Neural control of motor prostheses

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Neural interfaces (NIs) for motor control have recently become increasingly advanced. This has been possible owing to substantial progress in our understanding of the cortical motor system as well as the development of appropriate decoding methods in both non-human primates and paralyzed patients. So far, neural interfaces have controlled mainly computer screens and robotic arms. An important advancement has been the demonstration of neural interfaces that can directly control the subject's muscles. Furthermore, it has been shown that cortical plasticity alone can optimize neural interface performance in the absence of machine learning, which emphasizes the role of the brain for neural interface adaptation. Future motor prostheses may use also sensory feedback to enhance their control capabilities.

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Introduction

In the past decade, neural interfaces (NIs) that are able to read out brain signals for motor control have become increasingly popular and sophisticated [1–5]. Notwithstanding previous work using direct neural and non-invasive signals [6–8], the field took off in 1999 when Chapin *et al.* controlled a simple robot arm using signals from simultaneously recorded neurons in rat cortex [9]. NI systems with implanted recording electrodes were then refined and demonstrated to work in non-human primates using signals from primary motor, premotor, and the parietal cortex [10–13]. These studies demonstrated the possibility to control the continuous position of a two-dimensional or three-dimensional cursor, the selection of discrete targets, or walking patterns [14••].

Other groups have shown similar capabilities using non-invasive EEG signals [15–19], thereby challenging the need to use direct neural signals to operate neural prosthetics. However, EEG-based systems have a limited information transfer rate capacity and need substantial amount of training and attention to operate [2,4]. On the contrary, invasive systems still suffer from a limited lifetime (months to years instead of years to decades) owing to tissue reactions around the implanted sensors [20•,21•,22]. Technological improvements may overcome some or all of these shortcomings. Until then, the debate will probably continue.
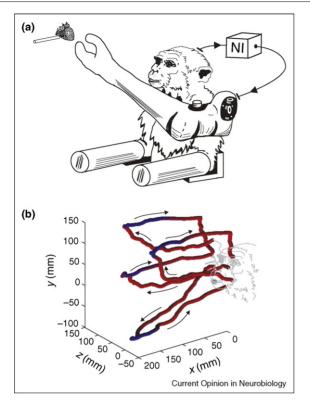
Human implants

Recently, it was demonstrated that invasive NIs can be functional in the brains of paralyzed patients [23••,24]. This is an important advancement for several reasons. First, the experiments have demonstrated that neural signals in the human motor cortex are similar to those of non-human primates. Neurons in the human cortex encode the position and velocity of imagined cursor tracking movements, which then could be used for the decoding of cursor movements [24]. This is significant, since it shows that the ongoing effort in discovering electrophysiological principles of motor control and decoding in non-human primates is transferable to humans. Second, it was possible to decode cursor and robotic control signals from motor cortex even years after the infliction of the brain lesion or spinal cord injury. This implies that the topographic reorganization of motor cortex is reversible after the injury or was never really complete. All this is good news for paralyzed patients who hope that results from animal studies can be transferred to the clinical setting soon.

Robotic arms

Previous NIs frequently controlled a cursor on a computer screen [11–13,25]. While this has considerable value in its own, for example to regain the capacity to operate a computer, an important application for paralyzed patients would be to substitute natural hand or arm function. This was recently demonstrated in monkeys. Using an implanted NI, monkeys were able to control a robotic arm and gripper and use it to feed themselves pieces of food (Figure 1A) [26••]. The NI recorded single and multiunit activity from the hand area of primary motor cortex and used population vector decoding to determine the three-dimensional position of the robotic arm as well as the gripper aperture. Using this arm, the monkey was able to grasp small food pieces that were placed in various positions in (3d) space and could transport them to the mouth (Figure 1B). These movements were not ballistic, but included online error correction and trajectory control by means of visual feedback. Interestingly, robotic control

Figure 1

Cortical control of a prosthetic arm for self-feeding. **A**. Setup with hand-restrained monkey controlling a prosthetic arm using a neural interface (NI). Food targets were presented randomly in space that the animal could grasp, bring to the mouth, and eat. **B**. Spatial trajectory of robotic endpoint position of four consecutive trials. Color indicates gripper aperture (red: open, blue: closed). Modified with permission from [26••].

appeared to be quite effortless and the animal was able to perform eye and head movements simultaneously with it. Transfer of this kind of robotic control to human patients would be an important next step, which could also meet recent efforts to develop dexterous robotic limbs for neuroprosthetic control [27,28].

Connecting to body muscles

Besides artificial devices like computer screens or robotic arms, paralyzed patients could also benefit from NI applications that directly control their muscles. Such an approach could avoid the need of a complicated and energy-consuming mechanical arm. Instead, it would restore motor function by directly connecting to the subject's limb.

A first proof of principle for such a system was recently demonstrated [29••]. Moritz *et al.* recorded neural activity of individual primary motor neurons in macaque monkeys and transformed these signals to stimulation signals that directly activated two opposing wrist rotation muscles (a pronator and a supinatior). To test the effectiveness of this NI, animals were trained to perform an instructed

wrist rotation task. Then, peripheral nerves of the performing arm were pharmacologically inactivated, which temporarily paralyzed the wrist rotation muscles. Activation of the NI then allowed the animal to perform the wrist rotation task despite the nerve block, hence demonstrating the effectiveness of the neuromuscular interface (Figure 2).
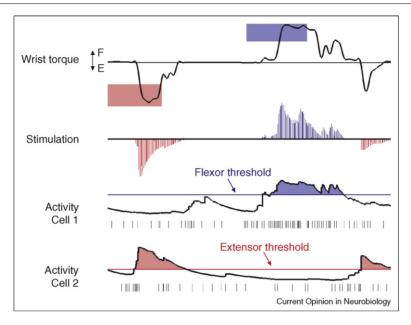
Connecting a NI directly to paralyzed muscles is very appealing and sounds like an ideal therapy for paralysis. Such an approach links NI research with the functional electrical stimulation (FES) community that uses muscle stimulation for rehabilitation [30,31••]. The combination of NIs with FES could lead to fully implantable systems that require no transdermal connections and no external devices, which would greatly improve the comfort, safety, and usefulness of such systems.

However, there are two main problems associated with this approach. The first one is that prolonged electrical stimulation induces muscle fatigue, which means that the muscle force in response to stimulation is not constant but progressively weakens over time. The second is the control problem of how to coordinate the many synergistic and antagonistic muscles precisely and meaningfully. Because of the common lack of proprioceptive and sensory feedback from paralyzed limbs, prosthetic control needs to rely entirely on visual feedback. This requires a lot of attention from the patient and is potentially worse than controlling a robot arm, where the control variable is usually position or velocity, but not acceleration (i.e. force). To establish direct muscle control, it will therefore be important to restore not only muscle activation, but also sensory feedback from the activated limb [32•,33••].

Cortical plasticity

A common approach to improve NI performance is to retrain the decoder at the beginning of each session or even continuously to account for possible changes of the neuronal ensemble and its tuning properties [9,11–13,25]. In addition, however, the brain adapts to the NI, which can be concluded from the observation that NI performance usually improves after the first decoding sessions. The brain and the NI therefore could act as two coupled controllers, which can lead to a potentially unstable system. But is external adaptation of the NI really necessary?

Previous experiments have shown that individual single units can adapt to an external decoder [6,8]. This idea was recently tested for the control of a NI for reaching [34••]. Ganguly and Carmena trained macaque monkeys to perform a center-out reach task and recorded neural ensemble activity in motor cortex. In the following decoding experiments, the weights of the external decoder were randomly permuted among the neurons and then fixed for the entire experiment. The neural ensemble activity adapted to this reshuffled decoder, leading to a decoding

Figure 2

Direct control of paralyzed muscles by cortical neurons. The monkey simultaneously modulates two neurons (cell 1 and cell 2) in motor cortex. Each cell controls a separate muscle group for antagonistic hand wrist rotation. Top: wrist torque curve produced by the muscles (F: flexion, E: extension) following presentation of the wrist torque targets (colored rectangles; red: extension, blue: flexion). Below: muscles are activated by proportional functional electrical stimulation (FES) when neural activity exceeds a threshold (red: extensor stimulation, blue: flexor stimulation). Modified with permission from [29••].

performance of >95% after about 10 decoding sessions. This demonstrates that high performance decoding is possible with brain adaptation only, provided the neural ensemble remains stable over time.

Furthermore, the same cortical ensemble could be trained for a new decoder that operates with a second set of reshuffled weights (Figure 3). Within a few sessions, the brain adapted also to the new decoder while conserving the performance of the old one. In other words, the brain could learn two independent decoders through the same NI and neural ensemble. Interestingly, the tuning properties of individual neurons differed substantially for the two decoders, indicating different cortical adaptation in the neural ensemble. Neural plasticity therefore is a powerful mechanism to excel NI performance, even to the point that no external learning is necessary. This could be of tremendous value for motor prosthetics.

Finger movements

A particular challenge for motor prosthesis is the control of dexterous hand and finger movements. Finger movements are highly complex and versatile, and humans spend much of their childhood learning to use their hands. From a control theoretical point of view, the difference between arm and hand movements is complexity. While reaching in space involves about three degrees of freedom, this number increases to 20 for moving a five-fingered hand. Currently, it is unclear how skillful hand movements are stored and retrieved in the brain, which makes effective

decoding hard. We have developed a simple decoder for hand grasping movements that is able to distinguish various grip types (power and precision grips) and wrist orientation from neural activity in the premotor and parietal cortex [35]. Such a NI is a first step, but more research is needed to determine which brain areas are suited best (e.g. motor, premotor, parietal cortex) to achieve dexterous finger control [28,31••,36].
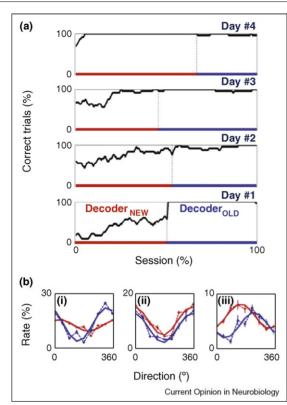
Future perspective

Basic research aiming at understanding the fundamental mechanisms of how the brain generates movements has become more and more relevant for clinical application. Currently, invasive and non-invasive decoding methods appear to be complementary [2,4]. Invasive methods seem to have a larger potential in decoding fidelity and information transfer rate, but the longevity of the implants still needs to be improved [20•]. It remains to be seen, which methods will be associated with better results and patient compliance in the long-term.

To improve the versatility of motor prostheses, an important enhancement would be to include sensory feedback from the actuated (artificial or natural) limbs. Such feedback could include tactile and proprioceptive information that can be sent either to a shared robotic controller [37] or to the nervous system [33••,38,39••]. In addition to other senses, such information could augment motor planning and execution, as it happens normally in healthy subjects. This corresponds to the emerging view that the motor

Figure 3

Emergence of stable cortical maps for neuroprosthetic control. **A**. Decoding performance over four consecutive days for predicting a center-out reaching task with a previously learned (blue epochs) or a new decoder (red epochs). Both decoders have differently assigned randomized weight parameters. Performance of the new decoder increases from chance to above 95% correct trials within 4 days while performance of the old decoder remains nearly perfect. **B**. Directional tuning of three example neurons (i–iii) during brain control with the new (red) and old decoder (blue); tuning curves of many neurons substantially change. Modified with permission from [34••].

system does not operate in isolation, but is tightly connected to sensory and cognitive networks [40•]. NI for motor prostheses should incorporate this fact for optimal performance.

Acknowledgements

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Schwartz AB, Cui XT, Weber DJ, Moran DW: **Brain-controlled interfaces: movement restoration with neural prosthetics**. *Neuron* 2006, **52**:205-220.

2. Donoghue JP: **Bridging the brain to the world: a perspective on neural interface systems**. *Neuron* 2008, **60**:511-521.

3. Linderman MD, Santhanam G, Kemere CT, Gilja V, O'Driscoll S, Yu BM, Afshar A, Ryu SI, Shenoy KV, Meng TH: **Signal processing challenges for neural prostheses**. *Signal Proc Mag, IEEE* 2008, **25**:18-28.

4. Hatsopoulos NG, Donoghue JP: **The science of neural interface systems**. *Annu Rev Neurosci* 2009, **32**:249-266.

5. Nicolelis MA, Lebedev MA: **Principles of neural ensemble physiology underlying the operation of brain-machine interfaces**. *Nat Rev Neurosci* 2009, **10**:530-540.

6. Fetz EE: **Operant conditioning of cortical unit activity**. *Science* 1969, **163**:955-958.

7. Wolpaw JR, McFarland DJ, Neat GW, Forneris CA: **An EEG-based brain-computer interface for cursor control**. *Electroencephalogr Clin Neurophysiol* 1991, **78**:252-259.

8. Kennedy PR, Bakay RA: **Restoration of neural output from a paralyzed patient by a direct brain connection**. *Neuroreport* 1998, **9**:1707-1711.

9. Chapin JK, Moxon KA, Markowitz RS, Nicolelis ML: **Real-time control of a robot arm using simultaneously recorded neurons in the motor cortex**. *Nat Neurosci* 1999, **2**:664-670.

10. Wessberg J, Stambaugh CR, Kralik JD, Beck PD, Laubach M, Chapin JK, Kim J, Biggs J, Srinivasan MA, Nicolelis MAL: **Real-time prediction of hand trajectory by ensembles of cortical neurons in primates**. *Nature* 2000, **408**:361-365.

11. Taylor DM, Tillery SI, Schwartz AB: **Direct cortical control of 3D neuroprosthetic devices**. *Science* 2002, **296**:1829-1832.

12. Musallam S, Corneil BD, Greger B, Scherberger H, Andersen RA: **Cognitive control signals for neural prosthetics**. *Science* 2004, **305**:258-262.

13. Santhanam G, Ryu SI, Yu BM, Afshar A, Shenoy KV: **A high-performance brain-computer interface**. *Nature* 2006, **442**:195-198.

14. Fitzsimmons NA, Lebedev MA, Peikon ID, Nicolelis MA:
•• **Extracting kinematic parameters for monkey bipedal walking from cortical neuronal ensemble activity**. *Front Integr Neurosci* 2009, **3**:3.
This study pioneers the field of restoring walking by decoding neural activity form motor cortex. Feasibility is demonstrated by predicting the kinematics of bipedal walking in rhesus macaques.

15. Birbaumer N, Kubler A, Ghanayim N, Hinterberger T, Perelmouter J, Kaiser J, Iversen I, Kotchoubey B, Neumann N, Flor H: **The thought translation device (TTD) for completely paralyzed patients**. *IEEE Trans Rehabil Eng* 2000, **8**:190-193.

16. Millan JR, Renkens F, Mourino J, Gerstner W: **Noninvasive brain-actuated control of a mobile robot by human EEG**. *IEEE Trans Biomed Eng* 2004, **51**:1026-1033.

17. Wolpaw JR, McFarland DJ: **Control of a two-dimensional movement signal by a noninvasive brain-computer interface in humans**. *Proc Natl Acad Sci U S A* 2004, **101**:17849-17854.

18. Blankertz B, Dornhege G, Krauledat M, Muller KR, Kunzmann V, Losch F, Curio G: **The Berlin brain-computer interface: EEG-based communication without subject training**. *IEEE Trans Neural Syst Rehabil Eng* 2006, **14**:147-152.

19. Birbaumer N, Cohen LG: **Brain-computer interfaces: communication and restoration of movement in paralysis**. *J Physiol* 2007, **579**:621-636.

20. Kipke DR, Shain W, Buzsaki G, Fetz E, Henderson JM, Hetke JF,
• Schalk G: **Advanced neurotechnologies for chronic neural interfaces: new horizons and clinical opportunities**. *J Neurosci* 2008, **28**:11830-11838.
A short review highlighting the state-of-the-art in chronic, microscale neural interfaces

21. Bjornsson CS, Oh SJ, Al-Kofahi YA, Lim YJ, Smith KL, Turner JN,
• De S, Roysam B, Shain W, Kim SJ: **Effects of insertion conditions on tissue strain and vascular damage during neuroprosthetic device insertion**. *J Neural Eng* 2006, **3**:196-207.

Qualitative and quantitative assessments of tissue damage were made for insertions using devices with different tip shapes and insertion speeds.

22. Szarowski DH, Andersen MD, Retterer S, Spence AJ, Isaacson M, Craighead HG, Turner JN, Shain W: **Brain responses to micro-machined silicon devices**. *Brain Res* 2003, **983**:23-35.

23. Hochberg LR, Serruya MD, Friehs GM, Mukand JA, Saleh M,
•• Caplan AH, Branner A, Chen D, Penn RD, Donoghue JP: **Neuronal ensemble control of prosthetic devices by a human with tetraplegia**. *Nature* 2006, **442**:164-171.
This seminal study demonstrates for the first time prosthetic control of a computer screen and a robotic gripper using motor cortical activity in humans.

24. Truccolo W, Friehs GM, Donoghue JP, Hochberg LR: **Primary motor cortex tuning to intended movement kinematics in humans with tetraplegia**. *J Neurosci* 2008, **28**:1163-1178.

25. Serruya MD, Hatsopoulos NG, Paninski L, Fellows MR, Donoghue JP: **Brain-machine interface: instant neural control of a movement signal**. *Nature* 2002, **416**:141-142.

26. Velliste M, Perel S, Spalding MC, Whitford AS, Schwartz AB:
•• **Cortical control of a prosthetic arm for self-feeding**. *Nature* 2008, **453**:1098-1101.
Monkeys are trained for the first time to continuously control a robotic arm and hand and use it for self-feeding.

27. Carrozza MC, Cappiello G, Micera S, Edin BB, Beccai L, Cipriani C: **Design of a cybernetic hand for perception and action**. *Biol Cybern* 2006, **95**:629-644.

28. Acharya S, Tenore F, Aggarwal V, Etienne-Cummings R, Schieber MH, Thakor NV: **Decoding Individuated Finger Movements Using Volume-Constrained Neuronal Ensembles in the M1 Hand Area**. *IEEE Trans Neural Systems Rehab Eng* 2008, **16**:15-23.

29. Moritz CT, Perlmutter SI, Fetz EE: **Direct control of paralysed
•• muscles by cortical neurons**. *Nature* 2008, **456**:639-642.
This study demonstrates for the first time direct neuronal control of hand muscles in the monkey, thereby implementing a neural interface that uses no external effector.

30. Lawrence M, Gross GP, Lang M, Kuhn A, Keller T, Morari M: **Assessment of finger forces and wrist torques for functional grasp using new multichannel textile neuroprostheses**. *Artif Organs* 2008, **32**:634-638.

31. Pohlmeyer EA, Oby ER, Perreault EJ, Solla SA, Kilgore KL,
•• Kirsch RF, Miller LE: **Toward the restoration of hand use to a paralyzed monkey: brain-controlled functional electrical stimulation of forearm muscles**. *PLoS One* 2009, **4**:e5924.
Monkeys were implanted with a multi-electrode array in motor cortex that was used to directly control a FES system. Animals were able to use this cortically controlled FES system to meaningfully contract four forearm muscles.

32. Fitzsimmons NA, Drake W, Hanson TL, Lebedev MA, Nicolelis MA:
• **Primate reaching cued by multichannel spatiotemporal cortical microstimulation**. *J Neurosci* 2007, **27**:5593-5602.
Owl monkeys performed reaching movements that were guided by cortical microstimulation delivered to primary somatosensory cortex through chronically implanted multielectrode arrays.

33. O'Doherty JE, Lebedev MA, Hanson TL, Fitzsimmons NA,
•• Nicolelis MA: **A brain-machine interface instructed by direct intracortical microstimulation**. *Front Integr Neurosci* 2009, **3**:20.
This study combines a NI with multi-electrode recordings in motor cortex with microstimulation of S1. Stimulation instructs monkeys to choose a specific reach target, which is then acquired by the brain machine interface.

34. Ganguly K, Carmena JM: **Emergence of a stable cortical map
•• for neuroprosthetic control**. *PLoS Biol* 2009, **7**:e1000153.
Monkeys were trained to use a cortical NI for center-our reaching solely by cortical adaptation, that is, without external training of the neural decoder.

35. Townsend B, Subasi E, Scherberger H: **Real time decoding of hand grasping signals from macaque premotor and paritetal cortex**. In *13th Annual Conference of the International Functional Electrical Stimulation Society 'From Movement to Mind' September 21–25*. Edited by Stieglitz T, Schuettler M.*Freiburg, Germany: Biomed Eng* 2008, **53(Suppl. 1)**.

36. Vargas-Irwin CE, Shakhnarovich G, Yadollapour P, Mislow JMK, Black MJ, Donoghue JP: **Evaluating the potential of primary motor and premotor cortex for mutltidimensional neuroprosthetic control of reaching and grasping actions**. *Society for Neuroscience*. Chicago, IL: Online; 2009.

37. Kim HK, Biggs SJ, Schloerb DW, Carmena JM, Lebedev MA, Nicolelis MA, Srinivasan MA: **Continuous shared control for stabilizing reaching and grasping with brain-machine interfaces**. *IEEE Trans Biomed Eng* 2006, **53**:1164-1173.

38. Patil PG, Carmena JM, Nicolelis MA, Turner DA: **Ensemble recordings of human subcortical neurons as a source of motor control signals for a brain-machine interface**. *Neurosurgery* 2004, **55**:27-35 discussion 35–28.

39. Marasco PD, Schultz AE, Kuiken TA: **Sensory capacity of
•• reinnervated skin after redirection of amputated upper limb nerves to the chest**. *Brain* 2009, **132**:1441-1448.
Amputee patients who had undergone targeted reinnervation surgery were examined for grating orientation and point localization thresholds to test the sensory capacity of the reinnervated skin.

40. Suminski AJ, Tkach DC, Hatsopoulos NG: **Exploiting multiple
• sensory modalities in brain-machine interfaces**. *Neural Netw* 2009.
Neurons in the primary motor cortex (MI) encode sensory information. Proprioceptive and visual feedback during passive movements elicited nearly identical activity in MI than active reaching.