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FEATURE ARTICLE
Distinctive Neurons of the Anterior Cingulate and Frontoinsular Cortex: A Historical Perspective

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Human anterior cingulate and frontoinsular cortices participate in healthy social-emotional processing. These regions feature 2 related layer 5 neuronal morphotypes, the von Economo neurons and fork cells. In this paper, we review the historical accounts of these neurons and provide a German-to-English translation of von Economo's seminal paper describing the neurons which have come to bear his name. We close with a brief discussion regarding the functional and clinical relevance of these neurons and their home regions.

Keywords: anterior cingulate cortex, cytoarchitecture, fork cell, insula, von Economo neuron

Introduction

Human cytoarchitectonic mapping has provided the anatomical framework for many aspects of contemporary neuroscience, including primate connectional anatomy and, more recently, human "connectomic" mapping; task-based functional imaging; nuanced lesion-deficit analyses; and many emerging aspects of developmental neuroscience. The early anatomists must have anticipated the timelessness of their work as they were carrying it out, section by section, stain by stain. In this manuscript, we review seminal work on the distinctive neuronal constituencies of anterior cingulate and frontoinsular cortex, seeking to highlight how relevant the pioneer neuro-cartographers remain to modern clinico-anatomical investigations.

The human anterior cingulate and frontoinsular cortices are agranular, peri-allocortical regions united by the conspicuous presence of large, slender, bipolar neurons located primarily in layer 5b. Among the early anatomists to notice and depict these cells (Betz 1874, 1881; Ramón y Cajal 1900, 1904), none took such an interest as did Constantin von Economo, who provided the first comprehensive description of these neurons, referring to them as "Stäbzellen" (rod cells) and "Korkzieherzellen" (corkscrew cells) as part of his celebrated cytoarchitectural atlas with George Koskinas (von Economo and Koskinas 1925):

"We now want to stress particularly just one more specific cell type that we call the rod or corkscrew cell … (Figure 44). These cells are only found at the crowns, curved regions, and inner wall of the frontal part of the cingulate gyrus, to a lesser extent in the posterior transitional gyral margin of the orbital portion of the frontal cortex that extends to the fronto-orbital insula and in its associated short accessory gyri of the anterior insula … The cell body is either narrow and pulled straight or somewhat crooked, other times taking on a torturous or even screw-like or corkscrew-like morphology. Small processes project laterally from the cell body, but the upper and lower tips of the cells have spine-like processes that are sometimes forked and can always be followed for relatively long distances up and down the tissue … The long axis of these straight or screw-shaped cells is always radial and perpendicular to the brain surface (compare Plate XLII H 30.5 cm/B 16.5 cm, and Plate XLVI H 11.5 cm/B 8 cm) (p. 66)."

The following year, in the definitive paper, von Economo (1926) consolidated many details regarding these rod and corkscrew cells, which have since been renamed von Economo neurons (VENs) in his honor (Allman et al. 2005). In the 1926 paper, which we provide in English translation following this commentary, von Economo further emphasized the curious topology of the VENs, which he found almost exclusively in anterior cingulate and frontoinsular cortices. He further noted progressive changes in VEN morphology during development. Presciently, he speculated on the phylogeny and function of these neurons. In particular, their restriction to the ancient "olfactory brain" fueled his hypothesis that VENs must have adopted new functions in humans. This insight soon proved relevant. As part of a comparative study of the insula's subregional boundaries, Maximilian Rose (1928) suggested that the insula of humans and apes could be distinguish from that of monkeys and small mammals by the presence of VENs in ventral anterior (agranular) insula, and he noted the particular abundance of these neurons in humans. The fortuitous rediscovery of the VENs in 1995 (Nimchinsky et al. 1995) stimulated more extensive comparative studies, which so far demonstrate VEN phylogenetic restriction to humans and other large-brained mammals with complex sociality, including great apes, cetaceans, and elephants (Nimchinsky et al. 1999; Hof and Van der Gucht 2007; Butti et al. 2009; Hakeem et al. 2009; Allman et al. 2010). Von Economo further proposed that the frontoinsular cortex might contain afferent representations of the autonomic nervous system, just as anterior cingulate was, even then, emerging as a cortical link to efferent sympathetic functions. Contemporary functional imaging, lesion-deficit, and anatomical studies support this notion, revealing anterior cingulate and frontoinsular contributions to a host of autonomic and social–emotional functions (Damasio 1999; Craig 2002; Critchley 2005; Heimer and Van Hoesen 2006; Seeley et al. 2007; Williamson and Allman 2010). Although von Economo was the first to provide a comprehensive description

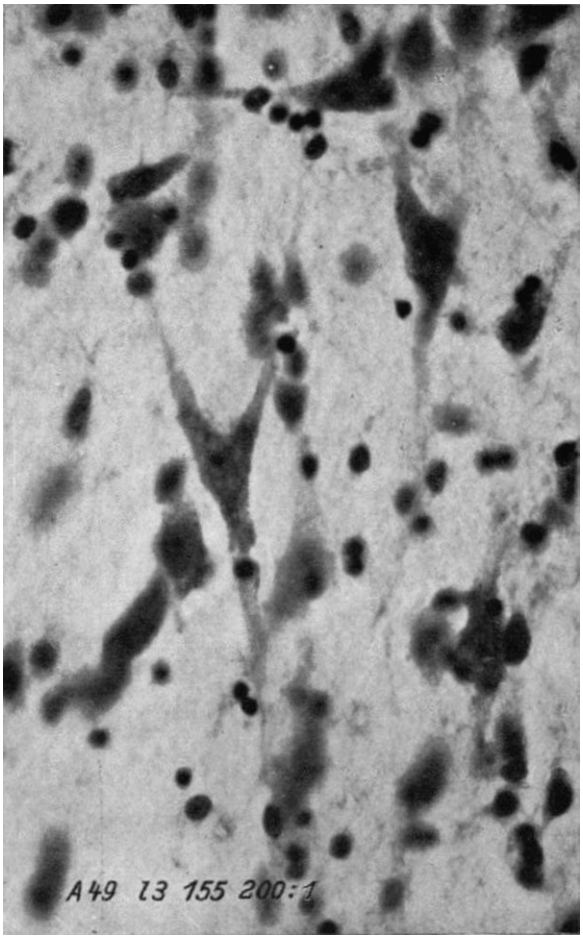

Figure 1. High magnification photomicrograph of frontoinsular cortex, layer 5, reveals a pair of characteristic fork cells. Figure reproduced from Ngowyang (1932).

of VEN morphology, distribution, and possible functional significance, it should be noted that these cells had been observed earlier by others, including Betz (1874, 1881) and Ramón y Cajal (1900, 1904). Ramón y Cajal noted the co-occurrence of VENs (referred to as large or giant fusiform cells) in anterior cingulate and insula, depicted their projection of large axons toward the white matter, and observed the absence of VENs from rodent and cat anterior cingulate homologues.

Ramón y Cajal and von Economo briefly noted a second large, intriguing human layer 5 neuron seen intermingling with the VENs in frontoinsula but not in anterior cingulate cortex (Ramón y Cajal 1900; von Economo and Koskinas 1925). Like VENs, these cells feature a single, long, thick basal dendrite, but unlike VENs they extend two large apical dendrites away from the soma (Fig. 1). Ngowyang (1932) published a dedicated description of these neurons, for which he offered the term "Gabelzellen" (fork cells). He called attention to the dense concentration of fork cells within the human frontoinsular cortex and their scarcity elsewhere:

"Within the folds of the human frontal telencephalon, we have now noticed yet another type of specialized cell in the ventral part of the anterior half of the insula . . . Each of these cells has a basal process directed towards the medulla (white matter), and two protoplasmic processes that are directed toward the cortical surface (Figure 1). As found in reviewing cresyl violet preparations, these processes are all strong, thick, elongated, and robustly stained. The nucleus is proportionally large, is oval or elliptical, and is usually located in the middle of the cell body. However, the cell body is smaller and shaped differently than that of other pyramidal cells in cortical layer V of this insula region and of pyramidal cells in layer III of other brain regions. An individual cell looks something like an isosceles triangle whose apex is directed down towards the medulla (Figure 2).

These cells are only found in the posterior part of Oscar Vogt's areas Ai 1 and Ai 2, anterior to the insula's juncture with the temporal lobe, specifically in layer Va; sometimes they occur singly in Vb; they impart a distinctive character to this region. . .They are grouped in clusters among the other, generally-elongated spindle cell elements, and together with them, give this part of the "insula belt" of von Economo a special appearance. Because of their shape, we call these cells *Gabelzellen* ("fork cells") . . . Furthermore, since the other elongated, spindle-forming cellular elements of this region are very similar to those in layer V of the anterior cingulate gyrus . . . and since both regions have agranular cortical architecture, the conspicuous presence of these fork cells in the insula provides a clear means to distinguish these two cortical areas." (pp. 672–673).

Ngowyang further observed scattered fork cells in the chimpanzee (Ngowyang 1932) and orangutan (Ngowyang 1936) but not in the cat (Ngowyang 1932), suggesting that fork cells might also exhibit a restricted mammalian phylogeny. After more extensive anatomical surveys with improved methods, he and others also noted a focal concentration of VEN and fork cell-like neurons in Ammon's horn (De Crinis 1933; Ngowyang 1936).

Based on meticulous anatomical and comparative studies that began more than a century ago, it seems clear that the human anterior cingulate and frontoinsular cortices should not be considered "primitive," as often suggested in contemporary writings. These regions feature phylogenetically restricted, morphologically unique layer 5 neurons, whose information processing capacities must in some way reflect their unusual dendritic arbors. We offer this anatomical and historical information to provide context for contemporary studies of anterior cingulate and frontoinsular function. Understanding these regions—and their unique neuronal architectures—may prove critical to deciphering how and why neurodevelopmental (Allman et al. 2005; Kaufman et al. 2008; Santos et al. 2010), psychiatric (Ellison-Wright et al. 2008; Bora et al. 2010), and neurodegenerative (Seeley et al. 2006; Kim et al. 2011 (this issue)) diseases impact these specialized human brain structures. Future efforts to protect, restore, or even replace affected neurons in these disorders will require a deep appreciation of region- and circuit-specific neuronal identities.

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Notes

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A New Type of Special Cells of the Cingulate and Insular Lobes

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Years ago, I discovered a peculiar cell type in layer V of the anterior rostral cingulate gyrus that, as far as I could find in the literature, had not previously been described and that I erroneously thought was a pathological formation (see page 63 and Plate VII, Figure 14a of reference von Economo (1918)). Since then, I have completed a detailed analysis of the cytoarchitecture of the whole cerebral cortex in a large number of adult brains (von Economo and Koskinas 1925); this analysis has shown that this peculiar cell type is indeed specialized to the cingulate gyrus and is found in only one other gyrus, the transverse insular gyrus. I first described the appearance and location of these cells and also included figures in a cytoarchitectonic study of the adult human brain (von Economo and Koskinas 1925), and they can easily be recognized in photographs of the accompanying atlas (Plates XLII, XLVI, and XLVII). To determine the nature of these cells, I have now studied them in juvenile brains and also with Bielschowsky's silver impregnation technique.

In adult brains (Fig. 1), these cells stain very darkly with protoplasmic dyes (thionin, toluidin blue, etc.) and have a remarkably elongated spindle-like form. Their morphology is unusually long, and they have such a narrow cell body that they often appear only like lines. The cells are radially oriented, practically perpendicular to the cortical surface. The long apical and basal dendrites have almost the same width as the cell body and slowly become narrower as they ascend or descend. Lateral dendrites are usually not seen, so the morphology of the cell looks peculiarly stiff and smooth. Therefore, they were called "rod cells" or "small rod cells." Sometimes one or both of the primary dendrites branches into 2. These branching dendrites frequently have a wavy morphology, to the degree that they appear to be twisted in a screw-like manner (Fig. 1) so that this type can be described as "corkscrew cells." Sometimes, the protoplasm appears to be wound or regularly constricted like a pearl necklace. In these cells, the cell body appears to be slightly pyramidal. The 2 principal dendrites can be followed into adjacent layers where they become thin and send out quill-like processes rather than sending out many processes like most neurons. The protoplasm usually appears to be homogeneously stained without any visible structures. The nucleus is usually very narrow and oblong along the axis of the cell, found in the center of the cell though near the cell wall. It does not appear to contain a nucleolus. The protoplasmic stain generally does not reveal an axon or axon hillock. All these characteristics might throw doubt on the claim that these cells are neurons. These cells are usually aligned parallel to each other in groups of 3 or more in layer V, surrounded by pyramidal neurons from which they diverge dramatically in form and length. It is difficult to accurately determine the size of these cells since it is difficult to determine where the cell body ends and the dendrites begin. The cell body can be said to range in length from 60–80 μm up to 100 μm but is only 7–10 μm thick. The dendrites easily reach a size of 60 μm so the total length of the cell is 160–200 μm or more.

I originally thought these cells were pathological structures, as I happened to find them first in diseased brains. Furthermore, the form is reminiscent of progressive paralysis and the corkscrew-like twistings are commonly seen in pathologically altered cells. However, as I have stated before, the analysis of a large number of normal adult brains proves that these cells are found again and again in layer Vb of the aforementioned areas, and in the absence of any pathological changes in the areas that would indicate a disease process. Therefore, we must conclude that these cells are specialized cells of these brain regions in normal brains. The intensity with which these cells are stained, their slender and dried-out appearance, the nucleus which does not resemble the nucleus of a healthy ganglion cell, and the twisted and prickly dendrites are therefore even more unique and obvious characteristics. Because these cells are only found in 2 areas of the so-called "olfactory brain," a region of the brain that is wasted away in humans, one might assume that the cells are the result of a regressive process and

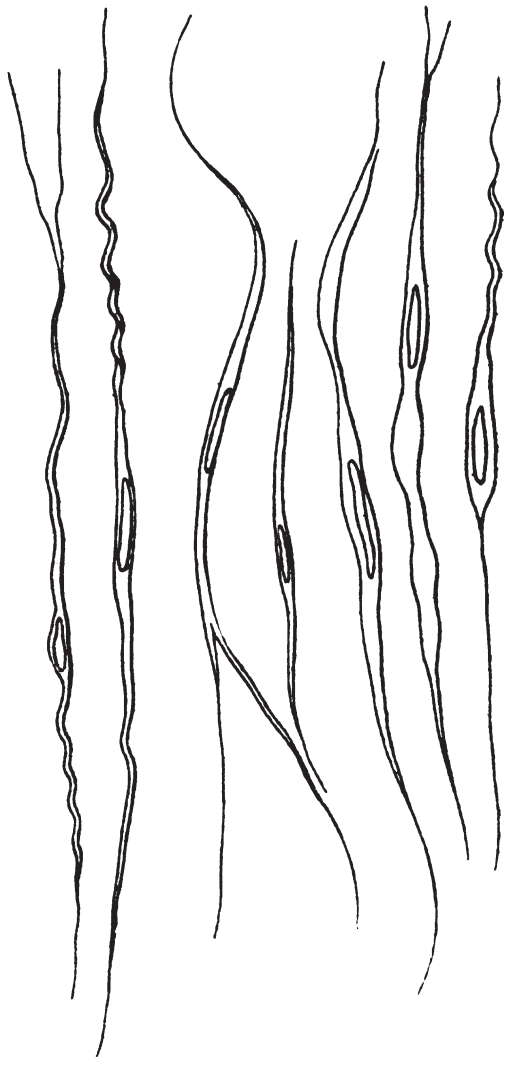

Figure 1.

perhaps are not neurons at all. To clarify this, I tested these areas with Bielschowsky's silver method and also searched for these cells in child brains.

The analysis of the silver-prepared tissues showed that in adults, these cells contain fibrils that cross the thin cell bodies, although these fibrils are stuck together and of irregular thickness and the pictures that one obtains of them are not very nice. The axon can also be commonly identified as it emerges horizontally from the center of the cell near the top of the nucleus and appears to stay in the same layer (see Fig. 2, *ax*). With the silver stain, it is possible to follow the dendrites much farther, but it is still not possible to determine where they arborize. The silver impregnation shows that we are assuredly dealing with specialized neurons.

The analysis of immature human brains, for example, the brain of an 8-year-old child (Fig. 3), also clearly shows these cells in the deep parts of layer V of the rostral cingulate gyrus with a protoplasmic dye. As in adults, they are narrow, stretched, and spindle-shaped and there is little difference between the thickness of the cell body and the origin of the dendrites, much less so than in other neurons, and the dendrites often have a corkscrew shape. However, there are some differences between juvenile and adult cells. In children, these cells do not appear to be as dried-out and slender as in adults, the cell body and dendrites appear to be rich in protoplasm, the nucleus is oval and larger than in the adult and contains an easily identifiable, round, deep blue-stained nucleolus. In the protoplasm, one can clearly see Nissl bodies capping the 2 ends of the nucleus and extending into the 2 dendrites. In the child brain, the cells have a peculiarly smooth appearance due to the relative lack of dendrites although occasionally one sees several lateral projections from the cell body. The primary dendrites sometimes split into 2 or more branches. Frequently, one can also observe the axon (*ax*) projecting horizontally from the cell body, and thionin staining of the child brain reveals the conical, thionin-free axon hillock. The axon projects from the center of the cell body into the surrounding neuropil of layer V as a thin, smooth, and wavy string. These characteristics are clearly shown in Figure 3 (surrounding pyramidal cells are included for comparison). Bielschowsky's silver stain also reveals long fibrils running along the axis of the cell through the principle dendrites and cell body that are more easily seen in the child than in the adult brain. Upon silver staining, the primary apical and basal dendrites could be followed far by tracing these stained fibrils. Nevertheless, I could not determine if the apical dendrite ended in the molecular layer or if the basal dendrite ended at the bottom of layer VI. I could follow the axon quite far horizontally; it seemed to stay in layer V, but I could not determine its target.

In somewhat older children (12½ years of age) the cells are similar to those of 8-year-olds (Fig. 4). The cells are easily identifiable by their narrow, stretched, and partially corkscrew-like morphology. However, they are already somewhat narrower than the cells of the 8-year-old child, seeming to contain less protoplasm. Still, one can clearly see the Nissl bodies especially as caps on ends of the nucleus. The whole picture so far suggests that these cells become narrower with time and that even though the cells are quite similar in children, in the 12½-year-old they are already beginning to look like the adult type.

To explain the morphological changes that take place in the cell form as the individual ages, it is not necessary to assume a wasting or degenerative process. There is another explanation for the narrowing of these specialized cells with time. These rod or corkscrew cells are found in 2 gyri in the deep ganglionic layer of the cortex. First, they are found in cingulate gyrus, particularly at its crest and its inner (inferior) wall facing the corpus callosum; they are best developed near regions of maximal cortical curvature. They are also found, although somewhat larger and more nicely developed, at the crest and region of maximal curvature of the transverse insular gyrus. The latter gyrus is a bridge-like curve that extends across the

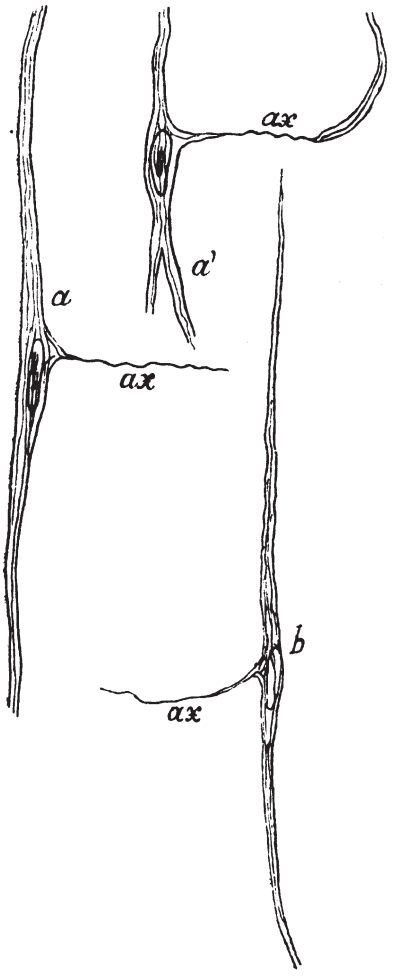

Figure 2.

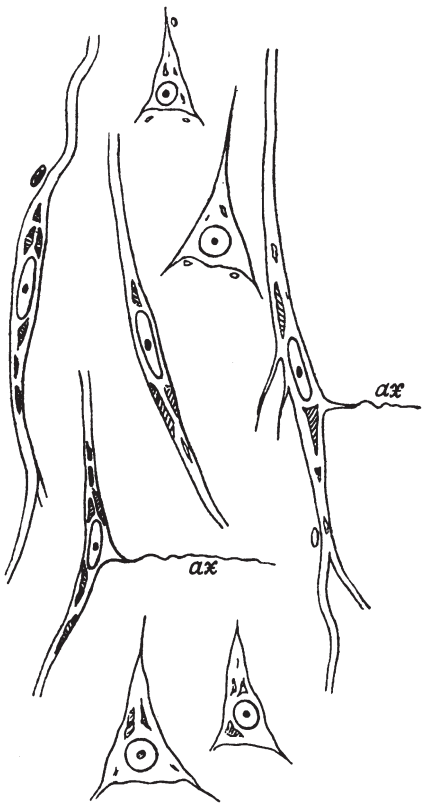

Figure 3.

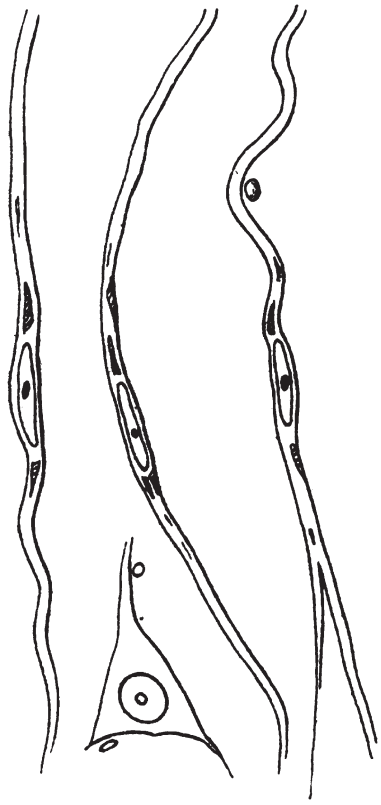

Figure 4.

orbital surface of the frontal lobe. It stretches from the area of the anterior medial third frontal gyrus abutting the olfactory sulcus out laterally toward the tip of the insula. The transverse insular gyrus is separated from the nearly parallel-running third frontal gyrus by the deep limiting sulcus of the anterior insula, which continues as a groove on the orbital surface [see Figure 24 and page 31 of von Economo and Koskinas (1925)]. The anterior wall of the transverse gyrus begins at the frontal anterior surface of the insula and does not contain any additional folds or short accessory gyri. In contrast to the very steep rostral surface of the transverse insular gyrus, its caudal aspect is rather shallow and abuts posteriorly the diminutive lateral olfactory gyrus, which, together with the lateral olfactory root, expands along the length of the basis of the frontal lobe and separates it from the anterior perforated substance. The finest examples of rod and corkscrew cells can be found in the crest and frontal edge of the transverse insular gyrus. In addition to both containing these specialized cells, the transverse insular gyrus and anterior cingulate gyrus have a similar cortical architecture despite their physical separation. Both are of "agranular cortical type 1," lacking the granular layers of the cortex. In the case of these 2 gyri, this cortical type has another peculiar property common to both regions: there is a notable tendency of all cortical cells to take on long, narrow, and stretched forms in adult brains. In the transverse insular gyrus, the stretching of the cells in most cortical layers is so pronounced that the cortex has a radially striated appearance. This stretching of all cells, even pyramidal cells, is most pronounced at cortical folds, where the cells can assume most unusual forms. Through this pulling along their axis the cells attain a spindle-like appearance, and one calls this condition a spindle transformation of cortical cells [see pp. 54 and 199 of von Economo and Koskinas (1925)]. Both the anterior cingulate gyrus and the transverse insular gyrus show such a spindle transformation of cortical cells, which increases until it reaches a maximum in adulthood. In other brain regions, cellular appearance or composition changes with development, such as the apparent increase in pyramidal cells in motor cortex or the increase in granule cells in primary sensory regions that becomes more and more pronounced as development proceeds. We can thereby explain the pathological appearance of the rod or corkscrew cells in the adult: characterized by their long narrow bodies in sharp contrast to the surrounding pyramidal cells, they are stretched to unbelievably narrow and unhealthy looking proportions by the 'spindle transformation' process as the brain reaches maturity.

To follow these facts, it is perhaps appropriate to propose an anatomical speculation about the possible significance of the insular cortex. Without drawing upon the many previous theories and attempts at physiopathological localization, I want to again point out, purely anatomically, the strong similarity between the 2 mentioned gyri: their identical cortical type 1, the spindle transformation of cortical cells that occurs in both, the specialized cells found therein, and the overdevelopment of cortical layer V, in which the cells are so densely arranged that they can be seen macroscopically as a band in stained tissue slices. In addition to these cytoarchitectonic similarities, there are gross anatomical relationships as well. The cingulate gyrus and its subrostral end (the carrefour of Broca or paraolfactory area) are connected to the medial olfactory root and its small medial olfactory gyrus; similarly the transverse insular gyrus and the anterior insula are unquestionably connected to the lateral olfactory root and its small lateral olfactory gyrus. Thus, there are gross anatomical correlates between the 2 areas. Both belong to a large part of the brain termed the olfactory brain. It is quite possible that in man, whose powers of olfaction have wasted away, most of this olfactory brain no longer processes olfaction but has taken on new functions through phylogenetic evolution. It does not seem unlikely that the anterior cingulate cortex, which is of efferent (motor) cortex type 1, considering its close associations with the sense of olfaction and the sympathetic nervous system and the assertion that for example bladder function may be localized there (Marburg and Czylarz), could primarily have efferent sympathetic functions. The structural similarity of frontal insular areas raises the possibility of finding a cerebral representation of the autonomic or sympathetic nervous systems in particular areas of the insula.

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