Literature reviews

Little-known neurons of the medial wall: a literature review of pyramidal cells of the cingulate gyrus

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Abstract

Objective: The purpose of this article is to provide an overview of the current state of knowledge of poorly understood and underresearched neuroanatomy of selected pyramidal cells of the medial wall of the cingulate gyrus.

Methods: A literature review was performed; and separate computerized literature searches of PubMed, Science Direct, Cochrane Library, Science Citation Index, SCOPUS, CINAHL, and the World Wide Web were used for each cell type using individual set time scales for the discovery of each cell. A narrative overview of the literature was developed using information from searches of computerized databases and authoritative texts.

Discussion: The medial walls of the cerebral hemispheres, notably the cingulate gyri, contain species-specific neuron fields that to date are not well known within the scientific community and yet have been implicated as the underlying cause of such varying conditions as dysgraphia and autism in children and obsessive-compulsive disorder and Alzheimer disease in adults. As these neurons are late to develop both phylogenetically and ontogenetically, it has been suggested that they may be particularly vulnerable to stressors that potentially could be an underlying factor in a wide range of neurodevelopmental and neuropsychiatric disorders.

Conclusion: It is considered that knowledge of these little-known pyramidal fields of the medial wall of the human brain is essential to the understanding of how the brain functions both in sickness and in health.

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Introduction

The cingulate gyri of the medial wall of the cerebral hemispheres contain neuron fields that are limited to certain species and that vary in numbers present and in both their structure and columnar arrangement. They

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are also unevenly distributed between the hemispheres, with a greater dominance of von Economo neurons (VENs) having been described in the right hemisphere of the human brain and those of certain great apes.¹⁻⁶ Only 15% of the total adult population of VENs are present at birth, the remaining 85% developing in a window between 4 months and 4 years postnatally. This puts them among a unique group of neurons known to develop postnatally.⁷ The presence of these neuron fields within the cingulate gyrus also lends weight to the argument that the cingulate gyrus should be considered as being isocortex as opposed to proisocortex.^{4,8} The gigantopyramidal field buried in the depth of the cingulate sulcus has been shown to be involved in the planning and execution of the fine motor control of the fingers, and the delayed development of these fields may explain why some children struggle to learn to write and use a fist grip.^{4,9} Calcium-binding calretinin neurons of the anterior cingulate like VENs have been found to be species specific, to date only having been found in the anterior cingulate of the human brain and that of the great apes.¹⁰ Furthermore, in common with VENs, their numbers increase stepwise, the lowest numbers being found in the orangutan, followed by the gorilla, then the chimpanzee, with the highest numbers being found in the human brain. Little is known concerning the precise function of the calcium-binding calretinin neurons of the anterior cingulate; but it has been suggested that they may be discrete projection neurons to specific motor centers involved with the control of vocalization, facial expression, and autonomic function.¹⁰

Although some of these cells were described as early as 1881, they have remained in relative obscurity until 1995; since then, interest in them has increased, leading to further research that potentially has far-reaching possibilities in terms of treatment of many neurodevelopmental/neuropsychiatric disorders. The purpose of this literature review is to provide a summary of the current literature that described these neurons.

Methods

Information was collected using a selective sampling strategy from the following sources using the Boolean operators (*von Economo cells* OR *spindle cells*) AND *anterior cingulate*; *von Economo neurons* AND *infraorbital area* OR *frontal pole*) AND *gigantopyramidal cells* AND *cingulate gyrus* AND *calcium-binding calretinin cells* AND *handedness* and was

fully reported. Separate computerized literature searches of PubMed, Science Direct, Cochrane Library, Science Citation Index, SCOPUS, CINAHL and the World Wide Web were used for each cell type using individual set time scales for the discovery of each cell. The temporal fields were 1925-2009 for VENs, 1976-2009 for gigantopyramidal cells, and 2001-2009 for Ca-binding calretinin cells. Articles chosen were limited to those concerning human studies, the great apes, cetaceans, dolphins, and the African and Indian elephants. Only articles published or translated into English were included. Hand searches of the references of retrieved literature were carried out by the authors. Texts and articles on second-generation neuron by the authors were also reviewed.

Results

von Economo neurons

History

von Economo neurons were first described by Betz¹¹ but were later described in detail by von Economo et al.¹ However, they remained in relative obscurity until 1995, when an article by Nimchinsky et al led to renewed interest in these cells that in turn led to numerous articles being published concerning their location,^{2,3,12,13} species in which they had been found,^{3,6,12,14} their structure,^{15,16} possible functions, and their role in various neuropsychiatric conditions.^{2,7,17,18} They were known as *spindle cells* until 2005, when Allman renamed them as *von Economo neurons* in honor of von Economo's work and to avoid confusion with the accepted use of the term in the field of oncology. In 2008, they were also reported to be present in the dorsolateral prefrontal cortex of humans.¹³

Phylogeny

Originally, spindle cells were described by Betz¹¹; but a more detailed description was provided by von Economo, particularly in terms of their location in limited areas of the cortex, namely, the anterior cingulate gyrus and the anterior region of the insula of the human brain.¹ It was not until 1995 that spindle cells were studied using modern neuroanatomical methods, namely, computer-assisted mapping and immunocytochemical techniques.² In 1999, it was reported that spindle cells had been found in layer Vb of the anterior cingulate cortex of pongids and hominids.¹² It was also

reported that there was a sliding scale in terms of both neuronal volumes and numbers present, the orangutan having the smallest and fewest cells, which increased in both size and numbers present through the gorilla, chimpanzee, and the bonobo, reaching the greatest size and greatest population in the human brain. In humans and bonobos, VENs occur in clusters of 3 to 6, whereas in the common chimpanzee and gorilla, they are found in clusters of 2 or 3 and, in the orangutan, they are present in very small numbers. There is also a sliding scale in terms of the percentage of VENs to pyramidal cells in layer V (Table 1).

In 2006,⁶ spindle cells were found to be present in the anterior cingulate and frontoinsula areas of sperm, killer, humpback, and fin whales; and it came as no surprise when, in 2009, VENs were discovered in both the African and Indian elephant brain.¹⁴ It was also reported in this article that the VENs had been found in the bottlenose dolphin and, in limited numbers, in the manatee.

Function

von Economo neurons represent a morphologic subpopulation of pyramidal cells that are limited to 3 locations in the human brain, with a bias toward a greater population in the right anterior cingulate and infraorbital areas. Being located in layer V would suggest that they are discrete projection neurons to other brain areas.¹⁹ Based on both clinical and imaging studies, it has been suggested that VENs may function in the ability to concentrate and to ignore irrelevant cues, in error correction, in working memory, in the ability to interpret and hence respond appropriately to social situations, and also in the subjective affective state and the capacity to have self-awareness.^{3,7,8}

Conditions associated with VENs

Abnormal structure and/or function of VENs has been implicated in a wide variety of neuropsychiatric disorders including Alzheimer's, depression, schizo-

phrenia, obsessive-compulsive disorder, phobic states, anxiety, akinetic mutism, autism, psychopathy, frontotemporal dementia, anorexia,^{2,3,7,8,12} attention deficit disorder, and attention-deficit/hyperactivity disorder.¹⁸

Gigantopyramidal neurons

History

In 1976, a distinct field of gigantopyramidal cells was described as being present in the human brain in layer Vb of the cingulate sulcus lying beneath and separate from the primary motor area 4 and extending into the lower wall of the superior frontal gyrus.^{4,5} This gigantopyramidal field lies in the midcingulate cortex just posterior to the VENs of the anterior cingulate.³ They are motor neurons involved in the activation of the musculature of the hand.⁹

Phylogeny

Braak's⁴ original articles were based on the study of human brain tissue. Imaging studies have demonstrated that the midcingulate motor area is strongly activated when the subject imagines or executes the precision grip.⁹ The precision grip can only be performed by some monkeys, the great apes, and humans.³ Neuronal activity in the supplementary motor area and the ventral cingulate cortex has been monitored during prehension in the monkey.^{3,9,20}

Function

Imaging studies have shown that the midcingulate area becomes active when the subject performs a precision grip opposing the thumb and index finger but also when the subject imagines such an activity.⁹ When the power grip is used, that is, the hand is wrapped around the object, the primary motor area is strongly activated. Therefore, the use of a pencil will activate the midcingulate area, whereas holding a dagger will activate the primary motor cortex.⁹ These findings would indicate that the midcingulate motor cortex contains phylogenetic specialized circuitry for planning and executing the precise manipulation of objects and writing.³

The 2 grip configurations—precision vs power—also produce differences in terms of hemispheric lateralization. The power grip in a right-handed individual predominantly activates the contralateral primary motor area, whereas the precision grip involves extensive activation of both hemispheres: the left primary motor area and the right midcingulate area.⁹

Table 1 The percentage of VENs to pyramidal neurons in layer V of the anterior cingulate and the number of VENs per cluster

	VENs to PCs	Cluster Size
Orangutan	0.6	1
Gorilla	2.3	2-3
Chimpanzee	3.8	2-3
Bonobo	4.8	3-6
Human	5.6	3-6

PC, Pyramidal cell.

Conditions associated with the gigantopyramidal field of the midcingulate area

As motor dysgraphia—a deficiency in the ability to write easily and legibly—may be due to deficient fine motor skills, it follows that should the gigantopyramidal fields of the midcingulate area fail to develop during early childhood, aspects of dysgraphia may be present. If this motor field is as vulnerable as the adjacent VENs field of the anterior cingulate, could similar environmental factors delay their development, thereby leading to the use of the fist grip via a functioning contralateral primary motor area?^{3,21,22} As dysgraphia is commonly associated with learning and behavioral disorders and these disorders are found to be comorbid, then it would seem that dysgraphia and poor expressive writing skills as a function of the ability to synchronize working memory, attention, and fine motor skills could be seen as the expression of an underfunctioning of both the anterior and midcingulate areas.^{18,23}

Calcium-binding calretinin neurons

History

In 2001, Hof et al¹⁰ described a previously unknown group of pyramidal neurons restricted to the superficial part of layer V of the anterior cingulate cortex of hominids. These pyramidal neurons are characterized by their immunoreactivity to the then recently described calcium-binding protein calretinin. Calretinin is one of 3 calcium-binding proteins and functions as a calcium buffer in certain neuronal populations.

Phylogeny

As with the VEN population of the anterior cingulate cortex calcium-binding calretinin neurons are limited in number in the orangutan and more numerous in both the common chimpanzee and gorilla, whereas in humans, they attain the highest numbers. As expansion of certain areas of cortex has been recognized as an expression of the evolution of the neocortex in primates, the discovery of the calcium-binding calretinin neurons adds weight to this evolutionary theory in terms of encephalization and thereby the possible integration necessary for higher cognitive functioning.¹⁰

Function

The precise function of these cells is not known, but it has been suggested that they may play an important role in the control of the autonomic

nervous system and/or be projection neurons to motor centers involved in the production of facial expression and vocalization.¹⁰

Conditions possibly associated with Ca-binding calretinin neurons

As so little is known concerning the function of these neurons, it is only possible to speculate that an underfunctioning of the population might disturb the complex functions subserved by the anterior cingulate and thereby cause the occurrence of conditions known to be associated with this area. If these cells are specific projection neurons involved in the production of facial expression and vocalization, then escape, that is, spontaneous depolarization, from this population could possibly cause blinking, grimacing, and involuntary vocalization as seen in the tic disorders and Tourette syndrome. Similarly, if they are involved in autonomic regulation, then low-grade activation of the sympathetic nervous system could cause gut symptoms by suppression of the normal activity of the enteric nervous system.

Discussion

The discovery of morphologic subpopulations of pyramidal cells in the anterior and midcingulate gyrus has made possible advancements in several important areas of brain research. In terms of primate neocortical evolution, these phylogenetic subpopulations may indicate an adaptive and anatomical modification critical in many cognitive processes.⁶ This phylogenetic specialization is considered to have arisen within the last 15 million years in hominids before the divergence of orangutans from the African great apes, with a greater proliferation occurring in the human line of descent.⁷ The discovery of spindle cells in certain whales, the bottlenose dolphin, manatee, and elephant has led to speculation of an independent paralleled evolution of VENs/spindle cells.^{3,6,12,14,17}

It is suggested that this late phylogenetic emergence may well make certain of these subpopulations particularly vulnerable to dysfunction and that the late ontological development of VENs may increase their vulnerability.⁷ Because of their predominantly postnatal development, VENs may well be influenced by environmental factors very much like the postnatally generated neurons of the dentate gyrus of the hippocampus. These cells have been found to be vulnerable to many stress-related events; and their

survival has been found to be enhanced by an enriched environment, physical activity, and serotonin-mediated mechanisms.²¹ Postnatally generated neurons in the entorhinal area have also shown to be dependent upon olfactory stimulation and the presence of brain-derived neurotrophic factor, which is enhanced by maternal care, in the hippocampus of rat pups. It may well be that these 2 opposing factors—stress vs enrichment—may impact upon the epigenome, which may cause significant change in terms of genetic expression, as in the case of Agouti mice research that clearly demonstrated the impact upon genetic expression of dietary changes,^{24–28} or a delay in the generation of certain neuronal subpopulations by late activation of homeobox genes.

The medial wall of the cerebral hemispheres, notably the cingulate gyrus, has in the last few years become the center of attention in a bid to find the underlying cause of the major neuropsychiatric disorders; and the discovery of the calcium-binding proteins has been germane to this research into the pathogenesis of such conditions as bipolar disorder and schizophrenia.^{29,30} Attention-deficit/hyperactivity disorder has been shown to be associated with reduced activation in the right lateral prefrontal cortex and anterior cingulate gyrus³¹; and as learning/behavioral disorders in children show distinct patterns of comorbidity,¹⁸ it may well be that, with further advancements in scanning even beyond virtual in vivo interactive dissection (VIVID scanning), the medial wall neuronal subpopulations will be shown to play a critical role in the pathogenesis of developmental delay (learning/behavioral disorders in comorbidity) as well as the later onset of conditions such as schizophrenia.

Current research into these neurons of the medial wall is limited to a few research facilities. It is hoped that, with greater exposure and general awareness of the possible functions of these neuron fields, more research can be put in place that may lead to a greater understanding of these cells both in sickness and in health.

Limitations

The limitation of this study is that it is a narrative review. The selection of databases was limited; other databases may have provided more robust information, and it is possible that some relevant literature was not included in this study. The summary of the materials found in this narrative review included only the authors' opinions and interpretation of the literature. Further more rigorous systematic reviews should be considered in the future. Because of the nature of this study, no clinical correlation should be made.

Conclusion

“The anterior cingulate cortex is a specialisation of neocortex rather than a more primitive stage of cortical evolution.”⁸ Its evolution would appear to parallel the process of encephalization particularly as the species identified to date as possessing morphologic subpopulation are those that have attained the highest levels of encephalization. However, such specialization may have come at a cost with regard to the human offspring that requires an extended period of nurturing in a process that has been called *juvenilization* and the vulnerability of the brain to environmental insults. It is suggested that reduced nurturing and poor nutrition may adversely affect brain maturation and that both neurodevelopmental disorders and many neuropsychiatric disorders may originate from the medial wall of the brain that is, from an ontological perspective, particularly vulnerable to stressors be it birth interventions, lack of omega 3, or food additives.^{32,33}

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