OPINION

Principles of neural ensemble physiology underlying the operation of brain–machine interfaces

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Abstract | Research on brain–machine interfaces has been ongoing for at least a decade. During this period, simultaneous recordings of the extracellular electrical activity of hundreds of individual neurons have been used for direct, real-time control of various artificial devices. Brain–machine interfaces have also added greatly to our knowledge of the fundamental physiological principles governing the operation of large neural ensembles. Further understanding of these principles is likely to have a key role in the future development of neuroprosthetics for restoring mobility in severely paralysed patients.

Recent demonstrations of direct, real-time interfaces between living brain tissue and artificial devices, such as computer cursors, robots and mechanical prostheses, have opened new avenues for experimental and clinical investigation[1–13]. Interest in these brain–machine interfaces (BMIs) has been kindled by the contribution that they may make to the treatment or rehabilitation of patients suffering from severe motor disabilities[6,8,9,14–17]. As such, BMIs have rapidly become incorporated into the development of 'neuroprosthetics', devices that use neurophysiological signals from undamaged components of the central or peripheral nervous system to allow patients to regain motor capabilities. Indeed, several findings already point to a bright future for neuroprosthetics in many domains of rehabilitation medicine[6,18–28]. For example, scalp electroencephalography (EEG) signals linked to a computer have provided 'locked-in' patients with a channel of communication[5,19,29–32].

BMI technology, based on multi-electrode single-unit recordings — a technique originally introduced in rodents[33–36] and later demonstrated in non-human primates[1,7,11–13,37–45] — has yet to be transferred to clinical neuroprosthetics. Human trials in which paralysed patients were chronically implanted with cone electrodes[5] or intracortical multi-electrode arrays[46] allowed the direct control of computer cursors. However, these trials also raised a number of issues that need to be addressed before the true clinical worth of invasive BMIs can be realized[6]. These include the reliability, safety and biocompatibility of chronic brain implants and the longevity of chronic recordings, areas that require greater attention if BMIs are to be safely moved into the clinical arena[46–48].

BMIs provide new insights[1,4,6–13] into important questions pertaining to the central issue of information processing by the CNS during the generation of motor behaviours[49–60]. Many recent review articles have covered BMI methods[6,10,25,61,62] and their potential implementation in medical rehabilitation[18–20,22–25,27,28], and so these issues will not be covered here. Instead, we focus on how modern BMI research has led to the proposal, and in some cases validation, of various physiological principles governing the operation of large populations of cortical neurons in behaving mammals (animals performing a given action or movement).

> "…in addition to offering hope for a potential future therapy for the rehabilitation of severely paralysed patients, BMIs can be extremely useful platforms to test various ideas for how populations of neurons encode information in behaving animals."

Neuronal ensemble recordings

Although the first multi-electrode recording experiments in rhesus monkeys date back to the mid 1950s[63,64], the current neurophysiological approach for sampling the extracellular activity of large populations of individual neurons in behaving animals emerged in the early 1980s[65–70]. At that time, most of the systems neuroscience community considered the single neuron to be the key functional unit of the CNS and, therefore, the main target for neurophysiological investigation[71,72]. Not surprisingly, the transition to neural ensemble recordings was slow and difficult. In addition to the enormous technological and technical barriers, few systems neurophysiologists saw any advantage in investing effort and resources into this paradigm shift. As a result, the concept of population coding[73–76], first proposed by Young[77] and further popularized by Hebb[78], played a distant second fiddle to the single-neuron doctrine[71,79–83] for many decades.

Today, the weight of evidence supports the idea that distributed ensembles of neurons define the true physiological unit of the mammalian CNS[73,84–86]. However, this does not mean that neurophysiologists have given up examining the degree to which animal behaviour can be affected by single-neuron activity[87–90]. Significant examples of the importance of single-neuron physiology to BMI research include the demonstration that single neurons can be conditioned to produce particular firing patterns if their activity is presented to primates as sensory feedback[91–94]. In these experiments, the firing of single cells became so well correlated to the desired motor output that primates could use this single-neuron activity to control the movements of a gauge needle[93] or drive a functional electrical stimulator to produce an isometric contraction[94].

During the past 25 years, the introduction of various new electrophysiological[33,36–38,41,43,65–70,95–99] and imaging methods[100–111] has allowed neurophysiologists to measure the concurrent activity of progressively larger samples of single neurons in behaving animals. Interestingly, the emergence of multi-electrode recordings as a new electrophysiological paradigm occurred in parallel with the development of BMIs. As researchers started to implant more than one micro-electrode in the brain, it was proposed that single-neuron recordings from the motor cortex might one day provide the source of signals to drive artificial devices designed to restore mobility in paralysed patients[112]. However, almost two decades went by before the first experiments were conducted to test the hypothesis[54] that highly distributed populations of broadly tuned neurons can sustain the continuous production of motor behaviours in real-time[1,11–13,113].

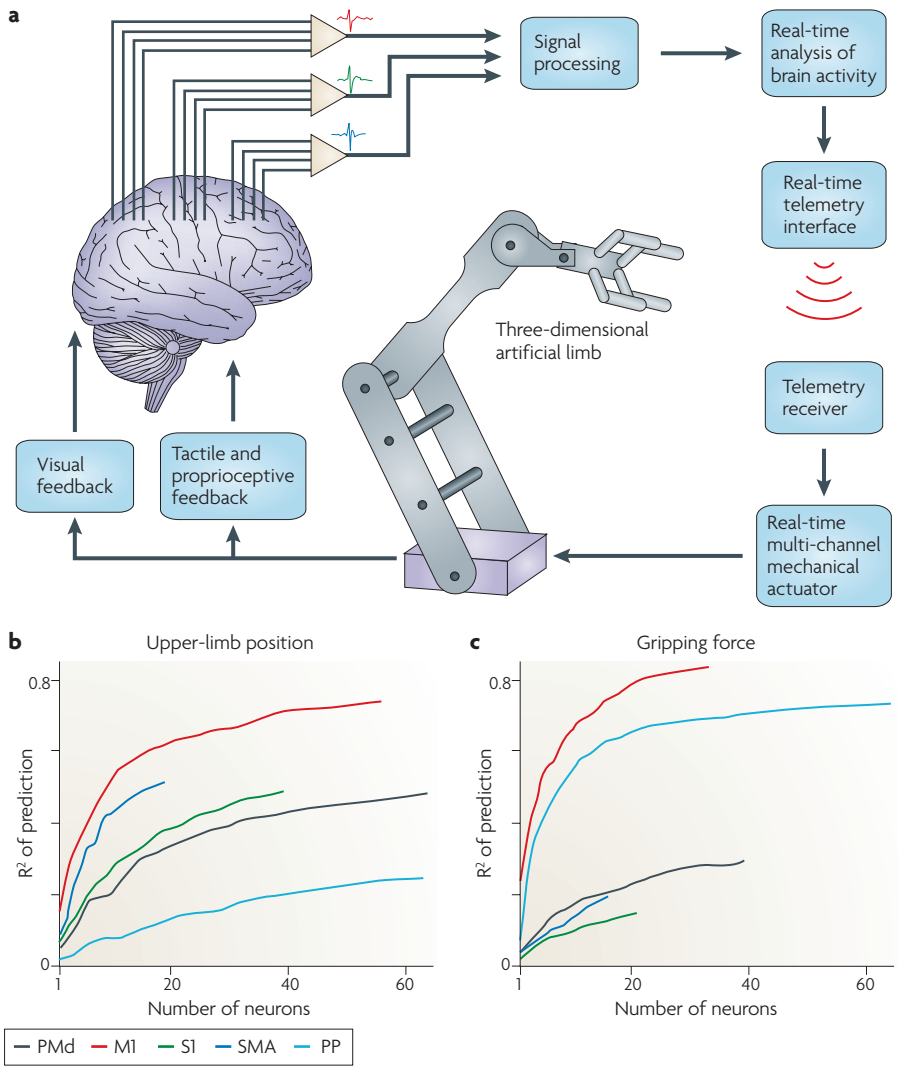

Figure 1 | **Principles of a brain–machine interface. a** | A schematic of a brain–machine interface (BMI) for reaching and grasping. Motor commands are extracted from cortical sensorimotor areas using multi-electrode implants that record neuronal discharges in large ensembles of cortical cells. Signal-processing algorithms convert neuronal spikes into the commands to a robotic manipulator. Wireless telemetry can be used to link the BMI to the manipulator. The subject receives visual and somatosensory feedback from the actuator, possibly through the microstimulation of cortical sensory areas. **b** | Neuronal dropping curves for the prediction of arm movements in rhesus macaques[1] calculated for the ensembles recorded in different cortical areas: the dorsal premotor cortex (PMd), the primary motor cortex (M1), the primary somatosensory cortex (S1), the supplementary motor area (SMA) and the posterior parietal cortex (PP). Neuronal dropping curves describe the accuracy (R^2) of a BMI's performance as a function of the size of the neuronal ensemble used to generate predictions. The best predictions were generated by the M1. Prediction accuracy improved with the increase of neuronal ensemble size. **c** | Predictions of hand gripping force calculated from the activity of the same cortical areas as in part **a**. Image in part **a** is modified, with permission, from REF. 8 © (2001) Macmillan Publishers Ltd. All rights reserved. Images in parts **b** and **c** are reproduced from REF. 1.

FIGURE 1a shows a basic BMI paradigm[8] in which the kinematic and dynamic parameters of upper- or lower-limb movements are predicted (or extracted) in real time from neuronal ensemble activity recorded by micro-electrode brain implants. In this context, the term prediction refers to the use of combined electrical neural ensemble activity to estimate time-varying kinematic and dynamic motor parameters a few hundred milliseconds (typically 100–1,000 ms) in the future. Multiple computational models are used to simultaneously extract various motor parameters (such as arm position and velocity, or hand gripping force) in real time from the extracellular activity of frontal and parietal cortical neurons. Computational models are first trained to predict motor parameters from the modulations of neuronal ensemble activity while animals perform motor tasks (typically reaching or grasping movements) with their own limbs. As the result of this training, the models generate a 'transform function' that matches neuronal activity patterns to particular movements. Next, the mode of operation is switched to 'brain control', in which the time-varying outputs of the computational models control the movements of an artificial device (such as a computer cursor or robot limbs) to reproduce the subject's voluntary motor intentions[6].

A somewhat different approach for model training implemented in invasive BMIs in monkeys[12] and non-invasive BMIs in humans[12,114] is based on a supervised adaptive algorithm that does not require subjects to perform limb movements, but rather adapts the model parameters so that the model output approximates ideal trajectories.

Principles of neural ensemble physiology

The advent of BMI research has advanced the field of multi-electrode recordings. Here we propose a series of principles of neural ensemble physiology (TABLE 1) that have been derived from, or validated by, BMI studies[1,6,7,11–13,42,115–119]. Ultimately, these principles may be used in the development of new neuroprosthetic devices (BOX 1).

The distributed-coding principle. Multi-electrode studies in New World[13,117,118] and Old World monkeys[1,42], rats and mice[86,120–122] consistently support the idea

that information about single motor parameters is processed within multiple cortical areas. BMI studies[1,42] have also revealed that real-time predictions of motor parameters can be obtained from multiple frontal and parietal cortical areas. This widespread representation of motor parameters defines the distributed-coding principle[73,84–86].

The analysis of neuron-dropping curves (NDCs) illustrates this principle well. NDCs depict a BMI's prediction accuracy as a function of the number of neurons recorded simultaneously during a given experimental session. NDCs are computed by first measuring the entire neuronal population's performance and then repeating the calculation after randomly chosen individual neurons are removed (dropped) from the original sample. In essence, NDCs measure the size of neuronal ensembles needed for a given BMI algorithm to achieve a certain level of performance. FIGURE 1b,c shows a series of NDCs that describe the contribution made by populations of neurons, located in different cortical areas, to the simultaneous prediction of multiple time-varying motor parameters during operation of a BMI by a rhesus monkey. This figure shows how the predictions of two such parameters — hand position (FIG. 1b) and gripping force[123] (FIG. 1c) — vary as a function of the size of the recorded neuronal population[1].

A widely distributed representation of each motor parameter does not necessarily mean that equally sized neuronal samples obtained from each of these cortical areas should yield similar levels of predictions[1] (FIG. 1b,c). For instance, in the example shown in FIG. 1, the prediction of hand position was, on average, better when randomly sampled populations of M1 neurons were used than when similar samples of posterior parietal cortex (PP) neurons were used. Moreover, the difference in prediction performance was much smaller between these two cortical areas when gripping force was used as the predicted parameter. However, NDC extrapolation to larger samples[13] indicates that, if a sufficiently large sample of PP neurons could be obtained, neural ensembles from the PP could eventually accurately predict both hand position and gripping force. Although the representation of motor parameters is distributed in the cortex, cortical areas nonetheless show a clear degree of specialization (but not in an absolute or strict sense). Additionally, modulations in neuronal activity in different cortical areas that seem to be similar (for example, increases in activity during rightward movements) may underlie different functions in the cortical motor programme transmitted to the spinal cord.

The observation of distributed representations of motor parameters obtained in BMI studies corresponds well with the proposition from previous neurophysiological research that brain areas represent information in a holographic manner, and that searching for explicit coding (of force, limb displacement or behavioural context) may be futile[124].

The single-neuron insufficiency principle. BMI studies have also revealed that, no matter how well tuned a cell is to the behavioural task in question, the firing rate of individual neurons usually carries only a limited amount of information about a given motor parameter[1,13,42]. Moreover, the contribution of individual neurons to the encoding of a given motor parameter tends to vary significantly from minute to minute[125]. Reliably predicting a motor variable, and achieving accurate and consistent operation of a BMI for long periods of time, therefore requires simultaneous recording from many neurons, and combining their collective ensemble firing[118]. Incidentally, the same single-neuron limitations have been observed in the rat somatosensory[126–128] and gustatory systems[86,129,130], and in the corticostriatal system of wild-type and transgenic mice[121]. We have called this principle the single-neuron insufficiency principle.

The insufficiency of single-neuron firing to precisely reproduce a given behavioural output has long been appreciated in studies in which averaging of neuronal activity over many trials was required to quantify a given neuron's behavioural function[131,132]. This analytical strategy is typically used when animals have attained a highly stereotyped behavioural performance, after being overtrained in a given task. Despite this caveat, single neurons have often been attributed very specific functions, and their inherent noisiness — clearly verified when single trials are analysed independently — has been disregarded[132]. In such studies, peri-event time histograms and directional tuning curves have emphasized a consistent relationship between the modulations of the firing rate of a single cell and behavioural parameters. As the attention of neurophysiological investigations started to shift towards ensemble recordings, neuronal variability, as opposed to consistency, came into focus, and neurophysiologists started to realize that modulations in neuronal firing are usually highly transient and plastic[86,133–137]. This led researchers to question the classic assertion that behavioural parameters are encoded only by the modulation of the firing rate of individual cells, and to the realization that the precise timing and correlations of neural ensemble firing should be taken more seriously[65–67,138]. Usually, in BMIs based on recordings from large neuronal populations, single-neuron noisiness is removed by ensemble averaging. In other words, as the population recorded becomes larger, variability in single-neuron firing declines in importance.

A recent study[139] documented significant single-neuron tuning stability over recording sessions that lasted several hours while monkeys performed a reaching task. Although this result initially seemed to contradict the earlier claim that there is single-neuron discharge variability[125], these two points of view proved to be consistent. The study demonstrating tuning stability focused on

Table 1 | **Principles of neural ensemble physiology**

Principle	Explanation
Distributed coding	The representation of any behavioural parameter is distributed across many brain areas
Single-neuron insufficiency	Single neurons are limited in encoding a given parameter
Multitasking	A single neuron is informative of several behavioural parameters
Mass effect principle	A certain number of neurons in a population is needed for their information capacity to stabilize at a sufficiently high value
Degeneracy principle	The same behaviour can be produced by different neuronal assemblies
Plasticity	Neural ensemble function is crucially dependent on the capacity to plastically adapt to new behavioural tasks
Conservation of firing	The overall firing rates of an ensemble stay constant during the learning of a task
Context principle	The sensory responses of neural ensembles change according to the context of the stimulus

Box 1 | **From ensemble principles to neuroprosthetic development**

Ultimately, we expect that the identification of principles of neural ensemble physiology will guide the development of a generation of cortical neuroprosthetic devices that can restore full-body mobility in patients suffering from devastating levels of paralysis, due either to traumatic or degenerative lesions of the nervous system. We believe that such devices should incorporate several key design features. First, brain-derived signals should be obtained from multi-electrode arrays implanted in the upper- and lower-limb representations of the cortex, preferably in multiple cortical areas. Custom-designed microchips (also known as neurochips), chronically implanted in the skull, would be used for neural signal-processing tasks. To significantly reduce the risk of infection and damage to the cortex, multi-channel wireless technology would transmit neural signals to a small, wearable processing unit. Such a unit would run multiple real-time computational models designed to optimize the real-time prediction of motor parameters. Time-varying, kinematic and dynamic digital motor signals would be used to continuously control actuators distributed across the joints of a wearable, whole-body, robotic exoskeleton. High-order brain-derived motor commands would then interact with the controllers of local actuators and sensors distributed across the exoskeleton. Such interplay between brain-derived and robotic control signals, known as shared brain–machine control[192], would assure both voluntary control and stability of bipedal walking of a patient supported by the exoskeleton.

Touch, position, stretch and force sensors, distributed throughout the exoskeleton, would generate a continuous stream of artificial touch and proprioceptive feedback signals to inform the patient's brain of the neuroprosthetic performance. Such signals would be delivered by multichannel cortical microstimulation directly into the patient's somatosensory areas. Our prediction is that, after a few weeks, such a continuous stream of somatosensory feedback signals, combined with vision, would allow patients to incorporate, through a process of experience-dependent cortical plasticity, the whole exoskeleton as an extension of their body.

These developments are likely to converge into the first reliable, safe and clinically useful cortical neuroprosthetic. To accelerate this process and make this milestone a clinical reality, a worldwide team of neurophysiologists, computer scientists, engineers, roboticists, neurologists and neurosurgeons has been assembled to launch the Walk Again Project, a non-profit, global initiative aimed at building the first cortical neuroprosthetic capable of restoring full-body mobility in severely paralysed patients.

mean firing characteristics, obtained by averaging hundreds of behavioural trials, to extract the preferred movement direction of single neurons. However, this study clearly showed that the firing rate of a single M1 neuron varied significantly from trial to trial (15–35 spikes per second). Only by averaging many trials were those authors able to obtain smooth directional tuning curves. The earlier study[125] examined a large population of individual neurons and focused on shorter behavioural epochs, during which they observed considerable variability. The difference between these studies therefore resides mainly in the temporal scale and the analytical procedure used to estimate short-term versus long-term changes in neuronal tuning properties.

In any neuronal population sample there are cells that are better tuned to a given motor parameter of interest. Such neurons are usually called task-related cells[140,141]. However, even these cells show significant variability in their discharges and need to be combined to produce accurate predictions of motor parameters[142].

Although single cells are generally insufficient for obtaining accurate BMI predictions, the performance of a single-cell BMI has been shown to improve with training[94]. Indeed, in our own studies using large neural ensembles to drive BMIs, we observed that both the firing patterns of individual cells and the correlation between cells underwent plastic changes that improved BMI accuracy[1,42,119].

The neuronal multitasking principle. BMI experiments also indicate that individual neurons, located in each of the cortical areas sampled, can participate in the encoding of more than one parameter at a given moment in time[1]. In other words, although individual cortical neurons might be better tuned to a given motor parameter, they can still contribute simultaneously to multiple, transient functional neural assemblies and therefore encode several motor parameters at once[78]. Here we name this the multitasking principle.

The multitasking principle, described here for BMI studies, is similar to the multimodal interactions observed previously in sensory and associational cortical areas[143–152]. However, as most of the BMI literature deals with the motor system, we prefer to use the term 'multitasking'. In our notation, a multitasking BMI controls several motor parameters simultaneously, for example several degrees of freedom of a multi-joint actuator.

BMI experiments in which monkeys used cortical activity to control the reaching and grasping movements of a robotic manipulator revealed that the firing of single cortical neurons was typically correlated to several motor variables, such as the manipulator position coordinates and its gripping force[1]. Recent experiments that aimed to use the combined activity of primate cortical neurons to reproduce patterns of bipedal locomotion[153] revealed that the firing of single neurons could contribute to the prediction of several motor variables related to leg movements[154–156], including the timing of movement onset, as previously observed for hand movements[116].

The neuronal mass principle. Further analysis of the NDCs shown in FIG. 1b,c shows that parametric reductions in the size of the neuronal population initially produce a minor reduction in overall prediction performance for each motor parameter in each of the sampled cortical areas[1,13,42]. However, below a certain critical population size the accuracy of the predictions starts to fall more rapidly and, at a certain level (fewer than ~10–20 neurons), becomes poor[1,13]. This suggests that BMIs based on recording the activity of just a few neurons are likely to perform poorly. According to the single-neuron insufficiency principle, predictive performance should increase continuously as a function of the growth in neural ensemble size. However, NDCs revealed that when the number of neurons used went above a certain population size (tens of neurons), the amount of predictive information obtained tended to remain virtually constant, regardless of the identity of the individual neurons sampled. This result is attributable to a significant decrease in the variance of NDCs for sufficiently large neuronal samples[116].

In other words, once a certain critical neuronal mass had been achieved, different, and sufficiently large, random samples of single neurons from a given cortical area (from different layers or different subregions) tended to yield similar levels of predictive information about a given motor parameter[1,42]. These results led us to propose the neuronal mass effect principle, which states that to achieve a sufficiently accurate and stable prediction of a given motor parameter, a neural ensemble has to recruit a crucial number of neurons at each moment in time. The neuronal mass needed to achieve stability depends on several factors, including the presence of highly tuned neurons in the population[116,142]. If these are missing, predictions gradually improve with neuronal sample size,

and the noise in the combined population activity is proportional to the square root of the number of neurons. The critical neuronal mass is also highly dependent on neuronal correlations, which limit the information that the population can contain[157,158]. Correlation makes neuronal encoding redundant. As a consequence, beyond a certain size the information represented by a neuronal population increases only marginally with the addition of new cells.

The minimal size of a neuronal sample needed to effectively control a BMI has become a controversial issue (for contrasting opinions, compare REFS 7,11,12 with REFS 1,6,9,13,42,116). On the basis of demonstrations that involved stereotypical and relatively simple upper-limb movements, several groups have argued that BMIs intended to restore upper-limb mobility could operate using small neuronal samples (<30 neurons)[7,11,12,159]. Despite this emphasis on the role of small neuronal samples, and results showing improvement in accuracy of small-sample BMIs with training[94], practical BMIs might not perform sufficiently well using signals from only a few neurons, for various reasons. For instance, it is unclear from the studies that used this approach whether small-sample BMIs can sustain the same level of performance over long periods of time[11,12,160]. Current recording techniques may not allow the sampling of high numbers of highly tuned neurons, or provide the kind of stability needed for such small-sample BMIs to remain effective for many months, let alone for many years. Additionally, small-sample BMIs may not be able to generalize their function to cope with newer or more complex behavioural tasks[153]. We therefore feel that it is likely that such an increase in behavioural demand will be met by only large neuronal populations. Evidence obtained in our laboratory indicates that this is precisely the case for BMIs aimed at reproducing both upper- and lower-limb movements[1,153].

The neural degeneracy principle. BMI studies also revealed that a single motor output is often associated with distinct spatiotemporal patterns of neural ensemble firing on the millisecond scale[118,161–164]. Following the nomenclature introduced by Reeke and Edelman[165], this principle, which states that identical behavioural outputs can be produced by distinct functional and transient neural ensembles, has been named the degeneracy principle.

Neural degeneracy is similar to neural redundancy in that different combinations of single neurons belonging to a neural circuit can produce different spatiotemporal firing patterns that end up encoding the same motor outputs[166]. Degenerate coding has been demonstrated in several neural circuits, including the pyloric network of the lobster, the song control system of the zebra finch and the order-encoding system of the locust[164], where it serves to represent low-dimensional information by a high-dimensional neural network in a fault-tolerant way.

BMIs based on neuronal ensemble recordings solve a similar problem: they map the activity of several hundred neurons onto the lower number of degrees of freedom of an artificial actuator. In these experiments, we have observed that similar movements, produced either by the animal's arm or by an artificial actuator, can result from distinct spatiotemporal patterns of neuronal population activity[125]. Therefore, if a sufficiently large population of neurons is recorded simultaneously, movements induced by a BMI can be reliably produced in each behavioural trial. Similarly, we observed that stereotypical steps in bipedally walking monkeys were associated with different patterns of motor cortex activations[153]. It follows from these considerations that the basic proportion between the recorded ensemble size and the number of controlled degrees of freedom should be preserved for BMI applications that require the production of complex motor behaviours in artificial actuators.

The plasticity principle. Experience-dependent plasticity in cortical neural ensembles[167,168] is essential for primates to learn to operate a BMI. As mentioned above, the strength of a single-neuron correlation to a given motor parameter is typically imprecise, varying as a function of time, internal state and learning, as well as the animal's expectation of the task outcome and reward[118,125,169]. Several studies have now documented the occurrence of cortical plasticity as animals learn to operate a BMI[1,12,42]. This phenomenon is characterized by changes in the tuning properties of individual neurons[12,42] and physiological adaptations at the level of neural ensembles, which include changes in firing covariance and spike timing[1]. Such changes in neuronal properties are undoubtedly related to basic plasticity mechanisms, such as changes in the strength of synaptic connections and gene expression. However, in BMI experiments such basic mechanisms are difficult to isolate from the population effects. For example, increases in the firing activity of a given neuron can result from multiple factors, such as changes in synaptic strength, increases in excitatory inputs or release of inhibition. Combinations of such factors manifest themselves as changes in neuronal tuning (the correlation of cell firing with a given motor parameter). In BMI studies, similar measurements of neuronal tuning are provided by the weights that prediction models assign to different neurons[142] and time-dependent correlations of neuronal rates with kinematic parameters[42].

As a rule, neuronal tuning tends to be modified and refined as a result of operant conditioning[93,94,161,170–179]. In BMI studies, cortical plasticity manifests itself in a series of physiological adaptations. For instance, during the transition from manual to brain control of a BMI[1,42] (when animals ceased to use their own limbs and started to control an actuator using their cortical activity directly), a significant portion of the recorded neurons, which were distributed across multiple cortical areas, progressively acquired tuning properties related to the kinematic properties of the robotic device used (FIG. 2). As a result, a fraction of these cortical neurons showed tuning to the kinematic properties of both the animal's biological arms and the robotic arm (FIG. 2a). Conversely, a subset of the recorded cortical neurons ceased to fire, or to show velocity or direction tuning, when animals stopped producing arm movements and controlled a robotic device without any overt motor behaviour[1,42] (FIG. 2b). Perhaps more surprisingly, a fraction of the recorded cortical neurons showed clear velocity and direction tuning that was related to the movements of the robotic prosthesis but not to the displacement of the animal's own arms[1,42] (FIG. 2c). Such tuning developed and became sharper during the period in which monkeys learned to operate the BMI without execution of overt body movements (brain control mode). The emergence of such tuning may explain why monkeys were able to control both robotic arms and legs using BMIs without generating corresponding body movements.

Besides changes in single-neuron tuning properties, a significant increase in firing covariance between pairs of neurons, located within and between multiple cortical areas, has also been observed when animals started operating a BMI without moving their own limbs[1] (FIG. 2d). As animals shifted back and forth between using their own limbs or the artificial actuator controlled by the BMI to solve a particular motor task, functional coupling between pairs of cortical neurons adapted dynamically. Interestingly, this

increase in neuronal pair covariance was observed not only within a given cortical area, but also between neurons located in distinct cortical fields[1].

The observation of such a broad repertoire of functional cortical adaptations during the operation of BMIs supports many far-reaching conclusions. First, they suggest that Old World monkeys may be capable of 'motor imagery'[180–183]: to imagine, in great detail, a series of complex motor sequences without necessarily producing body movements to execute such motor plans. Second, they imply that, at its limit, cortical plasticity may allow artificial tools to be incorporated as part of the multiple functional representations of the body that exist in the mammalian brain. If this proves

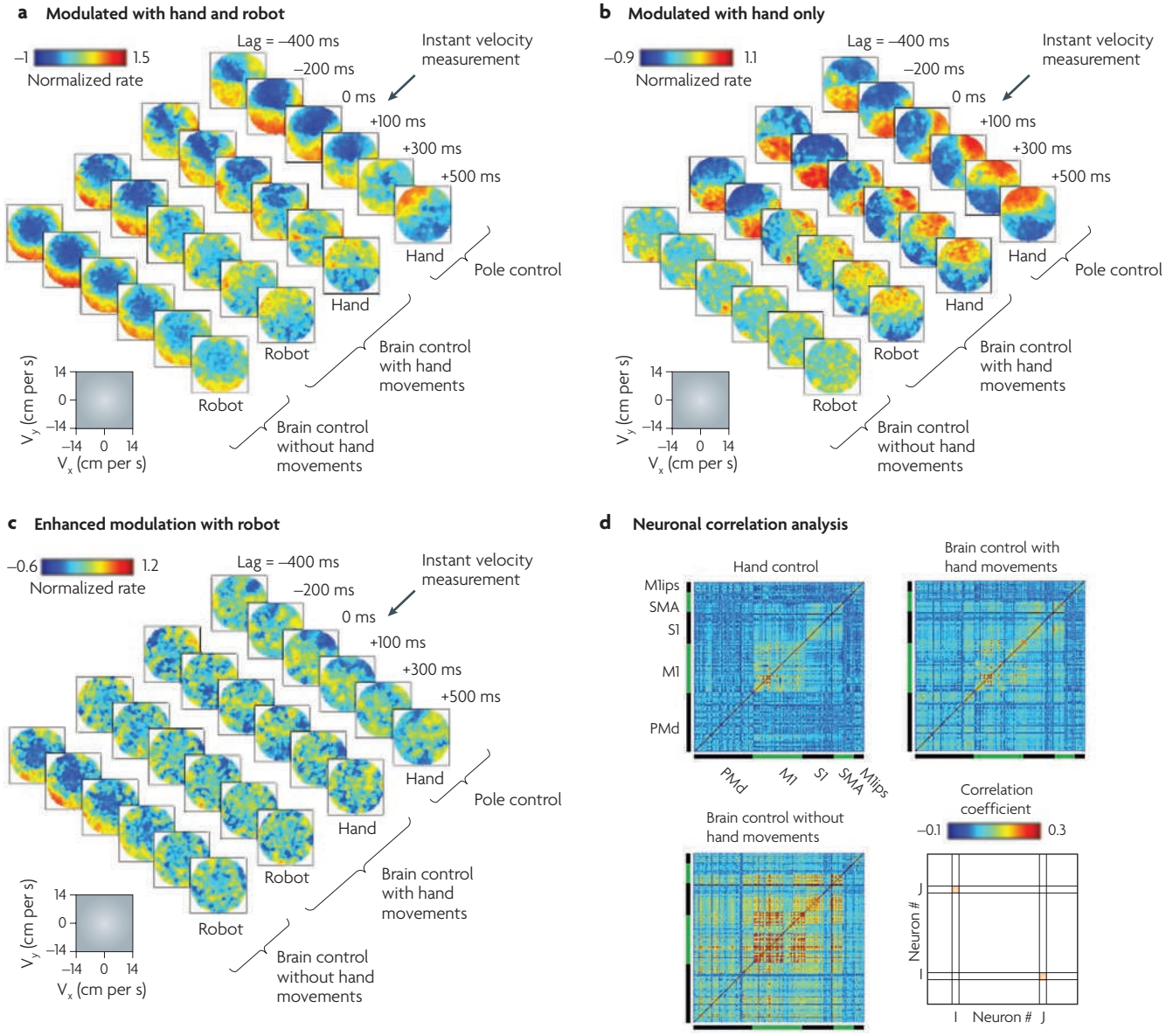

Figure 2 | **Neuronal activity during a reaching task.** The task illustrated was performed by a rhesus macaque that controlled a robotic actuator using a hand control or through a brain–machine interface (BMI; brain control). During BMI operation, the monkey either continued to move the pole with the hand (brain control with hand movements) or stopped moving its hand (brain control without hand movements). **a** | Activity of a primary motor cortex (M1) neuron during both pole and brain control. Colour-coded diagrams represent neuronal tuning to movement velocity (that is, the average neuronal rate as a function of hand or robot velocity), calculated at different lags (–400 ms to +500 ms) with respect to the time of velocity measurement. The diagrams labelled 'Hand' represent neuronal tuning to hand movements, and the diagrams labelled 'Robot' represent tuning to robot movements. During brain control without hand movements, this neuron became less tuned to hand movements (row of colour diagrams labelled 'Brain control with hand movements: hand'). Tuning to robot movements was maximal during brain control without hand movements (row labelled 'Brain control without hand movements: robot'). **b** | An M1 neuron modulated only when the monkey moved its hand. **c** | An M1 neuron that was not modulated during hand movements, but became tuned to the robot movements during brain control without hand movements. **d** | Analysis of pairwise correlations in firing between the neurons in the recorded ensemble, using data from REF. 1. Correlations increased during brain control, especially brain control without hand movements. The highest correlations were between the neurons recorded in the same cortical area. M1ips, primary motor cortex, hemisphere ipsilateral to the working hand; PMd, dorsal premotor cortex; S1, primary somatosensory cortex; SMA, supplementary motor area. Images in parts **a**–**c** are modified, with permission, from REF. 42 © (2005) Society for Neuroscience.

to be true, we would predict that continuous use of a BMI should induce subjects to perceive artificial prosthetic devices, such as prosthetic arms and legs, controlled by a BMI as part of their own bodies. Such a prediction opens the intriguing possibility that the representation of self does not necessarily end at the limit of the body surface, but can be extended to incorporate artificial tools under the control of the subject's brain. BMI research further stretches this puzzling idea by demonstrating that, once brain activity is recorded and decoded efficiently in real time, its capacity to control artificial devices can undergo considerable modification in terms of temporal, spatial, kinematic and kinetic characteristics, termed scaling[1,12]. In other words, not only can a BMI enact voluntary motor outputs faster than the subject's biological apparatus (temporal scaling), but it can also accomplish motor tasks at a distance from the subject's own body (spatial scaling), by controlling an actuator that is either considerably smaller (for example, a nano-tool) or considerably larger (for example, a crane) than the subject's own biological appendices.

Recently, another powerful way to induce cortical plasticity has been introduced to BMI research: multichannel, cortical microstimulation[115,184]. FIGURE 3 shows some of the findings obtained when chronic multichannel microstimulation of the primary somatosensory cortex was used to instruct owl monkeys on how to locate food rewards. During several months of microstimulation sessions, these monkeys progressively learned to detect the presence or absence of microstimulation, and to discriminate different temporal patterns of microstimulation pulses that indicated food location[115]. Moreover, the animals also learned new behavioural contingencies after changes were made in the direction of arm reach instructed by microstimulation. Interestingly, monkeys required less time to master a new set of rules as training progressed and new task contingencies were introduced, which allowed them more practice in handling microstimulation cues (FIG. 3b,c). So after being exposed to an original basic rule, monkeys learned a reversed task much more rapidly and, subsequently, more elaborate contingencies as well[115]. Although the basic mechanism involved in such 'rule generalization' was not uncovered, these results confirm the hypothesis that functional plasticity of cortical tissue can be induced by intracortical microstimulation[184]. This raises the question of whether chronic cortical microstimulation can trigger a process of functional adaptation that leads to the emergence of realistic perceptual experiences. Although there is no definitive answer to this question, it is interesting to note that people who were exposed to chronic patterned cutaneous stimulation, as an artificial replacement strategy for vision, learned to use such artificial sensory input to guide their movements and reported the development of qualitatively new perceptions[185,186]. Confirmation of new perceptual experiences after prolonged training with microstimulation would certainly be of considerable relevance for the design of future neuroprosthetic devices that aim to restore upper- and lower-limb mobility in severely paralysed patients.

With that long-term vision in mind, we have recently started to develop a new paradigm, named brain–machine–brain interface (FIG. 4), that will enable us to test whether monkeys can use neural ensemble activity to control the movements of artificial devices guided by instructions delivered directly to their somatosensory cortices by multichannel microstimulation.

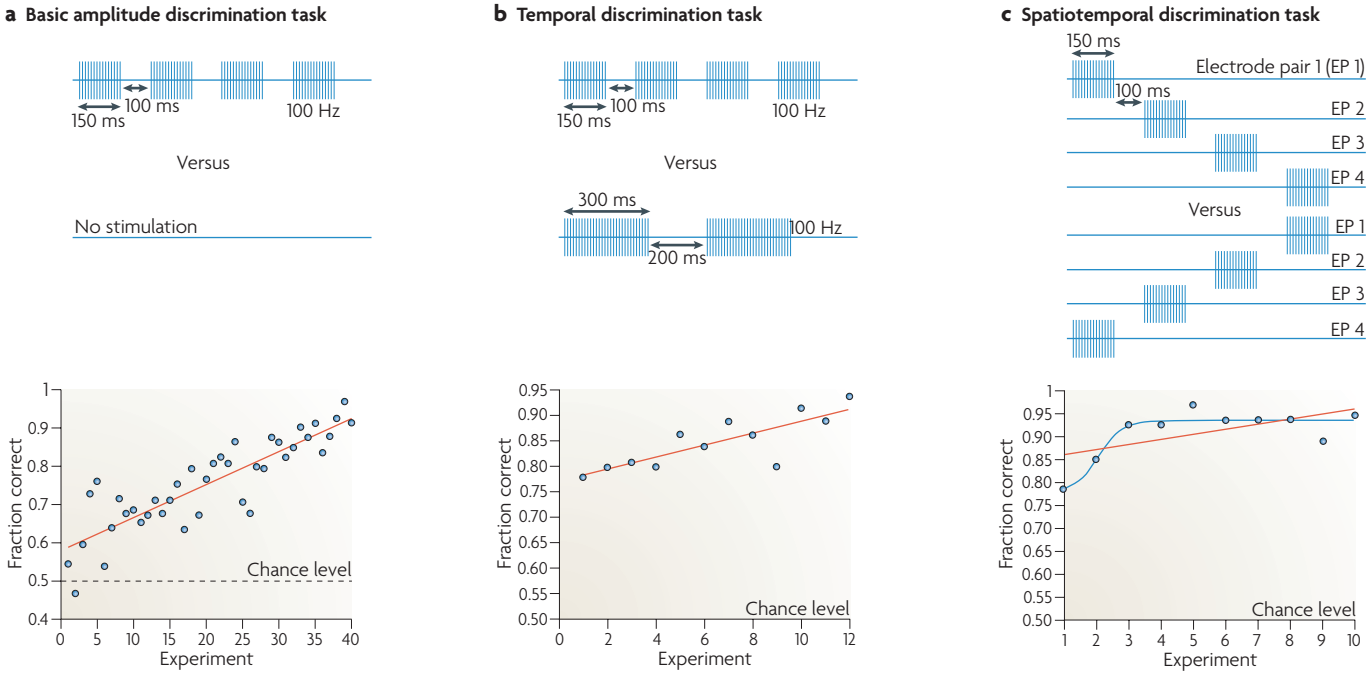

Figure 3 | **Discrimination of spatiotemporal microstimulation patterns by owl monkeys.** Microstimulation trains were delivered to the primary somatosensory cortex through chronically implanted multi-electrode arrays. The monkeys responded to microstimulation or its absence by selecting the target of reaching movements. Top panels illustrate microstimulation patterns; bottom panels show discrimination accuracy as the function of training day. **a** | A basic task in which the monkeys detected the presence or absence of microstimulation. The monkeys learned the task in 1 month. **b** | Discrimination of temporal patterns of microstimulation. The monkeys learned the task in 1 week. **c** | A spatiotemporal discrimination task during which waves of microstimulation were delivered through the electrode arrays. The monkeys learned the task in 3 days, and could then discriminate spatiotemporal patterns of cortical microstimulation. Moreover, after prolonged training with microstimulation they learned to interpret new microstimulation patterns faster. Figure is reproduced, with permission, from REF. 115 © (2007) Society for Neuroscience.

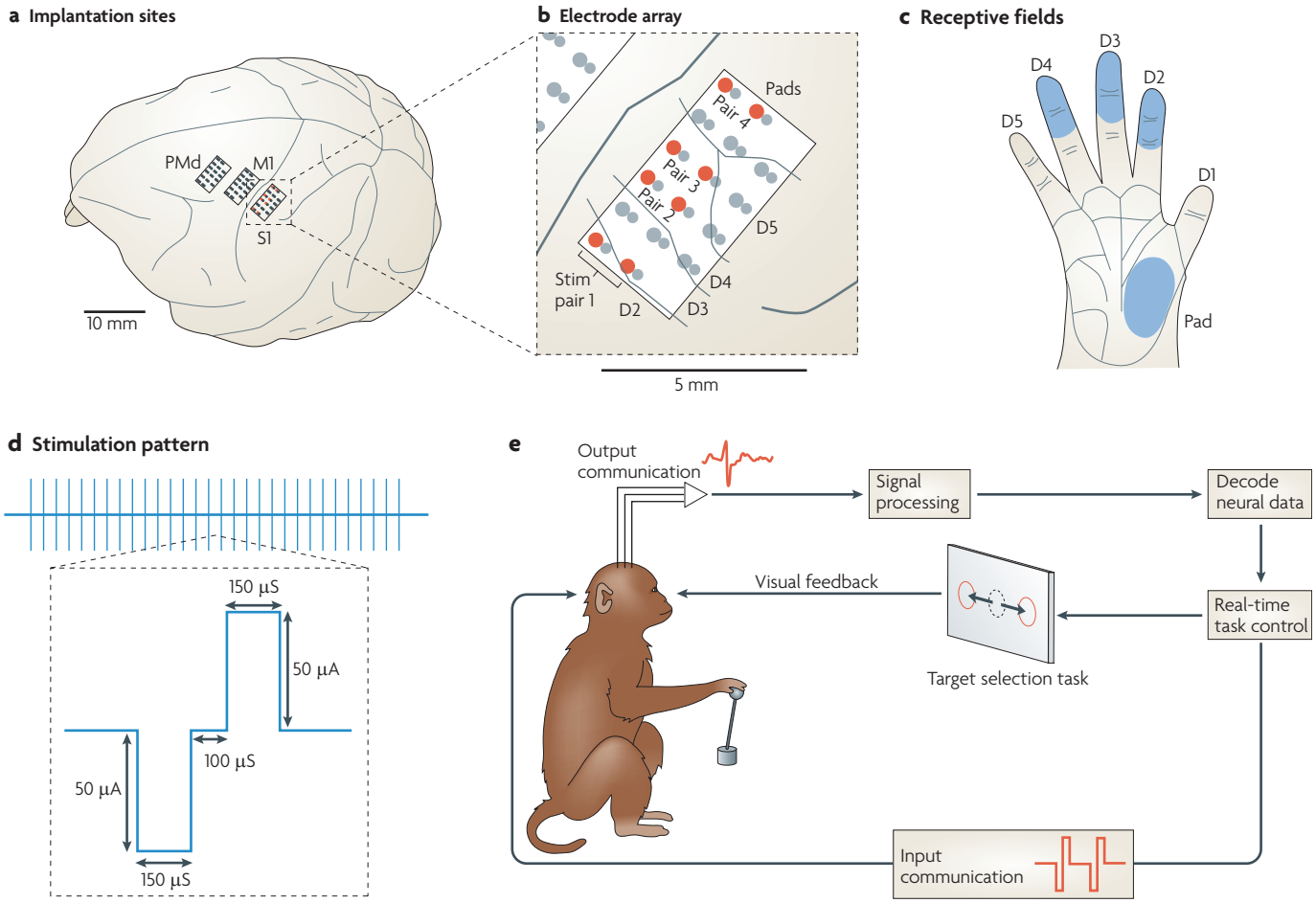

Figure 4 | **The concept of a brain–machine–brain (BMBI) interface with artificial sensory feedback.** In one possible implementation, depending on the presence or absence of microstimulation the monkeys perform brain–machine interface (BMI)-controlled reaching movements in different directions (right or left). Initially the monkeys acquire visual targets using a screen cursor moved by a hand-held joystick, and the directional instruction is delivered by mechanical vibration of the joystick handle. Manual control is then replaced by BMI control of cursor movements, and vibration is replaced by cortical microstimulation. **a** | Examples of possible sites of cortical implantation. Multi-electrode arrays are placed in the dorsal premotor cortex (PMd), the primary motor cortex (M1) and the primary somatosensory cortex (S1). PMd and M1 arrays are used to extract motor commands, and the S1 is the site of microstimulation. **b** | Examples of possible locations of S1 electrodes with respect to a somatotopic map determined using receptive field measurements. The multi-electrode array covers the representation of digits D2–D5 and of the hand pads. **c** | Receptive fields of the electrodes through which microstimulation is delivered. **d** | Parameters of microstimulation train (top) and microstimulation pulses. **e** | Schematic of the experiment, as described above.

The conservation of firing principle. Despite documenting clear and widespread changes in the single-neuron firing rate related to plastic modifications in neuronal velocity and duration tuning, and increases in firing covariance between pairs of cortical neurons, we have also observed that the global firing rate (total number of spikes) of the cortical neural ensembles recorded in our experiments usually remained unchanged as animals learned to operate a BMI[1]. This principle of neural ensemble firing conservation has also been observed in various other studies — including experiments conducted in New World monkeys, rats and mice — involving distinct cortical areas and various motor and sensory tasks[95,120–122,187–190]. These studies indicate that maintaining the total number of spikes for a range of behaviours could be a pervasive, homeostatis-like mechanism of cortical ensembles.

The context principle. Multi-electrode recordings in freely behaving animals have also opened new ways to examine a fundamental question in classic neurophysiology: how neurons respond to sensory stimuli that are applied passively or acquired actively by subjects. A study in behaving rats trained to perform a tactile discrimination task using only their facial whiskers addressed this issue directly[169]. This study revealed that neuronal modulations evoked by passively versus actively acquired tactile stimulation were strikingly different in their magnitude, adaptation rate and percentage of excitatory versus inhibitory sensory evoked responses in the primary somatosensory cortex (FIG. 5). A similar result has since been described in the rat primary gustatory cortex[191] and in the auditory cortex of marmosets[39].

Such marked neurophysiological differences indicate that the context in which animals sample their surrounding environment can radically alter the way cortical neural ensembles respond to incoming sensory information. Therefore, we named this principle the context principle.

Conclusions

The principles of neural ensemble physiology described above were either derived from, or confirmed by, a decade of BMI experiments. This demonstrates that, in

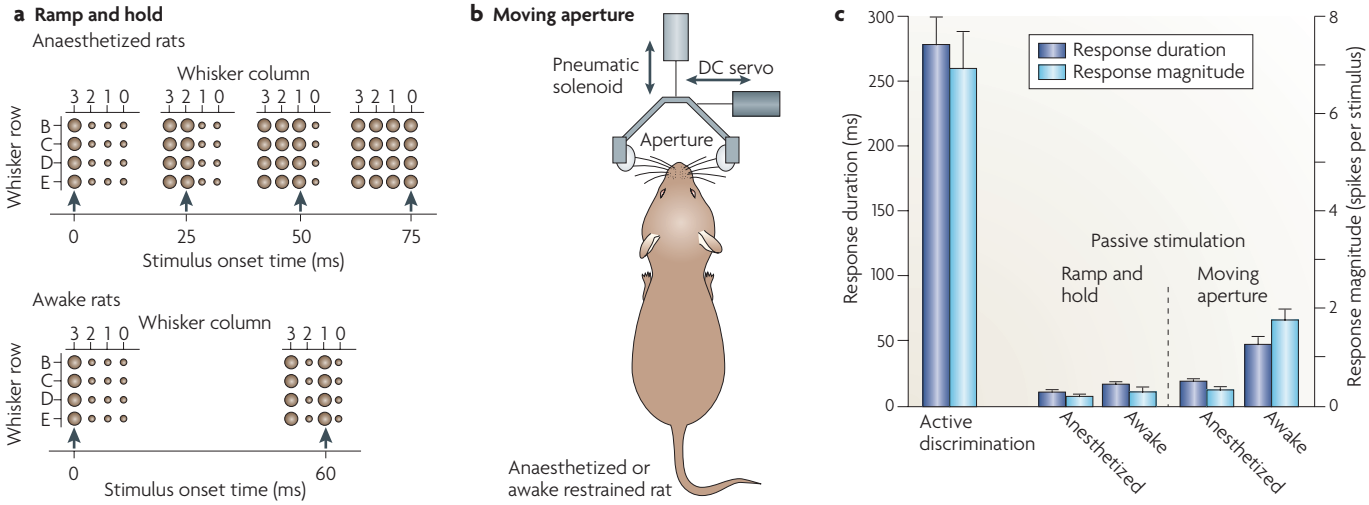

Figure 5 | **Neuronal responses in rat somatosensory cortex to passively applied stimuli versus active discrimination of the same stimuli.** **a** | Schematics illustrating the whiskers stimulated (arranged in rows and columns) and the stimulus timing. Multi-whisker ramp-and-hold stimuli were delivered to anaesthetized (top) or awake restrained (bottom) rats. Large circles represent stimulation of a particular whisker. Arrows show stimulation onsets. **b** | Schematic of stimulus delivery. The aperture was accelerated across the facial whiskers by the pneumatic solenoid and also simultaneously deflected laterally in varying amounts by the direct-current servo to accurately replicate the range of whisker deflection dynamics that occurred during active discrimination. **c** | Mean duration and magnitude of the responses evoked during active discrimination and during delivery of passive stimuli to anaesthetized or awake restrained rats. These results indicated that neuronal responses evoked in the primary somatosensory cortex by passively applied stimuli were strikingly different from those evoked by actively acquired tactile stimulation. Figure is reproduced, with permission, from REF. 169 © (2004) American Association for the Advancement of Science.

addition to offering hope for a potential future therapy for the rehabilitation of severely paralysed patients, BMIs can be extremely useful platforms to test various ideas for how populations of neurons encode information in behaving animals. Together with other methods, research on BMIs has contributed to the growing consensus that distributed neural ensembles, rather than the single neuron, constitute the true functional unit of the CNS responsible for the production of a wide behavioural repertoire.

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FURTHER INFORMATION
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Walk Again Project: http://www.walkagainproject.org
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