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Previews

Getting a grasp on BMIs: Decoding prehension and speech signals

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Wandelt et al. (2022) show that different grasps can be decoded from neural activity in the human supramarginal gyrus (SMG), ventral premotor cortex, and somatosensory cortex during motor imagery and speech, highlighting the attractiveness of higher-level areas such as the SMG for brain-machine interface applications.

From steering a heavy shopping cart through a crowded supermarket to scooping up rice with chopsticks, humans are experts at manipulating objects, using a wide variety of grasp types that differ in the fingers involved, their assumed shape, and the forces exerted. These capabilities are supported by the cortical grasp network, which involves brain areas such as the (pre)motor cortex, somatosensory cortex, and areas in the posterior parietal cortex (PPC). However, the ability to grasp objects can be lost because of paralysis from neurodegenerative diseases and brain or spinal cord injury, for example, tetraplegia. For those affected by paralysis, both the ability to independently interact with their environment and being able to successfully communicate are crucial (Anderson, 2004; Hecht et al., 2002). To address these issues, brain-machine interfaces (BMIs) are being developed to improve or restore lost sensorimotor and communication capabilities (Andersen et al., 2014; Pandarinath and Bensmaia, 2022; Willett et al., 2021).

Intracortical BMIs allow direct communication between the brain and an external device, such as a prosthetic hand. They rely on microelectrode arrays to record single-unit neural activity, which is then decoded to control devices such as robotic arms (Pandarinath and Bensmaia, 2022). For grasping applications, current BMIs typically target lower-level sensorimotor areas, which are situated closest to the periphery in the cortical hierarchy. Given their location, it might be expected that these areas most purely reflect relevant sensorimotor signals. However, decoding from higher-level regions within the grasp network might be attractive as these signal the *intention* of motor action. Not only might this intention be available earlier, leading to faster reaction times of the prosthetic, but it might also reflect aspects of the grasp holistically, such that the type of grasp can be decoded more easily. Exploiting such a signal might enable the prosthetic to execute whole grasp programs, rather than decoding mostly low-level signals such as finger trajectories and joint angles.

In this issue of *Neuron*, Wandelt et al. (2022) tackle this problem by testing whether and to what extent individual grasp types can be decoded during motor imagery from brain areas within the grasp network. Single-unit neural activity was recorded from three regions in a tetraplegic patient: the ventral premotor cortex (PMv), the primary somatosensory cortex (S1), and the supramarginal gyrus (SMG), which is a subregion of the PPC. The PMv provides cortical input to the primary motor cortex and has been associated with grasp planning, including hand shape and configuration (Davare et al., 2011). The PPC broadly encodes movement goals and plans or intention signals (Andersen et al., 2014), while the SMG itself is involved in the planning and execution of object and tool grasping, as well as object manipulation. Finally, sensory signals from the peripheral nervous system are processed by S1, such as proprioceptive information and tactile feedback, which are both relevant in the control of grasping (Delhaye et al., 2016; Pandarinath and Bensmaia, 2022).

The first part of the study employed a motor imagery task where the participant was asked to imagine performing one of five different grasps (Figure 1). Neural activity from the three regions was analyzed to investigate whether each grasp could be decoded. Activity was divided into time windows for each trial, including a "cue" phase, when the participant was shown the target grasp image, and an action phase, where either a "Go" or "No-Go" instruction was given. During Go trials the participant imagined performing the cued grasp. Under No-Go trials, the participant had to "cancel" imagining the grasp. This setup enabled the authors to test whether the participant could volitionally control the grasp imagery. Indeed, for the No-Go trials, grasps could only be decoded from the cue phase and not the action phase, demonstrating that the participant could successfully control the generation of motor imagery.

The authors found grasp-dependent neural activity in all three regions, with units tuned to different grasp types during both the cue and action phases in SMG and PMv and the action phase in S1. In all regions, some units were tuned to multiple grasps, as assessed by their firing rate profile. When combining the information from multiple neurons, grasps could be accurately decoded from the cue phase of both PMv and SMG and the action phase of all three regions. SMG recordings afforded almost perfect decoding, while accuracy dropped considerably for S1. Finally, the authors assessed how many units were needed to accurately classify grasps and found that both SMG and PMv supported classification from 50–100 neurons, well within the reach of current recording arrays.

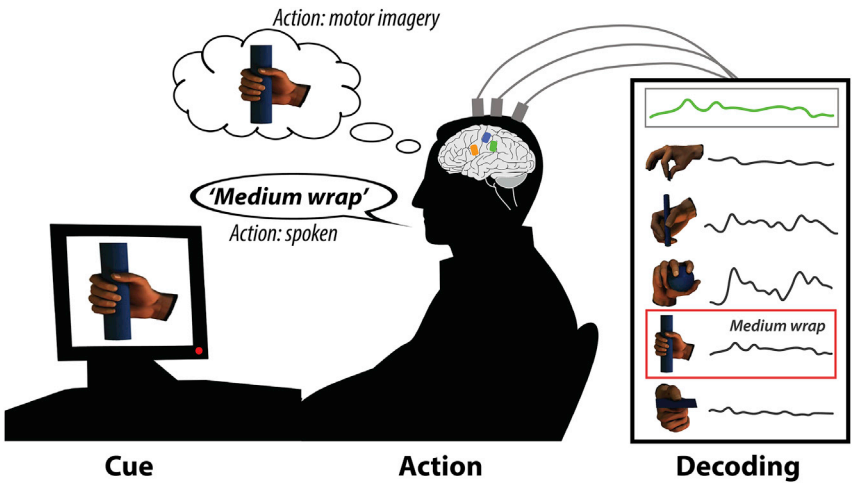

Figure 1. Decoding grasps from neural activity

One of five grasp types is indicated during the cue period. After a short delay, the participant either imagines performing the grasp action or speaks the name of the grasp during the action phase (middle). Neural responses are recorded via arrays implanted in the premotor cortex (orange), S1 (blue), and SMG (green). Grasp types are then decoded from the neural signals (right). Illustration created by the authors using image components in the public domain or taken from the original publication.

These investigations point to S1 providing less information than the two other areas. However, S1 can still play an important role in BMIs. Grasped objects can be of different sizes, weights, and shapes and may require the grasp to be subtly varied to accommodate these. This information is typically conveyed by cutaneous and proprioceptive signals, which project to S1 (Delhaye et al., 2016). More recently, BMI research has started to "close the loop"—by not only providing the ability to move external limbs but also to feel tactile sensations elicited by object interactions (Flesher et al., 2021). Accurate decoding from higher regions, rather than S1, frees up this region to deliver sensory feedback, reducing problematic signal artifacts caused by having nearby recording and stimulation probes (Andersen et al., 2014; Pandarinath and Bensmaia, 2022).

In contrast, SMG afforded robust grasp classification with few neurons. As a higher-level area, it is likely to be involved in more behaviors than just grasping. Could any of these additional functions be useful for a BMI to exploit? Paralysis can often affect the ability to communicate, and Wandelt et al. (2022) turned to this application next. They investigated whether both speech and motor imagery outputs could be decoded from neural activity in any of the three targeted regions. The action phase of the task was amended such that the name of the cued grasp was spoken instead. To test whether the SMG activity during speech was grasp related or whether more general single-unit language processing was possible, a control task was added: five colors were used as cues, and the name of the color was spoken in the action phase. Both spoken colors and grasps could be decoded from SMG, and units were mostly strongly tuned in the cue and action phases. Taken together with the earlier results, these findings suggest that the SMG could be a candidate for both speech and motor BMI applications.

While the neural activity during the action phase is likely directly related to the motor action, what the activity represents in the cue phase is less clear. Wandelt et al. (2022) present several possible explanations: activity might relate to visual processing of the grasp image, the beginning of a motor plan in preparation for grasp execution, or activating memories of the grasp. To answer this question, the authors tested whether neural activity from one task could be decoded by models trained on another task. For example, how well can spoken colors be decoded from a model trained on spoken grasps? Neural decoding was possible for the outcome of spoken grasps when trained on motor imagery (and vice versa) in the cue phase, but it was weakened in later phases. The authors suggest this could be due to divergence in motor plan formation between speech and grasps. However, the ability to decode grasps when the goal is different may suggest that not all of the cue phase activity is related to motor planning. In contrast, spoken colors could only be decoded from the model trained on colors, suggesting that the patterns of single-neuron activity in the SMG are tuned based on semantic content in the cue phase.

Overall, Wandelt et al. (2022) highlight the SMG as an attractive target for BMI applications. Not only is grasp-relevant activity available and decodable from this high-level area, but it might also play a promising role in speech BMIs. Future work toward practical BMIs will need to consider whether broad decoding of different grasp types is sufficient to afford precise and fine-tuned object manipulation. It is possible that some adjustments to grasp forces or contact locations might be controlled directly by a smart prosthetic device. However, it is also possible that this will require "closed-loop" design. Integrating somatosensory feedback by stimulating S1 and fine-tuning grasp decoding by integrating activity from lower-level motor areas such as PMv may go some way toward solving this problem. These are interesting questions to explore for future research that will pave the way toward practical devices but also further elucidate the role of different brain areas in the cortical grasp network.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Seq-ing the mechanisms of migraine

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The trigeminal ganglia (TG) play a crucial role in migraine pathophysiology. In this issue of *Neuron*, Yang et al. developed a single-cell atlas profiling the transcriptome and epigenome of mouse and human TG, thus providing a roadmap for therapeutic targeting.

Migraine is a severely debilitating condition that affects ~15% of the global population (Ashina et al., 2021; Ferrari et al., 2022). Migraine has a peak prevalence in mid-life, and women are 2–3 times more likely to be affected than men. It is the second leading cause of disability globally and the first in young women (Steiner et al., 2020). Thus, migraine results in significant lost productivity and decreased quality of life. Despite the incredibly high burden of migraine, headache disorders are relatively understudied, and research resources are sometimes scarce. However, a new paper by Yang et al. (2022) in this issue of *Neuron* is about to blow the field wide open.

Trigeminal ganglia (TG) play a critical role in the sensation of head pain. Neuronal cells within the TG innervate the meninges, and these primary afferents signal touch and pain sensation (Goadsby et al., 2017). The TG feeds into the trigeminal nerve, which splits into three branches—ophthalmic (V1), maxillary (V2), and mandibular (V3) nerves—and the TG regulate sensation and movement of the facial area. Primary afferents from the TG project into the brain stem and synapse onto neurons within the spinal trigeminal nucleus caudalis (Sp5C, TNC) as well as the C1-C2 regions of the cervical spinal cord. Although TG are located inside the head, they are outside the dura and arachnoid mater and are thus part of the peripheral nervous system. Given the location outside of the blood-brain barrier, cells within the TG are attractive therapeutic targets for migraine. For example, monoclonal antibodies targeting calcitonin gene-related peptide or its receptor have proven to be highly successful migraine therapies.

Yang et al. have developed an atlas profiling human and mouse TG using transcriptomic and epigenomic analysis with single-cell resolution (Yang et al., 2022). Until this publication, transcriptomic analysis of the TG was primarily performed in bulk tissue or focused on neuronal cell populations. Along with neuronal cells, the TG is also composed of non-neuronal cell types including satellite glia, fibroblasts, immune cells, epithelial cells, and Schwann cells. Through advancements in single-cell sequencing, it is possible to parse out the various cell types and determine their roles in perpetuating and modulating sensory signaling. Here, we highlight the impact of the work by Yang et al. in elucidating the conservation of TG gene expression and regulation in humans and mice, and the therapeutic implications of targeting these cell types.

The authors performed single-nucleus RNA-seq (snRNA-Seq) on human and mouse TG. Broadly, the transcriptional clusters of neuronal and non-neuronal cell types were conserved and showed high levels of overlap between species and across sex. For example, in both species both peptidergic (PEP) and nonpeptidergic nociceptors were highly enriched in TAC1 and SCN11A, respectively. This cross-species conservation validates and supports the continued use of mouse models for migraine in identifying novel targets and screening pharmacotherapies. Not surprisingly, human and mice TG did differ in some ways. For example, PEP nociceptors were more fractionally abundant in humans compared to mice. In addition, non-neuronal cell types in human TG were found to be more variable between subjects than neuronal cells, which likely reflects the heterogeneity between individual humans vs. an inbred mouse strain. One major strength of this study was the inclusion of both males and females. The authors did not observe abundant differences in the overall gene profile of cell types across sex but did confirm genes