INTUITIVE

INnovative Network for Training in ToUch InteracTIVE Interfaces

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Executive summary:

In this document we illustrate our method to achieve long-term recordings from large populations of cortical neurons simultaneously, while the distal digits are being reproducibly stimulated using a variety of combinations of haptic input features. We show that even in this very large population of neurons, each individual neuron is providing partly unique information for each combination, or a subset of combinations, of haptic input features. Combining information from a small subset of recorded neurons can thereby dramatically increase the decoding based on the neural information available in the system.

First representation of haptic input features across a population of cortical neurons

Deliverable 2.1, INTUITIVE

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INTRODUCTION

The aim of this deliverable is a first level description of the representation of haptic input features across a population of cortical neurons. This is a critical part of the aim of INTUITIVE to push forward the research frontiers in neuroscience, by gaining valuable knowledge on cortical information processing of data generated in wide populations of tactile afferents, whose activation is tuned to the skin biomechanics. Hence, it will help us to reach the goal of INTUITIVE to develop a new conceptual framework for tactile sensing and active perception where the signals of interdependent sensors are used to extract ultra-rich haptic information. For example, such results can be applied to develop biomimetic sensing for robotics and assistive devices. It will also help in developing algorithms for predictive coding of skin sensor dependency states performed across a population of peripheral and central neurons. All of which are central objectives for INTUITIVE.

In neuroscience studies such as the present one, the importance of using natural forms of skin stimulation, which unavoidably engages a large number of sensors across distributed skin areas (Jorntell et al., 2014; Oddo et al., 2017), is best understood in relation to the alternative scientific view proposed in the INTUITIVE project. Here, we are looking for the generic, fundamental brain mechanisms which apply to any skin-object interaction, a view that is based on considerations of the non-local laws of contact mechanics (Hayward, 2011), which stipulates that any natural type of skin-object interaction can be decomposed into a more generic set of haptic input features. Locally in the skin, this means that any type of interaction, or haptic input feature, is composed of a spatiotemporal evolution of skin sensor activation, and this is the minimal building block of human brain processing of haptic inputs. This differs from the pixelwise scheme of biological skin sensor data processing, which is currently prevailing in the literature, in the fundamental respect that tactile information is distributed across a large population of skin sensors that are non-independent. Thus, instead of viewing as a simple multiplication/summation of empirically defined properties for handful classes of tactile sensors, the tactile inputs should be viewed as spatiotemporal sub-manifolds of the high-dimensional space of the skin tissue's mechanical state. The features that arise in such skin-object interactions are spatiotemporal contact state evolutions across many tactile sensors, whose brain representation is a major scientific question that INTUITIVE wants to address, which is what we address in this study. This information is also an important key to begin to understand how predictive coding mechanisms for perception, another important scientific goal for INTUITIVE, are implemented in the neuronal circuitry. The study related to encoding of tactile stimuli (individual and collective) and its decoding by central neurons, investigated by ULUND, will be complemented by the work of ACA, which will investigate how soft skin material could modulate the tactile encoding. The understanding on tactile encoding will lead to new algorithm and models which can be used in artificial systems such

as robots to process tactile information as efficiently as in humans, at work carried out at ICL and BMW.

Here, we first wanted to explore the limits of that capacity in the neocortical network per se, i.e. what is the resolvability of highly similar spatiotemporal patterns of skin sensor information, provided in naturalistic, dynamic skin-object interactions. To address this issue, we needed to make invasive recordings of individual neurons in the neocortex. Invasive recordings require animal experiments and in the present set of experiments we recorded from the neocortex of the rat. In order to get the highest quality data from each experiment, we wanted to achieve recordings from 100's of neurons simultaneously, and we wanted the recordings from the specific neurons to last for a long time so that we could acquire large amounts of data. This would also allow us to get a much clearer picture of the differential tuning properties of neocortical neurons with respect to the haptic input features. The differential tuning properties across neurons is in itself a key goal, since this specific aspect of neocortical encoding of tactile events has potential paramount importance for our understanding of the limits of brain processing of haptic events. Hence, rather than relying on few parallel channels for recording individual neurons, we decided to take a more ambitious approach with several 100's of separate neurons recorded individually, spanning the full depth of the cortex including all layers, using the NeuroPixel probe (Jun et al., 2017). To generate the activation of tactile afferents, we used a new haptic display developed by ACA within the INTUITIVE project, which enables an infinite variety of spatiotemporal skin activation patterns, where each pattern is highly reproducible. The latter functionality is of the highest importance to be able to evaluate the specificity and resolution of the neocortical neuronal tuning to different haptic input features.

RESULTS

In order to record from a high number of cortical neurons in parallel in the paw region of the rat S1 neocortex (Oddo et al., 2017; Enander and Jorntell, 2019; Enander et al., 2019), we used the Neuropixels probe (Figure 1) (Jun 2017).

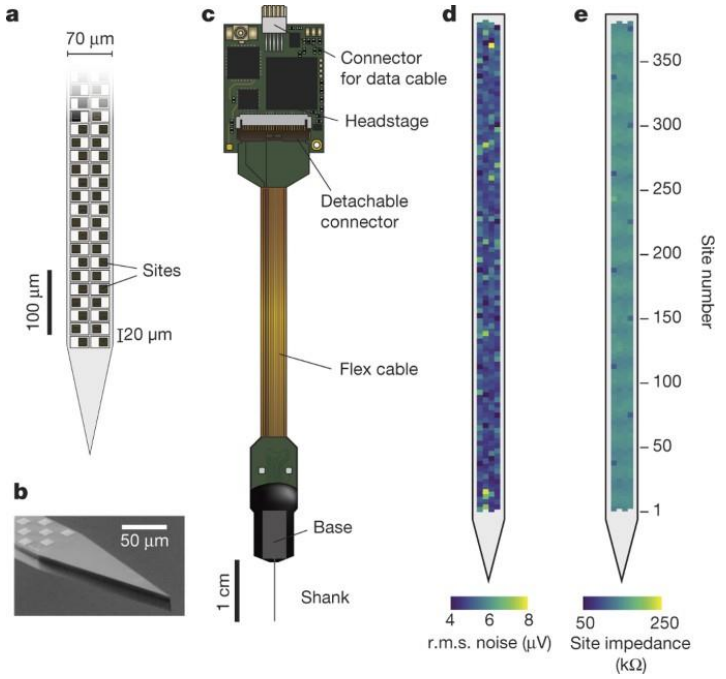

Figure 1: Neuropixels probe used to obtain recordings from multiple neurons simultaneously.

The Neuropixels probe contains 384 individual recording channels. In our recordings, each channel provide a low-noise signal where spikes from individual neurons were often clearly separable (Figure 2).

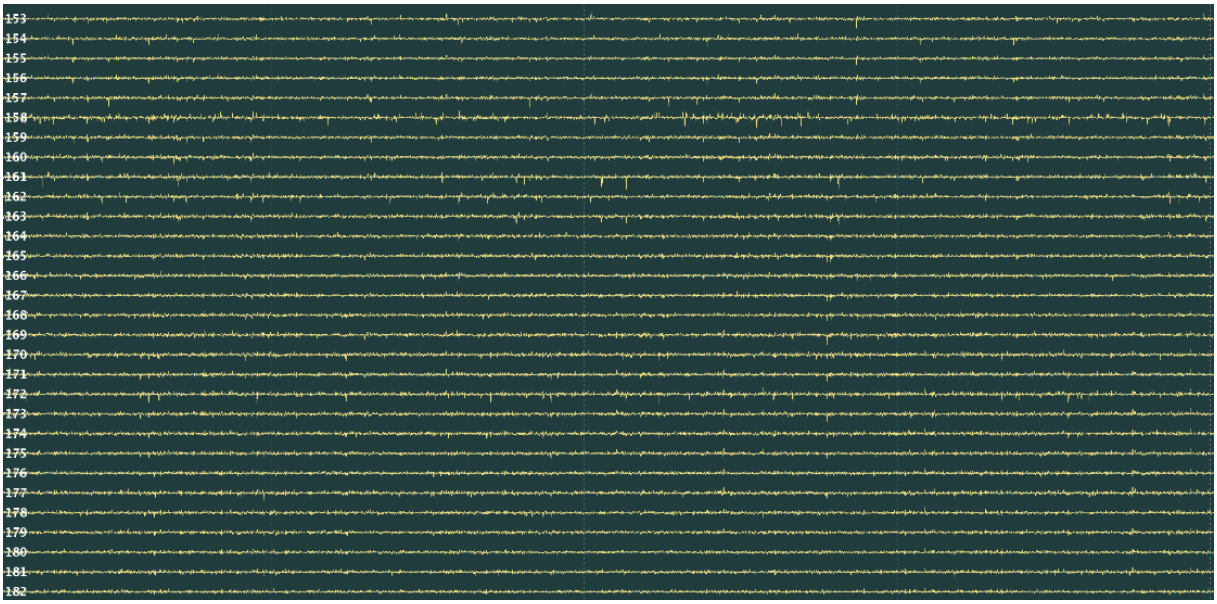

Figure 2: 800 ms of raw recording data from a subsection of the recording probe comprising 30 of its 383 recording channels. Peak-to-peak voltage for each channel was 0.05 mV.

In some cases, different neurons could be recorded from an overlapping set of recording channels (Figure 3A, illustrating 6 different neuronal units recorded from 6 neighboring channels, labelled channel I-VI). In this case, superimposed spikes of the different units could often be separated in at least a subset of the channels (Figure 3B). Different units with different morphology and different distances from the recording probe would be expected to result in spikes of different shapes being recorded (Figure 3C). In cases of doubt, we applied PCA to the spike shapes to verify their relative clusterability and thus their identification as being generated by separate neurons (Figure 3D).

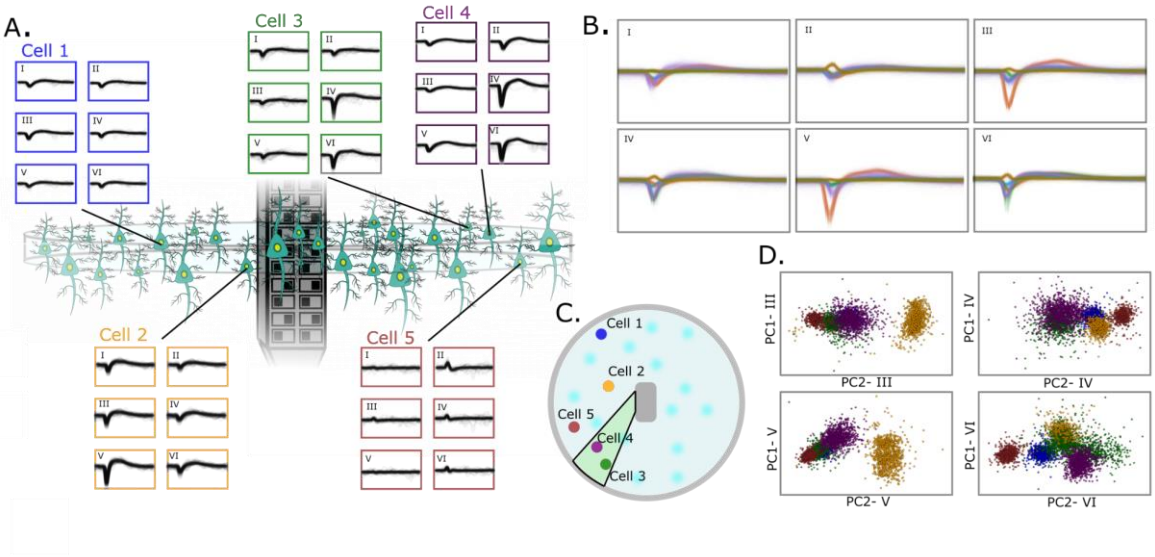

Figure 3: Sorting of neuronal units represented across overlapping neighboring channels. (A) 100 superimposed spikes each for 5 different cells (identified by the color codes framing each subpanel, same color code also apply to all other main panels) recorded across 6 channels. Note how their spike shapes and amplitudes varied across those channels. (B) Superimposed raw traces of the 5 different spikes across the 6 channels. (C) Hypothetic locations of the 5 different cells in relation to the recording probe. (D) PCA of the spike shapes for clustering analysis.

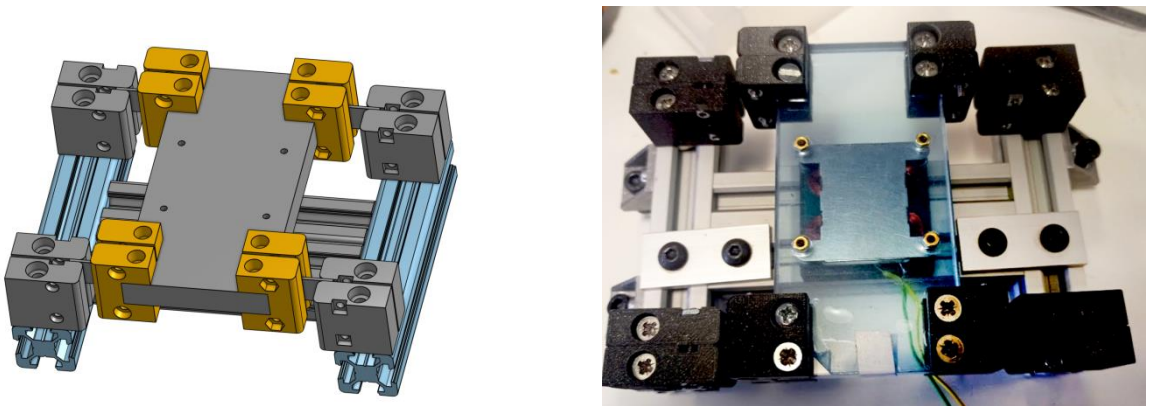

Figure 4. Haptic stimulation device developed by Actronika SAS in the INTUITIVE project (Deliverable 2.3).

The experiments consisted in continuous recordings of the neuronal activity across all channels, while intermittently delivering brief (300 ms or less) stimuli to the rat forepaw digits which were resting on a custom-made haptic stimulation device (Figure 4). The stimuli were one-dimensional vibrations of various superimposed frequencies (Figure 5). The stimuli were designed to be difficult to resolve, and when tested on ourselves as human subjects, these inputs were indeed hard to resolve.

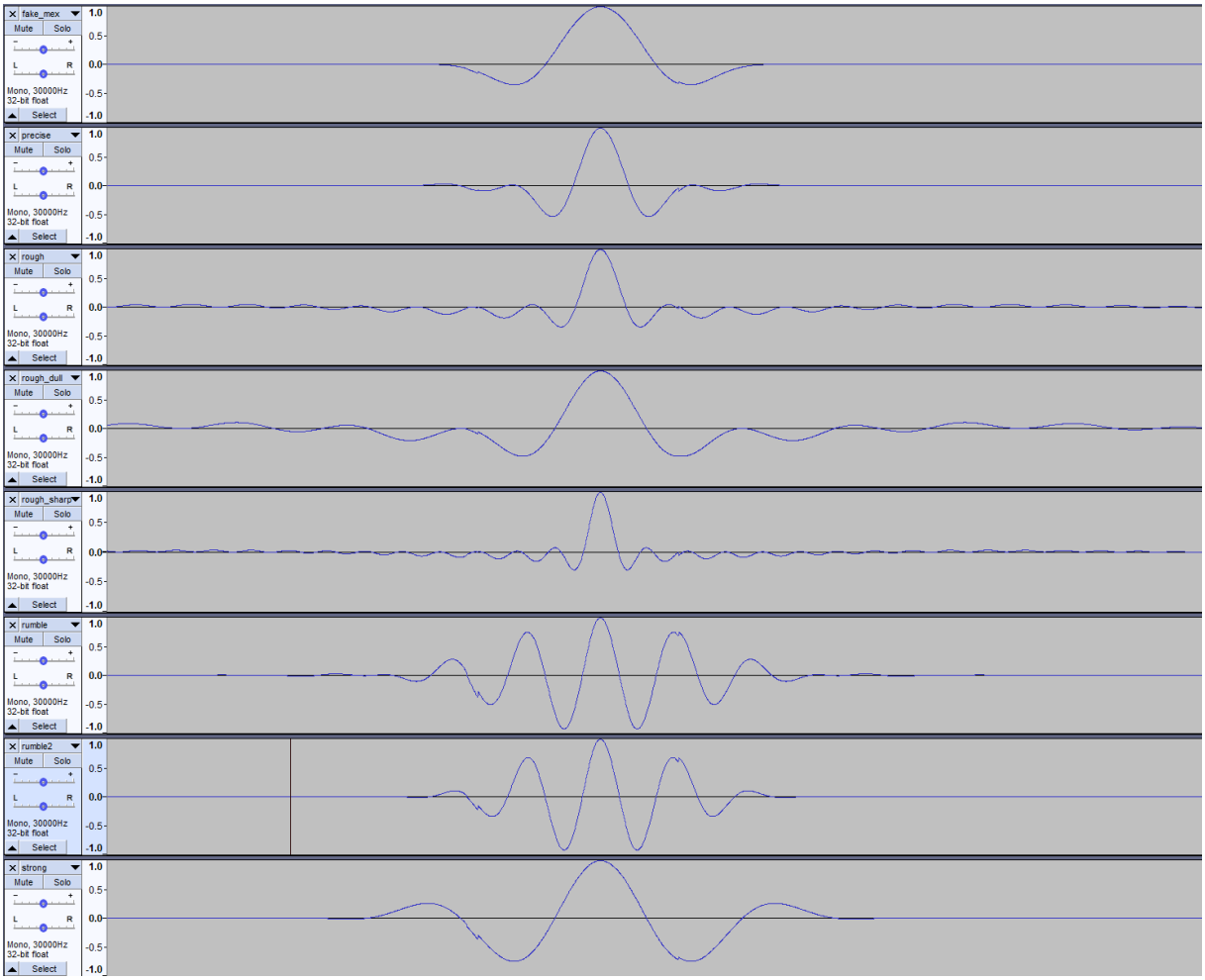

Figure 5: Stimulation patterns applied to the rat forepaw resting on the haptic display. The duration of each time window is 300 ms. The labels of the stimulation patterns are indicated in the respective subheadings to the left. The displacement (lateral movement of the display) is indicated in the y-axis.

Each stimulation pattern was repeated a high number of times, mixed in random order with the other stimulation patterns, at random intervals of 1.3-1.8 s. By isolating the spikes of individual neurons, we could first visualize the average responses to 200 repetitions of each stimulation pattern. We visualize these responses in peristimulus time histograms for two separate units (Figure 6). It can be seen that different patterns evoked different responses in the same unit (rows) whereas the same pattern evoked different responses in different units (columns).

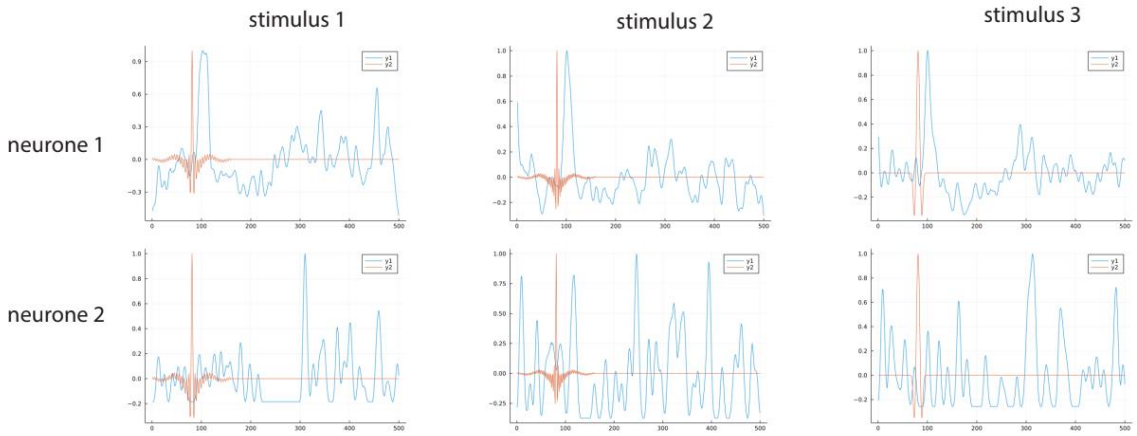

Figure 6: Mean responses of two of the neurons to three of the stimulation patterns, each repeated 200 times. (Stimulus1 = ‘precise’; Stimulus2 = ‘rough-sharp’; Stimulus 3 = ‘fake-mex’).

We first focused on the fact that the same neuron responded differently to each stimulus. But rather than looking at average responses, we wanted to quantify the probability with which each single response could be separated from all other responses evoked by other stimulation patterns. This is similar to the analysis that we have previously done for neuronal responses evoked via an electrotactile interface (Oddo et al., 2017; Enander and Jorntell, 2019; Enander et al., 2019; Wahlbom et al., 2019; Norrlid et al., 2021; Wahlbom et al., 2021; Etemadi et al., 2022), but here we instead used mechanical skin stimulation to evoked the responses. Also, whereas we previously applied a PCA followed by a kNN analysis, we here instead applied a Convolutional Neural Network (CNN) that was trained to separate responses evoked by the different stimuli (see Methods). Figure 7 reports the classication results of three different neurons. Notably, certain patterns were more easily separated by all three units, whereas some other patterns were more difficult to separate for all units. For example, ‘Rough-dull’ and ‘Rough-sharp’ were so easily confused with ‘Fake-mex’ that for two of the units responses evoked by the former stimulus was more often classified as being evoked by the latter stimulus for unit #483 and #488. Also ‘Rumble’ and ‘Rumble2’ patterns were often confused with each other. This was not surprising, given how small the differences between these stimuli were (Figure 5). However, for a high performing unit such as #704, more than half of the patterns were correctly classified by the neuron responses with a high probability-

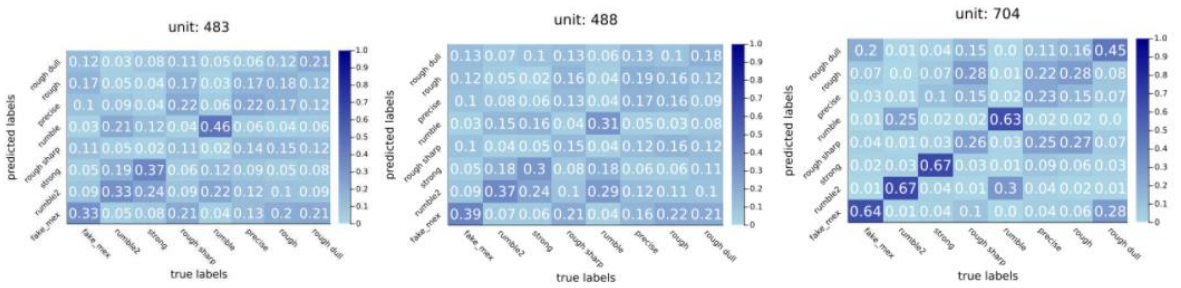

Figure 7: Classification scores for sample single neocortical neurons displayed in confusion matrices for three sample neurons.

We next focused on the fact that different neurons produced different responses to the same stimulus (Figure 6), which we have previously shown with an electrotactile interface (Oddo et al., 2017; Enander et al., 2019) to be indicative of complementary decoding, i.e. when one neuron fails to identify a particular stimulus presentation, the responses of other neurons may 'fill' in missing information, allowing the integrated brain circuitry to anyway being able to separate that particular evoked response. By concatenating the time series responses for any number of neurons for the CNN input, both the precision and the recall for any population of S1 neurons improved (Figure 8) and the improvement was better the higher the number of neurons that were included in the analysis. This data is more systematically presented in Figure 9. It can be seen that as the number of neurons increase, the accuracy increases and the variance around the responses decreases.

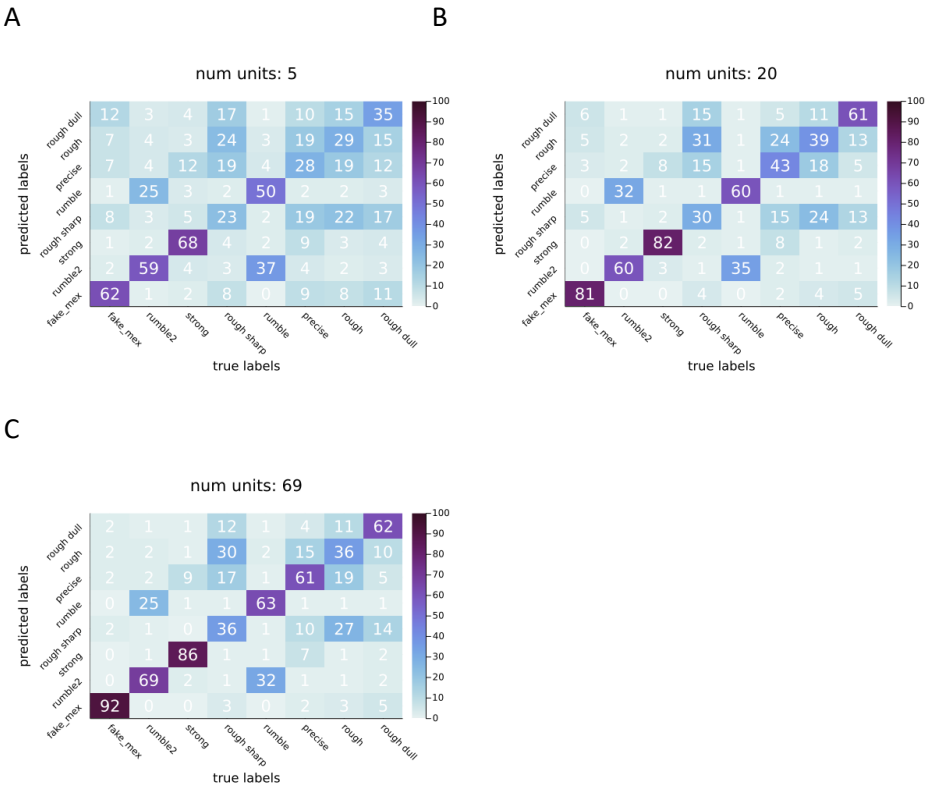

Figure 8: Decoding accuracy obtained by non-optimized combinations of different cortical neuronal units. (A) Decoding accuracy for 5 combined untits. (B) 20 combined units. (C) 69 combined units.

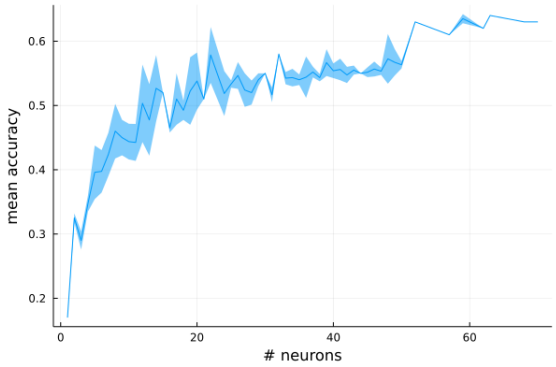

Figure 9: Mean accuracy as a function of # of combined units (non-optimized combinations).

DISCUSSION

We have shown that using a haptic display capable of delivering stimulations composed of a variety of closely related combinations of haptic input features, individual cortical neurons can separate these inputs. We have also shown that individual neurons can generate partly unique responses to these stimuli. This in turn was shown to support complementary decoding, i.e. where the information generated by the combined responses of a number of units is shown to be more accurate than the information generated by a single neuron. This is the first time that it is shown that complementary responses are present across a population of cortical neurons to natural haptic stimuli, even when these stimuli are closely related. Our findings suggest that the neural responses are more highly resolved than the perceptual reporting by humans, which in turn suggest that haptic interfaces of the type presented here may produce much more latent information in brain circuitry than a naïve person could identify. This in turn suggests that with training, this type of interfaces can produce richly resolvable, high dimensional percepts in humans.

METHODS

Experimental model and subject details

Adult Sprague-Dawley rats of male sex (N = 3, age: 12 ± 2 weeks, weight 250–380 g) were used in the acute experiments. Animals were maintained in the Lund University animal facilities under 12h light/dark condition. 2–3 rats were habituated in a cage of type 3H, before the experiments, and they were under ad libitum condition to have free access to food and water.

Institutional permission

The ethical approval for this study was received from the Lund/Malmö local animal ethics committee in advance (permit ID M13193-2017).

Surgical procedures

In order to make acute in vivo recordings, adult Sprague Dawley rats were initially prepared in the same way as in a previous study (Norrlid et al., 2021), briefly according to the following procedure: 1) The animal was sedated by inhaling air mixed with isoflurane gas (3%, for ~ 2 min); 2) To induce general anesthesia, a mixture of ketamine/xylazine (ketamine: 40 mg/kg and xylazine: 4 mg/kg, accordingly) was injected intraperitoneally; 3) an incision in the inguinal area of the hindlimb was made to insert a catheter in the femoral vein for continuous infusion of Ringer acetate and glucose mixed with anesthetic (ketamine and xylazine in a 20:1 ratio, delivered at a rate of ~5 mg/kg/h ketamine). After the initial preparation steps, the somatosensory cortex (SI); was exposed by removing a small part of the skull on the right-hand side (~2 × 2 mm), located at (from bregma): Ap: -1.0 - +0.1, ML: 3.0–5.0. A flap of dura was lifted and a small incision was made to facilitate the probe insertion.

The anesthetics used were chosen because they have previously been reported to not dramatically alter the neuronal recruitment order in spontaneous activity fluctuations and in stimulation-evoked responses as compared to the awake animal (Luczak and Bartho, 2012). As we have previously discussed extensively (Norrlid et al., 2021), anesthesia was required in order to achieve identical conditions for the haptic stimulation patterns over a sufficiently long period of time. It also served to minimize brain activity noise caused by uncontrollable movements and internal thought processes unrelated to the stimuli. The level of anesthesia was assessed both by regularly verifying the absence of withdrawal reflexes to noxious pinch of the hind paw and by continuously monitoring the irregular presence of sleep spindles mixed with epochs of more desynchronized activity, a characteristic of sleep. In order to prevent the exposed areas of the cortex from dehydrating, and to decrease the brain tissue movements, a thin layer of agarose (1%) was put on the exposed cortical areas. The animal was sacrificed by an overdose of pentobarbital at the end of the experiment.

Recording

Recordings were performed using Neuropixels microelectrode arrays (Jun et al., 2017). A custom made 3D printed attachment is used to connect the probe to a micromanipulator. Probes are then slowly lowered (10–20 μm s−1) until it reached the target depth (~4mm). Recordings were made in external reference mode where ground and reference were connected to a small incision made in the neck muscle. AP gain for the probes was set at 500 (300 Hz high-pass filter) with the recording software (http://billkarsh.github.io/SpikeGLX/).

Stimulation

During the recording, haptic stimulations were delivered through a tactile transducer for use with rodents, which is described in Deliverable D2.3, for 3-5 hours which enabled the possibility of obtaining a large dataset responses for each individual neuron recorded using highly controlled stimulations.

Spike sorting and unit identification

Recordings were automatically sorted offline using Kilosort software [https://proceedings.neurips.cc/paper/2016/file/1145a30ff80745b56fb0cecf65305017-Paper.pdf]. Obtained units are further manually inspected and selected based on their firing rate, inter spike intervals, waveforms and responses to the stimuli.

Data analysis

Spiking times within the onset of the stimulus to the following 250 ms immediately after are extracted for each neuron to create response peristimulus histograms, which enables qualitative inspection of the response of each individual neuron to simulations.

CNN decoding

Neural response to stimulations is clear based on the peristimulus histograms, however in order to quantify the degree to which neuron is able to tell these input patterns apart we performed a classification analysis using convolutional neural networks. The reason this approach is selected is previous evidence for CNN's success in classification of time series data (Sadouk, 2018) along with its ability to concatenate multiple neuronal activity across it's dimensions and extract information from a population without altering the classification algorithm, enabling a better controlled comparison between classifying the response of an individual neuron vs a population.

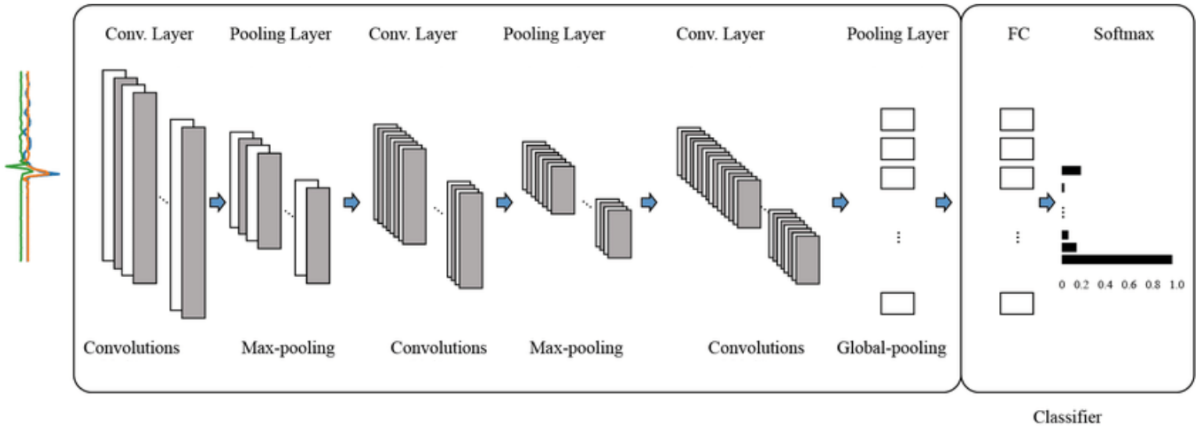

Figure 10: CNN pipeline for the time series data generated from an individual neuron

The Convolutional network designed to classify the input data that consists of sparse neural signals has an input convolutional layer of 20 randomly initialized masks of 5 ms window with a stride of 2 ms, followed by a max pooling layer of 3 ms non-linearized through rectified linear units (ReLU). The second convolutional layer is 10 randomly initialized masks of 10 features with max pooling of 5 features that go through another ReLU, which in turn attached to two densely connected layers of width 250 and 150 for classification, where the activation function for the last layer is a Softmax for assigning a probability for each time 250 ms window for what the neuron is likely to "think" that specific input is at each given stimulation instance.

The convolutional masks are randomly initialized from a uniform distribution between -1 and 1, and the dense layers are randomly initialized from another uniform distribution based on normalized Xavier initialization principle (Li et al., 2020). Training is performed with the batches of 50 windows of randomly selected patterns by optimizing the log loss cost function with preset momentum of a factor of ½ per 50 iterations of stagnated test loss. The code is written in Julia based on the Knet module.

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