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Novel analysis sheds new light on the mechanisms of brain development

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Scientists at the Allen Institute for Brain Science have taken an important step in identifying how the brain organizes itself during development. The findings, published in the *Journal of Comparative Neurology* today, describe – in more detail than ever before – the consequences of the loss of a key molecule involved in establishing proper brain architecture during brain development.

The study calls into question the current textbook explanation of abnormal brain development in a well-studied strain of mouse known as reeler, named for its abnormal "reeling" gait, which has been integral in understanding how neurons migrate to their correct locations during brain development. Whereas the reeler cortex has been described for many years as being "inverted" compared to the normal neocortex, the paper published today finds that this abnormal layering is far more complex, more closely resembling a mirror-image inversion of normal cortical layering. Furthermore, the degree of disorganization differs for different cell types in different parts of the brain, suggesting that the correct patterning of the brain involves a complex set of processes selective for specific cell types.

The approach used in this study capitalizes on the combination of systematic high-throughput histology with the wealth of highly specific cellular markers, which were identified by mining for genes with specific expression patterns in the Allen Mouse Brain Atlas, a genome-wide map of gene expression in the adult mouse brain. The authors used a novel approach to employ the most precise molecular markers to date

to identify features of cortical disorganization in the male reeler mouse that were unidentifiable with less specific methods previously available.

"To our surprise, we observed unexpected cellular patterning that is difficult to explain by current models of neocortical development," said Ed Lein, Senior Director, Neuroscience at the Allen Institute for Brain Science and senior author of the study. "These findings have major implications for mechanisms of how normal stereotyped functional brain architecture develops. These patterns suggest that there are a number of additional mechanisms beyond Reelin involved in the proper migration of newly generated neurons to their correct locations, and that different cell types use different cues in that process."

The reeler mouse has a spontaneous mutation in a gene called Reelin that has been implicated in autism. Studies of these mice, which are deficient in Reelin, have elucidated the involvement of this protein and its signaling pathway in the organization of the central nervous system during development, and particularly in cortical lamination, or layering, whereby newly generated neurons migrate from their birthplace to their proper positions in the developing cortex. In the normal cortex this process results in a highly ordered architecture with different neuronal cell types restricted to specific cortical layers. With Reelin deficiency as seen in reeler mice, the migration process of newly generated neurons into the cortex is highly disrupted.

Using in situ hybridization, a technique that allows for precise localization of specific genes, Lein and collaborators were able to follow developmental expression patterns through several stages of development to describe precise effects of Reelin deficiency in several brain areas during neurodevelopment. The authors were able to identify, locate, and track several specific cell types that are abnormally positioned in reeler mice.

Vivid imagery of cortical lamination illustrates the precise disorganization that occurs in reeler neurodevelopment compared to wild type mice. The paper includes 25 figures of compelling full-color, cellular-resolution imagery, one of which is featured on the journal's cover for this issue.

More information: *Journal of Comparative Neurology* 519: 2061-89. doi: 10.1002/cne.22655