NEURAL CODING

Togetherness for stability

Nature **605**, 713–721 (2022)

How sensory representations remain reliable despite considerable trial-to-trial and day-to-day variability in cortical neuronal responses remains insufficiently clear. To investigate this, Ebrahimi et al. performed longitudinal (across days) simultaneous large-scale imaging of the activity of thousands of neurons in primary and higher-order cortical areas, in mice performing a go/no-go visual discrimination task. Despite variability at the single-neuron level, decoder analyses revealed stable stimulus-type coding across sessions that emerged from fast, correlated fluctuations in the ensembles. Correlated fluctuations of task-related neurons resulted in redundancy in visual encoding across cortical areas, with fast dynamics. Furthermore, canonical correlation analyses identified ensemble co-fluctuation modes across cortical areas that orthogonally conveyed stimulus and decision information. These results provide insight into the population coding and inter-area communication that underlie the stability of sensory processing. *LAM*

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NEUROIMMUNOLOGY

Shared COVID- and chemo-fog

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Even after seemingly mild infection with SARS-CoV-2, many suffer from persistent cognitive impairment, or 'COVID brain fog', that resembles the 'chemo-fog' associated with cancer therapy. Chemo-fog is known to be mediated by microglial reactivity and subsequent neural dysregulation, and a study published in *Cell* investigated whether COVID recruits similar pathophysiological processes. In a mouse model of mild respiratory SARS-CoV-2 infection, the authors observed elevated cytokines and chemokines in serum and cerebrospinal fluid, increased microglial reactivity specifically in white matter, a loss of oligodendrocytes and myelin, and decreased hippocampal neurogenesis. These changes persisted for many weeks after the respiratory infection had cleared, and had human counterparts: brain tissue from patients with COVID-19 also showed white-matter-specific microglial reactivity and, intriguingly, cytokine CCL11 levels were higher in the plasma of patients with long-COVID who had 'brain-fog' than in plasma from patients without cognitive symptoms. Systemic CCL11 injection in mice induced white-matter microglial reactivity in hippocampus, along with impaired neurogenesis. Mild respiratory influenza in mice caused similar neuroinflammation and hippocampal pathology, but only transient subcortical white-matter changes. This work starts to unravel the mechanisms that underlie persistent COVID-related cognitive impairments, opening the door for future studies on how these mechanisms may depend on COVID-19 variant, vaccination status and age. *CA*

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FRAGILE X SYNDROME

A fragile imbalance

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Loss of expression of the mRNA-binding protein fragile X mental retardation protein (FMRP), encoded by the *FMR1* gene, causes fragile X syndrome (FXS), the most common inherited form of intellectual disability. A large body of work has demonstrated increased protein synthesis and exaggerated metabotropic glutamate receptor (mGluR)-dependent long-term depression (mGluR-LTD) in FXS model ($Fmr1^{-/y}$) mice, but the mechanisms that underlie these observations and how they contribute to the pathology of FXS have remained unclear. Using proteomics and TRAP-seq (translating ribosome affinity purification with sequencing) to examine ribosome-bound mRNA, Seo, Louros et al. observed upregulation of ribosomal genes in hippocampal CA1 synapses from $Fmr1^{-/y}$ mice and provided evidence for elevated ribosome levels in $Fmr1^{-/y}$ neurons. Consistent with earlier studies showing that increased ribosome availability favors the translation of short mRNAs, the authors found that $Fmr1^{-/y}$ mice had higher levels of translation of short mRNAs, which are enriched for house-keeping genes, and decreased translation of long mRNAs, which are enriched for synaptic genes and autism risk genes. Induction of mGluR-LTD in wild-type brain slices increased ribosomal-protein translation and recapitulated the length imbalance of translating mRNAs, and these effects of mGluR-LTD were occluded in slices from $Fmr1^{-/y}$ mice and could be blocked by selectively inhibiting the transcription of ribosomal RNA. Thus, the authors provide a mechanistic link between altered translation and aberrant synaptic plasticity in a model of FXS. *SW*

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Charlotte Arlt, Luis A. Mejia and Shari Wiseman