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Integrative Properties of Cortical Pyramidal Neurons

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English summary

The brain is among the most complex and most studied organs in our body. In the brain, external stimuli are integrated with internal stimuli such as memories and emotions to allow an organism to interact with their environment. While this sounds simple, it involves a wide array of cognitive capacities, ranging from perception to the allocation of attention to relevant stimuli, formation and retrieval of relevant memories and decision making and coordinating behavioral responses. Most advanced cognitive processes in mammals have been localized to the cerebral cortex. Located on the outer surface of the brain, the cerebral cortex is the most visible and most recognizable area of the mammalian brain. Its surface area differs widely between different species, ranging from 3-5 cm^2 in small insectivores and rodents to more than 1100 cm^2 in humans. Naturally, the number of neurons that can be found in different species also varies wildly; human cortex is thought to contain around 19-23 billion neurons, while the amount of neurons found in the cortex of the rat is much lower and is estimated between 21 and 30 million. However, it is difficult to directly relate global measures like brain size to intelligence or general cognitive abilities. Intrinsic connectivity of neurons and the electrophysiological ability to integrate signals is more important for understanding how the brain performs cognitive skills and this thesis was aimed at investigating these concepts.

One hallmark of the cortex is the division in layers and the different types of neurons that exist within each layer. In **Chapter 2** of this thesis, the precise structure of the axons of thick- and slender tufted neurons from layer 5 of the somatosensory cortex was studied. Individual neurons were filled with biocytin and subsequently stained after which automatic reconstruction of the entire axon was performed using a newly developed reconstruction pipeline. This allowed full 3D reconstruction of axon morphology and moreover, precise quantification of the length and distribution of the axons within the cortical area. The results showed that the two different neuron types in have distinct, parallel, intracortical projections properties. Slender tufted neurons project primarily to the more superficially situated L2/3, while thick tufted L5 neurons show more prominent lateral connections to neighboring areas. In addition, the total axonal length of slender tufted neurons was far greater than that of thick tufted neurons. The precise quantification of axonal length over the full 3D projection zone at the

micrometer level described in this study constitutes a major breakthrough, as this had not been achieved before. Modeling studies of cortical connectivity will greatly benefit from this ability to obtain precise, quantitative data on axon morphology.

Chapter 3 contains a further explanation of the method that was developed to reconstruct axons. Given the considerable length of individual axons and large number of bifurcations, reconstructing axonal morphology has always been labor intensive and has therefore not been carried out regularly. The newly developed semi-automated technique explained in this chapter greatly reduces the time spent axon reconstruction, and furthermore greatly reduces the risk of errors that exists with axon reconstructions performed by humans. This is a major advancement for unraveling the precise architecture of the cortex, as the semi-automated technique enables large-scale reconstruction of axons and therefore more precise quantification of cortical networks.

In **Chapter 4**, attention is focused to the prefrontal cortex (PFC), a brain area involved in higher order cognitive processes. While the primary sensory cortex is studied widely, much less is known about the cortical network and physiological properties of the PFC. Therefore, action potential firing and the occurrence of high-frequency action potential bursting was studied in L2/3 and L5 of the PFC. First, the frequency of action potential bursts at which calcium spikes occur was determined *in vitro*, then the presence of bursts at this critical frequency was investigated in awake animals. Action potential spiking at critical frequencies was observed among both L2/3 and L5 neurons, but the frequency with which bursts occurred was higher for L5 neurons compared to neurons in L2/3. Therefore, it was concluded that action potential spiking above a critical frequency and calcium electrogenesis, which has been strongly linked to this phenomenon, can be observed in the PFC of awake rats. These results suggest that association of segregated neuronal input to individual neurons might be achieved through a coincidence detection mechanism driven by calcium spikes.

Chapter 5 was aimed at determining the presence of action potential bursts and possible layer-specific activity during attention an attention task. The 5-choice serial reaction time task (5-CSRTT), in which rats learn to respond with a nose poke to brief presentation of a visual cue in order to obtain a reward, was used to assess attention behavior. Neural activity was studied by quantifying the expression of the immediate early gene c-fos, which can primarily be observed after high frequency bursts of action potentials. In order to study the effect of

attention on c-fos expression, rats were divided in a group with a high attentional load (short stimulus presentation) and a low attentional load (long stimulus presentation). Manipulating attentional load greatly affected behavioral performance but c-fos expression did not differ between the two experimental groups. Because of the small group sizes employed in this study, the results do not permit strong conclusions on the expression of c-fos during the 5-CSRTT or possible layer specificity. However, the study did provide valuable insights for the design of future studies.

In conclusion, the studies described have shed new light on anatomical and physiological aspects of cortical organization. The newly developed technique for high-throughput axon reconstructions can be used to perform axon reconstructions at a far greater scale and with high precision and will thereby permit better understanding of cortical wiring. The experiments performed in the PFC are an important step in unravelling the properties of a brain area that has been implicated in many cognitive behaviors and mental disorders but is far less understood than primary sensory areas. The studies reported in this thesis show that cellular mechanisms previously only described in sensory areas can also be observed in the PFC *in vivo.* These experiments therefore provide an important step in a more circuit-based approach of the study of the PFC.