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Historical paper

Von Economo neurons: Clinical and evolutionary perspectives

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ABSTRACT

Von Economo neurons (VENs) are projection neurons located in layer V of the anterior cingulate and frontoinsular cortex that are increasingly attracting the interest of the scientific community as many studies point to their involvement in neuropsychiatric conditions. In this review we provide a critical appraisal of both historic and recent literature on VENs that highlights the importance of clinicopathological studies in areas of research where animal models are not available. Current data suggest that VENs represent a specialized neuronal type with a characteristic morphology that evolved only in a restricted number of species most likely from a population of pyramidal neurons present in ancestral mammals in the context of specific adaptive pressures. VENs, which evolved among primates only in the hominoid lineage, are particularly vulnerable in neuropsychiatric conditions characterized by deficits in social skills and emotional function. Moreover, recent evidence on the neurochemical profile, morphologic features, and laminar and regional distribution of VENs suggests that this intriguing neuronal population could be critically involved in autonomic regulation.

1. The history of a discovery

Von Economo neurons (VENs) have been sporadically described and graphically documented in the literature for more than a century. First, Wladimir A. Betz (1881) described their morphology as follows: "These spindle-shaped cells of the cingulate gyrus are remarkably larger (twice or even three times as large), as the other [neurons] of the fifth layer." Later, Carl Hammarberg (1895) mentioned the presence of "spindle cells" in layer V of the *Gyrus centralis anterior* (the frontal gyrus) in the frontal lobe, and named it *Spindelzellenschicht* (the spindle cells layer). Spindle-shaped cells in layer V of the cingulate gyrus were then mentioned by Santiago Ramón y Cajal (1901–1902, 1904) who referred to them as "giant fusiform cells" in his histological study of the cortex. Interestingly, Ramón y Cajal (1901–1902, 1904) noted that the presence of such neuronal morphology was not common throughout the human cortex but was rather specific to the cingulate and insular cortices. In his description of the *gyrus cinguli*, he reported: "In the inferior layer some long and robust fusiform cells are scattered irregularly which reminds one of the cells characteristic of the insular cortex." During the first part of the 20th century, several authors briefly mentioned the presence of such spindle-shaped cells either in the human

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anterior cingulate or insular cortices (De Crinis, 1933; Flechsig, 1897, 1920; Goldstein, 1913; Juba, 1934; Marinesco and Goldstein, 1927; Ngowyang, 1932, 1936; Nikitin, 1909; Vogt and Vogt, 1919; Vogt, 1903; von Economo and Koskinas, 1925). In 1926 Constantin von Economo provided the only detailed description of the morphology and cortical distribution of these neurons (von Economo, 1926; for a modern translation of this paper see Seeley et al., in press) and was also the first to show that such cells are a specialized neuronal type of layer Vb of two well-defined cortical regions, the anterior cingulate cortex (ACC) and the frontoinsular (FI) cortex; (Fig. 1). Particularly, von Economo (1926) described "stick cells" (*Stabzellen*) or "staff cells" (*Stäbchenzellen*) as neurons displaying a spindle-like form and an unusual length, perpendicularly oriented to the pial surface, possessing apical and basal dendrites that are almost as wide as the cell body and that sometimes branch into two, as well as "rod cells" (*Stäbchenzellen*) and "corkscrew cells" (*Korkzieherzellen*) as "…absolutely spindle-shaped with regard to their vertical direction, and mostly form very long rod-like and also often spirally twined elements, extremely characteristic of this region". He also mentions that "Such cells are specific for this area, as they are not found anywhere else in the entire cerebral cortex, except, as we shall see later, in the anterior segment of the superior limbic [i.e., cingulate] gyrus." Moreover, von Economo (1927) described "…cells that are no longer fine pyramidal, but peculiarly elongated spindle (fusiform) cells, such that one might speak here of an actual cellular fusiform transformation (*Verspindelung*)" in layer III of the FI. Finally, he concludes that layer V of the FI presents a "veritable fusiform transformation of cells that is even more pronounced than in layer III".

After these initial descriptions, a few other authors acknowledged the presence of "spindle cells" in the human cortex (Braak, 1980; Juba, 1934; Ngowyang, 1932; Rose, 1927, 1928; Syring, 1956). In addition, VENs have been described in the subicular cortex and entorhinal cortex of the human hippocampal formation by Gü Ngowyang (1936), indicating that ACC and FI are not the only regions of the so-called limbic cortex that contains them (Fig. 2). It was only in 1995 that the first modern study of the morphology, distribution, and apparent numbers of the spindle cells was performed in the ACC (Nimchinsky et al., 1995), demonstrating their immunoreactivity to neurofilament protein as well as their rostrocaudal decrease in density, highlighting some variations to the classic morphology originally described by von Economo in 1926. These authors also provided the first evidence of spindle cells projecting subcortically, demonstrating that they are projection neurons. A few years later the same authors (Nimchinsky et al., 1999) reported the presence of spindle-shaped neurons in layer Vb of the ACC of great apes including bonobos (*Pan paniscus*), common chimpanzees (*Pan troglodytes*), gorillas (*Gorilla gorilla*), and orangutans (*Pongo pygmaeus* and *Pongo abelii*), and the absence of such neurons in other primates. In this context, it is interesting to note that *Spindelzellen* were reported by Maximilian Rose (1928) in his comparative work on the structure of the insula in the agranular insular cortex and in the claustrum of the ring-tailed lemur (*Lemur catta*). Moreover, Rose (1927) described *Spindelzellen* in layer Vb of the *Gyrus limbicus anterior* (the ACC) of human and chimpanzee, as well as lancet-shaped (*lanzettförmige*) pyramidal cells in layer V of the ACC of *L. catta*. Recent investigations on prosimians and small anthropoid primates did not confirm Rose's early observations in lemurs (Allman et al., 2010; Nimchinsky et al., 1999). Portraits of some of the pioneer neuroanatomists who investigated VENs and their drawings of these neurons are shown in Figs. 3 and 4, respectively.

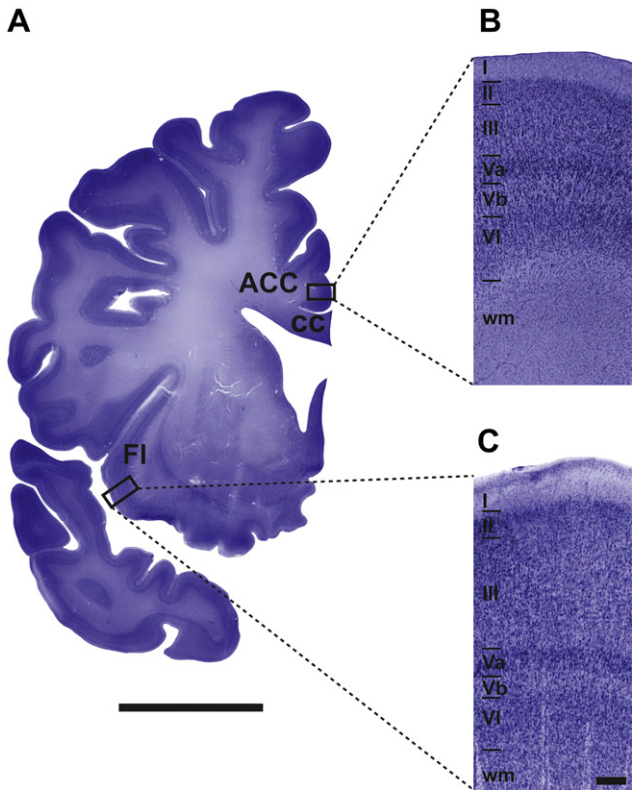

Fig. 1 – Gallocyanin-stained section of the left hemisphere of a human brain showing the localization of the VENs in ACC and FI (A); Panels (B) and (C) show photomicrographs of the cytoarchitecture of ACC (B) and FI (C). Scale bar = 3 cm (A); and 250 μm (B and C).

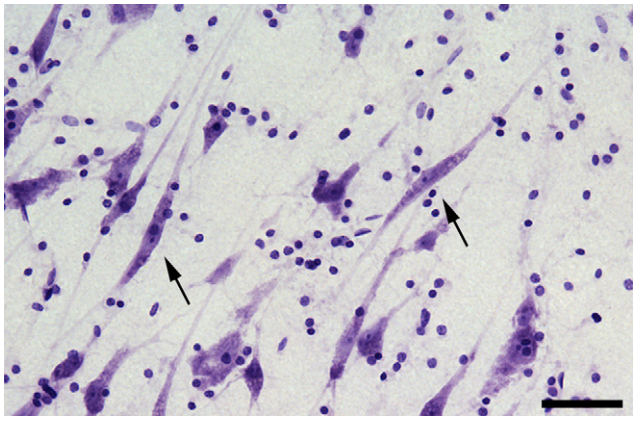

Fig. 2 – Photomicrograph showing VENs in the human subiculum. Arrows indicate VENs. Scale bar = 50 μm.