A Review of known properties of von Economo Neurons (VENs)

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1 Introduction

Although it is more than a hundred years since their discovery, very little is known about the neurophysiology, connectivity and functional roles of von Economo Neurons (VENs). They were described by Betz in 1874 and Ramón y Cajal in 1900, but Constantin von Economo was the first scientist who took a particular interest on them and provided the first detailed description of their morphology and cortical distribution [von26]. A historical review and the German to English translation of von Economo's original paper [von26] can be found in [SMG$^+$11]. He called them "Stäbzellen" (rod cells) and "Korkzieherzellen" (corkscrew cells), but today, in his honour, they are referred to as von Economo Neurons (VENs) [AWTH05]. He found them in Layer Vb of the regions of the human brain which we now call Anterior Insular Cortex (AIC) and Anterior Cingulate Cortex (ACC). He described them as having a remarkably elongated spindle-like form, with an unusually long morphology and are practically perpendicular to the cortical surface [von26].

VENs have a distinct morphology that sets them apart from pyramidal neurons. Evidence from stereological estimates show that VENs are generally larger than layer V pyramidal neurons and than fusiform neurons of layer VI [NVMH95, NGe99]. A characteristic feature of them is having a single basal dendrite which is as thick as the apical dendrite. Figure 1 shows an example of VENs in human AIC. VENs were 'rediscovered' in 1995 [NVMH95], which led to a renewed interest in these peculiar neurons. Apart from humans, they are also found in the homologue of AIC and ACC in great apes [ATH$^+$11], elephants [HSB$^+$09], dolphins [BSH$^+$09], whales [HVDG07], lesser apes [STA$^+$11] and in macaque monkeys [EFL12]. The VENs in macaques and other non-hominid primates are morphologically identical to their counterparts in humans, although in humans they are disproportionally bigger [EFL12]. In humans, VENs are more numerous in right than left AIC [ATH$^+$10].

VENs are usually found in clusters of three to six cells in humans, and singly or in small clusters of only two to three cells in the chimpanzee, gorilla, and orangutan. Humans possess the highest ratio of of VENs, relative to the number of pyramidal neurons in layer Vb (5.6%). Chimpanzees and gorillas display a lower density (3.8% and 2.3%, respectively), with a relatively sparse distribution in the orangutan (1.6%) [NGe99]. In macaque monkey it is reported to be in 2.0-3.0% range [EFL12]. These differences have been attributed to the fact that the Fronto-Insular (FI) region, which is the subset of AIC containing VENs, is relatively smaller in non-human primates compared to humans [ATH$^+$11].

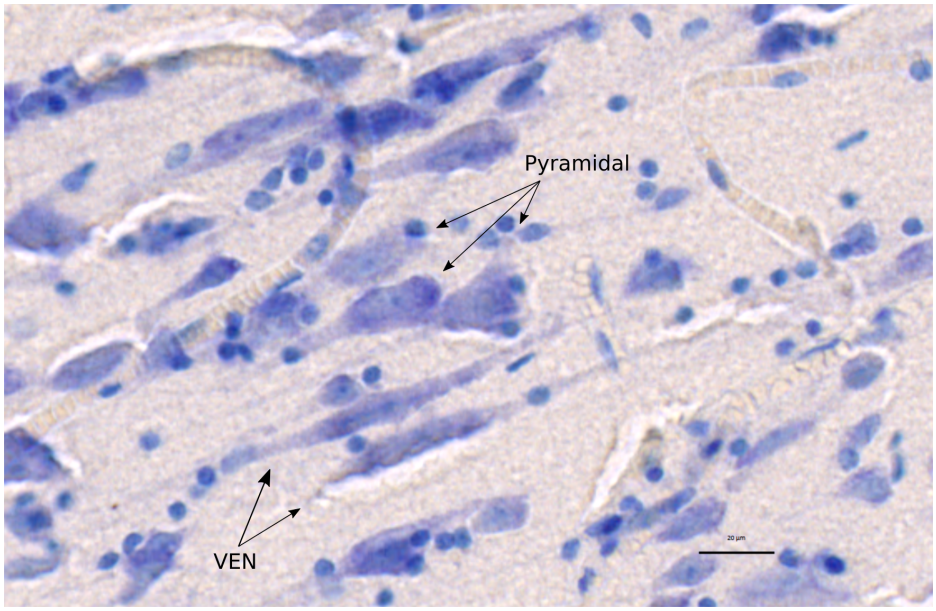

Figure 1: Cytoarchitecture of a sample of the anterior insular cortex of a human brain, obtained using Nissl staining technique. VENs and pyramidal neurons are visible in this image. Note that the lower VEN is only partially visible in this slice. The scale bar represents $20\mu m$ and the thickness of the slice is $50\mu m$. Courtesy of Ms. Felicitas Horn in MPI Biological Cybernetics.

A lot remains unknown about VENs but the current findings portray them as neurons with interesting properties which are instrumental in certain brain functions. In particular, the following two characteristics are worthy of special attention:

(i) VENs are fast, excitatory, long-range projection neurons;

(ii) VENs are instrumental in social cognition and awareness in humans.

2 Physiological and morphological properties of VENs

The large size of VENs, their simple dendritic structure and the fact that they are found only in Layer Vb support the idea that the evolution of VENs might be an adaptation to allow the gist of the information processed in a cortical column to be transferred rapidly to other brain structures. And the fact that they are found mostly in AIC and ACC and their selective degeneration in certain mental disorders [KSG+11] have provided evidence for the nature of the information that they transfer. This section reviews some notable properties of VENs.

VENs have high conduction velocity. So far, and to the best of my knowledge, there have been no direct measurements on the transmission velocity of VENs, but the current knowledge of neuroanatomical properties of neurons of different types and in different regions of the brain provides strong evidence for this claim. It is known that, at least for 'colossally projecting neurons', the diameter of the axon is correlated with the soma size of the parent neuron [TCI12], which is also demonstrated in earlier works on motor and somato-sensory cortices in primates [SP79]. And it has been shown in many studies that conduction velocity is correlated with axon diameter [GE27, GG39, Rus51, WB72]. Recently, using single-cell gene sequencing technology, it is shown that there is an increase in the expression of NEFH (neuro filament protein, heavy polypeptide) in VENs [YYY+18, DLN+16]. NEFH is strongly and positively related to axon calibre, a key determinant of conduction velocity in nerve cells [WYUS01].

It is also shown that mean firing frequency is low for thin fibres and high for thick ones, calculated in nine out of sixteen known fibre groups which span nearly the full range of axon diameters in five species [PNM+12]. Hence considering the observation that VENs have somas which are relatively bigger than pyramidal neurons, it seems reasonable to think they also posses higher spiking rate. But a recent ex-vivo measurement of putative VENs has shown the opposite effect [HMN+19]. There is an obvious need for retrograde studies on VENs to provide evidence for such qualitative physical properties and also to quantify them.

VENs are long-range projection neurons. VENs are located in Layer Vb, which characteristically sends subcortical projections [Bro78, GMM85, GMM90]. VENs express FEZF2 and CTIP2, two transcription factors essential for the developmental specification of sub-cerebral cortical projection neurons [CS13]. And they are nested in cortical areas in which information on the physiological states of the body is used to guide behavioural choices [Cra09], which

justifies their role as long-range projection neurons.

More importantly, tract tracing studies in monkeys, have provided direct evidence that VENs project to Periaqueductal grey (PAG) and parabrachial nucleus (PBN), which are key regions in autonomic network [SE17]. Also, there is more indirect evidence that hints VENs are involved in inter-hemispheric communications, which is obtained from studies in patients with Agenesis of the Corpus Callosum (AgCC) [KPM$^+$08]. I will elaborate more on that point in the following.

VENs are excitatory neurons. It has been shown that VENs express an isoform of the phosphate-activated glutaminase [EFL12]. And this indicates that they are glutamatergic excitatory neurons.

VENs are projection neurons for specialised communciations. One of the characteristic features of VENs, as mentioned already, is the fact that they posses only one basal dendrite. In contrast, pyramidal neurons usually have a basal tuft, consisting of dendrites that branch a few times before terminating. That probably means that VENs provide specialised communication channels to transfer a very specific type of information. This hypothesis is more plausible in light of recent findings that show dendrites can act as independent processing units, and that they perform local computations which are broadcast to the rest of the neuron or other neurons via dendritic transmitter and neuromodulator release [BH10].

3 Role of VENs in human awareness and social cognition

Studies of post-mortem brains of patients with behavioural variants of Frontotemporal Dementia (bvFTD), Alzheimer's Disease (AD) and control subjects showed that bvFTD causes a selective loss of VENs, which was absent in AD and in control subjects. A 70% decrease in numbers of VENs in ACC and AIC was observed in bvFTD patients, in striking contrast to an absence of selective loss of VENs in AD patients and control subjects [KSG$^+$11]. Moreover, in patients with bvFTD, the few VENs that did not undergo degeneration showed prominent alterations in morphology (swollen soma and twisted dendrite), distribution (very rare clustering), and presence of hyper-phosphorylated tau protein. These alterations in VEN numbers and morphology were present even in the initial stages of bvFTD [SZK12]. The degeneration of social graces in early stages of bvFTD can be explained by a loss of visceral-autonomic inputs to social-emotional systems

in ACC and AIC, and the selective loss of VENs is a strong evidence for their involvement in such networks. Conversely, the numbers of VENs is preserved in 'super-agers', which are those individuals who maintain sharp cognitive, emotional and social skills throughout ageing [GPP$^+$15].

Apart from, and even before the discovery of the selective loss of VENs in bvFTD, their localisation in AIC and ACC had been hinting towards their central role in autonomic and saliency networks of the brain. Based on current understanding of these networks, body homoeostasis information reaches the AIC and is integrated into decision-making and value attribution processes in the ACC and pre-frontal cortex [Cra03, Cra09, CCBR00]. Also, it was reported that human VENs were immunoreactive for the following three proteins: activating transcription factor 3 (ATF3) which is a protein involved in pain sensitivity; interleukin-4 receptor alpha chain (IL4Ra) which is a protein that mediates allergic reactions; and neuromedin B which is also expressed in the gut and may be involved in mediating the connection of visceral states and social awareness [ATH$^+$10]. A quantitative comparative analysis including humans, great apes, and lesser apes found that humans had a greater percentage of VENs that expressed IL4Ra and ATF3 than the apes [STA$^+$11]. This finding led to the hypothesis that these differences in biochemical phenotypes may be related to differences in interoceptive sensitivity that contribute to social behaviours.

And finally, major deficits in understanding non-literal language, humour and social interactions in patients with agenesis of the corpus callosum (AgCC) [BP00], led to the question of whether alterations in VENs occur in this condition. To test this hypothesis, a quantitative study of post-mortem brains showed that the number of VENs relative to pyramidal neurons decreases to approximately half their normal numbers in partial AgCC and are almost absent in complete AgCC, compared with control cases [KPM$^+$08]. The relative preservation of VEN numbers in partial AgCC is interpreted as support for the role of the remaining corpus callosum in preserving VEN connectivity, and together with observations from other neuropsychiatric disorders, as evidence for the role of VENs in social cognition.

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