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Cognitive neural prosthetics

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Research on neural prosthetics has focused largely on using activity related to hand trajectories recorded from motor cortical areas. An interesting question revolves around what other signals might be read out from the brain and used for neural prosthetic applications. Recent studies indicate that goals and expected value are among the high-level cognitive signals that can be used and will potentially enhance the ability of paralyzed patients to communicate with the outside world. Other new findings show that local field potentials provide an excellent source of information about the cognitive state of the subject and are much easier to record and maintain than spike activity. Finally, new movable probe technologies will enable recording electrodes to seek out automatically the best signals for decoding cognitive variables.

Neural prosthetics research has been a field of intense activity in recent years. It is by nature highly interdisciplinary and includes neuroscience, engineering, neurosurgery and neural informatics. Although the ultimate goal is a practical application, a basic understanding of the brain's neural codes and representations is a cornerstone of this research. Moreover, the brain–machine interfaces (BMIs) that are at the core of neural prosthetics afford a new method to study brain mechanisms and will allow, among other things, the testing of new theories of brain function.

Current studies that record the spike activity of neurons have focused primarily on deriving hand trajectory signals primarily, but not exclusively, from motor cortex [1–5]. Recordings from the cells are 'decoded' to control the trajectories of a robotic limb or a cursor on a computer screen. In addition, progress has been made in using EEG-based signals to derive neuroprosthetic commands [6]. This article examines what other signals, in particular high-level cognitive signals, can be recorded from single cells or local field potentials (LFPs) and used for controlling neural prosthetics.

Cognitive-based paradigms in monkey

Cognitive control signals can be derived from many higher cortical areas related to sensory–motor integration in the parietal and frontal lobes. The primary distinction is not the location from which recordings are made. Rather it is the type of information that is being decoded, and the strategy for using these signals to assist patients. Here we focus on the posterior parietal reach region (PRR) and the dorsal premotor cortex (PMd), but similar approaches can be used for interpreting cognitive signals from other brain areas. It is likely that some areas will be better than others depending on the cognitive signals to be decoded and the parts of the brain that are damaged.

PRR in non-human primates lies within a broader area of cortex, the posterior parietal cortex (PPC) [7,8]. The PPC is located functionally at a transition between sensory and motor areas and is involved in transforming sensory inputs into plans for action, so-called sensory–motor integration. The PPC contains many anatomically and functionally defined subdivisions. Of particular interest in recent years are areas within the intraparietal sulcus that are involved in planning eye movements (the lateral intraparietal area, LIP) [9], reach movements (PRR) [10], and grasping (the anterior intraparietal area, AIP) [11].

PRR has many features of a movement area, being active primarily when a subject is preparing and executing a movement [10,12]. However, the region receives direct visual projections and vision is perhaps its primary sensory input. Moreover, this area codes the targets for a reach in visual coordinates relative to the current direction of gaze (also called retinal or eye-centered coordinates) [12]. Similar visual coding of reaches has been reported in a region of the superior colliculus [13]. This coding in visual coordinates underscores the cognitive nature of the planning signal within PRR. It is coding the desired goal of a movement, rather than the intrinsic limb variables required to reach to the target. Moreover, PRR can hold the plan for a movement in short-term memory through persistent activity of its neurons. This intention-related activity provides a useful neural correlate of the intentions of the subject for subsequent decoding. The human homologue of PRR has recently been identified in fMRI experiments [14]. Less is currently known about the coordinates for coding in PMd. However, studies indicate that at least of subset of cells have properties similar to those found in PRR [15–17].

Decoding intended reaches

Experiments have recently been performed in monkeys in which reach intentions are decoded from neural activity in real time, and used to position a cursor on a computer screen – the so-called brain-control task [18] (Figure 1a). Arrays of electrodes were placed in the medial intraparietal area (MIP), a portion of PRR, area 5 (also in the posterior parietal cortex), and the PMd. Reach goals were decoded from activity present when the monkeys were planning the reach movements, but otherwise were sitting motionless in the dark and were not making eye

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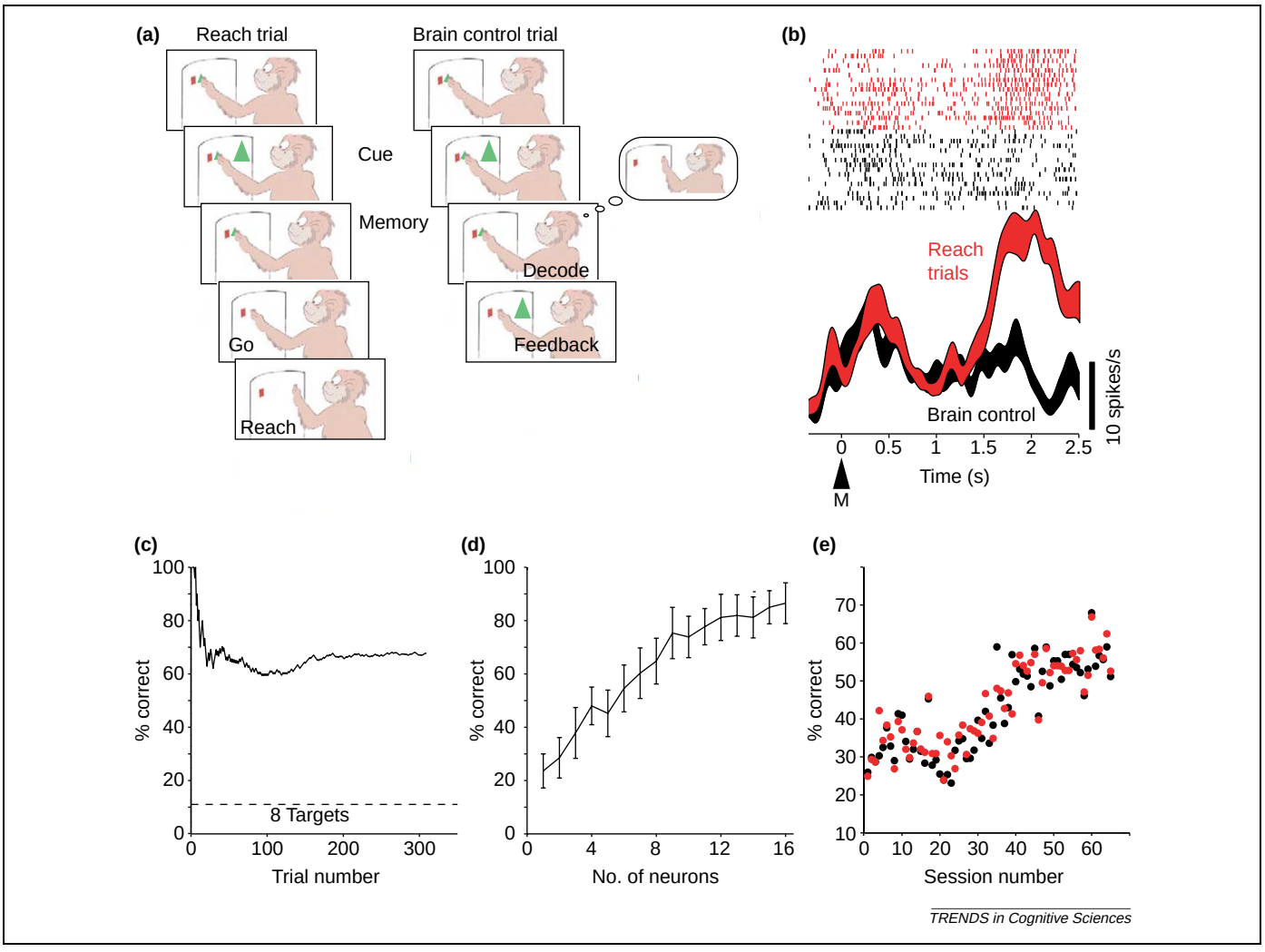

Figure 1. **(a)** The task for reach and 'brain-control' trials in the experiments of Musallam *et al.* [18]. 500 ms after the monkeys touched a central green cue and looked at a central fixation point (red), a peripheral cue (green) was flashed for 300 ms. For reach trials, the monkeys were rewarded if they reached to the target at the end of a 1500±300 ms memory period. During brain-control trials, data from 200 to 1100 ms of the memory period was used to decode the intended reach location. Monkeys were rewarded if the correct target was decoded. **(b)** Comparison of neural activity recorded in the posterior parietal reach region (PRR) during reach (red) and brain-control (black) trials. Each row of the upper rasters is a single trial aligned to the beginning of the memory period. Thickness of the post stimulus–time histogram (graph) represents the standard error calculated with the bootstrap method. M = start of memory period. **(c)** Cumulative performance of a brain-control session using 16 neurons recorded from the dorsal premotor cortex of one monkey. The overall percent correct in this session was 67.5%. **(d)** An off-line analysis using the same data, showing the effect of the number of cells on decode performance. However, the number of neurons that can achieve a high success rate still remained relatively low. **(e)** Offline decode results performed with an adaptive (red) and frozen (black) database for all the PRR recording sessions in consecutive order, for the same monkey whose data is shown in (c). There is no statistical difference between the two populations. Modified from [18].

movements (Figure 1a–c). Thus the cognitive signals in the brain-control task were free of any sensory or motor related activity. Generally only a small number of cells were required for successful performance of the task, with performance increasing with the number of neurons (Figure 1d).

Plasticity. Consistent with several studies of cortical plasticity [19], animals showed considerable learning in the brain-control task. The ability of the animals to position the cursor on the computer screen with their intentions improved considerably over a period of one to two months [18] (Figure 1e). This time course for learning is similar to that seen in motor cortex for trajectory decoding [2,4].

A closer analysis showed that the improvement in decoding was due to an increase in the amount of information carried by the neurons in the brain-control task [18]. A mutual information measure was calculated which quantifies the degree of spatial tuning of the neurons. This measure increased along with the increase in performance of the animals. Plastic changes are very useful for neural prosthetics, and will enable patients to optimize performance with training.

Adaptive and frozen databases. Each recording day began with the monkeys performing a series of reaches to touch different locations on a computer screen (Figure 1a). This segment of trials produced a database. Next the monkeys were instructed with a briefly flashed cue to plan to reach to different locations but without making a reach movement (Figure 1a). We then compared the activity with that in the database and, using a Bayesian decode algorithm, predicted where the monkeys were thinking about reaching. If the predicted reach direction corresponded to the cued location, then the animals received a drop of fluid reward and visual feedback was provided by re-illuminating the cued location. This approach was

necessary because we couldn't just say to the monkeys 'think about reaching to the target'.

However, this approach does open the question of whether reaches are necessary to build the database. This would of course be impossible for paralyzed patients. This point was directly addressed in off-line analysis by comparing the performance between 'adaptive' and 'frozen' databases. With the adaptive database, each time a successful brain-control trial was performed it was added to the database, and because the database was kept at the same number of trials for each direction, the earliest of the trials is dropped. Eventually only brain-control trials are contained within the database. In the case of the frozen database, the reach data was used throughout the brain-control segment. Both decodes were performed with the same data. As can be seen in Figure 1(e), both databases produce the same performance. Thus paralyzed patients can be simply asked to plan to make a reach and this planning activity can be used to build a database even though the patients cannot actually reach.

How much time is required to decode a goal? In the brain-control experiments the decode was based on a 900 ms period in which the animal was planning to reach. However, off-line analysis showed that the task could have been performed with time segments as short as 100 ms [18].

Expected value

Signals related to reward prediction are found in several brain areas [20]. In an eye movement region, area LIP of the posterior parietal cortex, Platt and Glimcher [21] found that cells code the expected value of rewards. Using a saccade task they showed that the neurons increased their activity when the animal expected a larger reward or the instructed saccade was more likely to be in the cells' receptive fields. Recently similar effects have been found for PRR neurons for amount of reward in the reaching task and the brain-control task [18]. PRR cells are also more active and better tuned when the animal expects higher probability of reward at the end of a successful trial (Figure 2c,d). Rather remarkably, PRR cell activity also shows a reward preference, being more active before the expected delivery of a preferred citrus juice reward than a neutral water reward (Figure 2a,b). The expected value in brain-control experiments could be read out simultaneously with the goal using offline analysis of the brain-control trials [18]. These experiments show that multiple cognitive variables can be decoded at the same time.

Local field potentials

It has recently been found that the local field potentials recorded in the posterior parietal cortex of monkeys contains a good deal of information regarding the animals' intentions. In area LIP, the eye movement area adjacent to PRR, the magnitude of the gamma band ($\sim$25–90 Hz) oscillations in LIP was found to be a good predictor of the direction in which monkeys planned to make saccades [22]. Interestingly, another useful oscillation in the local field potential in area LIP was present in the beta band, centered at around 20 Hz. This oscillation was not direction tuned, but rather indicated the behavioral state of the animal. When the animal was planning a saccade it slowly increased, whereas at the time of the eye movement it dramatically decreased in amplitude [22].

A direct comparison of the ability to decode intentions was made using the spikes and LFPs obtained from LIP [22]. A linear discriminant analysis was used to predict, from single trials, the direction of a planned movement. The performance for predicting direction was similar for spikes and LFPs. The decoding of the behavioral state was also examined; that is, whether the monkey was planning or executing a movement. The LFPs were better than spikes for the state decode [22]. The better performance of the LFP state decodes may reflect the activity due to circuits within LIP or inputs to LIP from external sources. Further work will be required to distinguish between the two. In motor cortex, LFPs evoked by limb movements can be decoded to predict the movement directions, with similar performance to spike decodes [23]. Electrocorticographic LFP recordings from human cortex have been used to control a one-dimensional cursor [24].

From a practical point of view, these LFPs are extremely useful for neural prosthetics applications. A major challenge for cortical prosthetics is to acquire meaningful data from a large number of channels over a long period of time. This is particularly challenging if single spikes are used because typically only a fraction of probes in an implanted electrode array will show the presence of spikes, and these spikes are difficult to hold over very long periods of time. However, as LFPs come from a less spatially restricted listening sphere, they are easier to record and are more stable over time. Thus it would be of great advantage to be able to use the LFPs for decoding when and where patients intend to make movements.

We now turn to some of the engineering issues that are relevant to the development of future cognitive neural prostheses.

Moveable electrodes for autonomous neuron isolation and tracking

Chronic recording experiments use electrodes that are introduced only once, and typically a large number of electrodes are implanted. These electrodes remain in place and are not moved and, as a result, the recordings are not optimal. Ideally, it would be advantageous to be able to adjust the electrodes and there are some systems which allow movement of chronically implanted electrodes with manual adjustment [25–29]. However, with permanent implants of large numbers of electrodes, such manual adjustment would be tedious and impractical for patients. This is especially true considering that the brain tissue moves with respect to the electrodes over time and would require constant adjustment of the positions of the electrodes. Automated movable probes would overcome many of these limitations.

Movable electrodes would be extremely well suited for cognitive-based prosthetics. Within different cortical areas there are various types of cells that code different parameters. For instance, in the frontal eye field one finds visual, visual-motor and motor cells [30–32]. A similar distinction can be made in area LIP, along with subsets of cells that carry information about eye and head position [33–35]. In both areas the cells for all of these attributes

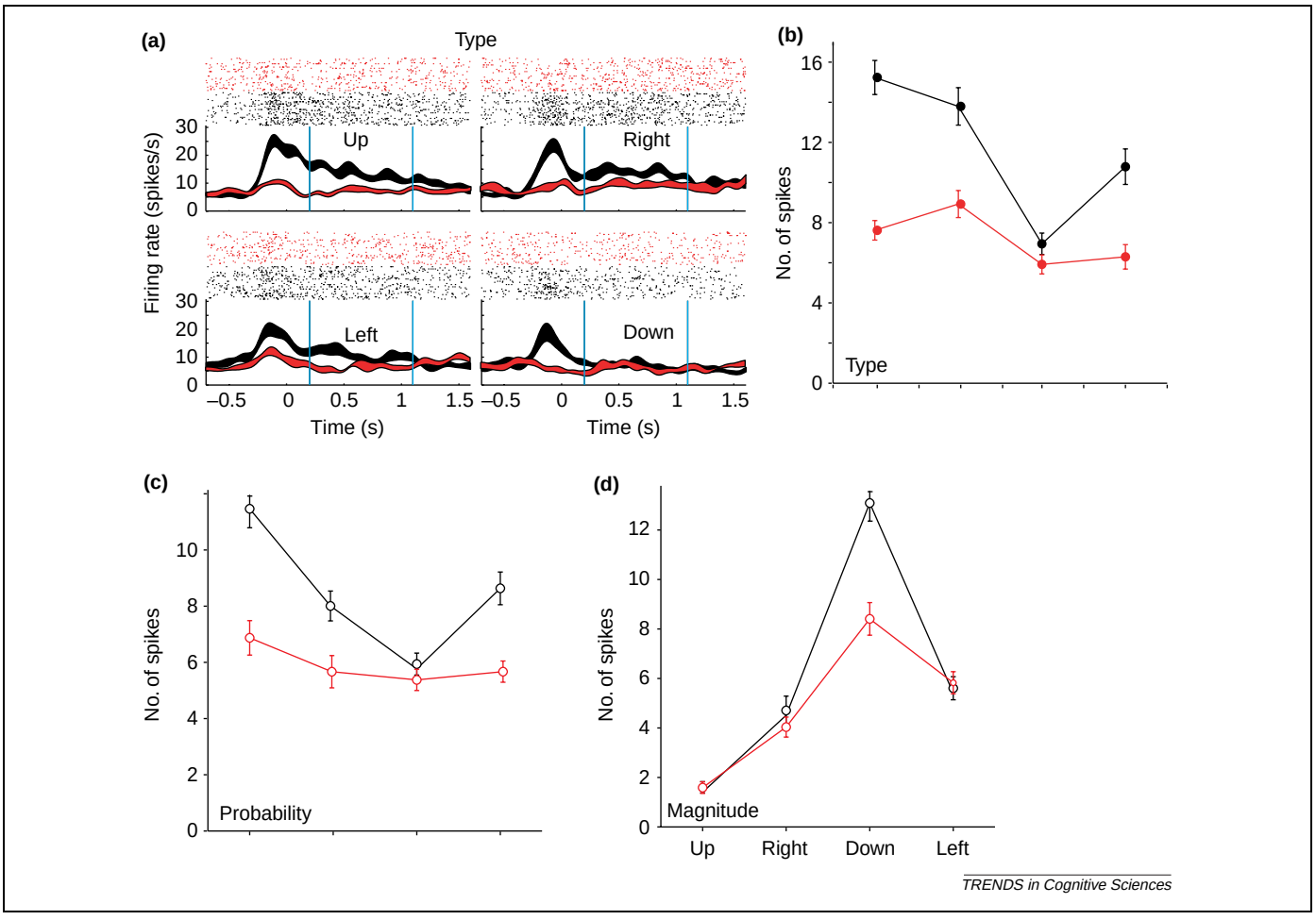

Figure 2. **(a)** Response of a neuron during brain-control trials in which reward type was varied: orange juice (black) versus water (red). Volume of juice and water was the same (0.12 ml). Rasters are aligned to the onset of the memory period. The direction of the intended reach (up, right, etc.) that elicited the responses is shown. Blue vertical lines superimposed on the graphs enclose the 900-ms memory segment used to calculate the tuning curves and the duration of the neural activity used to decode reach intention during brain-control trials. **(b)** Tuning curve of the neuron, which shows that it is more active before the expected delivery of a (preferred) orange juice reward than a neutral water reward. **(c,d)** Tuning curve calculated from the firing rates of two additional cells when the probability **(c)** and magnitude **(d)** of the reward was varied. Modified from [18]

have spatially selective response fields. To decode several variables, it would be ideal to choose the different cell types and, for each response type, further choose receptive fields that can tile the entire space. As an example, previous experiments that decoded intended reach directions in PRR concentrated on the cells that coded the planned movement in the absence of vision and actual movement [18]. This was a subset of the cells recorded with the fixed geometry electrode arrays, with other cells being responsive to vision or to movement execution. To search out cells coding the high-level movement plan would improve the decode performance substantially.

Cell selection would not be the only advantage of an autonomously controlled electrode technology. Autonomously moving probes could also improve the signal quality, stability and longevity of chronic recordings. The reported values of these neuronal signal metrics vary widely across different animals, cortical areas, and array designs. Although some arrays have provided useful signal for periods of up to a few years [36–38], the quality of single cell activation in most channels of fixed-geometry implanted electrode arrays noticeably degrades after a few weeks or months [39]. Factors contributing to this deleterious loss of signal include reactive gliosis [40,41] resulting from electrode movement in the tissue or bio-incompatibility of the electrode's surface material [42,43]. Another difficulty arises from the arrays' fixed electrode geometries, which cannot be adjusted once they are implanted. Consequently, the array's useful signal yield might be low, as the electrodes' active recording sites could lie in electrically inactive tissue, or be distant from cell bodies (which generally produce the largest extracellular signals). Even if the initial placement is satisfactory, fixed-geometry electrode arrays can drift in the brain matrix (owing to tissue movement caused by respiratory or circulatory pressure variations [44] and mechanical shocks due to body movements [45]). This drift can lead to the separation of the electrode from the vicinity of active cells, thereby lowering signal yield of the electrode array. (See Box 1 for recent advances in movable probe technology.)

Synthesis

In this article, we have outlined a new strategy for neural prosthetics that is based on the recording and decoding of signals related to the cognitive intentions of the subject. These cognitive control signals are derived from the

Box 1. Recent advances in movable probe technology

Clearly, the possibility to reposition electrodes automatically after implantation would significantly improve the quality and yield of neural recordings for prosthetics application, and allow specific cell types to be chosen. Recent engineering research has been directed to developing a new class of computer controlled multi-electrode systems that continually and autonomously adjust electrode positions under closed-loop feedback control so as to optimize and maintain the quality of the recorded extracellular signal [46,47].

The eventual goal is to use micro-electro-mechanical systems (MEMS) technology to produce a movable electrode array implant. One promising method is to use electrolysis techniques to move and lock the probes in place [49–52]. This movement is accomplished by passing electrical current within small bellows-chambers filled with fluid. The gas released by electrolysis increases pressure within the bellows and moves the electrode. The electrodes can be moved in the opposite direction by reversing the current flow and the use of a catalyst. Advantages of this electrolysis technique include relatively low driving voltage, low heat dissipation, the ability to lock electrodes in place without the need for continuous power dissipation, the ability to generate very high forces, and the ability to provide hundreds of microns of electrode displacement.

Another advance would be adding microfluidic delivery to the implant. These microfluidic systems would also work via electrolysis, and could potentially deliver anti-inflammatory agents to manage the effects of the electrodes' presence, or to deliver therapeutic and neurotrophic factors. The MEMS movable probes and microfluidic channels can be constructed as linear probe arrays (see Figure I). These arrays would comprise the electrodes/needles, micro-electrolysis systems, and control electronics. The individual chips with linear arrays would be stacked within a chamber, allowing the most flexibility in the overall geometry of the implanted array of electrodes and microfluidic channels. The depth of the individual chips can be adjusted coarsely using a motorized chip adjuster following surgery. After coarse adjustment, electrolysis actuators would provide the fine-tuning of the electrodes positions automatically and continuously. The integration of pre-processing electronics (e.g. pre-amplifiers, filters, and multiplexers) into a multi-electrode array front-end would improve recording performance by improving signal-to-noise ratio and buffering the signal of high impedance electrodes. Such a preprocessing chip has recently been developed [53].

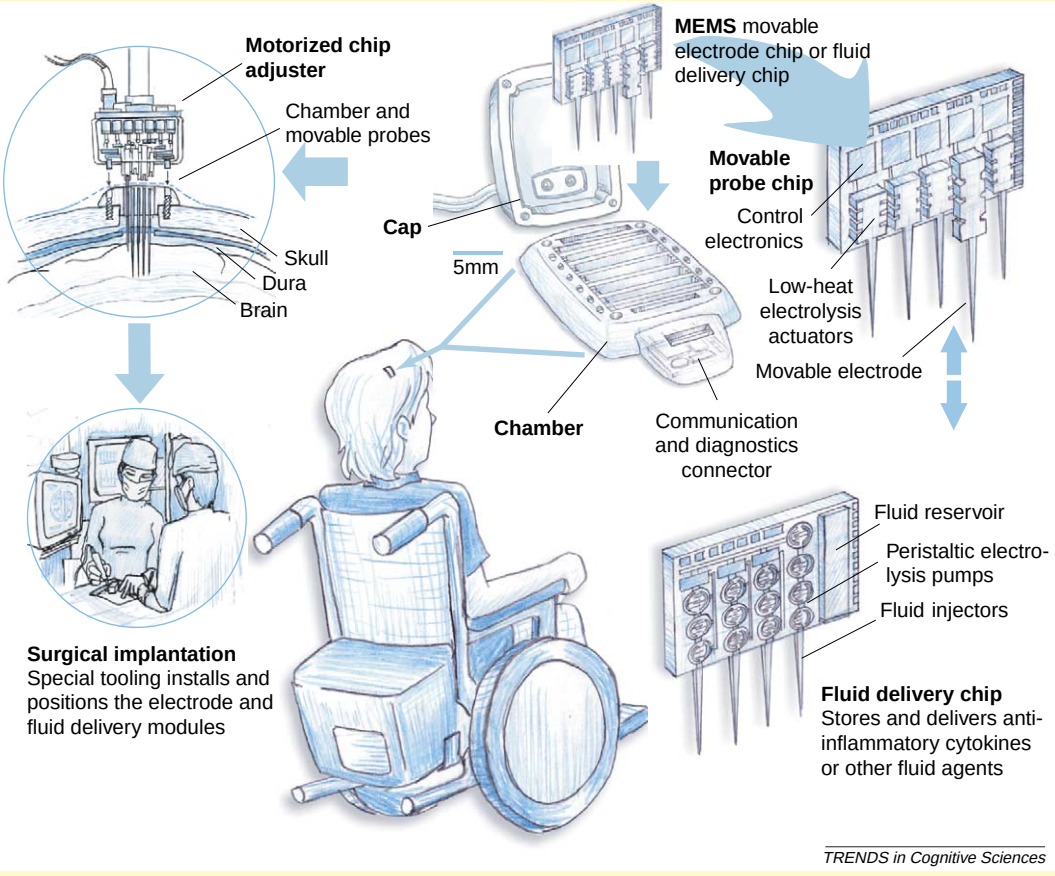

Figure I. Conceptual diagram illustrating a future neuroprosthetic system that combines arrays of movable electrodes and micro-fluidic delivery systems. The motorized chip adjuster would allow coarse control for placing the electrode arrays in the chamber beneath the skull. The movable electrodes and microfluidic injectors are designed as linear arrays on flat chips. These chips can be stacked in the chamber to allow versatility in the number and spacing of electrodes and injectors. The initial depth of each chip is set with the chip adjuster.

visual-motor system, taking advantage of the fact that humans have a dominant visual sense. However, this approach of using high-level cognitive signals can be extended to a variety of neuronal networks.

Some advances have already been made towards the goal of developing a cognition-based neural prosthetic. On the neurophysiological front, it has been shown that the intention to reach to a goal can be read out from PRR and PMd in monkeys and used to control the position of a cursor on a computer screen without the animals moving their limbs [18]. Furthermore, the cognitive variable of expected value has also been decoded from PRR in brain-control tasks [18]. LFPs can be used, along with spikes, as sources of neural signals for decoding cognitive variables.

Box 2. Neuroprosthetic control systems based on intelligent devices and supervisory control

Intelligent devices and hierarchical, supervisory control algorithms are required for cognitive-based prosthetic systems [54]. Any system that translates thoughts into action will require a computer interface, and often some electromechanical devices. Such systems must match the information that is decoded from the brain to the informational requirements of the computer interface and the commanded devices. On the brain side, the cognitive approach focuses on decoding high-level information at the abstract or symbolic level. The informational requirements on the electromechanical device side can vary widely with the type of device and intended task. For graphical computer interfaces, the problem of control system design reduces to matching the cognitive states of the brain to the symbolic states of the task. For instance, iconic menus on computer monitors can be used for communication with a wide range of devices from household utilities to computers for exploring the Internet.

Physical electromechanical devices require more detailed instructions. Supervisory control systems can convert symbolic level commands into detailed motor device commands, which are then carried out and monitored by the supervisory controller. There is much to be gained by pursuing this approach, as it has additional advantages for both the neuroprosthetic user and the system engineer. To interface the brain to different electromechanical devices, often only the lowest level of the control hierarchy need be re-engineered for the specific mechanical device. Similarly, the hierarchical nature of supervisory control should allow patients to learn much more quickly how to command a new device.

Because a patient's workspace will be limited, knowledge of that workspace, combined with the decoded desires of the subject, may be sufficient to successfully complete tasks using intelligent devices. For example, given the Cartesian coordinates of an intended object for grasping, a robotic motion planner [55] can determine the detailed joint trajectories that will transport a prosthetic hand to the desired location. Sensors embedded in the mechanical arm ensure that it follows the commanded trajectories, thereby replacing the function of proprioceptive feedback that is often lost in paralysis. Other sensors can allow the artificial arm and gripper to avoid obstacles and control the interaction forces with its surroundings, including grasping forces, thereby replacing somatosensory feedback. Only the intent to grasp or ungrasp an object is needed to supervise these actions. Hence, low-level physical details and interactions need not be specifically commanded from decoded brain signals. However, if available, motor signals can augment low level plans and controls.

Box 3. Questions for future research

- As PRR codes targets in eye coordinates, can the goals of movements be determined accurately across eye movements? Preliminary data suggest that they can [18]. Possible contributing factors for successful decodes despite eye movements include the fact that activity in PRR shifts with the eye movement to maintain the correct spatial coding of location [12], the pattern of eye and hand movements is highly stereotyped [56], and PRR activity also carries information about eye position [57].
- Does the fact that the main sensory input to PRR is vision make it versatile for learning brain-control tasks in paralyzed patients? Many forms of paralysis interrupt somatosensory inputs which are a major source of sensory feedback to motor cortex. On the other hand vision usually remains intact and can provide direct feedback signals regarding the performance of brain-control tasks.
- Does the fact that PRR is relatively anatomically removed from the motor and somatosensory pathways that are often damaged in paralysis render it more intact for the control of prosthetics in paralyzed patients?
- Will PRR signals be able to make rapid on-line adjustments of the operation of external devices controlled by the neural prosthetic? A patient with bilateral parietal lesions could not perform such on-line corrections [58], nor could healthy individuals during periods when PPC activity is disrupted by transcranial magnetic stimulation [59]. These results suggest that the PPC is essential for visually-guided, on-line corrections of movement trajectories.

Moreover, LFPs provide a better signal for specifying cognitive state changes than do spikes [22]. Another advantage of LFPs is that they are easier to record and more robust over time than spikes. Engineering advances include the development of algorithms for the automatic advancement of electrodes [46,47]. These algorithms will allow the cognitive-based prosthetic to select specific cell types to enable the best tiling of cognitive spaces and the ability to simultaneously read out substantial numbers of cognitive variables. These algorithms will also facilitate the increased yield, quality, and stability of signals for long term chronic recordings.

The read-out of intended goals is an important component of a cognitive-based prosthetic. Once the goals are determined, supervisory control systems and smart external devices will transform the high-level intentions to the low level computations required to obtain the goals (see Box 2). The decoding of expected value is also important, particularly for 'locked-in' patients who cannot move or speak. These signals can operate much like 'body language' by providing, on-line and in parallel with read-outs of other cognitive variables, the preferences, mood and motivational level of the patient.

This research suggests that a wide variety of cognitive variables can be decoded from patients. For instance, implants in speech areas might provide a direct readout of speech. This direct approach would be preferred to using more cumbersome letter-boards and time-consuming spelling programs. Implants in emotional centers could provide on-line readouts of the patients emotional states. Thus, future applications are likely to involve recordings from many areas to read out a substantial number of cognitive variables. In the future, cognitive-based and motor-based approaches will probably be combined in single prosthetic systems to capitalize on the benefits of both (see also Box 3).

It could be argued that the motor cortex should be the only location for reading out the subject's cognitive variables because many movement areas of cortex converge onto this one area. There are at least two reasons to not depend solely on motor cortex. One is that it produces a bottleneck that will reduce the number of cognitive variables that can be read out at any one time. For instance, one could access a patient's mood by asking him or her to move a cursor on a computer screen to a set of questions. However, this would preclude the motor cortex from performing other tasks at that time. It would be far better to read out this signal simultaneously from an area that directly processes the mood of the subject. The second reason is that the normal functional architecture of motor cortex is for generating commands for movement trajectories. It may be possible that motor cortex could be treated like an undifferentiated neural network and trained to perform any task. However, when neural networks are trained to do a large number of different tasks they tend to do each one poorly compared with being trained to perform

a small number of tasks [48]. What we are proposing instead is to use the intrinsic organization of the nervous system to provide multiple channels of communication and control. By using activity from several different parts of the brain and decoding several cognitive variables, a neural prosthetic can provide a patient with the maximum access to the outside world.

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