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Review Article

Von Economo neurons: A Review of the Anatomy and Functions

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Abstract

Von Economo neurons (VENs) are large bipolar neurons found in the anterior cingulate, frontoinsular and dorso-lateral prefrontal cortices of great apes and the humans. VENs are defined by their thin, elongated cell body and long dendrites projecting from the apical and basal ends. These neurons are mostly present in particularly high densities in cetaceans, elephants, and hominoid primates mainly, humans and apes. VENs have been shown to contribute in the specializations of neural circuits in species that share both large brain size and complex social cognition due to their location. This could possibly be due to the adaptation to rapidly relay of socially-relevant information over long distances across the brain. The VENs have been shown to be recently evolved cell type which may be involved in the fast intuitive assessment of complex social situations. As such, they could be part of the circuitry supporting human social networks. The VENs emerge mainly after birth and increase in number until four years of age. The presence of VENs in the frontoinsular cortex has been linked to a possible role in the integration of bodily feelings, emotional regulation and goal-directed behaviors. Some studies have shown decreased number of VENs in neuropsychiatric diseases in which social cognition is markedly affected. Some researchers have shown that selective destruction of VENs in the early stages of frontotemporal dementia implies that they are involved in empathy, social awareness, and self-control which is consistent with evidence from functional imaging.

Keywords: Von Economo Neurons; Humans; Apes; Frontoinsular cortex; Prefrontal Cortex; Frontotemporal dementia

Introduction

Von Economo neurons (VENs) are bipolar neurons found in the anterior cingulate, frontoinsular, and dorso-lateral prefrontal cortices of great apes which include humans, gorillas, chimpanzees, bonobos and orangutans [1,2]. These neurons, also called Spindle neurons are characterized by a large spindle-shaped cell body or soma with a tapering single apical axon in one direction. Whereas other types of neurons tend to have many dendrites, the polar shaped morphology of spindle neurons is unique [3,4]. These group of neurons were previously thought to be unique to the great apes but have more recently been found in cetaceans such as the humpback, fin, killer and sperm whales [5,6,7]. Because of their morphology and anatomical location, it has been speculated that VENs may play important role in intuitive choice in social situations and that their dysfunction may be a factor in autism and Alzheimer's disease [8,9]. VENs were first described by Constantin Von Economo in 1925, and their exclusivity to the great apes was discovered in 1999 by Allman and colleagues [1,10].

VENs are defined by their thin, elongated cell body and long dendrites projecting from the apical and basal ends [11]. These distinctive neurons are mostly present in anterior cingulate and fronto-insular cortex, with particularly high densities in cetaceans, elephants and hominoid primates mainly humans and apes [8,12]. This distribution suggests that VENs contribute to specializations of neural circuits in species that share both large brain size and complex social cognition, possibly representing an adaptation to rapidly relay socially-relevant information over long distances across the brain [13]. Recent evidence indicates that unique patterns of protein expression may also characterize VENs, particularly involving molecules that are known to regulate gut and immune function [13,14].

VENs are a recently evolved cell type which may be involved in the fast intuitive assessment of complex situations. As such, they could be part of the circuitry supporting human social networks [11,14]. It has been shown that VENs relay an output of fronto-insular and anterior cingulate cortex to the parts of frontal and temporal cortex associated with theory-of-mind, where fast intuitions are melded with slower, deliberative judgments [8,15]. VENs emerge mainly after birth and increase in number until the age of four years of age and that in autism spectrum disorders VENs fail to develop normally [16,17]. This failure might be partially responsible for the associated social disabilities that result from faulty intuition in autistic people. The presence of VENs in the frontoinsular cortex has been linked to a possible role in the integration of bodily feelings, emotional regulation, and goal-directed behaviors [7,12]. They have also been implicated in fast intuitive evaluation of complex social situations. Studies have reported a decreased number of VENs in neuropsychiatric diseases in which the dimension of social cognition is markedly affected [7,16].

The Structure and Anatomy of Economo Neurons

VENs are large, bipolar neurons with one large apical axon and

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a single basal dendrite. They are found exclusively in layer Vb of the anterior cingulate cortex (ACC) and fronto-insular cortex (FI) as shown in Figures 1 and 2, and have been identified in human dorso-lateral prefrontal cortex (DLPFC), Brodmann area [3,18]. Its large apical axon and high-volume, elongated soma is similar to that of the cortical pyramidal neuron, but the VEN lacks the pyramidal neuron's numerous basal dendrites, instead receiving inputs from a comparatively small subset of cortex; the average VEN is about 5 times larger than the average layer 5 pyramidal cells as shown in Figures 3 and 5 [5,8]. Their structural similarity to pyramidal neurons suggests that VENs may play a similar functional role, and because the speed at which neurons conduct information typically co-varies with the diameter of their axon, the large VENs may do so very quickly compared to other neurons as in Figure 3 [2,7]. VENs are relatively rare, comprising 1-2% of the total neurons in layer 5 of the ACC [4,19]. In FI, VENs are 30% more numerous in the right hemisphere than the left a hempispherization that occurs in the first four years of postnatal development in humans [2,11].

Ontogeny and Phylogeny

Von Economo neurons (VENs) develop late both ontogenetically and phylogenetically. Ontogenetically, VENs first appear in the 35th week of gestation; at birth only about 15% of the post-natal numbers are present, and at four years old, the adult numbers are present [2,8]. Analyses of over 30 mammalian species have failed to find VENs except in primates and cetaceans. Among primates including gibbons, VENs have only been found in the great apes, humans, gorillas, chimpanzees, bonobos, and orangutans [11,20]. Among the great apes, humans have the most VENs, both in terms of absolute number and relative percentage compared to total number of neurons [10]. In decreasing order of total number, VENs are found in humans, bonobos, chimpanzees, gorillas, and orangutans. Unlike in the other species exhibiting them, VENs in humans and bonobos are distributed in clusters of 3-6 neurons. In analyses of total number of VENs present in FI of both hemispheres, the average adult human was found to have 193,000 cells, a four year old human child had 184,000, the average human newborn had 28,200, a gorilla had 16,710, a bonobo had 2,159, and a chimpanzee had 1,808 [19,20]. That their relative abundance and clustering in species co-varies with a specie's phylogenetic proximity to humans has led to speculation that VENs are important to evolution and cognition [4,5]. That they occur in hominids and pongids but no other primates suggests that VENs evolved relatively recently approximately 15-20 million years ago, prior to the evolutionary divergence of orangutans and hominids [12,21]. Their discovery in some whales suggests a second, independent evolution of VENs, though they may not have the same function in both apes and cetaceans [21,22].

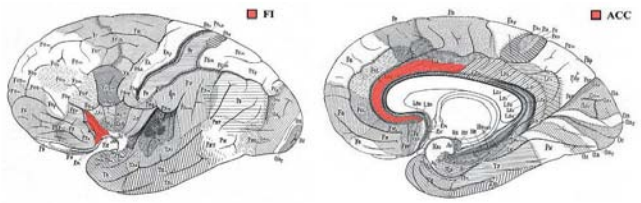

Figure 1: Regions of the brain containing Von Economo neurons (VENs). (a) A lateral view of the brain, with fronto-insular cortex (FI) shown in red. (b) A medial view of the brain, with anterior cingulate cortex (ACC) shown in red [10].

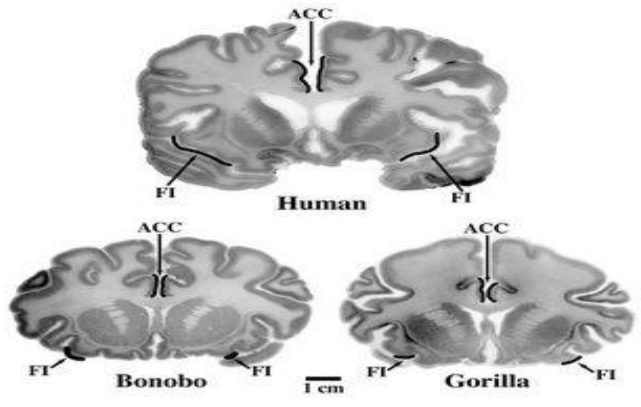

Figure 2: Location of the frontoinsular cortex (FI) and anterior cingulate cortex (ACC) on coronal brain sections [19,20].

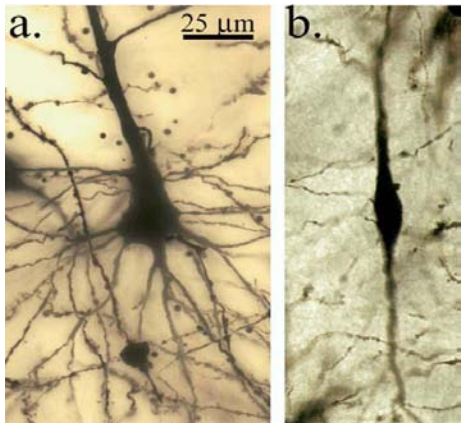

Figure 3: Photomicrographs of soma and proximal dendrites of (a) a pyramidal and (b) the VENs stained with the Golgi method [5].

The observation that spindle neurons only occur in a highly significant group of animals has led to speculation that they are of great importance in human evolution and/or brain function as in Figures 2 and 4. Their restriction among the primates to great apes leads to the hypothesis that they developed no earlier than 15-20

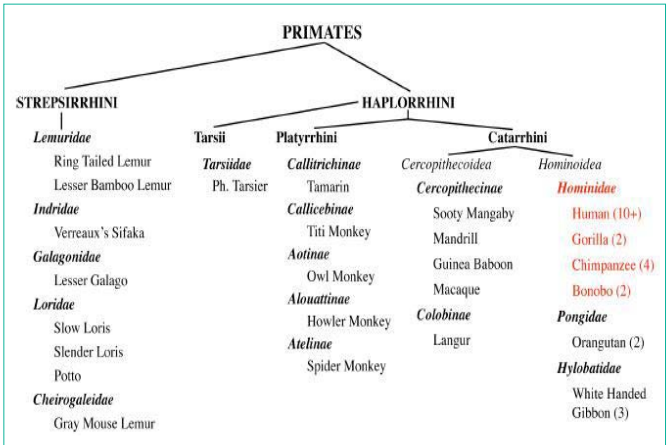

Figure 4: Primate cladogram detailing the species examined for VENs. Species in red have VENs in the FI. Pongids have VENs in the ACC only [1].

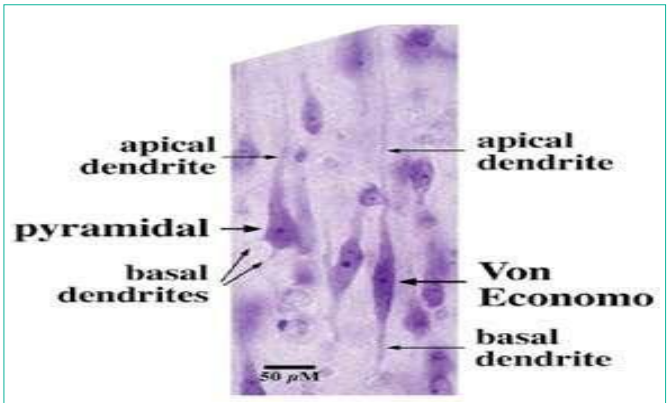

Figure 5: Von Economo neuron compared to Pyramidal neuron [5].

million years ago, prior to the divergence of orangutans from the African great apes. The discovery of spindle neurons in diverse whale species [6], has led to the suggestion that they are a possible obligatory neuronal adaptation in very large brains, permitting fast information processing and transfer along highly specific projections and that evolved in relation to emerging social behaviors [22]. Their presence in the brains of these species supports the theory, pointing towards the existence of these specialized neurons only in highly intelligent mammals, and may be an example of convergent evolution [6,23]. Though currently unknown where VENs ultimately project to, ACC and FI connect to numerous anatomical areas: prefrontal, orbito-frontal, insular and anterior temporal cortices, amygdala, hypothalamus, and various thalamic nuclei. Allman and others have speculated that VENs project information processed in FI and ACC to other parts of the brain, including Brodmann's area 10, in fronto-polar cortex [24,25].

All of the primates had more spindle cells in the fronto-insula of the right hemisphere than in the left. In contrast to the higher number of spindle cells found in the ACC of the gracile bonobos and chimpanzees, the number of fronto-insular spindle cells was far higher in the cortex of robust gorillas but no data for Orangutans was given [1,2]. An adult human had 82,855 such cells, a gorilla had 16,710, a bonobo had 2,159, and a chimpanzee had a mere 1,808 – despite the fact that chimpanzees and bonobos are great apes most closely related to humans [19,20].

Function and Behaviour

The FI and ACC, where VENs are located, are thought to be implicated in social reasoning, empathy, emotion, and monitoring of visceral autonomic activity, among other functions. ACC projects to the fronto-polar cortex, which has been implicated in cognitive dissonance and uncertainty [16]. Because their morphology suggests them as fast-projection neurons, and because of the functions of the areas they are thought to receive information from and project information to, it is speculated that VENs have an important role to play in intuition, which allows one to overcome uncertainty, make quick decisions and resolve cognitive dissonance [2]. Allman and Colleagues had reported that spindle neurons help channel neural signals from deep within the cortex to relatively distant parts of the brain [1]. They found that signals from the ACC are received in Brodmann's area 10, in the frontal polar cortex, where regulation of cognitive dissonance, disambiguation between alternatives is thought to occur. According to Allman and Others [1,2], this neural relay appears to convey motivation to act, and concerns the recognition of error. Self-control and avoidance of error, is thus facilitated by the executive gate-keeping function of the ACC, as it regulates the interference patterns of neural signals between these two brain regions.

In humans, intense emotion activates the anterior cingulate cortex, as it relays neural signals transmitted from the amygdala, a primary processing center for emotions to the frontal cortex, perhaps by functioning as a sort of lens to focus the complex texture of neural signal interference patterns. The ACC is also active during demanding tasks requiring judgment and discrimination, and when errors are detected by an individual. During difficult task or when experiencing intense love, anger or lust, activation of the ACC is increased. In brain imaging studies, the ACC has specifically been found to be active when mothers hear infants cry, underscoring its role in affording a heightened degree of social sensitivity.

The ACC is a relatively ancient cortical region and is involved with many autonomic functions, including motor and digestive functions, while also playing a role in the regulation of blood pressure and heart rate. Significant olfactory and gustatory capabilities of the ACC and fronto-insular cortex appear to have been usurped, during evolution, to serve enhanced roles related to higher cognition, ranging from planning and self awareness to role playing and deception. The diminished olfactory function of humans, compared to other primates, may be related to the fact that spindle cells located at crucial neural network hubs have only two dendrites rather than many, resulting in reduced neurological integration [5,19,21].

Abnormal spindle neuron development may be linked to several psychotic disorders, typically those characterized by distortions of reality, disturbances of thought, disturbances of language, and withdrawal from social contact. Abnormal VEN development has been implicated in autism [2], and selective degeneration of VENs has been observed in Alzheimer's and dementia [12]. Altered spindle neurons have been implicated in both schizophrenia and autism, but research into these correlations are at a very early stage. An initial study suggested that Alzheimer's disease specifically targeted Von Economo neurons however this study was performed with end-stage Alzheimer brains in which cell destruction was widespread. Later, it was found that Alzheimer's disease doesn't affect the VENS, but behavioral variant fronto-temporal lobe degeneration specifically targets these cell populations in the anterior cingulate cortex and the anterior insula early in the disease [12,18,25].

Conclusion

The von Economo neurons (VENs) are large bipolar neurons located in the frontoinsular cortex (FI) and limbic anterior (LA) area in great apes and humans but not in other primates. Stereological counts of VENs in FI and LA show them to be more numerous in humans than in apes. In humans, small numbers of VENs appear the 36th week postconception, with numbers increasing during the first 8 months after birth. There are significantly more VENs in the right hemisphere in postnatal brains; this may be related to asymmetries in the autonomic nervous system. VENs are also present in elephants and whales and may be a specialization related to very large brain size. The large size and simple dendritic structure of these projection

neurons suggest that they rapidly send basic information from FI and LA to other parts of the brain, while slower neighboring pyramids send more detailed information. Selective destruction of VENs in early stages of frontotemporal dementia (FTD) implies that they are involved in empathy, social awareness, and self-control in which VENs fail to develop normally in autism broad spectrum disorders which may be responsible for the associated social disabilities resulting from faulty intuition.

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