4 Summary and Reflections

4.1 Summary of results

In the above body of work, I describe the anatomy of the von Economo neurons. I have shown that the VENs in fronto-insula and anterior cingulate cortex form a single population when characterized on the basis of their dendritic architecture, and that, using this same criteria, this population is distinct from pyramidal neurons. In particular, I have shown that a typical VEN has a sparse dendritic tree, with less than half the total dendritic length of a typical pyramidal neuron.

I have additionally shown that the VENs express a rich array of surface receptors, many of which implicate these cells in the mediation of social decision making (see below). For example, I found that most VENs strongly express the D3 receptor, whereas only about half of the layer 5 pyramidal cells do, and that this expression is dense on the soma and on the apical dendrites. Other notable discoveries include the VEN expression of the 5HT-1b receptor, and the 5HT2b receptor, the latter of which is the first described occurrence of this receptor on cells in the human brain.

These results lend themselves to a hypothesis supporting the role of the VENs in fast decision making during uncertain circumstances, particularly in social contexts. We probed this hypothesis functionally by doing an fMRI study of humor, which activated both FI and ACC.

4.2 The social cognition hypothesis

In light of the above evidence, we hypothesize that the recently evolved von Economo neurons are a functional specialization of a circuit involved in making appropriate responses during quickly changing, ambiguous circumstances (Allman et al., 2005). Links between the von Economo cells and interoception – including, literally, "gut feelings" – could provide the basis for their role in fast decision making in the absence of explicit reasoning. In apes and humans, complex social interactions between conspecifics provide a forum in which this cognitive capacity would prove to be particularly useful. This is because participants must rapidly synthesize an enormous number of relevant but often ephemeral informational cues in order to act appropriately. We thus propose that von Economo cells mediate the rapid assessments and behavioral modifications required for the successful navigation of social interactions.

4.3 Future directions

As with any body of research, more work needs to be done. The receptor immunohistochemistry done in this paper is by no means exhaustive, and new antibodies are developed every year, increasing opportunities for exploration. Double labeling of various receptors will indicate if they are co-expressed; for example, V1a vasopressin (see Appendix) and D3 colocalization would further implicate these cells in mediating the rewarding aspects of social bonding. We can also further explore the role of the GTF2i protein that is absent in William's syndrome patients and upregulated in humans compared to other primates (see Appendix).

There are also additional, basic questions about the VENs that could be addressed in the future. For example, are the VENs inhibitory or excitatory? Certainly all of the available evidence suggests that they are excitatory – for example, they are projection neurons, and have a receptor profile similar to other layer 5 pyramidal neurons – but with the successful application of an antibody that recognizes GAD or EEAC, this question may be definitively answered. Another basic question that I was unable to explain during my tenure as a graduate student was the origin of the axon in these cells. In many Nissl-stained VENs, the axon appears to sprout from the side of the soma. However, confirming this will require either electron micrographs or the colocalization of axon-specific markers with somatic marker. Given the confluence of axons in the grey matter, this is not a straightforward task, and may require the application of an antibody specific to the axon hillock itself. Finally, I am extremely interested to see the results of the computational models of the von Economo Golgi stains. Will the VENs have a distinctive physiological "fingerprint" as a result of their unusual dendritic morphology? And if not, what else might have driven the evolution of a new cell shape so late in phylogeny?

There are additional ways to test the social cognition hypothesis (with respect to VENs) in addition to immunohistochemical and Golgi methods. Stereological counts of the VENs will be illuminating, particularly performed on brains of donors who had pathological disorders involving social dysfunction: autism, William's syndrome, acallosal agenesis, and fronto-temporal dementia. New and imaginative fMRI studies will bolster (or debunk) the hypothesis regarding FI and ACC coactivation during social interactions. Finally, lesion studies will permit us to assess whether damage to FI results in a selective deficit in social intelligence.

5 Appendix A – V1a Receptor and GTF-2ii in the VENs

Functional imaging paradigms associated with social behavior reliably activate both VE cell regions. For example, both ACC and FI are active during the act of lying (telling untruths), and they are both active when a subject receives an unfair offer while playing the Ultimatum game(Sanfey *et al.*, 2003; Spence *et al.*, 2004). Studies by Bartels and Zeki show both regions are active when subjects view the face of their love partner or child (Bartels and Zeki, 2000; Bartels and Zeki, 2004). Singer and colleagues showed in 2004 that both VE cell regions are active when a person feels empathy for pain, that is, when they know that their loved one, outside of the scanner, is being delivered an electric shock (Singer et al., 2004b). Interestingly, the extent of activation an individual shows under these conditions is directly correlated to that individual's score on a trait measurement for empathy. Finally, in a separate study, Singer and colleagues demonstrated that left FI is specifically active when subjects view faces of individuals who are reported to behave in a trustworthy fashion (Singer et al., 2004a).

5.1 Vasopressin V1a

Figure 16 VEN from ACC labeled with a V1a receptor antibody.

Fortunately, there is an excellent molecular model that allows us to specifically implicate the von Economo neurons in these various social behaviors. A body of work by Insel and Young indicates that the oxytocin and vasopressin V1a receptors mediate social bonding (Insel et al., 1998; Lim et al., 2004; Young et al., 2001). Insel and colleagues also suggest that these molecules may interact with dopamine to impart the rewarding aspects of social bonding (Insel *et al.*, 1998). I tested adult human ACC and FI tissue for reactivity to antibodies raised against the vasopressin V1a, V1b, V2 receptors and oxytocin receptor. My results show that the antibodies specific for the V1a receptor label a subpopulation of VE cells, as well as pyramidal neurons in layers 2/3 and 5 of ACC and FI (Figure 20). V1b receptors, while apparent on a subpopulation of large pyramidal cells in layer 5 of ACC, did not label the VENs. However, the pattern of labeling was interesting in that the apical dendrites labeled with the V1b receptor antibody formed columns that spanned layer 5 to layer 1. The vasopressin V2 and oxytocin receptor antibodies did not reveal any specific labeling.

5.2 GTF-2iRD1

One of the most remarkable immunocytochemical findings for the VENs is their strong dendritic staining with the antibody to a gene product for the gene GTF2iRD1 (see Figure 21). This finding is the result of collaboration between the Korenberg and Allman labs. GTF2iRD1 together with GTF2i are duplicated genes which are part of the set of genes that are deleted in William's syndrome (Pérez Jurado et al, 1998). The loss of this duplicated pair is associated with poor visuospatial abilities and possibly hypersocial behavior in this syndrome (Hirota et al, 2003; Korenberg, personal communication).

GTF21RD1's duplicate GTF2i is among the 25 most upregulated genes in an array of 7645 genes tested in a comparison between humans and chimpanzees (Preuss et al 2004). GTF2i expression is 2.5 to 4.2 times greater in humans than in chimpanzees. The gene products for GTF2i and GTF2iRD1 function both as transcription factors in the cell nucleus and signal transducers in the cytoplasm (Roy, 2001).

In the VENs, the gene products extend far out into the dendrites where they may mediate interactions between the dendritic periphery and gene transcription in the nucleus (Figures 21 and 22). This cytoplasmic labeling is constrained to layer 5 in humans and does not occur at all in monkeys. In monkey tissue, the antibody for this gene product labels cell nuclei only, without layer specificity (Figure 21).

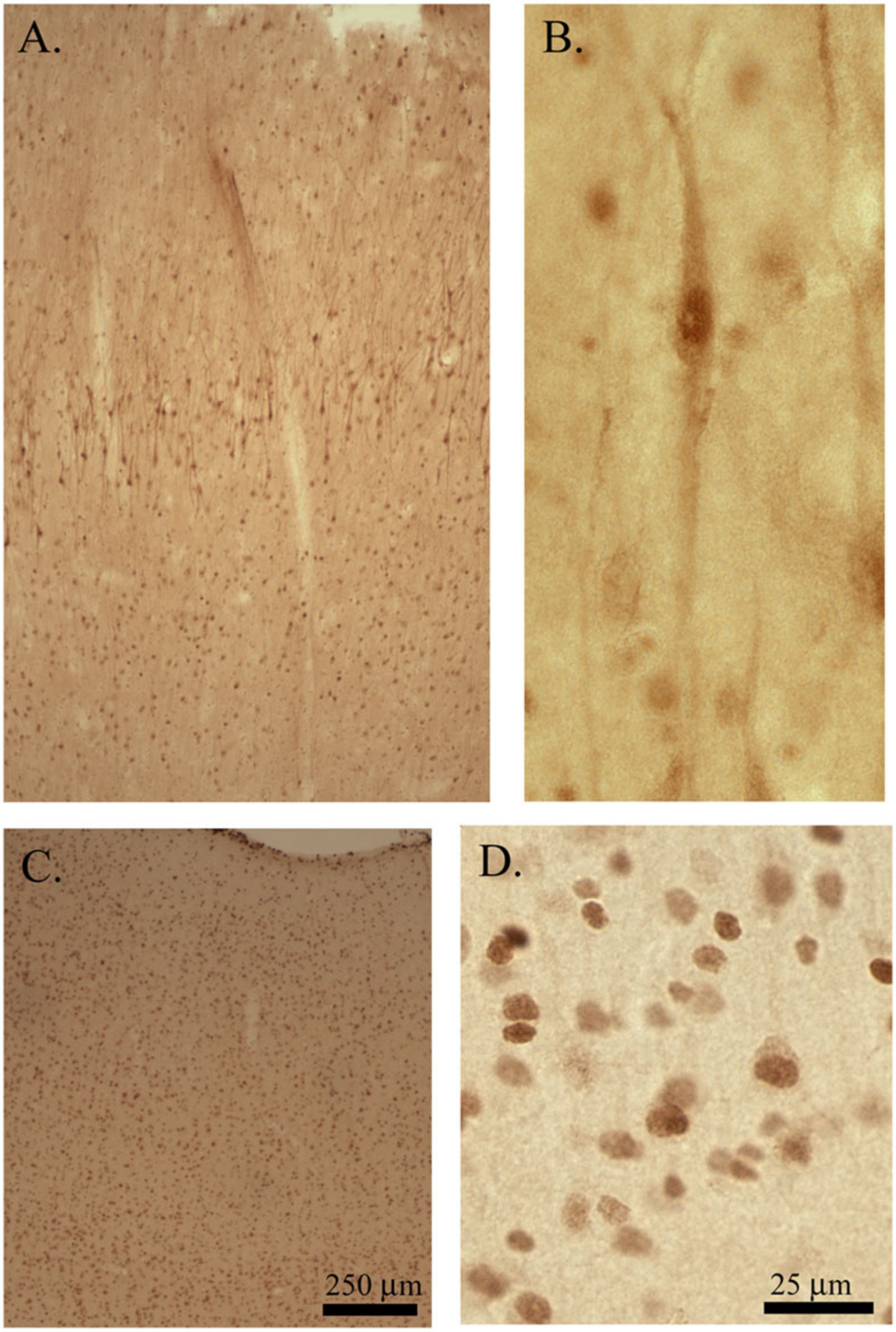

Figure 17. Labeling for the protein product of GTF2i-RD1, a gene that is deleted in William's syndrome. (A) Low power photomicrograph of human FI (16 year old male). Note extensive cytoplasmic labeling in layer 5. (B) High power image of a labeled von Economo neuron from the same specimen as in (A). (C) Low power photomicrogaph of macaque frontal cortex labeled with the same antibody as in (A) and (B). Note non specific nuclear labeling. Scale bar applies to both (A) and (C). (D). High power photomicrograph of neurons from (C). Scale bar applies to both (D) and (B).

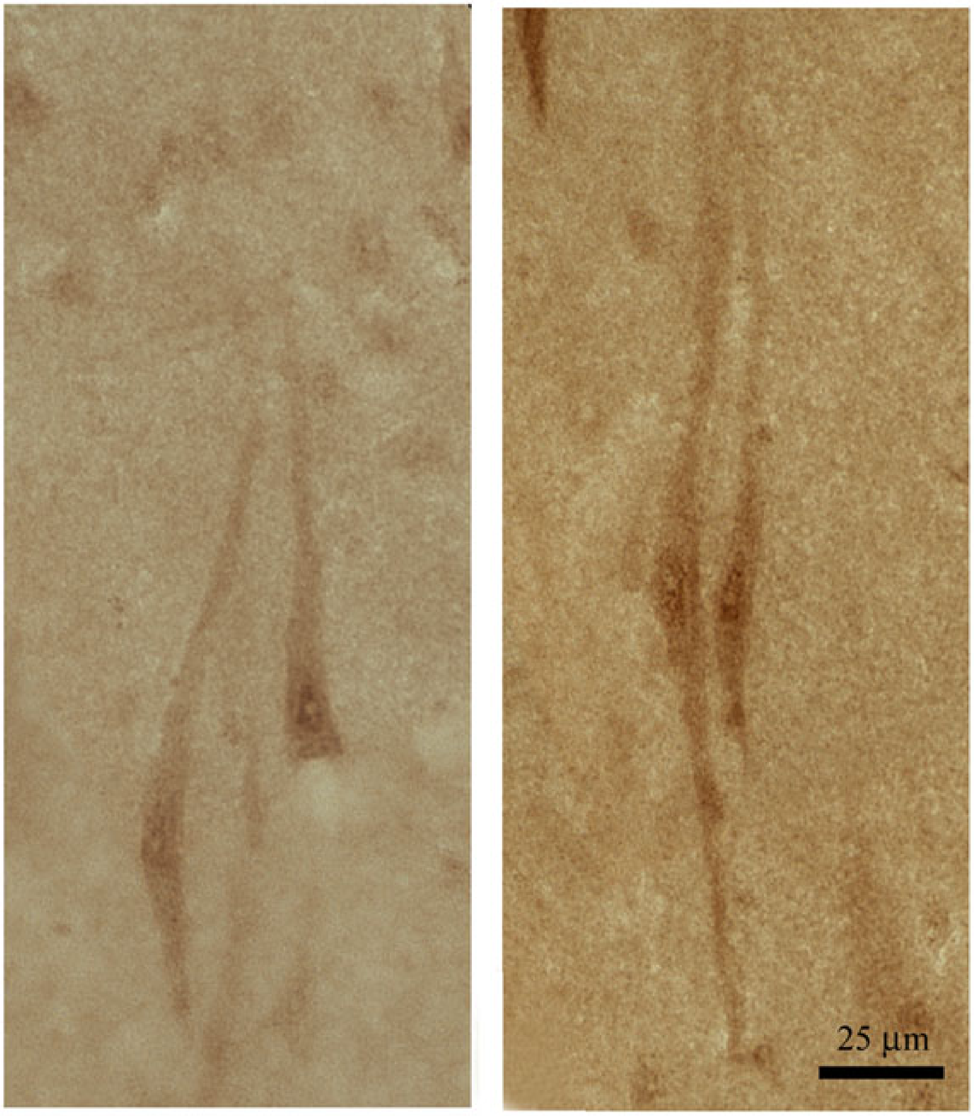

Figure 18 VENS and a pyramidal cell in ACC labeled with an antibody against the protein product of GTF2iRD1. Scale bar applies to both images.

6 Appendix B – Table of Immunohistological Results

Immunohistochemistry on human tissue is subject to inconsistencies that arise from variations in postmortem interval, fixation length, and postfixation storage time, not to mention all of the vagaries inherent in the art. For this reason, the following table should be taken with a grain of salt. For example, purely negative results, labeled “no labeling,” may not necessarily indicate that absence of that particular molecule, but merely that the antibody did not recognize it. Non-specific results – labeling of everything, including extracellular space – are also denoted by “no labeling.” Negative results are reportable only when a cell population that excludes the von Economo neurons is distinctly labeled by a particular antibody – for example, those for calbinden, calretinen, and parvalbumin. In some cases, the labeling profile does not lend itself to identification of the labeled elements by virtue of morphology. For example, the serotonin transporter antibody labels elements throughout the grey matter, but it is impossible to say whether the VENs are included in this labeling without a cytoplasmic or nissl counterstain. Use of fluorescent chromophores would be the best approach in these cases, for I tried in several instances to do double labeling with immunoprecipitation chromagens (i.e., DAB, TMB, and others), without satisfactory results.

antigen	VENs labeled?	comments
5HT-1b R	yes	Labels pyramids only in layer 2/3, neurons and fibers in layer 5, and fibers only in layer 6. Also labels pyramids in human BA 47, 6, 32, 9, and 10 and macaque frontal cortex.
5HT-2a R	faint	Non specific; labels all pyramids and VENs, similar to macaque results described by Goldman-Rakic.
5HT-2b R	yes	Layer 5 specific in ACC and FI. In macaque, labels frontal cortex with region specific profile.
5HT-2c R	no	No labeling
5HT-3 R	no	No labeling
β-3 adrenergic R	yes	Pyramids and VENs in layer 5 ACC; FI not tested
Calbindin	no	Layer 2/3 pyramids, glial cells in ACC
Calretinin	no	Small round bipolar cells in layer 2/3
Caspase-3	no	Pyramids, a few VENs
DAT	yes	Soma and apical of VENs, somas of layer 3 and 5 pyrs, punctate labeling throughout extracell space and white matter
GABAb R	yes	Deep layer labeling of pyramids and VENs. Most prominent on basal part of soma.
GAD	–	Labeled nucleoli only (?)
GAT-1	–	Labeled "cartridges" as reported previously, but was unable to determine whether they are apposed to VENs
GluR1	yes	Pyramids and VENs in layer 5 ACC; FI not tested
GluR2	yes	Pyramids and VENs in layer 5 ACC; FI not tested
HR1 R	no	No labeling
Kappa opioid R	no	No labeling
Map-2	yes	All neurons
Mu opoid R	no	No labeling
NMDAr1	yes	Pyramids and VENs in layer 5 ACC; FI not tested
Non-phosphoylated neurofilament	yes	Large pyramids in all layers and VENs
OxytocinR	no	No labeling
Phosphorylated neurofilament	–	Every axon
Parvalbumin	no	Multipolar non-spiny interneurons
Prolactin R	no	No labeling
Serotonin transporter	–	small punctate clusters in deep layers, many agains blood vessels
Tau	–	All fibers
Trk-b	yes	Somas and apical dendrites of VENs and layer 5 pyramids in ACC; FI not tested
Tryptophan hydroxylase	no	No labeling
Vasopressin R V1a	yes	Somatic, all pyramids and VENs
Vasopressin R V1b	no	Long apical dendrite labeling from Layer 5 pyramids up to Layer 1

Table 6 Table of immunohistochemical results. R = receptor.

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