Inhibitory interneurons of macaque primary visual cortex

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Summary

Inhibitory interneurons play a crucial role in cortical activity. This thesis examines the distribution of the subunits of AMPA and NMDA glutamate receptors on different classes of inhibitory cells expressing calcium binding proteins, in macaque V1. Furthermore, it provides evidence for differential impact of AMPA and NMDA receptor blockers in a complex visual task, with a specific interneuronal effect. It also seeks to bridge rodent and primate interneuronal classifications. To these ends, we used a variety of anatomical, physiological and pharmacological techniques. Importantly, we employed objective automated data analysis routines for anatomical data and provided numerous new insights into systematic mapping of interneurons, reconciling previously contradictory evidence.

In **Chapter II** we investigated whether the distribution of calcium binding proteins (CBPs) in inhibitory interneurons is similar between rodents (mice) and primates (macaque monkeys). Our results revealed both similarities and differences between the two species, with a higher differentiation of sub-layer CBP pattern in macaque. These data are potentially useful for translating mouse data to primate applications.

In **Chapter III** we analysed the AMPA receptor expression pattern of different inhibitory interneuronal populations, as defined by the calcium binding proteins they express. We found that there are two classes of inhibitory interneurons according to these criteria: PV-immunoreactive (PV-IR) cells that exhibit a high probability of expressing the AMPAR subunits GluA2 and GluA3, as opposed to CB-IR and CR-IR that have a high probability of expressing GluA1 and GluA4.

In **Chapter IV** we extended this analysis to the NMDA receptor and again found a dichotomy between PV-IR cells on the one hand, and CB-IR and CR-IR cells on the other. We found that PV-IR cells have a relatively low probability of expressing all GluN2 subunits, and therefore functional NMDARs, while CB-IR and CR-IR cells have a high probability of expressing all GluN2 subunits. The GluN2 expression was mostly restricted to the cell body in PV-IR cells, and much more extensive in CB-IR and CR-IR neurons.

In **Chapter V** we tested the effects of AMPA and NMDA blockers in a texture-defined figure-ground segregation task in macaque. This task has been previously demonstrated to elicit distinct phases in V1 activity for feed-forward and recurrent processing. The early, feed-forward, signal is similar for the figure and ground conditions. The late, recurrent, signal is enhanced for figure and supressed for the ground condition. We found that AMPA blockers reduced the feed-forward signal associated with the task, while NMDA blockers lead to a reduction in the difference between figure- and ground-elicited recurrent activity. The GluN2B subunit-specific blocker Ifenprodil lead to a distinct reduction in the recurrent activity difference, characterized by higher ground activity compared to the control condition. This effect suggests a GluN2B mediated reduction in local inhibitory activity.

This body of work gathers systematic evidence for the classification of inhibitory interneurons in macaque cortex. In this, it identifies a relationship between receptor expression pattern and functional properties, that transcends morphological heterogeneity. Our data suggest that fast spiking PV-IR cells are highly likely to express the GluA2 and GluA3 AMPAR subunits, and less likely to express any GluN2 NMDAR subunits. Intermediate-spiking CB-IR and CR-IR cells on the other hand, are highly likely to express the GluA1 and GluA4 AMPAR subunits and all GluN2 NMDAR subunits. In this context, we also established the impact of glutamate receptor blockers in a complex visual task, and found mostly AMPA driven feed-forward, and NMDA driven recurrent activity. We also found a specific GluN2B mediated recurrent inhibitory effect. Since our receptor data show no difference between the expression of the GluN2B subunit and other GluN2 subunits on different cell types, this effect is most likely mediated by feed-back projections targeting specific receptors. Additionally, we found evidence relating mouse inhibitory neuronal populations to their primate counterparts, accompanied by an evolutionary increase in complexity of their distribution pattern. Identifying such large scale rules for neuronal behaviour is an essential step in understanding how diversity ensues, and how basic cellular properties give rise to complex neuronal processing.