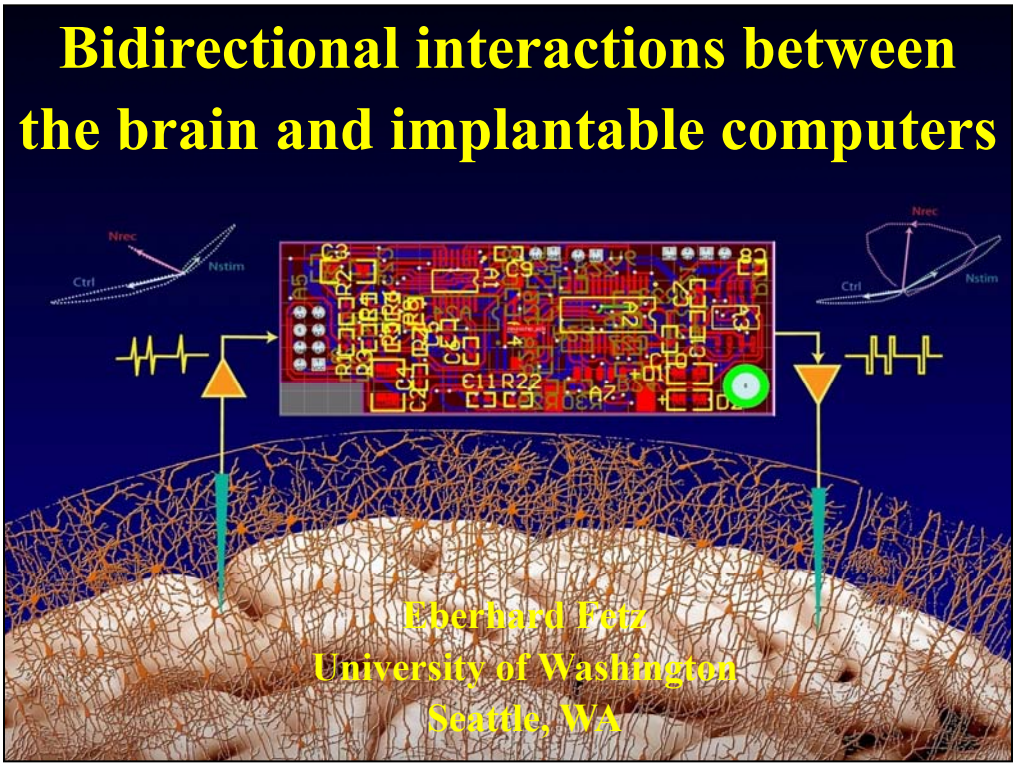
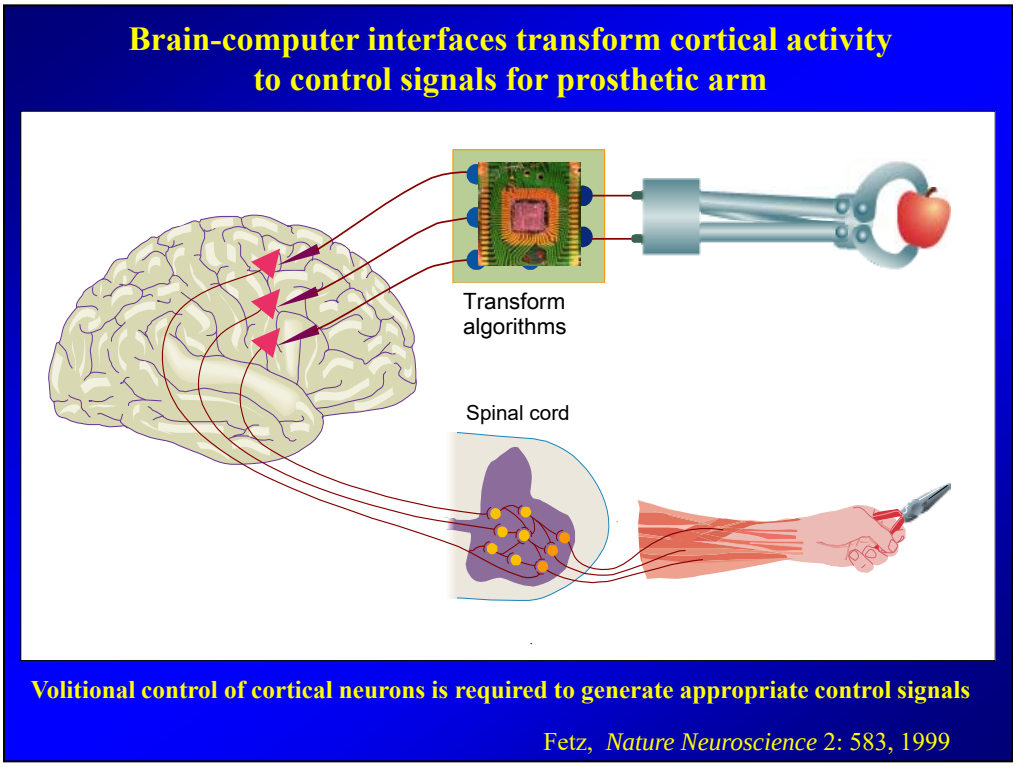
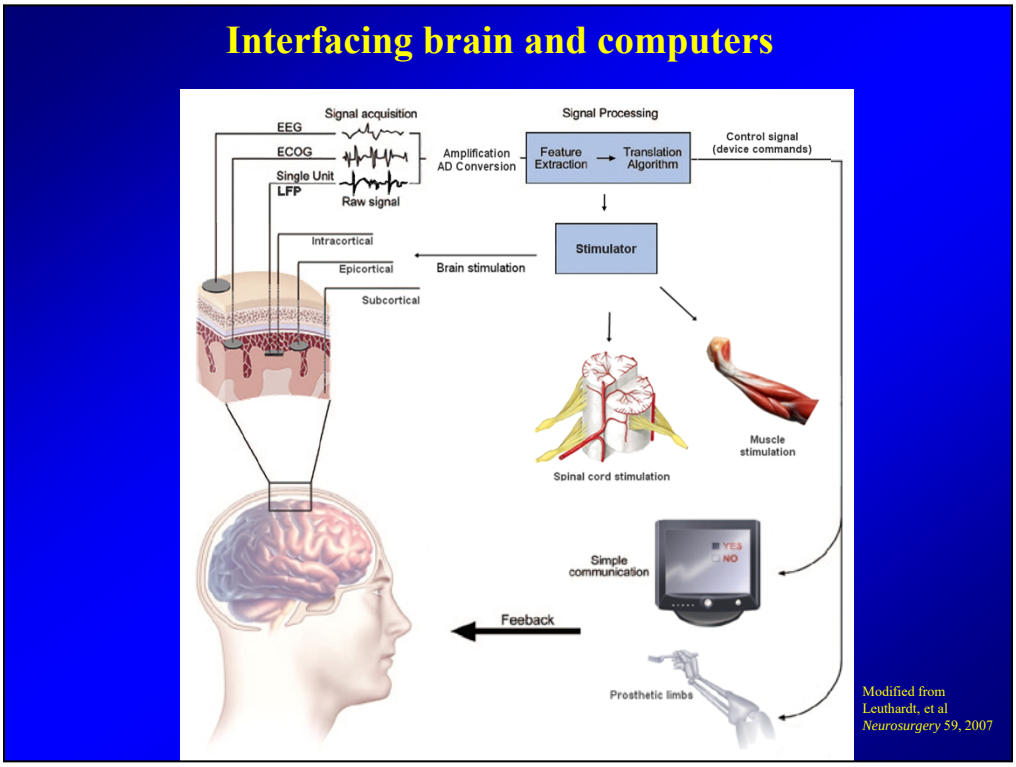


"Bidirectional Interactions between the Brain and Implantable Computers". This title would be unremarkable if the word implantable were removed. Our brains have many bidirectional interactions with computers. They are complementary information processing systems. Computers have gotten ever smaller. Smart phones and watches are about as small as computers can get and still allow us to interact through normal sensory and motor channels (*Show iPhone*). However we can make computers still smaller and make them interact directly with brain through electrodes. This will open many interesting possibilities for functional interactions. The question is what are these possibilities and the consequences?

The basic idea is illustrated here. Bidirectional Brain Computer Interfaces take neural activity from the brain and convert it in real-time to stimuli that can be delivered back to the brain, or spinal cord or muscles. This creates an artificial closed loop that the brain could learn to incorporate into normal behavior, particularly with chronically implantable circuitry that allows long-term adaptation. Closed loop stimulation can also create synaptic plasticity. I'll discuss some first steps toward exploring the consequences of such direct bidirectional connections in non-human primates.



You're all familiar with the traditional BCI. In one scenario neural activity can be tapped and converted to control signals for a prosthetic arm. A great source for such neural activity is motor cortex, which has big fat pyramidal cells that are normally used to generate flexible volitional movements via biological connections to the spinal cord. So it's understandable that subjects can learn to activate these cells in new ways to control external devices.



In the basic BCI paradigm brain signals are converted to control of a cursor or prosthetic arm.

Brain signals obtainable from several levels:

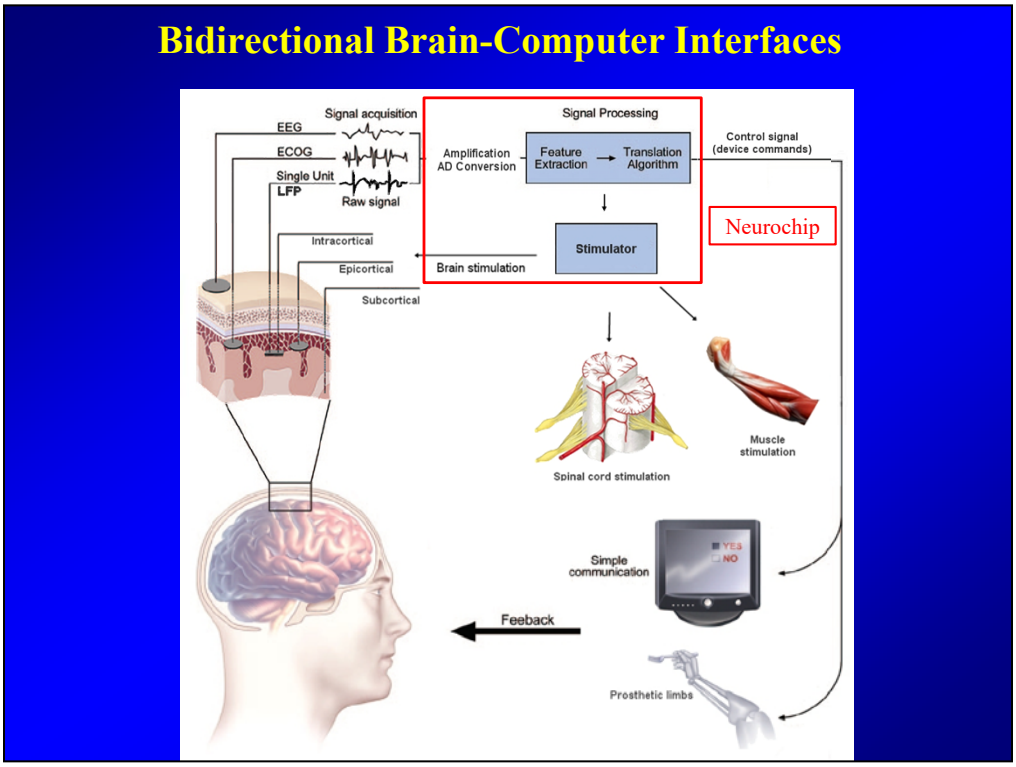
EEG, recorded from the surface of scalp is least invasive and least effective.

ECoG from the surface of the brain is better but also involves an invasive implant.

Single neurons provide the most effective signals but also require the most invasive techniques.

The closed-loop paradigm involves stimulation delivered back to arm, SC or brain, again at various levels.

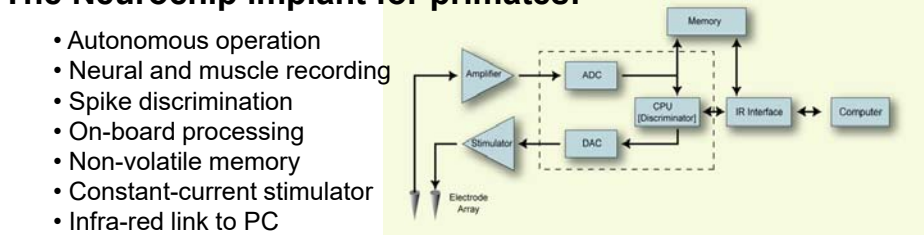
This is what we have incorporated into a small implantable device called the Neurochip.

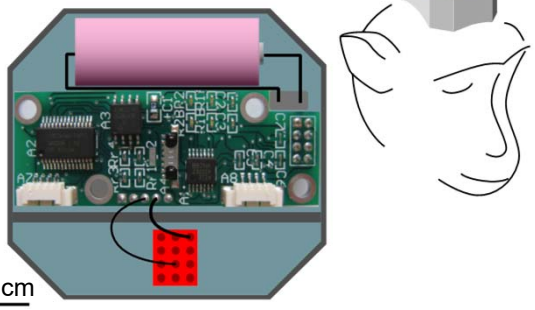


These components of the loop can be incorporated in electronic circuits small enough to be portable and operate autonomously. We have developed such a system in an implantable device called the Neurochip.

The Neurochip implant for primates:

- Autonomous operation
- Neural and muscle recording
- Spike discrimination
- On-board processing
- Non-volatile memory
- Constant-current stimulator
- Infra-red link to PC
- Battery-powered





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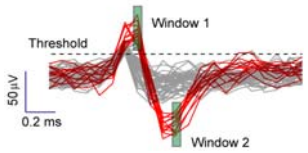


Mavoori, Jackson et al. *J. Neurosci. Meth*. 148: 71, 2005

By implant we are here talking about a head-fixed device.

And the so-called Neurochip is actually a printed circuit board populated with off-the-shelf components. These are connected to electrode arrays and powered by a battery

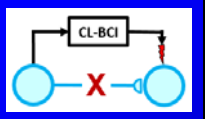
The circuit consists of an amplifier, a computer chip that can be programmed for example to detect action potentials with a time-amplitude window discriminator and convert these to pulses that trigger stimuli.

Data is stored to on-board memory. The whole thing operates autonomously during free behavior and sleep.

Closed-loop BCIs: Three types of applications

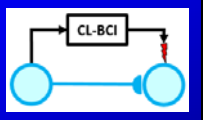
1. **Create artificial connections**

   Can bridge lost biological connections



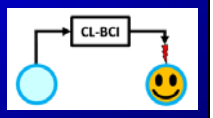
2. **Create synaptic (Hebbian) plasticity with activity-dependent stimulation**

   Can strengthen weak connections



3. **Deliver stimulation at intracranial reward sites**

   Can operantly condition neural activity during free behavior



There are three major types of applications for CL-BCIs that we'll discuss.

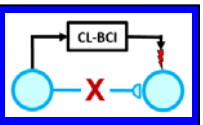
1. create artificial connections. Which the brain can adapt to and incorporate. In particular, an important clinical application is to bridge lost biological connections, as schematized here (right).

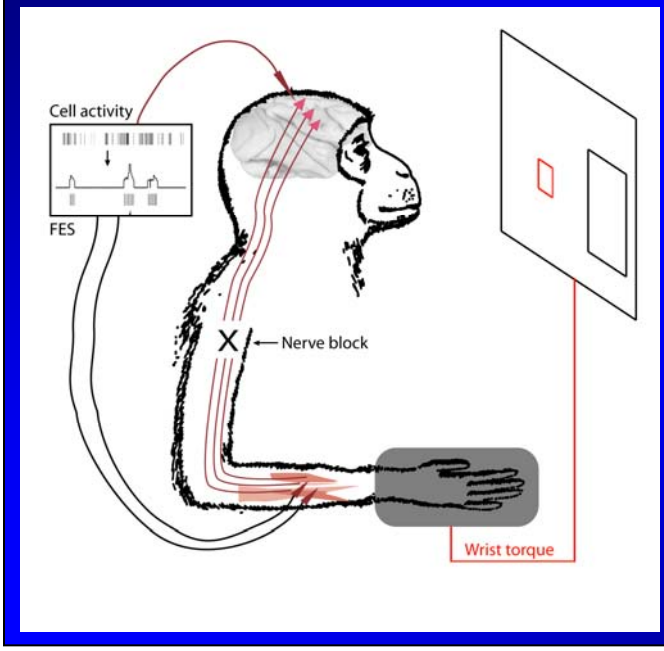
2. create synaptic plasticity. Spike-triggered stimulation creates synchrony that can strengthen synaptic connections. A clinical application is for targeted strengthening of weakened connections as in stroke or spinal cord injury.

3. The third application is to deliver stimulation to intracranial reward sites. This can be used for example to operantly condition neural activity during free behavior.

So I want to show you several examples of each of these.

Functional connections via closed-loop BCI: cortical spikes control FES of muscles





Activity of cortical cell triggers electrical stimulation of paralyzed muscles, allowing monkey to reach the force target

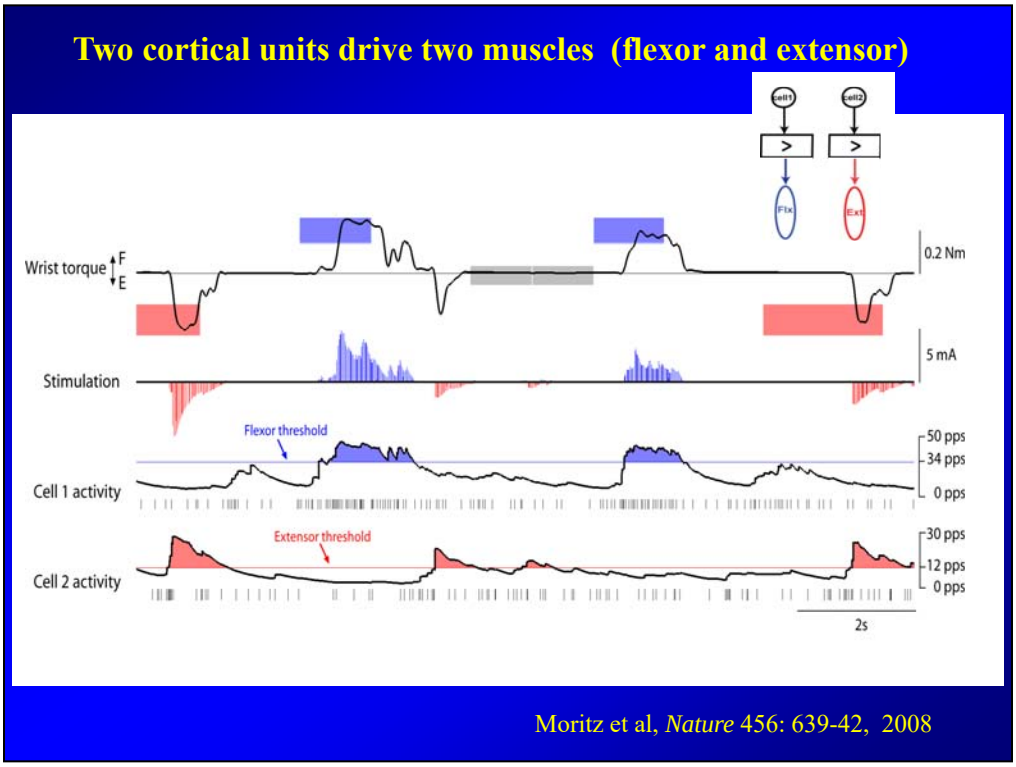
Moritz, Perlmutter Fetz, *Nature* 456: 639-42, 2008

The first example of bridging a lost connection is the demonstration that monkeys can learn to drive cortical cells connected to paralyzed muscles via the CL-BCI.

In this experiment led by Chet Moritz, the intact monkey first used force generated by the hand to move a cursor into a target for applesauce reward.

Then nerve was blocked and the monkey learned to control the cursor with cortical cell activity for about 20 -30 minutes.

Then the cell controlled functional electrical stimulation of muscles, which generated the force that controlled cursor.

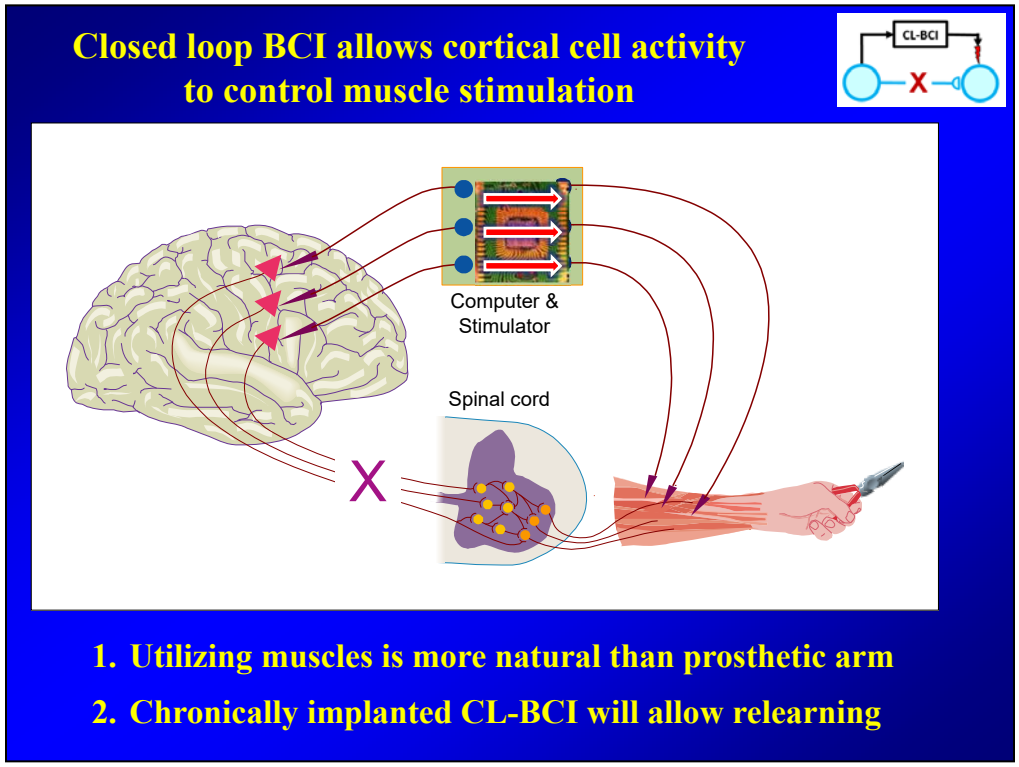


In this example flexion and extension torques were generated by FES of flexor and extensor muscles controlled by 2 different cells.

The torque trace show isometric torque generated to get into alternating flexion and extension targets.

For example stimulation of flexor muscle was proportional to the firing rate of cell 1 above a threshold level.

An important finding in this study was that the cells did not need to be normally related to wrist movement. During the 20 minutes of cell training the monkey learned to volitionally control the activity of essentially any motor cortex cell, and this quickly transferred to controlling the torque output.



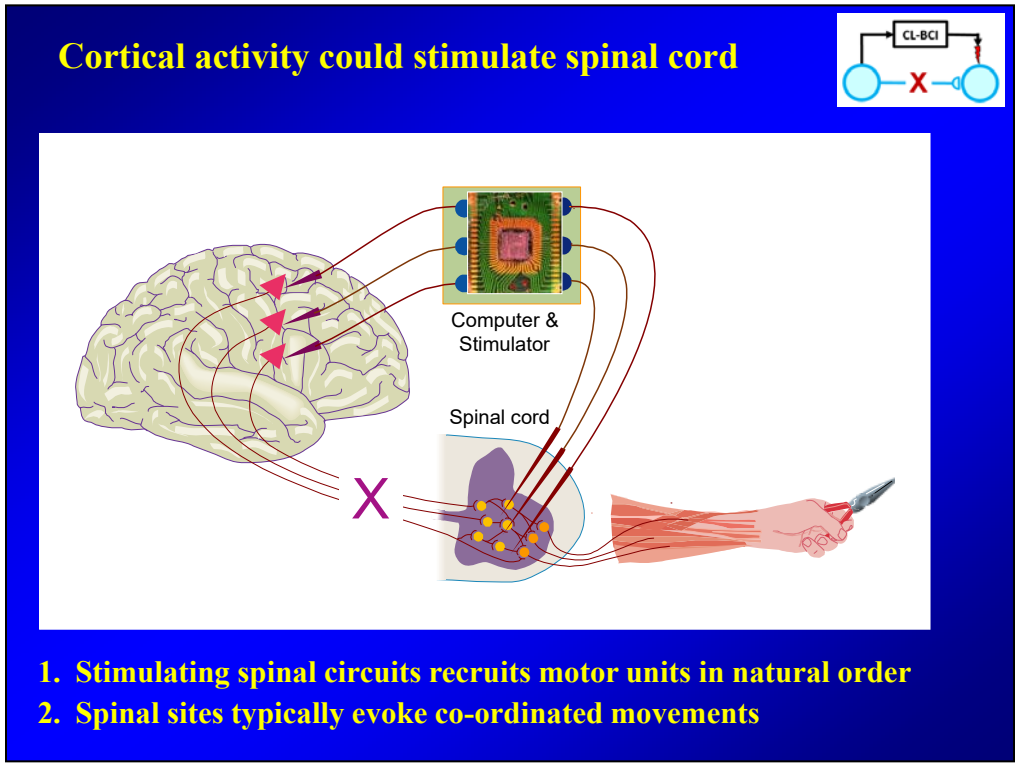
So a closed-loop BCI can connect cortical cells to muscle stimulation.

One can decode patterns of motor cortex cell activity and convert them to muscle stimulation, as done by Lee Miller and colleagues, or connect them directly and allow relearning of appropriate patterns.

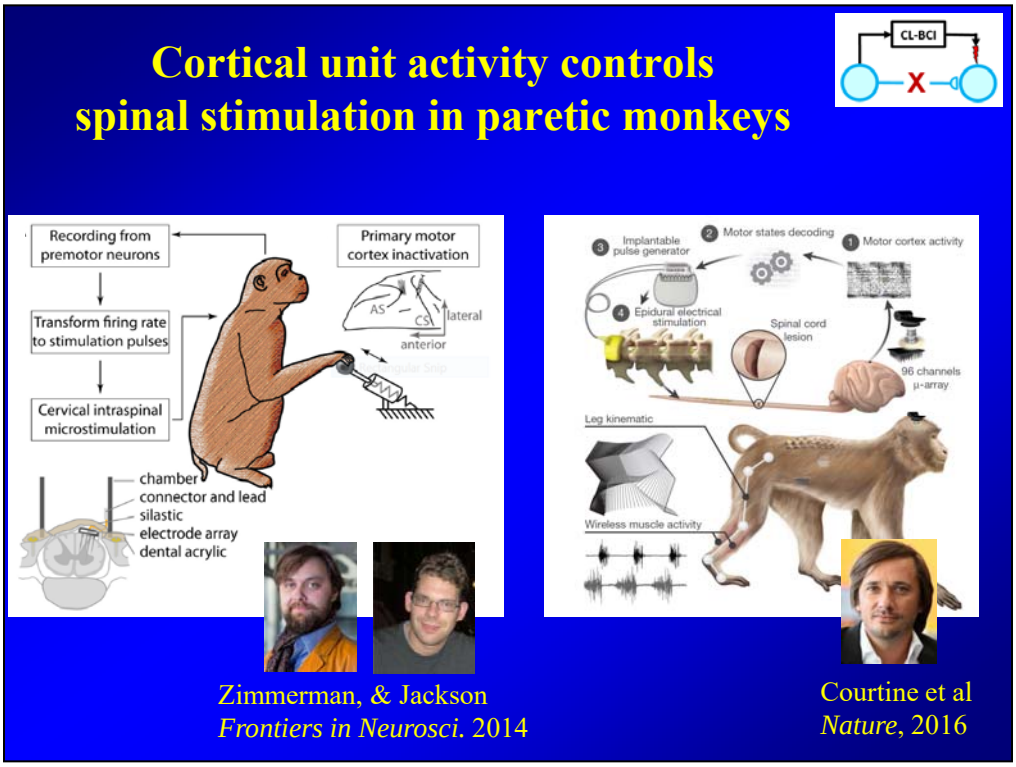
An implanted devices allows long-term learning. This is possible due to the amazing motor adaptation capacity of the brain.

However this strategy of muscle stimulation is limited for finely controlled coordinated movements since electrical stimulation recruits motor units in reverse of natural recruitment order. Stimulation activates large, rapidly fatiguing motor units first.

Secondly, direct FES becomes problematic for synergistic contractions of multiple muscles.

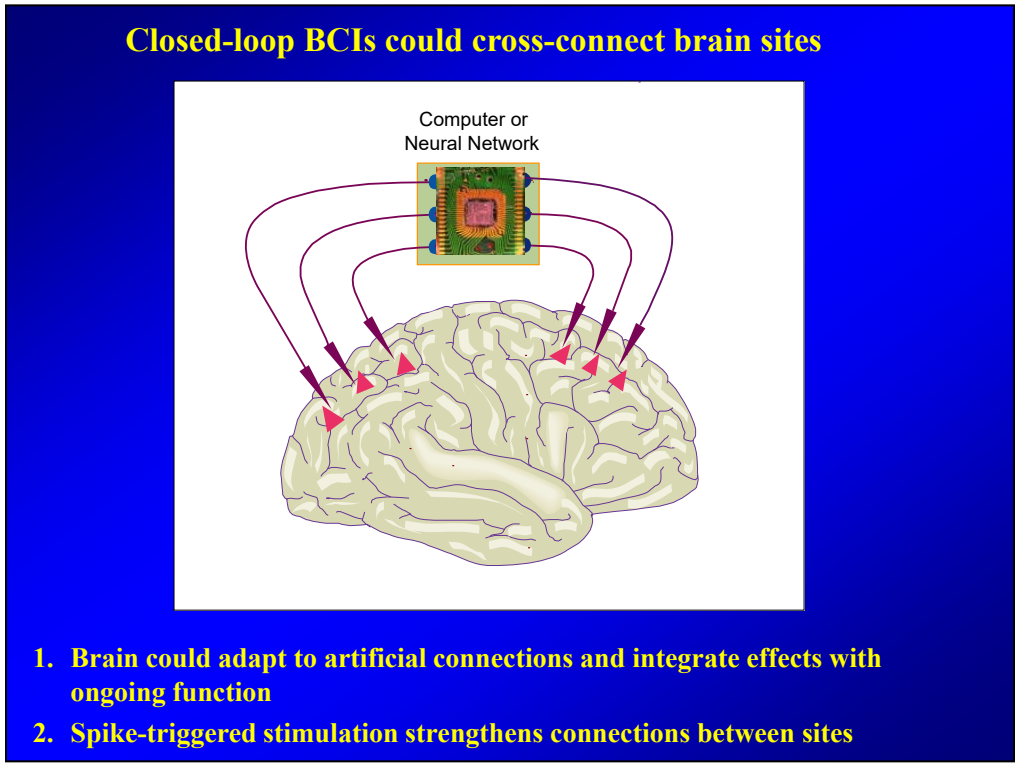


Intraspinal stimulation has several advantages over muscle stimulation.
Motor units are recruited in their natural order, from small to large.
Intraspinal stimulation typically activates combinations of synergistic muscles.
There are now several examples of connecting cortical cells to spinal stimulation for purposes of recovering function



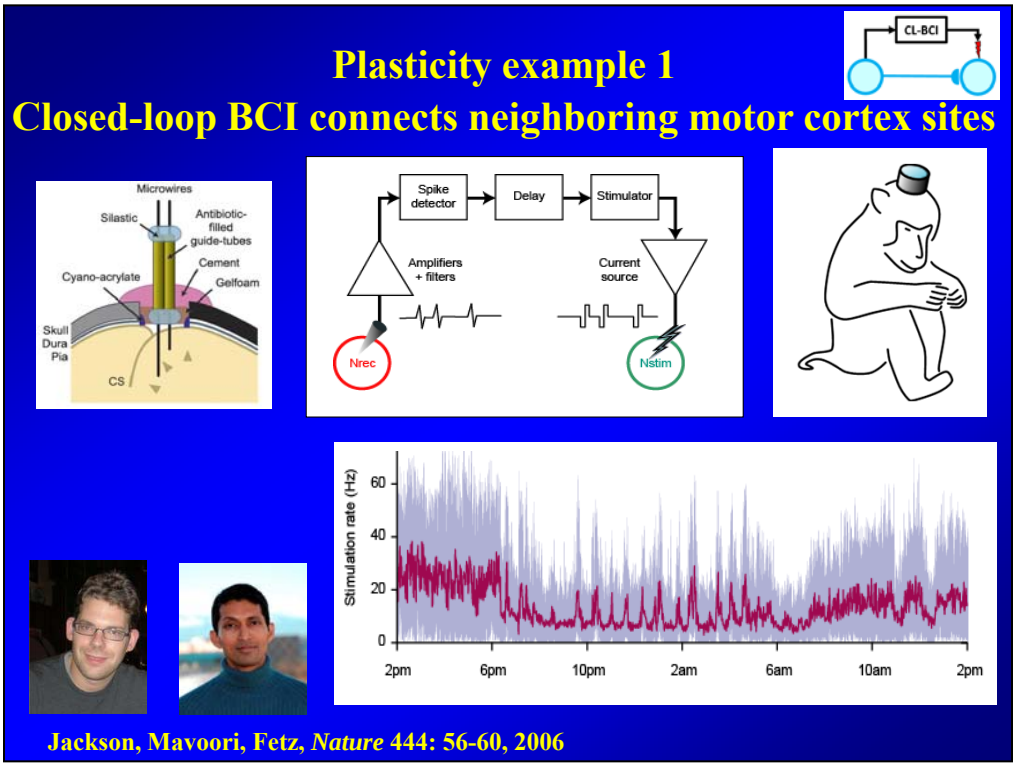
Zimmerman and Jackson trained monkeys to pull handle and then made them paretic by injecting muscimol into primary motor cortex. Neural activity in premotor cortex was then converted to appropriate intraspinal stimulation, which improved task performance.

In a second example Courtine et al used motor cortical unit activity to gate epidural spinal stimulation that activated pattern-generating circuits to promote locomotion.



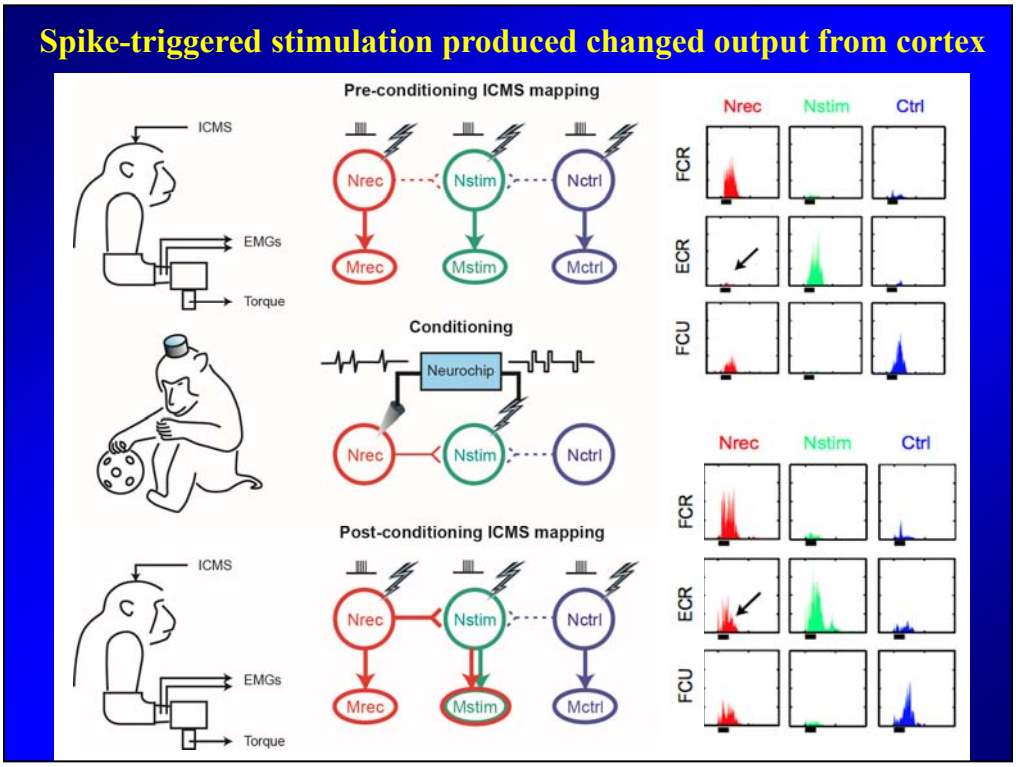
Beyond corticospinal and corticomuscle applications, the closed-loop paradigm could also cross-connect any number of brain sites, enabling many different experiments, depending on the sites.

In these scenarios a potential consequence is that spike-triggered stimulation can produce plasticity in synaptic connections between the sites.



This leads us to the first example of synaptic plasticity produced by a CL-BCI connecting motor cortical sites .

In this work of Andy Jackson and Jaideep Mavoori, spikes were recorded at one site, Nrec, and triggered stimuli delivered a neighboring site called Nstim. The wire electrodes could record the same cells over multiple days and during free behavior. Stimulus intensities were in tens of microamps, low enough to produce evidence of small twitches with bursts of cell activity, but these did not interfere with movement. After day one or two, the output effects from Nrec changed.



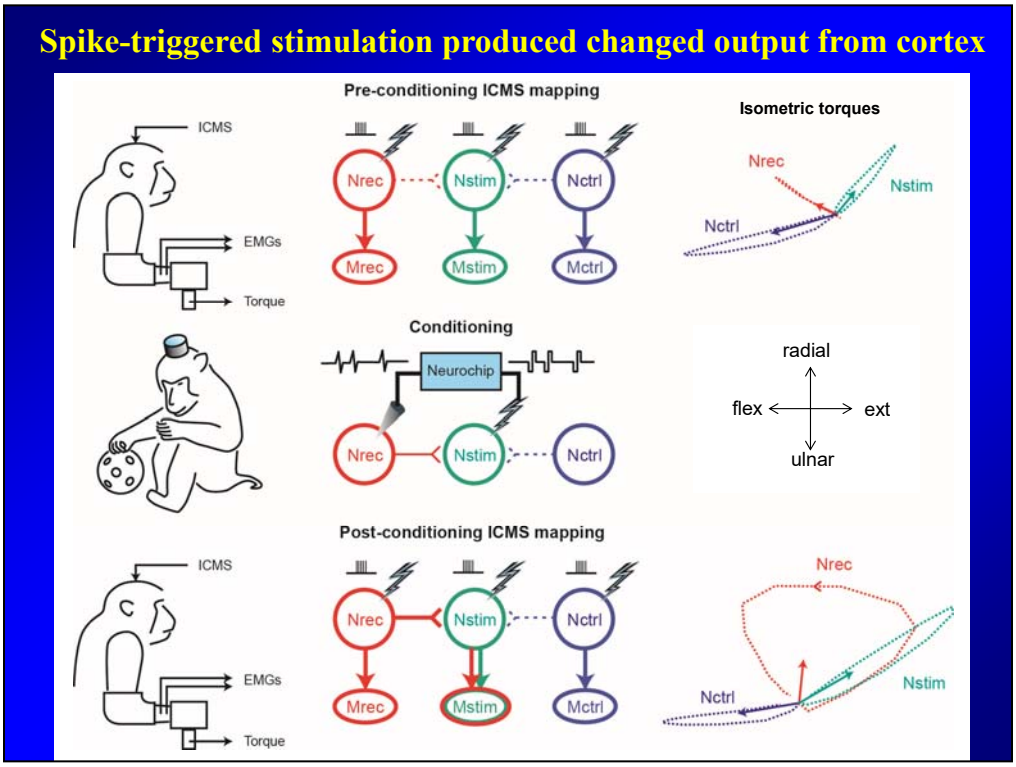
Here's the schematic summary of the experiment.

Before conditioning with spike-triggered stimulation the output effects evoked from trains of intracortical microstimulation were documented with the monkey seated in a primate chair. In this case the stimulation of 3 sites, which included a control site, evoked responses primarily in 3 different muscles.

Then spike-triggered stimulation was delivered continuously for 2 days.

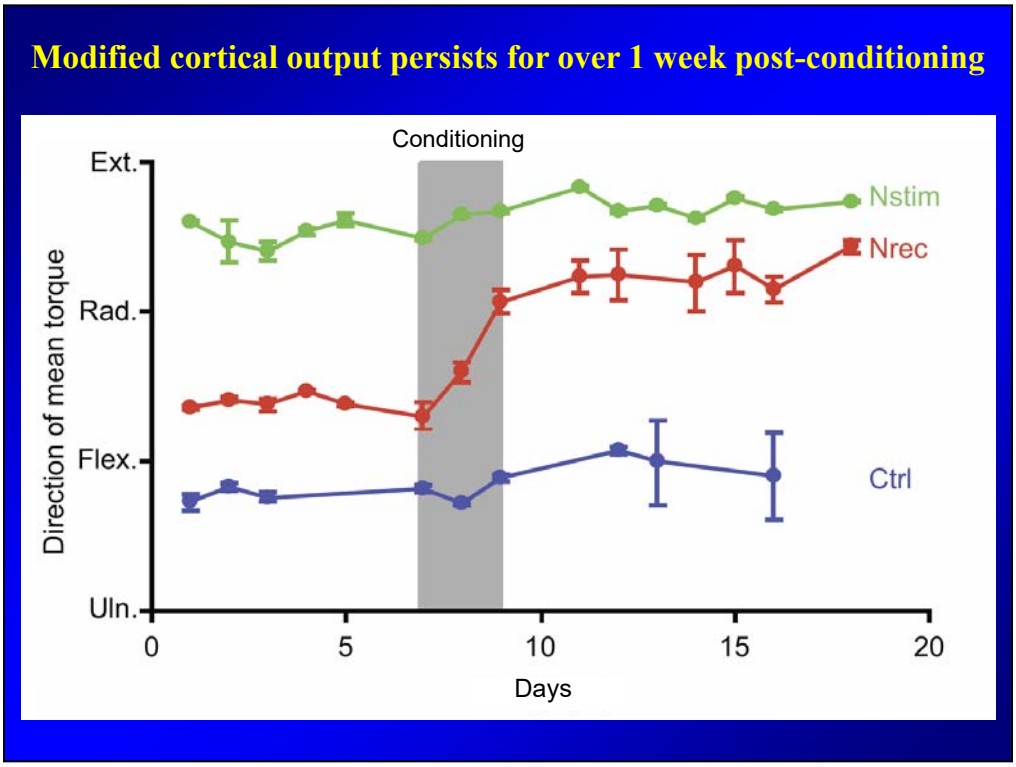
Following this conditioning the outputs from Nrec site had changed: they now co-activated the Nstim muscle, ECR.

A plausible explanation is that the connections from Nrec to Nstim were strengthened due to spike-triggered stimulation.

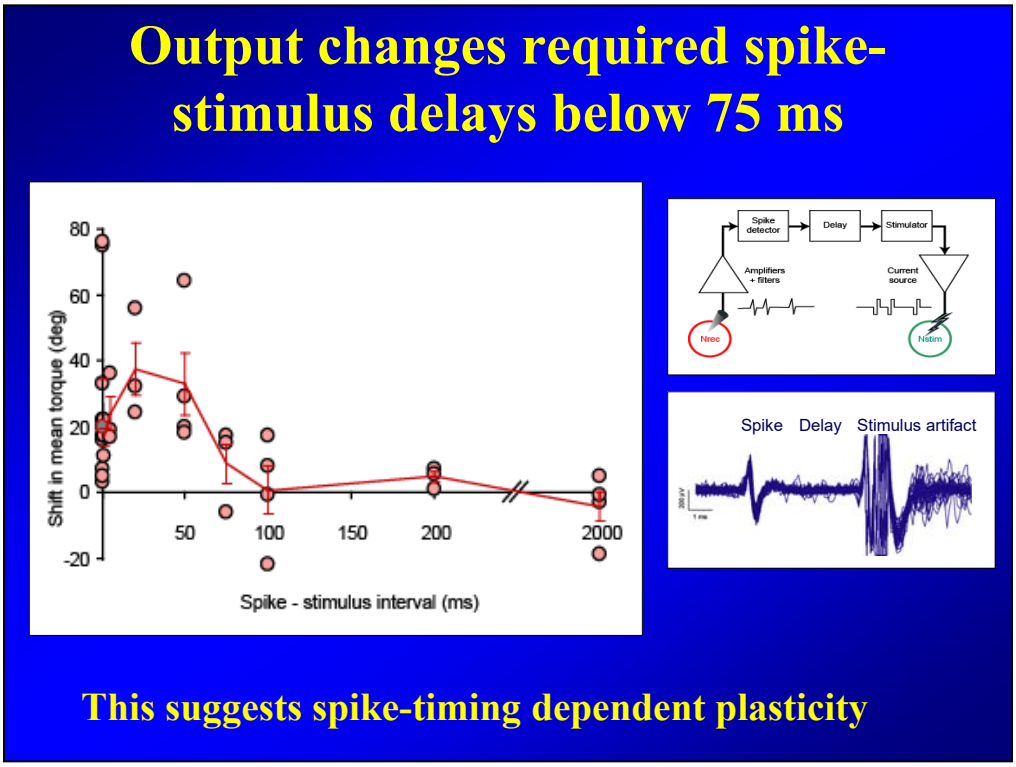


Another way to document outputs was in terms of isometric torques in flexion-extension and radial-ulnar directions evoked by the cortical stimulus trains.

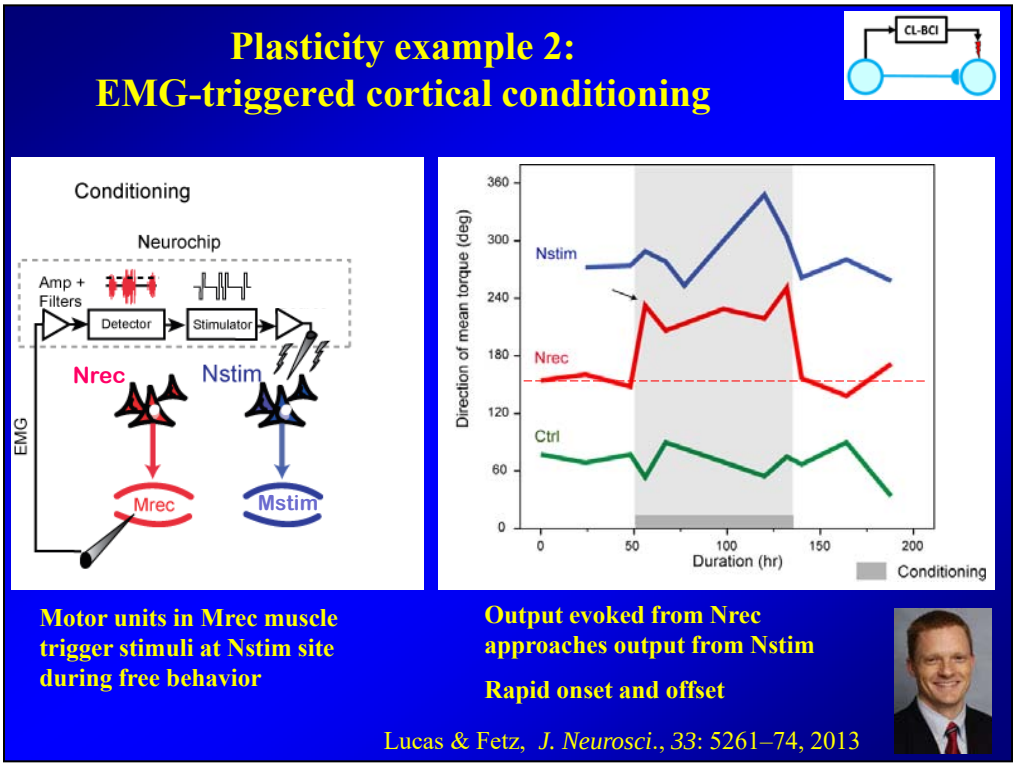
Following the conditioning stimulating the Nrec site now evoked torque trajectories that including Nstim direction. This moved the mean torque (arrow) closer to that from Nstim.



Here's a plot of the daily mean torques evoked by stimulating the three sites, before and after the spike-triggered stimulation conditioning . One interesting observation was that the changes in torque output from Nrec lasted for 10 days after end of conditioning.



A second notable result was that for different experiments using different spike-stimulus delays the changes in output torques were obtained with delays below 75 ms. This is consistent with the time window for spike-timing dependent plasticity.

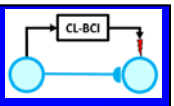


The second plasticity example uses a very similar paradigm, except that cortical stimulation was triggered not by cell activity but muscle activity.

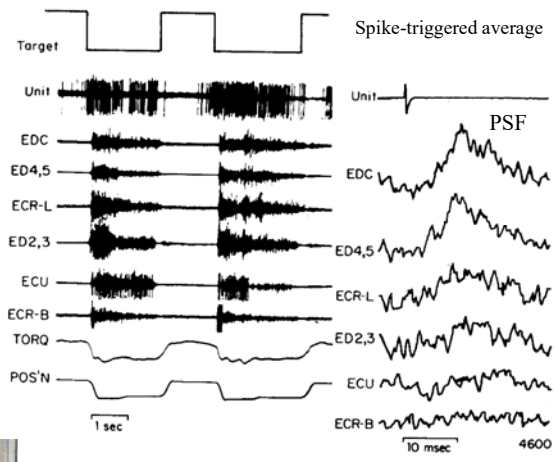
This produced similar changes in outputs evoked from the Nrec site. The significance here is that non-invasively recorded EMG signals can be used as surrogates for cortical signals.

The changes reverted more quickly, perhaps due to less precise timing of stimuli triggered from EMG.

Plasticity example 3: corticospinal connections

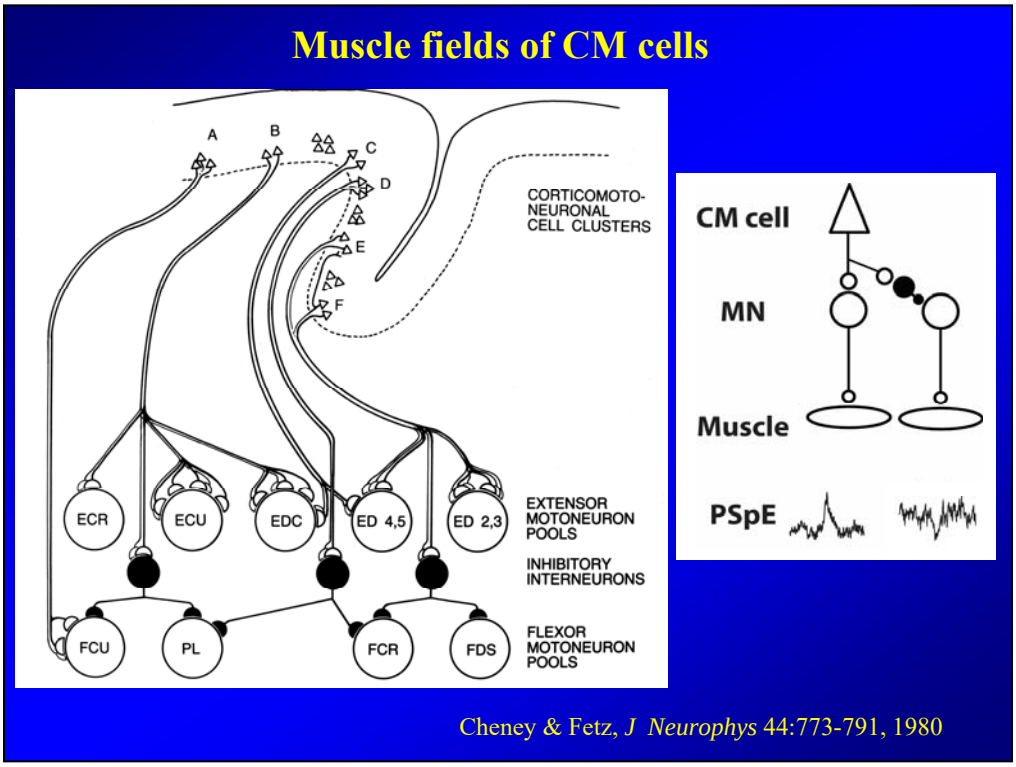


Corticomotoneuronal cells produce post-spike facilitation in STAs of EMG



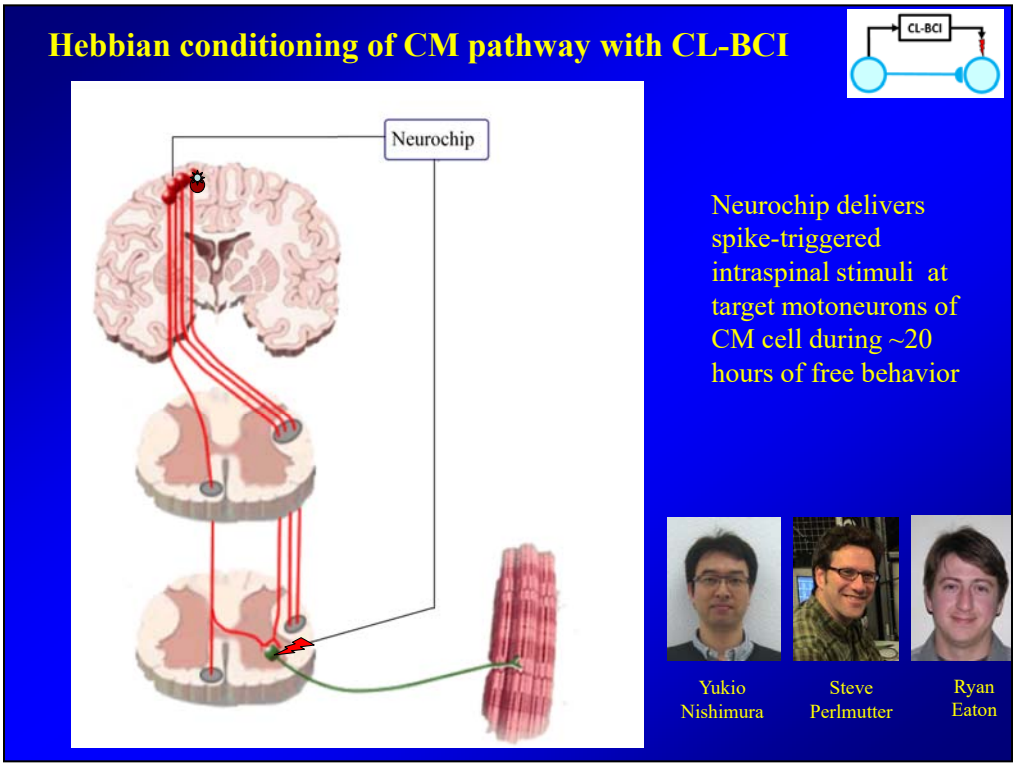
Cheney & Fetz, *J Neurophys* 44: 773-791, 1980

The third example concerns plasticity in corticospinal connections. This was documented directly for corticomotoneuronal cells. These so-called CM cells have output effects on muscles as shown by post-spike effect in spike-triggered averages (STA) of rectified EMG: In this example the STA revealed post-spike facilitation (PSpF) at 10 ms. Such PSF was probably mediated by direct CM connections, which we know exist in the primate.



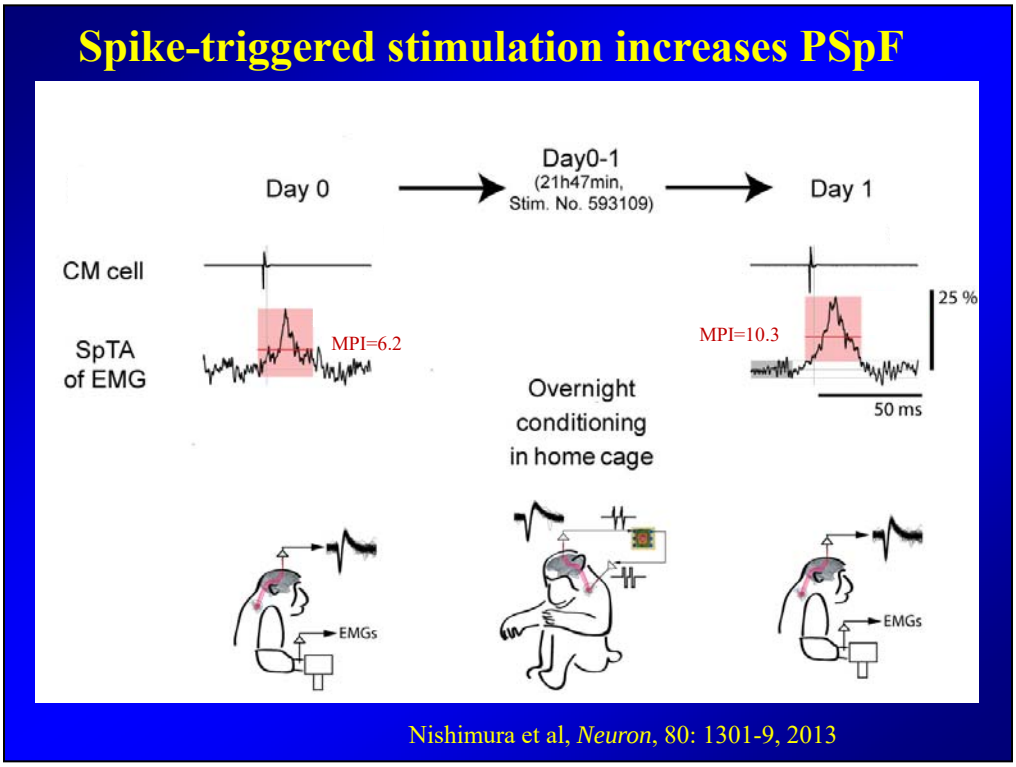
Here's a schematic summary of the correlational linkages found for CM cells shown in terms of distribution of terminals.

Single CM cells typically produced post-spike facilitation in a group of muscles. And a third of these also produced post-spike suppression in antagonists of the facilitated muscles, probably mediated by inhibitory spinal interneurons. The set of all muscles showing post-spike effects are called the cell's muscle field.



Yukio Nishimura et al used indwelling wire electrodes to record CM cells over multiple days. This is the first notable achievement making the experiment possible.

Second, the Neurochip delivered spike-triggered stimuli through intraspinal electrodes at spinal sites that evoked responses in target muscles, so they stimulated the target motoneurons of the CM cell at a fixed delay.

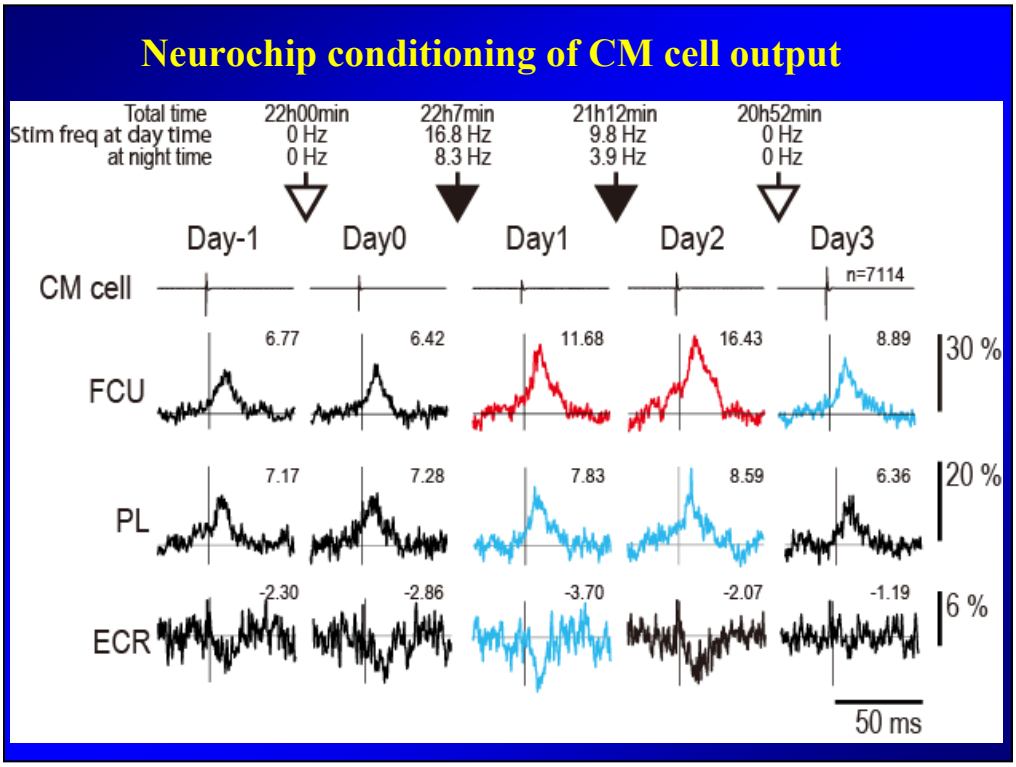


On the first day we identified PSpF magnitude with monkey performing standard target tracking task. Mean percent increase over baseline (MPI) measures the strength of the CM connection.

Spike-triggered stimulation was then delivered for 22 hrs of free behavior.

SpTAs during performance of the same target tracking task, under the same conditions of EMG revealed an increase in PSpF.

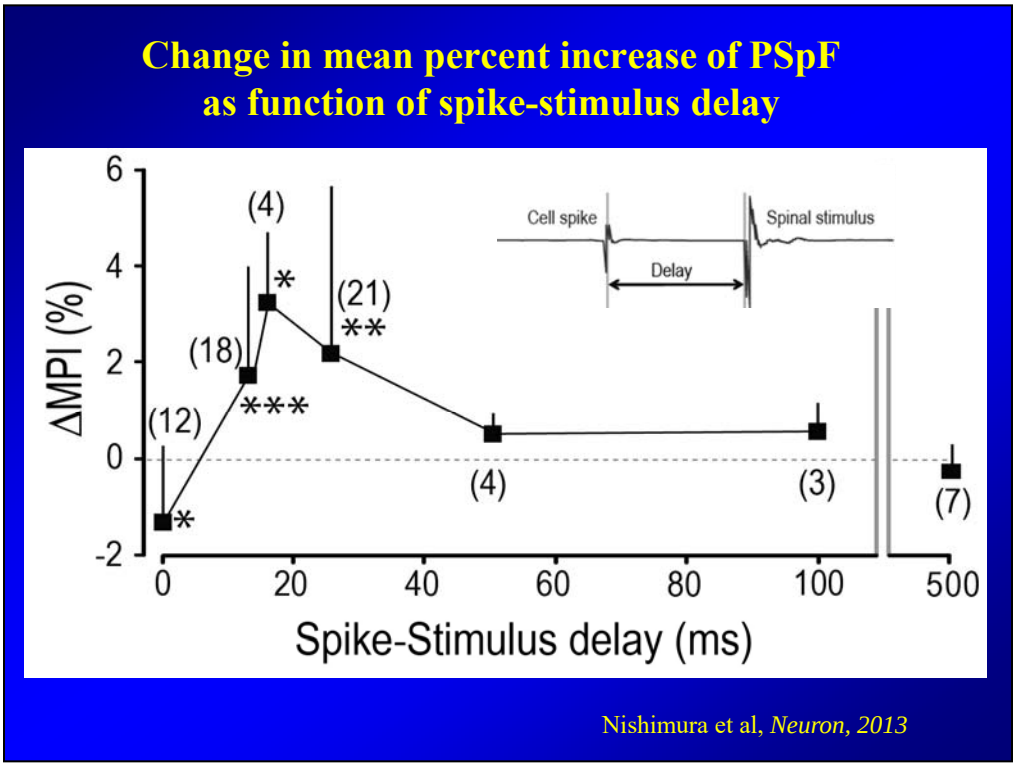
This is significant because it showed for the first time conditioning effects directly for single cell. Moreover, the conditioning was induced with patterns of normal activity during free behavior.



This experiment shows PSpF was stable over 2 days without conditioning. It increased after 22 hr of conditioning. PSpF remained higher 21 h after end of conditioning (FCU).

A second target muscle (PL) also showed an increase in PSpF.

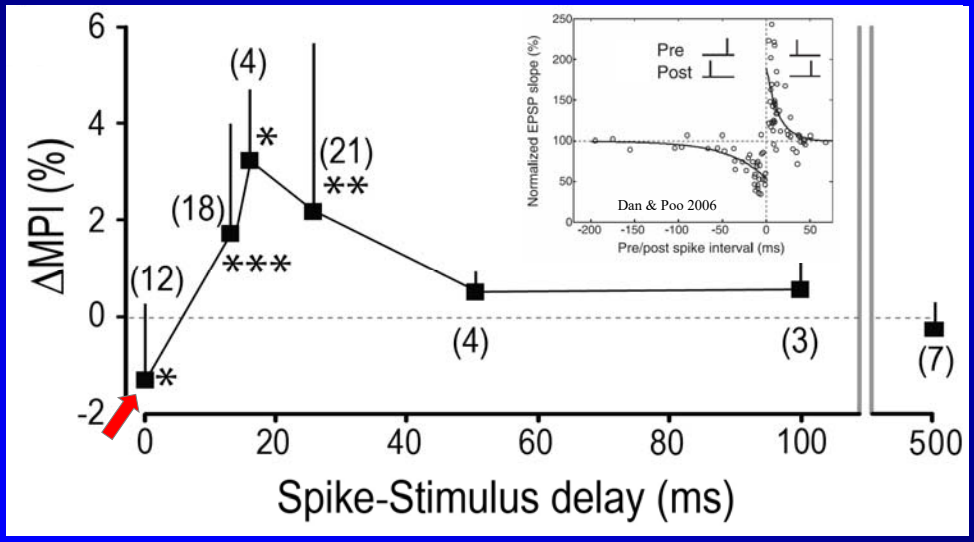
Post-spike suppression in ECR also increased after the first day, but in this case showed more variability, perhaps due to the disynaptic linkage.



Here's a summary of the change in mean percent increase of PSpF as function of spike-stimulus delay used during conditioning for multiple CM cell-muscle pairs.

The MPI increased if motoneurons were activated in the range 20-30 ms. There was no effect at longer delays, which is a good control for stimulation alone.

At zero delay spinal neurons are stimulated before descending input, decreasing synaptic strength



Nishimura et al, *Neuron, 2013*

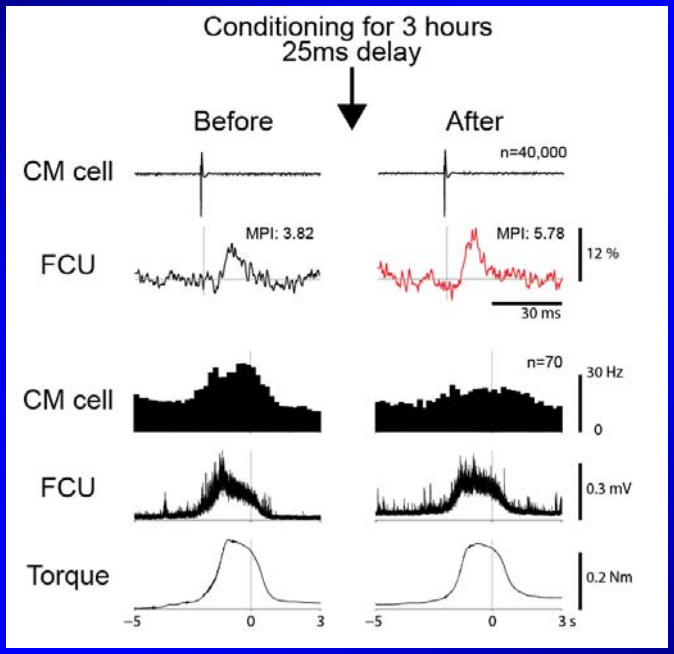
Note the interesting effect at zero delay: this produced a significant decrease in PSpF.

In this case target the motoneurons were activated electrically prior to arrival of the descending corticospinal impulses.

Consistent with the bidirectional Spike Timing Dependent Plasticity rule that synaptic strength is reduced when postsynaptic activation consistently occurs before the presynaptic input.

We would like to emphasize that this conditioning was done *in vivo* in non-human primates, with a normal neural mileau and activity.

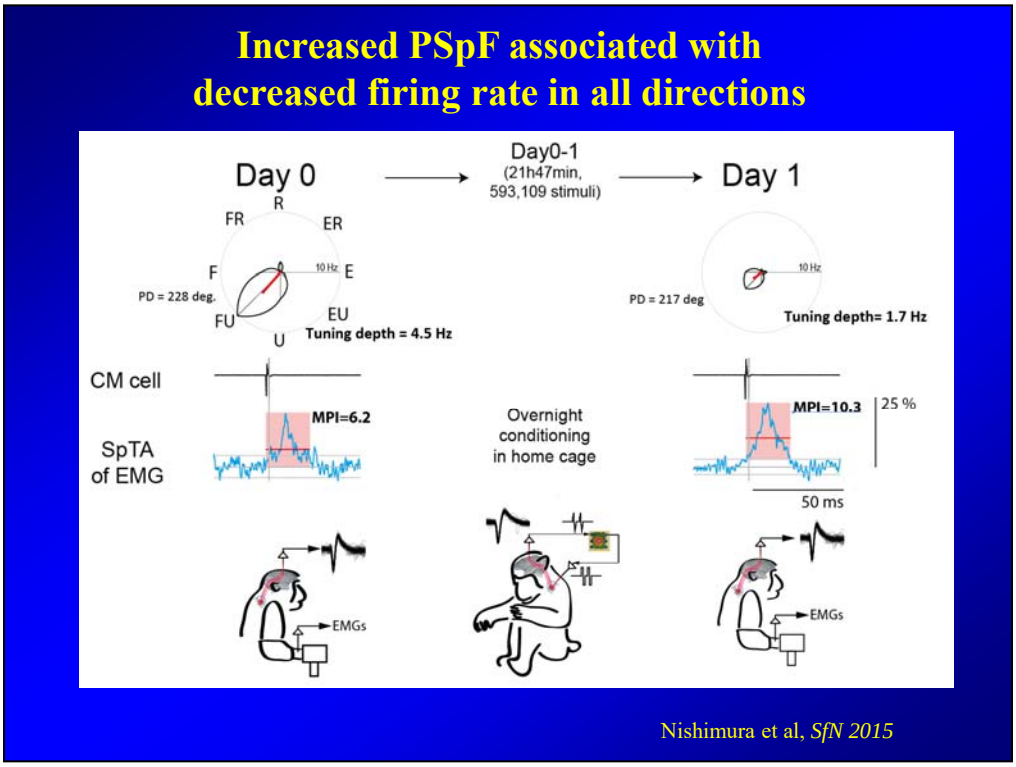
Increased PSpF is associated with decreased firing rate



Nishimura et al, *SfN 2015*

An unexpected finding was a change in firing rate after conditioning. Here the increased PSpF was associated with a decrease in firing rate.

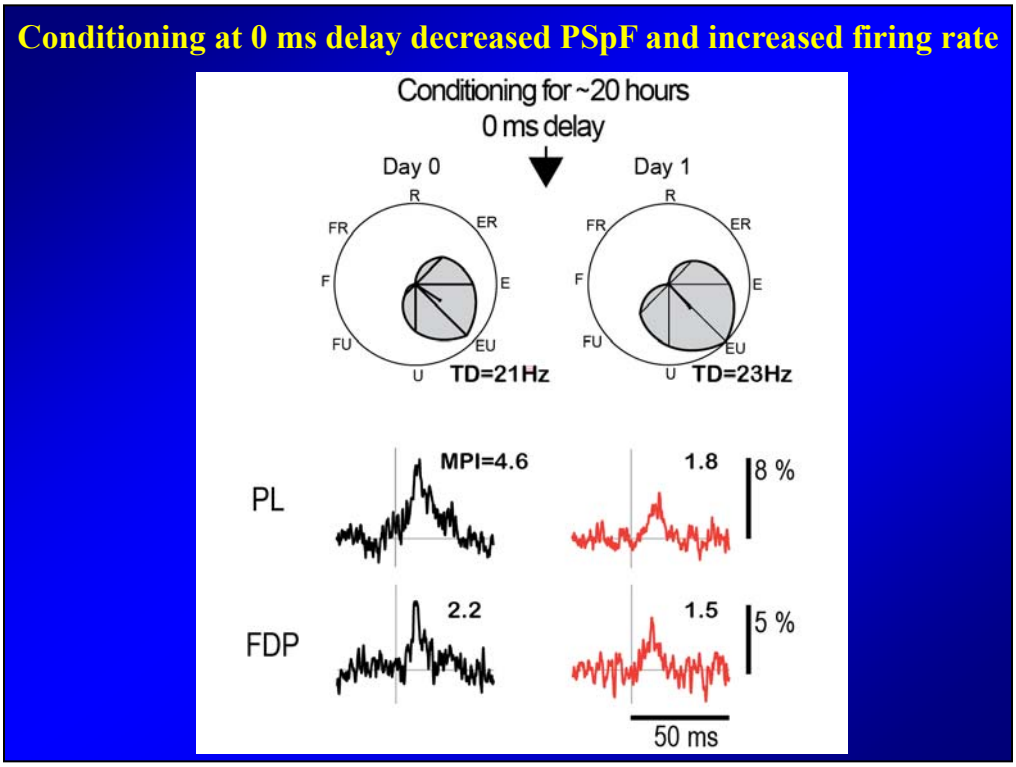
In this case 3 hours of conditioning produced larger post-spike effect, and the CM cell fired less for the same target force and EMG.



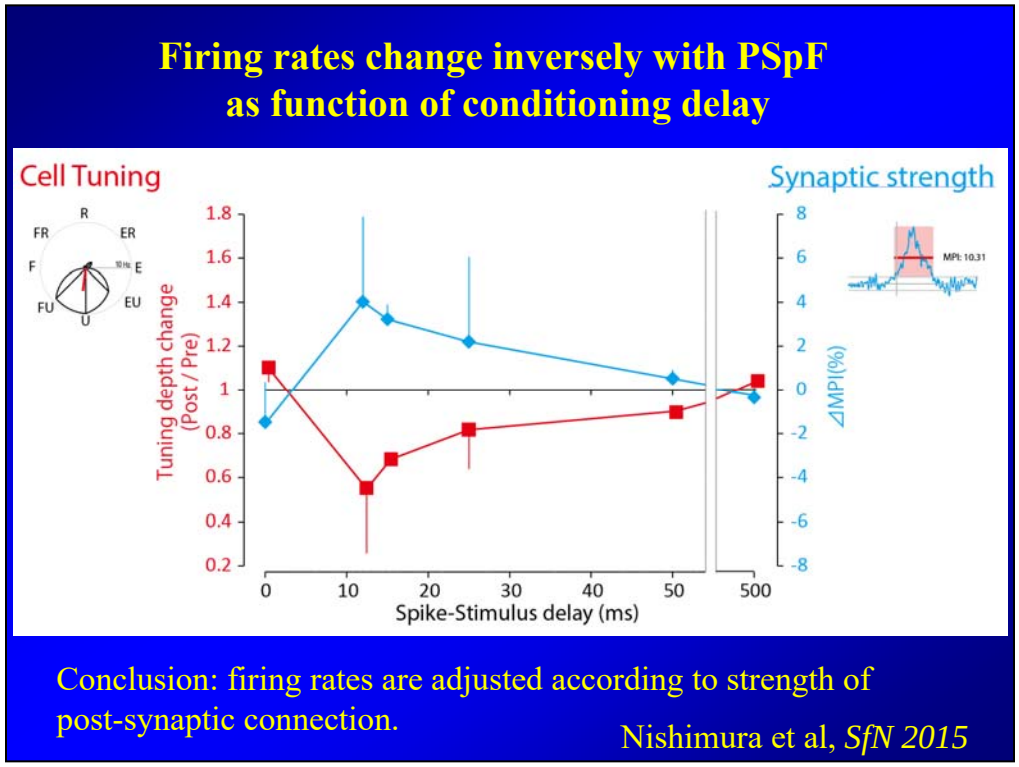
Another case of increased PSpF is shown with the associated tuning curve: the rate decreased in all directions.

This is surprising, since a change in PSpF represents a tiny effect. How does this produce a compensatory decrease in the firing rate?

One could imagine that this is simply due to boosting of cell output effects by spinal stimulation and so the monkey learned that less activity produces same effect. However, it's not that simple.



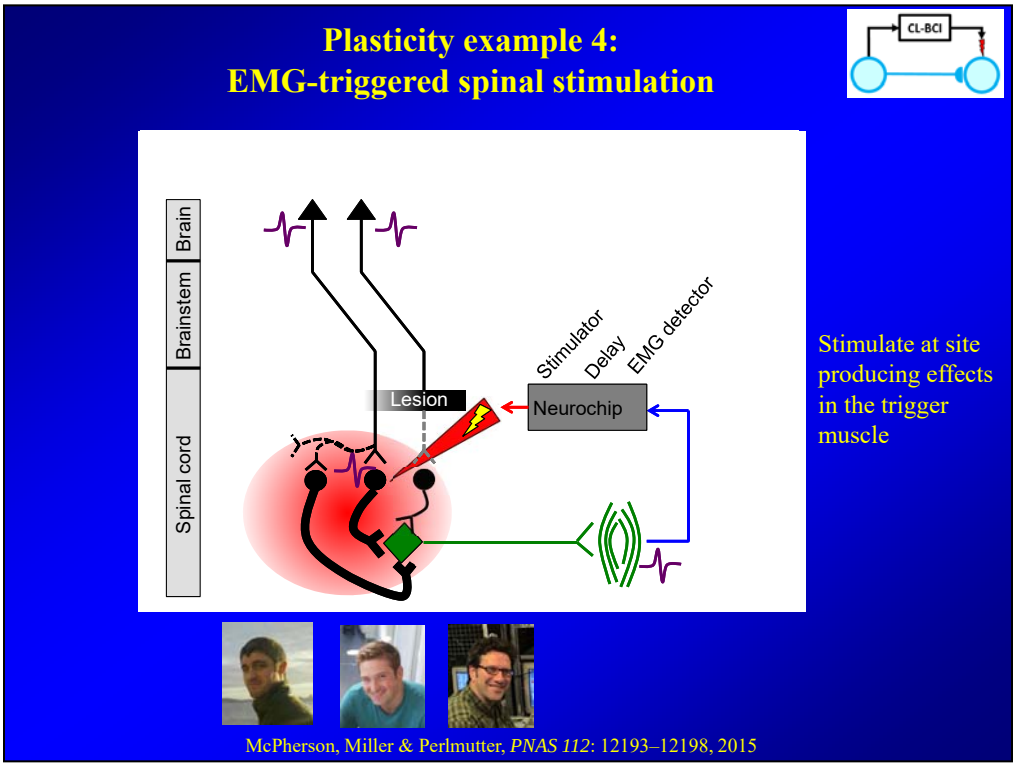
Here is a case of conditioning with zero delay which produced a decrease in PSpF. This was associated with a slight increase in activity as shown in the tuning curve.



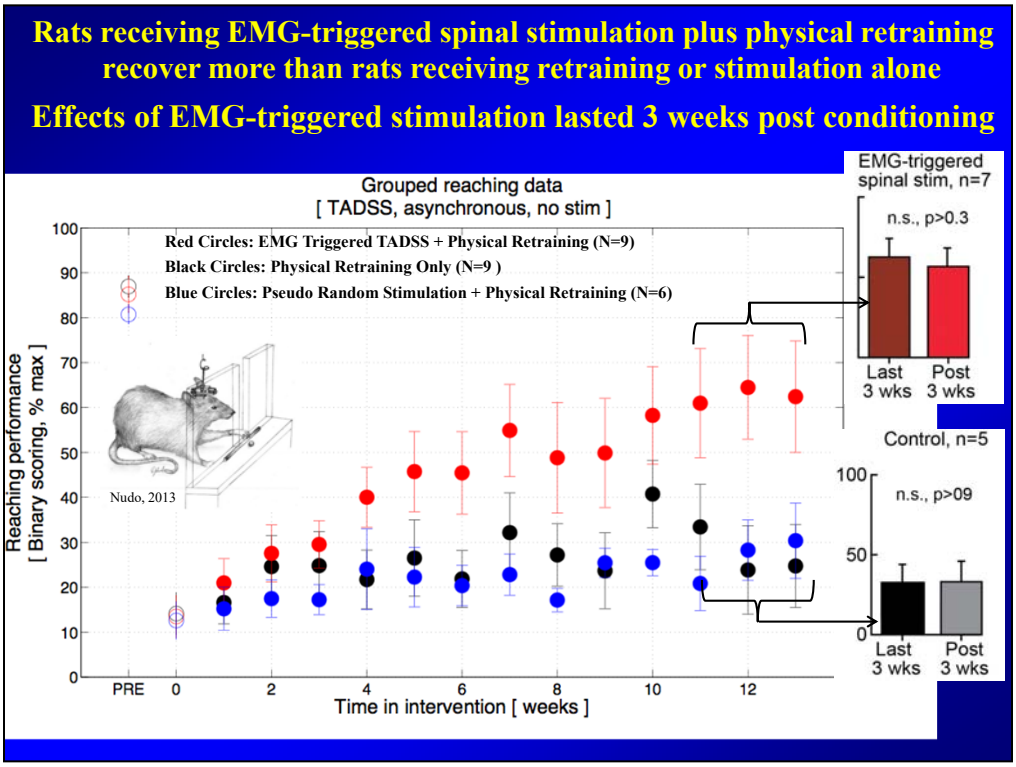
Plotting change in tuning depth against change in PSpF shows inverse relation for the range of spike-stimulus delays.

This indicates a unexpected and surprising degree of calibration of firing rate with post-spike effect.

These results are surprising because PSpF is tiny effect relative to what it takes to activate motoneurons. This looks like highly consistent inverse tuning. The explanation is still largely a mystery. (If anyone has any insights about mechanism, please see me after the talk.)



Moving on, our fourth example of plasticity induced by closed-loop conditioning involves EMG triggered intraspinal stimulation in rats. The rats were rendered paretic by contusion spinal cord injury. In this study by Steve Perlmutter, Jacob McPherson and Ryan Miller, the idea is that synchronized stimulation and descending commands could strengthen corticospinal connections.Delivering stimuli at sites of motoneuronal activity is called "Targeted Activity-Dependent Spinal Stimulation" (TADSS)

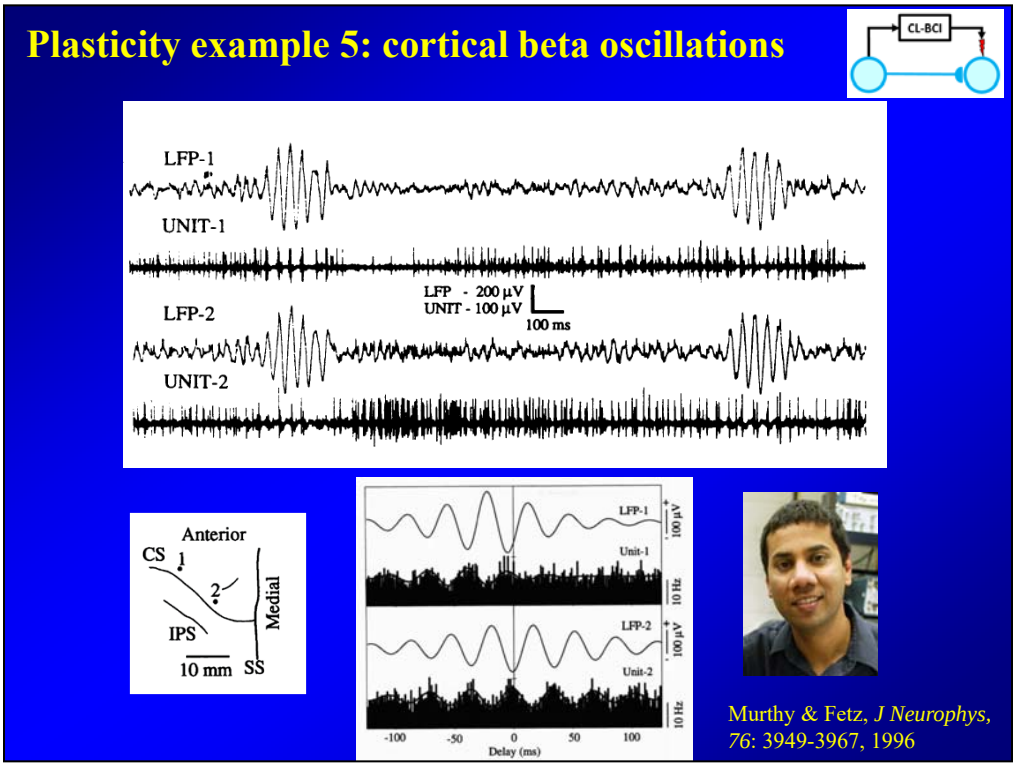


These plots show grouped data for reaching performance through a slot as a function of days after spinal cord injury. The group receiving EMG-triggered TADSS (red) showed greater improvement in reaching than either those receiving training alone (black) or matched random spinal stimulation (blue). So activity-dependent stimulation was critical for improvement.

Also interesting is the observation that the benefits outlasted conditioning sessions.

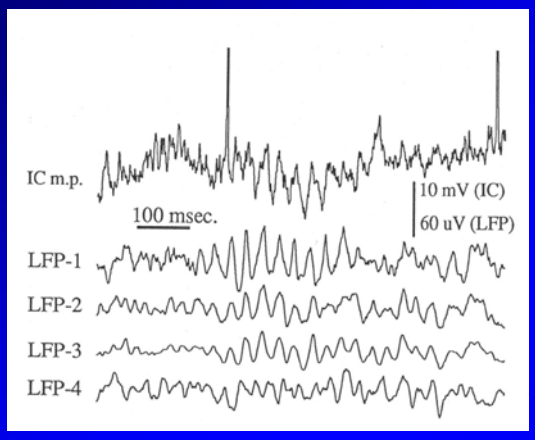
The two red bars at right compare the average reaching performance of the TADSS group during the last 3 weeks of conditioning, and their performance on the subsequent 3 weeks without stimulation. The absence of a statistically significant difference indicates that the conditioned changes lasted 3 weeks beyond the end of TADSS treatment.

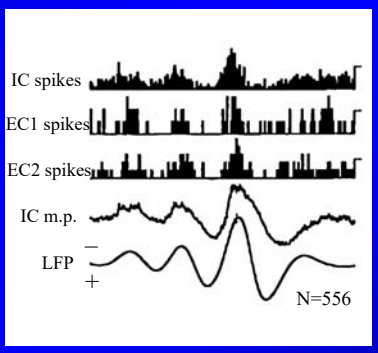
(OK, how are we doing? I realize I'm hitting you with a heavy dose of data, but hopefully you can hang in there. I'm encouraged by recalling previous SfN talks that were uncompromising in their detail. And since we've all had an extra hour of sleep with your permission I'm going to plow on to our last example of plasticity, using cortical oscillations.)



The fifth example of plasticity produced by activity dependent stimulation involves synchronization with cortical oscillations. The properties of these oscillations were documented in monkey motor cortex by Venky Murthy. Episodes of oscillations in local field potentials (LFPs) occur simultaneously over wide areas. The activity of many neurons become entrained, as shown in cycle-triggered average of firing rate. Cortical units tend to spike during the negative phase.

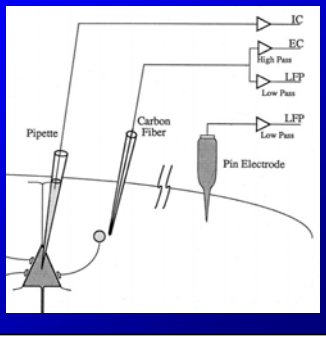
Cortical LFP oscillations correlate with intracellular depolarizations





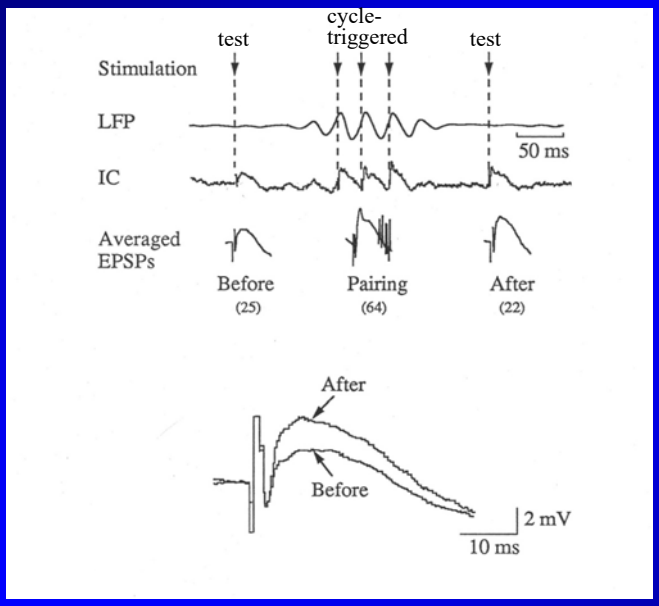
Daofen Chen

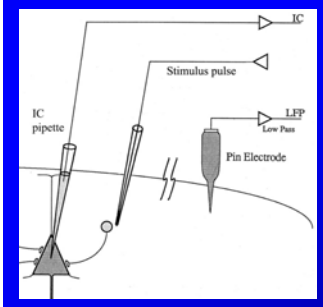
Michikazu Matsumura



Even when cortical cells are not firing with oscillation their membrane potentials can show oscillatory depolarization. This was found by Daofen Chen, who recorded in vivo intracellular activity in monkey motor cortex neurons, using intracellular recording techniques pioneered by the late Mitch Matsumura.

Stimulation during oscillations modifies subsequent EPSPS





Chen, Ph.D. thesis, 1993

Daofen found that phase-dependent stimulation during oscillatory episodes changes subsequent connectivity. Here's a schematic of the experiment. EPSP's were evoked in a cell by stimuli delivered to a nearby site. Test stimuli occurred at a low frequency until an oscillatory episode occurred; then the stimuli were delivered at a particular phase of the oscillations. When conditioning stimuli were delivered during the depolarizing phase the size of the EPSPs evoked **after** the episode were larger than those evoked by the last test pulse prior to the conditioning. This suggests a transient change in excitability subsequent to phase-triggered stimulation. Unfortunately this is a difficult experiment and only a few observations of this effect could be obtained

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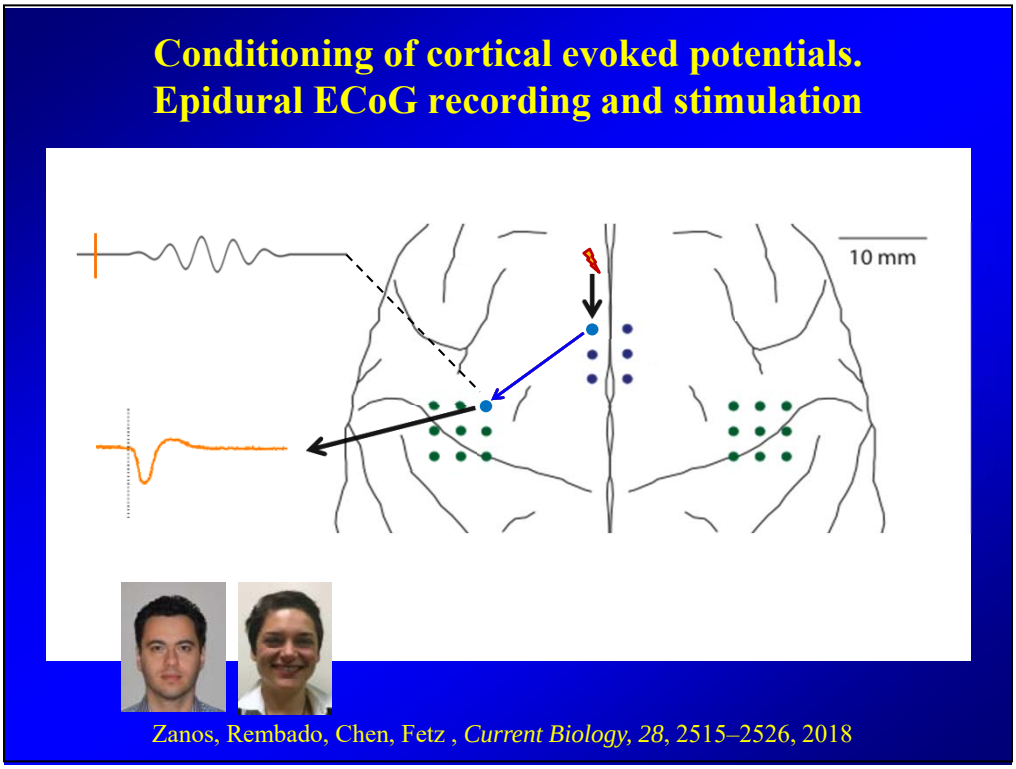
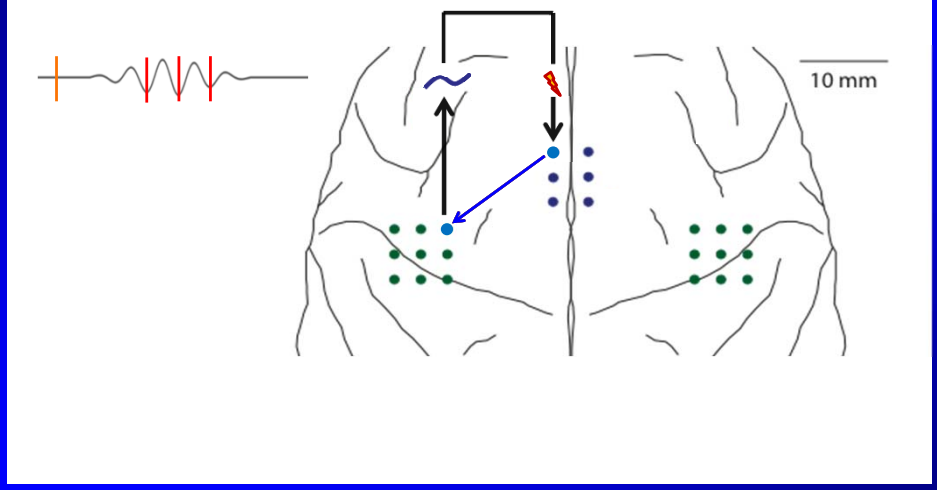


The phenomenon has been documented more systematically by Stavros Zanos and Irene Rembado with evoked cortical surface potentials recorded in the electrocorticogram (ECoG).

Here, stimulating a site in SMA evoked a cortical surface potential in M1.

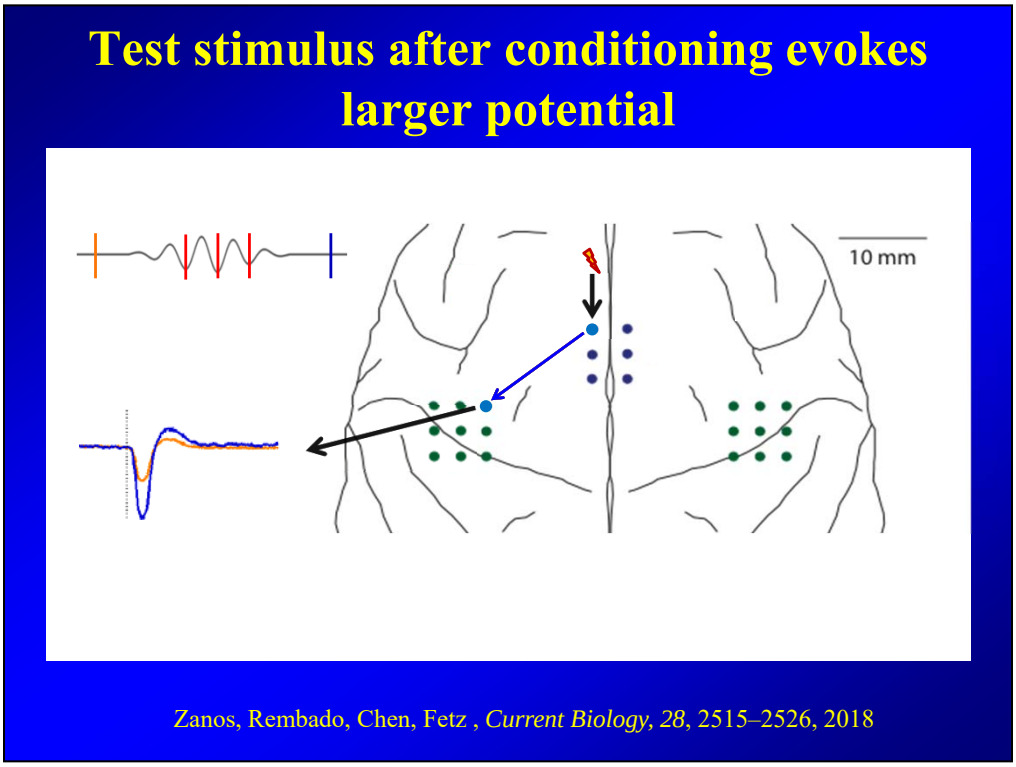
The orange trace shows the average of a number of such potentials, evoked by the last stimuli preceding spontaneous oscillatory episodes in M1.

Conditioning: cycle-triggered stimulation during oscillatory episodes

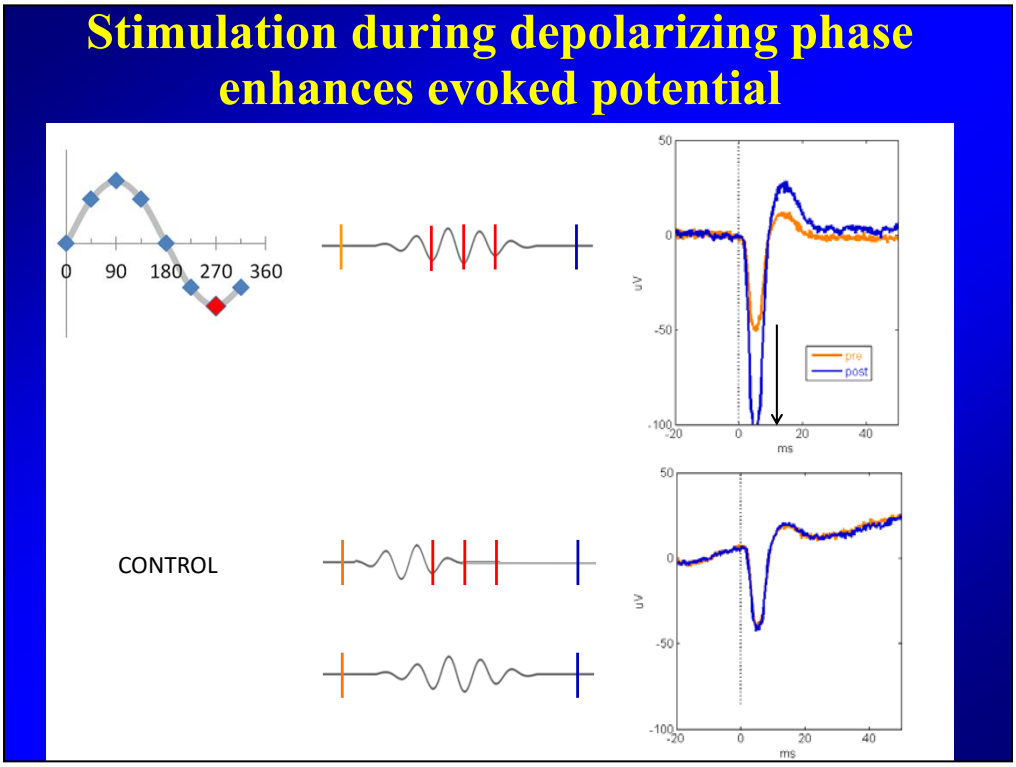


Zanos, Rembado, Chen, Fetz , *Current Biology, 28*, 2515–2526, 2018

During each oscillatory episode, cycle-triggered stimuli were delivered in SMA during the negative phases of the ECoG oscillations in M1.



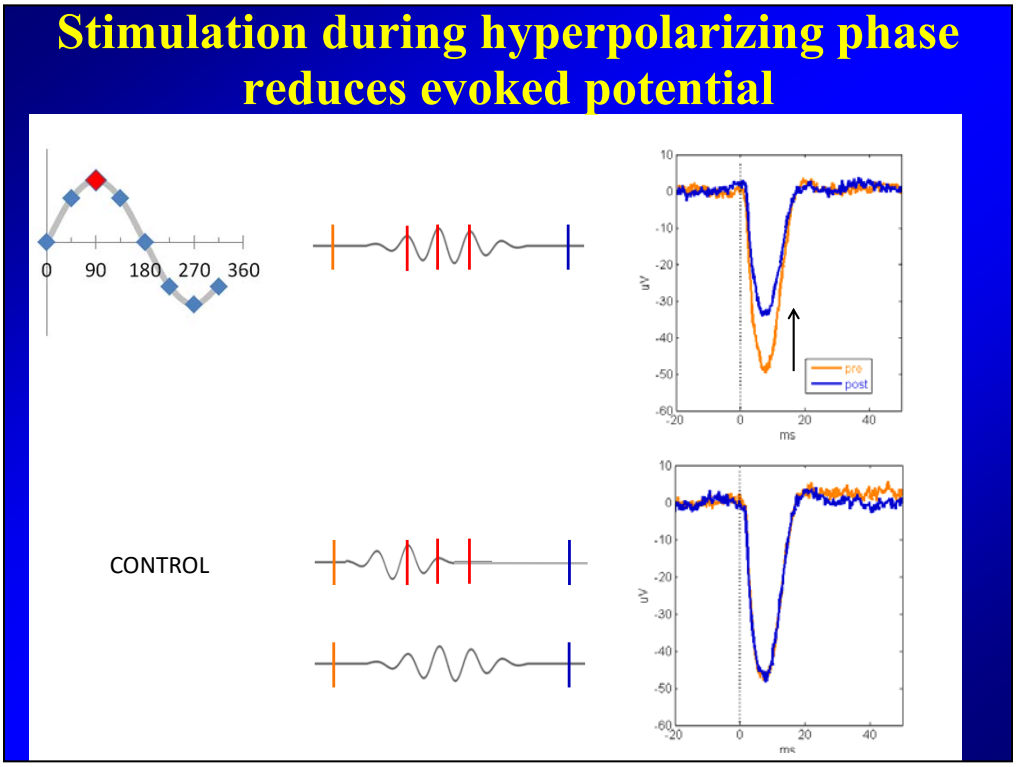
The first test stimulus after the oscillatory episode evoked a larger potential in M1 (blue trace).



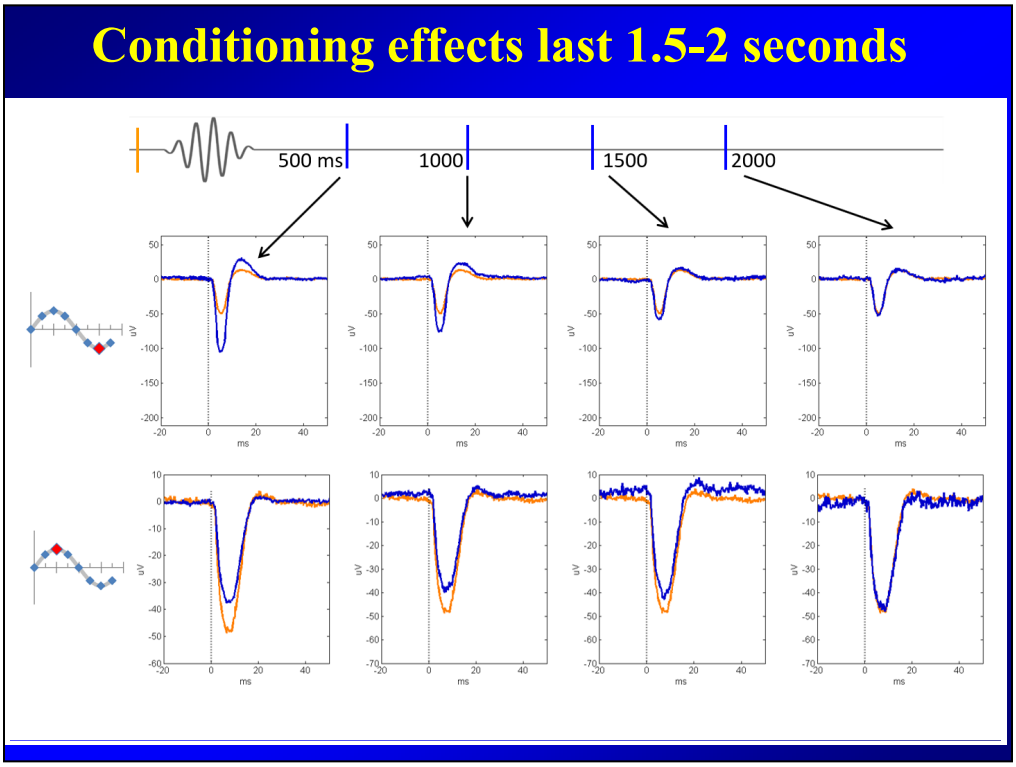
When stimuli were delivered during the depolarizing phase of oscillations the average cortical evoked potentials before and after episodes showed an increase in amplitude.

In the upper control, the same pattern of stimulation was delivered, but unrelated to oscillatory episodes; this produced no change in the evoked potentials.

In the second control, no stimulation was delivered during the episodes and again there was no change in the amplitude of potentials evoked before and after the episodes. These controls show that oscillations alone and stimulation alone were insufficient to produce a change in the evoked potentials.



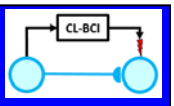
The changes depended on phase of stimulus delivery. When stimuli were delivered during the hyperpolarizing phase of oscillations the average cortical evoked potentials before and after episodes showed a decrease in amplitude.



Responses evoked by successive test stimuli delivered every 500 ms decreased, and showed that the effects last 1.5-2 seconds.

This indicates that oscillatory episodes produce transient post-episode changes in synaptic connectivity, in a phase-dependent manner. There is evidence that such oscillatory episodes reflect top-down attention, in which case these changes could play a role in attention-enhanced learning.

Timing of plasticity effects



Type	induction	duration
1. Cycle-triggered stim	3-6 cycles	2 sec
2. EMG-cortex	25+ min	0.5 – 24h
3. Cortico-spinal	3 -22 h	1-3+ days
4. Cortico-cortical	1-2 days	7+ days
5. EMG-spinal	13 weeks	3+ weeks

The timing of events in the five closed-loop conditioning experiments showed that the duration of plasticity effects generally covaried with the duration of induction.

1. Cycle-triggered stimulation involved the briefest induction period, typically 3 - 6 cycles, and lasted the shortest amount of time post conditioning

2. Tim Lucas showed that EMG-triggered cortical stimulation induced cortical plasticity in tens of minutes and conditioned changes lasted half an hour to 24 hours.

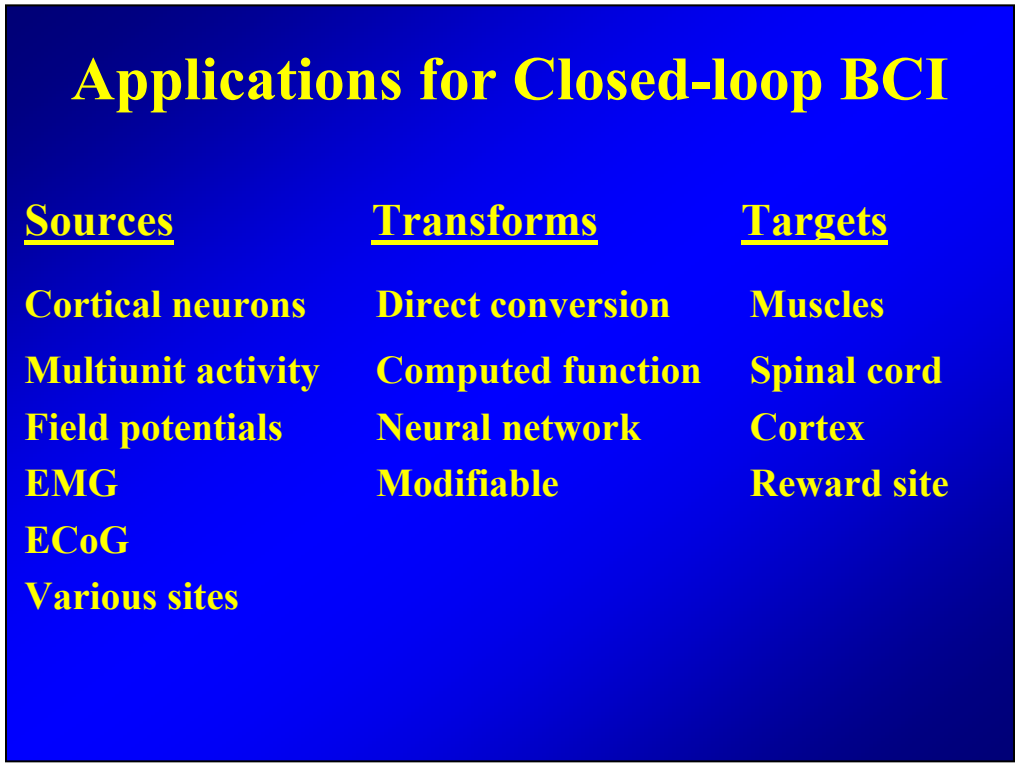
3. Yukio Nishimura showed that cortico-spinal stimulation triggered from spikes of CM cells induced changes in CM terminals after 3- 22 hrs and these changes lasted several days.

4. Andy Jackson induced intracortical plasticity with 24 hours of cortico-cortical spike-triggered stimulation and effects lasted 7-10 days

5. Steve Perlmutter and colleagues delivered EMG triggered spinal stimulation in rats with spinal cord injury. Reaching performance improved over 13 weeks of EMG triggered spinal stimulation, and the improvements lasted at least 3 weeks after the end of conditioning.

So in general longer conditioning induction times led to longer duration of post-conditioning effects.

These are just numbers that were used. The relation between conditioning time and duration of effects needs to be more systematically investigated.

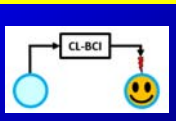


There are many applications for the closed-loop conditioning paradigm, depending on sources of the signal, the site of stimulation and the transform.

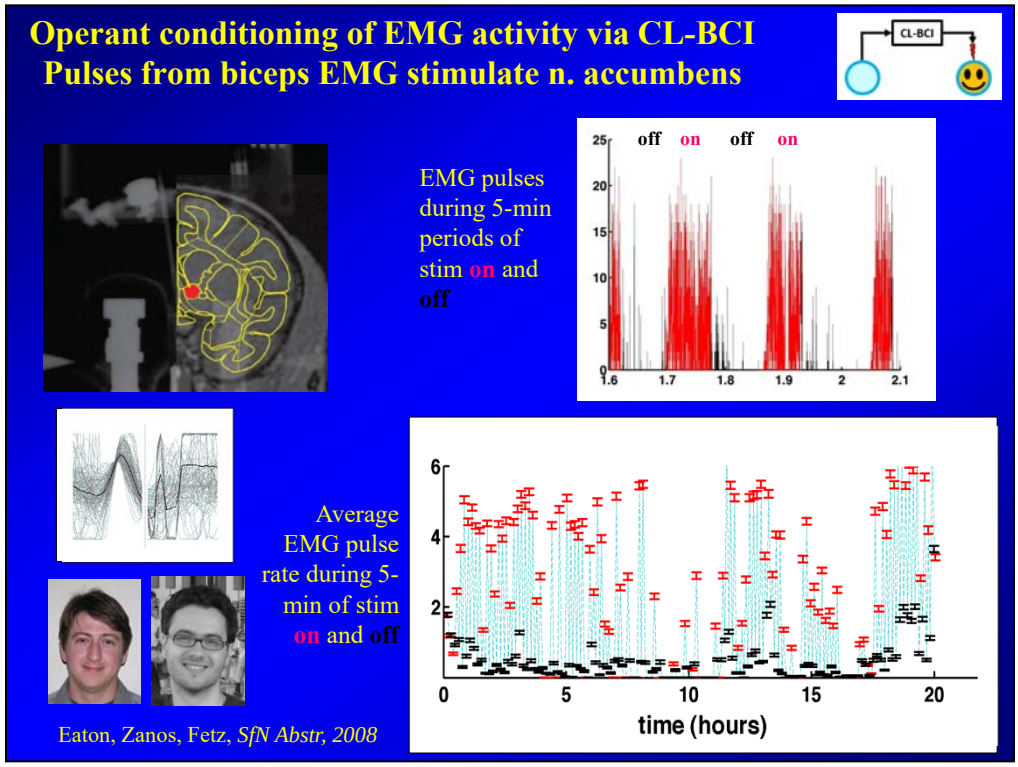
Neural activity can be recorded at many levels and different sites in the brain. The target sites are similarly diverse. The transform can directly convert recorded activity to proportional stimulation or be a computed function of the neural activity. Multichannel input can also be converted to output via artificial neural networks. The possible scenarios are limitless.

Applications for Closed-loop BCI

Sources	Transforms	Targets
Cortical neurons	Direct conversion	Muscles
Multiunit activity	Computed function	Spinal cord
Field potentials	Neural network	Cortex
EMG	Modifiable	Reward site
ECoG		
Various sites		

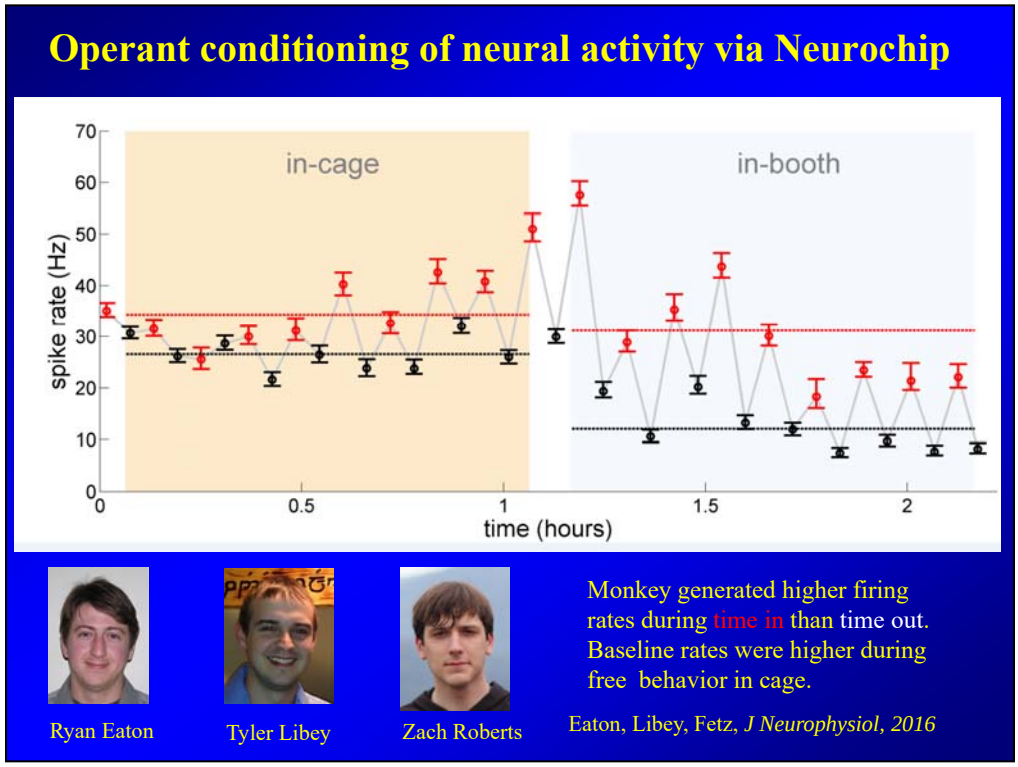


One final example of a closed-loop BCI involves stimulating an intracranial reinforcement site from EMG or neural activity. This is our third type of closed loop paradigm.



Ryan Eaton & Stavros Zanos used triggers from Biceps activity to deliver stimuli at a reinforcing site in nucleus accumbens. The Neurochip was programmed to alternately deliver 5 min periods of accumbens stimulation on and 5 min with stimulation off. There was no other feedback.

This plot shows that the stimulus rates are higher during on periods (red symbols), and continued to be so for almost 20 hours, except for pauses, probably sleep. During the on periods the monkey was seen flexing his elbow.

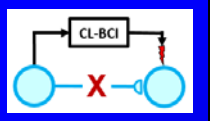


The same paradigm was used to operantly condition cortical unit activity with the monkey in the cage and in behavioral booth. The monkey generated higher firing rates when intracranial reinforcement was triggered from unit activity (redsymbols). The difference was more robust in the booth than with free movements in the cage, when there is lots of competing behavior.

Future possibilities for this conditioning paradigm is to test volitional control of patterns in multiple neurons and test the temporal coding hypothesis.

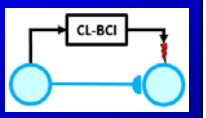
Closed-loop activity-dependent stimulation

For functional recovery



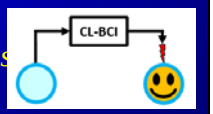
- **Corticospinal (NHP)**: Nishimura et al, *Frontiers,* 2016
- **Cortico-muscle (NHP)**: Ethier et al, *Nature*, 2012
- **Cortico-muscle (human)**: Bouton et al, *Nature*, 2016, Ajiboye et al, *Lancet*, 2017
- **Hippocampus multichannel CL-BCI (NHP & human)**: Deadwyler, Hampson, Berger et al, *Exp. Neurol.*, 2018; *J. Neural Eng.*, 2018

For neural plasticity



- **Cortico-cortical (rodent)**: Guggenmos, Nudo et al, *PNAS* 2013; Rebesco, Miller et al, *Front. System Neurosci.*, 2010

For operant conditioning



- **Amygdala spindling (chimpanzee)**: Delgado et al, *Brain Res*

So far I've focused largely on some examples from our lab, But there are many other studies of closed-loop activity-dependent stimulation. I wish there were more time to do them all justice. To cite just a few examples:

For functional recovery, other studies have investigated corticospinal and corticomuscle connections in the NHP. For example, Lee Miller and colleagues demonstrated that activity in population of cortical neurons could be decoded and used to deliver appropriate patterns of activity in paralyzed muscles.

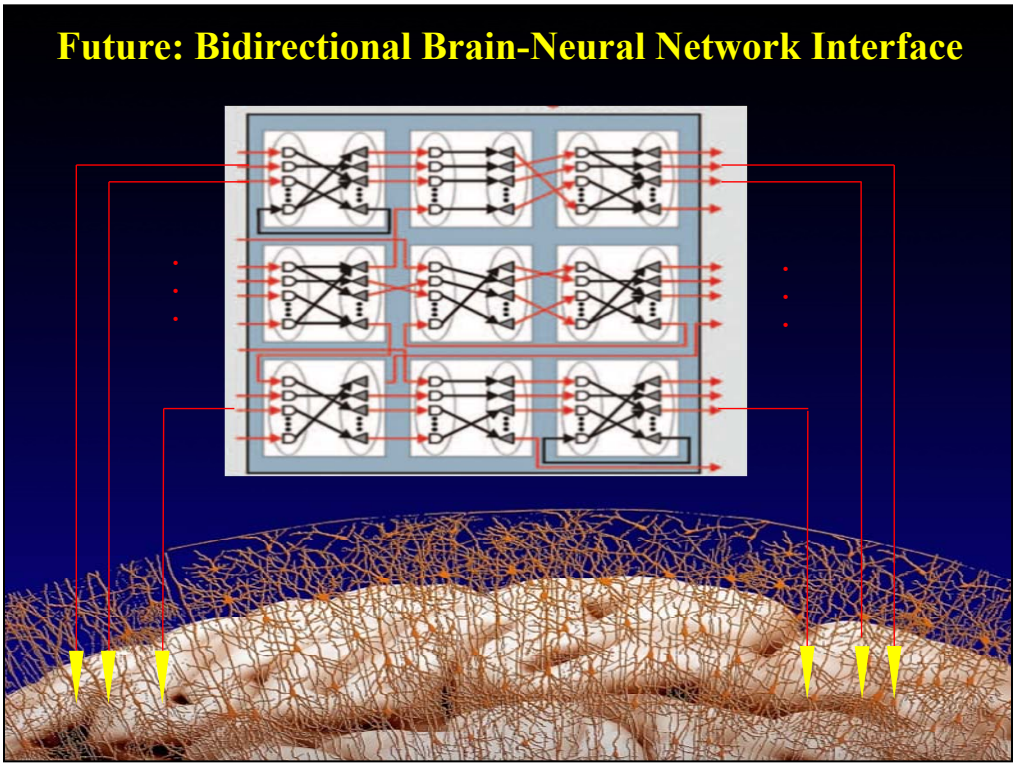
Also in human primates cortical cell activity can trigger transcutaneous functional electrical stimulation of muscles.

In the area of augmentation of function, Berger and colleagues have shown that multiunit activity can be converted to multichannel stimulation in hippocampus of monkeys and humans to boost performance in memory tasks.

Regarding neural plasticity, the labs of Randy Nudo and Lee Miller have shown the efficacy of spike-triggered stimulation in rodent cortex and demonstrated behavioral consequences.

Finally Jose Delgado many years ago implemented a wireless closed loop paradigm to trigger brain stem stimulation from amygdala spindles in the chimpanzee. Fortunately he performed this amazing experiment before such work with chimpanzees became taboo.

These are just a few examples from many more closed-loop BCI studies published and currently underway. And many more will be undertaken in the future. So what can we expect in the future?



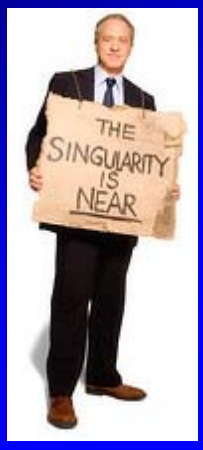
Looking ahead, I'm excited about the possibility of using a neuromorphic neural network chip in the loop rather than a conventional serial computer. This will exploit the parallel processing capabilities of large artificial neural networks and interface them directly with biological neural networks. This could create a sort of computational co-processor for the brain, which the brain could learn to exploit and incorporate.

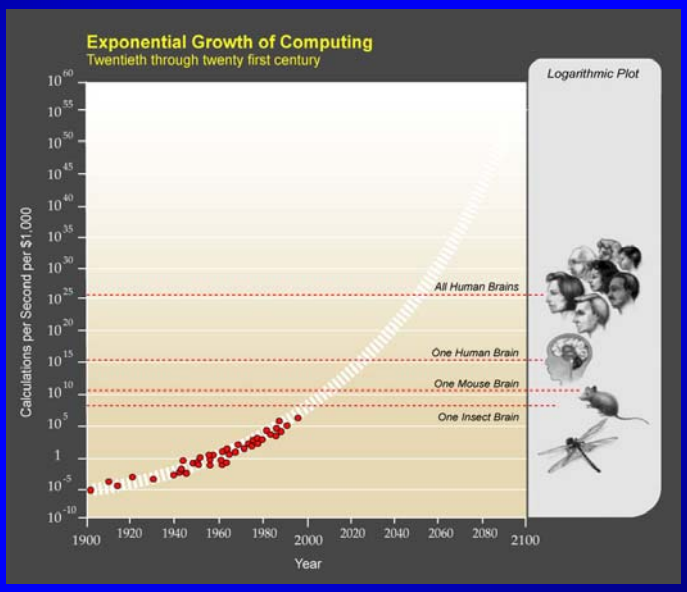
Obviously this is still a science-fiction scenario. A serious limitation for information processing comes from the electrode interfaces, which limit the ability to extract relevant information over long times and deliver effective input to the brain. These bottle-necks are no match for the efficacy of normal sensory and motor channels to transmit information. Nevertheless, the brain has remarkable adaptive abilities to generate appropriate output signals for intended results, and to interpret strange but consistent stimulus inputs. Who knows how the brain will adapt to such a novel interface when provided over a long time? I see this as an issue for empirical investigation rather than a-priori judgement.

But a major technical challenge is to reliably record unit activity in the face of simultaneous occurrence of asynchronous stimulation artifacts. This issue can hopefully be resolved, perhaps with optogenetic stimulation that

produces less electrical artifacts, or with sufficient computational power to eliminate them. In any case, I think that in a few decades we will have advanced significantly toward direct symbiotic interactions between brains and artificial neural networks.

Technologies are advancing exponentially





Kurzweil, The Singularity is Near, 2005

For inspiration about the possibilities, Ray Kurtzweil has pointed out that advances are increasing exponentially in many areas, including computer power, nanotechnology, understanding of brain function, neural network simulations, etc. Moreover all of these will combine to create new paradigms. What seems like science fiction today could well be reality tomorrow. A few decodes ago who would have thought you could carry in your pocket a powerful computer with access to the internet and GPS, a jukebox, an amazing camera, not to mention cell phone?

I believe that technologies for more powerful and direct interactions between the brain and implantable computers will become a reality in the lifetime of the students here, who will be fortunate enough to witness this and perhaps contribute to making it happen.

With that I close by thanking all the talented members of the lab that have worked on these projects.

And in particular thanks to our amazing programmer, Larry Shupe, who continues to write new software for the Neurochip to meet ever more demands. The specs for the latest and most powerful version of the Neurochip are on our website, if anyone is interested. And finally, many thanks for the support of these funding agencies and thanks to you for your attention.