Comment

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Can a single brain cell be surprised?

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A recent study by Buonomano et al. reports two important contributions; namely, empirical evidence for prediction error-like responses in single cells, using ex vivo preparations and optogenetics. Second, it foregrounds the role of asymmetric coupling in generating itinerant dynamics required for temporal prediction in neuronal circuits.

Evidence for prediction error signalling at the level of single cells is particularly prescient for the translation of basic science into a clinical setting. This follows from the growing excitement about the potential of using in vitro and ex vivo preparations to understand the cellular and molecular mechanisms of synaptopathy in neuropsychiatric and neurodegenerative disorders. For example, in schizophrenia research, one of the most reliable (in vivo) paradigms rests upon the mismatch negativity. Being able to reproduce the implicit prediction error responses in single cells—embedded in an organotypic slice of the brain—is something that was unimaginable several years ago. The particular benefit of studying mismatch or prediction error responses is that they index the kind of synaptic plasticity that many regard as the locus of pathophysiology in several brain disorders; especially those that can be construed as functional dysconnection syndromes resulting from the aberrant modulation of synaptic efficacy.

These kinds of responses—to mismatches, omissions and violations—speak to current formulations of predictive processing in the brain; in particular, those that appeal to predictive coding accounts of neuronal self-organisation. These accounts predominate in theoretical neurobiology and cognitive neuroscience. And are increasingly the focus of detailed electrophysiological studies of the requisite canonical microcircuits. In this regard, the findings of Buonomano et al. [1], are remarkable: the identification of single neurons—that show prediction error responses—could be among the first lines of definitive empirical evidence for predictive coding. Hitherto, evidence for predictive coding has relied upon the (usually, non-invasive) electrophysiology of neuronal populations, which cannot disentangle the contributions of individual cells or cell types[2,3].

From the perspective of the mismatch negativity, one can interpret the responses reported in ref. 1 as omission-related responses. In other words, neuronal responses to the absence of a predicted stimulus. Crucially, these responses were evinced in well-characterised single (excitatory, pyramidal) neurons. This is entirely consistent with proposals for canonical microcircuits, in which superficial pyramidal cells are generally thought to report prediction errors, and broadcast them to higher levels in cortical hierarchies[4]. In predictive coding schemes, neuronal message passing—along axonal connections—can be summarised in terms of prediction errors that ascend cortical hierarchies to update higher level representations, which then reciprocate descending predictions. Predictions of lower level representations are then used to form prediction errors that—through recurrent and asymmetric message passing—vitiate themselves. In other words, each level of the cortical hierarchy is in the game of minimising prediction errors by informing—and being informed by—the levels to which they are connected.

From a computational perspective, descending predictions can be read as being generated under a (generative or world) model of how states of the world generate the sensorium. Crucially, this places certain constraints on the nature of neuronal dynamics that must recapitulate the cause-effect structure in the sensed world. One aspect—that characterises these dynamics—is that they are universally far-from-equilibrium and necessarily feature non-dissipative dynamics.

The asymmetry in connectivity between excitatory subpopulations reported in ref. 1, speaks to this universal theme; namely, the breaking of detailed balance and the emergence of non-dissipative (a.k.a., solenoidal) dynamics. In short, asymmetry in the coupling of sparsely connected dynamical systems is necessary for the itinerant behaviour that characterises biotic self-organisation; ranging from oscillations through to lifecycles: from biorhythms to reproduction. This is evident at every scale of analysis, from turbulence in cortical field characterisations through to Red-Queen dynamics in evolution[5–9]. Indeed, much of the empirical evidence for predictive coding rests upon functional asymmetries in the exchange between prediction and prediction error units[10–13].

While most hierarchical predictive coding schemes foreground the role of bottom-up (ascending) and top-down (ascending) messages, general formulations consider lateral interactions[14]; especially when considering the role of neuromodulation, the encoding of uncertainty or its complement, precision[4,10]. Furthermore, exactly the same principles apply to heterarchical and non-hierarchical generative models: see for example[15]. This suggests that the findings reported Buonomano et al. [1], not only furnish evidence for predictive coding in the brain but suggest the capacity for predictive processing may be found in any neuronal culture, circuit or organoid; paving the way for in vitro and other neuromorphic models of sentience.

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References

1. Liu, B. & Buonomano, D. Ex vivo cortical circuits learn to predict and spontaneously replay temporal patterns. *Nat. Commun.* **1**, 1 (2025). https://doi.org/10.1038/s41467-025-58013-z.
2. Walsh, K. S., McGovern, D. P., Clark, A. & O'Connell, R. G. Evaluating the neurophysiological evidence for predictive processing as a model of perception. *Ann. N Y Acad. Sci.* **1464**, 242–268 (2020).
3. Hodson, R., Mehta, M. & Smith, R. The empirical status of predictive coding and active inference. *Neurosci. Biobehav. Rev.* **157**, 105473 (2024).
4. Shipp, S. Neural elements for predictive coding. *Front Psychol.* **7**, 1792 (2016).

5. Deco, G. & Kringelbach, M. L. Turbulent-like dynamics in the human brain. *Cell Rep.* **33**, 108471 (2020).
6. Gu, S. et al. The energy landscape of neurophysiological activity implicit in brain network structure. *Sci. Rep.* **8**, 2507 (2018).
7. Jiang, D.-Q., Qian, M. & Qian, M.-P. *Mathematical Theory of Nonequilibrium Steady-States* (Springer, 2004).
8. Zhang, F., Xu, L., Zhang, K., Wang, E. & Wang, J. The potential and flux landscape theory of evolution. *J. Chem. Phys.* **137**, 065102 (2012).
9. Ao, P. Global view of bionetwork dynamics: adaptive landscape. *J. Genet. Genomics* **36**, 63–73 (2009).
10. Bastos, A. M. et al. Canonical microcircuits for predictive coding. *Neuron* **76**, 695–711 (2012).
11. Bastos, A. M. et al. A DCM study of spectral asymmetries in feedforward and feedback connections between visual areas V1 and V4 in the monkey. *Neuroimage* **108**, 460–475 (2015).
12. Arnal, L. H. & Giraud, A. L. Cortical oscillations and sensory predictions. *Trends Cogn. Sci.* **16**, 390–398 (2012).
13. Hovsepyan, S., Olasagasti, I. & Giraud, A.-L. Combining predictive coding and neural oscillations enables online syllable recognition in natural speech. *Nat Commun.* **11**, 3117 (2020).
14. Bogacz, R. A tutorial on the free-energy framework for modelling perception and learning. *J. Math. Psychol.* **76**, 198–211 (2017).
15. Isomura, T. Active inference leads to Bayesian neurophysiology. *Neurosci. Res.* **175**, 38–45 (2022).

Author contributions

The author conceived and wrote this commentary.

Competing interests

The author declares no competing interests.

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