Inhibitory interneurons of macaque primary visual cortex

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Chapter VI

General discussion

The current results confirm that it is possible to divide inhibitory interneurons of macaque primary visual cortex into two relevant categories that bridge between the various existent classification criteria (**Chapter I**), and correlate with calcium binding proteins (CBPs) they express. To these criteria we added that of receptor expression, which may be the key to explaining the functional dichotomy of interneurons (Zaitsev et al. 2005).

Objective quantification

A significant contribution of the current work is the use of automated objective thresholding and counting algorithms (Wouterlood 2005; Wouterlood et al. 2008; Boulland et al. 2009; Beliën and Wouterlood 2012) for deriving appropriate measures for our anatomical research questions (Kooijmans, Self, et al. in preparation; Kooijmans, Sierhuis, et al. in preparation; Kooijmans et al. 2014, **Chapters II, III, IV**). We believe that, next to good histological and stereological practices (Braitenberg and Schüz 1998), the use of such objective quantification methods brings a new level of reliability and replicability to anatomical studies.

Species correspondence

The existence of a large degree of architectural correspondence between rodents and primates is a basic assumption for the use of rodent models for the development of theories and therapies with primate (human) reach. We therefore compared the cross-species relevance of two standard inhibitory interneuron labelling schemes, for the two most representative species utilized as research models of these phylogenetic orders – mouse (rodents) v. macaque (primates).

The first one, based on CBPs only (PV, CB and CR), is standard for macaque (Kooijmans, Self, et al. in preparation; Kooijmans, Sierhuis, et al. in preparation; Härtig et al. 1996; Sherwood et al. 2007; Disney and Aoki 2008; Kooijmans et al. 2014), and could be applied to both species successfully. Our results also show higher complexity in interneuronal layer expression profiles of macaque primary visual cortex, as compared to mouse, and demonstrate this quantitatively for the first time (Kooijmans,

Sierhuis, et al. in preparation, **Chapter II**). We also found preserved quantitative features between mouse and macaque, as the layer profile of CR-IR cells, as well as the PV to CB ratio. The CB to PV relationship is interesting as the two populations appear to have complementary effects, exhibit complementary layer depth distributions with alternating peaks in macaque, while originating from the same sub-cortical progenitor population (Ma et al. 2013). The other labelling scheme (PV, SST, 5HT3aR), that distinguishes between largely distinct inhibitory interneuronal populations in mouse cortex (Lee et al. 2010; Rudy et al. 2011), identifies no cell bodies in macaque V1 for 5HT3aR and only very few for SST (Hendry, et al. 1984; Campbell et al. 1987; Jakab and Goldman-Rakic 2000; Watakabe, et al. 2009; Kooijmans, Sierhuis, et al. in preparation, **Chapter II**). Thus, the latter labelling procedure cannot be applied in macaque V1, and cannot be used to bridge inhibitory neuronal architecture across the two species.

Considering the cross-species applicability of the CBP-based labelling scheme, we believe that it constitutes a better basis for the extension of results from rodents to primates, despite achieving less clear-cut population boundaries in mouse (Kooijmans, Sierhuis, et al. in preparation; Park et al. 2002; Gonchar et al. 2007, **Chapter II**). The fuzzier CBP-IR populations in rodent become sharper in macaque, while preserving overall expression ratios (Kooijmans, Sierhuis, et al. in preparation, **Chapter II**), and may be regarded as a cue for evolutionary differentiation of inhibitory populations, rather than a suboptimal labelling scheme.

Linking anatomy and function

The functionality of neuronal populations is influenced by the manner in which they process incoming signals. This depends both on the source of incoming signals, as well as the receptors the target neurons express. We demonstrated that inhibitory interneurons can be divided into two different classes depending on the glutamate receptors they express (Kooijmans, Self, et al. in preparation; Kooijmans et al. 2014, **Chapters III & IV**). The first category includes parvalbumin immunoreactive (PV-IR) cells, which are more likely to express the GluA2 and GluA3, rather than

the GluA1 and GluA4 AMPA receptor (AMPAR) subunits (Kooijmans et al. 2014, **Chapter III**), and also have a low probability of expressing all GluN2 NMDA receptor subunits (Kooijmans, Self, et al. in preparation, **Chapter IV**). The second category includes CB-IR and CR-IR cells, which are more likely to express the GluA1 and GluA4 AMPAR subunits (rather than GluA2 and GluA3), and highly express all GluN2 NMDA. The expression patterns for both GluA and GluN2 subunits on macaque PV-IR population suggest lower synaptic calcium influx through both AMPA and NMDA glutamate receptors, as compared to CB-IR and CR-IR cells. The predicted difference in calcium influx overlaps with firing properties of macaque interneurons and is likely to impact functional properties of the two populations it delineates.

Pharmacology

The observations we made regarding receptor expression suggest that it is possible to selectively block GluA2-lacking AMPARs on CB-IR and CR-IR inhibitory cells using pharmacological methods (Koike et al. 1997; Strømgaard et al. 2005; Hull et al. 2009; Kooijmans et al. 2014) This is an important contribution, as it could allow for specific impact of a globally delivered drug.

In a different pharmacological approach, we established that the input of the primary visual cortex is regulated by different glutamate receptors as a function of feed-forward or feed-back connectivity (Self et al. 2012, **Chapter V**). The layers targeted by feed-forward and feed-back projections to macaque V1 are distinct (Rockland and Pandya 1979; Lund 1988; Rockland 1994). In rodents however, Gonchar and colleagues showed that both FF and FB projections target similar (PV-IR) GABA-ergic interneuronal populations, however in different layers (Gonchar and Burkhalter 2003), and with different sub-cellular localization (Gonchar and Burkhalter 1999). Overall, it is still unclear whether the pharmacological effect we observed in macaque (Self et al. 2012, **Chapter V**) is due to connection specificity to different neuronal targets, or to different synaptic targets, on similar neuronal populations. Further investigation is needed to establish the detailed target specificity of FF and FB in macaque V1.

Concluding remarks

We propose the division of inhibitory interneurons into two functional classes (Kooijmans, Self, et al. in preparation; Zaitsev et al. 2005; Kooijmans et al. 2014, **Chapters, III, IV**). Morphological variety (Ramón y Cajal 1899; Jones 1984; Kisvarday et al. 1986; Kisvárday et al. 1990; DeFelipe and Jones 1998; Nieuwenhuys et al. 2007; Ascoli et al. 2008; DeFelipe et al. 2013) is a valid criterion for identifying numerous types of inhibitory interneurons, and remains a determining factor in how neurons integrate incoming input, as well as how they deliver it to their targets. Morphology may however be a by-product of different local architectural requirements and connectivity, superimposed on a far smaller physiological diversity, as previously shown by Zaitsev and colleagues (2005). Our proposed classification is therefore additional support for exploring how a specific cell type acquires its morphology and how this impacts functionality, in a population morphologically more diverse than excitatory cells.

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