Development and modulation of mouse and human cortical circuitry

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SUMMARY

The cerebral cortex is a complicated structure, comprising many different types of neurons and glia, which are organised into cortical layers, and connected through a number of mechanisms and rules that remain largely unknown. Development of the cortex consists of a tightly regulated series of events that ultimately results in this intricately interconnected structure.
The individual neurons that make up the cortex are born from progenitors, migrate to their appropriate position in the cortex and develop highly specialised morphological structures during early brain development. The precise shapes of these axons and dendrites not only help determine the cells to which a neuron connects via synapses, but also the way in which synaptic inputs from these connections are processed electrically within the cell. Thus, the form of a neuron is a major determinant of its function.
The morphology of neurons varies drastically between, and within, different cortical layers. It is unknown whether this diversity is reflected in the development of these different types of neurons. While the cortex is a moderately uniform structure, and the basic layout is similar, there are variations on this theme across cortical areas. The medial prefrontal cortex, for example, lacks a layer 4 in rodents. In humans, the development of the prefrontal cortex is protracted compared to other cortical areas, like primary sensory cortex. Whether this is also the case in rodents is debated.

In **chapter 2**, I examine the development of the dendritic morphology of pyramidal neurons in layers 3 and 5 of the medial prefrontal cortex. Neurons in layer 5 are larger and show more extensive dendritic arborisation than neurons in layer 3. In terms of development, however, I show that there are minor variations in the development of the dendrites of neurons from these layers, but that the overall developmental patterns are similar for both. Furthermore, these patterns resemble those found previously for other cortical areas in rodents, indicating that the development of the medial prefrontal cortex follows a similar timeline to that of other parts of the cortex.

The other important determinant of the way in which neurons integrate incoming synaptic inputs are their intrinsic membrane properties. The cell membrane of a neuron contains ion channels that allow the neuron to regulate the electrical potential across the membrane. The expression and localisation of these ion channels determines, for example, the membrane time constant, which affects the way in which distinct synaptic inputs are integrated over time.
Using the same cohort of layer 3 and 5 pyramidal neurons studied in chapter 2, in **chapter 3** I assess the development of intrinsic membrane properties of these cells. Similar to the results obtained for dendritic morphology, while there are large differences in actual

values of intrinsic properties between neurons from layers 3 and 5, the developmental patterns are roughly the same for neurons in both layers. Synaptic transmission, on the other hand, develops differently between layers, with excitatory transmission increasing more rapidly onto neurons in layer 3, while inhibition lags behind. This is not the case in layer 5 neurons, in which excitatory and inhibitory input increase in step with each other. This discrepancy leads to differences between layers in the balance between excitation and inhibition, and may thus be of importance when studying neurodevelopmental disorders.

In **chapter 4**, I study the effect of the intellectual disability gene Oligophrenin-1 (*Ophn1*) on the development of pyramidal neurons in medial prefrontal cortex, using the datasets compiled in chapters 2 and 3 as a reference. *Ophn1* encodes a Rho-GAP that inhibits the function of RHOA, CDC42 and RAC1. Thus, lack of OPHN1 might lead to constitutive activation of these targets, which is known to play a role in dendrite outgrowth. While studies of OPHN1 have shown dendritic spine growth to be affected, data on dendritic growth are less consistent. Furthermore, OPHN1 has been shown to be important for synaptic vesicle recycling and thus for synaptic fidelity upon high frequency stimulation. Indeed, I find that knockout of *Ophn1* has no major effects on the development of dendritic morphology. Synaptic transmission, on the other hand, is affected, most likely due to decreased synaptic function in response to high frequency stimulation. Interestingly, this effect is transient, and dependent on both age of the animal and cortical layer. This indicates that *Ophn1*, and possibly also other genes implicated in neurodevelopmental disorders, is differentially regulated between cortical layers as well as during development, which should be taken into account when devising future therapeutic strategies.

Group I metabotropic glutamate receptors (mGluRs) have been implicated in neurodevelopmental disorders, particularly Fragile X Syndrome. Results from studies using rodent models of the disease have been promising and have led to several clinical studies targeting group I mGluRs in patients. However, it is not known whether mGluRs function similarly in human cortex as they do in rodents. In **chapter 5**, I show that activation of group I mGluRs depresses excitatory synapses onto human pyramidal neurons. In addition, group I mGluR activation transiently increases the frequency of excitatory synaptic events, and leads to a prolonged increase in the frequency of inhibitory synaptic events, which are likely mediated by somatostatin-expressing Martinotti neurons, as has been shown previously in rodent studies. I thus confirm that group I mGluRs function similarly in human and rodent cortex.