Smart Neuroprosthetics: Brain-Machine Interfaces for the 21st Century

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Section I: Concept and Scientific Basis

The grand challenge for the 21st century will be to build an interface between our brains and electronic systems. Tom Kalil, Deputy Director for Policy for the White House Office of Science and Technology Policy, speaking about “Grand Challenges” asked: "What if people with prosthetic legs climb mountains and people with prosthetic arms play the piano.” The robotic technology needed for such feats already exists, as demonstrated by the DEKA Arm and others. However, what is lacking is a robust, high-performance control signal from the brain to control these prostheses.

While some brain-machine interface systems currently exist in prototype form, their performance is extremely limited. Currently, all devices that interface computers with the body use passive electrodes, and require that each electrode is individually wired and connected to remote electronics. **We propose to develop a new generation of brain-machine interfaces** that use active, flexible electronics to interface with the brain at 1000 times higher spatial resolution than today’s clinical devices. **We will use this new technology to design 'smart neuroprosthetics'** in three domains: motor control, sensory perception, and cognitive abilities. Our overall goal is a 'one size fits all', general purpose programmable device that can be easily adapted to solve various problems such as manipulating robotic arms for tetraplegic patients, building adaptive hearing aids that dynamically improve acoustics for people with hearing loss, or providing cognitive enhancement for autism spectrum disorders. This technology opens a new window into understanding brain function, and building truly high-performance brain-machine interfaces, based on studies performed at NYU (**Fig. 1**).

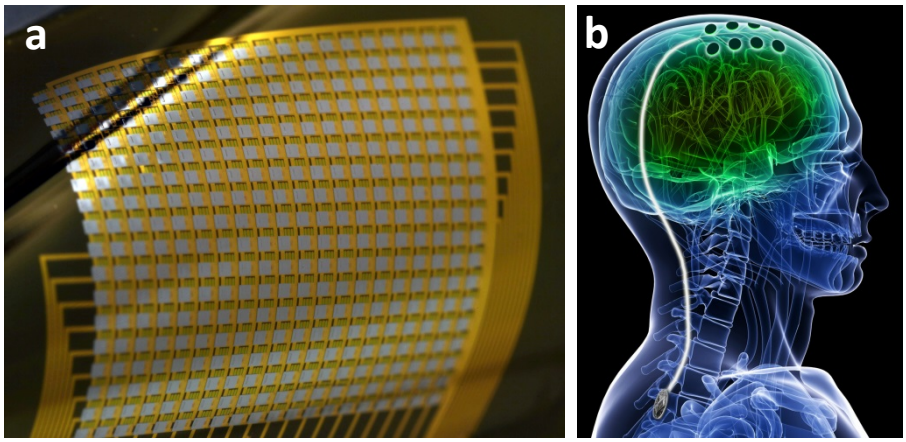

Figure 1. Technology for smart neuroprosthetics. **a,** high-resolution (500 µm spacing), flexible, active electrode array with 360 amplified and multiplexed electrodes. Only 39 wires are needed to sample from all of the electrodes. **b,** future implantable, high-performance, bi-directional neuroprosthetic systems

New developments in translational research demonstrate that submillimeter resolution will dramatically improve the efficacy of diagnostic and therapeutic brain computer interface devices[1–6]. Unfortunately, using current technology it is impossible to build a high-resolution (<1 mm) interface over broad regions (8 cm × 8 cm) of the brain, as an electrode array with thousands of passive contacts will also require thousands of wires to be individually connected. To overcome this limitation, we have developed new implantable electrode array technology that incorporates active, flexible silicon electronics (Fig. 1). We have demonstrated extremely flexible arrays of 360 recording electrodes that integrate an amplifier and multiplexer directly under each electrode in a sheet of thin polyimide[7]. These electrode arrays can sample micro-electrocorticographic (µECoG) signals from the surface of the brain at high temporal (>10 kHz/ channel) and high spatial resolution (<500 µm electrode spacing), while requiring only a few wires to be connected.

In this proposal, we will develop robust, high-performance, bi-directional neuroprosthetic systems using large-area, high-resolution arrays of recording and stimulating electrodes. This technology could overcome the limitations of current penetrating electrode approaches to brain-computer interfaces, which may only function 6-12 months[8] before signal quality on most electrodes is substantially diminished. In contrast, highly flexible arrays of subdural electrodes can maintain signal quality over extended periods of time with minimized injury and irritation to neural tissues. Arrays of thousands of μECoG electrodes covering motor cortex will convey more useful information for brain-machine interface systems than the arrays of 100 penetrating electrodes currently used. Furthermore, flexible arrays could be folded into the central sulcus, enabling access to rarely interfaced regions of brain, and allowing simultaneous recording from motor cortex and stimulation of sensory cortex on the opposite side.

Solving this problem is a "Grand Challenge" uniquely suited for NYU over the next decade. As described in this competition proposal, our laboratories at NYU collectively have the precise expertise, creativity, and technical prowess to develop these new devices. We also each have a long track record of productivity and funding success. The resources provided by the Grand Challenge proposal will allow us to synergize our efforts to solve this important problem, building devices that will transform science and medicine over the next decade. Our proposal is also connected to the heart of the Obama administration's BRAIN Initiative (Brain Research through Advancing Innovative Neurotechnologies). Going forward, we plan on interfacing with national BRAIN funding mechanisms, leveraging the resources provided by this Grand Challenge award to achieve sustainable funding for this urgently-needed research program.

Section II: Technical Approach and Experimental Design

Our goal is to build a next-generation, general-purpose telemetric (wireless) neuroprosthetic device for repairing and augmenting human abilities. The design of each device will be based on high-resolution electrode technology already developed and being refined in the Viventi lab, as discussed above (**Fig. 1**). Using this technological development and seed funding from the NYU Grand Challenge Award Competition, **we will demonstrate performance improvements in brain-machine interfaces in three major areas: motor control, sensory processing, and cognitive performance**. In each case we will begin by validating the utility of the neuroprosthetic device by recording neural activity in animals (non-human primates and rodents), focusing on various regions of the cerebral cortex. This region of the central nervous system is ideal for our experiments, as cortical circuits are involved in motor control, behavioral planning, sensory processing, and memory formation. Moreover, as the cortex is the outer part of the brain, it is the most accessible region in terms of electrode placement. After optimizing the technology on each test-bed for monitoring and manipulating neural activity, perception and behavior in pre-clinical animal models, we will begin to work towards clinical trials and use in human subjects.

1. Motor prosthesis (Lead PIs: Pesaran, Viventi)

Brain-machine interfaces to restore motor function record neural activity to infer a subject's intentions and control an external actuator, such as a prosthetic device. Developing such brain-machine interface systems to restore dexterous arm and hand movements is challenging because the arm and hand are incredibly complex systems. Restoring arm-hand movements requires control over the many joint movements that are required to position and shape the hand. How to neurally control many-degree-of-freedom arm and hand movements is an open question that lies at the cutting edge of brain-machine interface systems.

Work in the Pesaran lab, currently funded by DARPA, defines the state-of-the-art in high-dimensional neuroprosthetic control. We have simulated an anatomically-complete, 27-dimensional (7-D arm and 20-D hand) upper limb extremity as an avatar in a virtual reality environment. The avatar responds to processed neural signals with low-latency, <40 ms, and we have shown the avatar can be effectively controlled by non-human primates. In these experiments, monkeys view a virtual world presented on a 3-D monitor. In the virtual world, the anatomically-correct avatar is displayed on their shoulder, and we track their torso movements using infra-red cameras to maintain the placement of the avatar on their shoulder. We then present objects to the animals in the virtual world. By directly modulating the activity of populations of neurons in their brain, the monkey controls the avatar to reach out and grasp an object to earn a juice reward. We measure the rate at which they can successfully grasp objects placed at different locations and orientations in the virtual world. We then measure performance while varying the difficulty of the task, for example by requiring more precise grasp configurations.

To date, our work has been based on neural signals obtained within the motor and premotor cortices using electrodes that penetrate the brain. Penetrating electrodes allow us to record the activity of individual neurons as well as the population activity in the local field potential. Using spiking activity, which is commonly-believed to be the highest quality neural signal obtainable, we have found that using advanced, non-linear decoding algorithms based on support-vector regression we can control entire articulated virtual limb with high accuracy (~0.8 median reconstruction accuracy, where reconstruction performance is measured as the correlation between actual trajectories of all 27 dimensions of movement and decoded trajectories based only on neural signals). Recently, in a very surprising finding, we have shown that we can decode complex 27-D movement trajectories using local field potential signals with as much accuracy as spiking activity (similar median reconstruction performance of ~0.8). To achieve this level of performance, we need to record neural activity from ~100 penetrating electrodes over broad, many cm-squared, regions of the primate brain.

Our new decoding method based on local field potentials sets the stage for the current effort. Unlike conventional spiking signals, our method uses signals that can be recorded from the surface of the brain using electrodes that do not penetrate brain tissue, and in some cases non-invasively from scalp potentials. Thus a large-area high-resolution array of recording electrodes will enable a high-performance motor prosthesis that rivals the performance achieved with penetrating electrodes. Work for this proposal will directly test this prediction.

The first step will be to record surface brain activity from the macaque motor cortex and use this activity to manipulate a complex, jointed robotic arm through 6-7 degrees of freedom with high accuracy. We will use a large-scale array of μECoG electrodes that covers the same regions of the brain that we are currently recording from to achieve the performance of penetrating electrodes. We already know that local field potentials recorded at the surface do not contain as much as information as local field potentials recorded in the brain[9]. Performance is reduced by approximately 50%. However, using flexible, high-density arrays of surface electrodes we can record from an order of magnitude more sites from the same regions than we can using penetrating electrodes. Access to this increased neural information density will allow us to achieve our milestones based on current performance using penetrating electrodes.

The second step will be take advantage of the longevity of recordings at the surface to exceed current performance. **Specifically, we aim to monitor stable motor cortex activity for at least one year in a given**

subject. We will train animals to control the prosthesis in the virtual environment using processed neural signals from the high-density surface array to control the high-dimensional effector system with better performance than is currently possible. Our current ability to train subjects to perform brain-machine interface control is limited because the signals present on penetrating electrodes decline substantially over time. This means that the neural substrate upon which the subject depends to refine and learn better control is changing, fundamentally undermining the learning process. With surface electrodes, we will not suffer the limitations of penetrating electrodes and the neural signals will be far more stable over time. We expect that the increased stability of surface recordings will allow subjects to learn over longer time periods and hence achieve our milestone and exceed current performance. Once stable recordings can be obtained and used to accurately manipulate avatars and high degree-of-freedom robotic arms, **we will advance to clinical trials in paralyzed humans**.

2. Sensory prosthesis (Lead PIs: Sanes, Viventi)

Hearing loss profoundly diminishes the human brain's ability to acquire language during development and process speech in adulthood. This is true even when hearing aids are used to amplify sounds, or when cochlear implants are used to directly stimulate auditory nerve fibers. Simply put, hearing loss causes wholesale changes to central nervous system (CNS) synaptic and membrane properties, especially in the cortex[10]. Therefore, one broad research strategy to address the perceptual deficits that attend hearing loss is to ask whether CNS processing and plasticity can be harnessed to overcome the perceptual deficits. Here, **we propose to build a 'smart hearing aid'**: a brain-machine interface that transforms and optimizes the incoming sound signal to take full advantage of the processing capacity of the deaf CNS.

The core approach uses a large array of electrodes to monitor neural activity across the entire primary auditory cortex while rodents perform auditory perceptual tasks. Gerbils will be used as the gerbil auditory system more closely matches that of humans than other rodents. Perceptual skill will be assessed with amplitude modulation (AM) detection and discrimination tasks. The small amplitude fluctuations present in speech are necessary and sufficient for comprehension, and AM

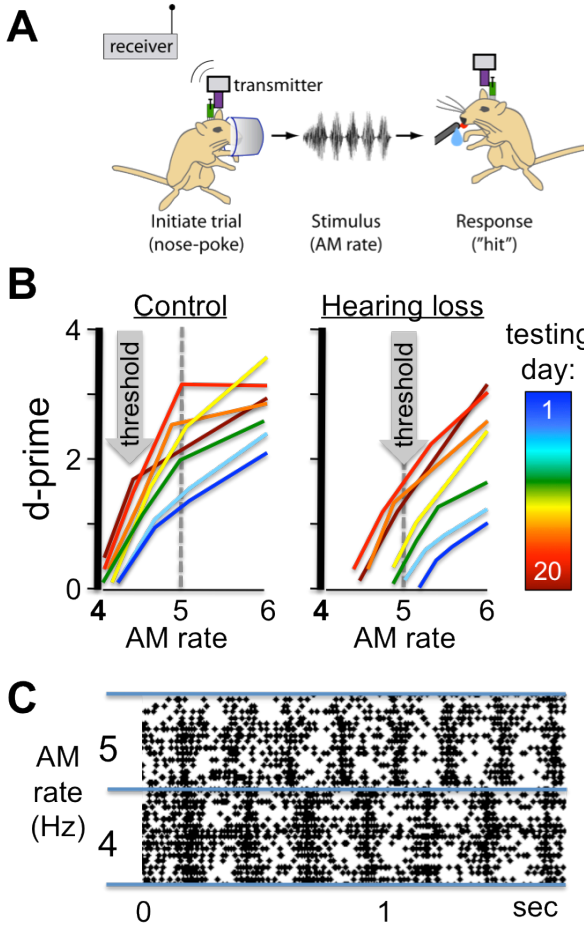

Figure 2. Recording auditory cortex responses during auditory psychophysics. **a**, Auditory cortex neurons are recorded from telemetrically (transmitter, receiver) while animals initiate trials, listen to a sound (stimulus), and then determine whether to respond (hit). **b**, When animals are trained to discriminate a 4 Hz AM rate from higher modulation rates, control animals improve rapidly and reach a low threshold (4.3 Hz), whereas hearing loss animal take longer to achieve asymptotic performance which is at a higher threshold (5 Hz). **c**, A raster histogram is displayed for one recording site during the behavioral testing, and displays good phase locking to both 4 and 5 Hz AM stimuli.

detection is significantly impaired by hearing loss[11–18]. Therefore, tests of AM perceptual skills in rodents may be relevant to human speech perception.

The neural readout will consist of local field potential responses from the auditory cortex using the electrode technology developed in the Viventi lab. Many of the technical advances that emerge from a cortical readout to control robotic limbs (as in the motor prosthesis described above) will be used to obtain a sensitive neurometric correlate to the acoustical stimuli. This will permit us to reference an animal's perceptual abilities directly to a neural readout from the electrode array. For example, normal adult rodents can be trained to discriminate between an AM rate of 4 Hz and a slightly higher rate (von Trapp and Sanes, unpublished observations). Therefore, we will first determine the neurometric readout from a large electrode array that is reliably associated with successful discrimination.

The Sanes lab has recently demonstrated significant perceptual deficits in animals reared with hearing loss, for both AM detection and discrimination[19]. Hearing loss animals also take longer to reach their best performance levels (**Fig. 2**). Therefore, hearing loss animals will be implanted with large electrode arrays and trained to perform an AM task. For example, if hearing loss animals are trained to discriminate between an AM rate of 4 Hz and a slightly higher rate, then we expect performance to be poorer than that of control animals. With a robust correlation between AM discrimination threshold and neural signal in control animals, we will test the core hypothesis: that **auditory cortex neural responses reliably predict correct performance**.

The first proof-of-principle experiment will test the effect of transiently inducing hearing loss on normal animals with bilateral earplugs. We predict that identical auditory cortex responses will correlate with correct performance even though sound signals will be raised to compensate for the earplugs. The second experiment addresses the hypothesis in hearing loss animals with impaired AM discrimination thresholds. We predict that hearing loss animals will display normal perceptual skills when the stimulus waveform is adjusted so as to elicit a control-like neural responses. This approach circumvents all current technologies that ignore central auditory changes.

Once we understand the relation between sound signals, neural responses, and behavioral performance, **we will build an adaptive 'smart hearing aid' that dynamically modifies incoming acoustic input** based on the neural signal measured from high density surface electrodes measured with our neuroprosthetic recording device. This device is essentially an iPod-style earphone that monitors and adjusts incoming acoustic signals to correct for reductions observed in the neural measurements. One of the major complaints from current hearing aid users is that when ambient background noise is too loud, the amplified sounds from the hearing aid become almost painful; many hearing aid users turn off their hearing aids in noisy environments such as restaurants. We will use active noise reduction combined with selective amplification just to a level that produces accurate responses in the cortex, but not to higher potentially distracting or painful levels. **This device will be tested in normal and hearing-impaired human listeners.**

3. Cognitive prosthesis (Lead PIs: Froemke, Long, Viventi)

In the previous sections above, neuroprosthetic devices have been designed to enable movement (e.g., in paralyzed subjects) or to strengthen or reestablish a sensory input (e.g., in the profoundly hearing impaired). However, the application of this technology to cognitive performance has been much more limited to date. Existing procedures such as deep brain stimulation show promise for leveraging central neural systems involved

in cognition and control of brain state, but there is little information about when and where deep brain stimulation should best be applied to improve cognitive performance. Here we will take advantage of existing FDA approval for deep brain stimulation-based devices, combining stimulation of neural systems that release neurochemicals involved in attention and learning together with high-resolution recording of brain activity, **to build a neuroprosthetic device for boosting performance in cases of impaired learning, memory, and social cognition**.

The central nervous system generates behaviors in a manner that depends on current sensory input combined with knowledge gained from past experience. In sections 1 and 2 above, we discuss the application of our devices when either the final motor effectors or the initial incoming sensory stimuli are defective. However, the inability to generate correct behavioral responses may in many cases come from a failure of the intermediate cognitive processes, such as the functions of neural circuits to: amplify and adequately attend to important features of the physical or social environment (for example, in speech, language, and autism spectrum disorders), suppress uninformative or maladaptive input (in attention deficit disorder) or prevent pathological forms of neural activity (in the case of epilepsy). How might we implement a neuroprosthetic device to enable the brain to correctly perform these essential tasks?

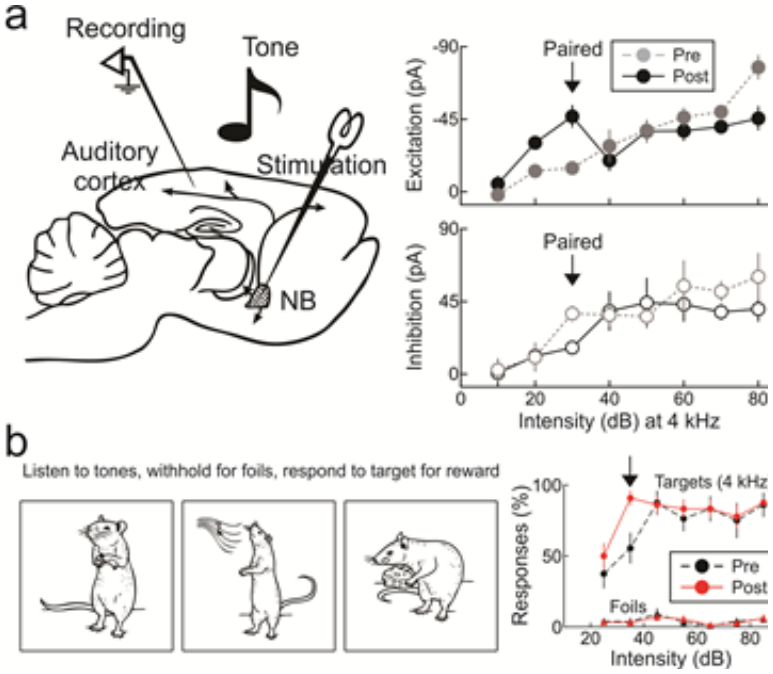

Figure 3. Auditory cortical synaptic plasticity improves sensory perception. **a**, Physiology. Left, *in vivo* whole-cell recording from adult auditory cortical neuron. Quiet (30 dB) tones were paired with acetyl-choline modulation via nucleus basalis (NB) stimulation. Right, excitatory responses at 30 dB increased (top) while inhibitory responses decreased (bottom) for 20+ min. **b**, Behavior. Animals were trained to respond to a 4 kHz tone at any intensity for food reward. Right, behavior before (black) and 1-2 hrs after (red) NB pairing with 35 dB tones (arrow). After pairing, detection ability improved at 35 dB, due to increased responses at 4 kHz ('targets', circles) with no change to false alarm rates for other tones that were not rewarded ('foils', triangles).

To address this idea, there are two required elements in our approach: 1) an intervention designed to alter how neural circuits process incoming sensory information, and 2) a precise readout of the cellular/circuit impact of this change. As detailed below, the investigators in this proposal are uniquely suited with complementary technical expertise, allowing us to work together to develop this novel approach and to develop a well-calibrated cognitive neuroprosthetic device that can enhance the processing capabilities of the central nervous system for improved behavioral output and control.

Neuromodulators such as acetylcholine and oxytocin have a large impact on sensory processing and behavior in rodents, primates, and humans. For instance, the Froemke lab has examined how acetylcholine can enable long-term synaptic plasticity in the adult rat auditory

cortex[20], increasing auditory cortex responses to behaviorally-important sounds[21]. Specifically, we used wireless stimulation of cholinergic basal forebrain (the 'nucleus basalis', an area important for attending to important sensory stimuli which is severely impacted in Alzheimers disease), to drive acetylcholine release when a quiet sound was played. In vivo intracellular recordings showed that this procedure greatly increased the strength of cortical synapses to these sounds (**Fig. 3a**). Animals who responded to these sounds were given a food reward (a 'tone recognition' task). Our nucleus basalis stimulation method enhanced their abilities to correctly hear and respond to these sounds that seemed barely perceptible before stimulation (**Fig. 3b**).

However, the cellular and circuit changes that result from this approach are not well understood, limiting our ability to effectively utilize mechanisms of neuroplasticity for behavioral improvement, especially in pathological cases. To address mechanisms of modulator-induced synaptic sharpening during behavior, and generalize these changes across impaired animals, **we will use a novel recording method developed by the Long lab that enables long-lasting intracellular recordings in freely behaving animals**[22,23]. We plan to record from individual neurons in auditory cortex with the Long lab motorized intracellular microdrive (**Fig. 4**), while leveraging mechanisms of modulation and plasticity with deep brain stimulation techniques refined in the Froemke lab. In contrast to the studies of motor and sensory processing, much less is known about the neural circuits involved in cognition, thus our first aim is precisely to obtain this information using state-of-the-art recording and stimulation methods in a robust animal model of goal-directed behavior (**Fig. 3**).

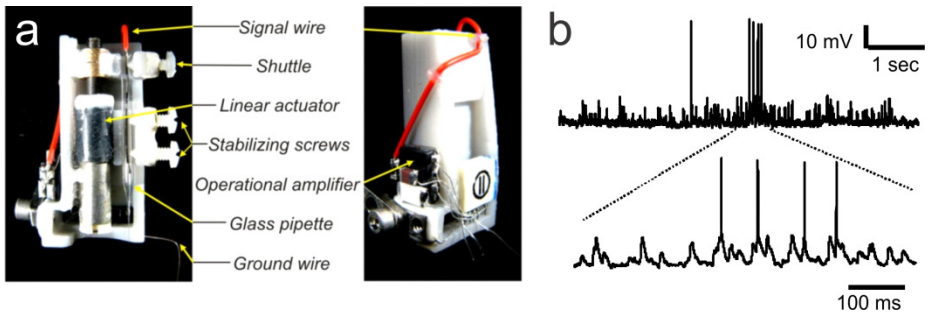

Figure 4. a, Motorized microdrive for intracellular recordings from moving animals (Long et al., 2010). **b**, Recordings using the intracellular microdrive from mouse hippocampus (M. Long, unpublished

First, we will determine how neuromodulatory systems engage mechanisms of cortical plasticity to affect synaptic strength in the adult mouse auditory cortex. As a suitable test-bed, we will examine a pair of modulatory systems centrally involved in two animal models of cognitive performance that we have found to depend strongly on activity in the auditory cortex. We will examine the modulatory action of the acetylcholine system of the nucleus basalis (involved in focusing attention on salient or behaviorally-relevant sensory stimuli) and the oxytocin system of the paraventricular nucleus of the hypothalamus (involved in social behavior). Correspondingly, we will examine behavioral performance of adult mice implanted with electrodes on both a learning and memory task as well as a task involving social recognition (described below). By comparing these systems we will be able to determine which neuromodulatory system or systems might most effectively enable neuroplasticity and improved behavioral performance under various circumstances, distinct behavioral episodes, or in different neuropathological conditions.

Our initial goal is to determine how pairing neuromodulation with sensory stimulation (a pure tone) leads to long-term changes in synaptic strength and spiking activity. We hypothesize that both acetylcholine and oxytocin lead directly to a decrease in synaptic inhibition, facilitating the emergence of stable long-term increases in excitatory and spiking responses to paired stimuli. In essence, this process should increase the

salience of stimuli paired with neuromodulation. Neuromodulatory release will be triggered either by electrical stimulation using implanted stimulation electrodes; or with optogenetic activation via a miniature fiber optic cable, implanted in transgenic animals expressing special light-activated ion channels in specific modulatory neurons. This potential for powerful, selective control of certain modulatory subpopulations is a main reason we will use mice for testing our cognitive neuroprosthetic device.

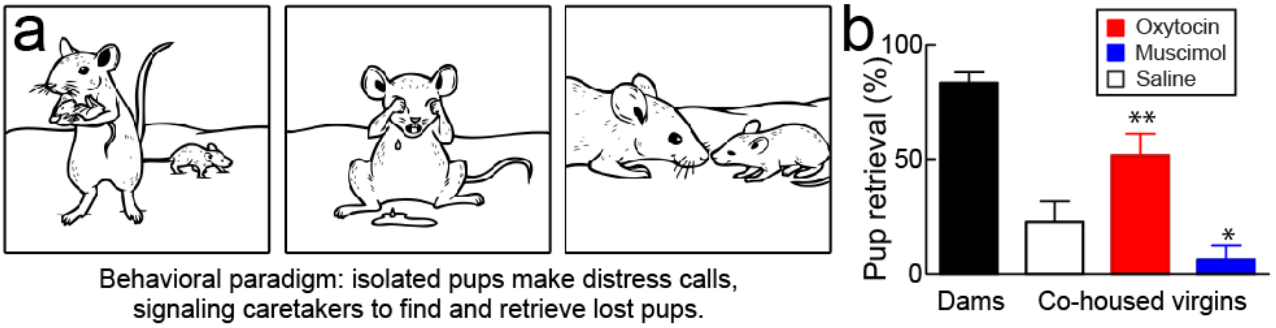

Figure 5. Oxytocin enhances auditory social behavior. **a**, Co-carers find and retrieve pups. **b**, 12 hrs co-housing, ~25% of saline-infused virgin co-carers (white) retrieve pups; this number of animals increased to ~50% after oxytocin infusion via cannula into the auditory cortex (red), and was impaired when the left auditory cortex was inactivated with the inhibitory GABA agonist muscimol (blue).

Similar to the experimental design for the smart hearing aid above, we will then examine behavioral performance on two behaviors that each require signal processing in the auditory cortex: a learning and memory task involving recognition of rewarded target tones (**Fig. 3b**), and a social cognitive task involving appropriate responses to distress vocalizations made by young animals (**Fig. 5**). In the first task, animals are trained to respond to a 4 kHz tone for a food reward- other tones are unrewarded and animals must withhold behavioral responses. In the social recognition task, adult animals are co-housed with a mother and her pups and tested for adequate attention to the young mouse pups- in particular, co-housed animals can learn that when pups are isolated from the nest, they make ultrasonic distress calls, alerting the mother or the other co-carer to orient to these isolation calls, fetching the pup and returning it to the nest (**Fig. 5a**). Virgin females and males do not initially behave in this manner, but after co-housing with a mother and pups, these inexperienced animals can also learn to fetch pups. New results from the Froemke lab have shown that this behavior is enhanced by oxytocin (**Fig. 5b**, red) and is impaired if the auditory cortex is transiently silenced with the inhibitory drug muscimol (**Fig. 5b**, blue). We will test control animals as well as animals with specific cognitive impairments. For example, the Simons Foundation- a nonprofit organization focused on funding research in autism spectrum disorders- has popularized a mouse model of Fragile X syndrome. We will examine neuromodulation, synaptic plasticity, and auditory behavioral performance in these animals, **asking if modulator systems and cortical neuroplasticity can effectively improve behavior in these cognitively-challenged animals**.

We will then use high-density surface electrode recordings with the Viventi system to record network activity simultaneously across hundreds of neurons as normal and learning-impaired animals engage in the tone recognition task. **This technology will be used to construct a cognitive prosthetic device, that conjointly monitors cortical activity and behavioral performance; if behavioral performance is sub-optimal, the device will stimulate release of neuromodulation to boost the neural signals and thus improve behavior.** We will optimize our deep brain stimulation procedures based on the population of neural responses that we measure,

as related to behavioral performance. Our strategy and goal is similar to the design of the motor and sensory prosthetic devices above: essentially, we aim to produce a target neural response, highly correlated in control animals with correct behavioral performance (responses to the target tone, withholding responses to non-target tones). If neural activity is too weak, we will engage the nucleus basalis (to release acetycholine for the tone recognition task) or the hypothalamus (to release oxytocin for the social recognition task). In case these systems themselves seem to be compromised in our model of cognitive impairment, we will assess the function of other complementary neuromodulatory systems such as the dopaminergic ventral tegmental area or the noradrenergic locus coeruleus, both currently also under study in the Froemke lab.

Our ultimate aim is to implement a similar technology in humans, taking advantage of existing FDA approval for deep brain stimulation devices in humans with Parkinson's, obsessive-compulsive disorders, epilepsy, and other neurological or psychiatric conditions. These studies in animals will fuel pre-clinical trials, to generate DARPA and NIH research funding for clinical trials in conjunction with NYU neurosurgeons and other extramural collaborators at UCSF and Harvard. Using non-invasive or minimally invasive recording technology in the case of severe impairments, such as autism spectrum disorders, we hope to improve social cognition and learning and memory in these critical cases for which other forms of treatment are sorely lacking.

Section III: Milestones and Measures of Success

Using this technological development and seed funding from the NYU Grand Challenge Award Competition, **we will demonstrate performance improvements in brain machine interfaces in three major areas**:

1. Motor prosthesis (Lead PIs: Pesaran, Viventi)

The Pesaran lab has currently demonstrated 6-7 degree-of-freedom control using the 27-D effector using penetrating electrodes in non-human primate (macaque) primary motor cortex. We have also demonstrated a high correlation coefficient (~0.8) between original movement and movement trajectories reconstructed from brain activity for each dimension of the system.

Criteria for success: 1) Implement virtual reality avatar control and robotic limb movement in non-human primates with high-density surface electrode recordings; 2) begin clinical trials for patients with paralysis and tetraplegia.

Milestone #1: Replicate 6-7 degree-of-freedom control with high reconstruction accuracy (~0.8) using μECoG from high-density surface electrode recordings. (Year 1)

Milestone #2: Improve control to 10-15 degree-of-freedom, which would saturate current state-of-the-art robotic systems. The interface with the brain will be shown to have stable and reliable performance for >1 year. (Year 2)

Milestone #3: Clinical trials in human patients. (Years 3+)

2. Sensory prosthesis (Lead PIs: Sanes, Viventi)

Criteria for success: 1) Identification of cortical responses from a large electrode array that are reliably associated with correct performance on AM perceptual tasks; 2) transform AM stimulus attributes to elicit

control-like neural response from auditory cortex of animals with hearing loss, and observe improvement in perceptual skills; 3) train hearing loss animals with transformed AM stimuli and observe improved auditory learning.

Milestone #1: Using our next-generation brain-machine interfaces developed under the proposed research plan, we will measure responses in auditory cortex that are reliably associated with AM detection and discrimination. We will then validate the experimental model by determining whether these responses can still be measured after acute hearing loss induced in these. Since acute hearing loss can be reversed (i.e., earplug removal), it will also be possible to determine if unexpected results are due to permanent damage.

In animals that display impaired AM discrimination thresholds, we will test the core prediction: **normal perceptual abilities will be observed behaviorally if auditory responses can be evoked in cortical neurons**. Therefore, we will modify the acoustic stimuli to elicit neural activity patterns that are associated with normal discrimination thresholds in control animals. Several features of the amplitude modulated waveform can be adjusted so as to elicit a normal neural response: carrier band, average level, envelope rise and decay time, and depth of modulation. This approach circumvents those current technologies that ignore central auditory changes, and lead to improved perception and auditory learning. (Year 1)

Milestone #2: Using the next-generation brain machine interfaces developed under the proposed research plan, we will determine how AM cues can be modified to support control perceptual abilities. With these optimized stimuli, we will train animals with hearing loss and determine whether the rate of perceptual skill acquisition is improved. (Year 2)

Milestone #3: Develop the smart hearing aid that dynamically adjusts acoustic input to correct for background noise and equalize losses in neural signals. (Year 3+)

3. Cognitive prosthesis (Lead PIs: Froemke, Long, Viventi)

Criteria for success: 1) Use mechanisms of neuroplasticity to improve cognitive abilities in animals with learning and memory impairments; 2) record

Milestone #1: Using in vivo intracellular recordings in the auditory cortex of freely-moving mice, we will use single neurons as a monitor for network dynamics. We will measure intracellular responses in single neurons with the Long lab microdrive, asking how the acetylcholine and oxytocin neuromodulator systems lead to long-term changes in synaptic and spiking activity. (Year 1)

Milestone #2: By combining this approach with neural stimulation in behaving animals, we will determine which brain areas most effectively modulate the cerebral cortex to enhance processing of sensory stimuli during behavioral tasks, one involving remembering the significance of a sensory input for food reward, and another task involving learning to correctly respond to social information (pup isolation calls). We have already demonstrated the feasibility of these recordings in anesthetized animals[18,19], and thus recording in awake animals is a tangible goal in the near future. (Year 2)

Milestone #3: Develop a multi-channel EEG system for non-invasively recording similar neural activity in humans, using recorded activity as a form of bio-feedback for guiding behavioral performance and improving human perceptual abilities through deep brain stimulation in cases of cognitive impairment. (Years 3+)

Section IV: External Partners and Community Mobilization

We have an established collaboration with all of the required external partners for this project. The Viventi lab focuses on the design and validation of the electrode arrays and supporting systems and collaborates with the Rogers lab at the University of Illinois at Urbana-Champaign for clean-room fabrication. This collaboration has spanned over five years and will continue through the project duration. The Rogers lab will fabricate the electrode arrays used in the animal studies in this proposal. The Viventi lab has also collaborated with Gert Cauwenberghs at the University of California San Diego for the past two years to develop the high channel count implantable wireless systems that will be used in this proposal[24].

The Viventi lab has filed five patent applications on the technology in this proposal. The patents have been licensed to mc10, a start-up company with ~30 employees developing the next generation of consumer and medical products using high-performance flexible electronics. The Viventi lab is actively collaborating with mc10 to develop the medical applications of this technology. The results of this grand challenge proposal will be rapidly translated to human use through our existing connections to mc10.

For the human studies proposed for years 3+, mc10 will build multiplexed recording electrodes based on previously proven designs[7] using commercial processing techniques. Commercial fabrication by mc10 will create devices that are sufficiently reliable, safe and robust for human use. Fabrication will begin at a commercial semiconductor foundry, X-FAB (Erfurt, Germany), where designs will be fabricated on a traditional rigid substrate. Engineers at MC10, in collaboration with commercial partners Semprius, Inc, will use proven micro-transfer printing technology[25] to remove a portion of the chiplets from their inflexible silicon wafer source and place them onto the flexible substrate. Hundreds of chiplets can be transferred in a single processing step, for example transferring 400 chiplets to cover 1 cm^2. Subsequent steps using the same transfer stamp can cover additional 1 cm^2 areas with 400 electrodes, producing final arrays in different clinical configurations, such as 4×4 cm devices containing 6,400 contacts and 8x8 cm devices containing up to 25,600 contacts. As commercial processing at X-FAB allows much finer feature sizes than our previous work[26], local amplification and filtering can occur at each electrode, while using less overall silicon. This will allow us to produce large area devices at significantly reduced cost. These arrays will be shipped to NYU for testing and use in human studies.

We have extensive collaborative ties to neurosurgery and neurology departments to facilitate the human studies in years 3+. The Pesaran and Viventi labs collaborate with the NYU Comprehensive Epilepsy Center on human studies in epilepsy patients, the Long lab collaborates with the Department of Neurosurgery at the University of Iowa on functional mapping in epilepsy patients using focal cooling, and the Froemke lab collaborates with clinicians in the Departments of Neurosurgery, Neurology, Psychiatry, and Otolarnygology, as well as extramurally with investigators at the University of California, San Francisco and Harvard.

Finally, we will work closely with the Office of Industrial Liaison (OIL) / Technology Transfer to file patent applications on new technology developed over the course of the grand challenge project and to rapidly license this technology to industry for commercialization.

References

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2. Schevon, C. a *et al.* Microphysiology of epileptiform activity in human neocortex. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society* **25**, 321–30 (2008).

3. Stead, M. *et al.* Microseizures and the spatiotemporal scales of human partial epilepsy. *Brain : a journal of neurology* **133**, 2789–97 (2010).

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5. Leuthardt, E. C. *et al.* Using the electrocorticographic speech network to control a brain-computer interface in humans. *Journal of neural engineering* **8**, 036004 (2011).

6. Kellis, S. *et al.* Decoding spoken words using local field potentials recorded from the cortical surface. *Journal of neural engineering* **7**, 056007 (2010).

7. Viventi, J. *et al.* Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo. *Nature Neuroscience* **14**, 1599–605 (2011).

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9. Markowitz, D. a, Wong, Y. T., Gray, C. M. & Pesaran, B. Optimizing the decoding of movement goals from local field potentials in macaque cortex. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **31**, 18412–22 (2011).

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18. Park et al. Temporal modulation transfer functions for child and adult cochlear implant and normal-hearing listeners. *Conference on Implantable Auditory Prostheses* 109 (2011).

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20. Froemke, R. C., Merzenich, M. M. & Schreiner, C. E. A synaptic memory trace for cortical receptive field plasticity. *Nature* **450**, 425–9 (2007).

21. Froemke, R. C. *et al.* Long-term modification of cortical synapses improves sensory perception. *Nature neuroscience* **16**, 79–88 (2013).

22. Long, M. a & Lee, A. K. Intracellular recording in behaving animals. *Current opinion in neurobiology* **22**, 34–44 (2012).

23. Long, M. a, Jin, D. Z. & Fee, M. S. Support for a synaptic chain model of neuronal sequence generation. *Nature* **468**, 394–9 (2010).

24. Ha, S. *et al.* Biopotential Recording IC for High-Density ECoG Flexible Active Electrode Array. *European Solid-State Circuits Conference (in review)* (2013).

25. Bower, C. a., Menard, E., Bonafede, S. & Burroughs, S. Transfer-printed microscale integrated circuits. *2009 59th Electronic Components and Technology Conference* 618–623 (2009).doi:10.1109/ECTC.2009.5074077

26. Viventi, J. *et al.* Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo. *Nature neuroscience* **14**, 1599–605 (2011).

Appendix Material

1. Management and Staffing Plan

The partners in this application have an established collaboration record spanning several years. To coordinate the activities in this proposal and supplement frequent informal meetings, monthly Skype teleconferences with the entire research team will be held to discuss results and challenges. At least every three months, an in-person meeting for all 5 PIs, plus the postdocs and graduate students involved in the project will occur to update everyone on the progress in each of the three research thrusts, as well as brainstorm new ideas. The location of the meeting will rotate between uptown, downtown and Brooklyn. A representative from the NYU Office of Industrial Liaison (OIL) will be invited to these meetings every 6-12 months to evaluate and highlight specific technologies to be patented.

The lab directors on this project will decide as a group what to publish, and alternate last authorship depending first upon who does the work and second the subject of publications. All work is collaborative and inclusive of partners involved in the research, provided they have made appropriate contributions to the research. Lab directors will senior author papers first authored by members of their lab or if they are the primary supervisors of specific projects. Authorship will be made strictly by academic criteria, specifically in order of the amount of contribution to the manuscript, as agreed upon by the participants.

The partners in the proposed research have a track record of successful collaboration, exceptional academic leadership in their respective areas and extensive experience with successfully managing significant projects.

Bijan Pesaran

Dr. Pesaran has a strong background in neural engineering, experimental and computational neuroscience and has the expertise necessary to successfully lead the proposed Motor prosthesis work. At NYU he has established a lab that seeks to unravel the neural mechanisms of sensory-motor processes performed by populations of neurons and implements novel brain-machine interfaces. Dr. Pesaran has successfully competed for several young investigator awards and is currently-funded by the DARPA ReNET program to develop many-DOF brain-machine interfaces. The first set of peer-reviewed studies from his lab are now published. These qualifications dove-tail with the goals of the current application and will take the important step of developing innovative approaches to developing naturalistic arm-hand control for advanced robotic devices.

Jonathan Viventi

Dr. Viventi creates new tools for neuroscience research and technology to diagnose and treat neurological disorders, such as epilepsy. His research leverages innovations in flexible electronics, low power analog circuits, and machine learning to create new technology for interfacing with the brain at a much finer scale and with broader coverage than previously possible. Using these tools, Dr. Viventi collaborates with neuroscientists and clinicians to explore the fundamental properties of brain networks in both health and disease. Dr. Viventi also works closely with industry, including filing five patents and several licensing agreements. His work has been featured as cover articles in *Science Translational Medicine* and *Nature Materials*, and has also appeared in *Nature Neuroscience*, the *Journal of Neurophysiology*, and *Brain*. Through the NYU Grand Challenge Competition, this research will form the basis of a new generation of diagnostic and therapeutic brain-computer interface (BCI) devices that are flexible, high-resolution, minimally invasive and wireless.

Rob Froemke

Dr. Froemke studies the organization and plasticity of cortical synapses, and the relations between circuit dynamics and control of perception and behavior. He uses several techniques in vivo and in vitro, including electrophysiology, 2-photon microscopy, behavioral methods, and computational analyses, to ask two main questions.

1) Neural circuitry and plasticity of mammalian motivated behavior. Motivated actions, such as food seeking, mating, and parental care are fundamental aspects of animal and human behavior. We study the representation of sensory stimuli in the auditory and frontal cortex of rats and mice using in vivo whole-cell recording, multi-electrode recording, and behavioral analysis. Recently Dr. Froemke has published a paper in Nature Neuroscience[21] using a custom-built wireless neuroprosthetic device to stimulate neuromodulator release and improve auditory perceptual abilities.

2) Long-term synaptic plasticity in cortical networks. Mechanisms of cortical plasticity seem to be disrupted in learning impairments and language disorders; conversely, engaging these mechanisms by training programs and prosthetic devices will help repair damaged brains in pathological conditions. Dr. Froemke studies interactions between excitation, inhibition, and the activation of various neuromodulatory systems.

Dan Sanes

Dr. Sanes has a 30 year background in neural development. This includes training, published research, and collaborations in each facet of the proposed experiments, especially synaptic plasticity. Dr. Sanes also has an equally long and broad background in the hearing sciences. He has led research projects that examine auditory processing in vivo from brainstem to cortex, as well as those that explore the underlying synaptic mechanisms. The emphasis of his lab's research for the past 12 years has considered the impact of hearing loss on synapse function. He has shown that sensorineural and conductive hearing loss lead to rapid, systematic changes in the strength of nearly all synaptic connections examined; in general, early hearing loss leads to a dramatic decrease of inhibitory synaptic strength and an increase in excitatory strength. These findings suggest that the deaf central auditory nervous system may operate quite differently when it is activated (for example, by a cochlear electrical prosthesis), and draw attention to the risk of considering only peripheral factors when trying to explain the perceptual deficits associated with early hearing loss. In Dr. Sanes' recent behavior and in vivo physiology experiments, he has identified a correlation between deficits in AM detection and AM depth encoding in auditory cortex.

Michael Long

Michael Long, a systems neuroscientist with 15 years of electrophysiological experience, has performed intracellular recordings in both in vitro and in vivo preparations. During his postdoctoral years, he developed a novel method for recording the intracellular membrane potential from single neurons in freely behaving animals. This method, originally designed for recording motor control neurons in songbirds, has been recently adapted for use with rodent and nonhuman primate preparations. He will use this experience, coupled with the expertise in auditory cortex and the basal forebrain from Robert Froemke, to help design and test a cognitive neuroprosthetic device. As the principal investigator on four concurrently funded proposals, Michael Long has organized separate teams of scientists in his laboratory to successfully pursue a variety of research goals.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Bijan Pesaran, Ph.D.	Associate Professor of Neural Science
eRA COMMONS USER NAME (credential, e.g., agency login) BP31.NYU	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Cambridge, UK	B.A.(Hons)	6/95	Physics
California Institute of Technology, Pasadena, CA	Ph.D.	6/2002	Physics
California Institute of Technology, Pasadena, CA	Postdoc	12/2005	Neuroscience

B. Positions and Honors

1995 – 1996 Consultant, Theoretical Physics Research, Bell Labs, Murray Hill, NJ
1996 – 2001 Senior Technical Associate, Theoretical Physics Research, Bell Labs, Murray Hill, NJ
2006 – 2012 Assistant Professor of Neural Science, New York University, New York, NY
2012 – present Associate Professor of Neural Science, New York University, New York, NY
2013 – present Visiting Assistant Professor, Princeton Neuroscience Institute, Princeton University, NJ
2013 – present C V Starr Visiting Scholar, Princeton Neuroscience Institute, Princeton University, NJ

1994 Nuffield Foundation Summer Research Fellow
1995 Royal Society Summer Research Fellow
1997 NSF Graduate Student Fellowship
1997 Sloan Center for Theoretical Neurobiology Fellowship
2004 Burroughs-Wellcome Fund Career Award in the Biomedical Sciences
2007 James D. Watson Program Investigator Award
2007 Alfred P. Sloan Research Fellowship
2008 McKnight Scholar Award
2010 NSF CAREER Award

C. Selected peer-reviewed articles

Most relevant to current application

Pesaran B, Nelson MJ and Andersen RA (2008). Free choice activates a decision circuit between frontal and parietal cortex. *Nature* 453(7193):406-9.

Markowitz DA, Wong YT, Gray CM, **Pesaran B**. (2011) Optimizing the decoding of movement goals from local field potentials in macaque cortex. *J Neurosci.* 31(50):18412-22.

Dean HL, Martí D, Tsui E, Rinzel J, **Pesaran B**. (2011) Reaction time correlations during eye-hand coordination: behavior and modeling. *J Neurosci*. 16;31(7):2399-412.

Hagan MA, Dean HL, **Pesaran B.** (2012) Spike-field activity in parietal area LIP during coordinated reach and saccade movements. *J Neurophysiol*. 107(5):1275-90.

Dean HL, Hagan MA, **Pesaran B**. (2012). Only coherent spiking in posterior parietal cortex coordinates looking and reaching. *Neuron*. Feb 23;73(4):829-41.

Additional recent publications of relevance to the field (in chronological order)

Mitra PP and **Pesaran B** (1999). Analysis of dynamic brain imaging data. *Biophys J* 76:691-708.

Pesaran B Pezaris JS, Sahani M, Mitra PP and Andersen RA (2002). Temporal structure in neuronal activity during working memory in macaque parietal cortex. *Nature Neurosci* 5:805-811.

Shenoy KV, Meeker D, Cao S, Kureishi, S, **Pesaran, B**, Buneo C, Batista AP, Mitra PP, Burdick JW and Andersen RA (2003). Neural prosthetic control signals from plan activity. *Neuroreport*. 14:591-596.

Andersen RA, Burdick JW, Musallam, S., **Pesaran B** and Cham JG (2004). Cognitive neural prosthetics. *Trends Cog Sci* 8:486-493
Andersen RA, Musallam S and **Pesaran B** (2004). Selecting signals for neural prosthetics. *Curr. Op. Neurobiol* 14(6):720-726
Pesaran B, Nelson MJ and Andersen RA (2006) Dorsal premotor neurons encode the relative position of the hand, eye and goal during reach planning. *Neuron* 51(1):125-134.
Lee B, **Pesaran B** and Andersen RA (2007). Translation speed compensation in MSTd. *J Neurosci* 27(10):2582-91.
Gershman SJ, **Pesaran B** and Daw ND. (2009) Human reinforcement learning subdivides structured action spaces by learning effector-specific values. *J Neurosci* 29(43):13524-31.
Pesaran B (2010) Neural correlations, decisions and actions. *Curr Opin Neurobiol* 20(2):166-71.
Pesaran B, Nelson MJ and Andersen RA (2010) A relative position code for saccades in dorsal premotor cortex *J Neurosci* 30(19):6527-37.
Banerjee A, Dean HL, **Pesaran B**. (2010) A likelihood method for computing selection times in spiking and local field potential activity. *J Neurophysiol.* 104(6):3705-20.
Markowitz DA, Shewcraft RA, Wong YT, **Pesaran B**. (2011) Competition for visual selection in the oculomotor system. *J Neurosci.* Jun 22;31(25):9298-306.
Gunduz A, Brunner P, Daitch A, Leuthardt EC, Ritaccio AL, **Pesaran B**, Schalk G. (2012) Decoding covert spatial attention using electrocorticographic (ECoG) signals in humans. *Neuroimage*. 60(4):2285-93.
Banerjee A, Dean HL, **Pesaran B**. (2012) Parametric models to relate spike train and LFP dynamics with neural information processing. *Front Comput Neurosci.* 6:51.
Gunduz A, Brunner P, Daitch A, Leuthardt EC, Ritaccio AL, **Pesaran B**, Schalk G. (2012) Decoding covert spatial attention using electrocorticographic (ECoG) signals in humans. *Neuroimage*. 60(4):2285-93.

D. Current Research Support

Burroughs-Wellcome Fund Career Award (P.I., Pesaran) 9/1/04-12/31/14
"Cortical mechanisms for hand-eye coordination"
Understand the cortical mechanisms for freely-selected, coordinated hand-eye movements and their organization across frontal and parietal cortex using multiple area, multiple electrode recordings in the behaving monkey.

CRCNS NIMH R01 (P.I. Nathaniel Daw)
"Reinforcement learning in multi-dimensional action spaces" 5/01/09 - 4/30/14
This project proposes a theoretical reinforcement learning framework for more realistic learning and decision problems involving multiple effectors, and leverages it in experiments probing how the brain copes with learning and decision-making in these cases.

R03 DC010475-01 (P.I. Pesaran)
"Auditory-articulatory representations for speech production" 12/1/09 – 11/30/13
The long-term goal of this research is to give people with severe motor disorders the ability to speak and communicate. I propose to take a step toward this goal by uncovering the neural code for speech production using recordings of electrical activity in the human brain.

NSF CAREER 0955701 (P.I. Pesaran)
"Neural circuit mechanisms of coordinated eye and hand movements" 2/1/10 – 1/31/15
This proposal tests hypotheses about how the coupling between the timing of coordinated eye-hand behaviors depends on cooperation and inhibition between saccade and reach representations.

DARPA N66001-11-1-4205 (P.I. Pesaran) 10/1/11 – 9/30/14
"Reliable High-bandwith Cortical Control of Unconstrained, Many-Degree-Of-Freedom Movement"
The objective of this effort is to advance brain interface technologies to provide significant benefits in the control of many-degree-of-freedom artifical arm and hand prosthetic devices that will help amputees and other patients who have lost the use of their arm and hand.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Viventi, Jonathan	Assistant Professor of Electrical and Computer Engineering, Assistant Professor of Neural Science Polytechnic Institute of New York University
eRA COMMONS USER NAME (credential, e.g., agency login) JVIVENTI	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
Princeton University, Princeton, NJ	B.S.E.	2000-2003	Electrical Engineering
Princeton University, Princeton, NJ	M.Eng.	2003-2004	Electrical Engineering
University of Pennsylvania	Ph.D.	2006-2010	Bioengineering
University of Illinois at Urbana-Champaign and University of Pennsylvania	Postdoctoral	2010-2011	Brain Machine Interface Devices

B. Positions and Honors

Positions and Employment

2011 – Assistant Professor of Electrical and Computer Engineering
Polytechnic Institute of New York University, Brooklyn, NY
2011 – Assistant Professor of Neural Science
New York University, New York, NY
2010 – Consultant, MC10, Inc., Boston, MA
2006 – Founder, N2MB Racing LLC, Holiday, FL
2006 – 2009 Consultant, Qualcomm, Inc., Bridgewater, NJ
2004 – 2006 Architecture and Algorithms Engineer, Flarion Technologies, Inc. (acquired by Qualcomm)

Honors

2012 Citizens United for Research in Epilepsy (CURE) - Taking Flight Award
2011 Grass Foundation – AES Young Investigator Travel Award
2010 Ruth L. Kirschstein-National Service Research Award
2010 Beckman Institute Postdoctoral Fellowship
2010 Mahoney Institute of Neurological Sciences / Neuroscience Graduate Group Flexner Award for best neuroscience thesis at the University of Pennsylvania
2010 Solomon R. Pollack Award for best thesis in the Dept. of Bioengineering at University of Pennsylvania
2010 Neural Interfaces Conference Travel Award
2009 Nano/Bio Interface Center Graduate Research Award for the best graduate research at the University of Pennsylvania on Nanotechology applied to Biology
2003, 2004 Two Outstanding Teaching Assistant Awards from the Princeton University Electrical Engineering department
2003 National Finalist in NASA-sponsored design competition, RASC-AL

Patent Applications

1. Conformable Actively Multiplexed High-Density Surface Electrode Array for Brain Interfacing, International Application No. PCT/US2012/040482, U.S. Application No. 13/486,726, June 3, 2011
2. High-Speed, High-Resolution Electrophysiology In-Vivo using Conformal Electronics. International Application No. PCT/US10/60425, US Application No. 12/968,637, December 15, 2010
3. Implantable Biomedical Devices on Bioresorbable Substrates. International Application No. PCT/US10/50468, US Application No. 12/892,001, September 28, 2010.
4. Self-Adaptive Bio-Signal Sensing and Modulation Device. International Application No. PCT/US2010/035584, May 20, 2009
5. Flexible and Scalable Sensor Arrays for Recording and Modulating Physiologic Activity. International Application No.: PCT/US2009/036956, March 12, 2008 * licensed to industry

C. Selected Peer-reviewed Publications

[1] **J. Viventi**, D.-H. Kim, L. Vigeland, E. S. Frechette, J. a Blanco, Y.-S. Kim, A. E. Avrin, V. R. Tiruvadi, S.-W. Hwang, A. C. Vanleer, D. F. Wulsin, K. Davis, C. E. Gelber, L. Palmer, J. Van der Spiegel, J. Wu, J. Xiao, Y. Huang, D. Contreras, J. a Rogers, and B. Litt, "Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo.," *Nature Neuroscience*, vol. 14, no. 12, pp. 1599–605, Dec. 2011.

[2] D.-H. Kim, N. Lu, R. Ghaffari, Y.-S. Kim, S. P. Lee, L. Xu, J. Wu, R.-H. Kim, J. Song, Z. Liu, **J. Viventi**, B. de Graff, B. Elolampi, M. Mansour, M. J. Slepian, S. Hwang, J. D. Moss, S.-M. Won, Y. Huang, B. Litt, and J. A. Rogers, "Materials for multifunctional balloon catheters with capabilities in cardiac electrophysiological mapping and ablation therapy.," *Nature Materials*, no. March, pp. 1–8, Mar. 2011.

[3] J. A. Blanco, M. Stead, A. Krieger, W. Stacey, D. Maus, E. Marsh, **J. Viventi**, K. H. Lee, R. Marsh, B. Litt, and G. A. Worrell, "Data mining neocortical high-frequency oscillations in epilepsy and controls.," *Brain : a journal of neurology*, Sep. 2011.

[4] **J. Viventi**, D.-H. Kim, J. D. Moss, Y.-S. Kim, J. a. Blanco, N. Annetta, a. Hicks, J. Xiao, Y. Huang, D. J. Callans, J. a. Rogers, and B. Litt, "A Conformal, Bio-Interfaced Class of Silicon Electronics for Mapping Cardiac Electrophysiology," *Science Translational Medicine*, vol. 2, no. 24, pp. 24ra22–24ra22, 2010.

[5] D.-H. Kim, **J. Viventi**, J. J. Amsden, J. Xiao, L. Vigeland, Y.-S. Kim, J. a Blanco, B. Panilaitis, E. S. Frechette, D. Contreras, D. L. Kaplan, F. G. Omenetto, Y. Huang, K.-C. Hwang, M. R. Zakin, B. Litt, and J. a Rogers, "Dissolvable films of silk fibroin for ultrathin conformal bio-integrated electronics.," *Nature Materials*, no. April, pp. 1–8, Apr. 2010.

[6] J. a Blanco, M. Stead, A. Krieger, **J. Viventi**, W. R. Marsh, K. H. Lee, G. a Worrell, and B. Litt, "Unsupervised classification of high-frequency oscillations in human neocortical epilepsy and control patients.," *Journal of Neurophysiology*, vol. 104, no. 5, pp. 2900–12, Nov. 2010.

[7] A. Ritaccio, M. Beauchamp, C. Bosman, P. Brunner, E. Chang, N. Crone, A. Gunduz, D. Gupta, R. Knight, E. Leuthardt, B. Litt, D. Moran, J. Ojemann, J. Parvizi, N. Ramsey, J. Rieger, **J. Viventi**, B. Voytek, J. Williams, and G. Schalk, "Proceedings of the third international workshop on advances in electrocorticography.," *Epilepsy & Behavior*, vol. 25, no. 4, pp. 605–13, Dec. 2012.

[8] A. Ritaccio, D. Boatman-Reich, P. Brunner, M. C. Cervenka, A. J. Cole, N. Crone, R. Duckrow, A. Korzeniewska, B. Litt, K. J. Miller, D. W. Moran, J. Parvizi, **J. Viventi**, J. Williams, and G. Schalk, "Proceedings of the second international workshop on advances in electrocorticography.," *Epilepsy & Behavior*, vol. 22, no. 4, pp. 641–50, Dec. 2011.

[9] **J. Viventi** and J. A. Blanco, "Development of high resolution, multiplexed electrode arrays: Opportunities and challenges," in *2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2012, pp. 1394–1396.

[10] T. Kim, N. S. Artan, **J. Viventi**, and H. J. Chao, "Spatiotemporal compression for efficient storage and transmission of high-resolution electrocorticography data," in *2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2012, vol. 35, no. 3, pp. 1012–1015.

[11] H. Bink, Y. Lai, S. R. Saudari, B. Helfer, **J. Viventi**, J. Van der Spiegel, B. Litt, and C. Kagan, "Flexible organic electronics for use in neural sensing," in *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2011, pp. 5400–5403.

[12] A. C. Chamberlain, **J. Viventi**, J. A. Blanco, D.-H. Kim, J. A. Rogers, and B. Litt, "Millimeter-scale epileptiform spike patterns and their relationship to seizures," in *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2011, vol. 2011, pp. 761–764.

D. Research Support

Ongoing Research Support

CURE Taking Flight Award Viventi (PI) 01/01/2012 – 12/31/2012

CURE: Citizens United for Research in Epilepsy

Responsive patterned microstimulation to abort seizure initiating patterns

The major goals of this project are to design and test multiplexed stimulation circuits in flexible, active electrode arrays and to validate that specifically designed spatiotemporal micro-stimulation patterns can disrupt or silence pathologic activity such as micro-seizures or HFOs.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Froemke, Robert Crooks	Assistant Professor of Otolaryngology, Physiology & Neuroscience, Skirball Institute, NYU Medical; Center for Neural Science, NYU
eRA COMMONS USER NAME (credential, e.g., agency login) RFROEMKE	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Tufts University, Medford MA	B.A.	11/98	Computer Science
University of California, Berkeley CA	Ph.D.	05/04	Molecular & Cell Biology
University of California, San Francisco CA	Postdoctoral	04/10	Otolaryngology

Positions and Employment

2010- Assistant Professor, New York University School of Medicine, Skirball Institute Program in Molecular Neurobiology; Departments of Otolaryngology, Physiology & Neuroscience; Kimmel Center for Stem Cell Biology; Center for Neural Science.

Other Experience and Professional Memberships

2000 Neural Systems & Behavior Course, Marine Biological Laboratory, Woods Hole, MA
2000- Member, American Association for the Advancement of Science
2000- Member, Society for Neuroscience
2004 Grass Fellow, Marine Biological Laboratory, Woods Hole, MA
2005- Member, Association for Research in Otolaryngology
2007 Okinawa Computational Neuroscience Course, Okinawa, Japan
2008 Methods in Computational Neuroscience, Marine Biological Laboratory, Woods Hole, MA
2009 Teaching Assistant, Biology of Memory Course, Cold Spring Harbor Laboratory, NY
2010 Kavli Institute for Theoretical Physics, UC Santa Barbara
2012- Co-Director, Biology & Disorders of Learning and Memory, Cold Spring Harbor Laboratory, NY

Honors

2001 Howard Hughes Medical Institute Predoctoral Fellowship
2002 Outstanding Graduate Student Instructor, University of California, Berkeley
2004 First place, General Scientific Meeting presentation, Marine Biological Laboratory
2005 Jane Coffin Childs Postdoctoral Fellowship
2006 Sandler Translational Research Postdoctoral Fellowship
2007 Tamagawa Dynamic Brain Forum Travel Award
2008 K99/R00 Career Award, NIDCD
2011 Whitehead Fellowship
2012 Alfred P. Sloan Research Fellowship
2012 Pew Scholarship
2012 Klingenstein Fellowship

Selected Peer-reviewed Publications (From 24 peer-reviewed publications)

1. Froemke RC, Carcea I, Barker AJ, Yuan K, Seybold B, Martins ARO, Zaika N, Bernstein H, Wachs M, Levis PA, Polley DB, Merzenich MM, Schreiner CE. Long-term modification of cortical synapses improves sensory perception. **Nature Neuroscience** 2013; 16:79-88. PMID: 23178974

2. Tukey DS, Ferreira JM, Antoine SO, D'amour JA, Ninan I, Cabeza de Vaca S, Incontro S, Wincott C, Horwitz JK, Hartner DT, Guarini CB, Khatri L, Goffer Y, Xu D, Titcombe RF, Khatri M, Marzan DS, Mahajan SS, Wang J, Froemke RC, Carr KD, Aoki C, Ziff EB. Sucrose ingestion induces rapid AMPA receptor trafficking. **Journal of Neuroscience** 2013; 33:6123-6132 PMID: 23554493.
3. Southwell DG, Paredes MF, Galvao RP, Jones DL, Froemke RC, Sebe JY, Alfaro-Cervello C, Tang Y, Garcia-Verdugo JM, Rubenstein JL, Baraban SC, Alvarez-Buylla A. Intrinsically determined cell death of developing cortical interneurons. **Nature** 2012; 491:109-113. PMID: 23041929
4. Hunzinger JF, Chan VH, Froemke RC. Learning complex temporal patterns with resource-dependent spike timing-dependent plasticity. **Journal of Neurophysiology** 2012; 108:551-566. PMID: 22496526
5. Froemke RC, Martins ARO. Spectrotemporal dynamics of auditory cortical synaptic receptive field plasticity. **Hearing Research** 2011; 279:149-161. PMID: 21426927
6. Dorrn A, Yuan K, Barker AJ, Schreiner CE, Froemke RC. Developmental sensory experience balances cortical excitation and inhibition. **Nature** 2010; 465:932-936. PMID: 20559387
7. Southwell D, Froemke RC, Alvarez-Buylla A, Stryker MP, Gandhi SP. Cortical plasticity induced by inhibitory neuron transplantation. **Science** 2010; 327:1145-1148. PMID: 20185728
8. Urakubo H, Honda M, Froemke RC, Kuroda S. Requirement of an allosteric kinetics of NMDA receptors for spike-timing-dependent plasticity. **Journal of Neuroscience** 2008; 28:3310-3323. PMID: 18367598
9. Froemke RC, Merzenich MM, Schreiner, CE. A synaptic memory trace for cortical receptive field plasticity. **Nature** 2007; 450:425-429. PMID: 18004384
10. Kenet T, Froemke RC, Schreiner CE, Pessah IN, Merzenich MM. Perinatal exposure to a non-coplanar PCB alters tonotopy, receptive fields and plasticity in rat primary auditory cortex. **Proceedings of the National Academy of Sciences USA** 2007; 104:7646-7651. PMID: 17460041
11. Froemke RC, Tsay IA, Raad M, Long JD, Dan Y. Contribution of individual spikes in burst-induced long-term synaptic modification. **Journal of Neurophysiology** 2006; 95:1620-1629. PMID: 16319206
12. Froemke RC, Poo MM, Dan Y. Spike-timing-dependent plasticity depends on dendritic location. **Nature** 2005; 434:221-225. PMID: 15759002
13. Froemke RC, Dan Y. Spike-timing-dependent synaptic modification induced by natural spike trains. **Nature** 2002; 416:433-438. PMID: 11919633

Ongoing Research Support

R01 NIDCD DC012557 Froemke (PI) 2012-2017
Synaptic basis for perceptual learning in primary auditory cortex
The goal of this study is to directly examine the relation between adult cortical synaptic plasticity and perceptual learning via the noradrenergic modulatory system. Role: PI

Pew Scholarship 2012-2016
Neural basis of learned social behavior
The goal of this study is to determine how oxytocin affects learned social behavior. Role: PI

Klingenstein Fellowship 2012-2015
Plasticity of excitatory-inhibitory balance in the auditory cortex
The goal of this study is to determine the network dynamics and mechanisms that calibrate and balance excitation and inhibition in the developing auditory cortex. Role: PI

Alfred P. Sloan Research Fellowship 2012-2014
Synaptic plasticity in the cerebral cortex
The goal of this study is to examine the behavioral consequences of cortical synaptic plasticity. Role: PI

K99/R00 NIDCD DC009635-05 Froemke (PI) 2008-2013
Synaptic basis for perceptual learning in primary auditory cortex
The goal of this study is to directly examine the relation between adult cortical synaptic plasticity and perceptual learning via the cholinergic modulatory system. Role: PI

Dan H. Sanes May 2013

CURRICULUM VITAE

EDUCATION

B.S.	1978	Univ. of Massachusetts, Amherst	Zoology
M.S.	1981	Princeton University	Biology
Ph.D.	1984	Princeton University	Biology

PROFESSIONAL APPOINTMENTS

1984-1986 Postdoctoral Fellow, University of Virginia School of Medicine
1986-1987 Postdoctoral Fellow, Yale University School of Medicine
1987-1991 Asst Professor, Dept. Otolaryngology, NYU School of Medicine
1991-1993 Asst Professor, Center for Neural Science, New York University
1993-2000 Associate Professor, Center for Neural Science, New York University
1998-2004 Director, Center for Neural Science, New York University
2000- Professor, Center for Neural Science, New York University

PROFESSIONAL SOCIETIES

Member, New York Academy of Sciences
Member, Acoustical Society of America
Member, Association for Research in Otolaryngology
Member, Society for Neuroscience

ACADEMIC RECORD & FUNDING

1988-1990 Sloan Foundation Fellow
1989-1994 NIDCD First Award
1993-1996 NSF Award
1993-1995 March of Dimes Award
1994-2000 NIDCD RO1
1996-1999 NSF Award
1998- Scientific Advisory Board, National Organization for Hearing Research
1999 Visiting Scholar, Physiology Department, Fukuoka University, Japan
2000-2005 NIDCD RO1
2005-2010 NIDCD RO1
2006 Hugh Knowles Visiting Professor, Northwestern University
2007 Visiting Scholar, University of Munich
2008-2012 Visiting Scholar, Communication Sci & Disorders, Northwestern Univ
2009-2014 NIDCD RO1
2009-2012 Section Editor, Hearing Research
2010-2015 NIDCD RO1
2010 Fellow, American Association for the Advancement of Science
2010-2013 Councilor, Association for Research in Otolaryngology
2010- Member, AUD Study Section, NIH
2012 Director, Gordon Research Conference: Auditory System
2012- Reviewing Editor, Journal of Neuroscience

SELECTED PUBLICATIONS

Sanes DH (1993) The development of synaptic function and integration in the central auditory system. J Neurosci 13: 2627-2637.

Sanes DH, Takács C (1993) Activity-dependent refinement of inhibitory connections. Eur J Neurosci 5: 570-574.

Kotak VC, Sanes DH (1996) Developmental influence of glycinergic inhibition: Regulation of NMDA- mediated EPSPs. J Neurosci 16: 1836-1843.

Kotak VC, Korada S, Schwartz IR, Sanes DH (1998) A developmental shift from GABAergic to glycinergic transmission in the central auditory system. J Neurosci 18: 4646-4655.

Thornton S, Semple MN, Sanes DH (1999) Development of auditory motion processing in the gerbil inferior colliculus. Eur J Neurosci 11: 1414-1420.
Vale C, Sanes DH (2000) Afferent regulation of inhibitory synaptic transmission in the developing auditory midbrain. J Neurosci 20: 1912-1921.
Kotak VK, Sanes DH (2000) Long-Lasting Inhibitory Synaptic Depression is Age- and Calcium-Dependent. J Neurosci 20: 5820-5826.
Vale C, Schoorlemmer J, Sanes DH (2003) Deafness disrupts chloride transport and inhibitory synaptic transmission. J Neurosci 23: 7516-7524.
Kotak VC, Fujisawa S, Lee FA, Karthikeyan O, Aoki C, Sanes DH (2005) Hearing loss raises excitability in the auditory cortex. J Neurosci 25: 3908-3918.
Kotak VC, Breithaupt AD, Sanes DH (2007) Developmental hearing loss eliminates LTP in the auditory cortex. Proc Natl Acad Sci USA 104: 3550-3555.
Yu X, Sanes DH, Zou J, Aristizabal O, Wadghiri YZ, Turnbull DH (2007) Large-scale reorganization of the tonotopic map in mouse auditory midbrain revealed by MRI. Proc Natl Acad Sci USA 104: 12193-12198.
Xu H, Kotak VC, Sanes DH (2007) Developmental conductive hearing loss disrupts temporal properties in the auditory cortex. J Neurosci 27: 9417-9426.
Yu X, Zhou J, Babb JS, Johnson G, Sanes DH, Turnbull DH (2008) Statistical mapping of sound-evoked activity in the mouse auditory midbrain using Mn-enhanced MRI. NeuroImage 39: 223-230.
Kotak VC, Takesian AE, Sanes DH (2008) Hearing Loss Prevents the Maturation of GABAergic Transmission in the Auditory Cortex. Cerebral Cortex 18: 2098-2108.
Xu H, Kotak VC, Sanes DH (2010) Normal hearing is essential for cortical inhibitory long-term potentiation. J Neurosci 30: 331-341.
Takesian AE, Kotak VC, Sanes DH (2010) Maturation of $GABA_B$ receptor-dependent inhibitory short-term plasticity depends on auditory experience. J Neurosci 30: 2716-2727.
Sarro EC, Sanes DH (2010) Prolonged maturation of auditory perception and learning in gerbils. Dev Neurobiol 70: 636-648.
Rosen MJ, Semple MN, Sanes DH (2010) Exploiting development to evaluate auditory encoding of amplitude modulation. J Neurosci 30: 15509-15520.
Jercog PE, Svirskis G, Kotak VC, Sanes DH, Rinzel J (2010) Asymmetric excitatory synaptic dynamics underlie interaural time difference processing in the auditory system. PLoS Biol 8(6): e1000406.
Sarro EC, Sanes DH (2011) The cost and benefit of juvenile training on adult perceptual skill. J Neurosci 31: 5383–5391.
Sanes DH, Woolley SMN (2011) A behavioral framework to guide research on central auditory development and plasticity. Neuron 72: 912-929.
Takesian AE, Kotak VC, Sanes DH (2012) Age-dependent effect of hearing loss on cortical inhibitory synapse function. J Neurophysiol 107: 937-947.
Rosen MJ, Sarro EC, Kelly JB, Sanes DH (2012) Diminished behavioral and neural sensitivity to sound modulation is associated with moderate developmental hearing loss. PLoS One 7(7):e41514.
Sanes DH, Harris WA, Reh TA (2012) Development of the Nervous System, Third Edition, Academic Press: San Diego.
Overath T, Zhang Y, Sanes DH, Poeppel D (2012) Sensitivity to temporal modulation rate and spectral bandwidth in the human auditory system: fMRI evidence. J Neurophysiol 107: 2042-2056.
Kotak VC, Takesian AE, MacKenzie PC, Sanes DH (2013) Rescue of inhibitory synapse function following developmental hearing loss. PLoS One 8(1): e53438.
Ter-Mikaelian M, Semple MN, Sanes DH (in resubmission) Effects of spectral and temporal disruption on cortical encoding of gerbil vocalizations. J Neurophysiol
Takesian AE, Kotak VC, Sharma N, Sanes DH (in resubmission) Hearing loss differentially disrupts thalamic drive to two cortical interneurons. J Neurophysiol

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Long, Michael Alan	Assistant Professor (Otolaryngology/Physiology and Neuroscience/Center for Neural Science)
eRA COMMONS USER NAME (credential, e.g., agency login) miclong	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Rhodes College	BS/BA	05/97	Biology/Psychology
Brown University	PhD	05/03	Neuroscience
MIT	Postdoctoral	12/09	Neuroscience

B. Positions and Honors

Positions and Employment

2003-2009 Postdoctoral Fellowship, McGovern Institute for Brain Research, MIT, Cambridge, MA
2010- Assistant Professor, NYU School of Medicine, New York, NY

Awards

2002 Dorthea and Sidney A. Fox Fellowship, Brown University
2005 Minisymposium co-chair, SFN Meeting, Washington DC
2012 Esther A & Joseph Klingenstein Fellowship Award in the Neurosciences
2012 Rita Allen Foundation Scholars Award
2012 New York Stem Cell Foundation Neuroscience Investigator Award

Other Experience and Professional Memberships

2000 Neurobiology course, Marine Biological Laboratory, Woods Hole, MA
2003- Member, Society for Neuroscience
2005 Co-organizer, Minisymposium ("Electrical Synaptic Transmission"), Society for Neuroscience
2010- Organizer, Neuroscience Colloquium, New York University
2011- Program Committee, Computational and System Neuroscience (CoSyNe) Conference

C. Selected peer-reviewed publications

Primary research

1. **Long MA**, Jin D and Fee MS (2010). Support for a synaptic chain model of sequence generation. Nature (Research Article), 468: 394-399. PMCID: PMC2998755
2. Arfin SK, **Long MA**, Fee MS, and Sarpeshkar R (2009). Ultra-Low-Power chronic wireless neural stimulation of the songbird brain. J Neurophys (Innovative Methodology); 102(1):598-605. PMCID: PMC2712256
3. **Long MA** and Fee MS (2008). Using temperature to analyze temporal dynamics in the songbird motor pathway. Nature (Research Article), 456, 189-194. PMCID: PMC2723166
4. **Long MA**, Cruikshank SJ, Jutras MJ, Connors BW (2005). Abrupt maturation of a spike-synchronizing mechanism in neocortex. J Neurosci; 25(32):7309-16. PMID: 16093380
5. **Long MA**, Jutras MJ, Connors BW, Burwell RD (2005). Electrical synapses coordinate activity in the suprachiasmatic nucleus. Nat Neurosci, 8:61-66. PMID: 15580271
6. **Long MA**, Landisman CE, Connors BW (2004). Small clusters of electrically coupled neurons generate synchronous rhythms in the thalamic reticular nucleus. J Neurosci, 24(2):341-9. PMID: 14724232
7. Ozden I, Venkataramani S, **Long MA**, Connors BW, Nurmikko AV (2004). Strong coupling of nonlinear electronic and biological oscillators: Reaching the "amplitude death" regime. Phys Rev Lett, 93(15): 158102. PMID: 15524944

8. Landisman CE, **Long MA**, Beierlein M, Deans MR, Paul DL, Connors BW (2002). Electrical synapses in the thalamic reticular neurons J Neurosci, 22(3): 1002-1009. PMID: 11826128
9. **Long MA**, Deans MR, Paul DL, Connors BW (2002). Rhythmicity without synchrony in the electrically uncoupled inferior olive. J Neurosci, 22(24): 10898-905. PMID: 12486184

Reviews

1. **Long MA** and Lee AK (2012). Intracellular recording in behaving animals. Curr Opin Neurobio., 22(1): 34-44. PMCID: PMC3408887
2. Fee MS and **Long MA** (2011). New methods for localizing and manipulating neuronal dynamics in behaving animals. Curr Opin Neurobio., 21(5): 693-700. PMCID: PMC3223334
3. Connors BW and **Long MA** (2004). Electrical synapses in the mammalian brain. Annu Rev Neurosci, 27: 393-418. PMID: 15217338

Book Chapters

1. Fee MS and **Long MA** (2013) Neural mechanisms of vocal sequence generation in the songbird, Birdsong, Speech and Language: Converging mechanisms, Edited by Johan J. Bolhuis and Martin Everaert, MIT Press.

D. Research Support

ACTIVE

R01NS075044 09/01/2011-06/30/2016 4.8 calendar months
NIH/NIDCD $211,786
"Synaptic and circuit mechanisms of learned vocal production"
We proposed to use the intracellular motorized microdrive that I had previously developed in order to measure network activity at the level of single neurons in behaving animals.
Role: PI

09/01/2011-08/31/2013 0 calendar months
Deutsche Forschungsgemeinschaft (DFG) $31,548
"Synaptic and circuit mechanisms of learned vocal production in the zebra finch"
This award was given to Daniela Vallentin by a German foundation.
Role: Advisor

07/01/2012-06/30/2015 0 calendar months
Klingenstein Fellowship Award $50,000
"Establishing a functional role for newly generated neurons in the adult brain"
We proposed to use 2-photon targeted recordings in order to measure the activity of newly born neurons in behaving animals.
Role: PI

09/01/2012-08/31/2017 1.2 calendar months
Rita Allen Foundation $100,000
"Population dynamics within a forebrain motor sequence generator"
We proposed to use calcium imaging and anatomical reconstruction in order to test predictions concerning circuit architecture within a forebrain sequence generator.
Role: PI

01/01/2013-12/31/2017 1.2 calendar months
NYSC Foundation $300,000
"Optical interrogation of a vertebrate motor circuit during natural behavior"
We proposed to use calcium imaging and a variety of perturbations in order to understand the flexibility of a forebrain sequence generator.
Role: PI

5 T32 GM 7308-36 07/01/2012-06/30/2013 0 calendar months
NIH/NIGMS $22,032
"Medical scientist research service award"
This training grant funds Daniel Okobi, an MD/PhD within my laboratory.

3. Budget

Budget Item	Year 1	Year 2
Salaries- postdoctoral research fellows	63,000	126,000
Equipment	16,608	0
Animals	5,000	15,000
Supplies and manufacturing	11,196	11,196
Travel	1,000	1,000
Total	96,804	153,196

4. Budget Narrative

The $250,000 funding will be used to support electrode array fabrication ($16,000), animal experiment costs ($20,000), custom equipment fabrication costs ($6,392), a data acquisition system from National Instruments ($16,608), and hiring two postdocs in engineering and neuroscience for 18 months to support the research ($63,000/year apiece, including fringe costs). A small amount ($1,000/year) will be set aside to support travel and meetings among the five investigators at the three NYU campuses- we will meet quarterly to review progress, and annually to provide a full assessment and progress report as to the status of our brain-machine interface technology.

In the first year, we will hire and train two postdocs: an engineer in the Viventi lab at NYU Poly to build the devices, and a neuroscientist to work between the Froemke, Long, and Sanes labs on implanting these devices in rodents. Existing personnel funded through complementary mechanisms in each of our labs will be mobilized as necessary to conduct these studies. Equipment will be obtained and constructed in year 1, and we will scale up the animal studies using that equipment in year 2.

We anticipate that this research will lead to large-scale extramural funding. There are already significant efforts to improve and enhance neural interface technology sponsored by DARPA through the RE-NET program. The Pesaran lab is already being supported by the DARPA RE-NET program to develop many-degree-of-freedom neuroprosthetic control using penetrating electrodes. This research program will extend that support to cover surface electrodes. The Froemke lab has NIH R01 funding to study neuroplasticity and cognitive enhancement using a small number of wired depth electrodes; this research program will enable this to scale up to many more electrodes for telemetric, wireless stimulation and recording.