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Preserved cortical somatotopic and motor representations in tetraplegic humans

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Abstract

A rich literature has documented changes in cortical representations of the body in somatosensory and motor cortex. Recent clinical studies of brain–machine interfaces designed to assist paralyzed patients have afforded the opportunity to record from and stimulate human somatosensory, motor, and action-related areas of the posterior parietal cortex. These studies show considerable preserved structure in the cortical somato-motor system. Motor cortex can immediately control assistive devices, stimulation of somatosensory cortex produces sensations in an orderly somatotopic map, and the posterior parietal cortex shows a high-dimensional representation of cognitive action variables. These results are strikingly similar to what would be expected in a healthy subject, demonstrating considerable stability of adult cortex even after severe injury and despite potential plasticity-induced new activations within the same region of cortex. Clinically, these results emphasize the importance of targeting cortical areas for BMI control signals that are consistent with their normal functional role.

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Introduction

How plastic is the adult cortex? Knowing the degree of plasticity is paramount for recovery from strokes and other neurological injuries that involve cortical motor areas. This topic is the subject of many animal studies [1,2], though missing neurophysiology evidence in humans may be critical. In ascending the phylogenetic tree, motor behavior has shown encephalization, with increasing direct cortical control of movement [3–5]. A rat with a motor cortex lesion does not lose the ability to execute movements but rather has trouble learning new motor behaviors [6]. On the other hand, a human with a stroke to motor cortex will exhibit some early recovery, with evidence for neuroplasticity but often has severe and lasting paralysis in proportion to damage, especially to the corticospinal tract [7–11]. Likewise, strokes to primary sensory areas produce disturbances of somatic sensation [12].

Interestingly, new insights are beginning to emerge with the advent of invasive brain–machine interfaces (BMIs) [13–19]. These studies are typically done in humans with cervical spinal cord injuries that produce tetraplegia; the paralysis of all four limbs. Likewise, the major somatosensory pathways are severed, leaving the participants without feelings of touch or body position below the level of the injury. Participation in clinical studies typically starts several years after injury, thus providing a novel window into cortical behavior following long-standing and severe injury.

The cortical implants for these studies are typically small arrays of microelectrodes, with 96 recording electrodes on a chip measuring 4 × 4 mm [16,20]. The implants record neural population activity and thus can determine the functional properties of small patches of the cortex and, by extension, the circuits associated with these cortical patches. Recent electrode designs allow microstimulation through the same electrodes, enabling bidirectional BMIs [21–24]. These recording and stimulating capabilities can be used to assess functional structure and learning within cortical circuits that are directly impacted by severe injury.

Organization of healthy cortex

Studies on laboratory animals and humans suggest the cerebral cortex is differentiated into many regions of functional specialization. Early anatomical studies divided the cortex based on cytoarchitectonic distinctions of cell body type, cortical layers, and cell density. Subsequent studies adding more indicators, including mylearchitecture and functional magnetic resonance imaging, have proposed maps of 180 distinct regions

[25]. At the same time, any percept or behavior will activate many cortical areas: monkey studies have shown that eye position signals can be found throughout the cortex of non-human primates [26,27] and that idiosyncratic behaviors can activate most of the cortex of rodents [28,29]. These latter observations suggest that there can be more global components to the activation of cerebral cortex and that even simple behaviors require the networked interactions of many specialized regions dispersed across the brain [30,31].

Another level of organization occurs within cortical subregions, often characterized by an orderly mapping across cortex of variables associated with the brain regions' function. For example, primary somatosensory and motor cortices are organized into topographic maps of the body [27,32,33]. These maps often seem complex [34], but can be predicted by models that map high-dimensional function onto the two-dimensional cortical sheet [35,36].

Plasticity of cortical representations in laboratory animals

Many of the studies in animal plasticity looked at how cortical maps change with experience or injury. Groundbreaking studies by Merzenich and Kaas showed that amputations could change these maps, with adjoining sensory representations occupying the deafferented cortex. Perhaps the most dramatic example of cortical plasticity was a report of facial representations moving into the cortical territory normally occupied by the limb following years-long forelimb deafferentation in the monkey [1,37]. Such changes depend on the degree and location of injury, and brain area under investigation [38,39].

Imaging studies in humans

Functional magnetic resonance imaging studies in humans have allowed non-invasive probing of topography after brain lesions and injury. With amputation, more cortex is activated with stimulation of intact parts of the body and with more bilateral activation of the two hemispheres [40–43]. Further, compensatory use of the preserved hand, mouth, or feet may drive novel representations into the deprived cortex [44–46]. However, neural representations of the missing limb remain: for amputations of the hand, attempted or imagined movements of missing limbs remain represented [41,47–49] and movement imagery of missing limbs recruits larger regions of cortex [50]. Thus, there seems to be some expansion of activation and plasticity even while structure persists.

Brain–machine interfaces

Given that cortex partially reorganizes and partially persists after deafferentation, an important question emerged with the introduction of brain–machine interfaces: how would years of lack of normal input and output affect the functional architecture of somatosensory and motor cortex, and how might this change as an individual gains experience with the BMI? At one extreme, the areas that previously encoded portions of the body lost to injury could undergo substantial loss of structure, disrupting the ability of subjects to volitionally control neural activity patterns. However, previous demonstrations of cortical plasticity introduced the possibility that the somatosensory and motor cortex could be retrained. In the extreme, if the cortex of adults is very plastic, an implant could be made in any area of cortex and trained to perform sensory or motor functions. This possibility was suggested by pioneering studies of Fetz et al., who showed that monkeys could be trained to generate arbitrary patterns of activity in one or two neurons within tens of minutes [51,52]. Similar short-term changes can be found in subdural electrocorticograms [53]. Another possibility was that the original structure of the cortex remained largely intact after injury and could be re-engaged or re-tasked for brain–machine interface applications.

Early clinical BMI studies demonstrate conserved function

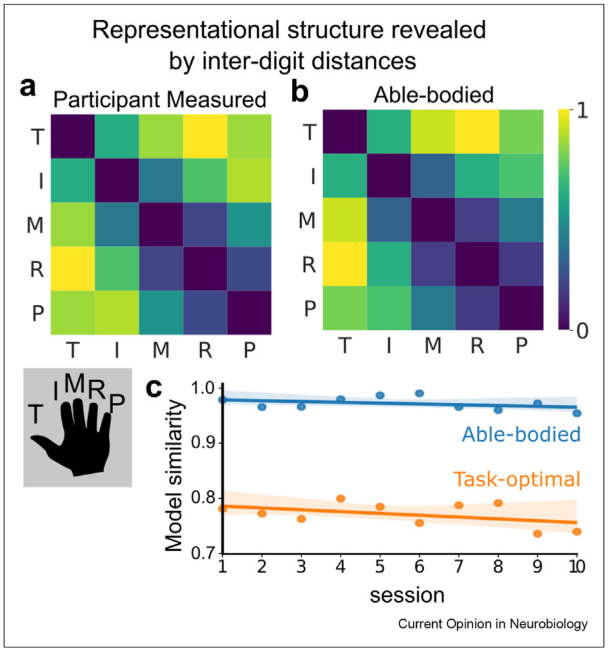
The first BMIs targeted motor cortex as a source of signals. Single motor cortex neurons showed direction tuning for intended movements similar to motor cortex in healthy laboratory animals [13]. Moreover, neural encoding of intended movement was present immediately and did not require retraining despite years of paralysis [20,54]. Using around one hundred neurons, paralyzed participants could move cursors on a computer screen or control the path of a robotic limb.

We have implanted arrays into human posterior parietal cortex (PPC) as a source of BMI signals. The PPC is situated between sensory cortices and motor and prefrontal cortex and is essential for sensorimotor transformations for sensory guided behaviors. We hypothesized that higher-order integrative processing within PPC would provide information complementary to the movement trajectories decodable from motor cortex. Supporting information from monkeys demonstrated that the early plan to move and simultaneous sequences of movements were encoded in PPC [55,56]. The ability to decode high-level information complementary to movement trajectories and the belief that higher-level signals would be better preserved, being further removed from the injury, inspired the move to implant PPC in humans. In human clinical studies, we have implanted regions within the PPC that are activated by grasping movements based on fMRI targeting in the participants before implantation [16].

We found that, similar to the monkey, human PPC encodes movement plans and high-level behavioral actions

[16,57]. The participants were able to engage these neural circuits through motor imagery. Interestingly, the volitional control of single neurons was easy for the participants, similar to the pioneering studies of Fetz et al. [51,52]. However, we found that subjects used imagined movements that were part of the natural movement repertoire [58,59]. Further, these neurons were highly specific; for example, firing when the participant thought about moving the hand to the mouth, but not for movements with similar arm or mouth kinematics. These results suggest that cortical activation is most efficacious when tapping into representations that are part of the natural functional role of the region. We have recently found that even the fine details of finger movements are preserved in tetraplegic individuals [Figure 1, [60]]. In the study of finger movements, a human clinical participant was able to control a BMI by attempting to move her fingers. The neural representational structure during these finger movements had a characteristic structure (1a) that was nearly identical to what is reported in able-bodied individuals (1b). This structure was maintained across experimental sessions (1c) despite contributing to BMI errors. These results suggest that detailed features of motor representations are remarkably preserved and engaged for BMI control.

Figure 1



Neural prosthetic control of individual fingers enabled by preserved motor representations. a) The representational structure (RS) of population neural activity BMI control of a virtual hand. RS was computed as the pairwise distances between fingers (see inset) revealing a clear reproducible pattern across repetitions (adapted from Guan et al., 2021). b) The RS of fMRI signals during overt finger movements in able-bodied individuals (adapted from Ejaz et al., 2015). c) Participant RS closely matches able-bodied RS. Similarity of patient RS (a) and able-bodied RS (b) across sessions (blue) compared to similarity of patient RS (a) and task-optimal RS (orange). Patient RS structure was consistent across time despite leading to BMI errors.

Diverse mixing of signals in PPC and M1

Although we found grasp and reach planning and sequence encoding in PPC, we also found encoding of many more variables, including action verbs, observed actions, memory recognition, movement strategies (to imagine versus attempting movement), and intended movements of all parts of the body, both on the contralateral and ipsilateral side [61—65]. So many variables encoded in a small number of neurons was possible because individual cells responded to a mixture of variables. Research in monkeys and rodents had also demonstrated this mixed variable encoding [66]. Whereas these reports indicated a random mixing of variables, we found statistical structure and referred to the phenomenon as partially mixed selectivity [61,64]. The mixing had an intuitive hierarchy; for instance, similar encoding of variables in the two hands could account for the transfer of learning between them [67]. An advantage from a neuroprosthetic perspective is that a single small implant can decode a myriad of intended movements.

The motor cortex also shows more mixing than would be expected from earlier animal studies [18]. However, even though motor cortex may encode more variables than expected, an implant in the hand knob of the motor cortex shows much stronger tuning for the contralateral hand than other body parts. Meanwhile, PPC represents movement of all body parts on a more equal footing.

A recent study reports some degree of planning activity in the hand-knob region of motor cortex [68]. We find some degree of planning activity when the motor cortex is not required to hold the effector over a target before a planned movement; in other words, if it is not given something to do. However, if motor cortex is required to steady the cursor before a movement command, then we find little planning activity. Thus planning activity is very context dependent for motor cortex but not PPC. This result may in part explain prior imaging and electrophysiological mapping studies which show expanded activity after injury, as described above. Connections that exist with other parts of the nervous system become “revealed” when its main inputs and outputs are injured, but the structure of the area remains intact for years and is the dominant driver of activity when it is reanimated by controlling a BMI.

Somatosensation after injury

Subjects with spinal cord lesions often suffer a loss of somatosensation, including touch and the sense of body position (proprioception), in addition to paralysis. Sensory loss is critical because somatosensory feedback is required for many behaviors such as handling objects dexterously. A robotic hand can be directed toward an object for grasping using vision as feedback. However, once the object is grasped, somatosensation is essential for dexterous manipulation. To provide this necessary information, a bidirectional interface includes sensors on the robotic hand that can control stimulation of the deafferented somatosensory cortex [24].

The presumption underlying this artificial re-innervation approach is that the user will interpret stimulation to deafferented cortex as touch to the corresponding deafferented body part. To work, the somatosensory cortex must still contain sufficient structure to convey the locations of stimuli on the previous homunculus (body map) in somatosensory cortex. Recent studies using intracortical microstimulation have demonstrated that somatotopy remains in the contralateral hand and in the lower and upper limbs [22,23,69]. This natural sensory feedback is crucial for BMI control: A recent report shows that a brain-controlled robotic limb takes less time to perform an object transfer task when intracortical microstimulation writes-in sensations [24].

Preserved sensory processing could also be identified during neural recordings: Imagination of particular somatosensations or the locations of touch can activate neurons in the PPC [70,71]. Interestingly, actual touch and imagined touch shared the same neural substrates [70]. Cognitive recruitment of sensory and motor circuits [72,73] may help preserve cortical representations when external sensory inputs are removed.

Another aspect of providing somatosensation is psychological, enabling a sense of embodiment to the participants [74,75]. No doubt the sense of ownership provided by feedback from assistive devices will increase the user's confidence and enjoyment when using BMIs. The major point of the stimulation-evoked sensations, for this short review, is that the body map, and pathways to other parts of the brain, which likely cooperate in the conscious awareness of touch and body position, remain intact despite evidence for reorganization. Again, despite potential unmasking [76] or use-dependent plasticity [45,46], the underlying structure of representations remains sufficiently intact that the subject perceives sensations from the deafferented regions of the body.

Distinct functional properties between S1 and PPC remain after spinal cord injury

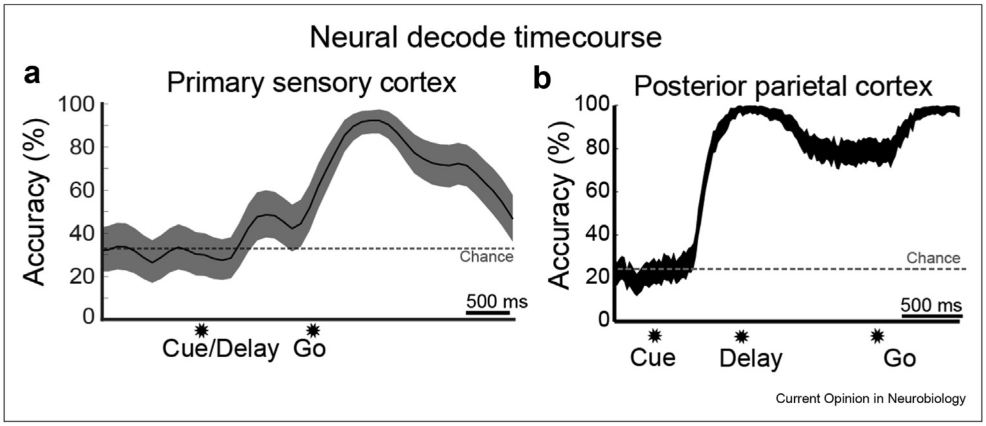
One way to establish preserved function is to ask whether the functional distinctions between regions are preserved after injury. As mentioned above, PPC appears to encode variables in a higher-dimensional space than motor cortex does, although some variables can leak in when motor cortex is not engaged in its primary function of continuous guidance of movement. A similar question can be asked of somatosensory cortex. In delayed movement tasks to visual cues, similar to tasks used in PPC and M1, there is little tuning for the visual targets or motor plans even though the subjects are not required to hold the original cursor position (Figure 2a) [77]. This difference can be compared to substantial visual and planning components in PPC during a similar task (Figure 2b) [16]. A parsimonious interpretation is that planning regions have a closer anatomical/functional connection to motor cortex than to primary somatosensory cortex, and that planning activity leaking to somatosensory cortex is just a bridge too far. This result again shows that the functional specificity of cortical regions remains years after spinal cord lesion.

Interestingly, S1 encodes imagined movement in this task, consistent with early movement activity in healthy monkeys [78,79]. This imagined movement activity codes the vector of the hand to the target, which implies that the visual target, presented in retinal coordinates, has been processed by areas outside of somatosensory cortex. A likely interpretation is that S1 activity is driven by an efference copy of motor commands and is part of the system that predicts the sensory outcomes of movement [80]. Such movement encoding opens the possibility that a single implant in primary somatosensory cortex can augment brain control through recording and enable sensory feedback through stimulation.

Learning

The above experiments indicate that a good deal of the original structure of the somatosensory and motor systems remain intact years after spinal cord lesions that interrupt both the outflow of motor cortex and the inflow to somatosensory cortex. It could be hypothesized that, through learning, BMIs can reprogram these pre-injury structures. This remains an avenue of active investigation, especially regarding the timescale and types of learning that are possible. Single-session learning experiments demonstrate that neural structures are remarkably robust. The primary demonstrations of learning involved using cognitive strategies, for instance, re-aiming, without altering the structure of circuits within the area [81–83]. However, requiring extensive and novel changes in neural activation patterns for behavioral success over long periods (> weeks) can generate seemingly fundamental alterations in neural activity patterns [84,85]. There are at least two important caveats to consider: First, it is unclear whether such activity patterns are novel, or whether they describe activity patterns for unsampled behaviors, such as off-effector movements. This may explain variable rates of skill acquisition. Second, learning new motor behaviors fit within our general understanding of motor cortex function, and thus it remains to be

Figure 2



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Visual and planning activity is restricted to high-level cortices in tetraplegic individuals. a) Accuracy of target location decode through time (95% ci) during planning and execution of imagined reaches in primary somatosensory (S1, a) and posterior parietal cortex (PPC, b). Visual cue and planning activity is found in S1 but not PPC. Adapted from Jafari et al., 2020 and Aflalo et al., 2015.

demonstrated whether cortical regions can learn outside their natural domain. For example, the demonstration that motor cortex can learn new activity patterns to control a cursor does not necessarily imply primary visual cortex could do the same.

Conclusions

The advent of BMIs has provided valuable new insights on the degree of plasticity after severe injury to somatosensory and motor systems. The good news, for BMIs, is that there is sufficient structure remaining for their effective therapeutic use. Another important finding is that, given this maintenance of functional organization, it is best to implant areas of the brain for BMI applications that are similar to the natural functions of those brain areas. This allows users to use pre-existing neural structures for fast intuitive neural control. Slow-learning systems may extend the repertoire of control signals that can be decoded from implanted regions. However, acquiring new patterns requires significant effort, and it remains to be seen whether this learning is constrained to specific domains. Thus, electrode arrays should not be implanted anywhere in cortex hoping to reorganize the area, but rather should be implanted in regions that are congruent with the applications. These studies also reinforce the concept of using higher-level association cortex for cognitive neural prosthetics, in which more complex or abstract applications may benefit from the high-dimensional multi-faceted information intrinsic to these areas.

There is also a surprisingly large number of variables encoded within small volumes of human cortex, achieved by single neurons being selective for several different variables. The mixing is generally not random but rather has statistical structure and is referred to as partially mixed selectivity. The number and type of variables represented depends on the tasks being performed by the subject and are thus context dependent. Although mixed selectivity has been reported in association cortical areas of healthy laboratory animals, it is currently not known to what extent spinal cord injury may contribute to the very high degree of mixed selectivity found in the cortex of tetraplegic humans and is an important topic for future research.

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Conflict of interest statement

Nothing declared.

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** of outstanding interest

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