A novel high channel-count system for acute multi-site neuronal recordings

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Abstract— **Multi-site recording represents a suitable condition to study microphysiology and network interactions in the central nervous system and, therefore, to understand brain functions. Several different materials and array configurations have been proposed for the development of new probes utilized to record brain activity from experimental animal models. We describe new multi-site silicon probes that broaden the currently available application base for neuroscientists. The array arrangement of the probes recording sites was extended to increase their spatial resolution. Probes were integrated with a newly developed electronic hardware and novel software for advanced real-time processing and analysis. The new system, based on 32- and 64-electrode silicon probes, proved very valuable to record field potentials and single unit activity from the olfactory-limbic cortex of the *in vitro* isolated guinea-pig brain preparation and to acutely record unit activity at multiple sites from the cerebellar cortex *in vivo*. The potential advantages of the new system in comparison to the currently available technology are discussed.**

Index Terms— **Silicon probes, silicon-on-insulator, multichannel recording, electrophysiology.**

I. Introduction

There is undisputed general consensus among neuroscientists that the functional properties of our brain are considerably more than the sum of its constituents [1]. At least one important component of this nonlinear increase in computational power comes from the extremely dynamic and extensive network of interconnections in the central nervous system (CNS; [2, 3]). In order to under-stand the flow of information and the processing schemes used by the CNS, distributed and simultaneous observations of the functioning nervous system are demanded to view the activity of as many neurons in parallel as possible [4]. Microelectrode arrays constructed out of various materials (metal, silicon) and organized in diverse geometries such as micro-wires [5, 6], linear arrays [7, 8], planar arrays [9], tetrodes [10, 11], have been developed over the past decades and are cur-rently commercially available. Multi-site probes are used in combination with appropriate preamplifier/headstages and amplifier/filter chains to comprise a working neural recording setup. However, the technical challenge of multiplying the number of recording channels in the amplification, proc-essing and analysis stages has significantly increased the cost and complexity of experimental setups, limiting their wider distribution and use. To date, there are only a relatively small number of multichannel recording systems available, servicing a relatively small number of neuroscience applications. The present report demonstrates the results of our attempt to improve and broaden the application base through the development of a new, turn-key multi-site neuronal recording system. We focused on developing and improving the multi-site electrode array to extend the range of electrode types, and increase the spatial resolution of the probe. Probes were integrated with ad hoc electronic hardware to maximize the signal to noise ratio of the recording system and with software driving the system to simplify its operation and improve real time processing and analysis. Finally, we demonstrate the usability of the system on in-vitro and in vivo preparations to allow compari-sons with other commercially available systems.

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II. Methods

The realized system comprised of a new set of experimental probes with three smooth sidewalls and high recording site density. The probes are connected via a flexible cable to a small size multi-channel preamplifier, to a programmable gain main amplifier and finally to a DSP-based data acquisition system running a software capable of performing wavelet-based signal analysis in real time and of collecting simultaneous records from 32 or 64 (up to 128) channels.

The probes

In order to cover the largest possible target area in the tissue under investigation 16 different electrode arrays with 32 or 64 recordings sites were implemented by Acreo AB (Kista,

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Sweden). The probe shank was kept as thin as possible (~25µm to ~38µm at the active part for 32- and 64-channel probes respectively). Each probe has a tapered tip with the first electrode site 210 µm from the tip. The overall length of the probe shaft varied greatly between designs, from 15mm to 4mm. The non-active part of the shank broadened in profile to 200µm for the 32 site design and to 300µm for our 64 site design, to provide mechanical support and strength. This tapered design prevented probe buckling during insertion into brain tissue. The probe thickness varied, depending upon the Silicon-on-Insulator (SOI)-wafer used (see below), from 20µm to 30µm. Topological and surface properties of the probes were modified to improve implantation [12] and allow for acute multi-site recordings in the delicate tissues of the rat cerebellum [13] and guinea pig cortex [14-16]. Although we did not attempt to add active on-probe microelectronics or signal conditioning, we developed a reproducible silicon probe fabrication process that allows on-demand reconfiguration of the positions of the recording sites on the probes [17] and a flexible in-built interconnect that mates to a newly designed headstage.

SOI fabrication technology originally developed for realizing high-speed microprocessor chips was used in the fabrication of the electrode probes. Our fabrication process for the 32 site probes is described in detail elsewhere [18] and was improved in the 64 site process mainly by decreasing the trace width and space width of the lithographical processes.

Preliminary results from insertion mechanics testing with the probes indicate that the probes have a lower insertion force and smaller dimpling as compared to single channel tungsten probes of comparable dimensions [19]. Figure 1 shows typical results of the micromachining process.

where the impedance spectra of each probe site was routinely measured with a fast 3-point impedance measuring setup [19, 20].

Realized silicon probes are wire-bonded to a ~10 cm long polyimide connector board. The resulting connected probe is mechanically very flexible while at the same time retaining a small form factor. The bonding area is insulated with epoxy and is sufficiently stiff to be mounted directly on a standard, single electrode, screw-on electrode-holder. The connection side of the flex-board mates to a standard high-density Zero-Insertion-Force (ZIF) connector (Molex 52559, 0.5 mm pitch, SMT), which is in turn mounted to the input of a new modular preamplifier box (TREC, Thomas Recording GmbH, Giessen, Germany). The high flexibility of the connector boards allows for the physical rearrangement of the headstage preamplifiers around the preparation without disturbing the probe mounted on the micromanipulator. Both 32 and 64 channel flex-boards are used for their respective probe counterparts. The 64-channel connector features a Y-shape which allows them either to connect a single 64 channel headstage (TREC PA64) or to a pair of 32 channel headstages (TREC PA32).

Modular Amplification

The flex-boards are designed to be mounted to a miniaturized low-noise 64 channel preamplifier/headstage (TREC PA64) with a very low input voltage noise density of 7.9nV/√Hz and a low total harmonic distortion of the signal of 0.0002% THD at a load of 1kΩ. The input section of the 64 channel preamplifier was matched to the high impedance multi-site silicon probes to optimize the signal to noise ratio of the recorded signal. The single ended input preamplifier has high input impedance (1GΩ) and amplifies the signal by 24dB

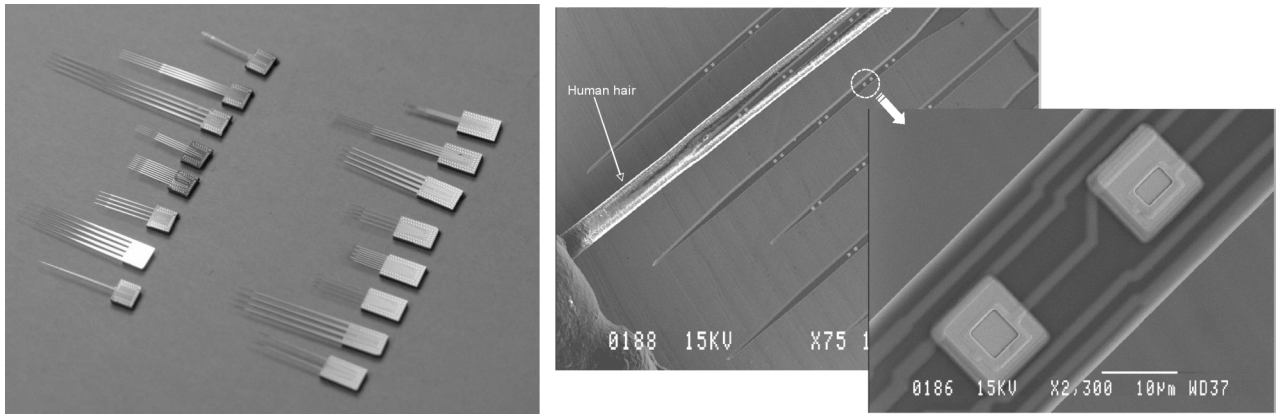

Figure 1 Example of microfabricated probes: left) Complete set of unconnected probes with 32 or 64 recording sites. right) EM-close ups of one of the 64-site probe's shafts on a human hair (thin arrow), displaying a stereotrode arrangement of sites.

The size of 10x10 μm^2 for standard recording sites together with the platinum electrode material resulted in a typical electrode-electrolyte interface of about 2.3 MΩ at 1 kHz. At least one larger electrode site was added to each design (ca. 1000μm^2) to allow electrolytic lesion of the tissue, which could be used to localize the probe track after histological follow-up procedures.

The ready-made probes were freed from the wafer and mounted in a custom made jig under microscopic control,

on each of the 64 channels. The preamplifier is accumulator powered with a power consumption optimized to a minimum quiescent current (400µA/channel). The preamplifier is housed in a small and lightweight metal cabinet, which can be connected to setup ground. The programmable gain main amplifier (PGMA, TREC) consists of five logical sections: an input stage, two amplification stages and two filtering stages. The input section is an AC-coupled differential input amplifier that subtracts the voltages at the two input leads on each

channel and multiplies the difference by a digitally selectable gain factor, thus removing common mode noise. This section guarantees for achieving high common mode rejection ratio (>100dB) and very low noise (< 21nV/√Hz). The programmable gain main amplifier has 64 of these differential input circuits. Each channel is software controlled, whereas the gain on each channel can be selected via a frontpanel interface unit, but also via the DAQ software, described below. The filter sections are responsible for the low (0.06Hz / 2nd order) and high (15kHz / 4th order) cutoff-frequencies. The amplifier section is separated into two pre-filter and one post filter section.

Data Acquisition

Amplified signals with a voltage range of ±10V are acquired with a M67 Digital Signal Processor card (Innovative Integration, Thousand Oaks, CA). Each PCI bus processor card carries a Texas Instruments TMS320C6701 VLIW signal processor, which processes digital signals coming from 32 separate sigma-delta analogue-to-digital converters (OMINIBUS card AD16, Innovative Integration). These A/D converters can simultaneously sample 32 channels at 16 bit resolution with a maximum sampling rate of up to 195 kHz per channel. When the system was configured to run with 64 channels, two M67 boards were used and synchronized via the SyncLink connection.

Real-time Analysis

The recording application software streams all incoming data to disk and provides real time monitoring of the data in one or more raw data, blue-plots, frequency spectra, and filtered data windows and selectable audio output. All data are stored using the non-proprietary hierarchical data format HDF5 [21] to keep the data as open as possible and allow the use of widely available post processing and analysis routines.

Real-time wavelet transform analysis [22, 23] is implemented using fast wavelet algorithms, which decompose the signal into equivalent numbers of Daubechies 2, 4 and 6 wavelet coefficients [24-27]. The sub-band decomposition property of the wavelet transformation provides, as a first important advantage, the means to easily filter signals by just dropping specific sub-bands with linear phase shift, thus maintaining fast signal shape integrity. Further use of the wavelet transform is made by performing user controlled noise reduction on the signals [28]. This leads to a significant reduction in signal entropy and thus opens the possibility of effectively compressing the data. Furthermore, real-time wavelet analysis is used for spike-detection on the coefficients at different wavelet levels [29].

By performing a simple threshold operation on the coefficients at particular levels [30] or on a non-linear energy operator [31], we defined spike events with high reliability, assessed manually by overlaying 8 msec long sweeps of the raw recording around the detected spikes. Unfortunately, due to the shift-variance of the Discrete Wavelet Transform spike clustering based on wavelet coefficients did not provide satisfactory results in realtime. [32].

Isolated guinea pig brain in vitro

Brains were isolated from young adult Hartley guinea-pigs (150-200 g; Charles River Laboratories, Comerio, Italy) according to the standard technique described in details elsewhere [14-16]. After barbiturate induction of anesthesia (125 mg/kg thiopental i.p), the animal was perfused with a cold, complex saline solution (see below) through the aorta to reduce brain temperature during the dissection. The brain was carefully removed and transferred to a perfusion chamber under hypothermic conditions (15° C). A custom-made polyethylene canula was inserted and secured to the basilar artery and perfusion of the whole brain was ensured at a rate of 5.5ml/min. Faster (8.25 ml/min) and slower (4.38 ml/min) perfusion rates were also utilized (see Results). The perfusate (composition NaCl 126 mM, KCl 3mM, KH2PO4 1.2 mM, MgSO4 1.3 mM, CaCl2 2.4 mM, NaHCO3 26 mM, glucose 15 mM, 3% dextran MW 70,000) was oxygenated with a 95% O2-5% CO2 gas mixture (pH 7.3). Experiments were carried out at 32 °C. Extracellular recordings were performed in different brain regions with silicon probes (see Results). Bipolar stimulation of the lateral olfactory tract (LOT) was performed to evoke potentials in olfactory/limbic cortices [33]. The experimental protocol was reviewed and approved by the Committee on Animal Care and Use and by the Ethics Committee of the Istituto Nazionale Neurologico, in accordance with the International policy on care and use of laboratory animals.

Cerebellar rat cortex

Surgery was performed on adult, male Sprague-Dawley rats (300-500 g; Iffa Credo, Brussels, Belgium) anaesthetized with Ketamine/Xylazine, following procedures described previously [34, 35]. The rat was placed in a stereotaxic frame and a single midsagittal skin incision was made on the head, the soft tissues retracted, and the peristeum of the posterior part of the skull removed. The cisterna magna was punctured to drain the cerebrospinal fluid in order to reduce cerebellar pulsation and the squamous part of the occipital bone was removed to expose Crus I and II of the cerebellum. The dura was removed and the craniotomy was covered by either warm agar in phosphate buffered saline or paraffin oil.

Extracellular single and multi-unit recordings were made with silicon probes positioned either along or perpendicular to the transverse axis of Crus I or II (see Figure 5). The probe was lowered vertically into the cerebellar cortex using hydraulic micropositioners. Probe signals were amplified (bandpass 400-20kHz), digitized and discriminated with a PC-controlled Multichannel Neuronal Acquisition Processor (Plexon, Inc., Austin, Texas, USA). Tactile stimulation of facial dermatomes was performed with a mechanical stimulation device delivering 10ms tap stimuli at a rate of 1 Hz. After the experiments rats were sacrified by an overdose of sodium pentobarbital. The experimental protocol was approved by the Local Ethical Committee of the University of Antwerp and in accordance with the International policy on care and use of laboratory animals.

III. Experimental Results

The recording system for 32 and 64 channels was tested in the cortex of guinea pig brain maintained in vitro [36] and in the cerebellar cortex of anesthetized rats [13, 37].

Field potentials and single units in the cortex of the isolated guinea pig brain in vitro

The new silicon probes were utilized to record extracellular field potentials generated by the synchronous activation of population of neurons in the olfactory/limbic cortices of the isolated brain of the guinea pig maintained in vitro by arterial perfusion. To validate the use of silicon probes, laminar profiles were performed in the dentate gyrus of the hippocampus following electrical stimulation of the lateral olfactory tract (arrow), as illustrated in Figure 2. The upper part of the panel illustrates the potentials simultaneously recorded at 20 adjacent recording sites, selected out of the 32 available channels. The field potential profile is also shown in the middle panel, with the indication of the depth at which recordings were performed. The electrode track was reconstructed on histological sections cut after fixing the brain with a mixed aldehydes solution (photograph on the right of Fig. 2). Current source density (CSD) analysis was performed on the fieldpotential laminar profile by applying the current-source density equation [33], to identify and localize the spatio-temporal distribution of the current sinks and sources responsible for the generation of the field potentials and, therefore, to describe the neuronal circuit activated in this area. The contour CSD plot in the lower panel of figure 2 confirmed the presence of a CSD sink (continuous lines) in the molecular layer of the dentate gyrus (ML), where the olfactory-driven input carried by the afferent fibers of entorhinal cortex neurons terminate. A source (dotted lines) was observed in the granule cell layer (GCL).

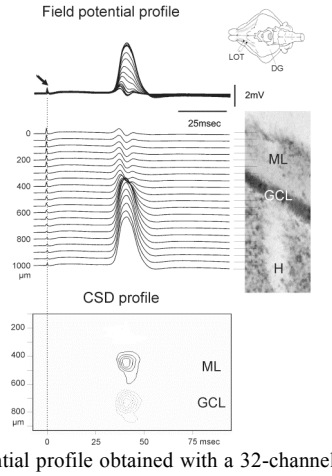

Figure 2 Field potential profile obtained with a 32-channel ACREO silicon probe in the dentate gyrus of the isolated guinea pig brain. The traces represent the average of 7 responses to lateral olfactory tract (LOT; arrow) stimulation (see scheme on the upper right corner). Superimposed (upper panel) and separated traces simultaneously recorded across the dentate gyrus are shown. Each trace was simultaneously recorded at different depths with a probe inserted in the tissue (20 recording sites out of 32 are shown). In the lower panel, the contour plot of the sink/source distribution obtained by performing current source density analysis on the laminar potential profile is illustrated. Sinks and sources are illustrated by continuous and dotted lines, respectively.

Silicon probes were also tested to record extracellular unit activity from single cells in the in vitro isolated guinea-pig preparation. The simultaneous recording from 4 different sites, separated by 100 µm are shown in Figure 3. The filter setting utilized in this experiment (highpass filter at 0.1Hz and low-pass filter at 5kHz) allowed the recording of slow events as well as fast activities generated by single cells. Unit discharges can be recorded as fast spikes generated by two different neurons marked by the asterisk and the filled circle, respectively, in Figure 3. It can be concluded that the multichannel, multi-shaft -probes are ideal to perform extracellular simultaneous recording of field potentials and unit activity from cells with diverse depth localization in an isolated animal brain maintained in vitro.

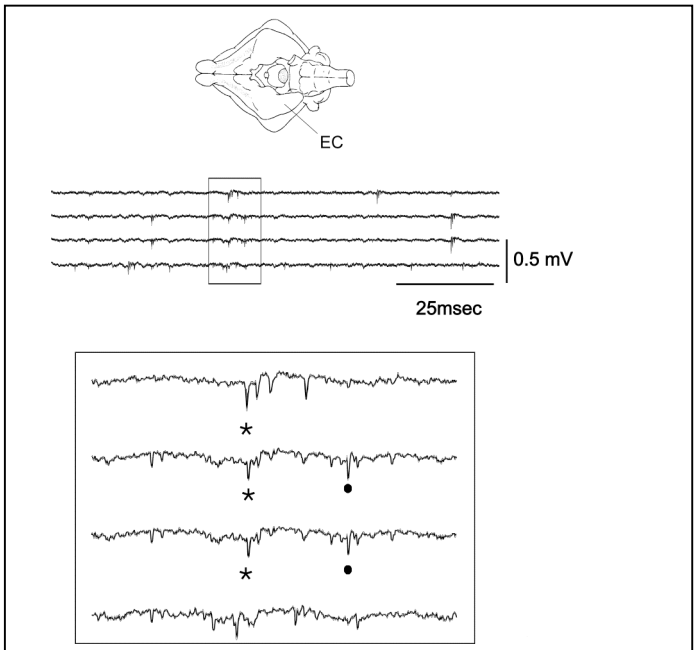

Figure 3 Single unit recordings performed with an ACREO silicon probe in the entorhinal cortex (EC in the drawing of the ventral view of the guinea-pig brain). Recordings were simultaneously performed at 4 sites separated by 100 µm on a single shaft. The activities of two units (marked by asterisk and filled circle) outlined by the box are illustrated at fast time resolution in the lower panel.

The study in the isolated guinea pig brain preparation also demonstrated that these silicon probes can be successfully reused at least 10 times in acute *in vitro* experiments without signs of deterioration of the recording sites. After use, each probe was carefully rinsed in double distilled water and stored at room temperature.

Spike Recordings from Cerebellum

Whereas silicon probes of older fabrication have been used to record from rats cortex for quite some time, the lack of publications on their use to record from the delicate cerebellum is a striking evidence for the difficulty of this task. The ACREO silicon probes tested here were particularly

designed to optimize implantation insertion and to minimize disastrous dimpling of the cerebellar surface. In acute experiments, probes were successfully implanted along and perpendicular to the cerebellar parallel fibers without significant dimpling disturbing the recording of signals from all recording sites. The results from these records gave us unique insights into the organization of cortical dynamics of the rat's cerebellum [37]. Of particular interest was the correlation of firing patterns between identified neuronal subtypes in different layers of the cerebellar cortex. Figure 4 shows examples of captured multi- and single unit action potentials during spontaneous activity recorded from the cerebellar cortex area Crus IIa using an 4x8 probe. Single units were isolated by standard spike sorting methods, i.e. cluster analysis of two first coefficients of principal components [38]. Several putative Purkinje and Golgi cells could be identified based on the shape of the action potential and single unit firing patterns. On several sites more than one unit could be isolated (Data not shown).

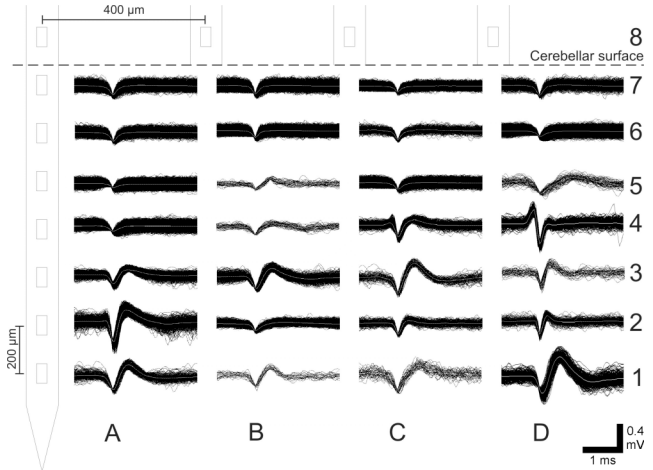

Figure 4 Extracellular action potential waveforms of multi- and single unit recordings of spontaneous activity from the cerebellar cortex Crus IIa of an anesthetized rat using an ACREO 4x8 probe. Single units could be identified as putative Purkinje cells (A2, C3, D1, D3) and Golgi cells (A1, B1, C1).

When placing the probe along the parallel fibre (PF) axis it is possible to study the processing of cerebellar signals along hypotesized PF beams of activity. Mapping of cerebellar response patterns to tactile stimuli to the facial skin [35] yielded complex data sets and, in accordance with previous results, showed that most recording sites of the probe are within the excited volume of tissue. In Figure 5, a 8x4 probe is used to record evoked activity from multi- and single units along a PF in Crus IIa corresponding to the receptive field of the rat's facial skin. The earliest response to stimulation appears on shafts C and D, indicated by a putative ascending signal pathway activating PFs at this location in the upper layers. Spike interval histograms with site C4 as reference (REF) indicate a transmission of activity moving in both directions along the probe and PF from shaft C. A timeshift of peak response from upper to lower layers could also be observed in some instances (e.g. G4 to G1).

Combining different stimulus protocols (position on skin, frequency of stimulation) with different recording positions of the probe within one or several receptive fields on the cerebellar surface is generating valuable data for detailed

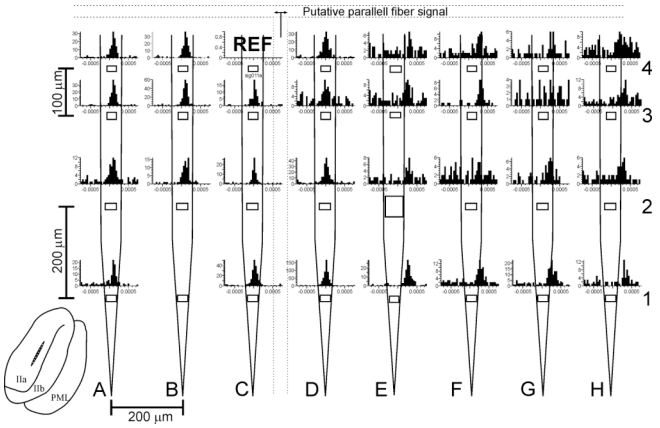

Figure 5 Spike interval histogram from multi- and single unit recordings of activity evoked in the cerebellum from tactile stimulation of the facial skin of an anesthetized rat using an ACREO probe that features 8 parallel shafts separated by 200µm, each carrying 4 recording sites with 100 and 200µm separation. Timeshift of peak activity can be observed from region of shaft C (action potentials recorded at site C4 serve as trigger = REF) in both directions of the probe. Recording position in Crus IIa is indicated in lower left inset.

studies of the dynamics of cerebellar networks during sensory processing. The ACREO silicon probes have proved to be a most suitable tool to study this problem as they allow simultaneous recording from multiple sites in multiple layers, allowing us to distinguish activity from several sites in the granular and molecular layers of cerebellar cortex simultaneously.

IV. Discussion and Outlook

This system was developed as part of a European Union project, to foster the use of multi-site neuronal recordings with high channel counts and make this technology available to the average neurophysiology researcher. This goal was achieved by realizing a turn-key system, which condenses the unique knowledge of several disciplines into a single measuring device. A variety of multi-site neural probes were developed to encompass a broad spectrum of electrophysiological recording paradigms and maximize the number of recording sites relative to the amount of displaced neural tissue. The probes achieve an unprecedented high site density that should translate to excellent spatial resolution. Current design space covers probes with one to 8 shafts and 32 to 64 recording sites distributed over a planar area of $400x400\mu m^2$ up to $1500x2000\mu m^2$. Mated to the modular recording hardware, the system is capable of recording simultaneously 64 channels with 16 bit resolution and more than 20 kHz bandwidth. Being modular by design, the core 32-channel system was shown to be expanded up to 128 channels, and still be capable of full bandwidth recordings.

Analysis of extracellular field potentials is critical to understand the dynamic interactions between populations of

neurons and to reconstruct synaptic networks that contribute to the generation of brain activity. When field recordings are performed at single sites in a cortical structure it is impossible to understand whether the recorded activity is generated by the cortex where the electrode is positioned or whether the activity represents a far field generated elsewhere and volume-conducted through the tissue. To verify the local generation of the recorded potentials a reversal of the activity should be observed across the cortical depth. The use of multichannel silicon probes offers the unique opportunity to record simultaneously from different positions of the brain during the generation of spontaneous and stimulus-evoked activity. Simultaneous recordings at different sites within a cortical structure are critical to investigate laminar profiles of activity. These can then be processed to reconstruct neuronal networks on the basis of either the identification of extracellular current sink/sources responsible for the generation of field potentials (cortex) or the propagation of signals along fiber tracts (cerebellar cortex). It has been demonstrated that in most cortical areas laminar analysis can be usefull in identifying and accurately localizing current generators if spacing between recording sites is no more than 50 µm on the same shaft [39-42]. The linear array design was especially useful in recording from cerebellar cortex as the circuitry in this structure is linearly organized around the PF beams, the orientation of which can be macroscopically recognized allowing for implantation of probes either parallel or perpendicular to the PF beam.

Moreover, probes characterized by multiple shafts (4-6), each carrying 6 to 10 recording sites (32-64 sites probes) were central to analyze the pattern of correlation and propagation of brain activity (not shown) and to record unit activity from multiple subregions of a cortical area, such as the olfactory-entorhinal cortex. Such a complex probe arrangement has not been reported on since recently [43, 44] and is still not available commercially.

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