[1] Neuropsychiatric genome-wide association studies (GWASs), including those for autism spectrum disorder and schizophrenia, show strong enrichment for regulatory elements in the developing brain. However, prioritizing risk genes and mechanisms is challenging without a unified regulatory atlas. Across 672 diverse developing human brains, we identified 15,752 genes harboring gene, isoform, and/or splicing quantitative trait loci, mapping 3739 to cellular contexts. Gene expression heritability drops during development, likely reflecting both increasing cellular heterogeneity and the intrinsic properties of neuronal maturation. Isoform-level regulation, particularly in the second trimester, mediated the largest proportion of GWAS heritability. Through colocalization, we prioritized mechanisms for about 60% of GWAS loci across five disorders, exceeding adult brain findings. Finally, we contextualized results within gene and isoform coexpression networks, revealing the comprehensive landscape of transcriptome regulation in development and disease.

[2] The complexity and heterogeneity of schizophrenia have hindered mechanistic elucidation and the development of more effective therapies. Here, we performed single-cell dissection of schizophrenia-associated transcriptomic changes in the human prefrontal cortex across 140 individuals in two independent cohorts. Excitatory neurons were the most affected cell group, with transcriptional changes converging on neurodevelopment and synapse-related molecular pathways. Transcriptional alterations included known genetic risk factors, suggesting convergence of rare and common genomic variants on neuronal population-specific alterations in schizophrenia. Based on the magnitude of schizophrenia-associated transcriptional change, we identified two populations of individuals with schizophrenia marked by expression of specific excitatory and inhibitory neuronal cell states. This single-cell atlas links transcriptomic changes to etiological genetic risk factors, contextualizing established knowledge within the human cortical cytoarchitecture and facilitating mechanistic understanding of schizophrenia pathophysiology and heterogeneity.

[3] Recent studies suggest that human-associated bacteria interact with host-produced steroids, but the mechanisms and physiological impact of such interactions remain unclear. Here, we show that the human gut bacteria *Gordonibacter pamelaeae* and *Eggerthella lenta* convert abundant biliary corticoids into progestins through 21-dehydroxylation, thereby transforming a class of immuno- and metabo-regulatory steroids into a class of sex hormones and neurosteroids. Using comparative genomics, homologous expression, and heterologous expression, we identify a bacterial gene cluster that performs 21-dehydroxylation. We also uncover an unexpected role for hydrogen gas production by gut commensals in promoting 21-dehydroxylation, suggesting that hydrogen modulates secondary metabolism in the gut. Levels of certain bacterial progestins, including allopregnanolone, better known as brexanolone, an FDA-approved drug for postpartum depression, are substantially increased in feces from pregnant

humans. Thus, bacterial conversion of corticoids into progestins may affect host physiology, particularly in the context of pregnancy and women's health.

[4] Flies groom in response to competing mechanosensory cues in an anterior-to-posterior order using specific legs. From behavior screens, we identified a pair of cholinergic command-like neurons, Mago-no-Te (MGT), whose optogenetic activation elicits thoracic grooming by the back legs. Thoracic grooming is typically composed of body sweeps and leg rubs in alternation, but clonal analysis coupled with amputation experiments revealed that MGT activation only commands the body sweeps: initiation of leg rubbing requires contact between the leg and thorax. With new electron microscopy (EM) connectome data for the ventral nerve cord (VNC), we uncovered a circuit-based explanation for why stimulation of posterior thoracic mechanosensory bristles initiates cleaning by the back legs. Our previous work showed that flies weigh mechanosensory inputs across the body to select which part to groom, but we did not know why the thorax was always cleaned last. Here, the connectome for the VNC enabled us to identify a pair of GABAergic inhibitory neurons, UMGT1, that receives diverse sensory inputs and synapses onto both MGT and components of its downstream circuits. Optogenetic activation of UMGT1 suppresses thoracic cleaning, representing a mechanism by which mechanosensory stimuli on other body parts could take precedence in the grooming hierarchy. We also anatomically mapped the pre-motor circuit downstream of MGT, including inhibitory feedback connections that may enable rhythmicity and coordination of limb movement during thoracic grooming. The combination of behavioral screens and connectome analysis allowed us to identify a neural circuit connecting sensory-to-motor neurons that contributes to thoracic grooming.

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