Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *New Perspectives on Neurobehavioral Evolution*

The von Economo neurons in the frontoinsular and anterior cingulate cortex

John M. Allman, Nicole A. Tetreault, Atiya Y. Hakeem, Kebreten F. Manaye, Katerina Semendeferi, Joseph M. Erwin, Soyoung Park, Virginie Goubert, and Patrick R. Hof

Division of Biology, California Institute of Technology, Pasadena, California

Address for correspondence: John Allman Caltech, M.C. 216-76-1200 E. California Blvd. Pasadena, CA 91125. cebus@caltech.edu

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. Our 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, consistent with evidence from functional imaging.

Keywords: frontotemporal dementia; autism; schizophrenia; empathy; disgust; self-awareness; hemispheric specialization

Introduction

In their comprehensive study of the cytoarchitecture of the human cerebral cortex, von Economo and Koskinas[1,2] described large bipolar neurons in the frontoinsular (FI) cortex and in the limbic anterior (LA) area, which wraps around the genu of the corpus callosum and extends posteriorly to the midcingulate (see Fig. 1). von Economo[3,4] called these specialized neurons the rod and corkscrew cells, referring to the straight and twisted variants of this distinct class of neurons. These unusual cells had previously been observed by many classical neuroanatomists, including Betz[5] and Ramón y Cajal,[6] but von Economo[3,4] made a more complete description of their morphology and mapped their specific locations in human cortex. They have often been termed "spindle cells,"[7,8] but because of possible confusion with other uses of this term, we have opted to call them von Economo neurons, or VENs.

The VENs are projection neurons and are substantially larger than their pyramidal cell neighbors.[8,9] They possess a single large basal dendrite, distinguishing them from pyramidal neurons, which have an array of smaller basal dendrites.[10] This single large basal dendrite may have resulted from a transformation during evolution of the genetic programs for pyramidal neuron development to modify the basal dendrite to concentrate its growth in the primary component and suppress the secondary and tertiary branching. The VENs have a narrow dendritic arborization that spans the layers of the cortex and may be able to sample and rapidly relay the output from a columnar array of neurons.[10] The apical and basal dendrites of the VENs are remarkably symmetrical; this architecture suggests that the VENs may be comparing inputs to these two symmetrical dendrites.[10] The VENs in LA are filled retrogradely with the carbocyanin tracer DiI after it is deposited in the cingulum

doi: 10.1111/j.1749-6632.2011.06011.x

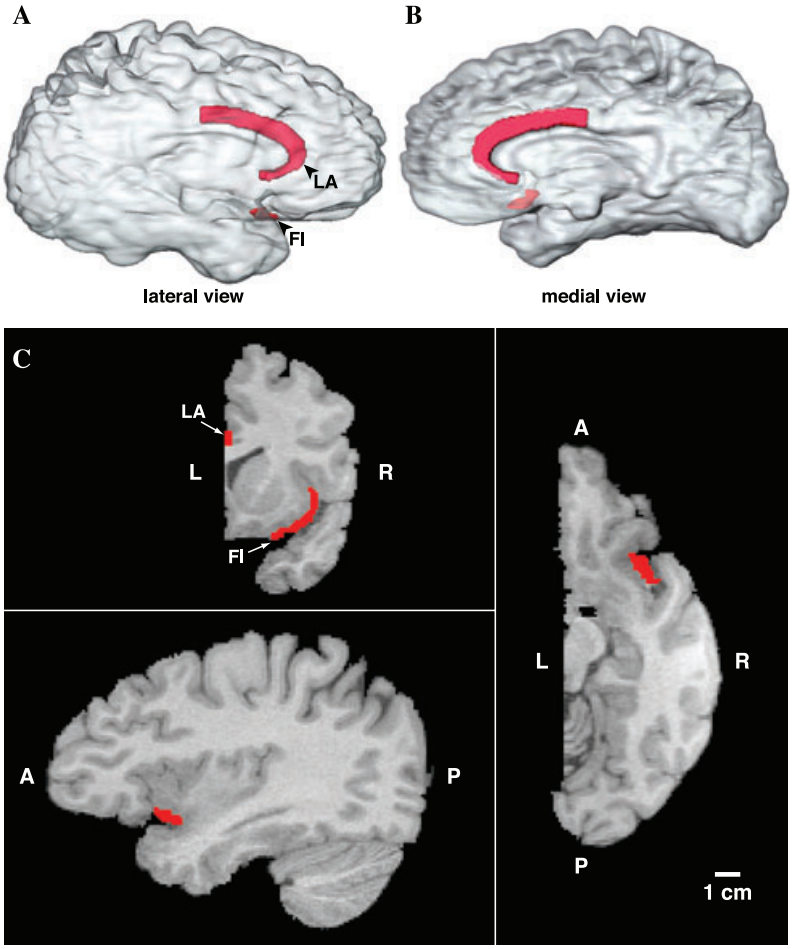

Figure 1. **The location of the VEN-containing areas FI and LA indicated (in red) on the MR scan images of the right hemisphere of a young adult human female. A and B are three-dimensional reconstructions of the hemisphere. C shows frontal (upper left), parasagittal (lower left), and horizontal (right) slices through the hemisphere.**

bundle, so the VENS are likely to be projection neurons with axonal connections extending through the underlying white mater to other parts of the brain.[7] The VENs' large size and preferential staining with the antibody for nonphosphorylated neurofilament are also characteristic features of cortical projection neurons.[7,11] The VENs are thus a significant output from FI and LA, and a consideration of the functions of these areas provides clues as to the kinds of information relayed by the VENs to other parts of the brain.

In anthropoid primates, the posterior insula and anterior cingulate cortex receive differentiated inputs subserving pain, itch, warmth, cooling, and sensual touch, which are central components of highly evolved mechanisms for physiological homeostasis.[12,13] The VEN-containing areas, FI, which are located in inferior anterior insula and LA, may be a further elaboration of these mechanisms, which, while retaining some aspects of their basic regulatory functions, have extended to include aspects of the awareness of self and others and decision making under uncertain conditions. In an exhaustive meta-analysis of the imaging data, the inferior anterior insula has been found to be consistently activated by peripheral autonomic changes.[14] One such connection between autonomic arousal and decision making is suggested by the findings of Critchley *et al.*,[15] who found that anterior insula was activated when subjects had increased galvanic skin responses. The activity of anterior insula also varied as a function of uncertainty during the anticipatory

period in a gambling task.[16] Preuschoff *et al.*[17] found that the region of anterior insula closely matching the location of FI was specifically activated during "risk prediction error," when a loss as the consequence of a gambling decision was revealed to the subject. The anterior inferior insula, also in a location closely corresponding to FI, is strongly activated by negative feedback in the form of frowning faces in a decision task involving a high degree of uncertainty.[18] Frowning faces also activated a site corresponding to the posterior part of LA.[18] The region corresponding to FI on the right side is activated when subjects scrutinize facial expressions to discern intentions.[19] The integrative functioning of the lateral part of FI in response to negative feedback is illustrated in a series of experiments by Jabbi *et al.*,[20] who elicited activity in this VEN-rich region through experiences involving disgust mediated by taste, by the observation of someone else responding to a disgusting taste, and by imagining a disgusting taste. These data, together with many other experiments, suggest that anterior insula and cingulate cortex are involved in the recognition of error and the initiation of adaptive responses to error and negative feedback.[21–24] Anterior insula and cingulate cortex are major components of the system for the flexible control of goal-directed behavior.[25] The area LA also includes portions located near the genu of the corpus callosum that are profoundly involved in emotional states; there is substantial functional heterogeneity within the cortex comprising LA, with VENs occurring throughout this structure (see Ref. 26 for a review). The following sections are an attempt to describe some of the complexity of this system.

Anterior insula and anterior cingulate cortex are activated by social error signals

Anterior insula and anterior cingulate cortex are activated by situations that involve social error, a defect in the social network in which the individual is participating, or a change in state of one of the participants. For example, these structures are activated by resentment,[27] deception,[28] embarrassment,[29] and guilt.[30] They are also activated by feelings of empathy for the suffering of others, another type of social error signal.[31] A meta-analysis of nine brain imaging studies involving empathy revealed consistent activation in FI and the adjacent superior anterior insula (SAI) as well as in the posterior part of LA in approximately the same region as was activated by frowning faces.[32] In mothers, FI in the right hemisphere responds to the cries of distressed infants,[33] which are powerful social error signals. The anterior insula (including both superior and inferior components) was activated when partners in the prisoner's dilemma game failed to reciprocate cooperative moves made by the subject, another type of social error signal.[34] Anterior insula and anterior cingulate cortex are activated by prosocial signals such as love and trust,[35,36] which suggests that these structures register both negative and positive aspects of the states of social networks. The responses of FI and LA are parametrically related to how humorous subjects judge cartoons to be; the humorous content of the cartoons typically involved social errors.[37]

VENs in neuropsychiatric disorders

The VENs are implicated in several neuropsychiatric illnesses. In a stereological study, Seeley *et al.*[38–40] found that the VENs are specifically and selectively attacked in the early stages of the behavioral variant of frontotemporal dementia (FTD), in which empathy, social awareness, and self-control are severely diminished. The VEN population of ACC is reduced by an average of 74% in these patients, and many of the surviving VENs are severely dysmorphic. The destruction of the VENs in FTD results from two distinct molecular mechanisms in different patients. One mechanism is related to abnormal isoforms of the tau protein, and the other is related to abnormal expression in the cytoplasm of VENs of the DNA-binding protein TDP-43.[38,40] The VENs are also reduced in FI.[39] In contrast, Seeley *et al.*[38,39] found that the VENs were not significantly reduced in Alzheimer's dementia (AD), although a reduction had been reported in an earlier study that did not use stereological methods.[7]

Agenesis of the corpus callosum is another condition in which abnormal social behavior may be linked to reduced VEN populations. Patients with agenesis of the corpus callosum often have impoverished and superficial relationships, suffer from social isolation, and have interpersonal conflicts both at home and at work due to misinterpretation of social cues.[41] Kaufman *et al.*[42] found that the VENs were reduced by 50% in a subject with partial

agenesis of the corpus callosum and by 90% in a subject with complete agenesis when compared to adult controls. The VEN loss could not be attributed to the reduction or absence of the corpus callosum itself, because the VEN concentration in FI was normal in another subject whose corpus callosum was destroyed as the result of a stroke 15 years before her death. Because the surgical sectioning of the corpus callosum does not disrupt social behavior,[43] the social deficit in agenesis of the corpus callosum may be related to VEN loss.

There are many features of autism that suggest that the VENs may be involved in this disorder.[44,45] An initial stereological study of the number of VENs in area FI in four autistic subjects plus controls did not confirm this conjecture.[46] However, a second stereological study of VENs in dorsal ACC in nine autistic subjects plus controls found that the autistic subjects fell into two groups, one with significantly higher numbers of VENs than controls, and the other with significantly fewer VENs than controls.[47] Thus the controls occupied a middle zone with little overlap with the high or low VEN autism groups. The results of Simms *et al.*[47] suggest that two different mechanisms influence the number of VENs in autism, possibly through different effects on migration and survival. A very recent study done in FI found a significantly higher ratio of VENs to pyramids in autistic subjects as compared to controls.[48] As in FTD, in autism the VENs may be vulnerable to more than one pathological process contributing to the disorder as it manifests in different individuals. The higher ratio of VENs to pyramids may paradoxically be associated with a reduction in activity in FI. A strong linkage between reduced activity in the right anterior insula in autistic subjects versus controls in social tasks was revealed in a meta-analysis of 24 functional imaging studies.[49]

Finally, the VENs have been implicated in schizophrenia. The VENs in the right hemisphere in ACC are reduced in number in early onset schizophrenia when compared with later-onset schizophrenia, bipolar disorder, and normal controls.[50]

VEN locations and stereological counts

The locations of the VEN-containing areas FI and LA are illustrated in three-dimensional transparent reconstructions of the right hemisphere of a human brain in Figure 1. In Figure 2, every VEN is plotted for a section through FI and adjacent cortex from a chimpanzee, a gorilla, and a human. To the left of each section is a corresponding low-power photomicrograph of the section. The VEN-containing area is largely confined to the region of high flexure in the chimpanzee but extends medially in the gorilla and even farther in the medial direction in the human. The transition between FI and SAI corresponds to a gradient in VEN density rather than a sharp border. The cytoarchitecture of area LA and the location of the VENs in this part of anterior cingulate cortex are illustrated by von Economo[2] and Nimchinsky *et al.*[7,8]

The VENs are illustrated at higher magnification in Figure 3, which shows that they have very similar morphology in the great apes and humans. In primates, the VENs are present in FI only in great apes and humans. This is the same taxonomic distribution as was found for the VENs in LA,[8] which suggests that the VENs emerged as a specialized neuron type in the common ancestor of great apes and humans. However, in orangutans we found only one out of seven individuals examined to have a substantial VEN population in FI and LA.

Our key stereological findings are represented in the form of graphs (Figs. 4–6); a more extensive account of the stereological findings together with the methods employed is given by Allman *et al.*[51] Figure 4 shows that the VENs are more numerous in humans than in apes, but that the VENs constitute a higher percentage of the total neurons in the regions of interest in apes than in humans. In LA, one of the individual apes (a gorilla) stands out as having considerably more VENs than the others, approaching the lower end of the human range. The VEN count was similarly elevated relative to the other apes in this same gorilla in FI on the left side and also approached the lower end of the human range for this structure; unfortunately, postmortem damage to right FI in this individual made it impossible to make a stereological count for this structure in the right hemisphere. The relative abundance of VENs in this gorilla is also illustrated in comparison to a chimpanzee in Figure 2. This individual gorilla had an exceptionally enriched environment.[52] Although we can conclude nothing definitive from this isolated observation, it does raise the possibility that VEN abundance may be related to environmental influences.

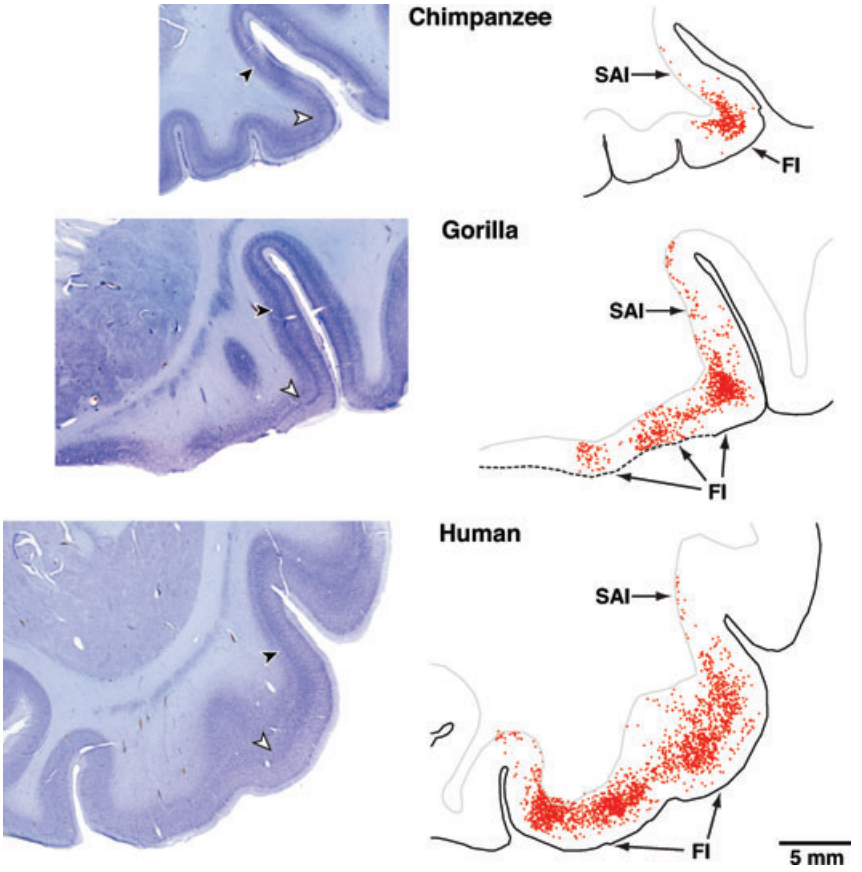

Figure 2. Photomicrographs of frontal sections through area FI in a 39-year-old male chimpanzee, a 27-year-old male gorilla, and a 1.6-year-old male human. On the right side are outlines of the corresponding sections in which the location of each VEN has been plotted. There are 354 VENs plotted in the chimpanzee, 919 in the gorilla, and 2415 in the human plotted by scanning through the different depth planes with a 40× oil immersion lens with the aid of Stereoinvestigator software. The sections were 100 μm thick. All images are represented at the same scale. The sections are from FI on the right side except for the gorilla, in which FI was damaged during histological processing, and instead the left FI has been used and the image reversed for ease of comparison with the other cases. The locations of the higher magnification photomicrographs shown in Figure 4 are indicated by arrows in the low power photomicrographs. FI, frontoinsular cortex; SAI, superior insular cortex.

VENs emerge mostly postnatally and are more abundant in the right hemisphere

We examined FI and LA in fetal brains at postconception ages of 32 weeks ($n = 1$), 33 weeks ($n = 1$), 34 weeks ($n = 3$), and 35 weeks ($n = 2$), and no VENs were found. In one 36-week postconception brain, small numbers of VENs were present in FI and LA. Figure 5 shows that the VENs exist in relatively low numbers in FI at birth; in LA, the VENs were so rare that we were not able to make stereological estimates in the brains of neonates. In the late-term neonate (42 weeks postconception), the number of VENs in FI was considerably higher than in the normal-term neonates (38 to 40 weeks postconception), suggesting that the number of VENs in FI increases immediately after the normal time of birth. The number of VENs is significantly greater in the postnatal brains relative to the neonatal brains. The percentage of total neurons that are VENs is relatively stable in adulthood and is similar to the percentages observed by Seeley *et al.*[38]

Figure 6 illustrates the ratio between the number of VENs in the right hemisphere and that in the left. In newborns, there is no clear hemispheric preference, but nearly all of the postnatal humans and all of the apes show a clear predominance of VENs in the right hemisphere in both FI and LA. In FI, nearly all the postnatal cases have 20–40% more VENs in the right hemisphere, except for the 8-month-old

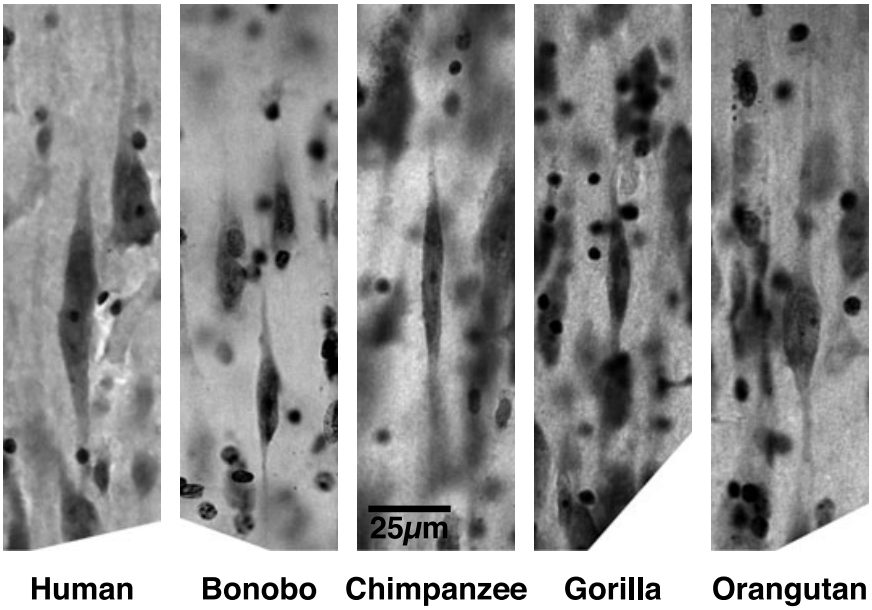

Figure 3. **VENs in area FI of humans and great apes. Photomicrographs are of Nissl-stained sections. All panels share the scale indicated in the central panel.**

infant, which is an extreme outlier. In ACC, nearly all the cases show a rightward predominance, but the numbers are much more variable than in FI. It is interesting in this context that the VENs are vulnerable in the right hemisphere in ACC in early onset schizophrenia.[50]

The VENs mostly emerge postnatally, which can be seen in their numbers, concentrations, and the formation of the hemispheric predominance of VENs on the right side in the first few months after birth. This emergence could come about by the transformation of another cell type into the VENs or by postnatal neurogenesis. The long, thin spindle shape of the VENs with their sometimes undulating apical and basal dendrites closely resembles that of migrating neurons with undulating leading and trailing processes, and this is particularly evident in infant brains.[11] Although there are many technical difficulties in experimentally resolving whether the VENs arise by transformation or postnatal neurogenesis, future research should reveal whether either of these possibilities is correct.

An important finding in our study is the larger number of VENs in the right hemisphere than the left except in very young subjects, and thus that the rightward asymmetry emerges during the first few months of postnatal life. Stereological evidence for hemispheric differences in neuron number in primates (including humans) is very limited. Uylings *et al.*[53] found a trend toward a larger number of total neurons in the left hemisphere of Broca's area for a population of five female brains. Sherwood *et al.*[54] found that right–left differences in the density of parvalbumin-positive interneurons in layers 2 and 3 of primary motor cortex in chimpanzees is linked to hand preference.

However, there is excellent evidence that the anterior cingulate cortex is larger on the right side from a structural MRI study of 100 young adult subjects. One study found that ACC is 13% larger on the right side, while the size of posterior cingulate cortex is the same in both hemispheres.[55] There are also structural MRI data for 142 young adults that suggest FI is enlarged by about the same amount on the right side.[56] The significantly increased number of VENs in the right hemisphere in FI and ACC is among the few demonstrations of hemispheric differences in neuron number based on stereological techniques, and these rightward predominances correspond to size differences in FI and ACC observed in structural MRI studies done in large populations of adult human subjects. The fact that

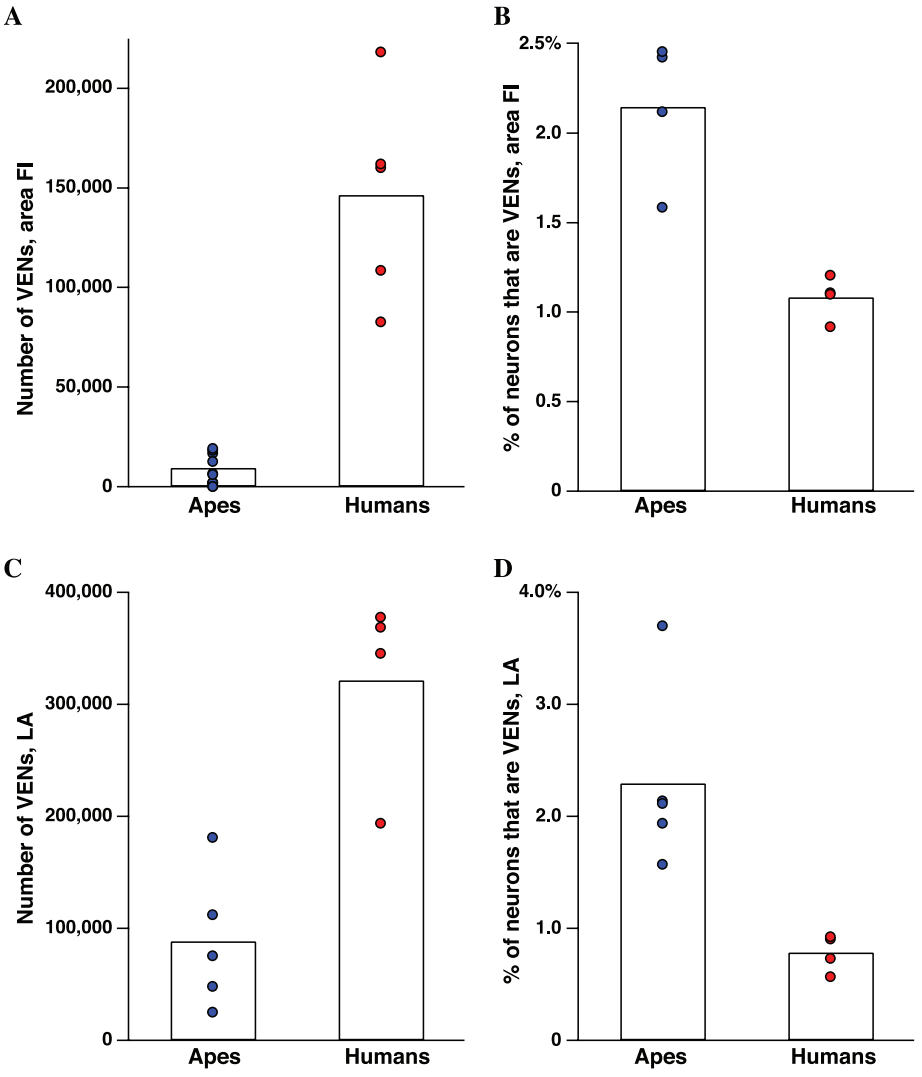

Figure 4. **A comparison of the number and proportion of VENs in area FI and ACC of adult humans and great apes. Bars indicate the average of all data points in a given column. (A) The number of VENs in area FI (both hemispheres combined). FI contains many more VENs in humans than in great apes ($P = 0.001$). (B) The percentage of neurons in area FI that are VENs. Although the great apes have a smaller total number of VENs in FI, they have a higher proportion of VENs to non-VEN neurons in FI ($P = 0.029$). (C) The number of VENs in ACC (both hemispheres combined). As in area FI, humans have more VENs than the great apes ($P = 0.016$), although this difference is less great in ACC. (D) The percentage of neurons in ACC that are VENs. Again, as in FI, the great apes have a higher percentage of neurons that are VENs ($P = 0.016$). All comparisons are Mann–Whitney *U*-tests.**

these hemispheric differences are present in both humans and great apes suggests that they may have existed in the common ancestor of both groups. There is recent evidence from a developmental MRI study based on 316 right-handed subjects that the anterior insular and posterior orbitofrontal cortex is thinner on the right side than the left at age four in normal subjects but progresses by age 20 to be significantly thicker, by about 0.3 mm, on the right side than the left.[57] The rightward asymmetry in cortical thickness for the region containing FI in the adult brain is consistent with previous MRI studies done in adults and with the rightward asymmetry in VEN numbers in our study; however, in our study

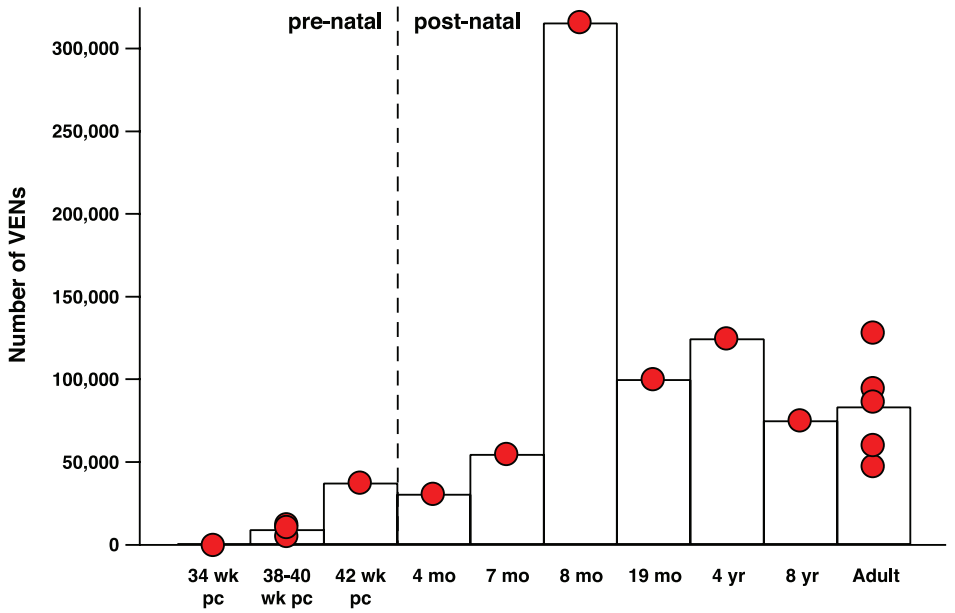

Figure 5. **The number of VENs increases after birth. The number of VENs in right hemisphere FI in humans of different ages. VEN numbers are low in neonates and increase after birth. The 8-month-old individual examined had markedly more VENs in the right hemisphere than any other subject in this study; this might possibly be due to individual variation. The right hemisphere VEN measurement in this individual was repeated with similar results. The difference between the number of VENs in right FI for pre- and postnatal subjects was statistically significant ($P = 0.0029$), and this significance remained when the 8-month-old individual was removed from the comparison ($P = 0.0040$). The number of VENS in left FI and in both hemispheres together was also significantly different for pre- and postnatal individuals ($P = 0.0056$ for both). Significance was determined using the Mann–Whitney *U*-test.**

we found a rightward asymmetry in VEN numbers throughout postnatal life. Thus, the rightward predominance of VEN numbers develops before the predominance in cortical thickness in this cortical region.

What is the biological significance of the rightward hemispheric asymmetry of the VENs in FI and ACC? The VEN asymmetry may be related to asymmetry in the autonomic nervous system in which the right hemisphere is preferentially involved in sympathetic activation, as would result from negative feedback and subsequent error-correcting behavior; the left hemisphere is preferentially involved in parasympathetic activity associated with reduced tension or calming responses.[58] Following this reasoning, there may be more VENs on the right side because the responses to negative feedback require more complex and more urgent behavioral responses than do situations that are calming and involve reduced tension. Many of these experiments probably have in common a right FI response similar to that which has been specifically linked to sympathetic arousal as measured by the galvanic skin response.[15] A meta-analysis of coactivation of amygdala and insula involving 955 responses in 86 papers reported coactivation between the amygdala and inferior anterior insula on both sides but found it to be more pronounced on the right.[14] In a meta-analysis of 23 functional imaging studies conducted in children and adolescents performing various executive functioning tasks such as go versus no-go, which typically involve intense focus and self-control, Houdé *et al.*[59] found that in children the most consistent site of activation was in anterior insula on the left side, while in adolescents the most consistent site of activation was the inferior anterior insula corresponding to FI on the right side. Thus, the right FI becomes strongly engaged in executive functioning and self-control in adolescents. Houdé *et al.*[59] say that this change "is consistent with the fact that adolescents are often psychologically embedded in a period of great emotional reactivity and

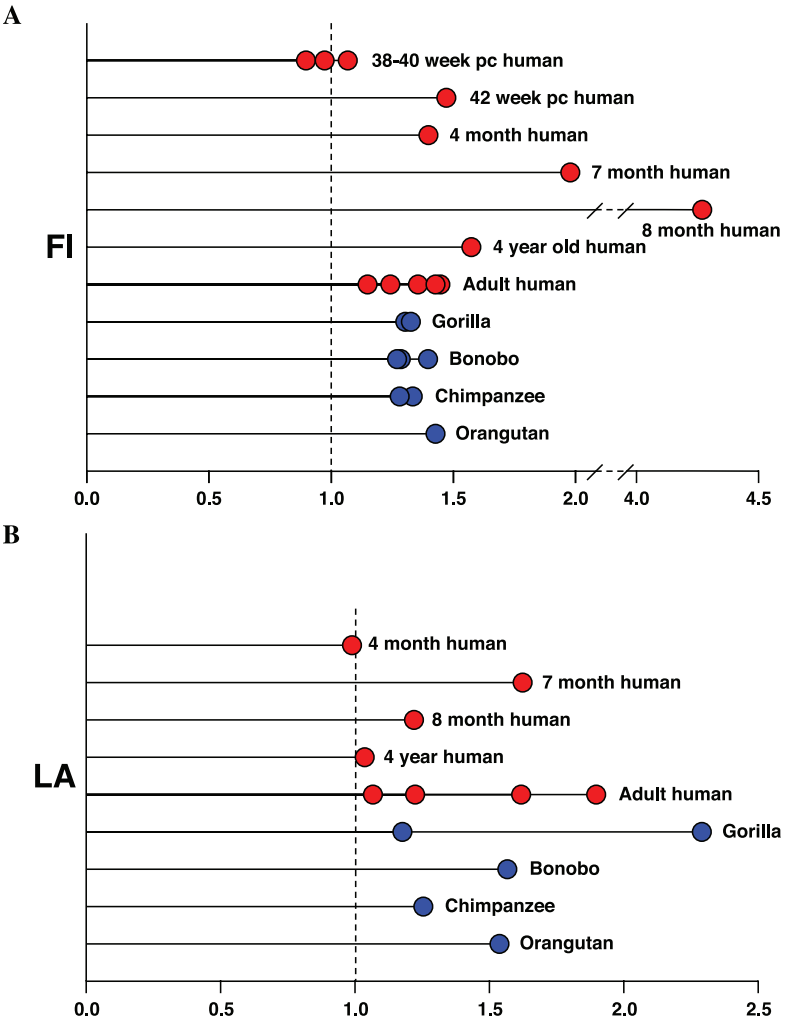

Figure 6. The ratio of the number of VENs in the right hemisphere to the number of VENs in the left hemisphere. (A) In postnatal humans and great apes, there are consistently more VENs in FI on the right side. This ratio develops after birth. In neonates, the numbers in each hemisphere are almost even, while in infants, juveniles, and adults there are many more VENs in the right hemisphere. When the numbers of VENs in the right and left hemispheres were compared for FI in the postnatal cases, the difference was statistically significant both with and without the 8-month-old outlier ($P = 0.0039$ for all postnatal humans and $P = 0.0078$ without the 8-month-old case). For postnatal apes and humans combined, the hemispheric difference for FI was significant at $P < 0.0001$. (B) The ratio of VENs in right and left LA. This ratio is less consistent than in area FI, but in almost all cases there are more VENs on the right side. When the number of VENs in the right and left hemispheres in postnatal humans was compared for LA, the result was statistically significant ($P = 0.03$). When postnatal apes and humans were combined, the difference was significant at $P = 0.001$. Significance was determined using the Mann–Whitney U-test.

sensitivity with negative feelings. Recognizing the necessity of being wrong is necessary to achieve high levels of adult adaptation and maturity in cognitive control. Our result might reflect a key transition around the time of adolescence toward increased influence of negative feedback (i.e., error detection and/or anticipation) on cognitive control" (Ref. 59).

There is also some evidence of preferential leftward activation in FI and ACC involving positive and affiliative emotions.[13,35,60] The left anterior cingulate cortex was preferentially activated when subjects relaxed and reduced their sympathetic arousal through biofeedback.[61] There is evidence that the right hemisphere of the brain is related to

sympathetic arousal and the left hemisphere to parasympathetic quietude.[58,62,65] This autonomic asymmetry is consistent with the proposal that the right hemisphere responds to the unexpected and the left hemisphere to more routine stimuli.[64] There is also evidence for this autonomic asymmetry from electrical stimulation of the insular cortex on the right and left sides in human subjects.[65] Craig[58] suggests that sympathetic activation on the right side and consequent energy expenditure by the organism, and parasympathetic activation on the left and energy conservation together, function to serve as a balancing mechanism for managing the organism's energy resources. These mechanisms involve in part highly conserved circuits in the vagal complex that regulate respiration and the production of vocalizations throughout vertebrates.[66]

VENs in evolution

In immunocytochemical studies, many VENs in FI and LA express gastrin-releasing peptide (GRP) and neuromedin B (NMB), which are bombesin hormones involved in gastric function and peristalsis in the gut and satiety in the brain.[46,67] GRP and NMB are expressed in very specific populations of neurons in anterior insula and anterior cingulate cortex in mice in the *in situ* hybridization maps in the Allen Brain Atlas (http://www.brain-map.org/). These findings, together with the presence of VENs in the apparent homologs of FI and ACC in such phylogenetically diverse mammals such as apes, humans, elephants, and whales, suggest that they are derived from common populations of neurons in anterior insula and anterior cingulate cortex that were present in primitive mammals.[68–70] The existence of VENs in primates is not related to relative brain size or encephalization.[51] Instead, it appears to be related to absolute brain size. The VENs are present in primates with adult brain sizes greater than about 300 g and in elephants and whales, which also have very large brains. We suggest that large brain size and complex social behavior both favor specialized neural systems for rapid communication within brain circuits. Large brains may be inherently slower because of the greater distances over which messages must be sent. Large brains also suffer from the limitations associated with packing large myelinated axons into a restricted space. The corpus callosum in large brains has small numbers of very large axons.[71] These very large axons may relay the gist of the information between the hemispheres, which is then followed by more detailed information communicated by smaller, slower conducting axons. These very large axons would thus enable the fast communication between the hemispheres that would otherwise be limited by size and distance in large brains while conforming with the packing constraint that would not allow the scaling up of all axons because of spatial limitations. We suggest that there is an analogous temporal division of labor between the VENs and the neighboring pyramids, which may serve as a compromise between the needs for rapid communication and the inability to enlarge all axons.[71] We believe that the large size and simple dendritic architecture of the VENs supports the conjecture that they are built for speed. We predict that the axon calibers of the VENs are larger than in the neighboring pyramids and that the VEN axons are faster conducting than their neighbors. The evolution of the VENs may be an adaptation related to large brain size allowing the gist of the information processed within a cortical column to be relayed rapidly to other brain structures. This putative rapid relay may be particularly important for the relay of social decisions, although not restricted to the social domain.[26,41] Complex social behavior is often fast paced, and this puts a premium on the capacity to respond quickly to changing conditions. A basic function of FI may be to register feedback crucial for initiating fast adaptive responses to changes, which would be consistent with the activity of FI preceding linked activity in ACC and other cortical areas.[72]

We found two interesting differences between the distribution of VENs in humans and in apes. The first difference between humans and apes is the relationship between VEN location and agranular insular cortex, i.e., insular cortex lacking a layer 4. In humans, area FI, which is defined by the presence of VENs, appears to correspond to most of agranular insular cortex, as delineated by Rose.[73] However, in apes, area FI appears to correspond to a smaller part of the total agranular insular cortex. This difference may explain why there are typically considerably more VENs in humans than in apes. The second difference between humans and apes is that the density of VENs relative to other neurons is significantly higher for apes than humans in FI and ACC. One possible explanation for this surprising finding is that there may be other specialized neuronal

populations that are differentially expanded in humans relative to apes.

The anterior insula and VENs may be linked to awareness

Recent work suggests that the anterior insula is involved in awareness.[74–76] This connection with awareness was initially suggested in an fMRI experiment by Kikyo and Ohki,[77] in which they observed activity in anterior insula when subjects reported the subjective sense of knowing a word before recalling it in a memory task, which these authors called the "feeling of knowing." More recently, in an experiment employing a behavioral paradigm in which objects gradually emerge from noise, Ploran *et al.*[74] found that the activity of anterior insula was strongly linked to the moment when the subjects became aware of the identity of the object.[74] More recent work from the same group has identified several components of this activity, including one in inferior anterior insula, particularly on the right side.[75] Devue *et al.*[78] found foci of activity in FI and LA in subjects when viewing their own faces as compared with the familiar faces of colleagues, suggesting that these foci may be involved in discriminating self from other. We have proposed[44] that the VENs and related circuitry are involved in rapid intuition, which, like perceptual recognition, involves immediate effortless awareness rather than the engagement of deliberative processes. Recently, Aziz-Zadeh *et al.*[79] found that when subjects were solving anagrams and arrived at rapid insightful solutions ("aha" moments), both anterior insula and anterior cingulate cortex were activated. These aspects of awareness are not limited to body states, but involve visual and linguistic experiences as well, suggesting the hypothesis that the role of anterior insula in awareness may include most or all aspects of perception and cognition. An extension of this hypothesis is that the VENs in FI serve as a fast relay of this information to other parts of the brain.

Acknowledgments

The authors would like to thank Drs. Barbara Wold, Chet Sherwood, Bill Seeley, and A. D. Craig for their invaluable comments and discussion. We thank Drs. Micheal Tyszka and Jason Kaufman for the MRI imaging of the ape brains. We thank Drs. Kristen Tillisch and Emeran Mayer for the MR images of the young adult human subject. We thank Dr. Heidi Griffith for her help in collecting some of the human stereological data. We also thank Archibald Fobbs, curator of the Yakovlev and Welker Brain Collections, and Dr. Adrianne Noe, Director of the National Museum of Health and Medicine, for their crucial role in preserving these collections and making them available to us and to the broader scientific community. In the Hof lab, technical help was provided by B. Wicinski and S. Harry. Several of the great ape brains involved in this study were on loan to the "Great Ape Aging Project" from zoological gardens that are accredited by the Association of Zoos and Aquariums (AZA) and that participate in the Ape Taxon Advisory Group (Ape-TAG). We especially appreciate the contribution of zoo veterinarians and staff in collecting and providing specimens. Additional human tissue was obtained from the National Institute of Child Health and Human Development Brain and Tissue Bank for Developmental Disorders. Some comparative specimens were collected under the "Comparative Neurobiology of Aging Resource," NIH/NIA grant AG14308, J. Erwin, PI. This research was supported by the James S. McDonnell Foundation, the David and Lucille Packard Foundation, the Simons Foundation, and the National Institute of Mental Health.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. von Economo, C. & G. Koskinas. 1925. *Die Cytoarchitectonik der Hirnrinde des erwachsenen Menschen.* Springer. Berlin.
2. von Economo, C. 2009. *Cellular Structure of the Human Cerebral Cortex*. Translated by L.C. Triarhou. Karger. Basel.
3. von Economo, C. 1926. Eine neue Art Spezialzellen des Lobus cinguli und Lobus insulae. *Zschr. ges. Neurol. Psychiat.* **100:** 706–712.
4. Seeley, W., A. Craig, P. Hof, *et al*. 2011. Distinctive neurons in anterior cingulated and frontoinsular cortex: a historical perspective. *Cereb. Cortex*. In press. doi:10.1093/cercor/bhr005.
5. Betz, W. 1881. Ueber die feinere Structur der Gehirnrinde des Menschen. *Zentralbl. Med. Wiss.* **19:** 193–195, 209–213, 231–234.
6. Ramón y Cajal, S. 1899. *Textura del Sistema Nervioso del Hombre y de los Vertebrados, Tomo II*. Nicolás Moya. Madrid.
7. Nimchinsky, E.A., B.A. Vogt, J.H. Morrison & P.R. Hof. 1995. Spindle neurons of the human anterior cingulate cortex. *J. Comp. Neurol.* **355:** 27–37.
8. Nimchinsky, E.A., E. Gilissen, J.M. Allman, *et al*. 1999. A neuronal morphologic type unique to humans and great apes. *Proc. Natl. Acad. Sci. USA* **96:** 5268–5273.

9. Allman, J.M., A. Hakeem, J.M. Erwin, *et al*. 2001. Anterior cingulate cortex: the evolution of an interface between emotion and cognition. *Ann. N.Y. Acad. Sci.* **935:** 107–117.
10. Watson, K.K., T.K. Jones & J.M. Allman. 2006. Dendritic architecture of the von Economo neurons. *Neuroscience* **141:** 1107–1112.
11. Allman, J., A. Hakeem & K. Watson. 2002. Two phylogenetic specializations in the human brain. *Neuroscientist* **8:** 335–346.
12. Craig, A.D. 2003. A new view of pain as a homeostasis emotion. *Trends Neurosci.* **26:** 303–307.
13. Craig, A.D. 2009. How do you feel—now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* **10:** 59–70.
14. Mutschler, I., B. Wieckhorst, S. Kowalevski, *et al*. 2009. Functional organization of the human inferior insular cortex. *Neurosci. Lett.* **457:** 66–70.
15. Critchley, H.D., R. Elliott, C.J. Mathias & R.J. Dolan. 2000. Neural activity relating to generation and representation of galvanic skin conductance responses. *J. Neurosci.* **20:** 3033–3040.
16. Critchley, H.D., C. Mathias & R. Dolan. 2001. Neural activity in the human brain relating to uncertainty and arousal during anticipation. *Neuron* **29:** 537–545.
17. Preuschhoff, K., S. Quartz & P. Bossaerts. 2008. Human insula activation reflects risk prediction errors as well as risk. *J. Neurosci.* **28:** 2745–2752.
18. Ullsperger, M. & D.Y. von Cramon. 2004. Neuroimaging of performance monitoring: error detection and beyond. *Cortex* **40:** 593–604.
19. Baron-Cohen, S., H.A. Ring, S. Wheelwright, *et al*. 1999. Social intelligence in the normal and autistic brain: an fMRI study. *Eur. J. Neurosci.* **11:** 1891–1898.
20. Jabbi, M., J. Bastiaansen & C. Keysers. 2008. A common anterior insula representation of disgust observation, experience and imagination shows divergent functional connectivity pathways. *PLos One* **8:** e2939.
21. Gehring, W.J., B. Goss, M.G.H. Coles, *et al*. 1993. A neural system of error detection and compensation. *Psychol. Sci.* **4:** 385–390.
22. Dehaene, S., M.I. Posner & D.M. Tucker. 1994. Localization of a neural system for error detection and compensation. *Psychol. Sci.* **5:** 303–305.
23. Klein, T.A., T. Endrass, N. Kathmann, *et al*. 2007. Neural correlates of error awareness. *Neuroimage* **34:** 1774–1781.
24. Lamm, C., T. Singer. 2010. Role of anterior insular cortex in social emotions. *Brain Struct. Funct.* **214:** 579–591.
25. Dosenbach, N.U., D.A. Fair, F.M. Miezin, *et al*. 2007. Distinct brain networks for adaptive and stable task control in humans. *Proc. Natl. Acad. Sci. USA* **104:** 11073–11078.
26. Williamson, P.C. & J.M. Allman. 2010. *The Human Illnesses: Neuropsyciatric Disorders and the Nature of the Human Brain.* Oxford University Press. New York.
27. Sanfey, A.G., R.J. Rilling, J.A. Aronson, *et al*. 2003. The neural basis of economic decision-making in the ultimatum game. *Science* **300:** 1755–1758.
28. Spence, S.A., T.F. Farrow, A.E. Herford, *et al*. 2001. Behavioural and functional anatomical correlates of deception in humans. *Neuroreport* **12:** 2849–2853.
29. Berthoz ,S., J.L. Armony, R.J.R. Blair & R.J. Dolan. 2002. An fMRI study of intentional and unintentional (embarrassing) violations of social norms. *Brain* **125:** 1696–1708.
30. Shin, L.M., D.D. Dougherty, S.P. Orr, *et al*. 2000. Activation of anterior paralimbic structures during guilt-related script-driven imagery. *Biol Psychiat.* **48:** 43–50.
31. Singer, T., B. Seymour, J. O'Doherty, *et al*. 2004a. Empathy for pain involves the affective but not sensory components of pain. *Science* **303:** 1157–1162.
32. Lamm, C., J. Decety & T. Singer. 2011. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *Neuroimage* **54:** 2492–2502.
33. Lorberbaum, J.P., J.D. Newman, A.R. Horwitz, *et al*. 2002. A potential role for thalamocingulate circuitry in human maternal behavior. *Biol. Psychiat.* **51:** 431–445.
34. Rilling, J., D. Goldsmith, A. Glenn, *et al*. 2008. Neural correlates of the affective response to unreciprocated cooperation. *Neuropsychologia* **46:** 1265–1266.
35. Bartels, A. & S. Zeki. 2004. The neural correlates of maternal and romantic love. *Neuroimage* **21:** 1155–1166.
36. Singer, T., S.J. Kiebel, J.S. Winston, *et al*. 2004. Brain responses to the acquired moral status of faces. *Neuron* **41:** 653-662.
37. Watson, K.K., B.J. Matthews & J.M. Allman. 2007. Brain activation during sight gags and language-dependent humor. *Cereb. Cortex* **17:** 314–324.
38. Seeley, W.W., D.A. Carlin, J.M. Allman, *et al*. 2006. Early fronto-temporal dementia targets neurons unique to apes and humans. *Ann. Neurol.* **60:** 660–667.
39. Seeley, W.W., J.M. Allman, D.A. Carlin, *et al*. 2007. Divergent social functioning in behavioral variant fronto-temporal dementia and Alzheimer disease: reciprocal networks and neuronal evolution. *Alzheimer Dis. Assoc. Disord.* **21:** S50–S57.
40. Seeley, W.W. 2008. Selective functional, regional, and neuronal vulnerability in fronto-temporal dementia. *Curr. Opin. Neurol.* **21:** 701–707.
41. Paul, L.K., W.S. Brown, R. Adolphs, *et al*. 2007. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. *Nat. Rev. Neurosci.* **8:** 287–299.
42. Kaufman, J.A., L.K. Paul, K.F. Manaye, *et al*. 2008. Selective reduction of Von Economo neuron number in agenesis of the corpus callosum. *Acta. Neuropathol.* **116:** 479–489.
43. Shorvon, S. 2005. *Handbook of Epilepsy Treatment*. Wiley. New York.
44. Allman, J., K. Watson, N. Tetreault & A. Hakeem. 2005. Intuition and autism: a possible role for von Economo neurons. *Trends Cogn. Sci.* **9:** 367–373.
45. van Kooten. 2008. Autism counts. Dissertation, Maastricht University.
46. Kennedy, D.P., K. Semendeferi & E. Courchesne. 2007. No reduction of spindle neuron number in frontoinsular cortex in autism. *Brain Cogn.* **64:** 124–129.
47. Simms, M.L., T.L. Kemper, C.M. Timbie, *et al*. 2009. The anterior cingulate cortex in autism: heterogeneity of qualitative and quantitative cytoarchitectonic features suggests possible subgroups. *Acta Neuropathol.* **118:** 673–684.
48. Santos, M., N. Uppal, C. Butti, *et al*. 2011. Von Economo neurons in autism: a stereological study of the

frontoinsular cortex in children. *Brain Res.* **1380:** 206–217.
49. Di Martino, A., K. Ross, L. Uddin, *et al*. 2009. Processes in autism spectrum disorders: an activation likelihood estimation meta-analysis. *Biol. Psychiat.* **65:** 63–74.
50. Brune, M., A. Schobel, R. Karau, *et al*. 2010. Von Economo neuron density in anterior cingulate cortex is reduced in early onset schizophrenia. *Acta Neuropathol*. **119:** 771–778.
51. Allman, J.M., N.A. Tetreault, A.Y. Hakeem, *et al*. 2010. The von Economo neurons in frontoinsular and anterior cingulate cortex in great apes and humans. *Brain Struct. Funct.* **214:** 495–517.
52. Patterson, F. & W. Gordon. 2002. Twenty-seven years of Project Koko and Michael. In *All Apes Great and Small* B. Galdikas, N. Briggs, L. Sheeran, G. Shapiro & J. Goodall, Eds.: 165–176, vol. I. Kluwer Press. New York.
53. Uylings, H., A. Jacosen, K. Zilles & K. Amunts. 2006. Left-right asymmetry in volume and number of neurons in adult Broca's area. *Cortex* **42:** 652–658.
54. Sherwood, C.C., E. Wahl, J.M. Erwin, *et al*. 2007. Histological asymmetries of primary motor cortex predict handedness in chimpanzees. *J. Comp. Neurol.* **503:** 525–537.
55. Gündel, H., A. López-Sala, A.O. Ceballos-Baumann, *et al*. 2004. Alexithymia correlates with the size of right anterior cingulate. *Psychosom. Med.* **66:** 132–140.
56. Watkins, K.E., T. Paus, J.P. Lerch, *et al*. 2001. Structural asymmetries in human brain: a voxel-based statistical analysis of 142 brains. *Cereb. Cortex* **11:** 868–877.
57. Shaw, P., F. Lalonde, C.Lepage, *et al*. 2009. Development of cortical asymmetry in typically developing children and its disruption in attention-deficit/hyperactivity disorder. *Arch. Gen. Psychiat.* **66:** 888–896.
58. Craig, A.D. 2005. Forebrain emotional asymmetry: a neuroanatomical basis? *Trends Cogn. Sci.* **912:** 566–571.
59. Houdé, O., S. Rossi, A. Lubin & M. Joliot. 2010. Mapping numerical processing, reading, and executive functions in the developing brain: an fMRI meta-analysis of 52 studies including 842 children. *Develop. Sci.* **1:** 1–10.
60. Ortigue, S., S. Grafton & F. Bianchi-Demicheli. 2007. Correlation between insula activation in self-reported quality of orgasm in women. *Neuroimage* **37:** 551–560.
61. Critchley, H.D., R.N. Melmed, E. Featherstone, *et al*. 2001. Brain activity during biofeedback relaxation: a functional neuroimaging investigation. *Brain* **124:** 1003–1012.
62. Wittling, W. 1995. Brain Asymmetry in the control of autonomic-physiological activity. In. *Brain Asymmetry*. R.J. Davidson & K. Hugdahl, Eds.: 305–356. MIT Press. Cambridge.
63. Rogers, L. & R. Andrew. 2002. *Comparative Vertebrate Lateralization.* Cambridge University Press. Cambridge.
64. MacNeilage, P.F., L.J. Rogers & G. Vallortigara. 2009. Origins of the left and right brain. *Sci. Am.* **301:** 60–67.
65. Oppenheimer, S.M., A. Gelb, J.P. Girvin & V.C. Hachinski. 1992. Cardiovascular effects of human insular cortex stimulation. *Neurology* **42:** 1727–1732.
66. Bass, A.H., E.H. Gilland & R. Baker. 2008. Evolutionary origins for social vocalization in a vertebrate hindbrain-spinal compartment. *Science* **321:** 417–421.
67. Stimpson, C., N. Tetreault, J. Allman, *et al*. 2010 Biochemical specificity of von Economo neurons in hominoids. *Am. J. Hum. Biol.* **23:** 22–28.
68. Hof, P.R. & E. Van Der Gucht. 2007. Structure of the cerebral cortex of the humpback whale, *Megaptera novaeangliae* (Cetacea, Mysticeti, Balaenopteridae). *Anat. Rec.* **290:** 1–31.
69. Butti, C., C.C. Sherwood, A.Y. Hakeem, *et al*. 2009. Total number and volume of Von Economo neurons in the cerebral cortex of cetaceans. *J. Comp. Neurol.* **515:** 243–259.
70. Hakeem, A.Y., C.C. Sherwood, C.J. Bonar, *et al*. 2009. Von Economo neurons in the elephant brain. *Anat. Rec. (Hoboken)* **292:** 242–248.
71. Wang, S.S., J.R. Shultz, M.J. Burish, *et al*. 2008. Functional trade-offs in white matter axonal scaling. *J. Neurosci.* **28:** 4047–4056.
72. Sridharan, D., D.J. Levitin & V. Menon. 2008. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc. Natl. Acad. Sci. USA* **105:** 12569–12574.
73. Rose, M. 1928. Die Inselrinde des Menschen und der Tiere. *J. Psychol. Neurol.* **37:** 467–624.
74. Ploran, E., S. Nelson, K. Velanova, *et al*. 2007. Evidence accumulation and moment of recognition: Dissociating perceptual recognition processes using fMRI. *J. Neurosci.* **27:** 11012–11924.
75. Nelson, S., N. Dosenbach, A. Cohen, *et al*. 2010. Role of the anterior insula in task-level control and focal attention. *Brain Struct. Funct.* **214:** 669–680.
76. Craig, A.D. 2010. The sentient self. *Brain Struct. Funct.* **214:** 563–577.
77. Kikyo, H., K. Ohki, Y. Miyashita. 2002. Neural correlates for feeling-of-knowing: an fMRI parametric analysis. *Neuron* **36:** 177–186.
78. Devue, C., F. Collette, E. Balteau, *et al*. 2007. Here I am: the cortical correlates of visual self-recognition. *Brain Res.* **143:** 169–182.
79. Aziz-Zadeh, L., J. Kaplan & M. Iocoboni. 2009. "Aha": the neural correlates of verbal insight solutions. *Human Brain Map.* **30:** 908–916.