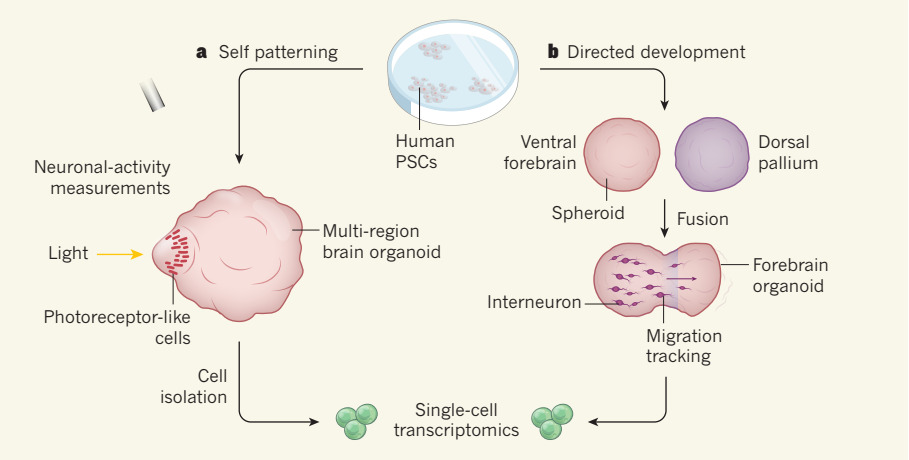

Figure 1 | Two routes to a mini-brain. Structures called organoids that resemble regions of the embryonic human brain can be grown *in vitro* from human pluripotent stem cells (PSCs), which can give rise to every cell type in the body. **a**, Quadrato *et al.*[6] induced PSCs to form a cell layer that self-patterned into organoids composed of multiple brain regions. Measurements of neuronal activity revealed that the organoids contain cells that respond to light in a similar way to photoreceptor cells of the retina, demonstrating that neurons can mature in organoids. The authors isolated single cells and analysed the gene-expression profiles (transcriptomes) to determine the range of cell types in the organoids. **b**, Birey *et al.*[7] used signalling molecules to direct the development of 3D structures called spheroids that resemble two regions of the forebrain (the ventral forebrain and dorsal pallium). Spheroid fusion led to the formation of forebrain-like organoids. Imaging revealed that neurons called interneurons migrated from the ventral to the dorsal region, providing information on brain-region interactions. These authors also performed single-cell transcriptomics.

equivalent to that in the cortex of an embryonic human brain. Individual neuronal projections (dendrites) often made multiple synapses, suggesting that complex networks form by this stage. Quadrato *et al.* found that these synapses could fire, and periods of coordinated firing indicated that organoids contained active neuronal networks.

Finally, the authors showed that a subpopulation of neurons had lowered firing rates after exposure to light. Coupled with transcriptomic data suggesting that organoids contained light-sensing retinal neurons called photoreceptor cells, these data indicate that organoids could be used to investigate how neuronal networks are modulated by physiological stimuli.

It is of note that Quadrato and colleagues found extensive differences in cell composition between organoid batches. This highlights the need to control organoid engineering so as to improve reproducibility when studying disease mechanisms, for example. In the second study, Birey *et al.*[7] (page 54) take a leap in this direction.

The authors used a controlled-patterning protocol to generate 3D structures, which they called spheroids, that resemble one of two forebrain regions: the ventral forebrain, which produces inhibitory neurons called interneurons; and the dorsal pallium, which contains excitatory neurons. Single-cell transcriptomics showed that the spheroid cells were remarkably similar to those from corresponding regions of the human fetal brain.

Next, Birey and colleagues placed spheroids of different types next to each other, and allowed them to fuse over a few days to form forebrain-like organoids. Interneurons from the ventral spheroids migrated into the dorsal regions — similar to the migration route taken by these interneurons *in vivo*. After migration, the interneurons matured. The authors detected stronger neuronal firing in fused organoids after interneuron migration than before.

The researchers used live-cell imaging to track individual interneurons, comparing their behaviour with that of equivalent cells in the human and mouse brain. Certain human-specific aspects of migration were accurately replicated in the fused organoids, presenting exciting possibilities for studying the genes that mediate migration. Indeed, Birey *et al.* next used their system to study the neurodevelopmental disorder Timothy syndrome, which is associated with mutations in a protein that regulates interneuron migration[8].

The authors produced fused forebrain organoids from PSCs that had been generated by inducing mature differentiated cells from patients with Timothy syndrome to become pluripotent. The patient-derived interneurons migrated less efficiently than controls. This is probably due to a defect in the interneurons themselves, rather than in the dorsal environment, because migration remained defective when the researchers fused patient-derived ventral spheroids to wild-type dorsal spheroids. Birey *et al.* have therefore succeeded in generating a controlled 3D system that has both excitatory and inhibitory neuronal activity, and that can effectively model an interneuron migratory disorder.

Both studies reveal the power of high-throughput, single-cell transcriptomics to quantify cell-type diversity in brain organoids. These methods will be valuable for studying how cell composition and gene-expression networks are dysregulated during disease. Nevertheless, it is unclear how transcriptomes will vary between organoid batches, between different stem-cell lines generated from the same patient, and between patients with the same disease. This is particularly important when comparing patient and control organoids, and should be addressed in detail.

It was known[4] that organoid neurons could create synapses. However, serial electron microscopy is a new and elegant approach to studying detailed synaptic structures in organoids, and, it is hoped, to studying the complete map of neuronal networks. It remains to be seen how neurons 'decide' to connect with one another in these complex and heterogeneous tissues, and whether the connections mirror those in the developing human brain.

Much work shows that brain tissue engineered from induced PSCs can accurately model neuronal-progenitor behaviour[9]. The new studies showcase how brain-organoid technology can be improved to study the interactions between brain regions and the way in which mature neurons might function in a coordinated network. Time will tell just how much information these mini-brains can provide. ■

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CORRECTION

The News & Views 'Biochemistry: Origin of a key player in methane biosynthesis' (*Nature* **543,** 49–50; 2017) by Tadhg P. Begley indicated that a paper by Moore *et al.* (*Nature* **543,** 78–82; 2017) solved an outstanding problem — the biosynthesis of coenzyme F_{430}. However, a paper (K. Zheng *et al. Science* **354,** 339–342; 2016) that solved this problem was published shortly before the work by Moore and colleagues. A corrigendum for the paper by Moore *et al.* can be found on page 116.