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Monkey Models for Brain-Machine Interfaces: The Need for Maintaining Diversity

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***Abstract*—Brain-machine interfaces (BMIs) aim to help disabled patients by translating neural signals from the brain into control signals for guiding prosthetic arms, computer cursors, and other assistive devices. Animal models are central to the development of these systems and have helped enable the successful translation of the first generation of BMIs. As we move toward next-generation systems, we face the question of which animal models will aid broader patient populations and achieve even higher performance, robustness, and functionality. We review here four general types of rhesus monkey models employed in BMI research, and describe two additional, complementary models. Given the physiological diversity of neurological injury and disease, we suggest a need to maintain the current diversity of animal models and to explore additional alternatives, as each mimic different aspects of injury or disease.**

***Index Terms*—Brain-computer interfaces, neural prostheses, animal models.**

I. Introduction

NEUROLOGICAL injury and disease often result in the permanent loss of motor and sensory function. In some cases the disability is so severe that it is not possible to feed oneself or even communicate. BMIs are a new class of electronic medical systems that aim to improve the quality of life for disabled patients. These systems interface with the central nervous system and use neural signals from the brain to control prosthetic devices (e.g., [1]). In recent years, first-generation BMIs developed with rhesus monkey animal models have translated from the laboratory into an FDA Phase-I clinical trial focused on tetraplegics and ALS patients (BrainGate I & II, [2–7]).

Next-generation BMIs aim to further improve the quality of life of disabled patients and expand to larger patient populations, such as amputees and paraplegics. These next-generation systems may meet this goal if performance, robustness, and functionality can be increased substantially [8, 9]. But what types of monkey models are best suited to develop next-generation BMIs? It is currently unclear if a single animal model can capture all aspects of injury and disease or mimic different physiological conditions observed in patient populations. Thus, we suggest that maintaining and expanding the diversity of available monkey models is critical.

We briefly review four major existing rhesus models, and briefly describe two emerging models. We note that there are several other models not covered here, that either exist or are possible. These models may employ pharmacological, lesioning, or electrical micro-stimulation methods. Together, this set of animal models should help provide a diverse resource for laboratory research being conducted, which may prove essential for the successful translation of next-generation BMIs.

II. Rhesus monkey models

There appear to be four widely used rhesus monkey models. These have been employed in recent BMI laboratory experiments, and are listed in Table I. We note that the animal model used while training these systems may be different from the animal model used while evaluating BMI performance. However, for simplicity, we have categorized these references based only on the animal model used in evaluation of BMI performance.

A. Arm restrained, no EMG modulation

In the first model, the monkey's contralateral arm is restrained and monitored for task-modulated muscle activity[1]. The absence of this muscle activity does not require enforcing electromyography (EMG) silence, but rather that EMG activity not change within or across behavioral trials. This model has been employed by Schwartz and colleagues, where it was used in a control experiment to see if neural cursor control could be maintained without arm movements or EMG modulation [11].

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[1]The contralateral arm with respect to the electrode-array implant. The ipsilateral arm is also often restrained since motor cortical activity is also related to ipsilateral arm movements (e.g., [10]) However the ipsilateral arm's EMG activity is seldom if ever measured.

TABLE I
CURRENT AND EMERGING MONKEY MODELS

Current Monkey Models	References
A) Arm restrained, no EMG modulation	[11–15]
B) Arm restrained, no EMG measurement	[18–20]
C) Arm not restrained, not visible	[11, 20–26]
D) No arm movement, nerve block	[27, 28]
Emerging Monkey Models	**References**
E) Optogenetics	[9, 29–31]
F) Freely moving	[32–36]

This model has also been employed by Nicolelis, Carmena, and colleagues [12, 13] as well as by Andersen, Shenoy, and colleagues, albeit measuring EMG in separate experiments to assure no EMG modulation during an "instructed-delay" period [14, 15].

This monkey model "looks like a paralyzed patient," which may be beneficial to BMI research insofar as there are no arm movements or muscle contractions that would lead to sensory signals. These signals, including vision, somatosensation, and proprioception, could feed back to the cortical area driving the BMI and could influence BMI control. Such sensory input could be viewed as a potential confounding factor, as it is presumably not present in paralyzed patients as a potential source of useful information, or it could be viewed as an important opportunity for increasing performance [16]. There also appear to be two open questions with this model. The first is whether the range and pattern of possible neural activity is constrained, by virtue of the animal being restricted to not move the arm or modulate EMG activity. Paralyzed patients would presumably not have this neural constraint since the injury or disease prevents neural activity from reaching muscles, regardless of its range or pattern. Second, we ask whether all relevant muscle groups can be monitored to assure no task-relevant EMG modulation given that the homunculus is highly fractured and individual neurons may respond with respect to multiple muscle groups. This is a practical concern, but one that is brought into focus by recent studies highlighting how individual neurons in the nominal arm area of primary motor cortex contain considerable hand and finger movement related activity [17].

B. Arm restrained, no EMG measurement

The second model again restrains the monkey's contralateral arm, but does not measure EMG activity. Some finger, hand, and arm movement as well as force generation is therefore allowed. This model has been employed by Schwartz, Vaadia, and colleagues [18–20].

This monkey model "looks a bit less like a paralyzed patient" because there may be some visible movement. This allowed movement may be beneficial, as described above, because the neural population under observation may be less constrained. This second model also recognizes, implicitly, that it is challenging to record from all relevant muscles to confirm that there is no EMG modulation. Instead, small movements and small amounts of force production are allowed. An open question with this model is whether muscle co-contraction, isometric force production against the arm restraint, and/or small movements are producing sensory signals that could feed back to the cortical area driving the BMI.

C. Arm not restrained, not visible

The third model does not restrain the monkey's contralateral arm. It also does not allow the arm to be viewed by the animal, as was the case for the first two monkey models. This model has been employed by Schwartz, Donoghue, Andersen, Vaadia, Batista, Yu, Shenoy, and colleagues [11, 20–26].

This monkey model "looks less like a paralyzed patient" because there is frank visible (to an observer, not the animal) movement. This movement may again be beneficial because the neural population under observation may be less constrained or altogether unconstrained. There appear to be two open questions with this model. The first is how to interpret the presumed presence of proprioceptive and somatosensory signals that feed back to the cortical area driving the BMI, as a result of arm movements. Second, several groups have observed that sometimes monkeys stop moving their arms and the BMI continues to operate. It would appear that monkeys can continue to operate what is in essence the first or second animal model after voluntarily transitioning to keeping the arm motionless [12, 21, 22]. This may suggest that the difference between these three animal models is not large from the perspective of BMI algorithm design and operation.

D. No arm movement, nerve block

The fourth monkey model employs a local anaesthetic to block much, if not all, of the efferent motor signals going to the arm as well as afferent sensory signals coming from the arm. This is a newer model and has been employed by Fetz, Miller, and colleagues [27, 28].

This monkey model "looks like a paralyzed patient" since the arm, hand, and fingers are (temporarily, reversibly) paralyzed and sensory information is substantially attenuated. As such, this model may closely mimic a spinal cord injury patient. This model may also be beneficial, as described above, because the neural population under observation may be less constrained or altogether unconstrained. There appear to be several open questions with this model, largely due to its recent development. The first stems from the observation that nerve blocks are peripheral nerve interventions, whereas spinal cord injury patients have lesions in the central nervous system. Second, the degree of afferent activity block is presumably difficult to verify (i.e., daily nerve conduction studies are not feasible). Third, nerve block is a temporary, acute intervention, whereas spinal cord injury is a chronic condition. As a result, adaptive or deteriorative changes in the cortex of a patient with spinal cord injury are presumably not modeled. The daily novelty of paralysis may also be a distraction to the animal and could even present cue conflict (i.e., can see the arm, but can't move or feel it). These factors could lead to different cortical neural activity than would be present in the chronic patient case. Fourth, the pharmacokinetics of the local anaesthetic result in a gradual return of motor and sensory function over the course of a long experiment. This is potentially

complicated by the difficulty of verifying the degree of sensory block and mitigating its day-to-day variability.

Finally, the technical complexities are non-trivial, including surgically implanting a nerve cuff and drug reservoir, injection-filling the reservoir periodically, and animal husbandry following experiments. While not necessarily a limitation, this additional technical complexity is a consideration when selecting animal models. As discussed below, optogenetic and freely moving monkey models also have additional technical complexity.

E. Optogenetics

One emerging model that could potentially (temporarily, reversibly) emulate paralysis, stroke, or other disorders is an "*optogenetic monkey model*." Optogenetics provides a method for exciting or inhibiting neural activity while simultaneously recording, and does so with high spatial (individual neuron, specific neuron types, specific projection pattern) and temporal (millisecond timescale) resolution. Several optogenetic methods have recently been translated to rhesus monkeys [29–31]. With these methods it may be possible to use light to reversibly mimic injury and disease: "synthetic cord injury" (e.g., inhibit activity in descending motor fibers with NpHR), "synthetic stroke" (e.g., inhibit activity within an illumination-defined volume of gray matter with NpHR), and "synthetic spasticity" (e.g., excite activity at specific rhythms with ChR2, or elevate baseline activity with SFO). It may also be possible to use these methods as part of the BMI system itself to, for example, "write in" artificial sensory information coming from sensors built in to prosthetic hands [9].

F. Freely moving

Another emerging model that could potentially be used to understand more naturalistic and freeform movements, and is relevant for designing BMIs to assist amputees who live active lives, is a "*freely moving monkey model*." It is now possible to build miniature head-mounted systems to record from multi-electrode arrays, transmit these data wirelessly to a nearby receiver, and use modern computer vision and markerless motion tracking techniques for high-precision behavioral measurement [32–34]. In combination, this enables monkeys to move freely and perform a variety of naturalistic tasks while studying how populations of neurons control movement. This could lead to a more comprehensive understanding of cortical motor control across a wide range of naturalistic movements and behavioral contexts, and thereby better mimic the lifestyle of arm amputees as well as model healthy humans [35]. The freely moving monkey model also enables studies exploring chronic neural stimulation, including stimulation contingent on specific neural activity, and has been employed to demonstrate motor plasticity [36].

III. Discussion

A range of rhesus monkey models is currently being employed to help advance BMI design, and their translation to disabled patients. First-generation BMIs have shown substantial promise and are currently part of a clinical trial. With the desire to provide even greater benefit to the current patient populations, as well as to help more patients who suffer from a wider range of disabilities, next-generation systems are coming into focus. A central question to this new endeavor is what types of rhesus models are currently available, and what new models might be needed. We have attempted to provide a brief review of the existing models, categorized into four broad types, as well as an overview of two emerging monkey models currently under development. Two additional points are worth highlighting.

First, animal models are essential and appear to be working fairly well. As such, this diversity of models ought to be maintained. BMIs are still in their early days, and considerable additional basic science, basic engineering, and pre-clinical testing are essential. The current animal models have already led to a clinical trial and, equally importantly, the basic BMI system architecture appears to work with little design modification when switching between animal models. This suggests that rhesus monkey models are both appropriate to translational BMI efforts, and that such a diverse set of animal models may map well across a range of physiological conditions. It could be that the different animal models each mimic a different neurological injury or disease, and having a set of BMIs that each operate well with one or more of these models is prudent.

Second, we ought to not only maintain the diversity of rhesus models, but also continue to investigate new ones. These new animal models may provide the field with useful platforms for examining various pathological presentations. It is important to recognize that BMIs aim to assist patients with a variety of different neurological injuries and disease. A wide variety of pathology can result in debilitating loss of motor function while preserving cortical areas. Although cervical spinal cord injury is the prototypical example, traumatic injury can occur anywhere along the pathway, from cortex to subcortical structures to the distal limb. Many other mechanisms for loss of function also exist, including neurodegenerative diseases, autoimmune conditions, neuropathies, and myopathies. This suggests that different monkey models may be needed to mimic these varied pathologies. Even within the sub-class termed "upper spinal cord injury" there is a whole spectrum of actual injuries and associated dysfunctions that may leave a patient with varied impairments from moderate paresis to full paralysis, with or without concomitant sensory deficits. Similarly, then, a rich and growing spectrum of monkey models is presumably required to cover the range of spinal cord injuries as, ultimately, it is unlikely that a single monkey model will suffice.

IV. Conclusion

A range of rhesus monkey models currently exists for BMI research, and they can be broadly categorized into four types. Two additional types of rhesus models that are emerging were also reviewed briefly. We suggest that this diversity of models is important, should be maintained, and expanded as part of the overall effort to design and translate next-generation BMIs.

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