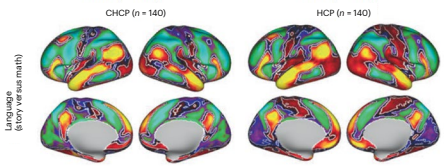
Neuroscience

The Chinese Human Connectome Project



Differences in brain activity in the HCP and CHCP cohorts during a language task. Reproduced with permission from Ge, J. et al. *Nat. Neurosci*. 26, 163–172 (2023), Springer Nature.

Large-scale multimodal magnetic resonance imaging (MR) studies have been instrumental in probing the structure, connectivity and function of the brain. However, such studies have largely focused on populations living in the Western world. To diversify into subjects with a different background, Jia-Hong Gao from Peking University and his colleagues have started the Chinese Human Connectome Project (CHCP).

The team has acquired structural, diffusion, and resting-state and task-based functional MRI data from 366 adults of Han Chinese origin. These neuroimaging data are paired with behavioral, physiological and genetic data. The researchers used essentially the same procedures as those employed by the Human Connectome Project (HCP). Thus, within the limitations of between-study confounding factors, data from these two studies should be comparable. For such comparisons of the neuroimaging data, the researchers focused on 140 subjects for each whose MRI data were of high quality and who had similar demographics.

Based on structural MRI and resting-state functional MRI, the researchers observed differences in some brain areas between the CHCP and HCP cohorts, mainly in higher processing centers of the brain. The most striking differences were, however, apparent in the functional MRI data acquired during a language task, whereas brain activity during a motor task was highly similar. These observations may reflect the substantial differences in the English and Mandarin languages and the underlying processing. Furthermore, the researchers observed differences in brain activity during other tasks involving complex cognitive processes.

The MRI data are publicly available, and the researchers are also working to make associated physiological and genetic data available, although this may be more difficult. Nevertheless, the MRI data form a valuable resource for exploring genetic, cultural and environmental effects on brain development and activity. The researchers plan to expand the resource by increasing the sample size and recruiting participants in a larger age range. They also intend to conduct a traveler study, which would address potential confounding factors associated with the different study sites, scanners and other variation between the CHCP and the HCP, making these two efforts even more directly comparable.

Nina Vogt

Nature Methods

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Immunology

ENTERing the world of immune cells

The adaptive immune system is finely tuned by diverse highly specific ligand-receptor interactions. Being able to decode these interactions at the single-cell level will further our understanding of the complexities of the immune response.

To this end, researchers at Stanford University led by Howard Chang have developed ENTER, a method that leverages lentiviral-mediated cell entry to deorphanize ligand–receptor pairs. First the team engineered lentiviruses expressing a mutant vesicular stomatitis virus protein G (VSV-G) that allows them to bind low-density lipoprotein receptors on host cells without infecting them. When a ligand of interest is co-expressed with the VSV-G, the viruses specifically binds the cells expressing the cognate receptor, allowing these cells to be isolated and further analyzed.

This VSV-G modular viral display system for deciphering ligand–receptor pairing has enabled high-throughput, large-scale T cell receptor (TCR) and B cell receptor (BCR) profiling (Dobson, C.S. et al. *Nat. Methods* **19**, 449–460; 2022).

Similarly, researchers have now engineered viruses to display a single-chain antigen–MHCI (major histocompatibility complex I) to identify the cognate TCRs. This approach was then extended to B cells, where an optimized transmembrane domain was engineered for the surface display of B cell antigens. For example, viruses were engineered to display the receptor-binding domain from SARS-CoV-2 and could be used to detect cells expressing the cognate BCR with high specificity.

Next, the researchers demonstrated that ENTER could be used to deliver cargo to T or B cells in an antigen-specific manner. When they delivered the GFP transgene, 82% of the target T cells and only 0.22% of non-target T cells expressed the fluorescent protein. As a proof of concept, the team engineered peptide–MHC-displaying viruses to deliver a suicide gene to antigen-specific T cells for targeted cell killing.

To further extend the applications of this approach, the researchers then combined ENTER with a droplet-based single-cell RNA-sequencing pipeline. This method, called ENTER-seq, could simultaneously map antigen specificity, TCR repertoire and single T cell gene expression profiles. Using ENTER-seq, the team delved into the memory T cell repertoire in cytomegalovirus seropositive individuals.

ENTER and ENTER-seq are versatile methods not only for deorphanizing immune ligand–receptor pairs but also for high-content screening of single T cells.

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Nature Methods

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