimensionality from 1024 to 101 and concluded with a LogSoftmax layer for generating categorical log probability distributions per time step. The text pathway employed a 1D CNN (input and output channels of 1024, kernel size of 2, stride of 2), followed by a dimension-reducing linear projection layer and a LogSoftmax layer. We use the CTC loss function from PyTorch for loss calculation, with the "zero_infinity" parameter enabled to handle padding. The blank identifiers were set to 100 for speech and 0 for text outputs. The final model loss was a weighted combination of the CTC losses for speech and text, with weights of 0.6 and 0.4, respectively. The learning rate was halved after 5000 steps, and the model was trained with 10000 steps with a batch size of 16. While training, the model was evaluated every 100 steps on the validation set. After the training, the model checkpoint with the lowest validation loss was selected.

For the EMG, the model was implemented with CNN feature extractor and Transformer encoder [22]. The CNN had 4 Residual Blocks with 768 hidden dims, kernel size of 3, and downsampling strides with [1, 2, 2, 2], respectively. The Transformer encoder had six layers of an 8-head self-attention network followed by a feedforward layer with 3072 hidden units and a 0.2 dropout rate. The input features were concatenated with relative-positional embeddings. The transformer outputs were then fed into two separate branches: one for speech and one for text. Each branch consisted of a ConvTranspose1D to upsample the input by the factor of 2, followed by a linear classifier. The log softmax was applied to infer categorical log probability distributions at each time step for each modality. The loss computation uses the CTC loss function from PyTorch's

functionals with "zero_infinity" set to true. The blank identifiers for speech and text outputs are 100 and 0, respectively. The final model loss is the weighted sum of the CTC losses for speech and text, with weights [0.9, 0.1]. The learning rate was halved every after 6000, 10000, and 15000 steps, and the model was trained with 20000 steps with a batch size of 4. While training, the model was evaluated every 500 steps on the validation set. After the training, the model checkpoint with the lowest validation loss was selected. During training and validation, utterances with EMG lengths above 20000 are excluded; however, all utterances are retained during testing, regardless of EMG length.

Supplementary figures

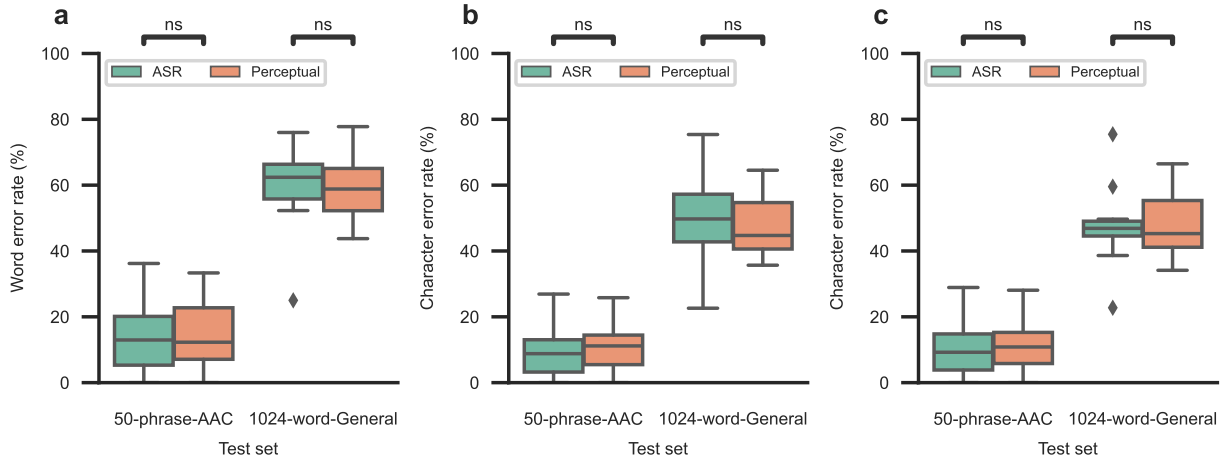

Figure S1. Automatic speech recognition is suitable for speech-BCI evaluation. Real-time decoding performance of speech synthesis using predicted transcripts gathered from perceptual evaluations or automatic speech recognition using the Whisper speech transcription model [16] (Method S3). **a.** Phoneme error rates. **b.** Word error rates. **c.** Character error rates. **a-c.** Performances between ASR and perceptual transcripts were not significantly different, suggesting automatic speech recognition is now ready for use in speech-BCI evaluation ($ns > .05$ for all metrics, Two-tailed Wilcoxon signed-rank test with 6-way Holm-Bonferonni Correction for multiple comparisons; Statistics compare $n = 10$ total pseudo-blocks; see Supplementary Table S1. P=1.0 for all comparisons). Using speech recognition on the 50-phrase-AAC set, we observed a median PER of 9.23% (99% CI [3.74, 16.4]). Median WER was 12.9% (99% CI [5.26, 25.0]), and median CER was 8.80% (99% CI [3.13, 14.3]). For the 1024-word-General set, we observed a median PER of 49.9% (99% CI [42.1, 61.6]). Median WER was 62.4% (99% CI [53.6, 75.6]), and median CER was 48.8% (99% CI [40.2, 61.5]).

Supplementary tables

Supplementary Table S1. Comparisons for real-time text-to-speech decoding.

Dataset	Metric	Comparison 1	Comparison 2	Statistic	Corrected P-value
1024-word-General	WER	Speech	Chance (speech)	1.842e+04	1.172e-02
1024-word-General	WER	Text	Chance (text)	1.842e+04	1.172e-02
1024-word-General	CER	Speech	Chance (speech)	1.842e+04	1.172e-02
1024-word-General	CER	Text	Chance (text)	1.842e+04	1.172e-02
1024-word-General	PER	Speech	Chance (speech)	1.842e+04	1.172e-02
1024-word-General	PER	Text	Chance (text)	1.842e+04	1.172e-02

Each comparison is a two-sided Wilcoxon signed-rank test between n=10 pseudoblocks for the 1024-word-General set. 6-way Holm-Bonferroni correction for multiple comparisons applied.

Supplementary Table S2. Comparisons for real-time direct speech decoding.

Dataset	Metric	Comparison 1	Comparison 2	Statistic	Corrected P-value
50-phrase-AAC	PER	Speech	Chance (speech)	1.842e+04	3.662e-04
50-phrase-AAC	PER	Text	Chance (text)	1.842e+04	3.662e-04
50-phrase-AAC	WER	Speech	Chance (speech)	1.842e+04	3.662e-04
50-phrase-AAC	WER	Text	Chance (text)	1.842e+04	3.662e-04
50-phrase-AAC	CER	Speech	Chance (speech)	1.842e+04	3.662e-04
50-phrase-AAC	CER	Text	Chance (text)	1.842e+04	3.662e-04
1024-word-General	PER	Speech	Chance (speech)	1.842e+04	1.172e-02
1024-word-General	PER	Text	Chance (text)	1.842e+04	1.172e-02
1024-word-General	WER	Speech	Chance (speech)	1.842e+04	1.172e-02
1024-word-General	WER	Text	Chance (text)	1.842e+04	1.172e-02
1024-word-General	CER	Speech	Chance (speech)	1.842e+04	1.172e-02
1024-word-General	CER	Text	Chance (text)	1.842e+04	1.172e-02

Each comparison is a two-sided Wilcoxon signed-rank test between n=15 pseudo-blocks for 50-phrase-AAC and n=10 pseudoblocks for 1024-word-General. 6-way Holm-Bonferroni correction for multiple comparisons was used for each dataset.

Supplementary Table S3. Comparisons for real-time decoding speed.

Dataset	Metric	Comparison 1	Comparison 2	Statistic	P-value
50-phrase-AAC	WPM	Streaming	Metzger '23	1.842e+04	1.023e-43
1024-word-General	WPM	Streaming	Metzger '23	1.842e+04	1.499e-32

Each comparison is a two-sided Wilcoxon signed-rank test between n=15 pseudo-blocks for 50-phrase-AAC and n=10 pseudoblocks for 1024-word-General.

Supplementary Table S4. Comparisons for long-form speech-synthesis and text-decoding.

Dataset	Metric	Comparison 1	Comparison 2	Statistic	Corrected P-value
1024-word-General	PER	Speech	Chance	0.000e+00	1.156e-164
1024-word-General	PER	Text	Chance	0.000e+00	1.156e-164
1024-word-General	WER	Speech	Chance	0.000e+00	1.156e-164
1024-word-General	WER	Text	Chance	0.000e+00	1.156e-164
1024-word-General	CER	Speech	Chance	0.000e+00	1.156e-164
1024-word-General	CER	Text	Chance	0.000e+00	1.156e-164

Each comparison is a two-sided Wilcoxon signed-rank test between n=1000 bootstrapped median metrics for the 1024-word-General set. 3-way Holm-Bonferroni correction for multiple comparisons applied.

Supplementary Table S5. Comparisons for modality generalization.

Dataset	Metric	Comparison 1	Comparison 2	Statistic	Corrected P-value
ECoG	PER	Streaming RNN-T	Chance	0.000e+00	1.717e-05
ECoG	PER	Full-context RNN-T	Chance	0.000e+00	1.717e-05
ECoG	PER	Full-context CTC	Chance	0.000e+00	1.717e-05
ECoG	WER	Streaming RNN-T	Chance	0.000e+00	1.717e-05
ECoG	WER	Full-context RNN-T	Chance	0.000e+00	1.717e-05
ECoG	WER	Full-context CTC	Chance	0.000e+00	1.717e-05
ECoG	CER	Streaming RNN-T	Chance	0.000e+00	1.171e-03
ECoG	CER	Full-context RNN-T	Chance	0.000e+00	1.171e-03
ECoG	CER	Full-context CTC	Chance	0.000e+00	1.717e-05
MEA	PER	Streaming RNN-T	Chance	0.000e+00	2.747e-04
MEA	PER	Full-context RNN-T	Chance	0.000e+00	2.747e-04
MEA	PER	Full-context CTC	Chance	0.000e+00	2.747e-04
MEA	WER	Streaming RNN-T	Chance	0.000e+00	2.747e-04
MEA	WER	Full-context RNN-T	Chance	0.000e+00	2.747e-04
MEA	WER	Full-context CTC	Chance	0.000e+00	2.747e-04
MEA	CER	Streaming RNN-T	Chance	0.000e+00	2.747e-04
MEA	CER	Full-context RNN-T	Chance	0.000e+00	2.747e-04
MEA	CER	Full-context CTC	Chance	0.000e+00	2.747e-04
EMG	PER	Streaming RNN-T	Chance	0.000e+00	1.758e-02
EMG	PER	Full-context RNN-T	Chance	0.000e+00	1.758e-02
EMG	PER	Full-context CTC	Chance	0.000e+00	1.758e-02
EMG	WER	Streaming RNN-T	Chance	0.000e+00	1.758e-02
EMG	WER	Full-context RNN-T	Chance	0.000e+00	1.758e-02
EMG	WER	Full-context CTC	Chance	0.000e+00	1.758e-02
EMG	CER	Streaming RNN-T	Chance	0.000e+00	1.758e-02
EMG	CER	Full-context RNN-T	Chance	0.000e+00	1.758e-02
EMG	CER	Full-context CTC	Chance	0.000e+00	1.758e-02

Each comparison is a two-sided Wilcoxon signed-rank test between n=20 pseudo-blocks for ECoG, n=12 pseudoblocks for MEA, and n=10 pseudoblocks for EMG. 9-way Holm-Bonferroni correction for multiple comparisons was used for each dataset.

Supplementary Table S6. Decoding performance of models with and without auditory feedback.

Dataset	Metric	Modality	Feedback	Median	99% CI
1024-word-General	PER	Speech	Auditory feedback	42.22	[30.20, 59.34]
1024-word-General	PER	Speech	No feedback	40.16	[36.11, 49.91]
1024-word-General	PER	Text	Auditory feedback	26.88	[18.60, 35.62]
1024-word-General	PER	Text	No feedback	24.23	[17.22, 27.59]
1024-word-General	WER	Speech	Auditory feedback	59.10	[41.29, 77.27]
1024-word-General	WER	Speech	No feedback	53.20	[43.48, 65.22]
1024-word-General	WER	Text	Auditory feedback	36.67	[26.92, 42.89]
1024-word-General	WER	Text	No feedback	29.00	[21.66, 36.36]
1024-word-General	CER	Speech	Auditory feedback	43.89	[28.41, 56.64]
1024-word-General	CER	Speech	No feedback	40.15	[33.58, 46.57]
1024-word-General	CER	Text	Auditory feedback	26.37	[19.05, 32.14]
1024-word-General	CER	Text	No feedback	21.61	[17.18, 27.47]

Median error rates (%) and confidence intervals with and without feedback and measured in three forms: phoneme (PER), word (WER), and character (CER). ASR is applied to get the transcript from the decoded speech waveform.

Supplementary Table S7. Comparisons for with and without auditory feedback.

Dataset	Metric	Modality	Comparison 1	Comparison 2	Statistic	Corrected P-value
1024-word-General	PER	Speech	Auditory feedback	No feedback	2.6000E+01	9.2188E-01
1024-word-General	PER	Text	Auditory feedback	No feedback	1.5000E+01	4.6484E-01
1024-word-General	WER	Speech	Auditory feedback	No feedback	2.2000E+01	9.5277E-01
1024-word-General	WER	Text	Auditory feedback	No feedback	8.0000E+00	1.7166E-01
1024-word-General	CER	Speech	Auditory feedback	No feedback	2.7000E+01	1.0000E+00
1024-word-General	CER	Text	Auditory feedback	No feedback	1.0000E+01	2.7728E-01

Each comparison is a Two-sided Wilcoxon Signed-Rank test between n=10 pseudo-blocks with 5 trials for 1024-word-General. 2-way Holm-Bonferroni correction for multiple comparisons was applied within metrics.

Supplementary Table S8. Region ablation decoding accuracy.

Dataset	Metric	Modality	Training data hours (weak range)	Median	99% CI
1024-word-General	PER	Speech	Excluding PrCG	48.02	[31.74, 53.72]
1024-word-General	PER	Speech	Excluding PoCG	43.55	[35.50, 50.67]
1024-word-General	PER	Speech	Excluding TG	43.45	[31.90, 50.29]
1024-word-General	PER	Speech	Excluding PreCG & PoCG	79.43	[74.06, 82.01]
1024-word-General	PER	Text	Excluding PrCG	26.33	[20.32, 31.77]
1024-word-General	PER	Text	Excluding PoCG	22.60	[20.85, 29.14]
1024-word-General	PER	Text	Excluding TG	19.75	[17.03, 24.00]
1024-word-General	PER	Text	Excluding PreCG & PoCG	70.32	[66.47, 74.85]
1024-word-General	WER	Speech	Excluding PrCG	60.58	[43.27, 69.54]
1024-word-General	WER	Speech	Excluding PoCG	56.43	[43.56, 62.39]
1024-word-General	WER	Speech	Excluding TG	53.59	[38.63, 64.08]
1024-word-General	WER	Speech	Excluding PreCG & PoCG	96.12	[94.78, 101.96]
1024-word-General	WER	Text	Excluding PrCG	30.78	[28.04, 42.40]
1024-word-General	WER	Text	Excluding PoCG	29.63	[26.79, 38.00]
1024-word-General	WER	Text	Excluding TG	24.97	[19.61, 30.38]
1024-word-General	WER	Text	Excluding PreCG & PoCG	78.68	[75.00, 84.09]
1024-word-General	CER	Speech	Excluding PrCG	46.72	[33.51, 53.90]
1024-word-General	CER	Speech	Excluding PoCG	42.91	[35.05, 51.53]
1024-word-General	CER	Speech	Excluding TG	44.16	[31.65, 49.28]
1024-word-General	CER	Speech	Excluding PreCG & PoCG	76.30	[72.10, 79.66]
1024-word-General	CER	Text	Excluding PrCG	26.22	[20.28, 32.21]
1024-word-General	CER	Text	Excluding PoCG	22.63	[20.19, 30.53]
1024-word-General	CER	Text	Excluding TG	19.15	[16.84, 22.49]
1024-word-General	CER	Text	Excluding PreCG & PoCG	69.98	[64.60, 72.46]

Median error rates (%) and confidence intervals Extended Data Fig. 8.

Supplementary Table S9. Comparisons of different region ablations.

Dataset	Metric	Modality	Comparison 1	Comparison 2	Statistic	Corrected P-value
1024-word-General	PER	Speech	all channels	Excluding PrCG	2.6000E+01	1.0000E+00
1024-word-General	PER	Speech	all channels	Excluding PoCG	2.5000E+01	1.0000E+00
1024-word-General	PER	Speech	all channels	Excluding TG	1.0000E+01	1.9336E-01
1024-word-General	PER	Speech	all channels	Excluding PreCG & PoCG	0.0000E+00	5.8594E-03
1024-word-General	PER	Text	all channels	Excluding PrCG	9.0000E+00	1.9336E-01
1024-word-General	PER	Text	all channels	Excluding PoCG	2.4000E+01	1.0000E+00
1024-word-General	PER	Text	all channels	Excluding TG	2.1000E+01	1.0000E+00
1024-word-General	PER	Text	all channels	Excluding PreCG & PoCG	0.0000E+00	5.8594E-03
1024-word-General	WER	Speech	all channels	Excluding PrCG	2.2000E+01	1.0000E+00
1024-word-General	WER	Speech	all channels	Excluding PoCG	2.1000E+01	1.0000E+00
1024-word-General	WER	Speech	all channels	Excluding TG	9.5000E+00	1.9336E-01
1024-word-General	WER	Speech	all channels	Excluding PreCG & PoCG	0.0000E+00	5.8594E-03
1024-word-General	WER	Text	all channels	Excluding PrCG	1.3000E+01	1.9336E-01
1024-word-General	WER	Text	all channels	Excluding PoCG	2.0000E+01	1.0000E+00
1024-word-General	WER	Text	all channels	Excluding TG	1.9000E+01	1.0000E+00
1024-word-General	WER	Text	all channels	Excluding PreCG & PoCG	0.0000E+00	5.8594E-03
1024-word-General	CER	Speech	all channels	Excluding PrCG	2.5000E+01	1.0000E+00
1024-word-General	CER	Speech	all channels	Excluding PoCG	2.4000E+01	1.0000E+00
1024-word-General	CER	Speech	all channels	Excluding TG	9.0000E+00	1.9336E-01
1024-word-General	CER	Speech	all channels	Excluding PreCG & PoCG	0.0000E+00	5.8594E-03
1024-word-General	CER	Text	all channels	Excluding PrCG	9.0000E+00	1.9336E-01
1024-word-General	CER	Text	all channels	Excluding PoCG	2.2000E+01	1.0000E+00
1024-word-General	CER	Text	all channels	Excluding TG	2.0000E+01	1.0000E+00
1024-word-General	CER	Text	all channels	Excluding PreCG & PoCG	0.0000E+00	5.8594E-03

Each comparison is a Two-sided Wilcoxon Signed-Rank test between n=10 pseudo-blocks for 1024-word-General. 3-way Holm-Bonferroni correction for multiple comparisons was applied within metrics and modalities.

Supplementary Table S10. Decoding accuracy by the length of training data.

Dataset	Metric	Modality	Training data hours (weak range)	Median	99% CI
1024-word-General	PER	Speech	58.4 (6-71)	44.57	[36.98, 56.57]
1024-word-General	PER	Speech	29.4 (54-71)	45.24	[34.29, 54.36]
1024-word-General	PER	Speech	8.6 (68-71)	70.42	[67.05, 76.65]
1024-word-General	PER	Text	58.4 (6-71)	20.40	[13.86, 32.00]
1024-word-General	PER	Text	29.4 (54-71)	25.08	[19.52, 32.40]
1024-word-General	PER	Text	8.6 (68-71)	52.99	[46.86, 55.21]
1024-word-General	WER	Speech	58.4 (6-71)	58.96	[47.54, 67.92]
1024-word-General	WER	Speech	29.4 (54-71)	59.00	[45.28, 71.29]
1024-word-General	WER	Speech	8.6 (68-71)	87.33	[78.20, 90.57]
1024-word-General	WER	Text	58.4 (6-71)	27.36	[16.60, 42.67]
1024-word-General	WER	Text	29.4 (54-71)	32.62	[22.54, 38.77]
1024-word-General	WER	Text	8.6 (68-71)	62.98	[54.72, 68.63]
1024-word-General	CER	Speech	58.4 (6-71)	46.39	[39.21, 53.11]
1024-word-General	CER	Speech	29.4 (54-71)	46.59	[37.80, 54.04]
1024-word-General	CER	Speech	8.6 (68-71)	69.16	[66.80, 74.64]
1024-word-General	CER	Text	58.4 (6-71)	19.76	[13.03, 32.21]
1024-word-General	CER	Text	29.4 (54-71)	26.25	[19.09, 32.34]
1024-word-General	CER	Text	8.6 (68-71)	51.20	[45.93, 55.09]

Median error rates (%) and confidence intervals in Extended Data Fig. 9.

Supplementary Table S11. Comparisons of different training data length.

Dataset	Metric	Modality	Comparison 1	Comparison 2	Statistic	Corrected P-value
1024-word-General	PER	Speech	58.4 (6-71)	29.4 (54-71)	2.0000E+01	1.0000E+00
1024-word-General	PER	Speech	58.4 (6-71)	8.6 (68-71)	0.0000E+00	5.8594E-03
1024-word-General	PER	Speech	29.4 (54-71)	8.6 (68-71)	0.0000E+00	5.8594E-03
1024-word-General	PER	Text	58.4 (6-71)	29.4 (54-71)	1.5000E+01	5.8008E-01
1024-word-General	PER	Text	58.4 (6-71)	8.6 (68-71)	0.0000E+00	5.8594E-03
1024-word-General	PER	Text	29.4 (54-71)	8.6 (68-71)	0.0000E+00	5.8594E-03
1024-word-General	WER	Speech	58.4 (6-71)	29.4 (54-71)	1.9000E+01	1.0000E+00
1024-word-General	WER	Speech	58.4 (6-71)	8.6 (68-71)	0.0000E+00	5.8594E-03
1024-word-General	WER	Speech	29.4 (54-71)	8.6 (68-71)	0.0000E+00	5.8594E-03
1024-word-General	WER	Text	58.4 (6-71)	29.4 (54-71)	1.9000E+01	6.7840E-01
1024-word-General	WER	Text	58.4 (6-71)	8.6 (68-71)	1.0000E+00	5.8594E-03
1024-word-General	WER	Text	29.4 (54-71)	8.6 (68-71)	1.0000E+00	5.8594E-03
1024-word-General	CER	Speech	58.4 (6-71)	29.4 (54-71)	2.4000E+01	1.0000E+00
1024-word-General	CER	Speech	58.4 (6-71)	8.6 (68-71)	0.0000E+00	5.8594E-03
1024-word-General	CER	Speech	29.4 (54-71)	8.6 (68-71)	0.0000E+00	5.8594E-03
1024-word-General	CER	Text	58.4 (6-71)	29.4 (54-71)	1.4000E+01	5.8008E-01
1024-word-General	CER	Text	58.4 (6-71)	8.6 (68-71)	0.0000E+00	5.8594E-03
1024-word-General	CER	Text	29.4 (54-71)	8.6 (68-71)	0.0000E+00	5.8594E-03

Each comparison is a Two-sided Wilcoxon Signed-Rank test between n=10 pseudo-blocks for 1024-word-General. 3-way Holm-Bonferroni correction for multiple comparisons was applied.

Supplementary Table S12. Comparisons for perceptual evaluations.

Dataset	Metric	Comparison 1	Comparison 2	Statistic	Corrected P-value
50-phrase-AAC	WER	ASR	Perceptual	1.842e+04	1.000e+00
50-phrase-AAC	CER	ASR	Perceptual	1.842e+04	1.000e+00
50-phrase-AAC	PER	ASR	Perceptual	1.842e+04	1.000e+00
1024-word-General	WER	ASR	Perceptual	1.842e+04	1.000e+00
1024-word-General	CER	ASR	Perceptual	1.842e+04	1.000e+00
1024-word-General	PER	ASR	Perceptual	1.842e+04	1.000e+00

Each comparison is a two-sided Wilcoxon signed-rank test between n=15 pseudo-blocks for 50-phrase-AAC and n=10 pseudoblocks for 1024-word-General. 6-way Holm-Bonferroni correction for multiple comparisons was used for each dataset.

Supplementary references

1. Metzger, S. L. et al. A high-performance neuroprosthesis for speech decoding and avatar control. Nature **620,** 1037–1046. ISSN: 1476-4687. http://dx.doi.org/10.1038/s41586-023-06443-4 (Aug. 2023).
2. Graves, A. Sequence transduction with recurrent neural networks. arXiv preprint arXiv:1211.3711 (2012).
3. Panayotov, V., Chen, G., Povey, D. & Khudanpur, S. Librispeech: an asr corpus based on public domain audio books in 2015 IEEE international conference on acoustics, speech and signal processing (ICASSP) (2015), 5206–5210.
4. Kingma, D. P. & Ba, J. Adam: A method for stochastic optimization. arXiv preprint arXiv:1412.6980 (2014).
5. Shi, Y. et al. Emformer: Efficient memory transformer based acoustic model for low latency streaming speech recognition in ICASSP 2021-2021 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP) (2021), 6783–6787.
6. Kim, J., Kong, J. & Son, J. Conditional variational autoencoder with adversarial learning for end-to-end text-to-speech in International Conference on Machine Learning (2021), 5530–5540.
7. Ito, K. & Johnson, L. The LJ Speech Dataset https://keithito.com/LJ-Speech-Dataset/. 2017.
8. Kushal, L. et al. Generative spoken language modeling from raw audio. Transactions of the Association for Computational Linguistics (2021).
9. Wu, P. et al. Deep Speech Synthesis from MRI-Based Articulatory Representations 2023. arXiv: 2307.02471 [eess.AS].
10. Casanova, E. et al. Yourtts: Towards zero-shot multi-speaker tts and zero-shot voice conversion for everyone in International Conference on Machine Learning (2022), 2709–2720.
11. Kong, J., Kim, J. & Bae, J. Hifi-gan: Generative adversarial networks for efficient and high fidelity speech synthesis. Advances in Neural Information Processing Systems **33,** 17022–17033 (2020).
12. Morrison, M. et al. Chunked autoregressive GAN for conditional waveform synthesis. International Conference on Learning Representations (2022).
13. Goodfellow, I. et al. Generative adversarial networks. Communications of the ACM **63,** 139–144 (2020).
14. Ren, Y. et al. Fastspeech 2: Fast and high-quality end-to-end text to speech. arXiv preprint arXiv:2006.04558 (2020).
15. Zen, H. et al. LibriTTS: A Corpus Derived from LibriSpeech for Text-to-Speech in Interspeech 2019 (2019), 1526–1530.
16. Radford, A. et al. Robust Speech Recognition via Large-Scale Weak Supervision 2022. https://arxiv.org/abs/2212.04356.

17. Willett, F. R. et al. A high-performance speech neuroprosthesis en. Aug. 2023.

18. Willett, F. et al. Data for: A high-performance speech neuroprosthesis en. 2023. https://datadryad.org/stash/dataset/doi:10.5061/dryad.x69p8czpq.

19. Gaddy, D. & Klein, D. Digital Voicing of Silent Speech 2020. https://arxiv.org/abs/2010.02960.

20. Gaddy, D. Silent Speech EMG 2020. https://zenodo.org/record/4064409.

21. Gaddy, D. & Klein, D. An Improved Model for Voicing Silent Speech (eds Zong, C., Xia, F., Li, W. & Navigli, R.) Online, Aug. 2021. https://aclanthology.org/2021.acl-short.23.

22. Gaddy, D. Voicing Silent Speech May 2022. http://www2.eecs.berkeley.edu/Pubs/TechRpts/2022/EECS-2022-68.html.

23. Graves, A., Fernández, S., Gomez, F. & Schmidhuber, J. Connectionist temporal classification: labelling unsegmented sequence data with recurrent neural networks in Proceedings of the 23rd international conference on Machine learning - ICML '06 (ACM Press, 2006). http://dx.doi.org/10.1145/1143844.1143891.

CLINICAL PROTOCOL
(original)

Title: A High-Performance ECoG-based Neural Interface for Communication and Neuroprosthetic Control

Study Sponsors/Investigators:

Redacted

Protocol Synopsis

Title	**A High-Performance ECoG-based Neural Interface for Communication and Neuroprosthetic Control**
Study Phase	Phase I
Device(s)	**Device Information:** Devices to be used in this study are grouped below according to FDA approval. **Cleared for temporary (<30 days) recording and monitoring of brain electrical activity under 510k:** • **NeuroPort Array, PN 6248 (K070272, K110010)** • **NeuroPort System, PN 5416 (K060523, K090957)** **Cleared for temporary (<30 day) use with recording, monitoring, and stimulation equipment for the recording, monitoring and stimulation of electrical signals on the surface of the brain under 510k:** • **PMT Subdural Cortical Electrodes, Model #2110TX-128-005 (K082474)** The Blackrock Microsystems Neuroport Array connector pedestal, a subcomponent of the Blackrock Microsystems NeuroPort Array, will be laser bonded to the PMT Subdural Cortical Electrode by Blackrock Microsystems. As documented below, this specific approach has already been tested in non-human primates (over at least an 18-month period, see below regarding published report). **Request for off-label use of the combined investigational device for 1 year, for the equivalent indication of recording and monitoring of brain electrical activity.**
Indication	Adults with neurological disorders (e.g. amyotrophic lateral sclerosis/ALS, spinal cord injury, multiple sclerosis, stroke) often develop disorders of movement and communication. We aim to determine the feasibility of ECoG based brain computer interface control of complex neuroprosthetic devices.
Sponsor Contacts	*Redacted*
Data Safety Monitor Board (DSMB)	*Redacted*

Treatment	The Blackrock Microsystems NeuroPort Array connector pedestal, NeuroPort System, and PMT Subdural Cortical Electrodes are currently cleared for monitoring of patients for up to 30 days. Here we to aim to use these systems combined for at least a 1-year period in subjects with neurological illness and disorders of communication to test feasibility for both neuroprosthetic control and for decoding speech from neural activity.
Study Sites	• *Redacted*
Study Design	This is a **single-center early feasibility study** of the use of an ECoG-based neural interface for testing the feasibility of using ECoG signals to control complex devices for motor and speech control in adults affected by neurological disorders of movement. A PMT Subdural Cortical Electrode array, bonded to the Blackrock Microsystems NeuroPort Array pedestal, will be surgically placed directly on the brain surface over the motor and language cortices of subjects with disorders of motor control. After implantation of the electrode and pedestal, the Neuroport Biopotential Processing System will be connected to the Neuroport Array pedestal to monitor and record neural signals. With this ECoG-based neural interface, study patients will undergo training and assessment of their ability to control a wearable hand robotic exoskeleton and to determine if ECoG brain signals can be decoded for language communication. This will be performed in two phases. <u>Phase 1: Optimize BCI system</u> In Phase 1, we will optimize the entire system to reliably detect neural activity to ensure that the recorded signals are stable and free of artifacts. Moreover, we will ensure that the neural signals are converted in real-time into cursor movements. During this phase, we will primarily examine cursor based control, decoding of parameters and 'disembodied' control (i.e. the subjects' arm will not interact with the mechanical system). This phase will be conducted in the outpatient office setting and/or the patient's home environment, based on patient preference and needs. We anticipate that this phase will take approximately 1 month; however, this may be longer or shorter for each subject depending on the level of control achieved. <u>Phase 2: Testing of BCI Control</u> In Phase 2, we will test feasibility for both neuroprosthetic control and for decoding speech from neural activity. We will begin to perform experimental testing with the system for control of a custom wearable hand exoskeleton robot that

	meets criteria for a non-significant risk device. As outlined in the sections below, we have multiple safety features to ensure that there is minimal risk for injury during the embodiment phase (i.e. the subjects arm is interacting with the exoskeleton). Throughout this period, neural signals will be recorded and analyzed, and tasks will be performed toward the development, assessment, and improvement of the neural interface system. We will assess quality of performance using kinematic parameters while performing required tasks. We will analyze stability of neural recordings and performance. To measure stability of the neural representation we will analyze the neural correlates of imagined movements. We will also assess changes in spatial correlation scales and other redundancy measures during learning and stable performance. We anticipate that testing will be conducted in the outpatient office or home setting based on the patient's preference and needs. In this phase, we will also continue to perform experimental testing with the system for control of a virtual communicating interface. Throughout this period, neural signals will be recorded and analyzed, and tasks will be performed toward the development, assessment, and improvement of the communication interface.
Objectives	In eight patients with severe disorders of movement control, we will surgically implant PMT Subdural Cortical Electrodes on the brain surface over the motor and language cortices. The electrode will be bonded to a Blackrock Neuroport Array pedestal, which can be connected to the NeuroPort System in order to process and record neural activity in real time. Using this neural interface, we will condition the patient to be able to control a wearable hand robotic exoskeleton, communicate with a computer system for typing and perform speech output tasks. We will utilize optimal neural plasticity mechanisms, a novel decoder framework, and advanced language modeling during BCI conditioning. Hypothesis: The underlying hypothesis is that ECoG recordings will allow severely paralyzed individuals to skillfully control complex neuroprosthetic devices for movement and communication. A closely related hypothesis is that the well-known stability of ECoG signals will allow us to maximally engage neural mechanism of plasticity and thereby optimize long-term skilled acquisition.
Patient Population	Study subjects will be adults with severe motor impairment secondary to a neurological disorder.

	<u>Inclusion Criteria</u> • Age > 21 • Limited ability to use upper limbs, based on neurological examination, due to stroke, amyotrophic lateral sclerosis (ALS), multiple sclerosis, cervical spinal cord injury, brainstem stroke, muscular dystrophy, myopathy or severe neuropathy • Disability, defined by a 4 or greater score on the Modified Rankin Scale, must be severe enough to cause loss of independence and inability to perform activities of daily living. • If stroke or spinal cord injury, at least 1 year has passed since onset of symptoms • Must live within a two-hour drive of UCSF <u>Exclusion Criteria</u> • Pregnancy or breastfeeding • Inability to understand and/or read English • Inability to give consent • Dementia, based on history, physical exam, and MMSE • Active depression (BDI > 20) or other psychiatric illness (active general anxiety disorder, schizophrenia, bipolar disorder, obsessive-compulsive disorder (OCD), or personality disorders (e.g. multiple personality disorder, borderline personality disorder, etc.) • History of suicide attempt or suicidal ideation • History of substance abuse • Co-morbidities including ongoing anticoagulation, uncontrolled hypertension, cancer, or major organ system failure • Inability to comply with study follow-up visits • Any prior intracranial surgery • History of seizures • Immunocompromised • Has an active infection • Has a CSF drainage system or an active CSF leak • Requires diathermy, electroconvulsive therapy (ECT), or transcranial magnetic stimulation (TMS) to treat a chronic condition • Has an implanted electronic device such as a neurostimulator, cardiac pacemaker/defibrillator or medication pump • Allergies or known hypersensitivity to materials in the Blackrock NeuroPort Array pedestal (i.e. silicone, titanium) or the PMT Subdural Cortical Electrode (silicone, platinum iridium, nichrome)

Sample Size	8 patients
Efficacy Assessments	Primary Endpoints: Feasibility of control of a wearable exoskeleton device and a communication interface.
Safety Assessments	• Physical examination at all study visits • Perform functional test of the PMT/Blackrock combined neural interface system prior to implantation • Surgical/ or nonsurgical protocol-defined adverse events recorded on adverse events case report forms and use of protocol-defined procedures for adverse event management • Assessment of suicidality using Columbia Suicide Severity Rating Scale, and assessment of changes using the Beck Depression and Anxiety Inventories, at monthly intervals.

1.0 Patient Eligibility

Study subjects will be adults with severe motor impairment secondary to a neurological disorder.

Inclusion Criteria

- Age > 21
- Limited ability to use upper limbs, based on neurological examination, due to stroke, amyotrophic lateral sclerosis (ALS), multiple sclerosis, cervical spinal cord injury, brainstem stroke, muscular dystrophy, myopathy or severe neuropathy
- Disability, defined by a 4 or greater score on the Modified Rankin Scale, must be severe enough to cause loss of independence and inability to perform activities of daily living.
- If stroke or spinal cord injury, at least 1 year has passed since onset of symptoms
- Must live within a two-hour drive of UCSF

Exclusion Criteria

- Pregnancy or breastfeeding
- Inability to understand and/or read English
- Inability to give consent
- Dementia, based on history, physical exam, and MMSE
- Active depression (BDI > 20) or other psychiatric illness (active general anxiety disorder, schizophrenia, bipolar disorder, obsessive-compulsive disorder (OCD), or personality disorders (e.g. multiple personality disorder, borderline personality disorder, etc.)
- History of suicide attempt or suicidal ideation
- History of substance abuse
- Co-morbidities including ongoing anticoagulation, uncontrolled hypertension, cancer, or major organ system failure
- Inability to comply with study follow-up visits
- Any prior intracranial surgery
- History of seizures
- Immunocompromised
- Has an active infection
- Has a CSF drainage system or an active CSF leak
- Requires diathermy, electroconvulsive therapy (ECT), or transcranial magnetic stimulation (TMS) to treat a chronic condition
- Has an implanted electronic device such as a neurostimulator, cardiac pacemaker/defibrillator or medication pump
- Allergies or known hypersensitivity to materials in the Blackrock NeuroPort Array pedestal (i.e. silicone, titanium) or the PMT Subdural Cortical Electrode (silicone, platinum iridium, nichrome)

2.0 Study Device(s)

Cleared for same indication with off-label use of device for at least 1 year:

- Blackrock NeuroPort Array, PN 6248
- Blackrock NeuroPort System, PN 5416
- PMT Subdural Cortical Electrodes, Model #2110TX-128-005

3.0 Study Procedure

Study Duration: The duration of this pilot study will be 6 years. We expect that all 8 patients will be recruited in the first 4-5 years, and data collection, device development and analysis will be completed in 6 years.

Patient recruitment and clinical characterization: Patients with motor impairments secondary to neurological disorders will be recruited from clinics specializing in the treatment of stroke, ALS, and general neurological disorders, at UCSF and the San Francisco VA Medical Center.

Enrollment procedures: Prior to enrollment into the study, an informal phone interview to schedule an office-based evaluation will take place, followed by three outpatient screening visits. During the first outpatient visit we will describe the trial in detail and answer all questions. Should the participant choose to continue, we will schedule another visit to conduct a physical exam and to perform screening labs to determine eligibility. During this visit we will screen for eligibility by 1) acquiring patient demographics, 2) reviewing medical history and measuring vital signs, 3) ensuring patients are not currently pregnant or plan to become pregnant, 4) obtaining a list of current medications being taken, 5) ensuring MMSE scores are within a reasonable range (≥18, also accounting for motor difficulties with taking the test), 6) obtain baseline patient-rated and investigator rated clinical global impression scales, 7) assess baseline health status with SF-36 Health Survey, 8) assess current depression and anxiety states with Beck Depression and Anxiety inventories (BDI and BAI, respectively), 9) determine suicidal ideation risk is minimal with Columbia Suicide Severity Rating Scale (C-SSRS) 10) perform a baseline neurological physical exam and 11) determine the disability rating using the modified Rankin Scale. An MRI and CT of the brain will also be obtained for future surgical planning and to further determine eligibility. Moreover, a ECG and chest x-ray will also be obtained. We will then schedule a third follow-up visit to review this data and to answer remaining questions.

Pre-operative care: Subjects will be administered Kefzol 2g IV within 60 minutes prior to surgical incision, and continued for 24 hours post-operatively. In case of allergy to Kefzol, Vancomycin 1gm IV will be used.

Surgery: After obtaining informed consent, subjects will undergo brief general anesthesia (typically ~ 3-4 hours) for the surgical procedure. This may be either IV or inhaled anesthetics. Patient will be given IV antibiotics prior to incision, and re-dosed if required. Induction and wake-up will take place in the operating room, and patients will be monitored in the post-anesthesia care unit (PACU) after surgery for 2-3 hours during the peri-operative period. Subject will then continue to recover on the surgical ward for 2 days.

Subjects will undergo surgical placement of an ECoG array over the nondominant (usually right-sided) sensorimotor and speech cortices. The basic operative procedure is similar to what is commonly performed for non-penetrating subdural grid placement in patients with intractable epilepsy, which is well tolerated and has few complications [35]. This surgery will be smaller in exposure given that coverage will be limited to the regions of interest, and

not broadly applied as used for epilepsy localization. Standard procedures for craniotomy at the surgical site will be followed. Briefly, a 5-6 cm curvilinear incision will be made over the anatomic hand representation of the cortex (i.e."hand knob") which is located 3 cm lateral to the midline. Localization will be confirmed using intraoperative Brainlab stereotactic neuronavigation. A craniotomy will then be performed, exposing the dural surface. A wide slit in the dura will be opened.

After identifying the location for the electrode grid implant, the position for the pedestal connector is determined on the adjacent or contra-lateral skull surface and marked. A separate 2 cm scalp incision will be made for the pedestal connector. Holes will be drilled for connector placement and the connector will be secured to the skull with 8 small titanium screws. Once the connector is placed, the electrodes and wire bundle are gently manipulated to position the electrodes so that they are resting on the cortical surface over the area of interest. The nonpenetrating ECoG microarray will be sutured to the dura to secure its position. After successful placement of the electrode grid, the dura will be sutured closed in a watertight fashion and the bone flap will be replaced and secured in place with a standard titanium cranial fixation plates and screws.

The surgical site will be irrigated with antibiotic lactated ringers solution. The fascia and skin will be closed with absorbable sutures over the covered craniotomy with a slit accommodating the passage of the connector. The wound will be dressed with a sealed surgical bandage. The expected blood loss for this procedure is 50 cc. The expected operative time is 3-6 hours.

The ECoG electrode array is manufactured by PMT Corporation, and is already FDA-cleared for temporary (<30 days) clinical monitoring of neural signals (K082474). The PMT Subdural Cortical Electrodes are a chronically implantable array containing 128 electrodes, with an electrode spacing of 4 mm, capable of recording from areas of the central nervous system for extended periods of time. The electrode contacts are composed of medical grade platinum iridium, and embedded in a thin sheet of medical grade silastic. The model number 2110 indicates a platinum iridium wire and platinum iridium contacts. Platinum iridium is a mechanically robust alloy electrode material used in commercial DBS leads (Petrossians, Whalen and Weiland 2016). The electrodes' contacts are molded into a silicone rubber matrix in a fixed pattern. This identical electrode is used routinely at our institution and others for seizure localization. In the past ten years, we have not encountered any adverse inflammatory reactions or bleeding specific to the electrode arrays itself (over 100 cases). Insulated wires extend from each electrode through a flexible silicone tube to the connector on the pedestal.

Post-Operative Care: Subjects will be recovered in the intensive care unit and observed for 24 hours before transferring to the ward. A postoperative head CT will be obtained to evaluate for any hemorrhage and to confirm the position of the array. IV antibiotics (Kefzol will used if there are no allergies) will be administered for 24 hours after surgery, followed by prophylactic antibiotics given up to suture removal plus 2 days. Patients will be switched to oral antibiotics as soon as possible. Subjects will undergo physical exam every day with monitoring of vital signs, neurological exam, and basic respiratory, cardiac, and gastrointestinal exams. In addition, the wound site will be inspected at all study visits.

Routine hygiene will consist of handwashing with soap/water and donning gloves using sterile technique when coming in contact with the percutaneous connector. The caregiver

and patient will be trained to clean the pedestal site according to specific instructions that will be given to them, to be performed at least once every seven days or as required.

An infection control protocol will be strictly followed. At early signs of infection or irritation the patient/caregiver should contact the study physician immediately. The surgical site will need to be cleaned twice or more during the day, while using extra meticulous hand hygiene. If skin erythema, edema, pain and/or warmth are present, the available drainage will be cultured and oral antibiotics will be started. Plain radiographs of the involved area, ESR, CRP, WBC, and blood cultures will be obtained. If there is no improvement within 72 hours, rapid progression of erythema, symptoms worsen, or if there are signs of systemic toxicity, parenteral antibiotics is warranted. If high fever or severe pain is present, nuchal rigidity, or progressive deterioration in level of consciousness, the participant should go to the hospital emergency room. All implanted hardware will be surgically removed if there is evidence of hardware infection.

Pain related to small craniotomies is usually self-limited. Pain scale ratings will be assessed every 4 hours and routine postoperative pain management will be used. This includes the following medications as needed: acetaminophen and/or Percocet (acetaminophen/hydrocodone). IV pain meds (morphine sulfate or dilaudid) will also be administered if needed. In our experience, most patients do not require IV analgesics beyond the first operative day for smaller craniotomies.

Study visits: As outlined above, system testing will occur through two phases. In the first phase, we will simply optimize the system; in the second phase, we will commence testing of the motor and communication neural interface systems.

In **Phase 1**, the main goal is to ensure reliable neural signal monitoring and optimization of the real-time systems. Initial study visits will occur at defined time points, similar to those normally used in clinical care. For example, we anticipate a visit at post-op day (POD) 10 and 14. During this time, we will simply monitor the neural signals and briefly test the real-time communication with the computer interface. We anticipate additional visits 1-3x/week, based on the patient's availability and preference, to continue to monitor signal stability and check for wound healing. During this phase, we will also offer in home testing of the system to minimize the burden. While the equipment may be kept at the subject's home, testing will only occur when study personnel are present. The total time period of Phase 1 will be approximately 1 months, the exact time will be customized for each patient.

In **Phase 2**, we will test feasibility for both neuroprosthetic control and for decoding speech from neural activity. We will begin to perform experimental testing with the system for control of a custom wearable hand exoskeleton robot that can be classified as a non-significant risk device. As shown in panel A, the exoskeleton system consists of a table top frame that allows x,y,z movement of the arm/hand (i.e. supported by a brace attached to the platform mount). Movements are limited to the natural workspace of each subject. The hand exoskeleton (panel B) will be mounted using a readily releasable magnetic mount. The hand system aims to allow control of the fingers and thumb using a motorized cable system attached to motors. This system will allow us to test restoration of reach to grasp functions in our subjects. As outlined in the Risk Analysis (Appendix D), we have multiple safety features to ensure that there is minimal risk for injury during the embodiment phase (i.e. the subjects interact with the exoskeleton).

Throughout this period, neural signals will be recorded and analyzed, and tasks will be performed toward the development, assessment, and improvement of the neural interface system. We will assess quality of performance using kinematic parameters while performing required tasks. We will analyze stability of neural recordings and performance. To measure stability of the neural representation we will analyze the neural correlates of imagined movements. We will also examine the stability of neural correlates on neuroprosthetic exoskeleton movements (e.g. spectral content, timing, spatial recruitment). We will assess changes in the spatial correlation scales and other redundancy measures during learning and stable performance. We anticipate that testing will be conducted in the outpatient office or home setting based on the patient's preference and needs.

In this phase, we will also continue to perform experimental testing with the system for control of a virtual communicating interface. Throughout this period, neural signals will be recorded and analyzed, and tasks will be performed toward the development, assessment, and improvement of the neural interface system. We will assess the ability to control a computer communication interface. To measure stability of the neural representation we will analyze the neural correlates of imagined speech. We will also examine the stability of neural correlates on a neuroprosthetic communication device (e.g. spectral content, timing, spatial recruitment).

Neural activity monitoring: Continuous neural signal data will be acquired from the 128-channel implanted PMT Subdural Cortical Electrodes and processed with the NeuroPort System hardware by Blackrock Microsystems. Broadly, the neural data will consist of ECoG neural activity from neurons in the vicinity of each recording electrode. The neural data will be actively monitored and recorded via the graphical user interface associated with the NeuroPort hardware commercially available via Blackrock. Data read and download are non-invasive and will be performed with the patient comfortably rested.

The NeuroPort System has been successfully deployed in monitoring neural activity in patients with motor control disorders (e.g. (Hochberg et al. 2012a, Pandarinath et al. 2015)). Blackrock Microsystems provides commercial software that allows real-time filtering, recording, and visualization of acquired neural data and also allows interfacing with other programming languages such as MATLAB (Mathworks, MA). Together, this allows the ability to create custom software such as communication device based on neural spiking activity, detailed further in the following section. Overall, the mix of commercial and custom software will allow for real-time signal processing, synchronization and control of the peripheral communication device, with parallel data streams to store data for offline analyses.

Online BMI control of a Wearable Hand Robotic Exoskeleton Device:
ECoG signals will be filtered and processed in real-time using a customized portable multi-channel neurophysiology workstation NeuroPort Biopotential Signal Processing System. We will bandpass each channel into multiple bands. Past experiments, including our own, suggest that movement related information is encoded in these bands.

Initialization Phase. We will use an adaptive filter to create a 'decoder' that maps neural activity to movement of the wearable exoskeleton device. Recent experiments suggest that such a filter can rapidly allow control of neuroprosthetic devices. We will train the filter

using 'imagined movements'. As paretic/paralyzed patients will not have access to normal overt movement related neural signals, we will use the neural basis of imagined movements for training. We anticipate that during the initial training phase, the filter will establish a set of weights between the object and neural signals. During this training phase, patients will observe a computer cursor on a screen. In order to compare visual versus visual + proprioceptive/tactile feedback signals during decoder conditioning, we will use the exoskeleton setup for decoder conditioning. The arm and hand will move in a stereotyped fashion while the subjects are instructed to 'imagine' actively tracking its path. Of note, we have experience with similar control of an exoskeleton system ((Ganguly et al. 2011, Ganguly et al. 2009)). As prior and as outlined below, the current system is developed by UC Berkeley. They have long-standing experience with kinematic monitoring, limb dynamics and exoskeleton development (Matthew et al. 2015, Matthew et al. 2016, Oskarsson et al. 2016).

Training Phase. Subjects will be allowed to practice tasks associated with arms/hand and object manipulation. The position of the exoskeleton end effector coordinates (x, y, z) will be under direct neural control. Preliminary experiments with an exoskeleton system showed that end effector control (position and orientation of the wrist) was more intuitive and efficient then position control of individual joints. For this initial phase, the motion will be restricted to a 2-dimensional plane for reaching and grasping objects. There are currently 9 tasks which involve interactions with both static and dynamic environments with various fixtures. We will first limit movements to a 2D environment. The additional degree of freedom involving grasp will be included based on proficiency. In addition, given that 'motivation' and reward are known to influence the overall learning process, a gamed-based training environment with specific goals and scoring systems were developed to engage the subject intellectually and to provide additional enrichment during the training phase.

Testing Phase. To assess robustness and stability of control over days we will assess performance characteristics in three tasks. A) Standard center-out task where subjects have to move to the center, engage a grasp, then move to a target and disengage the grasp to release of an object such as a ball. The workspace will be at 95% of the patient's natural reach. Target size will be kept at 5 cm. B) Reaching from a randomized starting and end position in the workspace of Task A. C) Task B except with the need to plan around obstacles that are placed in the direct path.

Online BMI control: Also during phase 2, neural activity will be used to control a real-time communication device using state of the art closed-loop decoders based on rapid changes in neural activity (Shanechi, Orsborn and Carmena 2016). The main advantage of such a decoder lies in its enhanced ability in discriminating user intent and its speed of operating at every event. Such decoders operate at much higher speeds (typically at 200Hz) over previously developed decoders that rely on averaging neural activity (typically at 10Hz). In addition, we will compare this decoder to more standard decoders (e.g. the Weiner Filter, the LMS filter, the Kalman filter and variants). As documented below, the main outcome measure will be the rate of communication using these approaches.

A virtual communication effector will be presented on a computer screen, custom written in the MATLAB programming environment. The interface between MATLAB and the NeuroPort System will be via commercial software provided by Blackrock Microsystems. The novel decoder will map neural activity to the communication interface. A language processing engine will be concurrently running in the background to model and predict the words and sentences. The following metrics will be utilized to measure performance of the decoder and communication device: selections per minute, accuracy, correct characters per minute (Bacher et al. 2015b) and the bitrate, an information theoretic approach to relate accuracy, time of task completion and complexity (Nuyujukian et al. 2014b, Thompson et al. 2014a). The performance of the novel decoder based communication device will be compared to traditional state space filtering decoders such as the Kalman Filter that has been previously successfully deployed in similar BMI paradigms (Gilja et al. 2012, Bacher et al. 2015b).

Development life cycle of the BMI motor control and communication software:
a) Scope: The intended use of the decoder is to allow the patient to achieve control of external devices and thereby select characters and letters to form sentences, as well as control a wearable hand exoskeleton. As such the operation of the BCI is therefore dependent on the functionality of the software.
b) Platform: The software will be developed on MATLAB (The Mathworks, MA) and MATLAB supported C/C++ complied programs (MEX files) and will be running on the data acquisition PC that interfaces with the Blackrock NeuroPort Array pedestal connector. We will use the software libraries that are part of the Blackrock Neuroport system to stream neural data into MATLAB in real-time.
c) Inputs and outputs: The inputs to the software will be the neural signals from the PMT Subdural Cortical Electrodes grid and the output of the software will consist of user controlled (via the user's neural signals) effector position, selections of characters, letters and numbers for communication purposes, in addition to control of a movements of a wearable hand exoskeleton.
d) Components: There are four distinct aspects of the software, three that operate 'behind the scenes' and one that serves as a Graphical User Interface for display. First, is the decoder itself that translates neural signals into user intentions. Second, is another parallel decoder that serves to discriminate when the patient has made a particular selection (or e.g. grasping actions). Third, is the software engine, that keeps track of the current selections made and generates a list of probable options using a statistical model of movement direction and language (Nadkarni, Ohno-Machado and Chapman 2011b). The fourth and final aspect of the decoder is the Graphical User Interface (GUI) that displays and controls the real-time position of end effector.
e) Safety: The software provides only visual feedback to the user and does not directly interface with the neural signal data acquisition process. The software only serves to allow the use to control the communication interface and the exoskeleton position.
f) Planning phase: In the planning phase, we will identify off-the-shelf components (such as language processing engines) and will aim to further refine and customize it in-house concurrently with the decoders and GUI.
g) Development phase: In the development phase, all components will be developed in parallel as discrete subunits of the overall functional system. A code repository will be maintained to keep track of the life cycle versions and code will be commented wherever

appropriate. During the development phase, debugging will be performed at every iteration and documented. The documentation and code will be maintained on secure hard drives.
h) Testing phase: There are two aspects of this phase. One is the performance testing of each of the four individual components and the other is the testing of the entire software. In lieu of actual neural signals, simulated neural signals will be delivered as input, with a known mapping between the input and output state as the ground truth is known a priori. This will allow testing the performance of the decoders (accuracy in estimated positions). The testing of the GUI and the software engine will be performed independently of the decoders by manually controlling the position of the effector. The testing of the GUI and the software engine will be assessed by the stability and reliability in updating effector position and exoskeleton movements, in the turnaround time of displaying the list of predictive words and actions based on current selections. The overall system testing will employ a combination of simulated neural signals and manual position control to assess the ability of the software in allowing a user to communicate and control a hand neuroprosthetic.
i) Error handling: Code will be written to specifically monitor potential sources of errors in real-time decoding due to either noise in neural signals or decoder weight drift that would necessitate recalibration and resetting of the GUI and software engine.
j) Software validation: The validation and formal design review for the overall software will be performed by members of the PI's laboratory not involved with the development and testing of the software prior to software deployment.
k) Resolution and maintenance: Active documentation and daily logs will be noted to keep track of the performance of the software and address issues such as version control, robustness and immediate resolution of unforeseen errors in the software.

Progression of phases: We anticipate phase 1 will last approximately 1month, but will vary based on each subject. Phase 2 will last at a minimum 10-11 months, a total amount of time of at least 1 year after PMT Subdural Cortical Electrodes implantation and neural interface monitoring and testing, a timeframe which has been performed or exceeded without adverse effects by previous studies using the PMT Subdural Cortical Electrodes and Blackrock Microsystems NeuroPort Array pedestal and NeuroPort System. In this study, recordings were made over 666 days in a non-human primate with no adverse events related to the implanted devices (Degenhart et al. 2016). The ECoG array is identical to that used for subdural grid placement in patients with intractable epilepsy, which is well tolerated and has few complications (Chang et al. 2010).

Activation of the brain recording function: All data collection in the study visits will be initiated by the study staff.

Conclusion of study: For each enrolled subject, if there have been no serious adverse events, we will present the option to continue with the study at the end of a 1-year period. If the subject chooses, we will continue with testing for another year. We will formally present this option every year for a period of 5 years. Notably, the subject will be reminded that he/she will have the option for surgical removal of the device at any point.

Removal of the ECoG grid and Connector pedestal: At the conclusion of the study, or earlier if medically indicated, the subdural cortical electrodes and connector pedestal will be

surgically removed. The skin incision and bone flap will be reopened and the electrode will be removed and discarded. The dura will be sutured tightly. The galea and scalp will be sutured closed. The expected blood loss is minimal (less than 10 cc), and the expected operative time is 30 minutes.

4.0 Clinical Measurements

Primary

This is a pilot study to test feasibility in eight subjects.

For BCI motor control, we will use outcome measures that are frequently used in preclinical studies of neuroprostheses (e.g. accuracy and reliability of cursor and limb control). As outlined below, the primary goal will be to gather statistics regarding the best achievable control using ECoG signals and state-of-the-art methods to allow motor neuroprosthetic control. For each of the parameters below we aim to describe the statistics as the mean and the variance (Bacher et al. 2015a, Nadkarni et al. 2011a, Nuyujukian et al. 2014a, Shanechi et al. 2016, Thompson et al. 2014b). Ultimately, we will compare these values to a wealth of published data regarding movements in able-bodied subjects, e.g.(Bacher et al. 2015a).

1. *Quality of performance* will be assessed using kinematic parameters while performing the required tasks. We will assess stability of the trajectories in the tasks. We will then assess ability for generalization from any region in the workspace to another random point. Position errors from the selected trajectory of the task as well as velocity and acceleration will be studied in both joint space and the end effector space.

2. *Recording and Performance Stability.* We will use previously established metrics to analyze stability of neural recordings (Shanechi et al. 2016, Thompson et al. 2014b) and performance. To measure stability of the neural representation we will analyze the neural correlates of daily imagined movements. We will also examine the stability of the neural correlates of neuroprosthetic movements (e.g. spectral content, timing, spatial recruitment).

3. *Spatial Scale.* An important question for ECoG recordings is the optimal spatial scale for the electrode grid. This has implications for maximizing the amount of information that can be obtained from the recording setup but also for defining the design specifications of implantable electronics (e.g. power requirements could vary greatly depending on the spatial and temporal resolution of the neural data required). We will look at changes in the spatial correlation scales and other redundancy measures during learning and stable performance.

The following metrics will further be utilized to measure performance of the decoder and communication device: selections per minute, accuracy, correct characters per minute (Bacher et al. 2015b) and the bitrate, an information theoretic approach to relate accuracy, time of task completion and complexity (Nuyujukian et al. 2014b, Thompson et al. 2014a). Physiological measurements related to neural activity will include statistical assessments of z-scored activity from single electrodes as well as population dynamics. Physiological measurements related to oscillatory activity will include: wide spectrum power-spectral

analysis as well as using specific frequency domain for mean log power (i.e. in the delta, theta, alpha, beta, gamma bands), coupling between the phase of low frequency rhythms and broadband gamma amplitude (phase-amplitude coupling, abbreviated PAC) (Canolty et al. 2006, Miller et al. 2010, Tort et al.).

Clinical measures and physiological measurements will be collected and recorded by members of the research and clinical team.

5.0 Data Management

All clinical and physiological data will be stored in encrypted and password-protected computers in the PI's laboratory that is always locked. If the Neuroport System is stored in the participant's residence, all research data will be maintained in accordance with UCSF standard encryption policy. In publications or presentations of the data, data will be grouped by case number in chronological order with no name identification. All patients will be asked to sign a separate consent for audio-video recording. When presenting videotape data at scientific conferences, we will utilize only videos from patients who have consented to have their videos shown. De-identified electrophysiological data may be shared with other researchers at other institutions.

6.0 Statistical Methods and Data Analysis

To assess the performance of the decoder, analyses will be performed on the kinematics associated with control, such as time to reach a target, trajectory curvature etc., in conjunction with measures associated with the communication device such as the bit rate, accuracy, characters per minute. The statistical reliability of the decoder will be assessed by non-parametric data permutation wherein the learned mapping between neural activity and the effector position will be artificially broken down and shuffled. Field potential data will be analyzed using wide spectrum power-spectral analysis as well as using specific frequency domain for mean log power (i.e. in the delta, theta, alpha, beta, gamma bands). We will also examine coherence and cross-frequency coupling between the channels (Canolty et al. 2006, Miller et al. 2010, Tort et al.). Using a repeated measures ANOVA statistical analysis, summary statistics for power in relevant frequency bands, control related power changes, and indices of phase-amplitude coupling will be compared at different time-points of control. Additionally, bootstrap statistical tests and general linear mixed models can be utilized to investigate potential statistical effects, given the small sample size. Mean, median, variance and median absolute deviation describing the statistics of each of the measured outcome (such as accuracy, effector position control) will be recorded for each subject.

Sample size calculation: This is a pilot study to assess the feasibility of an ECoG based implantable BCI device in patients with motor control disorders using intracranial recordings, a communication interface and a wearable hand exoskeleton. The collected pilot data will aid in determining the feasibility, reliability and future directions of the brain machine interface for communication and motor control. In addition, the pilot data will be used to formulate more detailed hypothesis on neural plasticity and BMI control in humans. As such, there is no formal sample size requirement for this pilot study.

Criteria for study success that would justify a larger subsequent trial:

1) Ability to use ECoG-based neural activity to control a neuroprosthetic device and communication interface.
2) No permanent serious adverse events occur (such as trauma with long-term motor deficit).
3) Benefits to the patient in regaining a sense of control over the ability to exert motor control and communicate in an efficient manner.

7.0 Regulatory Requirements

Prior to the start of the study, the following documents will be collected and filed:
- Signed protocol signature page
- Curriculum vitae of the PIs and Sub-investigators, updated within 2 years
- Current medical licenses for the PIs and all Sub-investigators
- Financial disclosure form signed by the PIs and all Sub-investigators
- Copy of the IRB approval letter for the study and the IRB Membership List
- Investigator Agreement

Investigator Obligations

Redacted will be responsible for ensuring that all study site personnel, adhere to all FDA regulations and guidelines regarding clinical trials, including guidelines for GCP (including the archiving of essential documents), both during and after study completion. Additionally, they are responsible for the subject's compliance to the study protocol.

All information obtained during the conduct of the study with respect to the patients' state of health will be regarded as confidential. This is detailed in the written information provided to the patient. An agreement for disclosure of any such information will be obtained in writing and will be signed by the patient.

Informed Consent

The investigators will obtain and document informed consent for each patient screened for this study. All patients will be informed in writing of the nature of the protocol and investigational therapy, its possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate prior to the initiation of study procedures.

Institutional Review Board

This protocol and relevant supporting data are to be submitted to the appropriate IRB for review and approval before the study can be initiated (UCSF, Human Research Protection Program, 3333 California Street, Suite 315, San Francisco, CA, 94118, FWA#00000068; IRB Registration 00000229, Lisa Denney, HRRP Director). Amendments to the protocol will also be submitted to the IRB prior to implementation of the change. The PIs are responsible for informing the IRB of the progress of the study and for obtaining annual IRB renewal. The IRB must be informed at the time of completion of the study and should be provided with a summary of the results of the study by the PIs. The PIs must notify the IRB in writing of any SAE or any unexpected AE according to ICH guidelines.

Data safety monitory board (DSMB) and safety monitoring plan

Treatment emergent adverse events that are assessed by the principal investigators as possibly, probably, or definitely related to surgical implantation or chronic cortical recording AND are unexpected or meet seriousness criteria (death, immediately life threatening, hospitalization >24 hours, persistent or significant disability, or significant

intervention required to prevent one of the previously-stated outcomes) will be recorded and reported to the IRB, device manufacturer and the FDA via the MedWatch online voluntary reporting form within 10 working days of the study team's knowledge of the event.

All such events will also be reported to the data safety monitor board (DSMB), led by a neurosurgeon at our home institution, who does not have direct involvement in this study but who has expertise in implantable devices, pain management and neurosurgery. The DSMB will meet regularly to review data related to the clinical trial, provide guidance and feedback, and review any adverse event reports. Treatment-related adverse events assessed as definitely, probably, or possibly related to study procedures and either serious or unexpected, noted by any study personnel will be reported within 10 working days of their knowledge of the event to the DSMB. The DSMB will then advise the PI on potential changes in procedures to improve safety. The safety endpoint will consist of all adverse events.

Throughout the clinical trial, should a serious adverse event occur that is assessed to be surgery related or not, or related to the presence of the electrode system, such as infection, the device will be removed and the study halted for the patient. Removal will be accomplished by re-opening the original incisions, temporary removal of the bone, and removal of the PMT Subdural Cortical Electrodes from the brain and NeuroPort Array pedestal from the skull. The dura will be re-sewn together and the bone fixed again with titanium screws

Furthermore, if there is a serious surgical or non-surgical adverse event, or with the onset of suicidality, the study will be halted for the patient.

If two patients meet one or more of these criteria (i. serious surgical or nonsurgery-related adverse event, or ii. onset of suicidality), the study will be halted until information is reviewed by the DSMB and FDA.

8.0 References

Ajiboye, A. B., J. D. Simeral, J. P. Donoghue, L. R. Hochberg & R. F. Kirsch (2012) Prediction of imagined single-joint movements in a person with high-level tetraplegia. *IEEE Trans Biomed Eng,* 59**,** 2755-65.

Anderson, K. D. (2004) Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma,* 21**,** 1371-83.

Bacher, D., B. Jarosiewicz, N. Y. Masse, S. D. Stavisky, J. D. Simeral, K. Newell, E. M. Oakley, S. S. Cash, G. Friehs & L. R. Hochberg (2015a) Neural Point-and-Click Communication by a Person With Incomplete Locked-In Syndrome. *Neurorehabil Neural Repair,* 29**,** 462-71.

Bacher, D., B. Jarosiewicz, N. Y. Masse, S. D. Stavisky, J. D. Simeral, K. Newell, E. M. Oakley, S. S. Cash, G. Friehs & L. R. Hochberg (2015b) Neural point-and-click communication by a person with incomplete locked-in syndrome. *Neurorehabilitation and neural repair,* 29**,** 462-471.

Bensmaia, S. J. & L. E. Miller (2014) Restoring sensorimotor function through intracortical interfaces: progress and looming challenges. *Nat Rev Neurosci,* 15**,** 313-25.

Birbaumer, N., N. Ghanayim, T. Hinterberger, I. Iversen, B. Kotchoubey, A. Kubler, J. Perelmouter, E. Taub & H. Flor (1999) A spelling device for the paralysed. *Nature,* 398**,** 297-8.

Bouchard, K. E., N. Mesgarani, K. Johnson & E. F. Chang (2013) Functional organization of human sensorimotor cortex for speech articulation. *Nature,* 495**,** 327-32.

Bouton, C. E., A. Shaikhouni, N. V. Annetta, M. A. Bockbrader, D. A. Friedenberg, D. M. Nielson, G. Sharma, P. B. Sederberg, B. C. Glenn, W. J. Mysiw, A. G. Morgan, M. Deogaonkar & A. R. Rezai (2016) Restoring cortical control of functional movement in a human with quadriplegia. *Nature,* 533**,** 247-50.

Canolty, R. T., E. Edwards, S. S. Dalal, M. Soltani, S. S. Nagarajan, H. E. Kirsch, M. S. Berger, N. M. Barbaro & R. T. Knight (2006) High gamma power is phase-locked to theta oscillations in human neocortex. *Science,* 313**,** 1626-8.

Carmena, J. M., M. A. Lebedev, R. E. Crist, J. E. O'Doherty, D. M. Santucci, D. F. Dimitrov, P. G. Patil, C. S. Henriquez & M. A. Nicolelis (2003) Learning to control a brain-machine interface for reaching and grasping by primates. *PLoS Biol,* 1**,** E42.

Chang, E. F., J. W. Rieger, K. Johnson, M. S. Berger, N. M. Barbaro & R. T. Knight (2010) Categorical speech representation in human superior temporal gyrus. *Nat Neurosci,* 13**,** 1428-32.

Chao, Z. C., Y. Nagasaka & N. Fujii (2010) Long-term asynchronous decoding of arm motion using electrocorticographic signals in monkeys. *Front Neuroengineering,* 3**,** 3.

Chestek, C. A., V. Gilja, P. Nuyujukian, R. J. Kier, F. Solzbacher, S. I. Ryu, R. R. Harrison & K. V. Shenoy (2009) HermesC: Low-Power Wireless Neural Recording System for Freely Moving Primates. *Ieee Transactions on Neural Systems and Rehabilitation Engineering,* 17**,** 330-338.

Churchland, M. M., J. P. Cunningham, M. T. Kaufman, J. D. Foster, P. Nuyujukian, S. I. Ryu & K. V. Shenoy (2012) Neural population dynamics during reaching. *Nature,* 487**,** 51-6.

Collinger, J. L., S. Foldes, T. M. Bruns, B. Wodlinger, R. Gaunt & D. J. Weber (2013) Neuroprosthetic technology for individuals with spinal cord injury. *J Spinal Cord Med,* 36**,** 258-72.

Degenhart, A. D., J. Eles, R. Dum, J. L. Mischel, I. Smalianchuk, B. Endler, R. C. Ashmore, E. C. Tyler-Kabara, N. G. Hatsopoulos, W. Wang, A. P. Batista & X. T. Cui (2016) Histological evaluation of a chronically-implanted electrocorticographic electrode grid in a non-human primate. *J Neural Eng,* 13**,** 046019.

Ganguly, K. & J. M. Carmena (2009) Emergence of a stable cortical map for neuroprosthetic control. *PLoS Biol,* 7**,** e1000153.

Ganguly, K., D. F. Dimitrov, J. D. Wallis & J. M. Carmena (2011) Reversible large-scale modification of cortical networks during neuroprosthetic control. *Nat Neurosci,* 14**,** 662-7.

Ganguly, K., L. Secundo, G. Ranade, A. Orsborn, E. F. Chang, D. F. Dimitrov, J. D. Wallis, N. M. Barbaro, R. T. Knight & J. M. Carmena (2009) Cortical representation of ipsilateral arm movements in monkey and man. *J Neurosci,* 29**,** 12948-56.

Gilja, V., C. A. Chestek, I. Diester, J. M. Henderson, K. Deisseroth & K. V. Shenoy (2011) Challenges and opportunities for next-generation intracortically based neural prostheses. *IEEE Trans Biomed Eng,* 58**,** 1891-9.

Gilja, V., P. Nuyujukian, C. A. Chestek, J. P. Cunningham, M. Y. Byron, J. M. Fan, M. M. Churchland, M. T. Kaufman, J. C. Kao & S. I. Ryu (2012) A high-performance neural prosthesis enabled by control algorithm design. *Nature neuroscience,* 15**,** 1752-1757.

Hochberg, L. R., D. Bacher, B. Jarosiewicz, N. Y. Masse, J. D. Simeral, J. Vogel, S. Haddadin, J. Liu, S. S. Cash & P. van der Smagt (2012a) Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature,* 485**,** 372-375.

Hochberg, L. R., D. Bacher, B. Jarosiewicz, N. Y. Masse, J. D. Simeral, J. Vogel, S. Haddadin, J. Liu, S. S. Cash, P. van der Smagt & J. P. Donoghue (2012b) Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature,* 485**,** 372-5.

Hochberg, L. R., M. D. Serruya, G. M. Friehs, J. A. Mukand, M. Saleh, A. H. Caplan, A. Branner, D. Chen, R. D. Penn & J. P. Donoghue (2006) Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature,* 442**,** 164-71.

Homer, M. L., A. V. Nurmikko, J. P. Donoghue & L. R. Hochberg (2013) Sensors and decoding for intracortical brain computer interfaces. *Annu Rev Biomed Eng,* 15**,** 383-405.

Huggins, J. E., P. A. Wren & K. L. Gruis (2011) What would brain-computer interface users want? Opinions and priorities of potential users with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler,* 12**,** 318-24.

Kennedy, P. R. (1994) 'Locked-in' patients. *Neurology,* 44**,** 366-7.

Kennedy, P. R. & R. A. Bakay (1998) Restoration of neural output from a paralyzed patient by a direct brain connection. *Neuroreport,* 9**,** 1707-11.

Kim, S. P., J. D. Simeral, L. R. Hochberg, J. P. Donoghue & M. J. Black (2008a) Neural control of computer cursor velocity by decoding motor cortical spiking activity in humans with tetraplegia. *Journal of Neural Engineering,* 5**,** 455-76.

--- (2008b) Neural control of computer cursor velocity by decoding motor cortical spiking activity in humans with tetraplegia. *J Neural Eng,* 5**,** 455-76.

Kubler, A., B. Kotchoubey, J. Kaiser, J. R. Wolpaw & N. Birbaumer (2001) Brain-computer communication: unlocking the locked in. *Psychol Bull,* 127**,** 358-75.

Leuthardt, E. C., K. J. Miller, G. Schalk, R. P. Rao & J. G. Ojemann (2006) Electrocorticography-based brain computer interface--the Seattle experience. *IEEE Trans Neural Syst Rehabil Eng,* 14**,** 194-8.

Leuthardt, E. C., G. Schalk, J. Roland, A. Rouse & D. W. Moran (2009) Evolution of brain-computer interfaces: going beyond classic motor physiology. *Neurosurg Focus,* 27**,** E4.

Leuthardt, E. C., G. Schalk, J. R. Wolpaw, J. G. Ojemann & D. W. Moran (2004) A brain-computer interface using electrocorticographic signals in humans. *J Neural Eng,* 1**,** 63-71.

Matthew, R. P., E. J. Mica, W. Meinhold, J. A. Loeza, M. Tomizuka & R. Bajcsy (2015) Initial investigation into the effect of an Active/Passive exoskeleton on hammer curl performance in healthy subjects. *Conf Proc IEEE Eng Med Biol Soc,* 2015**,** 3607-10.

Matthew, R. P., V. Shia, G. Venture & R. Bajcsy (2016) Generating physically realistic kinematic and dynamic models from small data sets: An application for sit-to-stand actions. *Conf Proc IEEE Eng Med Biol Soc,* 2016**,** 2173-2178.

Miller, K. J., D. Hermes, C. J. Honey, M. Sharma, R. P. Rao, M. den Nijs, E. E. Fetz, T. J. Sejnowski, A. O. Hebb, J. G. Ojemann, S. Makeig & E. C. Leuthardt (2010) Dynamic modulation of local population activity by rhythm phase in human occipital cortex during a visual search task. *Front Hum Neurosci,* 4**,** 197.

Monti, M. M., A. Vanhaudenhuyse, M. R. Coleman, M. Boly, J. D. Pickard, L. Tshibanda, A. M. Owen & S. Laureys (2010) Willful modulation of brain activity in disorders of consciousness. *N Engl J Med,* 362**,** 579-89.

Morrell, M. J. & R. N. S. S. i. E. S. Group (2011) Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology,* 77**,** 1295-304.

Nadkarni, P. M., L. Ohno-Machado & W. W. Chapman (2011a) Natural language processing: an introduction. *J Am Med Inform Assoc,* 18**,** 544-51.

Nadkarni, P. M., L. Ohno-Machado & W. W. Chapman (2011b) Natural language processing: an introduction. *Journal of the American Medical Informatics Association,* 18**,** 544-551.

Nicolelis, M. A. & M. A. Lebedev (2009) Principles of neural ensemble physiology underlying the operation of brain-machine interfaces. *Nat Rev Neurosci,* 10**,** 530-40.

Nuyujukian, D. S., J. Voutsinas, L. Bernstein & S. S. Wang (2014a) Medication use and multiple myeloma risk in Los Angeles County. *Cancer Causes Control,* 25**,** 1233-7.

Nuyujukian, P., J. C. Kao, J. M. Fan, S. D. Stavisky, S. I. Ryu & K. V. Shenoy (2014b) Performance sustaining intracortical neural prostheses. *Journal of neural engineering,* 11**,** 066003.

Oskarsson, B., N. C. Joyce, E. De Bie, A. Nicorici, R. Bajcsy, G. Kurillo & J. J. Han (2016) Upper extremity 3-dimensional reachable workspace assessment in amyotrophic lateral sclerosis by Kinect sensor. *Muscle Nerve,* 53**,** 234-41.

Pandarinath, C., V. Gilja, C. H. Blabe, P. Nuyujukian, A. A. Sarma, B. L. Sorice, E. N. Eskandar, L. R. Hochberg, J. M. Henderson & K. V. Shenoy (2015) Neural population dynamics in human motor cortex during movements in people with ALS. *Elife,* 4**,** e07436.

Pasley, B. N., S. V. David, N. Mesgarani, A. Flinker, S. A. Shamma, N. E. Crone, R. T. Knight & E. F. Chang (2012) Reconstructing speech from human auditory cortex. *Plos Biology,* 10**,** e1001251.

Schalk, G., K. J. Miller, N. R. Anderson, J. A. Wilson, M. D. Smyth, J. G. Ojemann, D. W. Moran, J. R. Wolpaw & E. C. Leuthardt (2008) Two-dimensional movement control using electrocorticographic signals in humans. *J Neural Eng,* 5**,** 75-84.

Schwartz, A. B. (2004) Cortical neural prosthetics. *Annu Rev Neurosci,* 27**,** 487-507.

Schwartz, A. B., X. T. Cui, D. J. Weber & D. W. Moran (2006) Brain-controlled interfaces: movement restoration with neural prosthetics. *Neuron,* 52**,** 205-20.

Selzer, M. E., S. Clarke, L. G. Cohen, G. Kwakkel & R. H. Miller. 2014. *Textbook of neural repair and rehabilitation*. Cambridge: Cambridge University Press.

Shanechi, M. M., A. L. Orsborn & J. M. Carmena (2016) Robust Brain-Machine Interface Design Using Optimal Feedback Control Modeling and Adaptive Point Process Filtering. *PLoS Comput Biol,* 12**,** e1004730.

Shenoy, K. V. & J. M. Carmena (2014) Combining decoder design and neural adaptation in brain-machine interfaces. *Neuron,* 84**,** 665-80.

Simeral, J. D., S. P. Kim, M. J. Black, J. P. Donoghue & L. R. Hochberg (2011) Neural control of cursor trajectory and click by a human with tetraplegia 1000 days after implant of an intracortical microelectrode array. *J Neural Eng,* 8**,** 025027.

Slutzky, M. W., L. R. Jordan, E. W. Lindberg, K. E. Lindsay & L. E. Miller (2011) Decoding the rat forelimb movement direction from epidural and intracortical field potentials. *J Neural Eng,* 8**,** 036013.

Spataro, R., M. Ciriacono, C. Manno & V. La Bella (2014) The eye-tracking computer device for communication in amyotrophic lateral sclerosis. *Acta Neurol Scand,* 130**,** 40-5.

Taylor, D. M., S. I. Tillery & A. B. Schwartz (2002) Direct cortical control of 3D neuroprosthetic devices. *Science,* 296**,** 1829-32.

Thompson, D. E., L. R. Quitadamo, L. Mainardi, S. Gao, P.-J. Kindermans, J. D. Simeral, R. Fazel-Rezai, M. Matteucci, T. H. Falk & L. Bianchi (2014a) Performance measurement for brain–computer or brain–machine interfaces: a tutorial. *Journal of neural engineering,* 11**,** 035001.

Thompson, D. E., L. R. Quitadamo, L. Mainardi, K. U. Laghari, S. Gao, P. J. Kindermans, J. D. Simeral, R. Fazel-Rezai, M. Matteucci, T. H. Falk, L. Bianchi, C. A. Chestek & J. E. Huggins (2014b) Performance measurement for brain-computer or brain-machine interfaces: a tutorial. *J Neural Eng,* 11**,** 035001.

Tort, A. B., R. Komorowski, H. Eichenbaum & N. Kopell (2010) Measuring phase-amplitude coupling between neuronal oscillations of different frequencies. *J Neurophysiol,* 104**,** 1195-210.

Wolpaw, J. R., N. Birbaumer, D. J. McFarland, G. Pfurtscheller & T. M. Vaughan (2002) Brain-computer interfaces for communication and control. *Clin Neurophysiol,* 113**,** 767-91.

CLINICAL PROTOCOL

(updated 8/23/2022)

Title:
A High-Performance ECoG-based Neural Interface for Communication and Neuroprosthetic Control

Protocol:
FDA reference number: G170242
UCSF-BMI-ECoG-2022-06

Study Sponsors/Investigators:

Redacted

Protocol Synopsis

Title	**A High-Performance ECoG-based Neural Interface for Communication and Neuroprosthetic Control**
Study Phase	Phase I
Device(s)	**Device Information:** Devices to be used in this study are grouped below according to FDA approval. **Cleared for temporary (<30 days) recording and monitoring of brain electrical activity under 510k:** ● **NeuroPort Array, PN 6248 (K070272, K110010)** **Seeking Special 510(k) (not yet submitted to FDA):** ● **Digital NeuroPort System (Modification to existing NeuroPort System - K042626)** **Cleared for temporary (<30 day) use with recording, monitoring, and stimulation equipment for the recording, monitoring and stimulation of electrical signals on the surface of the brain under 510k:** ● **PMT Subdural Cortical Electrodes, Model #2110TX-253-001 (K082474)** ● **PMT Subdural Cortical Electrodes, Model #2110TX-128-005 (K082474)** **Not cleared**: • **Blackrock Microsystems 256-channel pedestal connector (see Appendix E for justification of use)** • **Blackrock Microsystems CerePlex E256 digital head stage** The Blackrock Microsystems NeuroPort Array connector pedestal, a subcomponent of the Blackrock Microsystems NeuroPort Array, or the 256-channel Blackrock Microsystems connector pedestal will be laser bonded to the PMT Subdural Cortical Electrode by Blackrock Microsystems. As documented below, the combination device including the Blackrock Microsystems NeuroPort Array connector pedestal laser bonded to the PMT Subdural Cortical Electrode has already been tested in non-human primates (over at least an 18-month period, see below regarding published report). **Request for off-label use of the combined investigational device for 1 year, for the equivalent indication of recording and monitoring of brain electrical activity.**

Indication	Adults with neurological disorders (e.g. amyotrophic lateral sclerosis/ALS, spinal cord injury, multiple sclerosis, stroke) often develop disorders of movement and communication. We aim to determine the feasibility of ECoG based brain computer interface control of complex neuroprosthetic devices.
Sponsor Contacts	*Redacted*
Data Safety Monitor Board (DSMB)	*Redacted*
Treatment	The Blackrock Microsystems NeuroPort Array connector pedestal, NeuroPort system, and PMT Subdural Cortical Electrodes are currently cleared for monitoring of patients for up to 30 days. The Blackrock Microsystems 256-channel NeuroPort connector pedestal and CerePlex E256 digital head stage are not cleared by the FDA. Blackrock has modifications to the NeuroPort system for which they are seeking special 510(k) clearance. Here we to aim to use these systems combined for at least a 1-year period in subjects with neurological illness and disorders of communication to test feasibility for both neuroprosthetic control and for decoding speech from neural activity.

Study Sites	*Redacted*

Study Design	This is a **single-center early feasibility study** of the use of an ECoG-based neural interface for testing the feasibility of using ECoG signals to control complex devices for motor and speech control in adults affected by neurological disorders of movement. A PMT Subdural Cortical Electrode array, bonded to the Blackrock Microsystems NeuroPort Array pedestal or to the 256-channel NeuroPort pedestal, will be surgically placed directly on the brain surface over the motor and language cortices of subjects with disorders of motor control. After implantation of the electrode and pedestal, the NeuroPort Biopotential Processing System will be connected to the NeuroPort Array pedestal, or to the 256-channel NeuroPort pedestal, to monitor and record neural signals. With this ECoG-based neural interface, study patients will undergo training and assessment of their ability to control assistive robotic arms and to determine if ECoG brain signals can be decoded for language communication. This will be performed in two phases. <u>Phase 1: Optimize BCI system</u> In Phase 1, we will optimize the entire system to reliably detect neural activity to ensure that the recorded signals are stable and free of artifacts. Moreover, we will ensure that the neural signals are converted in real-time into cursor movements. During this phase, we will primarily examine cursor based control, decoding of parameters and 'disembodied' control (i.e. the subjects' arm will not interact with the mechanical system). This phase will be conducted in the outpatient office setting and/or the patient's home environment, based on patient preference and needs. We anticipate that this phase will take approximately 1 month; however, this may be longer or shorter for each subject depending on the level of control achieved. <u>Phase 2: Testing of BCI Control</u> In Phase 2, we will test feasibility for both neuroprosthetic control and for decoding speech from neural activity. We will begin to perform experimental testing with the system for control of an assistive robotic arms that meets criteria for a non-significant risk device. As outlined in the sections below, we have multiple safety features to ensure that there is minimal risk for injury during use of the robotic arms, including subject contact during object interaction and the embodiment phase (i.e. the subjects arm is interacting with the exoskeleton). Throughout this period, neural signals will be recorded and analyzed, and tasks will be performed toward the development, assessment, and improvement of the neural interface system. We will assess quality of performance using kinematic parameters while performing required tasks. We will analyze stability of neural recordings and performance. To measure stability of the neural representation we will analyze the neural correlates of imagined movements. We will also assess changes in spatial correlation scales and other redundancy measures during learning and stable performance. We anticipate that testing will be conducted in the outpatient office or home setting based on the patient's preference and needs.

	In this phase, we will also continue to perform experimental testing with the system for control of a virtual communicating interface. Throughout this period, neural signals will be recorded and analyzed, and tasks will be performed toward the development, assessment, and improvement of the communication interface.

Objectives	In eight patients with severe disorders of movement control, we will surgically implant PMT Subdural Cortical Electrodes on the brain surface over the motor and language cortices. The electrode will be bonded to a Blackrock NeuroPort Array pedestal or the Blackrock 256-channel NeuroPort pedestal, which can be connected to the Digital NeuroPort system in order to process and record neural activity in real time. Using this neural interface, we will condition the patient to be able to control assistive robotic arms, communicate with a computer system for typing and perform speech output tasks. We will utilize optimal neural plasticity mechanisms, a novel decoder framework, and advanced language modeling during BCI conditioning. Hypothesis: The underlying hypothesis is that ECoG recordings will allow severely paralyzed individuals to skillfully control complex neuroprosthetic devices for movement and communication. A closely related hypothesis is that the well-known stability of ECoG signals will allow us to maximally engage neural mechanism of plasticity and thereby optimize long-term skilled acquisition.

Patient Population	Study subjects will be adults with severe motor impairment secondary to a neurological disorder. <u>Inclusion Criteria</u> ● Age 21-75 years old ● Limited ability to use upper limbs and limited ability to use speech, based on neurological examination by a board-certified neurological specialist, due to stroke, spastic quadriplegic cerebral palsy (with no significant cognitive deficits based on formal neuropsychological testing), amyotrophic lateral sclerosis (ALS), multiple sclerosis, cervical spinal cord injury, brainstem stroke, muscular dystrophy, myopathy or severe neuropathy ● Disability, defined by a 4 or greater score on the Modified Rankin Scale, must be severe enough to cause loss of independence and inability to perform activities of daily living. ● If stroke or spinal cord injury, at least 1 year has passed since onset of symptoms ● Must live within a two-hour drive of UCSF <u>Exclusion Criteria</u> ● Pregnancy or breastfeeding ● Inability to understand and/or read English ● Inability to give consent ● Dementia, based on history, physical exam, and MMSE ● Active depression (BDI > 20) or other psychiatric illness (active general anxiety disorder, schizophrenia, bipolar disorder, obsessive-compulsive disorder (OCD), or personality disorders (e.g. multiple personality disorder, borderline personality disorder, etc.) ● History of suicide attempt or suicidal ideation within one's lifetime prior to enrollment, confirmed by a baseline negative Columbia Suicide Severity Rating Scale (C-SSRS) ● Comorbidities including uncontrolled hypertension, cancer, or major organ system failure. ● History of intracranial surgery ● History of substance abuse within the last year ● Ongoing anticoagulation which cannot be stopped in the peri-procedural period. ● Inability to comply with study follow-up visits ● Immunocompromised ● Has an active infection ● Has a CSF drainage system or an active CSF leak ● Requires diathermy, electroconvulsive therapy (ECT), or transcranial magnetic stimulation (TMS) to treat a chronic condition ● Has an implanted electronic device such as a neurostimulator, cardiac pacemaker/defibrillator or medication pump

	• Allergies or known hypersensitivity to materials in the Blackrock NeuroPort Array pedestal or Blackrock 256-channel pedestal (i.e. silicone, titanium) or the PMT Subdural Cortical Electrode (silicone, platinum iridium, nichrome)

Sample Size	8 patients
Efficacy Assessments	Primary Endpoints: Feasibility of control of assistive robotic arms and a communication interface.
Safety Assessments	● Physical examination at all study visits ● Perform functional test of the PMT/Blackrock combined neural interface system prior to implantation ● Surgical/ or nonsurgical protocol-defined adverse events recorded on adverse events case report forms and use of protocol-defined procedures for adverse event management ● Assessment of suicidality using Columbia Suicide Severity Rating Scale, and assessment of changes using the Beck Depression and Anxiety Inventories, at monthly intervals.

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Investigator Agreement / Protocol Signature Page

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1.0
Introduction

Restoration of function with assistive robotic arms and a communication interface are important goals of BCIs. Multiple neurological disorders can result in severe bilateral upper limb weakness or paralysis. Surveys of patients with quadriplegia provide important guidance about specific rehabilitation needs and preferences as well as targets for intervention. A survey of patients with tetraplegia resulting from SCI found that restoration of arm and hand function was of highest priority (Anderson 2004). Similarly, patients with ALS reported that direct neural control of a robotic arm would be of great importance (Huggins, Wren and Gruis 2011). While there has been extensive research into each disease process, little has been proven to be clinically effective for the rehabilitation of this chronic disability (Wolpaw et al. 2002).

In patients with conditions such as high cervical SCI, basilar strokes or advanced ALS, the effects can be particularly devastating as tetraplegia may be accompanied by paralysis of oral structures, leading to the loss of voluntary vocal function. Individuals with severe traumatic brain injury or high cervical injuries who require mechanical ventilation may also have limited capacity to communicate (Kennedy 1994, Kubler et al. 2001, Monti et al. 2010). Standard augmentative and alternative communication (AAC) devices are widely available but may not be suitable for individuals with severe or complete paralysis of the voluntary motor system (Selzer et al. 2014). For example, the most commonly used devices are gaze trackers that allow computer cursor control through eye movements (Spataro et al. 2014). However, eye tracking may have a limited role in advanced cases of ALS and after brainstem strokes, where eye movements are frequently affected (Birbaumer et al. 1999, Kennedy and Bakay 1998). They also require sustained visual attention and may create a high cognitive burden. Thus, it remains critical to develop novel technologies to help restore communication as well as upper limb function.

Brain-Computer Interfaces (BCIs) are a very promising method to significantly improve quality of life by restoring upper extremity function and communication ability in patients with motor and speech disabilities. Over the past decade, the rate and sophistication of research involving invasive BCIs have rapidly increased. BMIs have the potential to seamlessly integrate the computational power of artificial electronic systems with that of the nervous system. Multiple neural signals can be used in a BCI, including non-invasive EEG signals and other neural signals such as spikes and electrocorticography (ECoG) that require invasive placement of electrodes. Non-invasive BCIs have been studied for at least two decades. Known limitations of surface EEG recordings are a low 'signal-to-noise' and contamination by muscle activity (Wolpaw et al. 2002). Recent studies suggest that BMIs using invasive recording of neural signals (spikes or ECoG) can allow more rapid intuitive control over complex devices (Carmena et al. 2003, Leuthardt et al. 2009, Leuthardt et al. 2004, Schwartz et al. 2006, Taylor, Tillery and Schwartz 2002). A large basic science and clinical effort is currently devoted to BMIs based on invasive recordings of action potentials. However, it is increasingly clear that there are significant limits on possible translation of spikes

based recordings. It does not readily permit reliable long-term recordings (Chestek et al. 2009, Ganguly and Carmena 2009, Gilja et al. 2011, Hochberg et al. 2006).

Electrocorticography (ECoG) offers a promising alternative for BMIs (Pasley et al. 2012, Bouchard et al. 2013, Slutzky et al. 2011, Leuthardt et al. 2006, Ganguly et al. 2009). ECoG has the potential to serve as a robust source of neural signals that can be integrated into a clinically viable device. Specifically, it can be: (1) stably recorded over long-periods of time, (2) possesses sufficient 'signal-to-noise' and (3) is known to be rich in information about neural processes, (4) can allow long-term rapid control of multiple degrees of freedom (DOF). Because ECoG arrays lie on the brain surface, they can be stably monitored for very long periods of time (Nadkarni, Ohno-Machado and Chapman 2011a, Thompson et al. 2014b). This approach has been demonstrated clinically in tens of thousands of patients that have had arrays or stimulating electrodes made of the same materials implanted for years (for indications such as pain, movement disorders, or newer closed loop devices for epilepsy) (Nadkarni et al. 2011a).

A significant limitation of current ECoG studies and models is the use of able-bodied subjects in whom motor and sensory pathways are intact. The overwhelming majority of BMI experiments do not monitor physical movements or EMG signals during online BMI control. In addition, intact sensory feedback would likely facilitate learning BMI control. Disabled patients may not have access to such training signals (Bensmaia and Miller 2014). Moreover, it is well known that there is a major reorganization of sensorimotor areas following injury (e.g. after spinal cord injury) (Canolty et al. 2006, Churchland et al. 2012, Miller et al. 2010, Tort et al. 2010). Thus, it remains quite difficult to predict generalization of ECoG-based neuroprosthetic control to disabled patients. It remains unclear if ECoG based control of complex devices can be achieved in paralyzed patients.

Thus, this proposal aims to test feasibility of controlling assistive robotic arms and a communication interface using invasive electrocorticography (ECoG) in subjects with extensive motor disabilities. There have been two main approaches to BCI control, i.e. control of a motor prosthetic (mBCI) or a communication interface (cBCI) (Bensmaia and Miller 2014, Homer et al. 2013, Nicolelis and Lebedev 2009, Schwartz 2004, Shenoy and Carmena 2014). In general, the broader framework for communication is similar to motor control. In a motor BCI, a participant's intention to move is translated into commands for device control. The components of a motor BMI are (1) recordings of neural activity (2) algorithms to transform the neural activity into control signals, (3) an external device driven by these control signals and (4) feedback regarding the current state. Initial studies in able-bodied non-human primates as well as human subjects (e.g. undergoing epilepsy surgical monitoring) have demonstrated the general feasibility of neuroprosthetic control using ECoG based recordings (Leuthardt et al. 2006, Chao, Nagasaka and Fujii 2010, Schalk et al. 2008).

We propose to conduct an early feasibly (i.e. pilot clinical) trial of ECoG-based BMIs in subjects with motor disability. Preclinical studies have suggested that ECoG based recordings provide a viable alternative for clinical translation of BMI technology; however, it remains unclear if complex control can be achieved in patients with neurological disorders. This study will utilize devices cleared by the FDA for the same indication of recording and monitoring of brain electrical activity, but with off label use of the device for at least 1 year to meet the objectives outlined above. Specifically, we will use the Blackrock NeuroPort Array pedestal, or the Blackrock 256-channel

pedestal (not currently cleared by FDA), laser-bonded to PMT Subdural Cortical Electrodes, and connected to the NeuroPort Biopotential Signal Processing System, to acquire neural data. The digitized data will then be transmitted to a personal computer and decoded to direct motion of assistive robotic arms and a communication interface. This will allow individuals to use ECoG neural activity to control complex neuroprosthetic devices. **Demonstration of reliable prosthetic control using ECoG signals in disabled subjects would represent a major milestone. It would strongly motivate the development of implantable wireless ECoG recording systems that can be integrated with assistive robotic devices.**

The Blackrock Microsystems NeuroPort system and the NeuroPort Array have been successfully used in humans with neurological disorders. Several human studies have demonstrated successful long-term implantation of neuroprosthetic control using the Blackrock Microsystem NeuroPort microelectrode array with the NeuroPort system (Hochberg et al. 2012b, Hochberg et al. 2006, Kim et al. 2008a, Ajiboye et al. 2012, Simeral et al. 2011, Bouton et al. 2016). Thus far, at least six patients with tetraplegia have been implanted and monitored with the Blackrock NeuroPort Array and NeuroPort system from published reports. This human data supports chronic implantation of the devices in human patient populations by showing: 1) Chronic stable recordings from the cortex using the NeuroPort Signal Processing system connected to the Blackrock NeuroPort Array may be maintained for at least 5 years. 2) Extensive experience with the decoding of the neural data in humans using these devices 3) Proof of concept that individuals with tetraplegia resulting from neurological injuries could readily use motor cortex neural signals to control a computer cursor after an injury
3) Lack of significant adverse events associated with the devices observed over years after implantation

In this study, the PMT Subdural Cortical Electrodes will replace the Blackrock Microsystems NeuroPort Array microelectrode array for monitoring recordable electrical brain activity. The NeuroPort Array pedestal, or the Blackrock Microsystems 256-channel pedestal, will be bonded to the PMT Subdural Cortical Electrodes (in place of the Blackrock Microsystems NeuroPort Array electrode) in a custom-ordered device collaboratively built by the Blackrock Microsystems and PMT Corporation and sterilized by PMT Corporation. The feasibility of this approach has been demonstrated **in a non-human primate study (i.e. the PMT ECoG grid was connected to a Blackrock Microsystems pedestal connector to monitor neural signals for ~ 18 months)** (Degenhart et al. 2016). After implantation, the study explored the host-tissue response to the subdural ECoG grid implanted for 666 d, focusing on both cortical tissue health and fibrosis at the implant site, while also validating device performance by examining neural responses to overt reaching movements. They found that cortical thickness and neuronal density were both unaffected by the ECoG array implantation. As expected, the grid itself was found to be encapsulated in a fibrous envelope upon explantation. Despite this encapsulation, robust modulation of ECoG signals in recordings conducted 18 months after implantation were observed.

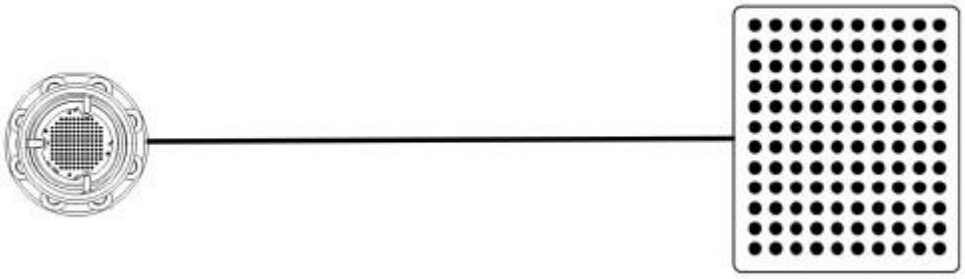


Figure 1: Diagram of pedestal connected to a 128-channel ECoG array

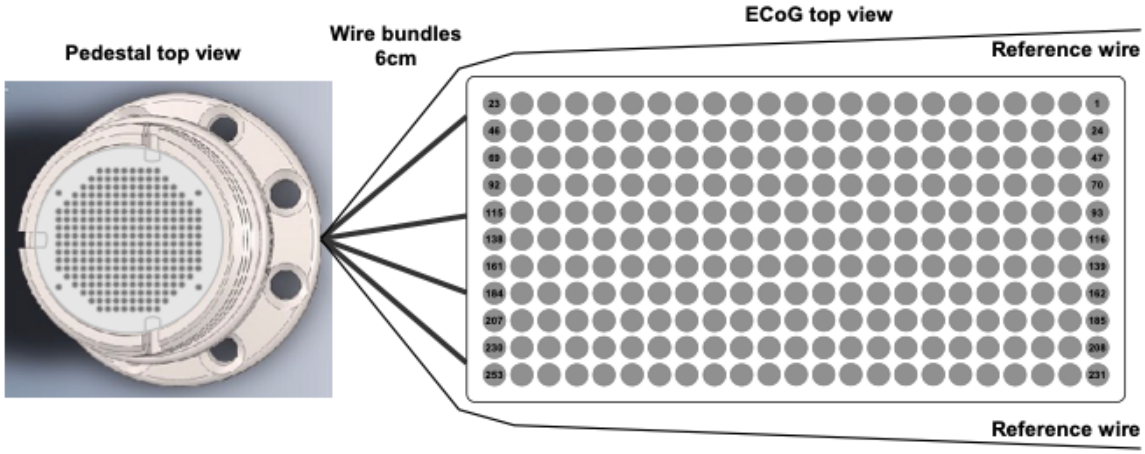


Figure 2: Diagram of pedestal connected to a 253-channel ECoG array

The current literature indicates that ECoG may provide a means by which stable chronic cortical recordings can be obtained with little neural tissue damage, and with a safety level comparable to chronic intracranial device implantations for the treatment of PD. For example, in human subjects, subdural ECoG arrays have been implanted in patients with epilepsy for over 1 year with corroborating evidence of viable long-term neural recordings (Morrell and Group 2011). The primary safety endpoint was achieved whereby the SAE rate for the ECoG system over the first 28 days (device related and not device related) was not worse than the prespecified literature-derived comparator for implantation of intracranial electrodes for seizure localization and epilepsy surgery. Moreover, the SAE rate for the ECoG system during the implant and first 84 days was not worse than the prespecified literature-derived comparator with DBS for PD (Morrell and Group 2011).

2.0 Clinical Study Outline

This study will use the Blackrock Microsystems NeuroPort Biopotential Signal Processing system to record data from the Blackrock Microsystems NeuroPort Array pedestal, or the 256-channel Blackrock Microsystems pedestal, bonded to PMT Subdural Cortical electrodes implanted over cortical areas over a period of at least 1 year. The processed neural signals received by the system will allow us to test the feasibility of training patients to use their neural activity to control assistive robotic arms and a communication interface.

2.1 Study Objectives

This study will allow us to test the feasibility of conditioning individuals with impaired motor ability to be able to control assistive robotic arms and a communication device using ECoG signals.

3.0 Investigational Plan

We aim to conduct a small pilot study to assess the feasibility of translating an ECoG-based interface to control complex neuroprosthetic devices in a severely disabled patient population. **Our underlying hypothesis is that ECoG recordings will allow disabled individuals to skillfully exert motor control of assistive robotic arms and generate verbal output using a computer communication interface.**

In a cohort of 8 subjects, we propose to record and monitor neural signals using subdural electrodes and a mounting and processing system which are already FDA cleared for the general indications of recording and monitoring of brain electrical activity. Specifically, the 510(k) documentation for the Blackrock NeuroPort system and NeuroPort Array states that it "is for temporary (< 30 days) recording and monitoring of brain electrical activity" (K060523 and K090957). The 510K documentation for the PMT Subdural Cortical Electrodes states that it is "cleared for temporary (<30 day) use with recording, monitoring, and stimulation equipment for the recording, monitoring and stimulation of electrical signals on the surface of the brain" (K082474). The Blackrock Microsystems 256-channel pedestal and 256-channel Blackrock Microsystems CereplexE256 digital headstage will also be used in this study (Appendix E). The Blackrock NeuroPort Biopotential Signal Processing System and NeuroPort Electrode Array have been used in human translational clinical studies to record neural activity over a number of months and years and enabled tetraplegic patients to volitionally control computer cursor position and an anthropomorphic prosthetic limb with 7 degrees-of-freedom (Ajiboye et al. 2012, Bouton et al. 2016, Collinger et al. 2013, Hochberg et al. 2012b, Hochberg et al. 2006, Kim et al. 2008b, Simeral et al. 2011). The PMT Subdural Cortical Electrodes have been used extensively in patients for epilepsy monitoring. The combination device of Blackrock Microsystems NeuroPort system, NeuroPort Array pedestal, and PMT Subdural Cortical Electrodes has been implanted in a nonhuman primate to successfully monitor overt reaching movements for 666 days without signal degradation or without significant damage to the brain cortex. We propose to perform long-term

monitoring and testing with the Blackrock/PMT combined system over similar time scales as the aforementioned studies, with the aim of motor and communication control.

We further propose that our investigational device will bear the statement, "CAUTION – Investigational device. Limited by United States law to investigational use."; all devices that will be used in this study will be labeled for investigational use and all labels and labeling will contain the investigational device statement .

Upon UCSF Institutional Review Board (IRB) approval of our investigational plan and protocol, we propose to conduct testing in two phases for each subject. We anticipate that study visits will be conducted in the outpatient office and/or home setting based on participant preference and other practicalities.

This is a single-center study of the use of a ECoG-based neural interface for testing the feasibility of using ECoG signals to control complex devices for motor and speech control in adults affected by neurological disorders with severely impaired motor and communication.

PMT Subdural Cortical Electrodes will be surgically placed directly on the brain surface over the motor and language cortices of subjects with severe disorders of motor control and communication. After implantation of the electrode, study patients will undergo training and assessment of their ability to control assistive robotic arms and determine if ECoG brain signals can be decoded for language communication. This will be performed in two phases.

Phase 1: Optimize BCI system
In Phase 1, we will optimize the entire system to reliably detect neural activity to ensure that the recorded signals are stable and free of artifacts. Moreover, we will ensure that the neural signals can be converted in real-time into cursor or external object movements. This phase will be conducted in the outpatient office setting and/or the patient's home environment, based on patient preference and needs. We anticipate that this phase will take ~1 month; we will, however, specifically tailor the period for each subject.

Phase 2: Testing of BCI Control
In Phase 2, we will test feasibility for both neuroprosthetic control and for decoding speech from neural activity. We will begin experimental testing with the system for control of assistive robotic arms that is classified as a non-significant risk device. As outlined in the sections below, we have multiple safety features to ensure that there is minimal risk for injury during use of the robotic arms, including subject contact during object interaction and the embodiment phase (i.e. the subject's arm is interacting with the exoskeleton).

Throughout this period, neural signals will be recorded and analyzed, and tasks will be performed toward the development, assessment, and improvement of the neural interface system. We anticipate that testing will be conducted in the outpatient office or home setting based on the patient's preference and needs. In this phase, we will also continue to perform experimental testing with the communication interface; we will assess the ability to control a communication interface. We anticipate that this phase will take a minimum of 10-11 months.

4.0
Patient Eligibility

Study subjects will be adults with severe motor impairment secondary to a neurological disorder.

Inclusion Criteria

- Age 21-75 years old
- Limited ability to use upper limbs and limited ability to use speech, based on neurological examination by a board-certified neurological specialist, due to stroke, spastic quadriplegic cerebral palsy (with no significant cognitive deficits based on formal neuropsychological testing), amyotrophic lateral sclerosis (ALS), multiple sclerosis, cervical spinal cord injury, brainstem stroke, muscular dystrophy, myopathy or severe neuropathy
- Disability, defined by a 4 or greater score on the Modified Rankin Scale, must be severe enough to cause loss of independence and inability to perform activities of daily living.
- If stroke or spinal cord injury, at least 1 year has passed since onset of symptoms
- Must live within a two-hour drive of UCSF

Exclusion Criteria

- Pregnancy or breastfeeding
- Inability to understand and/or read English
- Inability to give consent
- Dementia, based on history, physical exam, and MMSE
- Active depression (BDI > 20) or other psychiatric illness (active general anxiety disorder, schizophrenia, bipolar disorder, obsessive-compulsive disorder (OCD), or personality disorders (e.g. multiple personality disorder, borderline personality disorder, etc.)
- History of suicide attempt or suicidal ideation within one's lifetime prior to enrollment, confirmed by a baseline negative Columbia Suicide Severity Rating Scale (C-SSRS)
- Comorbidities including uncontrolled hypertension, cancer, or major organ system failure.
- History of intracranial surgery
- History of substance abuse within the last year
- Ongoing anticoagulation which cannot be stopped in the peri-procedural period.
- Inability to comply with study follow-up visits
- Immunocompromised
- Has an active infection
- Has a CSF drainage system or an active CSF leak
- Requires diathermy, electroconvulsive therapy (ECT), or transcranial magnetic stimulation (TMS) to treat a chronic condition
- Has an implanted electronic device such as a neurostimulator, cardiac pacemaker/defibrillator or medication pump
- Allergies or known hypersensitivity to materials in the Blackrock NeuroPort Array pedestal or the Blackrock 256-channel pedestal (i.e. silicone, titanium) or the PMT
  Subdural Cortical Electrode (silicone, platinum iridium, nichrome)

5.0
Study Device(s)

Cleared for same indication with off-label use of device for at least 1 year:

- Blackrock NeuroPort Array, PN 6248
- Blackrock NeuroPort system, PN 5416
- PMT Subdural Cortical Electrodes, Model #2110TX-128-005, Model #2110TX-253-001

Modifications to Blackrock NeuroPort System with same indication with off-label use of device for at least 1 year:

- Digital Hub, 10480
- NeuroPlex E, 10908

Not cleared:

- Blackrock Microsystems 256-channel pedestal connector (see Appendix E for justification of use)
- Blackrock Microsystems 256-channel CereplexE256 digital headstage (see Appendix E for justification of use)

6.0
Study Procedure

Study Duration: The duration of this pilot study will be 6 years. We expect that all 8 patients will be recruited in the first 4-5 years, and data collection, device development and analysis will be completed in 6 years.

Patient recruitment and clinical characterization: Patients with motor impairments secondary to neurological disorders will be recruited from clinics specializing in the treatment of stroke, ALS, and general neurological disorders, at UCSF.

Enrollment procedures: Prior to enrollment into the study, an informal phone interview to schedule an office-based evaluation will take place, followed by three outpatient screening visits. During the first outpatient visit we will describe the trial in detail and answer all questions. Should the participant choose to continue, we will schedule another visit to conduct a physical exam and to perform screening labs to determine eligibility. During this visit we will screen for eligibility by 1) acquiring patient demographics, 2) reviewing medical history and measuring vital signs, 3) ensuring patients are not currently pregnant or plan to become pregnant, 4) obtaining a list of current medications being taken, 5) ensuring MMSE scores are within a reasonable range ($\geq$18, also accounting for motor difficulties with taking the test), 6) obtain baseline patient-rated and investigator rated clinical global impression scales, 7) assess baseline health status with SF-36 Health Survey, 8) assess current depression and anxiety states with Beck Depression and Anxiety inventories (BDI and BAI, respectively), 9) determine suicidal ideation risk is minimal with Columbia Suicide Severity Rating Scale (C-SSRS) 10) perform a baseline neurological physical exam and 11) determine the disability rating using the modified Rankin Scale. An MRI and CT of the brain will also be obtained for future surgical planning and to further determine eligibility. Moreover, a ECG and chest x-ray will also be obtained. We will then schedule a third follow-up visit to review this data and to answer remaining questions.

Pre-operative care: Subjects will be administered Kefzol 2g IV within 60 minutes prior to surgical incision, and continued for 24 hours post-operatively. In case of allergy to Kefzol, Vancomycin 1gm IV will be used.

Surgery: After obtaining informed consent, subjects will undergo brief general anesthesia (typically ~ 3-4 hours) for the surgical procedure. This may be either IV or inhaled anesthetics. Patient will be given IV antibiotics prior to incision, and re-dosed if required. Induction and wakeup will take place in the operating room, and patients will be monitored in the post-anesthesia care unit (PACU) after surgery for 2-3 hours during the peri-operative period. Subject will then continue to recover on the surgical ward for 2 days.

Subjects will undergo surgical placement of an ECoG array over the dominant (usually left-sided) sensorimotor and speech cortices. The basic operative procedure is similar to what is commonly performed for non-penetrating subdural grid placement in patients with intractable epilepsy, which is well tolerated and has few complications [35]. This surgery will be smaller in exposure given that coverage will be limited to the regions of interest, and not broadly applied as used for epilepsy localization. For placement of the 253-channel electrocorticography array, the craniotomy will be the same size as for the 128-channel array. The craniotomy will also be smaller in exposure compared with the broader exposure for epilepsy localization, which usually includes placement of two 128-channel electrocorticography arrays. Standard procedures for craniotomy at the surgical site will be followed. Briefly, a 5-6 cm curvilinear incision will be made over the anatomic hand representation of the cortex (i.e."hand knob") which is located 3 cm lateral to the midline. Localization will be confirmed using intraoperative BrainLab stereotactic neuronavigation. A craniotomy will then be performed, exposing the dural surface. A wide slit in the dura will be opened.

After identifying the location for the electrode grid implant, the position for the pedestal connector is determined on the adjacent or contra-lateral skull surface and marked. A separate 2 cm scalp incision will be made for the pedestal connector. Holes will be drilled for connector placement and the connector will be secured to the skull with 8 small titanium screws. Once the connector is placed, the electrodes and wire bundle are gently manipulated to position the electrodes so that they are resting on the cortical surface over the area of interest. The nonpenetrating ECoG microarray will be sutured to the dura to secure its position. After successful placement of the electrode grid, the dura will be sutured closed in a watertight fashion and the bone flap will be replaced and secured in place with standard titanium cranial fixation plates and screws.

The surgical site will be irrigated with antibiotic lactated ringers solution. The fascia and skin will be closed with absorbable sutures over the covered craniotomy with a slit accommodating the passage of the connector. The wound will be dressed with a sealed surgical bandage. The expected blood loss for this procedure is 50 cc. The expected operative time is 3-6 hours.

The ECoG electrode array is manufactured by PMT Corporation, and is already FDA-cleared for temporary (<30 days) clinical monitoring of neural signals (K082474). The PMT Subdural Cortical Electrodes are a chronically implantable array containing 128 or 253 electrodes, with an electrode spacing of 4 mm or 3mm, capable of recording from areas of the central nervous system for extended periods of time. The electrode contacts are composed of medical grade platinum iridium, and embedded in a thin sheet of medical grade silastic. The model number 2110 indicates a platinum iridium wire and platinum iridium contacts. Platinum iridium is a mechanically robust alloy electrode material used in commercial DBS leads (Petrossians, Whalen and Weiland 2016).

The electrodes' contacts are molded into a silicone rubber matrix in a fixed pattern. PMT Corporation electrodes are used routinely at our institution and others for seizure localization. In the past ten years, we have not encountered any adverse inflammatory reactions or bleeding specific to the electrode arrays itself (over 100 cases). Insulated wires extend from each electrode through a flexible silicone tube to the connector on the pedestal.

Post-Operative Care: Subjects will be recovered in the intensive care unit and observed for 24 hours before transferring to the ward. A postoperative head CT will be obtained to evaluate for any hemorrhage and to confirm the position of the array. IV antibiotics (Kefzol will used if there are no allergies) will be administered for 24 hours after surgery, followed by prophylactic antibiotics given up to suture removal plus 2 days. Patients will be switched to oral antibiotics as soon as possible. Subjects will undergo physical exam every day with monitoring of vital signs, neurological exam, and basic respiratory, cardiac, and gastrointestinal exams. In addition, the wound site will be inspected at all study visits.

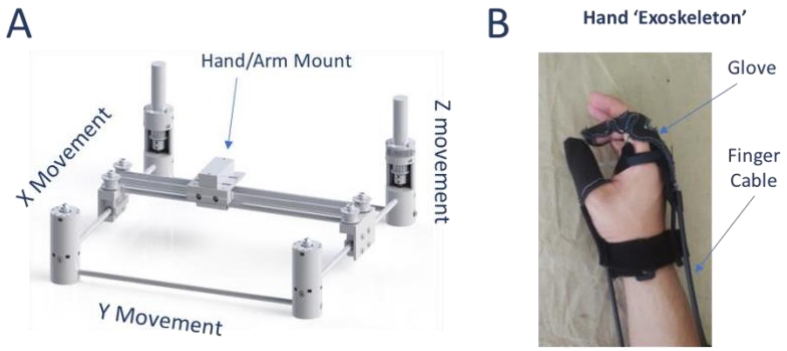
Routine hygiene will consist of handwashing with soap/water and donning gloves using sterile technique when coming in contact with the percutaneous connector. The caregiver and patient will be trained to clean the pedestal site according to specific instructions that will be given to them, to be performed at least once every seven days or as required.

An infection control protocol will be strictly followed. At early signs of infection or irritation the patient/caregiver should contact the study physician immediately. The surgical site will need to be cleaned twice or more during the day, while using extra meticulous hand hygiene. If skin erythema, edema, pain and/or warmth are present, the available drainage will be cultured and oral antibiotics will be started. Plain radiographs of the involved area, ESR, CRP, WBC, and blood cultures will be obtained. If there is no improvement within 72 hours, rapid progression of erythema, symptoms worsen, or if there are signs of systemic toxicity, parenteral antibiotics is warranted. If high fever or severe pain is present, nuchal rigidity, or progressive deterioration in level of consciousness, the participant should go to the hospital emergency room. All implanted hardware will be surgically removed if there is evidence of hardware infection.

Pain related to small craniotomies is usually self-limited. Pain scale ratings will be assessed every 4 hours and routine postoperative pain management will be used. This includes the following medications as needed: acetaminophen and/or Percocet (acetaminophen/hydrocodone). IV pain meds (morphine sulfate or dilaudid) will also be administered if needed. In our experience, most patients do not require IV analgesics beyond the first operative day for smaller craniotomies.

Study visits: As outlined above, system testing will occur through two phases. In the first phase, we will simply optimize the system; in the second phase, we will commence testing of the motor and communication neural interface systems.

In **Phase 1**, the main goal is to ensure reliable neural signal monitoring and optimization of the real-time systems. Initial study visits will occur at defined time points, similar to those normally used in clinical care. For example, we anticipate a visit at post-op day (POD) 10 and 14. During this time, we will simply monitor the neural signals and briefly test the real-time communication with the computer interface. We anticipate additional visits 1-3x/week, based on the patient's availability and preference, to continue to monitor signal stability and check for wound healing. During this phase, we will also offer in home testing of the system to minimize the burden. While the equipment may be kept at the subject's home, testing will only occur when study personnel are present. The total time period of Phase 1 will be approximately 1 months, the exact time will be customized for each patient.



In **Phase 2**, we will test feasibility for both neuroprosthetic control and for decoding speech from neural activity. We will begin to perform experimental testing with the system for control of assistive robotic arms including a custom wearable hand exoskeleton robot and a surface mounted robotic arm which can be classified as non-significant risk devices. As shown in panel A, the exoskeleton system consists of a table top frame that allows x,y,z movement of the arm/hand (i.e. supported by a brace attached to the platform mount). Movements are limited to the natural workspace of each subject. The hand exoskeleton (panel B) will be mounted using a readily releasable magnetic mount. The hand system aims to allow control of the fingers and thumb using a motorized cable system attached to motors. This system will allow us to test restoration of reach to grasp functions in our subjects. The surface mounted robotic arm is a commercially available investigational device for installation on wheelchairs of users with functional limitations or upper body disabilities. It is designed to support active tasks such as eating, drinking, and personal hygiene. There are three options available for control of the robotic arm, including joystick control, a graphical user interface, and an option offering developers to customize control of the robotic arm through a software interface. This system will allow us to test control of a surface mounted robotic assistive arm. However, for the purposes of this study, we will not mount the robotic arm on a wheelchair, but rather to a tabletop. There will be no direct physical contact between the Kinova robot arm and gripper and the participant. In addition, the participant is positioned greater than 48 inches inches away from the base of the robotic arm, rendering it physically impossible for the robot to contact the participant. As outlined in the Risk Analysis (Appendix B), we have multiple safety features to ensure that there is minimal risk for injury during the embodiment and use phase (i.e. the subjects interact with the exoskeleton and surface mounted robotic arm).

Throughout this period, neural signals will be recorded and analyzed, and tasks will be performed toward the development, assessment, and improvement of the neural interface system. We will assess quality of performance using kinematic parameters while performing required tasks. We will analyze stability of neural recordings and performance. To measure stability of the neural representation we will analyze the neural correlates of imagined movements. We will also examine the stability of neural correlates on neuroprosthetic control (e.g. spectral content, timing, spatial recruitment). We will assess changes in the spatial correlation scales and other redundancy measures during learning and stable performance. We anticipate that testing will be conducted in the outpatient office or home setting based on the patient's preference and needs.

In this phase, we will also continue to perform experimental testing with the system for control of a virtual communicating interface. Throughout this period, neural signals will be recorded and analyzed, and tasks will be performed toward the development, assessment, and improvement of the neural interface system. We will assess the ability to control a computer communication interface. To measure stability of the neural representation we will analyze the neural correlates of imagined speech. We will also examine the stability of neural correlates on a neuroprosthetic communication device (e.g. spectral content, timing, spatial recruitment).

Neural activity monitoring: Continuous neural signal data will be acquired from the 253 or 128channel implanted PMT Subdural Cortical Electrodes and processed with the Digital NeuroPort system hardware by Blackrock Microsystems. Broadly, the neural data will consist of ECoG neural activity from neurons in the vicinity of each recording electrode. The neural data will be actively monitored and recorded via the graphical user interface associated with the NeuroPort hardware commercially available via Blackrock. Data read and download are non-invasive and will be performed with the patient comfortably rested. For both the 128 and 253-channel system, the patient will have one or two high-definition multimedia interface (HDMI) connections from the digital headstage to the digital hub for data acquisition. To mitigate the risk of any pulling, snagging, or tension to this connection, we will position our patients such that there is no activity between the digital headstage and the digital hub. Additionally, to further mitigate any risk of head movement which could lead to pulling, we will offer our patients neck support during each session.

The NeuroPort system has been successfully deployed in monitoring neural activity in patients with motor control disorders (e.g. (Hochberg et al. 2012a, Pandarinath et al. 2015)). Blackrock Microsystems provides commercial software that allows real-time filtering, recording, and visualization of acquired neural data and also allows interfacing with other programming languages such as MATLAB (Mathworks, MA) or Python (Python Software Foundation, VA). Together, this allows the ability to create custom software such as communication device based on neural spiking activity, detailed further in the following section. Overall, the mix of commercial and custom software will allow for real-time signal processing, synchronization, and control of the peripheral communication device, with parallel data streams to store data for offline analyses.

Online BMI control of Assistive Robotic Arm Devices:
ECoG signals will be filtered and processed in real-time using a customized portable multi-channel neurophysiology workstation NeuroPort Biopotential Signal Processing System. We will bandpass each channel into multiple bands. Past experiments, including our own, suggest that movement related information is encoded in these bands.

Initialization Phase.

We will train a 'decoder' that maps neural activity to the movement of an assistive robotic arm device. Recent experiments suggest that such methods can rapidly allow control of neuroprosthetic devices. We will train the neural decoder using 'imagined movements'. As paretic/paralyzed patients will not have access to normal overt movement related neural signals, we will use the neural basis of imagined movements for training. During the training phase, patients will observe a

computer screen with either a cursor or a simulated robotic arm. Initial online decoder performance can be assessed in this virtual environment. We will then aim to transition to physical control of the assistive robotic arm devices (with all the safety constraints outlined in this submission).

In order to compare visual versus visual + proprioceptive/tactile feedback signals during decoder conditioning, we will use the exoskeleton setup for decoder conditioning. The arm and hand will move in a stereotyped fashion while the subjects are instructed to 'imagine' actively tracking its path. Of note, we have experience with similar control of an exoskeleton system (Ganguly et al. 2011, Ganguly et al. 2009). As prior and as outlined below, the current system is developed by the Robert Matthews, PhD and Ruzena Bajcsy, PhD (UC Berkeley). They have long-standing experience with kinematic monitoring, limb dynamics and exoskeleton development (Matthew et al. 2015, Matthew et al. 2016, Oskarsson et al. 2016).

The training of the Kinova robot arm will occur with the arm mounted on a table in front of him. The participant will be positioned greater than 48 inches from the robot to be outside the physical reach of the robotic arm and to account for any error. In this case, the subject will be able to control the endpoint of the Kinova robot along with orientation of its gripper and the grasper. Participants will practice object interactions such as picking up a ball and moving it to a second location. Testing of the robotic arm will only be performed with research study personnel present. Participants and caregivers will not use the robotic arm outside of testing with study personnel. In addition, the Kinova robotic arm will only be powered by a wall electrical outlet, and not by battery power.

While testing is conducted with the table mounted robotic arm, experimenters will visualize all channels of data in real-time and monitor for large variations in the recorded neural signals to detect the presence of noise or artifacts that may suggest electromagnetic interference. Additionally, we have implemented detections to determine if the recorded signals significantly differ from historical values or the baseline values recorded at the start of the session. If significant variations are detected, we will power off the robotic arm to determine if it is the source of the noise.

Training Phase. Subjects will be allowed to practice tasks associated with arms/hand and object manipulation. The position of the robotic arm end effector coordinates (x, y, z) will be under direct neural control. Preliminary experiments with an exoskeleton system showed that end effector control (position and orientation of the wrist) was more intuitive and efficient than position control of individual joints. For this initial phase, the motion will be restricted to a 2-dimensional plane for reaching and grasping objects. There are currently 9 tasks which involve interactions with both static and dynamic environments with various fixtures. We will first limit movements to a 2D environment. The additional degree of freedom involving grasp will be included based on proficiency. In addition, given that 'motivation' and reward are known to influence the overall learning process, a gamed-based training environment with specific goals and scoring systems were developed to engage the subject intellectually and to provide additional enrichment during the training phase.

Testing Phase. To assess robustness and stability of control over days we will assess performance characteristics in three tasks. A) Standard center-out task where subjects have to move to the center, engage a grasp, then move to a target and disengage the grasp to release an object such as a ball.

The workspace will be at 95% of the patient's natural reach. Target size will be kept at 5 cm. B) Reaching from a randomized starting and end position in the workspace of Task A. C) Task B except with the need to plan around obstacles that are placed in the direct path.

Online BMI control: Also during phase 2, neural activity will be used to control a real-time communication device using state of the art closed-loop decoders based on rapid changes in neural activity (Shanechi, Orsborn and Carmena 2016). The main advantage of such a decoder lies in its enhanced ability in discriminating user intent and its speed of operating at every event. Such decoders operate at much higher speeds (typically at 200Hz) over previously developed decoders that rely on averaging neural activity (typically at 10Hz). In addition, we will compare this decoder to more standard decoders (e.g. the Weiner Filter, the LMS filter, the Kalman filter and variants). As documented below, the main outcome measure will be the rate of communication using these approaches.

A virtual communication effector will be presented on a computer screen, custom written in the MATLAB or Python programming environment. The interface between MATLAB or Python and the Digital NeuroPort system will be via custom software or commercial software provided by Blackrock Microsystems. The novel decoder will map neural activity to the communication interface. A language processing engine will be concurrently running in the background to model and predict the words and sentences. The following metrics will be utilized to measure performance of the decoder and communication device: selections per minute, accuracy, correct characters per minute (Bacher et al. 2015b) and the bitrate, an information theoretic approach to relate accuracy, time of task completion and complexity (Nuyujukian et al. 2014b, Thompson et al. 2014a). The performance of the novel decoder based communication device will be compared to traditional state space filtering decoders such as the Kalman Filter that has been previously successfully deployed in similar BMI paradigms (Gilja et al. 2012, Bacher et al. 2015b).

Development life cycle of the BMI motor control and communication software:

a) *Scope:* The intended use of the decoder is to allow the patient to achieve control of external devices and thereby select characters and letters to form sentences, as well as control assistive robotic arm devices. As such the operation of the BCI is therefore dependent on the functionality of the software.

b) *Platform:* The software will be developed on MATLAB (The Mathworks, MA) and MATLAB supported C/C++ complied programs (MEX files) or (Python Software Foundation, VA) and will be running on the data acquisition PC that interfaces with the Blackrock NeuroPort Array pedestal connector or on a separate real-time processing machine (as in [Moses*, Metzger*, Liu* et al., 2021]). We will use the software libraries that are part of the Blackrock Digital NeuroPort system, potentially in coordination with custom software, to stream neural data into MATLAB or Python in real-time. All neural data will be streamed through the Blackrock Microsystems Neural Signal Processor before streamed by HDMI cord to MATLAB or Python in real-time.

c) *Inputs and outputs:* The inputs to the software will be the neural signals from the PMT Subdural Cortical Electrodes grid and the output of the software will consist of user controlled (via

the user's neural signals) effector position, selections of characters, letters and numbers for communication purposes, in addition to control of a movements of assistive robotic arms.

d) *Components:* There are four distinct aspects of the software, three that operate 'behind the scenes' and one that serves as a Graphical User Interface for display. First, is the decoder itself that translates neural signals into user intentions. Second, is another parallel decoder that serves to discriminate when the patient has made a particular selection (or e.g. grasping actions). Third, is the software engine that keeps track of the current selections made and generates a list of probable options using a statistical model of movement direction and language (Nadkarni, Ohno-Machado and Chapman 2011b). The fourth and final aspect of the decoder is the Graphical User Interface (GUI) that displays and controls the real-time position of the end effector.

e) *Safety:* The software provides only visual feedback to the user and does not directly interface with the neural signal data acquisition process. The software only serves to allow the use to control the communication interface and the robotic arm position.

f) *Planning phase:* In the planning phase, we will identify off-the-shelf components (such as language processing engines) and will aim to further refine and customize it in-house concurrently with the decoders and GUI.

g) *Development phase:* In the development phase, all components will be developed in parallel as discrete subunits of the overall functional system. A code repository will be maintained to keep track of the life cycle versions and code will be commented wherever appropriate. During the development phase, debugging will be performed at every iteration and documented. The documentation and code will be maintained on secure hard drives.

h) *Testing phase:* There are two aspects of this phase. One is the performance testing of each of the four individual components and the other is the testing of the entire software. In lieu of actual neural signals, simulated neural signals will be delivered as input, with a known mapping between the input and output state as the ground truth is known a priori. This will allow testing the performance of the decoders (accuracy in estimated positions). The testing of the GUI and the software engine will be performed independently of the decoders by manually controlling the position of the effector. The testing of the GUI and the software engine will be assessed by the stability and reliability in updating effector position and robotic arm movements, in the turnaround time of displaying the list of predictive words and actions based on current selections. The overall system testing will employ a combination of simulated neural signals and manual position control to assess the ability of the software in allowing a user to communicate and control a hand neuroprosthetic. *i) Error handling:* Code will be written to specifically monitor potential sources of errors in realtime decoding due to either noise in neural signals or decoder weight drift that would necessitate recalibration and resetting of the GUI and software engine.

j) *Software validation:* The validation and formal design review for the overall software will be performed by members of the PI's laboratory not involved with the development and testing of the software prior to software deployment.

k) *Resolution and maintenance:* Active documentation and daily logs will be noted to keep track of the performance of the software and address issues such as version control, robustness and immediate resolution of unforeseen errors in the software.

Progression of phases: We anticipate phase 1 will last approximately 1 month but will vary based on each subject. Phase 2 will last at a minimum 10-11 months, a total amount of time of at least 1 year after PMT Subdural Cortical Electrodes implantation and neural interface monitoring and testing, a timeframe which has been performed or exceeded without adverse effects by previous

studies using the PMT Subdural Cortical Electrodes and Blackrock Microsystems NeuroPort Array pedestal, and NeuroPort system. In this study, recordings were made over 666 days in a non-human primate with no adverse events related to the implanted devices (Degenhart et al. 2016). The ECoG array is identical in manufacture and material to that used for subdural grid placement in patients with intractable epilepsy, which is well tolerated and has few complications (Chang et al. 2010).

Activation of the brain recording function: All data collection in the study visits will be initiated by the study staff.

Conclusion of study: For each enrolled subject, if there have been no serious adverse events, we will present the option to continue with the study at the end of a 1-year period. If the subject chooses, we will continue with testing for another year. We will formally present this option every year for a period of 5 years. Notably, the subject will be reminded that he/she will have the option for surgical removal of the device at any point.

Removal of the ECoG grid and Connector pedestal: At the conclusion of the study, or earlier if medically indicated, the subdural cortical electrodes and connector pedestal will be surgically removed. The skin incision and bone flap will be reopened and the electrode will be removed and discarded. The dura will be sutured tightly. The galea and scalp will be sutured closed. The expected blood loss is minimal (less than 10 cc), and the expected operative time is 30 minutes.

7.0
Clinical Measurements

Primary

This is a pilot study to test feasibility in eight subjects.

For BCI motor control, we will use outcome measures that are frequently used in preclinical studies of neuroprostheses (e.g. accuracy and reliability of cursor and limb control). As outlined below, the primary goal will be to gather statistics regarding the best achievable control using ECoG signals and state-of-the-art methods to allow motor neuroprosthetic control. For each of the parameters below we aim to describe the statistics as the mean and the variance (Bacher et al. 2015a, Nadkarni et al. 2011a, Nuyujukian et al. 2014a, Shanechi et al. 2016, Thompson et al. 2014b). Ultimately, we will compare these values to a wealth of published data regarding movements in able-bodied subjects, e.g.(Bacher et al. 2015a).

1. *Quality of performance* will be assessed using kinematic parameters while performing the required tasks. We will assess stability of the trajectories in the tasks. We will then assess the ability for generalization from any region in the workspace to another random point. Position errors from the selected trajectory of the task as well as velocity and acceleration will be studied in both joint space and the end effector space.

2. *Recording and Performance Stability*. We will use previously established metrics to analyze stability of neural recordings (Shanechi et al. 2016, Thompson et al. 2014b) and performance. To measure stability of the neural representation we will analyze the neural correlates of daily imagined movements. We will also examine the stability of the neural correlates of neuroprosthetic movements (e.g. spectral content, timing, spatial recruitment).

3. *Spatial Scale*. An important question for ECoG recordings is the optimal spatial scale for the electrode grid. This has implications for maximizing the amount of information that can be obtained from the recording setup but also for defining the design specifications of implantable electronics (e.g. power requirements could vary greatly depending on the spatial and temporal resolution of the neural data required). We will look at changes in the spatial correlation scales and other redundancy measures during learning and stable performance.

The following metrics will further be utilized to measure performance of the decoder and communication device: selections per minute, accuracy, correct characters per minute (Bacher et al. 2015b) and the bitrate, an information theoretic approach to relate accuracy, time of task completion and complexity (Nuyujukian et al. 2014b, Thompson et al. 2014a). Physiological measurements related to neural activity will include statistical assessments of z-scored activity from single electrodes as well as population dynamics. Physiological measurements related to oscillatory activity will include: wide spectrum power-spectral analysis as well as using specific frequency

domain for mean log power (i.e. in the delta, theta, alpha, beta, gamma bands), coupling between the phase of low frequency rhythms and broadband gamma amplitude (phase-amplitude coupling, abbreviated PAC) (Canolty et al. 2006, Miller et al. 2010, Tort et al.).

Clinical measures and physiological measurements will be collected and recorded by members of the research and clinical team.

8.0
Data Management

All clinical and physiological data will be stored in encrypted and password-protected computers in the PI's laboratory that is always locked. If the Digital NeuroPort system is stored in the participant's residence, all research data will be maintained in accordance with UCSF standard encryption policy. In publications or presentations of the data, data will be grouped by case number in chronological order with no name identification. All patients will be asked to sign a separate consent for audio-video recording. When presenting videotape data at scientific conferences, we will utilize only videos from patients who have consented to have their videos shown. De-identified electrophysiological data may be shared with other researchers at other institutions.

9.0
Statistical Methods and Data Analysis

To assess the performance of the decoder, analyses will be performed on the kinematics associated with control, such as time to reach a target, trajectory curvature etc., in conjunction with measures associated with the communication device such as the bit rate, accuracy, characters per minute. The statistical reliability of the decoder will be assessed by non-parametric data permutation wherein the learned mapping between neural activity and the effector position will be artificially broken down and shuffled. Field potential data will be analyzed using wide spectrum power-spectral analysis as well as using specific frequency domain for mean log power (i.e. in the delta, theta, alpha, beta, gamma bands). We will also examine coherence and cross-frequency coupling between the channels (Canolty et al. 2006, Miller et al. 2010, Tort et al.). Using a repeated measures ANOVA statistical analysis, summary statistics for power in relevant frequency bands, control related power changes, and indices of phase-amplitude coupling will be compared at different timepoints of control. Additionally, bootstrap statistical tests and general linear mixed models can be utilized to investigate potential statistical effects, given the small sample size. Mean, median, variance and median absolute deviation describing the statistics of each of the measured outcomes (such as accuracy, effector position control) will be recorded for each subject.

Sample size calculation: This is a pilot study to assess the feasibility of an ECoG based implantable BCI device in patients with motor control disorders using intracranial recordings, a communication interface and assistive robotic arms. The collected pilot data will aid in determining the feasibility, reliability and future directions of the brain machine interface for communication and motor control. In addition, the pilot data will be used to formulate more detailed hypothesis on neural plasticity and BMI control in humans. As such, there is no formal sample size requirement for this pilot study.

Criteria for study success that would justify a larger subsequent trial:

1. Ability to use ECoG-based neural activity to control a neuroprosthetic device and communication interface.
2. No permanent serious adverse events occur (such as trauma with long-term motor deficit).
3. Benefits to the patient in regaining a sense of control over the ability to exert motor control and communicate in an efficient manner.

10.0
Regulatory Requirements

Prior to the start of the study, the following documents will be collected and filed:

- Signed protocol signature page
- Curriculum vitae of the PIs and Sub-investigators, updated within 2 years
- Current medical licenses for the PIs and all Sub-investigators
- Financial disclosure form signed by the PIs and all Sub-investigators
- Copy of the IRB approval letter for the study and the IRB Membership List
- Investigator Agreement

Investigator Obligations

Redacted will be responsible for ensuring that all study site personnel adhere to all FDA regulations and guidelines regarding clinical trials, including guidelines for GCP (including the archiving of essential documents), both during and after study completion.

Additionally, they are responsible for the subject's compliance to the study protocol.

All information obtained during the conduct of the study with respect to the patients' state of health will be regarded as confidential. This is detailed in the written information provided to the patient. An agreement for disclosure of any such information will be obtained in writing and will be signed by the patient.

Informed Consent

The investigators will obtain and document informed consent for each patient screened for this study. All patients will be informed in writing of the nature of the protocol and investigational therapy, its possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate prior to the initiation of study procedures.

Institutional Review Board

This protocol and relevant supporting data are to be submitted to the appropriate IRB for review and approval before the study can be initiated (UCSF, Human Research Protection Program, 3333 California Street, Suite 315, San Francisco, CA, 94118, FWA#00000068; IRB Registration 00000229, Lisa Denney, HRRP Director). Amendments to the protocol will also be submitted to the IRB prior to implementation of the change. The PIs are responsible for informing the IRB of the progress of the study and for obtaining annual IRB renewal. The IRB must be informed at the time of completion of the study and should be provided with a summary of the results of the study by the PIs. The PIs must notify the IRB in writing of any SAE or any unexpected AE according to ICH guidelines.

Data safety monitory board (DSMB) and safety monitoring plan

Treatment emergent adverse events that are assessed by the principal investigators as possibly, probably, or definitely related to surgical implantation or chronic cortical recording AND are unexpected or meet seriousness criteria (death, immediately life threatening, hospitalization >24 hours, persistent or significant disability, or significant intervention required to prevent one of the previously-stated outcomes) will be recorded and reported to the IRB, device manufacturer and the FDA via the MedWatch online voluntary reporting form within 10 working days of the study team's knowledge of the event.

All such events will also be reported to the data safety monitor board (DSMB), *Redacted*, who does not have direct involvement in this study but who has expertise in implantable devices, pain management and neurosurgery. The DSMB will meet regularly to review data related to the clinical trial, provide guidance and feedback, and review any adverse event reports. Treatment-related adverse events assessed as definitely, probably, or possibly related to study procedures and either serious or unexpected, noted by any study personnel will be reported within 10 working days of their knowledge of the event to the DSMB. The DSMB will then advise the PI on potential changes in procedures to improve safety. The safety endpoint will consist of all adverse events.

A Data and Safety Monitoring Board (DSMB), which includes an independent Medical Monitor and Neuroethics expert, will regularly assess reports of unanticipated study-related events. As a part of the DSMB, the independent medical monitor will receive mandatory adverse event reporting in the same timeframe as the DSMB. Apart from this, a report of accumulated adverse event data will be provided on a quarterly basis to the independent medical monitor for review.

Surgical and/or non-Surgical protocol defined adverse events will be recorded on adverse event case report forms. Any serious or unanticipated adverse events will be promptly reported to the DSMB, NIDCD, IRB and FDA in line with regulatory policies.

Throughout the clinical trial, should a serious adverse event occur that is assessed to be related to the presence or surgical implantation of the electrode system, such as infection, the device will be removed and the study halted for the patient. Removal will be accomplished by re-opening the original incisions, temporary removal of the bone, and removal of the PMT Subdural Cortical Electrodes from the brain and NeuroPort Array pedestal from the skull. The dura will be re-sewn together and the bone fixed again with titanium screws

Furthermore, if there is a serious surgical or non-surgical adverse event, or with the onset of suicidality, the study will be halted for the patient.

If two patients meet one or more of these criteria (i. serious surgical or nonsurgery-related adverse event, or ii. onset of suicidality), the study will be halted until information is reviewed by the DSMB and FDA.

References

Ajiboye, A. B., J. D. Simeral, J. P. Donoghue, L. R. Hochberg & R. F. Kirsch (2012) Prediction of imagined single-joint movements in a person with high-level tetraplegia. *IEEE Trans Biomed Eng,* 59**,** 2755-65.

Anderson, K. D. (2004) Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma,* 21**,** 1371-83.

Bacher, D., B. Jarosiewicz, N. Y. Masse, S. D. Stavisky, J. D. Simeral, K. Newell, E. M. Oakley, S. S. Cash, G. Friehs & L. R. Hochberg (2015a) Neural Point-and-Click Communication by a Person With Incomplete Locked-In Syndrome. *Neurorehabil Neural Repair,* 29**,** 46271.

Bacher, D., B. Jarosiewicz, N. Y. Masse, S. D. Stavisky, J. D. Simeral, K. Newell, E. M. Oakley, S. S. Cash, G. Friehs & L. R. Hochberg (2015b) Neural point-and-click communication by a person with incomplete locked-in syndrome. *Neurorehabilitation and neural repair,* 29**,** 462-471.

Bensmaia, S. J. & L. E. Miller (2014) Restoring sensorimotor function through intracortical interfaces: progress and looming challenges. *Nat Rev Neurosci,* 15**,** 313-25.

Birbaumer, N., N. Ghanayim, T. Hinterberger, I. Iversen, B. Kotchoubey, A. Kubler, J. Perelmouter, E. Taub & H. Flor (1999) A spelling device for the paralysed. *Nature,* 398**,** 297-8.

Bouchard, K. E., N. Mesgarani, K. Johnson & E. F. Chang (2013) Functional organization of human sensorimotor cortex for speech articulation. *Nature,* 495**,** 327-32.

Bouton, C. E., A. Shaikhouni, N. V. Annetta, M. A. Bockbrader, D. A. Friedenberg, D. M. Nielson, G. Sharma, P. B. Sederberg, B. C. Glenn, W. J. Mysiw, A. G. Morgan, M. Deogaonkar & A. R. Rezai (2016) Restoring cortical control of functional movement in a human with quadriplegia. *Nature,* 533**,** 247-50.

Canolty, R. T., E. Edwards, S. S. Dalal, M. Soltani, S. S. Nagarajan, H. E. Kirsch, M. S. Berger, N. M. Barbaro & R. T. Knight (2006) High gamma power is phase-locked to theta oscillations in human neocortex. *Science,* 313**,** 1626-8.

Carmena, J. M., M. A. Lebedev, R. E. Crist, J. E. O'Doherty, D. M. Santucci, D. F. Dimitrov, P. G. Patil, C. S. Henriquez & M. A. Nicolelis (2003) Learning to control a brain-machine interface for reaching and grasping by primates. *PLoS Biol,* 1**,** E42.

Chang, E. F., J. W. Rieger, K. Johnson, M. S. Berger, N. M. Barbaro & R. T. Knight (2010) Categorical speech representation in human superior temporal gyrus. *Nat Neurosci,* 13**,** 1428-32.

Chao, Z. C., Y. Nagasaka & N. Fujii (2010) Long-term asynchronous decoding of arm motion using electrocorticographic signals in monkeys. *Front Neuroengineering,* 3**,** 3.

Chestek, C. A., V. Gilja, P. Nuyujukian, R. J. Kier, F. Solzbacher, S. I. Ryu, R. R. Harrison & K. V. Shenoy (2009) HermesC: Low-Power Wireless Neural Recording System for Freely Moving Primates. *Ieee Transactions on Neural Systems and Rehabilitation Engineering,* 17**,** 330-338.

Churchland, M. M., J. P. Cunningham, M. T. Kaufman, J. D. Foster, P. Nuyujukian, S. I. Ryu & K. V. Shenoy (2012) Neural population dynamics during reaching. *Nature,* 487**,** 51-6.

Collinger, J. L., S. Foldes, T. M. Bruns, B. Wodlinger, R. Gaunt & D. J. Weber (2013) Neuroprosthetic technology for individuals with spinal cord injury. *J Spinal Cord Med,* 36**,** 258-72.

Degenhart, A. D., J. Eles, R. Dum, J. L. Mischel, I. Smalianchuk, B. Endler, R. C. Ashmore, E. C. Tyler-Kabara, N. G. Hatsopoulos, W. Wang, A. P. Batista & X. T. Cui (2016) Histological evaluation of a chronically-implanted electrocorticographic electrode grid in a non-human primate. *J Neural Eng,* 13**,** 046019.

Ganguly, K. & J. M. Carmena (2009) Emergence of a stable cortical map for neuroprosthetic control. *PLoS Biol,* 7**,** e1000153.

Ganguly, K., D. F. Dimitrov, J. D. Wallis & J. M. Carmena (2011) Reversible large-scale modification of cortical networks during neuroprosthetic control. *Nat Neurosci,* 14**,** 662-7.

Ganguly, K., L. Secundo, G. Ranade, A. Orsborn, E. F. Chang, D. F. Dimitrov, J. D. Wallis, N. M. Barbaro, R. T. Knight & J. M. Carmena (2009) Cortical representation of ipsilateral arm movements in monkey and man. *J Neurosci,* 29**,** 12948-56.

Gilja, V., C. A. Chestek, I. Diester, J. M. Henderson, K. Deisseroth & K. V. Shenoy (2011) Challenges and opportunities for next-generation intracortically based neural prostheses. *IEEE Trans Biomed Eng,* 58**,** 1891-9.

Gilja, V., P. Nuyujukian, C. A. Chestek, J. P. Cunningham, M. Y. Byron, J. M. Fan, M. M. Churchland, M. T. Kaufman, J. C. Kao & S. I. Ryu (2012) A high-performance neural prosthesis enabled by control algorithm design. *Nature neuroscience,* 15**,** 1752-1757.

Hochberg, L. R., D. Bacher, B. Jarosiewicz, N. Y. Masse, J. D. Simeral, J. Vogel, S. Haddadin, J. Liu, S. S. Cash & P. van der Smagt (2012a) Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature,* 485**,** 372-375.

Hochberg, L. R., D. Bacher, B. Jarosiewicz, N. Y. Masse, J. D. Simeral, J. Vogel, S. Haddadin, J. Liu, S. S. Cash, P. van der Smagt & J. P. Donoghue (2012b) Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature,* 485**,** 372-5.

Hochberg, L. R., M. D. Serruya, G. M. Friehs, J. A. Mukand, M. Saleh, A. H. Caplan, A. Branner, D. Chen, R. D. Penn & J. P. Donoghue (2006) Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature,* 442**,** 164-71.

Homer, M. L., A. V. Nurmikko, J. P. Donoghue & L. R. Hochberg (2013) Sensors and decoding for intracortical brain computer interfaces. *Annu Rev Biomed Eng,* 15**,** 383-405.

Huggins, J. E., P. A. Wren & K. L. Gruis (2011) What would brain-computer interface users want? Opinions and priorities of potential users with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler,* 12**,** 318-24.

Kennedy, P. R. (1994) 'Locked-in' patients. *Neurology,* 44**,** 366-7.

Kennedy, P. R. & R. A. Bakay (1998) Restoration of neural output from a paralyzed patient by a direct brain connection. *Neuroreport,* 9**,** 1707-11.

Kim, S. P., J. D. Simeral, L. R. Hochberg, J. P. Donoghue & M. J. Black (2008a) Neural control of computer cursor velocity by decoding motor cortical spiking activity in humans with tetraplegia. *Journal of Neural Engineering,* 5**,** 455-76.

--- (2008b) Neural control of computer cursor velocity by decoding motor cortical spiking activity in humans with tetraplegia. *J Neural Eng,* 5**,** 455-76.

Kubler, A., B. Kotchoubey, J. Kaiser, J. R. Wolpaw & N. Birbaumer (2001) Brain-computer communication: unlocking the locked in. *Psychol Bull,* 127**,** 358-75.

Leuthardt, E. C., K. J. Miller, G. Schalk, R. P. Rao & J. G. Ojemann (2006) Electrocorticographybased brain computer interface--the Seattle experience. *IEEE Trans Neural Syst Rehabil Eng,* 14**,** 194-8.

Leuthardt, E. C., G. Schalk, J. Roland, A. Rouse & D. W. Moran (2009) Evolution of braincomputer interfaces: going beyond classic motor physiology. *Neurosurg Focus,* 27**,** E4.

Leuthardt, E. C., G. Schalk, J. R. Wolpaw, J. G. Ojemann & D. W. Moran (2004) A braincomputer interface using electrocorticographic signals in humans. *J Neural Eng,* 1**,** 6371.

Matthew, R. P., E. J. Mica, W. Meinhold, J. A. Loeza, M. Tomizuka & R. Bajcsy (2015) Initial investigation into the effect of an Active/Passive exoskeleton on hammer curl performance in healthy subjects. *Conf Proc IEEE Eng Med Biol Soc,* 2015**,** 3607-10.

Matthew, R. P., V. Shia, G. Venture & R. Bajcsy (2016) Generating physically realistic kinematic and dynamic models from small data sets: An application for sit-to-stand actions. *Conf Proc IEEE Eng Med Biol Soc,* 2016**,** 2173-2178.

Miller, K. J., D. Hermes, C. J. Honey, M. Sharma, R. P. Rao, M. den Nijs, E. E. Fetz, T. J. Sejnowski, A. O. Hebb, J. G. Ojemann, S. Makeig & E. C. Leuthardt (2010) Dynamic modulation of local population activity by rhythm phase in human occipital cortex during a visual search task. *Front Hum Neurosci,* 4**,** 197.

Monti, M. M., A. Vanhaudenhuyse, M. R. Coleman, M. Boly, J. D. Pickard, L. Tshibanda, A. M. Owen & S. Laureys (2010) Willful modulation of brain activity in disorders of consciousness. *N Engl J Med,* 362**,** 579-89.

Morrell, M. J. & R. N. S. S. i. E. S. Group (2011) Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology,* 77**,** 1295-304.

Moses, D.A., Metzger, S.L., Liu, J.R., et al., (2021) Neuroprosthesis for Decoding Speech in a Paralyzed Person with Anarthria. *N Engl J Med,* 385, 217-227.

Nadkarni, P. M., L. Ohno-Machado & W. W. Chapman (2011a) Natural language processing: an introduction. *J Am Med Inform Assoc,* 18**,** 544-51.

Nadkarni, P. M., L. Ohno-Machado & W. W. Chapman (2011b) Natural language processing: an introduction. *Journal of the American Medical Informatics Association,* 18**,** 544-551.

Nicolelis, M. A. & M. A. Lebedev (2009) Principles of neural ensemble physiology underlying the operation of brain-machine interfaces. *Nat Rev Neurosci,* 10**,** 530-40.

Nuyujukian, D. S., J. Voutsinas, L. Bernstein & S. S. Wang (2014a) Medication use and multiple myeloma risk in Los Angeles County. *Cancer Causes Control,* 25**,** 1233-7.

Nuyujukian, P., J. C. Kao, J. M. Fan, S. D. Stavisky, S. I. Ryu & K. V. Shenoy (2014b) Performance sustaining intracortical neural prostheses. *Journal of neural engineering,* 11**,** 066003.

Oskarsson, B., N. C. Joyce, E. De Bie, A. Nicorici, R. Bajcsy, G. Kurillo & J. J. Han (2016) Upper extremity 3-dimensional reachable workspace assessment in amyotrophic lateral sclerosis by Kinect sensor. *Muscle Nerve,* 53**,** 234-41.

Pandarinath, C., V. Gilja, C. H. Blabe, P. Nuyujukian, A. A. Sarma, B. L. Sorice, E. N. Eskandar, L. R. Hochberg, J. M. Henderson & K. V. Shenoy (2015) Neural population dynamics in human motor cortex during movements in people with ALS. *Elife,* 4**,** e07436.

Pasley, B. N., S. V. David, N. Mesgarani, A. Flinker, S. A. Shamma, N. E. Crone, R. T. Knight & E. F. Chang (2012) Reconstructing speech from human auditory cortex. *Plos Biology,* 10**,** e1001251.

Schalk, G., K. J. Miller, N. R. Anderson, J. A. Wilson, M. D. Smyth, J. G. Ojemann, D. W. Moran, J. R. Wolpaw & E. C. Leuthardt (2008) Two-dimensional movement control using electrocorticographic signals in humans. *J Neural Eng,* 5**,** 75-84.

Schwartz, A. B. (2004) Cortical neural prosthetics. *Annu Rev Neurosci,* 27**,** 487-507.

Schwartz, A. B., X. T. Cui, D. J. Weber & D. W. Moran (2006) Brain-controlled interfaces: movement restoration with neural prosthetics. *Neuron,* 52**,** 205-20.

Selzer, M. E., S. Clarke, L. G. Cohen, G. Kwakkel & R. H. Miller. 2014. *Textbook of neural repair and rehabilitation*. Cambridge: Cambridge University Press.

Shanechi, M. M., A. L. Orsborn & J. M. Carmena (2016) Robust Brain-Machine Interface Design Using Optimal Feedback Control Modeling and Adaptive Point Process Filtering. *PLoS Comput Biol,* 12**,** e1004730.

Shenoy, K. V. & J. M. Carmena (2014) Combining decoder design and neural adaptation in brainmachine interfaces. *Neuron,* 84**,** 665-80.

Simeral, J. D., S. P. Kim, M. J. Black, J. P. Donoghue & L. R. Hochberg (2011) Neural control of cursor trajectory and click by a human with tetraplegia 1000 days after implant of an intracortical microelectrode array. *J Neural Eng,* 8**,** 025027.

Slutzky, M. W., L. R. Jordan, E. W. Lindberg, K. E. Lindsay & L. E. Miller (2011) Decoding the rat forelimb movement direction from epidural and intracortical field potentials. *J Neural Eng,* 8**,** 036013.

Spataro, R., M. Ciriacono, C. Manno & V. La Bella (2014) The eye-tracking computer device for communication in amyotrophic lateral sclerosis. *Acta Neurol Scand,* 130**,** 40-5.

Taylor, D. M., S. I. Tillery & A. B. Schwartz (2002) Direct cortical control of 3D neuroprosthetic devices. *Science,* 296**,** 1829-32.

Thompson, D. E., L. R. Quitadamo, L. Mainardi, S. Gao, P.-J. Kindermans, J. D. Simeral, R. Fazel-Rezai, M. Matteucci, T. H. Falk & L. Bianchi (2014a) Performance measurement for brain–computer or brain–machine interfaces: a tutorial. *Journal of neural engineering,* 11**,** 035001.

Thompson, D. E., L. R. Quitadamo, L. Mainardi, K. U. Laghari, S. Gao, P. J. Kindermans, J. D. Simeral, R. Fazel-Rezai, M. Matteucci, T. H. Falk, L. Bianchi, C. A. Chestek & J. E. Huggins (2014b) Performance measurement for brain-computer or brain-machine interfaces: a tutorial. *J Neural Eng,* 11**,** 035001.

Tort, A. B., R. Komorowski, H. Eichenbaum & N. Kopell (2010) Measuring phase-amplitude coupling between neuronal oscillations of different frequencies. *J Neurophysiol,* 104**,** 1195-210.

Wolpaw, J. R., N. Birbaumer, D. J. McFarland, G. Pfurtscheller & T. M. Vaughan (2002) Braincomputer interfaces for communication and control. *Clin Neurophysiol,* 113**,** 767-91.

Summary of Changes

1. Correction to our Clinical Protocol (page 30) wording to make it more precise and reflect the intended and appropriate device explantation criteria.

   Before Correction:
   "Throughout the clinical trial, should a serious adverse event occur that is assessed to be surgery related or not, or related to the presence of the electrode system, such as infection, the device will be removed and the study halted for the patient."

   After Correction:
   "Throughout the clinical trial, should a serious adverse event occur that is assessed to be related to the presence or surgical implantation of the electrode system, such as infection, the device will be removed and the study halted for the patient."

2. Change from the Blackrock Microsystems NeuroPort Biopotential Signal Processing system, otherwise known as the NeuroPort system (K060523, K090957), to utilize the newest versions of the Front End Amplifier and its power supply, and the Patient Cable, which are the Digital Hub 128, its power supply, and the NeuroPlex E, respectively.

3. Minor corrections to the wording of several exclusion criteria.

   Before correction:

   - Co-morbidities including ongoing anticoagulation, uncontrolled hypertension, cancer, or major organsystem failure.
   - History of substance abuse
   - History of suicide attempt or suicidal ideation
   - Allergies or known hypersensitivity to materials in the Blackrock NeuroPort Array pedestal (i.e. silicone, titanium) or the PMT Subdural Cortical Electrode (i.e. silicone, platinum iridium, nichrome)

   After correction:

   - Co-morbidities including uncontrolled hypertension, cancer, or major organ system failure.
   - Ongoing anticoagulation which cannot be stopped in the peri-procedural period.
   - History of substance abuse within the last year.
   - History of suicide attempt of suicidal ideation within one's lifetime prior to enrollment, confirmed by a baseline negative Columbia Suicide Severity Rating Scale (C-SSRS).
   - Allergies or known hypersensitivity to materials in the Blackrock NeuroPort Array pedestal or Blackrock 256-channel pedestal (i.e. silicone, titanium) or the PMT Subdural Cortical Electrode (i.e. silicone, platinum iridium, nichrome).

4. Addition of PMT Corporation 253-channel 3-mm-pitch electrocorticography array and the Blackrock Microsystems 256-channel connector pedestal and digital headstage to the clinical protocol.

5. Addition of the assistive robotic arm device to the clinical protocol to supplement the existing arm exoskeleton device.

6. Removal of "History of seizures" from the exclusion criteria.

7. Minor correction to wording in the surgical plan to specify laterality of device placement to the dominant (usually left) hemisphere.

8. Changes to the responsibilities of the Data Safety and Monitoring Board, including addition of an independent Medical Monitor and a Neuroethics expert who will assist in monitoring this study and additional adverse-event reporting requirements.

9. Minor correction to the software plan to specify that Python will be used to present the virtual communication effector and as the interface with the Digital NeuroPort system.

Note about the exploratory nature of the clinical trial

The following note is taken verbatim from a supplementary clinical-protocol file included in our prior publication. The reference for this publication is given at the end of the note.

This clinical trial is a Phase I single-center early feasibility study to evaluate the potential of ECoG-based neural interfaces for controlling advanced neuroprostheses that restore motor and communicative functions. Due to the exploratory nature of the trial and the limited number of trial participants, we did not pre-define specific methods and algorithms to evaluate using specific metrics. This is reflected in the primary endpoints for the efficacy assessments of the clinical trial, which are stated in the protocol as "Feasibility of control of a wearable exoskeleton device and a communication interface."

As a result, a variety of analysis methods will be applied to the datasets collected with the trial participants throughout the trial. Additionally, we did not formalize a statistical analysis plan alongside the protocol. In any reports (publications, presentations, etc.) of analyses that involve data collected as part of this clinical trial, the selection, measurement, statistical testing, and interpretation of outcome metrics will be informed by the relevant literature and performed to the highest standard of analytic and statistical rigor. This includes the present work, which describes a proof-of-concept spelling system controlled by silent attempts to speak and an ECoG-based neural interface with a single participant.

Metzger, S. L., J. R. Liu, D. A. Moses, M. E. Dougherty, M. P. Seaton, K. T. Littlejohn, J. Chartier, G. K. Anumanchipalli, A. Tu-Chan, K. Ganguly & and E. F. Chang (2022) Generalizable Spelling Using a Speech Neuroprosthesis in an Individual with Severe Limb and Vocal Paralysis. *Nature Communications*, 13(1), 6510.

Table 1 CENT 2015 checklist*****; CONSORT 2010 checklist items with modifications or additions for individual or series of N-of-1 trials; empty items in the CENT 2015 column indicate no modification from the CONSORT 2010 item

Section/ Topic	CONSORT 2010 No	CONSORT 2010 Item	CENT 2015 No	CENT 2015 Item
Title and abstract				
	1a	Identification as a randomised trial in the title This is a **single-center early feasibility study** of the use of an ECoG-based neural interface to test the feasibility of ECoG signals to control devices for motor and speech control in adults affected by neurological disorders of movement. Each participant receives the same intervention. **As such, this is not a randomized trial.**	1a	Identify as an "N-of-1 trial" in the title ***For series:*** Identify as "a series of N-of-1 trials" in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) The PMT Subdural Cortical Electrode array, bonded to the Blackrock Microsystems NeuroPort array pedestal or Blackrock Microsystems 253-channel array pedestal will be surgically placed directly on the surface of the brain in regions responsible for speech production and language perception in participants with disorders of motor control. Following surgical implantation of the array and pedestal, the NeuroPort Biopotential Processing System will be connected to the Blackrock Microsystems Neuroport array pedestal or 253ch pedestal to monitor cortical signals. With this ECoG-based neural interface, study participants will take part in recording sessions with researchers to train and assess their ability to control assistive robotic arms and communication outputs. This will be performed in two phases with clinical trial participants. <u>Phase 1: Optimize BCI system</u> In Phase 1, we will start with preliminary testing to optimize the system to reliably detect neural activity to ensure that the recorded signals are stable and free of artifacts. During this phase, we will work to ensure that we can control both the motor and speech control parts of the study. Based on patient preferences, this phase will be conducted in the outpatient office setting and/or the patient's home environment, based on patient preference and needs. This phase will likely take around one month, however, this may be longer or shorter for each subject depending on level of subject control.	1b	*For specific guidance, see CENT guidance for abstracts (table 2)*

Phase 2: Testing of BCI Control

In Phase 2, we will test feasibility for both neuroprosthetic control and for decoding speech from neural activity. We will begin this phase with testing to improve neuroprosthetic control with the robotic arm. As outlined in the sections below, we have multiple safety features to ensure that there is minimal risk for injury during use of the robotic arms, including subject contact during object interaction and the embodiment phase (i.e. the subjects arm is interacting with the exoskeleton). Throughout this period, neural signals will be recorded and analyzed, and tasks will be performed toward the development, assessment, and improvement of the neural interface system. We will assess quality of performance using kinematic parameters while performing required tasks. We will analyze stability of neural recordings and performance. To measure stability of the neural representation we will analyze the neural correlates of imagined movements. We will also assess changes in spatial correlation scales and other redundancy measures during learning and stable performance. We anticipate that testing will continue to be conducted in the outpatient office or home setting based on the patient's preference and needs.

In phase II, we will also continue to perform experimental testing for control of the virtual communication interface. Throughout this period, neural signals will continue to be recorded and analyzed, and tasks will be performed toward the development, assessment, and improvement of the communication interface.

Introduction

Background and objectives	2a	Scientific background and explanation of rationale	2a.1

Restoration of function with assistive robotic arms and a communication interface are important goals of BCIs. Multiple neurological disorders can result in severe bilateral upper limb weakness or paralysis. Surveys of patients with quadriplegia provide important guidance about specific rehabilitation needs and preferences as well as targets for intervention. A survey of patients with tetraplegia resulting from SCI found that restoration of arm and hand function was of highest priority (Anderson 2004). Similarly, patients with ALS reported that direct neural control of a robotic arm would be of great importance (Huggins, Wren and Gruis 2011). While there has been extensive research into each disease process, little has been proven to be clinically effective for the rehabilitation of this chronic disability (Wolpaw et al. 2002).

In patients with conditions such as high cervical SCI, basilar strokes or advanced ALS, the effects can be particularly devastating as tetraplegia may be accompanied by paralysis of oral structures, leading to the loss of voluntary vocal function. Individuals with severe traumatic brain injury or high cervical injuries who require mechanical ventilation may also have limited capacity to communicate (Kennedy 1994,

Kubler et al. 2001, Monti et al. 2010). Standard augmentative and alternative communication (AAC) devices are widely available but may not be suitable for individuals with severe or complete paralysis of the voluntary motor system (Selzer et al. 2014). For example, the most commonly used devices are gaze trackers that allow computer cursor control through eye movements (Spataro et al. 2014). However, eye tracking may have a limited role in advanced cases of ALS and after brainstem strokes, where eye movements are frequently affected (Birbaumer et al. 1999, Kennedy and Bakay 1998). They also require sustained visual attention and may create a high cognitive burden. Thus, it remains critical to develop novel technologies to help restore communication as well as upper limb function.

Brain-Computer Interfaces (BCIs) are a very promising method to significantly improve quality of life by restoring upper extremity function and communication ability in patients with motor and speech disabilities. Over the past decade, the rate and sophistication of research involving invasive BCIs have rapidly increased. BMIs have the potential to seamlessly integrate the computational power of artificial electronic systems with that of the nervous system. Multiple neural signals can be used in a BCI, including non-invasive EEG signals and other neural signals such as spikes and electrocorticography (ECoG) that require invasive placement of electrodes. Non-invasive BCIs have been studied for at least two decades. Known limitations of surface EEG recordings are a low 'signal-to-noise' and contamination by muscle activity (Wolpaw et al. 2002). Recent studies suggest that BMIs using invasive recording of neural signals (spikes or ECoG) can allow more rapid intuitive control over complex devices (Carmena et al. 2003, Leuthardt et al. 2009, Leuthardt et al. 2004, Schwartz et al. 2006, Taylor, Tillery and Schwartz 2002). A large basic science and clinical effort is currently devoted to BMIs based on invasive recordings of action potentials. However, it is increasingly clear that there are significant limits on possible translation of spikes based recordings. It does not readily permit reliable long-term recordings (Chestek et al. 2009, Ganguly and Carmena 2009, Gilja et al. 2011, Hochberg et al. 2006).

Electrocorticography (ECoG) offers a promising alternative for BMIs (Pasley et al. 2012, Bouchard et al. 2013, Slutzky et al. 2011, Leuthardt et al. 2006, Ganguly et al. 2009). ECoG has the potential to serve as a robust source of neural signals that can be integrated into a clinically viable device. Specifically, it can be: (1) stably recorded over long-periods of time, (2) possesses sufficient 'signal-to-noise' and (3) is known to be rich in information about neural processes, (4) can allow long-term rapid control of multiple degrees of freedom (DOF). Because ECoG arrays lie on the brain surface, they can be stably monitored for very long periods of time (Nadkarni, Ohno-Machado and Chapman 2011a, Thompson et al. 2014b). This approach has been demonstrated clinically in tens of thousands of patients that have had arrays or stimulating electrodes made of the same materials implanted for years (for indications such as pain, movement disorders, or newer closed loop devices for epilepsy) (Nadkarni et al. 2011a).

			2a.2	Rationale for using N-of-1 approach
	2b	Specific objectives or hypotheses	2b	
		In eight patients with severe disorders of movement control, we will surgically implant PMT Subdural Cortical Electrodes on the brain surface over the motor and language cortices. The electrode will be bonded to a Blackrock NeuroPort Array pedestal or Blackrock 253ch pedestal which can be connected to the Digital NeuroPort system to process and record neural activity in real time. Using this neural interface, we will condition the patient to be able to control assistive robotic arms, communicate with a computer system for typing and perform speech output tasks. We will utilize optimal neural plasticity mechanisms, a novel framework, and advanced language modeling during BCI conditioning. The underlying hypothesis is that ECoG recordings will allow severely paralyzed individuals to control complex neuroprosthetic devices for movement and communication. A closely related hypothesis is that the well-known stability of ECoG signals will allow us to maximally engage neural mechanism of plasticity and thereby optimize long-term skilled acquisition.		
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio This is an early-feasibility, single-arm clinical trial. We will enroll a cohort of 8 subjects where we propose to record and monitor neural signals using subdural cortical electrodes.	3a	Describe trial design, planned number of periods, and duration of each period (including run-in and wash out, if applicable) ***In addition for series:*** Whether and how the design was individualized to each participant, and explain the series design
	3b	Important changes to methods after trial start (such as eligibility criteria), with reasons	3b	

		Since the trial start, we have made a few changes to eligibility criteria to ensure we capture a representative patient population. 1. Added upper age limit of 75 to reduce the risk of enrolling patients with higher change of age-related cognitive decline 2. Included patients with spastic quadriplegic cerebral palsy (with no significant cognitive deficits based on formal neuropsychological testing) to ensure we include patients with disability due to a variety of neurological disorders 3. Added exclusion criteria to exclude patients with uncontrolled hypertension from the protocol, and to ensure patients taking anticoagulation medications can safely stop them during the perioperative period. Both of these modifications were done to ensure that surgical risk is minimized. 4. Removed history of seizures from inclusion criteria, as several participants may have had seizures which are now well controlled or absent, as well as the fact that our study device is used clinically for treatment of seizures. 5. Updated study device to include the 253ch electrocorticography array with 3mm spacing and the Blackrock Microsystems 253ch pedestal to the study protocol. This change was made to increase cortical coverage and increase density.		
Participant(s)	4a	Eligibility criteria for participants <u>Inclusion Criteria</u> ● Age 21-75 years old ● Limited ability to use upper limbs and limited ability to use speech, based on neurological examination by a board-certified neurological specialist, due to stroke, spastic quadriplegic cerebral palsy (with no significant cognitive deficits based on formal neuropsychological testing), amyotrophic lateral sclerosis (ALS), multiple sclerosis, cervical spinal cord injury, brainstem stroke, muscular dystrophy, myopathy or severe neuropathy ● Disability, defined by a 4 or greater score on the Modified Rankin Scale, must be severe enough to cause loss of independence and inability to perform activities of daily living. ● If stroke or spinal cord injury, at least 1 year has passed since onset of symptoms ● Must live within a two-hour drive of UCSF <u>Exclusion Criteria</u> ● Pregnancy or breastfeeding ● Inability to understand and/or read English ● Inability to give consent ● Dementia, based on history, physical exam, and MMSE	4a†	Diagnosis or disorder, diagnostic criteria, comorbid conditions, and concurrent therapies. ***For series:*** Same as CONSORT item 4a

● Active depression (BDI > 20) or other psychiatric illness (active general anxiety disorder, schizophrenia, bipolar disorder, obsessive-compulsive disorder (OCD), or personality disorders (e.g. multiple personality disorder, borderline personality disorder, etc.)

● History of suicide attempt or suicidal ideation within one's lifetime prior to enrollment, confirmed by a baseline negative Columbia Suicide Severity Rating Scale (C-SSRS) ● Comorbidities including uncontrolled hypertension, cancer, or major organ system failure. ● History of intracranial surgery

● History of substance abuse within the last year

● Ongoing anticoagulation which cannot be stopped in the peri-procedural period.

● Inability to comply with study follow-up visits

● Immunocompromised

● Has an active infection

● Has a CSF drainage system or an active CSF leak

● Requires diathermy, electroconvulsive therapy (ECT), or transcranial magnetic stimulation (TMS) to treat a chronic condition

● Has an implanted electronic device such as a neurostimulator, cardiac pacemaker/defibrillator or medication pump

4b	Settings and locations where the data were collected	4b†	

- University of California, San Francisco Medical Center
  505 Parnassus Ave
  San Francisco, CA 94143
- UCSF Sandler Neuroscience Center
  675 Nelson Rising Lane
  San Francisco, CA 94143
- UCSF Joan and Sanford I. Weill Neurosciences Building
  1651 4th Street
  San Francisco, CA 94158
- St. Mary's Medical Center
  450 Stanyan St, San Francisco, CA 94117
- The home of each participant.
- Medical office at 181 Andrieux St, Sonoma, CA 95476

		4c	Whether the trial(s) represents a research study

				and if so, whether institutional ethics approval was obtained
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered As mentioned above, this is an early-feasibility, phase I, pilot clinical trial with only one group. Each participant undergoes surgical implantation of intracranial electrodes for the purpose of testing the feasibility of using ECoG signals to control complex devices for motor and speech control in adults affected by neurological disorders of movement. Following implantation of the electrode and pedestal, the NeuroPort Biopotential Processing System will be connected to the NeuroPort Array pedestal or Blackrock Microsystem 253ch pedestal to monitor and record neural signals. With this ECoG-based neural interface, study patients will undergo training and assessment of their ability to control assistive robotic arms and to determine if ECoG brain signals can be decoded for communication and motor control.	5	The interventions for each period with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed <u>Primary Endpoints</u>: Feasibility of control of assistive robotic arms and a communication interface. Safety Assessments: ● Physical examination at all study visits ● Perform functional test of the PMT/Blackrock combined neural interface system prior to implantation ● Surgical/ or nonsurgical protocol-defined adverse events recorded on adverse events case report forms and use of protocol-defined procedures for adverse event management ● Assessment of suicidality using Columbia Suicide Severity Rating Scale, and assessment of changes using the Beck Depression and Anxiety Inventories, at monthly intervals.	6a.1	
			6a.2	Description and measurement properties

				(validity and reliability) of outcome assessment tools
	6b	Any changes to trial outcomes after the trial commenced, with reasons	6b	
		N/A		
Sample size	7a	How sample size was determined	7a	
		Sample size calculation: This is a pilot study to assess the feasibility of an ECoG based implantable BCI device in patients with motor control disorders using intracranial recordings, a communication interface and assistive robotic arms. The collected pilot data will aid in determining the feasibility, reliability and future directions of the brain machine interface for communication and motor control. In addition, the pilot data will be used to formulate more detailed hypothesis on neural plasticity and BMI control in humans. As such, there is no formal sample size requirement for this pilot study.		
	7b	When applicable, explanation of any interim analyses and stopping guidelines	7b	
		As this is an early feasibility, phase I, pilot clinical trial, there are no interim planned analyses.		
		Stopping guidelines:		
		Surgical and/or non-Surgical protocol defined adverse events will be recorded on adverse event case report forms. Any serious or unanticipated adverse events will be promptly reported to the DSMB, NIDCD, IRB and FDA in line with regulatory policies.		
		Throughout the clinical trial, should a serious adverse event occur that is assessed to be related to the presence or surgical implantation of the electrode system, such as infection, the device will be removed and the study halted for the patient. Removal will be accomplished by re-opening the original incisions, temporary removal of the bone, and removal of the PMT Subdural Cortical Electrodes from the brain and NeuroPort Array pedestal from the skull. The dura will be re-sewn together and the bone fixed again with titanium screws		
		Furthermore, if there is a serious surgical or non-surgical adverse event, or with the onset of suicidality, the study will be halted for the patient.		

		If two patients meet one or more of these criteria (i. serious surgical or nonsurgery-related adverse event, or ii. onset of suicidality), the study will be halted until information is reviewed by the DSMB and FDA.		
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence N/A, not a randomized trial.	8a	Whether the order of treatment periods was randomised, with rationale, and method used to generate allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size) N/A, not a randomized trial	8b	When applicable, type of randomisation; details of any restrictions (such as pairs, blocking)
			8c	Full, intended sequence of periods
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned N/A	9	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions As mentioned above, this study is an early feasibility, phase I, pilot clinical trial. As such, there is no random allocation sequence applied. Participants are enrolled by the study PI with assistance from IRB approved study clinicians and research coordinators.	10	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	11a	

		N/A		
	11b	If relevant, description of the similarity of interventions N/A	11b	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes As mentioned above, this is an early feasibility, phase I, pilot clinical trial. As such, there are no separate groups for comparison. To work towards our primary objective of feasibility of an ECoG-based neuroprosthesis for motor and communication restoration, we perform analyses to assess the overall performance overtime. The statistical reliability of the decoder will be assessed by non-parametric data permutation wherein the learned mapping between neural activity and the effector position will be artificially broken down and shuffled. Field potential data will be analyzed using wide spectrum power-spectral analysis as well as using specific frequency domain for mean log power (i.e. in the delta, theta, alpha, beta, gamma bands).	12a	Methods used to summarize data and compare interventions for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses N/A	12b	***For series:*** If done, methods of quantitative synthesis of individual trial data, including subgroup analyses, adjusted analyses, and how heterogeneity between participants was assessed, (for specific guidance on reporting syntheses of multiple trials, please consult the PRISMA Statement)

			12c	Statistical methods used to account for carryover effect, period effects, and intra-subject correlation
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome As this is an early feasibility, phase I, pilot clinical trial, each patient receives the same treatment, and are assessed as described above for the primary outcome. We have enrolled three participants in total, with two active participants. Both received the same intervention and were assessed for the same primary outcome.	13a.1	Number and sequence of periods completed, and any changes from original plan with reasons
			13a.2	***For series:*** The number of participants who were enrolled, assigned to interventions, and analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons N/A	13c	***For series:*** losses or exclusions of participants after treatment assignment, with reasons, and period in which this occurred, if applicable
Recruitment	14a	Dates defining the periods of recruitment and follow-up	14a†	

		Recruitment began during October of 2018, with enrollment of the participant included in these analyses in September 2022. The current participant will be offered the option to continue in the trial for a maximum length of five years. General Recruitment Protocol: Patients with motor impairments secondary to neurological disorders will be recruited from clinics specializing in the treatment of stroke, ALS, and general neurological disorders at UCSF. For each enrolled subject, if there have been no serious adverse events, we will present the option to continue with the study at the end of a 1-year period. If the subject chooses, we will continue with testing for another year. We will formally present this option every year for a period of 5 years. Notably, the subject will be reminded that he/she will have the option for surgical removal of the device at any point.		
	14b	Why the trial ended or was stopped N/A	14b	Whether any periods were stopped early and/or whether trial was stopped early, with reason(s).
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group One participant is included in our one group. Participant was 47 years old at enrollment who suffered a brainstem stroke at the age of 30 years old after which she was diagnosed with quadriplegia and anarthria.	15†	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups One participant is included in the analyses.	16	For each intervention, number of periods analysed. ***In addition for series:*** if quantitative synthesis was performed,

				number of trials for which data were synthesized
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) N/A. Primary outcome is feasibility of ECoG-based system.	17a.1	For each primary and secondary outcome, results for each period; an accompanying figure displaying the trial data is recommended.
			17a.2	For each primary and secondary outcome, the estimated effect size and its precision (such as 95% confidence interval) ***In addition for series:*** if quantitative synthesis was performed, group estimates of effect and precision for each primary and secondary outcome
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended N/A	17b	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	18	Results of any other analyses performed,

		N/A		including assessment of carryover effects, period effects, intra-subject correlation ***In addition for series:*** If done, results of subgroup or sensitivity analyses
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) N/A, no participants have been withdrawn due to any adverse events.	19	All harms or unintended effects for each intervention. *(for specific guidance see CONSORT for harms)*
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses As this is an early feasibility, phase I, pilot clinical trial, there are limitations of generalizability due to the sample size of the study. However, such limitations are mitigated by the fact that the collected pilot data will aid in the feasibility, reliability, and future directions of brain computer interfaces for communication and motor control, as well as future larger clinical trials which could better generalize.	20	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings Any findings in this early feasibility trial will be applied to future investigations into the use of an ECoG-based neuroprosthesis for motor and speech restoration. As this is a low-enrollment trial, there will not be a large enough number of participants to ensure generalizability. However, this is an early feasibility trial with no aims to generalize.	21	

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence Informed by the existing literature on the long-term viability of ECoG interfaces (Nadkarni, Ohno-Machado and Chapman 2011a, Thompson et al. 2014b, Nadkarni et al. 2011a), we expect that the benefit of gaining key knowledge and insights from this early feasibility trial concerning the suitability of an ECoG-based neuroprosthesis for motor and speech restoration are well justified given the known potential risks. Participants are informed of known potential risks and mitigation strategies, which are covered in the informed consent form and the clinical protocol. The findings of the current study, and of our prior work (Metzger, Liu, Moses et al 2022, Moses, Metzger, Liu, et al. 2021), within this clinical trial support the interpretation that ECoG interfaces are clinically viable for communication restoration, although continued development of the approach and further validation with other participants are necessary to affirm this.	22
Other information			
Registration	23	Registration number and name of trial registry The study was registered at ClinicalTrials.gov under the identifier NCT03698149.	23
Protocol	24	Where the full trial protocol can be accessed, if available The full clinical-trial protocol can be found as an attachment alongside the manuscript.	24
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders The following sources of funding supported our prior work (Moses, Metzger, Liu et al. 2021) and/or the current study: A research contract under Facebook's Sponsored Academic Research Agreement; the National Institutes of Health (grant NIH U01 DC018671-01A1); Joan and Sandy Weill and the Weill Family Foundation; the Bill and Susan Oberndorf Foundation; the William K. Bowes, Jr. Foundation; and the Shurl and Kay Curci Foundation.	25

*****It is strongly recommended that this checklist be read in conjunction with the CENT 2015 Explanation and Elaboration[24] for important clarification on the items. The copyright for CENT (including checklist) is held by the CENT Group and is distributed under a Creative Commons Attribution (CC-BY 4.0) license.
†Caution should be taken when reporting potentially identifying information pertaining to CENT items 4a, 4b, 14a, and 15.

References

Anderson, K. D. (2004) Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma,* 21**,** 1371-83.

Huggins, J. E., P. A. Wren & K. L. Gruis (2011) What would brain-computer interface users want? Opinions and priorities of potential users with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler,* 12**,** 318-24.

Wolpaw, J. R., N. Birbaumer, D. J. McFarland, G. Pfurtscheller & T. M. Vaughan (2002) Brain-computer interfaces for communication and control. *Clin Neurophysiol,* 113**,** 767-91.

Kubler, A., B. Kotchoubey, J. Kaiser, J. R. Wolpaw & N. Birbaumer (2001) Brain-computer communication: unlocking the locked in. *Psychol Bull,* 127**,** 358-75.

Kennedy, P. R. (1994) 'Locked-in' patients. *Neurology,* 44**,** 366-7.

Kennedy, P. R. & R. A. Bakay (1998) Restoration of neural output from a paralyzed patient by a direct brain connection. *Neuroreport,* 9**,** 1707-11.

Selzer, M. E., S. Clarke, L. G. Cohen, G. Kwakkel & R. H. Miller. 2014. *Textbook of neural repair and rehabilitation*. Cambridge: Cambridge University Press.

Spataro, R., M. Ciriacono, C. Manno & V. La Bella (2014) The eye-tracking computer device for communication in amyotrophic lateral sclerosis. *Acta Neurol Scand,* 130**,** 40-5.

Birbaumer, N., N. Ghanayim, T. Hinterberger, I. Iversen, B. Kotchoubey, A. Kubler, J. Perelmouter, E. Taub & H. Flor (1999) A spelling device for the paralysed. *Nature,* 398**,** 297-8.

Carmena, J. M., M. A. Lebedev, R. E. Crist, J. E. O'Doherty, D. M. Santucci, D. F. Dimitrov, P. G. Patil, C. S. Henriquez & M. A. Nicolelis (2003) Learning to control a brain-machine interface for reaching and grasping by primates. *PLoS Biol,* 1**,** E42.

Leuthardt, E. C., G. Schalk, J. Roland, A. Rouse & D. W. Moran (2009) Evolution of brain-computer interfaces: going beyond classic motor physiology. *Neurosurg Focus,* 27**,** E4.

Leuthardt, E. C., G. Schalk, J. R. Wolpaw, J. G. Ojemann & D. W. Moran (2004) A brain-computer interface using electrocorticographic signals in humans. *J Neural Eng,* 1**,** 63-71.

Taylor, D. M., S. I. Tillery & A. B. Schwartz (2002) Direct cortical control of 3D neuroprosthetic devices. *Science,* 296**,** 1829-32.

Schwartz, A. B., X. T. Cui, D. J. Weber & D. W. Moran (2006) Brain-controlled interfaces: movement restoration with neural prosthetics. *Neuron,* 52**,** 205-20.

Chestek, C. A., V. Gilja, P. Nuyujukian, R. J. Kier, F. Solzbacher, S. I. Ryu, R. R. Harrison & K. V. Shenoy (2009) HermesC: Low-Power Wireless Neural Recording System for Freely Moving Primates. *Ieee Transactions on Neural Systems and Rehabilitation Engineering,* 17**,** 330-338.

Ganguly, K., D. F. Dimitrov, J. D. Wallis & J. M. Carmena (2011) Reversible large-scale modification of cortical networks during neuroprosthetic control. *Nat Neurosci,* 14**,** 662-7.

Gilja, V., C. A. Chestek, I. Diester, J. M. Henderson, K. Deisseroth & K. V. Shenoy (2011) Challenges and opportunities for next-generation intracortically based neural prostheses. *IEEE Trans Biomed Eng,* 58**,** 1891-9.

Hochberg, L. R., M. D. Serruya, G. M. Friehs, J. A. Mukand, M. Saleh, A. H. Caplan, A. Branner, D. Chen, R. D. Penn & J. P. Donoghue (2006) Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature,* 442**,** 164-71.

Nadkarni, P. M., L. Ohno-Machado & W. W. Chapman (2011a) Natural language processing: an introduction. *J Am Med Inform Assoc,* 18**,** 544-51.

Thompson, D. E., L. R. Quitadamo, L. Mainardi, K. U. Laghari, S. Gao, P. J. Kindermans, J. D. Simeral, R. Fazel-Rezai, M. Matteucci, T. H. Falk, L. Bianchi, C. A. Chestek & J. E. Huggins (2014b) Performance measurement for brain-computer or brain-machine interfaces: a tutorial. *J Neural Eng,* 11**,** 035001.

Nadkarni, P. M., L. Ohno-Machado & W. W. Chapman (2011a) Natural language processing: an introduction. *J Am Med Inform Assoc,* 18**,** 544-51.

Moses, D.A., Metzger, S.L., Liu, J.R., et al., (2021) Neuroprosthesis for Decoding Speech in a Paralyzed Person with Anarthria. *N Engl J Med,* 385, 217-227.