“Corticogenesis from human pluripotent stem cells leads to the generation of pyramidal neurons with diverse and complex hodological properties”.

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Abstract

The cerebral cortex is the most complex structure of our brain. During evolution, the relative size of the cortex has increased considerably among higher mammals and new cortical areas involved in higher evolved functions have emerged. Here, we describe an intrinsic pathway of corticogenesis from human embryonic (ESC) and induced pluripotent (iPSC) stem cells leading to the sequential generation of first forebrain progenitors and later pyramidal neurons of all six layers identities in a time-dependent fashion, highly reminiscent of the *in vivo* situation. Moreover, the hESC-derived neurons followed a neuronal maturation program where late born neurons of about two months *in vitro* expressed a variety of genes involved in cortical neuronal function and where the majority of the neuronal population was characterized by the presence of synapses *in vitro*. Following transplantation into mouse neonatal brain, human ESC-derived cortical neurons integrated robustly into the host brain and established specific axonal projections and dendritic patterns corresponding to native cortical neurons. The differentiation and connectivity of the transplanted human cortical neurons complexified progressively over several months *in vivo*, culminating in the establishment of functional synapses with the host circuitry. Importantly, our data not only demonstrate *in vitro*, as well as *in vivo*, the cortical identity of the neurons differentiated from human ESC, but also provide a faithful model of human cortical development, from early neurogenesis to neuronal maturation and generation of neuronal circuits, with implications for the modelling and treatment of neuropsychiatric and neurological diseases and brain repair.