Information processing and storage by the human pyramidal neuron

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Summary

Our advanced cognitive abilities are generally considered as defining our humanity, yet what adaptations our brain has undergone to gain these faculties remains one of the central questions in neuroscience. Traditionally, answers to this question have been sought in the anatomy of our brain, pointing at its large size and large number of neurons. Yet upon further examination, our brain appears to have little exceptional or extra-ordinary features to which our outstanding cognitive abilities can be straightforwardly attributed. The question arises then, to what extent our advanced cognitive capacities may also be down to adaptations on a smaller scale, at the level of neurons and circuits. In this thesis, we explore the electrophysiological properties of human neurons and synapses in an effort to identify which features our neurons share with rodents, and in which they differ. To achieve this, we use whole-cell recordings from living human pyramidal neurons in slices of brain tissue resected during neurosurgery.

The first question addressed is how the dendritic arborisations of human neocortical pyramidal neurons compare to those of other species and how they affect dendritic signal propagation. Reconstructing close to a hundred biocytin-filled human neurons provided the first quantitative dataset on full dendritic trees of human pyramidal neurons. Comparison of their dendritic morphologies to those of mice and macaques showed that human layer 2/3 pyramidal neurons have almost three times as much dendrite and a distinct branching architecture. The effect of the distinct human dendritic arborisation on passive signal propagation was explored using computer modelling, which revealed strong attenuation of signals in human dendrites. This indicates that human neurons may rely heavily on local dendritic computation, but mechanisms may also exist to compensate this signal attenuation to some extent, such as a substantially lower specific membrane capacitance.

The extensive dendritic arborisations of human neurons support a vast amount of synapses, but little is known about their physiology; the properties of short-term plasticity and information transfer at human cortical synapses have never been studied directly. We therefore proceeded to characterise short-term plasticity at synapses between human layer 2/3 cortical pyramidal neurons. Human cortical synapses were found to all show short-term depression, similar to rodent synapses. In contrast to rodent synapses however, they recover much more rapidly from depression and are therefore capable of transferring much more information. Thus, when it comes to receiving information, human cortical pyramidal neurons not only receive an enormous volume of input, made possible by their large dendritic arborisations, but the inputs that they receive are also higher in information content, owing to fast recovering synapses. In order for human neurons to make use of all this information, they will have to be sensitive to the associated rapid fluctuations in synaptic inputs and be able to react quickly with their firing of action potentials. We tested how reliably human neurons can do so using an experimental paradigm called frequency tracking. Human neurons indeed turn out to be capable of encoding much more rapid fluctuations in inputs into the timing of their action potential than juvenile or adult mouse neurons, an ability supported by the faster onset kinetics of their action potentials.

Information is stored in the brain by activity-dependent modifications in the strength of connections between neurons. An important form of such neuron-level information storage, called spike timing-dependent plasticity, has not been investigated directly at a cellular level in the human brain. In the second part of this thesis, we therefore set out to characterise the rules, mechanisms and modulation of spike timing-dependent plasticity at human cortical synapses. We find that human synapses can undergo bidirectional changes in strength throughout adulthood with a wider and reversed temporal window compared to that generally found in juvenile rodents. Employing pharmacological and calcium imaging techniques, we found synaptic potentiation and depression at human synapses is gated by postsynaptic NMDA receptors and that dendritic L-type voltage-gated calcium channels recruited by back-propagating action potentials are important for synaptic strengthening.

Spike timing-dependent plasticity rules are not fixed, but plastic themselves and can be altered by the actions of neuromodulators such as acetylcholine. This thesis ends with an investigation focussed on nicotinic acetylcholine receptors, which show a distinct layer and cell-type specific expression in the neocortex. We aimed to identify to what extent this layer-specific expression translates to layer-specific modulation of spike timing-dependent plasticity rules. Starting in mouse medial prefrontal cortex, we found that endogenous acetylcholine release augments long-term potentiation of glutamatergic synapses on layer 6 pyramidal neurons by activating dendritic nicotinic receptors which amplify back-propagating action potentials. This is in contrast to layer 5 where long-term potentiation was shown before to be supressed by nicotine and so points to layer-specific control over spike timing-dependent plasticity rules by the cholinergic system. Returning to the human neocortex, we found comparable mechanisms were in place there, with functional nicotinic receptors having a similar laminar distribution and cholinergic modulation of synaptic plasticity being opposite in superficial versus deep cortical layers.

The findings presented in this thesis show that many basic electrophysiological features are shared between human and rodent neurons, but importantly, we have also come to identify a number of morphological and physiological differences which may strongly impact the way these cells process and storage information. When considering the origins of the cognitive capacities of the human brain, one therefore cannot merely point to its size and numbers of neurons, but must also take into account an array of neuron-level adaptations that may have large implications for the computational power of the system as a whole.