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Previews

Natural behavior relaxes zoning divisions in the brain

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Technological advances allow neurophysiologists to explore the brain during natural behaviors, revealing new functional principles and challenging old ones. In this issue of *Neuron*, Li[1] and colleagues show that the traditional parcellation of the marmoset frontal cortex does not apply to naturalistic conversations.

What would our social life look like if every frown or smile had to be repeated tens of times for the receiver to understand it? Foundational neuroscience experiments, spanning decades of exploration, relied on paradigms that needed tens or hundreds of repetitions of the same behavior or stimulus to extract meaningful information from single neurons. A major leap forward came with technological innovations that allowed neurophysiologists to monitor the activity of populations of neurons[2,3] and the subsequent demand for new analytical methods. Together, these developments revealed brain states emerging from the joint activity of neurons assembled in functional networks. Neural networks, often distributed across multiple brain areas, replaced single neurons as the functional unit of brain activity.[4] The collateral advantage of capturing the activity of entire networks of neurons was the replacement of reductionist and trial-based experimental designs with natural behaviors that are spontaneous, less predictable, and that carry the risk of never repetitively occurring. These challenges notwithstanding, the neurophysiology of natural behaviors offers a significant advantage for discovering neural dynamics and computational principles that evolved to serve the behaviors under scrutiny.[5]

In this issue, Li and colleagues[1] embraced this challenge. They abandoned the strictly scripted, trial-based experimental design and exploited instead the quasi-predictable sequence of natural vocal exchanges between marmosets. They simulated natural conversations (antiphonal calling) by delivering through speakers pre-recorded vocal calls that engage the listener monkey into responding to these calls with delays seen during natural behavior. They also recorded the spontaneous solicitation calls of the subject. Instead of timing the presentations of calls independently of the receiver's behavioral state, the pre-recorded calls were broadcast either as solicitation calls or as responses to calls of the subject. The resulting sequence of calls was temporally variable, even overlapping at times. They analyzed the activity of neurons in multiple areas of the frontal cortex both at the single-cell level, using traditional methods (e.g., peri-stimulus time histograms), and at the population level, using a method that considered the history of calls and was flexible enough to accommodate the temporal variability inherent to unconstrained behaviors. Accordingly, they applied a generalized linear model (GLM) that included behavioral state, calls heard, calls produced, and interactions between them as regressors. Previous experiments showed how critical it is to include behavioral state in these analyses, as the activity of neurons in the frontal cortex of marmosets predicted whether they would engage in a conversation with a conspecific seconds before they heard the invitation to respond.[6]

The traditional, cell-by-cell approach confirmed that the majority of neurons in the prefrontal cortex and the premotor cortex were responsive to facets of the ongoing communication. However, the GLM captured additional facets of dependence between brain activity and the receiving-emitting cycle of vocal communication. Through dimensionality reduction, the authors identified functional clusters related to the perceptual and motor elements of the communication but also to internal states and social context.

Remarkably, the functional clusters did not map onto the well-established functional parcellation of the primate frontal cortex.[7] The premotor and prefrontal cortical areas of a freely moving, unrestrained receiver and emitter of calls responded differently during the vocal exchange than what would be expected based on a trial-based design with behavioral restrictions. Moreover, the sliding-window GLMs suggested that both areas contributed to a continuously unfolding progression of neural states distributed over multiple subdivisions of the frontal cortex. Although not monitored by the authors, these states could be informed by body posture, head and eye movements, social decision-making, autonomic and energetic regulation, and perhaps even less obvious elements of the unfolding mental processes.

The zoning violation perpetrated by these functional clusters is not as surprising as it may appear at first glance, given that removing behavioral constraints may add new variables processed by neurons in both areas. Areas of the prefrontal cortex are highly interconnected with the premotor cortex, and both areas are required to contribute to the elaboration of spontaneous social behaviors. The current functional parcellation may have been established by tasks and behaviors that by design, or by necessity, elicited lower dimensional representations. By contrast,

high-dimensional representations evidenced by multidimensional selectivity at the individual cell level[8] may reveal *relative* rather than *absolute* cortical specializations. Indeed, the fluid transitions between absolute and relative specialization might be a better criterion of frontal homology across mammals than localization of function or hierarchical organization.[9] Highly social animals, like marmosets, need behavioral flexibility arising from high-dimensional representations to handle parallel streams of relatively unscripted behaviors. The quiet revolution toward natural behavior may dissolve the absolute functional parcellation and the strict division of labor among cortical areas.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Li, J., Aoi, M.C., and Miller, C.T. (2024). Representing the dynamics of natural marmoset vocal behaviors in frontal cortex. Neuron *113*, 3542–3550.e3. https://doi.org/10.1016/j.neuron.2024.08.020.

2. McNaughton, B.L., O'Keefe, J., and Barnes, C.A. (1983). The stereotrode: a new technique for simultaneous isolation of several single units in the central nervous system from multiple unit records. J. Neurosci. Methods *8*, 391–397. https://doi.org/10.1016/0165-0270(83)90097-3.

3. Steinmetz, N.A., Aydin, C., Lebedeva, A., Okun, M., Pachitariu, M., Bauza, M., Beau, M., Bhagat, J., Bohm, C., Broux, M., et al. (2021). Neuropixels 2.0: A miniaturized high-density probe for stable, long-term brain recordings. Science *372*, eabf4588. (6539). https://doi.org/10.1126/science.abf4588.

4. Yuste, R. (2015). From the neuron doctrine to neural networks. Nat. Rev. Neurosci. *16*, 487–497. https://doi.org/10.1038/nrn3962.

5. Miller, C.T., Gire, D., Hoke, K., Huk, A.C., Kelley, D., Leopold, D.A., Smear, M.C., Theunissen, F., Yartsev, M., and Niell, C.M. (2022). Natural behavior is the language of the brain. Curr. Biol. *32*, R482–R493. https://doi.org/10.1016/j.cub.2022.03.031.

6. Nummela, S.U., Jovanovic, V., de la Mothe, L., and Miller, C.T. (2017). Social context-dependent activity in marmoset frontal cortex populations during natural conversations. J. Neurosci. *37*, 7036–7047. https://doi.org/10.1523/JNEUROSCI.0702-17.2017.

7. Passingham, R.E., and Wise, S.P. (2012). The neurobiology of the prefrontal cortex: anatomy, evolution, and the origin of insight. OUP Oxford. https://doi.org/10.1093/acprof:osobl/9780199552917.001.0001.

8. Fusi, S., Miller, E.K., and Rigotti, M. (2016). Why neurons mix: high dimensionality for higher cognition. Curr. Opin. Neurobiol. *37*, 66–74. https://doi.org/10.1016/j.conb.2016.01.010.

9. Le Merre, P., Ährlund-Richter, S., and Carlén, M. (2021). The mouse prefrontal cortex: Unity in diversity. Neuron *109*, 1925–1944. https://doi.org/10.1016/j.neuron.2021.03.035.

Gastrointestinal tract cleavage of α-synuclein by asparaginyl endopeptidase leads to Parkinson's disease

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Pathologic α-synuclein (α-syn) aggregates from the gastrointestinal (GI) tract may contribute to Parkinson's disease (PD). Xiang et al.[1] report in *Neuron* that enteric nervous system-specific expression of asparaginyl endopeptidase (AEP)-truncated α-syn and tau spreads to the brain, synergistically causing PD-related neurodegeneration and neurobehavioral deficits.

Parkinson's disease (PD) is neuropathologically characterized by Lewy bodies (LBs) composed of pathologic α-synuclein (α-syn). LB dementia (LBD), which ranks as the second most prevalent dementia after Alzheimer's disease (AD), encompasses dementia with LBs (DLB) and PD dementia (PDD) and is distinguished by the timing of onset of dementia relative to motor symptoms in PD.[2] Remarkably, 50% of PDD/DLB cases display co-existing AD pathology, while up to 50% of AD patients exhibit concurrent LB pathology.[2] AD pathology, which is neuropathologically characterized by tau neurofibrillary tangles and β-amyloid plaques, hastens the progression of LB pathology, influences the pattern of LB pathology, and exacerbates the cognitive decline in LBD.[3] α-Syn pathology in PD is thought to originate, in part, in the gastrointestinal (GI) tract and spreads to the central nervous system via neuronal connections along both ascending and descending

