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Classics never get old: neurotransmitters shape human cortical interneuron migration

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While key developmental functions of neurotransmitters have been described in rodent neural progenitors, there is a lack of understanding of their roles in the human fetal brain. A new study published in *The EMBO Journal* demonstrates that human cortical interneurons that are moving in fused brain organoids express a large repertoire of neurotransmitter receptors whose activation fine tunes selective migration strategies.

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See also: **S Bajaj *et al*** (December 2021)

The exquisite organization of the cerebral cortex reflects the elaborated patterns of generation, migration, and functional maturation of neurons and glia that contribute to its morphogenesis (Gupta *et al*, 2002). The execution of these biological events involves the computation of extracellular cues that are sensed and transduced into key intracellular signaling by neural cells at all developmental steps. Among them, neurotransmitters are released in the embryonic brain where they act beyond their canonical role in neurotransmission as early signals for brain development (Nguyen *et al*, 2001). Neural precursors express a large repertoire of neurotransmitter receptors whose activation can directly or indirectly trigger intracellular molecular cascades that modulate early biological steps, such as proliferation or migration in the cortical wall (Nguyen *et al*, 2003; Manent *et al*, 2006; Avila *et al*, 2013; Murthy *et al*, 2014). While most observations have been made in rodents, the functional significance underlying the activation of such receptors in human progenitors and immature neurons only starts to be revealed. Working with live human embryonic brain sample is ethically and technically challenging; therefore, prepatterned and fused brain organoids (also called brain assembloids) were recently engineered in vitro by three laboratories to follow the migration of human cortical interneurons in health and disease (Bagley *et al*, 2017; Birey *et al*, 2017; Xiang *et al*, 2017).

In this issue of *The EMBO Journal*, Bajaj *et al* (2021) show that some neurotransmitters, naturally present in the embryonic brain, orchestrate the complex migratory behavior of human cortical interneurons generated within fused brain organoids. This *tour de force* has been made possible after improvement of the model to generate cells that more faithfully recapitulate features of cortical interneurons. In mammals, interneurons are generated by progenitors located in the medial and caudal ganglionic eminences of the ventral forebrain (Anderson *et al*, 1997). These cells use a directed migration along tangential streams to integrate the cortical wall from where they disperse using a multidirectional migration mode to further settle via a more confined migration mode in their *bona fide* cortical layer. The development of a new quantitative analytic pipeline for long-term tracking of individual interneuron migration trajectories revealed that human cortical interneurons distribute in three main migration clusters (directed, exploratory, and confined) and that they use similar migration strategies to reach the dorsal region of fused brain organoids, as compared with those observed in the mouse that invade the cortical wall *in vivo* (Fig 1). In addition, single-cell analysis of purified human cortical interneurons that actively migrate to dorsal regions of fused brain organoids showed diverse maturation trajectories and the expression of specific neurotransmitter receptors whose pharmacological modulation alters their migration behavior. More specifically, the authors demonstrated that activation of GABA, glutamate, and glycine receptors controls the directed migration of human interneurons, as seen *in vivo* in the mouse forebrain migratory streams. Also, serotonin may act as guidance cue to underlie the exploratory migration allowing interneurons to acquire a multidirectional migration mode to disperse and further settle in their cortical layers. This last step involves a confined migration, which seems also to depend on the activation of a specific subtype of GABA receptor.

These observations are key because they suggest that an important part of the multimodal migration of cortical interneurons that allow them to reach the cortex is cell-intrinsically programmed. In addition, they suggest that neurotransmitters act directly and/or indirectly as an additional layer of control to favor the interneuron migration modes adapted to progress efficiently within the forebrain parenchyma and further settle in their *ad hoc* cortical layer. Alterations to brain chemistry and in particular to neurotransmitter levels are observed in patients suffering from psychiatric disorders. It is

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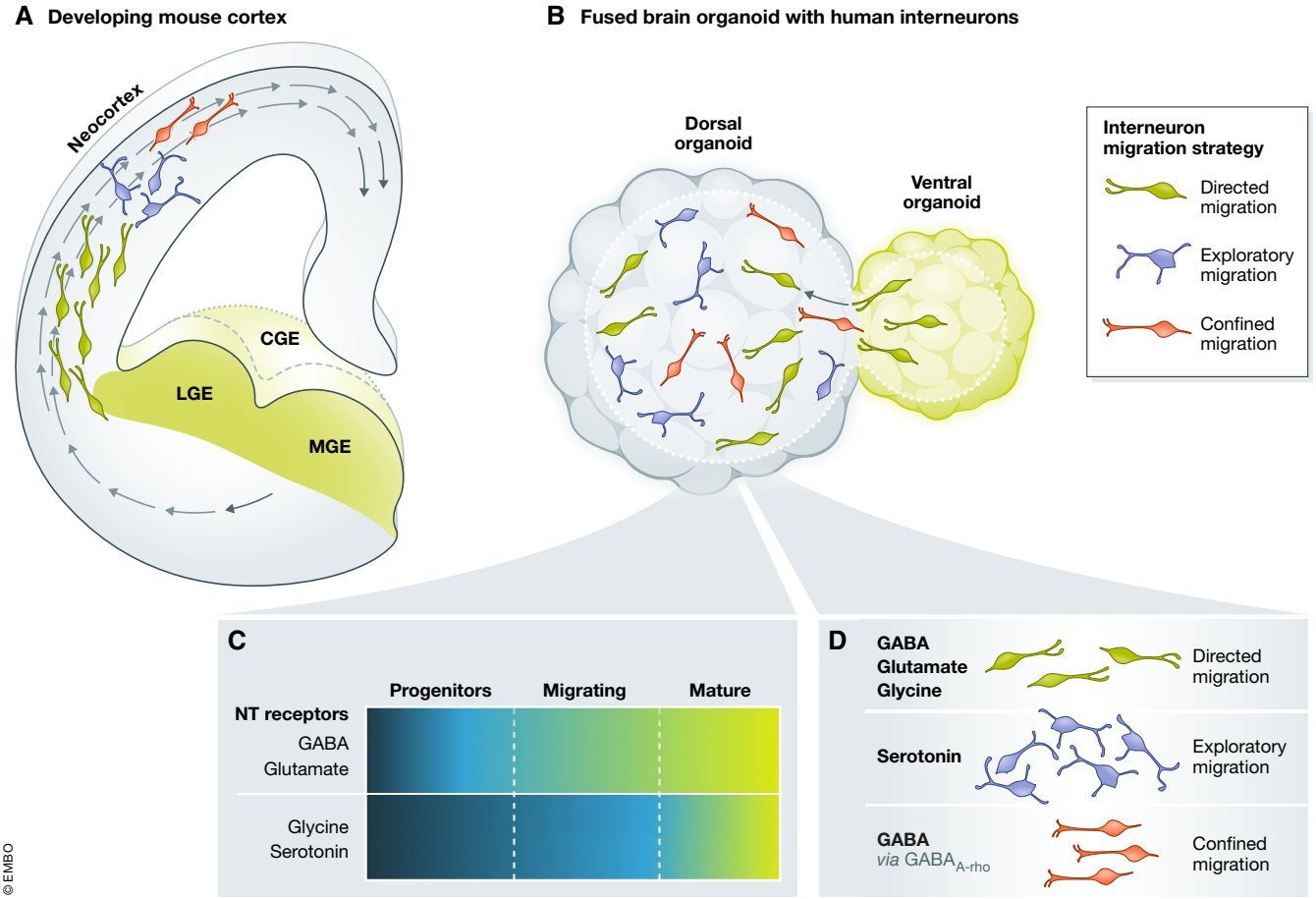

Figure 1. Neurotransmitters control the migration of cortical interneurons in human fused brain organoids.

(A) During cortical development mouse interneurons migrate long distances toward their final destination within the cortex. Interneuron migration is a dynamic and multimodal process where three different main behaviors can be described: directed (green cells), exploratory (blue cells), and confined (red cells). Arrows show the tangential migration pathway. (B) The fusion of brain organoids allows the tracking of human interneuron migration *in vitro*. Arrow shows direction of cell migration. (C) Representative heatmap of the expression level of neurotransmitter (NT) receptor genes in human cortical interneurons at distinct differentiation steps. (D) Schematic overview showing that GABA, glutamate, and glycine regulate direct tangential migration of human interneurons, while serotonin acts as a guidance cue for exploratory tangential migration, and GABA promotes confined migration via activation of $GABA_{A\text{-}rho}$ receptors. CGE: caudal ganglionic eminence; LGE: lateral ganglionic eminence; MGE: medial ganglionic eminence; NT: neurotransmitter.

thus tempting to speculate that changing the landscape of neurotransmitter gradients in the developing brain may interfere with the migration of interneurons into the cortex, thereby affecting proper brain function during adulthood.

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References

Anderson SA, Eisenstat DD, Shi L, Rubenstein JL (1997) Interneuron migration from basal forebrain to neocortex: dependence on Dlx genes. *Science* 278: 474 – 476

Avila A, Vidal PM, Dear TN, Harvey RJ, Rigo JM, Nguyen L (2013) Glycine receptor alpha2 subunit activation promotes cortical interneuron migration. *Cell Rep* 4: 738 – 750

Bagley JA, Reumann D, Bian S, Levi-Strauss J, Knoblich JA (2017) Fused cerebral organoids model interactions between brain regions. *Nat Methods* 14: 743 – 751

Bajaj S, Bagley J, Sommer C, Vertesy A, Wong S, Krenn V, Lévi-Strauss J, Knoblich J (2021) Neurotransmitter signaling regulates distinct phases of multimodal human interneuron migration. *EMBO J* 40: e108714

Birey F, Andersen J, Makinson CD, Islam S, Wei W, Huber N, Fan HC, Metzler KRC, Panagiotakos G, Thom N *et al* (2017) Assembly of functionally integrated human forebrain spheroids. *Nature* 545: 54 – 59

Gupta A, Tsai LH, Wynshaw-Boris A (2002) Life is a journey: a genetic look at neocortical development. *Nat Rev Genet* 3: 342 – 355

Manent JB, Jorquera I, Ben-Ari Y, Aniksztejn L, Represa A (2006) Glutamate acting on AMPA but not NMDA receptors modulates the migration of hippocampal interneurons. *J Neurosci* 26: 5901 – 5909

Murthy S, Niquille M, Hurni N, Limoni G, Frazer S, Chameau P, van Hooft JA, Vitalis T, Dayer A (2014)

Serotonin receptor 3A controls interneuron migration into the neocortex. *Nat Commun* 5: 5524

Nguyen L, Rigo JM, Rocher V, Belachew S, Malgrange B, Rogister B, Leprince P, Moonen G (2001) Neurotransmitters as early signals for central nervous system development. *Cell Tissue Res* 305: 187 – 202

Nguyen L, Malgrange B, Breuskin I, Bettendorff L, Moonen G, Belachew S, Rigo JM (2003) Autocrine/paracrine activation of the GABA(A) receptor inhibits the proliferation of neurogenic polysialylated neural cell adhesion molecule-positive (PSA-NCAM+) precursor cells from postnatal striatum. *J Neurosci* 23: 3278 – 3294

Xiang Y, Tanaka Y, Patterson B, Kang YJ, Govindaiah G, Roselaar N, Cakir B, Kim KY, Lombroso AP, Hwang SM *et al* (2017) Fusion of regionally specified hPSC-derived organoids models human brain development and interneuron migration. *Cell Stem Cell* 21: 383 – 398.e7