SPATIAL NAVIGATION

Grids and the city

Nature **604**, 104–110 (2022)

Urban upbringing and living have been associated with adverse mental health outcomes, but their effects on cognitive abilities are not well understood. Coutrot et al. addressed this issue using data from 397,162 participants across 38 countries playing 'Sea Hero Quest', a mobile video game designed to measure spatial navigation ability. The authors found that people who grew up in cities had worse spatial navigation skills than people with rural or suburban backgrounds, and that this effect was constant across the lifespan. The difference in navigation skills varied strongly between countries, with the largest effects observed in countries whose cities have a grid-like street pattern. Intriguingly, people performed better in video game environments with topographical similarity to their childhood environment. Having grown up in cities with high street-network entropy was associated with mastering high-entropy game levels, whereas having grown up in low-entropy, grid-like environments led to a performance advantage on simple and regular game layouts. This work highlights the long-term effects of urban design on human cognition and motivates future studies on the mechanisms by which urbanicity shapes navigation skills during childhood. *CA*

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ALZHEIMER'S DISEASE

Glia heterogeneity in AD

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Astrocytes and oligodendrocytes, two major and heterogeneous glial cell populations, are involved in several distinct aspects of the pathophysiology of Alzheimer's disease (AD). Considering the complexity of AD and the heterogeneity of both astrocyte and oligodendrocyte populations, it is important to address whether specific astrocyte and oligodendrocyte subtypes are altered and how they contribute to AD.

In a recently published article, Sadick, Liddelow and colleagues performed single-nucleus transcriptomic analysis of human post-mortem samples of prefrontal cortex from individuals with AD and age-matched non-symptomatic donors. The study was focused on late-onset dementia and individuals with the *APOE* ε2/3 genotype, who have been underrepresented in other sequencing studies of AD. The authors also stringently evaluated the pathological load of the donor tissue and improved astrocyte capture by sorting, which addressed the issue of astrocyte under-sampling in single-nucleus sequencing. Sadick, Liddelow and colleagues identified five transcriptionally distinct oligodendrocyte clusters, none of which exclusively associated with disease state, sex, or donor age. Differential gene expression analysis showed oligodendrocyte cluster-specific changes and both common and cluster-specific changes in the astrocyte population in the samples from donors with AD. The authors discussed some of the identified genes that were differentially expressed according to cell cluster and provide some insight into the potential functions of the oligodendrocyte and astrocyte subtypes in AD. Integration of the single-nucleus transcriptomic data generated here and in three previously published studies of AD revealed consistent identification of oligodendrocyte and astrocyte subtypes, while integration with human and mouse spatially resolved transcriptomic datasets showed that astrocyte subtypes are heterogeneously distributed across cortical layers. This study is an extensive resource that describes the subtype-specific transcriptional changes that occur in two major cell types and provides insight into their potential roles in AD. It will be exciting to elucidate the functional contributions of specific oligodendrocyte and astrocyte subtypes in AD. *EF*

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DOPAMINE

Dopamine surprises

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Action potentials are generally thought to originate near the neuronal soma and then to propagate along axons into synaptic terminals, where they trigger neurotransmitter release. However, a recent paper in *Science* indicates that midbrain dopamine (DA) neurons and their terminals in the striatum may be an exception. Using the DA sensor $GRAB_{DA2m}$, Liu et al. detected spontaneous DA release in striatal slices, which do not contain DA neuron cell bodies. It is known that the axons of cholinergic (ACh) interneurons intermingle with DA axons in the striatum and can stimulate DA release, and indeed the authors found that spontaneous DA release in striatal slices was blocked when they inhibited nicotinic acetylcholine receptors (nAChRs). By directly recording from individual DA axons, Liu et al. observed action potentials in individual axons in response to current injection or application of an nAChR agonist. These action potentials could also be triggered by optogenetic stimulation of ACh neurons. Finally, they found evidence that this mechanism is engaged in vivo during movement and when mice are presented with flashes of light. Liu et al. speculate that that these local action potentials may spread through the DA axon network, allowing ACh to 'broadcast' DA release, and they think that this may allow a mode of DA signaling with greater spatial control than soma-initiated firing. *SW*

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