

## How the human neocortex folds - a novel role of the extracellular matrix

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Neocortical expansion is thought to underlie the cognitive traits that are unique to humans. This evolutionary expansion is accompanied by cortical folding, which starts to form from around gestational weeks (GW) 20. However, what causes it remains largely unknown. Extracellular matrix (ECM) has been previously implicated in neocortical expansion and here we investigate the potential role of ECM in the formation of neocortical folds. We focus on three specific ECM components localized in the human fetal cortical plate: hyaluronan and proteoglycan link protein 1 (HAPLN1), lumican and collagen I (collectively, HLC). Addition of HLC to cultures of human fetal neocortex (11-22 GW) caused local changes in tissue stiffness, induced cortical plate folding, increased hyaluronic acid (HA) in the cortical plate and required the HA-receptor CD168 and its downstream ERK signaling. Importantly, loss of HA reduced HLC-induced and 22 GW physiological nascent folds and this process was altered in samples with neurodevelopmental disorders, indicating it may be a useful system to study such disorders.

**Primary author(s) :** LONG, Katherine (MPI-CBG)

**Presenter(s) :** LONG, Katherine (MPI-CBG)

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