

# Two Phylogenetic Specializations in the Human Brain

JOHN ALLMAN, ATIYA HAKEEM, and KARLI WATSON

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

In this study, two anatomical specializations of the brain in apes and humans are considered. One of these is a whole cortical area located in the frontal polar cortex (Brodmann's area 10), and the other is a morphologically distinctive cell type, the spindle neuron of the anterior cingulate cortex. The authors suggest that the spindle cells may relay to other parts of the brain—especially to area 10, the outcome of processing within the anterior cingulate cortex. This relay conveys the motivation to act. It particularly concerns the recognition of having committed an error that leads to the initiation of adaptive responses to these adverse events so as to reduce error commission. This capacity is related to the development of self-control as an individual matures and gains social insight. Although the anterior cingulate deals with the individual's immediate response to changing conditions, area 10 is involved in the retrieval of memories from the individual's past experience and the capacity to plan adaptive responses. The authors suggest that these neurobehavioral specializations are crucial aspects of intelligence as defined as the capacity to make adaptive responses to changing conditions. The authors further hypothesize that these specializations facilitated the evolution of the unique capacity for the intergenerational transfer of the food and information characteristic of human extended families. *NEUROSCIENTIST* 8(4):335–346, 2002

**KEY WORDS** *Anterior cingulate cortex, Area 10 of Brodmann, Spindle cells*

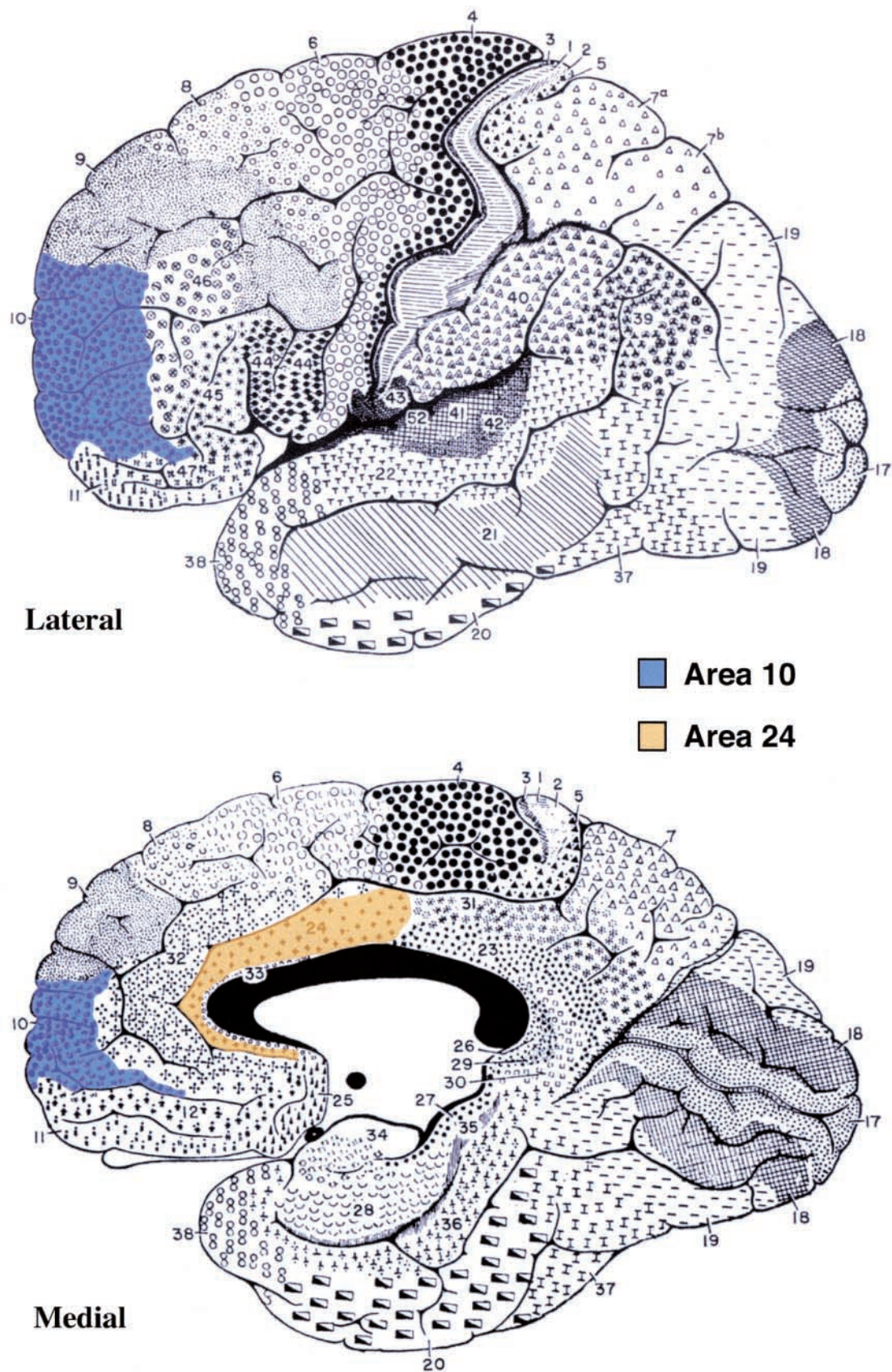
Recently, our colleagues have identified a class of neurons that are unique to humans and our closest relatives, the great apes (bonobos, common chimpanzees, gorillas, and orangutans) (Nimchinsky and others 1999). These neurons are large, spindle-shaped cells located in layer 5 of the anterior cingulate cortex, which is labeled in orange on the brain map in Figure 1. The spindle cells are characterized by their bipolar shape resulting from the large apical dendrite extending toward the pial surface of the cortex and the single large basal dendrite extending toward the underlying white matter (see Fig. 2). Apart from these two very large dendrites, there are typically no other dendrites branching from the vicinity of the cell body. The volume of the average spindle cell is four times greater than that of the average layer 5 pyramidal neuron (Nimchinsky and others 1999). The spindle cells are largest and most abundant in humans and decline in density in the following progression: bonobos > common chimpanzees > gorillas > orang-

utans (Nimchinsky and others 1999). They are not present in lesser apes (gibbons). Thus, within the hominoids, the group comprising humans and apes, the density of spindle cells declines with approximately the phylogenetic distance from humans. Spindle cells are not present in the 22 species of monkeys and prosimians examined or in 30 nonprimate species (Nimchinsky and others 1999). The spindle cells likely arose in the common ancestor of the great apes and humans, a dryopithecine ape probably living in East Africa about 15 million years ago (Szalay and Delson 1979). Very recently, Hof and his colleagues (2001) have reported another specialized population of anterior cingulate neurons present only in apes and humans. These neurons are also located in layer 5 but are pyramidal cells containing the calcium-binding protein calretinin. Like the spindle cells, these specialized neurons are most abundant in humans. The anterior cingulate cortex, as a whole, is a specialized region of neocortex, characterized by a reduced or absent layer 4 and a well-developed layer 5, which are features of motor areas. Anterior cingulate cortex appears to be present in all mammals but is larger and anatomically differentiated in primates (Brodmann 1909; Allman and others 2001).

Frontal polar cortex, area 10 of Brodmann (1909), which is labeled in blue in Figure 1, is a similar phylogenetic specialization in hominoids. Area 10 possesses a well-differentiated layer 4 and can be easily identified in histological sections. Area 10 is large, both absolutely and relatively, in humans; it is smaller but well devel-

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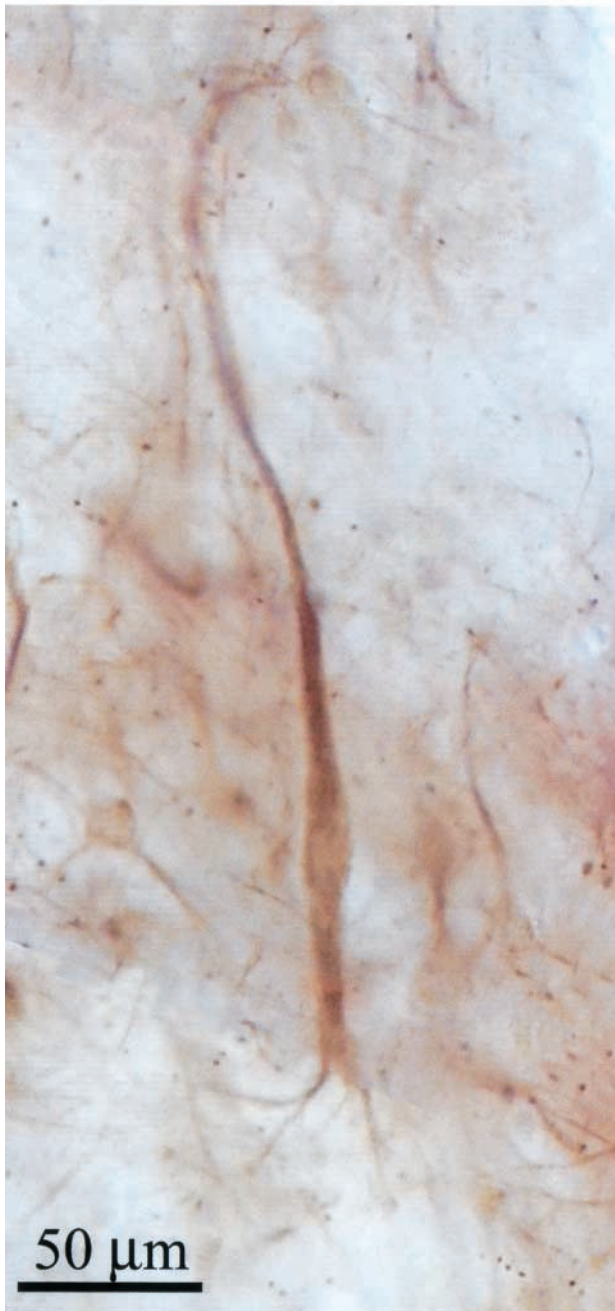
**Address correspondence to:** John Allman, Division of Biology, California Institute of Technology, Pasadena, CA 91125 (e-mail: cecus@caltech.edu).



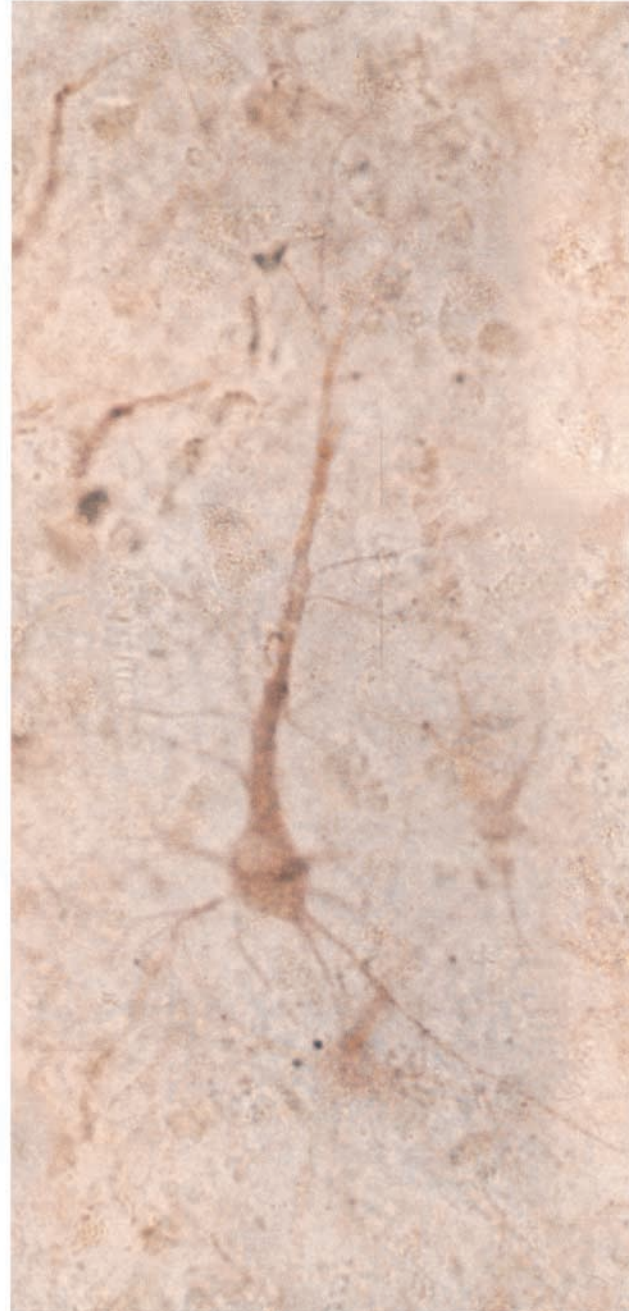
**Fig. 1.** Brodmann's (1909) map of the human cerebral cortex based on cell architecture.



## Spindle Cell



## Pyramidal Cell



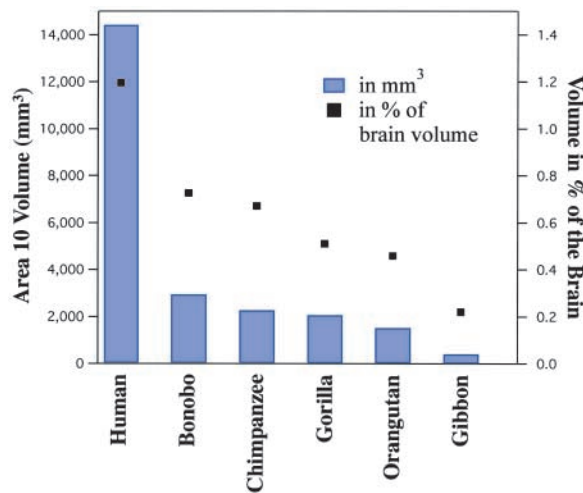
**Fig. 2.** Nonphosphorylated neurofilament staining of a spindle cell and a pyramidal cell in layer 5 of the anterior cingulate cortex.

oped in the great apes and much smaller in gibbons and monkeys (see Fig. 3) (Brodmann 1909; Semendeferi and others 2001). Within the hominoid species, area 10 declines in size in the same order as the decline in density of the spindle cells. However, unlike the spindle cells, area 10 is not a unique specialization of humans and great apes but is much larger in these than in other primates (Brodmann 1909; Semendeferi and others 2001). In this review, we will explore the evidence for functional specializations related to the spindle cells of

the anterior cingulate cortex and to the frontal polar cortex and how they may be linked to each other and to evolution of behavioral specializations in humans.

### Functional Studies of Anterior Cingulate Cortex

A clue to the possible functions of the spindle cells comes from another distinctive set of large neurons, the gigantopyramidal cells in layer 5 of the mid-cingulate



**Fig. 3.** The relative and absolute size of area 10 in humans and apes, modified after Semendeferi and others (2001).

cortex (Braak 1976). The gigantopyramidal cells are located just posterior to the spindle cell field, buried in the cingulate sulcus. These cells are motor neurons that control the muscles. In imaging experiments, the mid-cingulate motor area is strongly activated when the subject performs the precision grip in which the thumb and index finger grasp an object (Ehrsson and others 2000). Only humans and some monkeys and apes can perform the precision grip, which is necessary for the fine manipulation of objects. The precision grip produces stronger activation of the mid-cingulate motor cortex than the power grip in which all the fingers wrap around the object to be manipulated. The power grip produces stronger activity in the primary motor cortex. Similarly, the mid-cingulate cortex is more strongly activated when the subject makes small, precisely controlled movements, whereas in the primary motor cortex, activity increases with the force exerted by the subject (see Fig. 4) (Ehrsson and others 2001a). The mental imagery of hand movements also selectively activates the cingulate motor area (Ehrsson and others 2001b). These findings indicate that the mid-cingulate motor cortex contains phylogenetic specialized circuitry for executing the precise manipulation of objects.

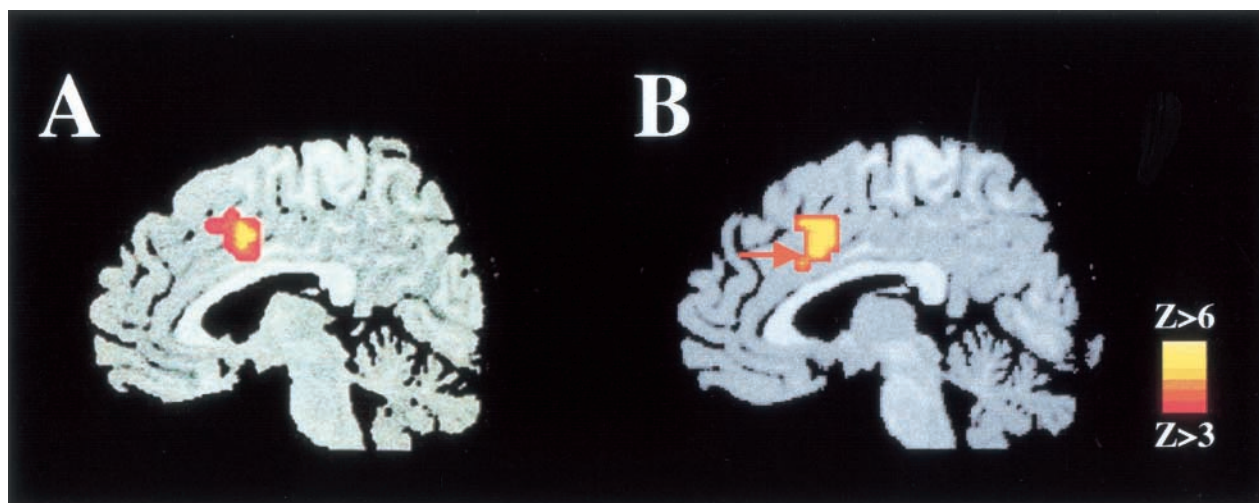
At present, we have little direct knowledge of the functions of the spindle cells, but we can make inferences from functional studies of the anterior cingulate cortex and from the morphology of the spindle cells. Anterior cingulate cortex participates in functions that are commonly associated both with emotional states and with cognition. It controls autonomic functions such as heart rate and blood pressure, the generation of vocalizations (Pool and Ransohoff 1949; Jurgens 1998), and the production and recognition of facial expressions (Smith 1945; George and others 1993). The experience of virtually any intense emotion, whether it be anger, love, or lust, is associated with the activation of the anterior cingulate cortex (Dougherty and others 1999; Bartels and Zeki 2000; Bush and others 2000; Redouté

and others 2000). States of intense behavioral drive such as pain, hunger, thirst, and breathlessness are also related to strong activity in the anterior cingulate cortex (Liotti and others 2001). However, the dorsal part of the anterior cingulate cortex is powerfully activated during the performance of cognitively demanding tasks. In an analysis of more than 70 PET and functional magnetic resonance imaging (fMRI) studies involving attention-demanding cognitive tasks, Bush and his colleagues (2000) found the centers of activation to be consistently located in the dorsal part of the anterior cingulate cortex (see Fig. 5). This activation increases with task difficulty (Paus and others 1998). Interestingly, the dorsal part of the anterior cingulate is also activated in recent fMRI studies in which the subjects are experiencing intense drive states such as love and lust (Bartels and Zeki 2000; Redouté and others 2000). The commonality between elicitation of activity in the dorsal part of the anterior cingulate cortex in cognitive functioning and drive states is that both involve intense mental focus.

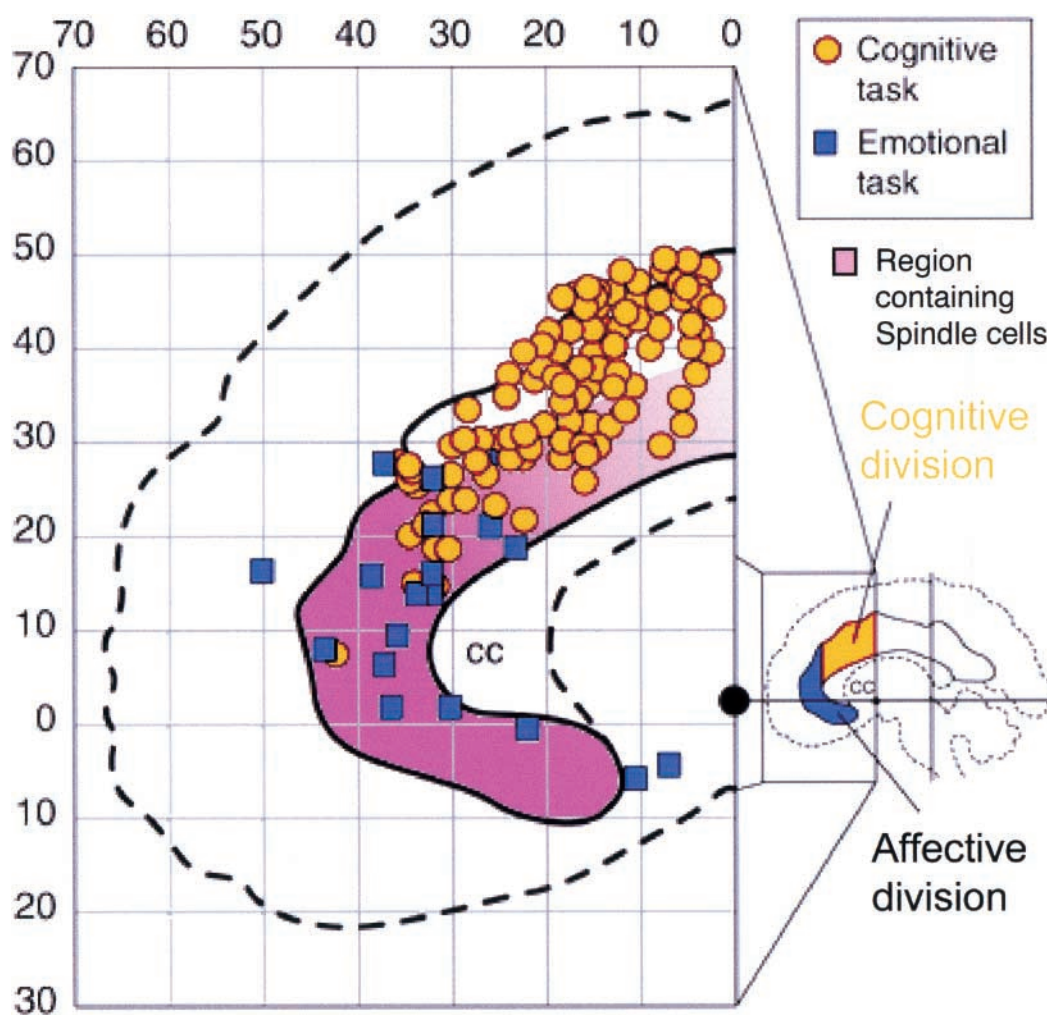
In electro-encephalographic (EEG) studies, a 4 to 7 Hz signal (the frontal midline theta rhythm) arises from the dorsal part of the anterior cingulate cortex when the subject is engaged in problem solving, and the amplitude of this signal increases with task difficulty (Gevins and others 1997). This signal is attenuated when the subject is anxious and restored when the anxiety is relieved with drugs (Suetsugi and others 2000). Thus, there is a dimension to anterior cingulate cortex activity that ranges from restless anxiety, poor problem solving, and an attenuated EEG signal to focused problem solving, superior performance, and an increased frontal midline theta rhythm. All of us have probably experienced anxiety-related interference with concentration or, conversely, the relief from anxiety associated with intense and successful problem solving. These experiences probably reflect this dimension of anterior cingulate functioning. When the subject makes an error, there is a change in the EEG activity arising from the anterior cingulate cortex, which is termed *error-related negativity* (Dehaene and others 1994; Bush and others 2000). Direct electrophysiological recordings from the anterior cingulate cortex in neurosurgical patients confirm the relationship with error commission, task difficulty, and the source of this EEG signal (Wang and others 2001).

Although the relationship between error recognition and anterior cingulate function has been most extensively investigated in human subjects, it was originally discovered in electrophysiological recordings from monkeys (Niki and Watanabe 1979; Brooks 1986). Shidara and Richmond (2001) have shown that activation of neurons in the anterior cingulate cortex is related to the expectation of reward in behaving monkeys. These studies support the concept that the anterior cingulate cortex is continuously monitoring changes in feedback from the individual's interaction with his or her environment that affect survival and reproduction and initiate behavioral responses to maintain or improve these conditions. These studies also indicate that the error recognition and correcting function of the anterior cingulate cortex





**Fig. 4.** Activation of the mid-cingulate cortex when performing the precision grip relative to the power grip (A) and when using the minimum force necessary relative to stronger force (B) (Ehrsson and others 2000, 2001a).

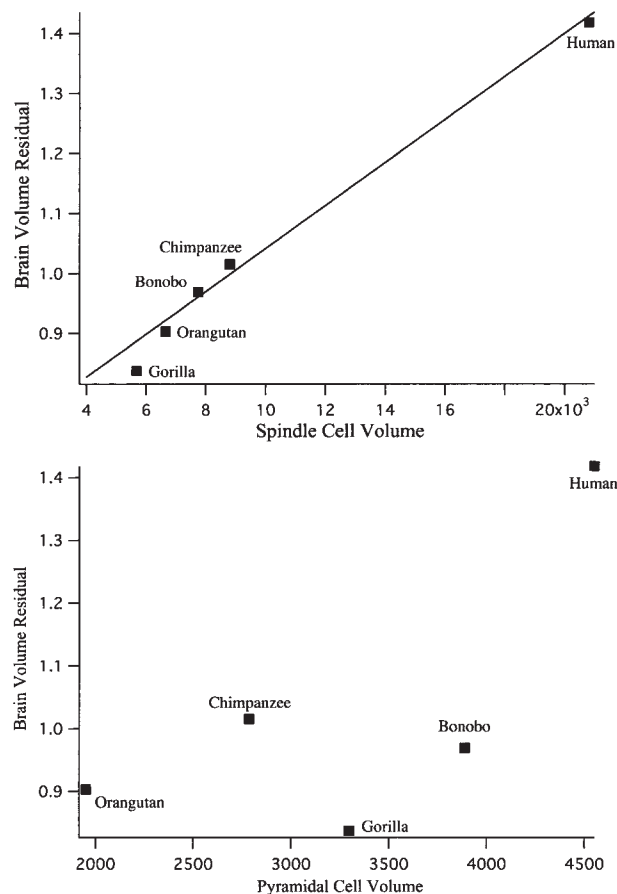


**Fig. 5.** Centers of activation in brain imaging studies of the anterior cingulate cortex, modified after Bush and others (2000). Each dot or square indicates a separate study. Note that the separation between sites activated by emotional states and cognitive tasks is not perfect, and in each case the zone of activation extends over larger regions of the cingulate cortex. The cortex containing spindle cells is indicated by the purple shading, as based on Nimchinsky and others (1995). The gradient in shading indicates the anterior to posterior gradient in the density of spindle cells.

evolved before the spindle cells appeared in an ancestral hominoid about 15 million years ago.

The spindle cells may serve to augment and relay the error-correcting information to other parts of the brain. The spindle cells are located in layer 5, which typically relays the output of cortical processing to other cortical areas and subcortical structures. The axons of the spindle cells are known to project into the underlying white matter (Nimchinsky and others 1995), but the sites of termination of these axons have not yet been determined. The cell body and dendrites of the spindle cells contain a rich concentration of nonphosphorylated neurofilaments, which are a characteristic feature of neurons with large axons (see Fig. 2) (Hoffman and others 1987; Nimchinsky and others 1995). The average volume of the cell bodies of spindle cells varies as a function of relative brain size (encephalization) across humans, bonobos, chimpanzees, gorillas, and orangutans (see Fig. 6). This relationship is not a general feature of layer 5 neurons because it does not hold for pyramidal cells in the anterior cingulate cortex. Because cell body size probably scales with the size of the axonal arborization, the arborizations of spindle cells may scale with encephalization. These observations suggest that the spindle cells may have widespread connections with other parts of the brain and that they may participate in the broadcast to error recognition and correcting information to many effector systems within the brain. The morphology of the spindle cells also suggests another aspect of their functioning. Mainen and Sejnowski (1996) have noted that pyramidal neurons with a prominent apical dendrite tend to fire in regular bursts with intervals of several hundred milliseconds between bursts. They propose that the action potentials invade the large apical dendrite, which after a brief delay can reexcite the cell body and give rise to a rapid burst of spikes. The spindle cell is morphologically like a super pyramidal cell with two large dendrites. This morphology could result in an even more pronounced cycle of bursts and intervals, which could contribute to the prominent EEG signals originating from the anterior cingulate cortex.

Abnormalities in the physiological activity and anatomy of the anterior cingulate cortex are present in most of the major neuropsychiatric disorders. The spindle cells are reduced in number in Alzheimer's disease (Nimchinsky and others 1995). Reduced size of the anterior cingulate cortex, as revealed in structural MRIs, is a major risk factor to the subsequent development of dementia in elderly subjects (Killiany and others 2000). The anterior cingulate cortex is reduced in both size and metabolic activity in autistic patients versus control subjects, as revealed in structural MRI and PET studies (Haznedar and others 2000). Both the size and activity of the ventral part of the anterior cingulate cortex are reduced in depressed patients (Drevets and others 1997). There is a substantial reduction in the density of layer 2 nonpyramidal neurons in the anterior cingulate cortex of patients who suffer from bipolar depression and schizophrenia (Benes and others 2001). The activity in the ventral part of the anterior cingulate cortex is increased in



**Fig. 6.** The average volumes of the cell bodies of spindle cells and pyramidal cells from layer 5 of the anterior cingulate cortex in humans and great apes plotted against relative brain (brain volume residuals). The spindle cell volumes are correlated with relative brain size ( $r^2 = 0.99$ ;  $P = 0.001$ ). The pyramidal cells are not significantly correlated with relative brain size ( $r^2 = 0.49$ ;  $P = 0.196$ ).

patients with obsessive-compulsive, phobic, and anxiety disorders when subjects are presented with stimuli that aggravate their symptoms (see Fig. 5) (Rauch and others 1994, 1996; Bush and others 2000). These symptom provocation studies suggest that the hyperactivation or possibly the breakdown in the coherence of the error message originating from the ventral anterior cingulate cortex is responsible for the obsessive, phobic, and anxious thoughts in these patients. As mentioned earlier, the frontal midline theta rhythm is attenuated in anxious subjects (Suetsugi and others 2000).

Large strokes involving the anterior cingulate cortex produce akinetic mutes, patients who lie in their hospital beds and say or do little. However, with strong arousal, these patients can move or speak a few words, revealing that they are not paralyzed. If these patients recover, they report that they felt "empty" and had "no will" to say or do anything during the acute period following their strokes (Damasio and Van Hoesen 1983). Small lesions in the anterior cingulate cortex reduce the anxiety produced by chronic pain but also reduce the patient's

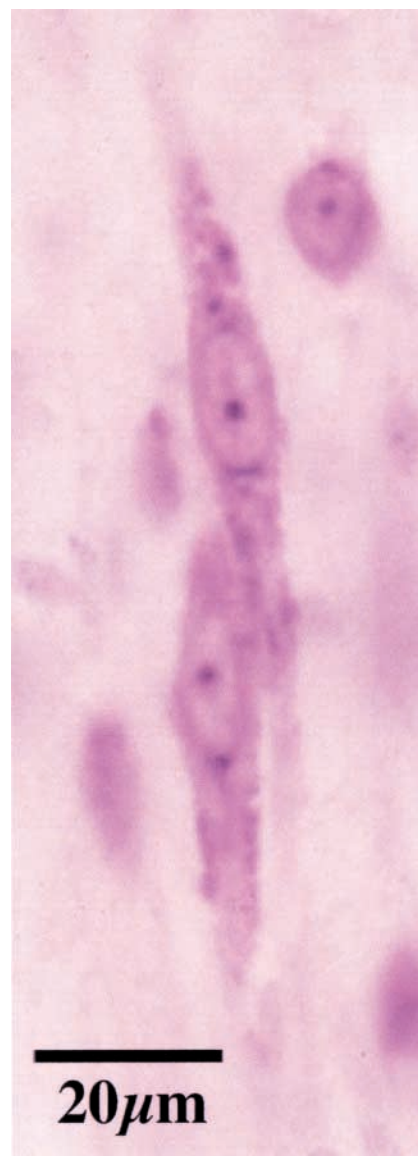
capacity to generate responses to novel stimuli (Cohen and others 1999).

The cingulate cortex contains two phylogenetic specializations characteristic of higher primates. The mid-cingulate motor cortex controls precise, volitional hand movements. The anterior cingulate cortex controls thought and adaptive behavior. The functions of the anterior cingulate cortex are the analog of precise manipulation in the realm of thought processes. The anterior cingulate cortex is implicated in volition, the experience of intense drive states, self-awareness and control, the discrimination of information from conflicting cues, focused problem solving, and error recognition. The spindle cells are a phylogenetically recent specialization within hominoids that may relay information concerning these functions to other parts of the brain, especially to another phylogenetic specialization in hominoids, the frontal polar cortex (area 10).

### The Development of Spindle Cells

Spindle cells have been described at embryonic day 224 in the anterior cingulate cortex of a fetal chimpanzee (Hayashi and others 2001). However, in our examination of the ontogenetic series of human brains at the National Museum of Health and Science, the spindle cells are not discernible in late-term fetal brains or at birth in humans but rather appear to migrate into the anterior cingulate cortex beginning several months after birth. Our observations are not in conflict with the prenatal development of the spindle cells in chimpanzees because human babies are much less developed at birth than chimpanzee infants. It is possible that the spindle cells are present earlier in development and only change their shape, but there are several reasons to suspect that they are migrating into the anterior cingulate cortex. In human infants, the spindle cells often appear in pairs and sometimes in vertical chains of three or four neurons, which suggest that they might be tracking an anatomical or chemical path (see Fig. 7). Sometimes the spindle cells in infants have long, undulating leading and trailing processes that resemble flagella, which also suggests that they might be migrating (see Fig. 8). This morphology led Von Economo (1929) to describe these neurons as the “corkscrew cells.”

Posner and Rothbart (1998) have proposed that the anterior cingulate cortex is involved in the behavioral maturation of self-control as an individual progresses through life from infancy to adulthood. Both the anterior cingulate cortex and area 10 are activated when subjects retrieve episodic memories, that is, when they engage in tasks that require remembering specific events in the past (see Fig. 9) (Lepage and others 2000). The capacity to use past experience as a guide to respond to current events in one’s life is an important aspect of the process of developing self-control and behavioral maturation. Posner and Rothbart’s maturation hypothesis is also supported by the steady increase in the metabolic activity of the anterior cingulate cortex from childhood to young adulthood (Von Bogaert and others 1998). In

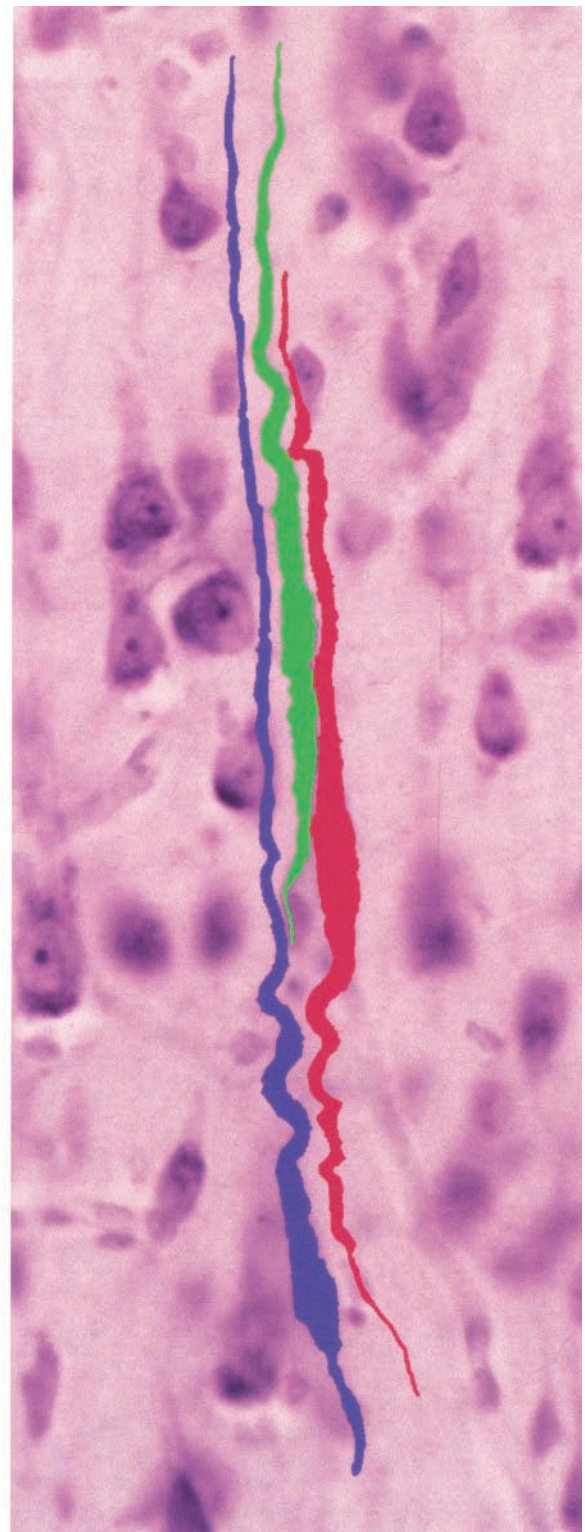
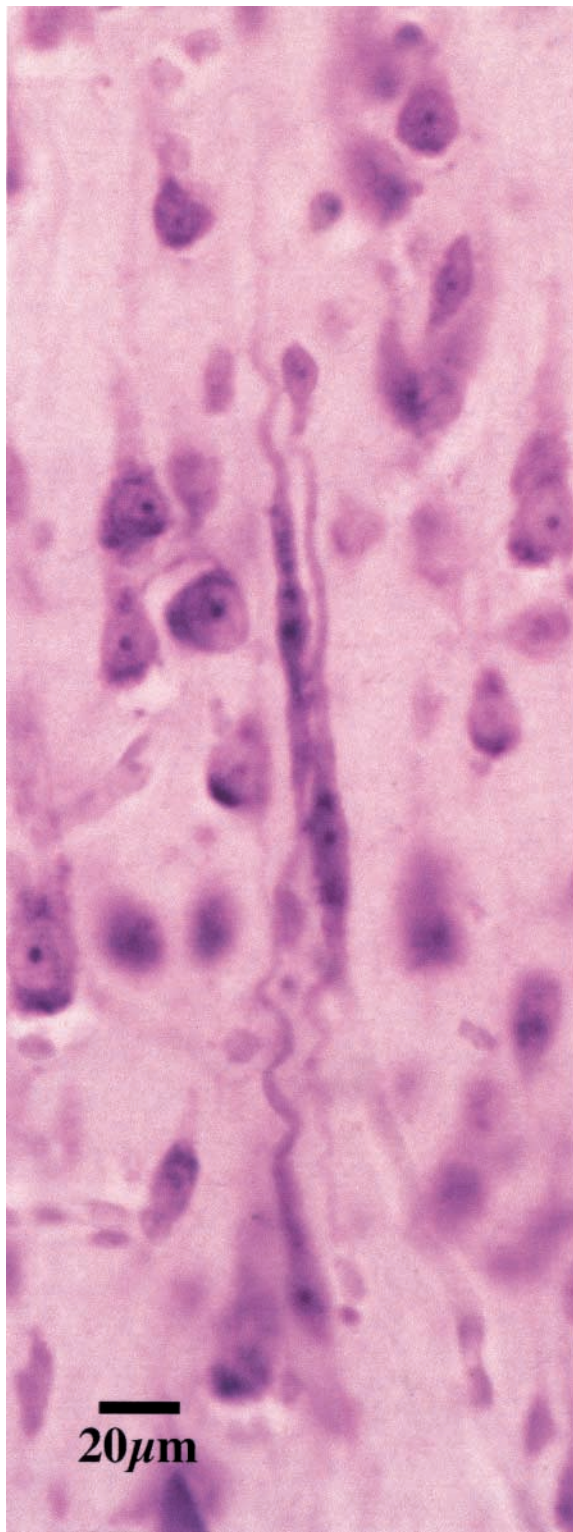


**Fig. 7.** A pair of spindle cells in the anterior cingulate cortex of a 4-month-old human infant from the Yakovlev Brain Collection at the National Museum of Health and Science.

the classic condition of lack of self-control, attention deficit hyperactivity disorder, subjects presented with the conflicting cue task do not exhibit a response in the anterior cingulate cortex, whereas this task elicits a strong response in normal subjects (Bush and others 1999). Finally, there also is evidence of increased activation of the anterior cingulate cortex in individuals with greater social insight (Lane and others 1997). The spindle cells, which appear to arise postnatally, may have a role in all of the slowly maturing functions of the anterior cingulate cortex.

The postnatal development of the spindle cells could be relevant to the pathogenesis of psychiatric disorders because there is evidence that the survival of other populations of postnatally generated neurons is heavily



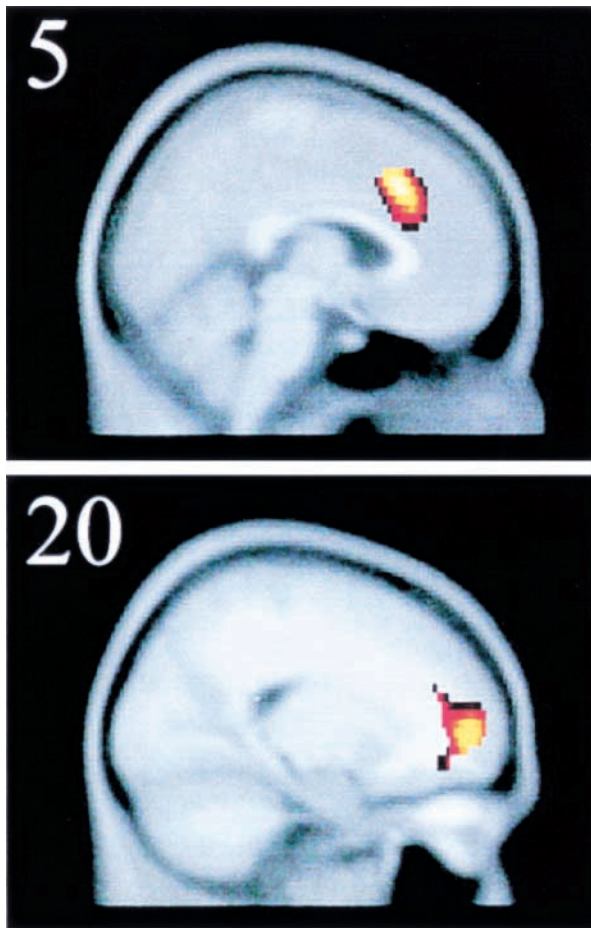


**Fig. 8.** A cluster of three possible migratory spindle cells in the anterior cingulate cortex of a 4-month-old human infant from the Yakovlev Brain Collection at the National Museum of Health and Science. Note the flagella-like undulations in the apical and basal dendrites.

influenced by environmental factors. For example, the postnatally generated neurons in the dentate gyrus of the hippocampus are vulnerable to many stress-related

events, and their survival can be enhanced by enriched environments, physical activity, and serotonin-mediated mechanisms (Gould and others 1997; Jacobs and others





**Fig. 9.** Coactivation of the anterior cingulate cortex and area 10 in the retrieval of episodic memory in a PET imaging study by Lepage and others (2000). The area 10 activation was obtained in a slice 20 mm from the midline.

2000). If the survival of the spindle cells is similarly influenced by environmental conditions during infancy, it is conceivable that positive environments could favor spindle cell survival and enhance emotional stability, self-control, and cognitive functioning later in life and that unfavorable environments could lead to the death of spindle cells and increased vulnerability to psychiatric or learning disorders. Because neuron death is also necessary for the normal development of the brain (Kuida and others 1998), it is also possible that in some instances, the excessive survival of spindle cells might contribute to the genesis of psychiatric disorders associated with hyperactivity of the anterior cingulate cortex, such as obsessive-compulsive disorder, which is characterized by excessively active vigilance and error-correcting behavior.

#### Frontal Polar Cortex: Area 10

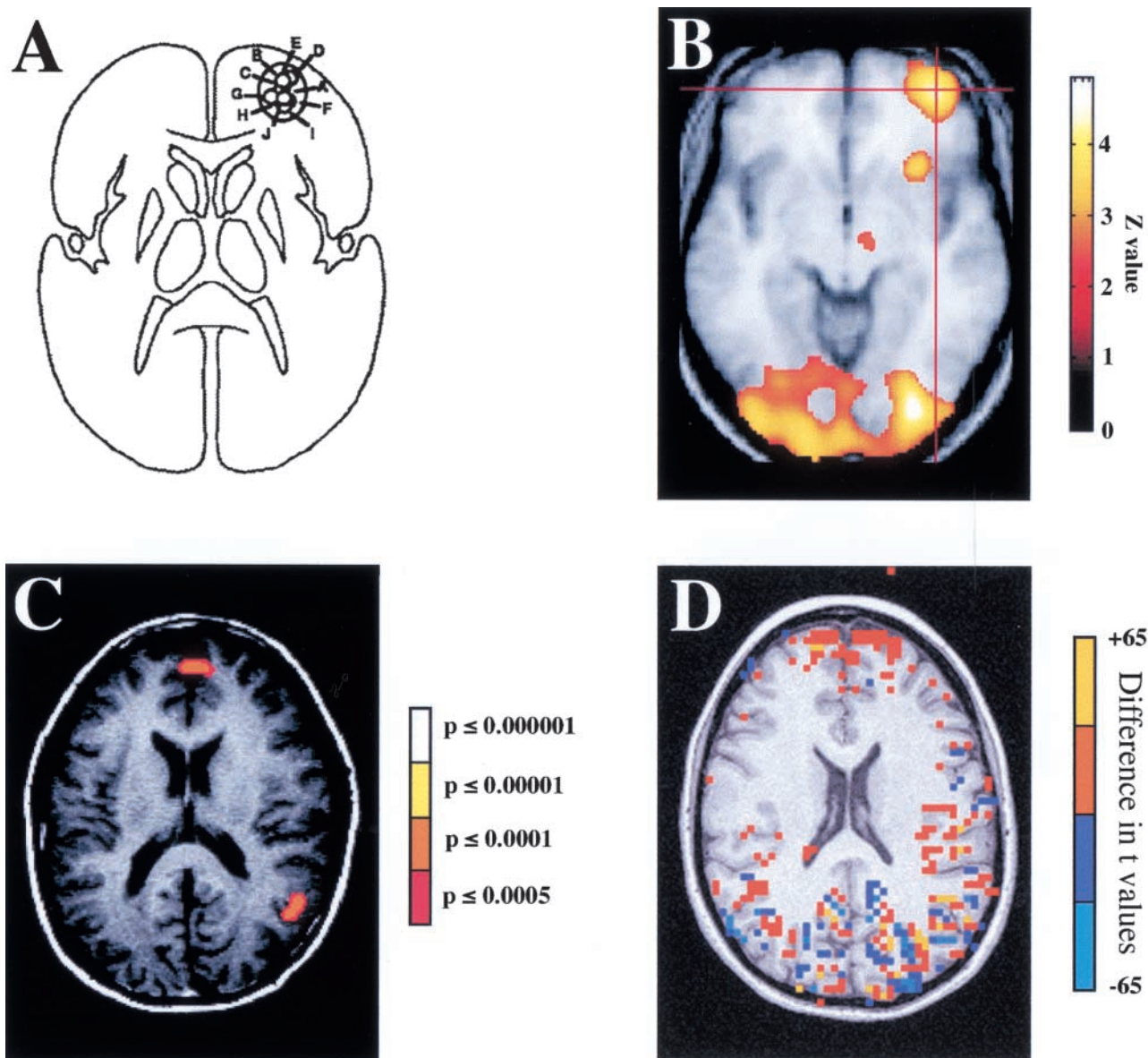
Much less is known about the functions of area 10 than for the anterior cingulate cortex. The best functional data come from PET and fMRI studies that indicate that the lateral part of area 10 is involved in episodic as opposed

to semantic memory (Buckner 1996; Lepage and others 2000). Episodic memory is related to specific events in one's past as opposed to general (semantic) knowledge. The lateral part of area 10 is consistently activated by both verbal and nonverbal episodic memory in a large number of studies (see Fig. 10A) (Buckner 1996). Just below the part of area 10 activated in the studies of episodic memory, there is another part that is activated when subjects choose between small, likely rewards and large, unlikely rewards (see Fig. 10B) (Rogers and others 1999). The anterior cingulate cortex is also activated in making these reward-related decisions, which provides further functional evidence linking this structure with area 10.

Recently, the medial part of area 10 has been activated in a study in which subjects were presented with emotionally charged moral dilemmas requiring them to choose a course of action affecting the lives of others (see Fig. 10C) (Greene and others 2001). The medial and anterior parts of area 10 are activated when subjects develop a successful decision-making strategy in a simulated auction involving real monetary rewards (see Fig. 10D). This activation may be related to the recollection of the outcome of recent bids (episodic memory), the assessment of reward probability, and the choice of a strategy for the next bid. The anterior cingulate was also activated in this bidding task. Taken together, these findings suggest a functional linkage between the anterior cingulate cortex and area 10, in which the anterior cingulate monitors the current state of reward and punishment and signals the need for behavioral adaptation, whereas area 10 compares the current state with past experience and on this basis makes choices governing future behavior. The subject is likely to be consciously aware of many of these processes, and consciousness may be an important and perhaps crucial aspect of the individual's behavioral adaptation to changing rewards and penalties. This behavioral adaptation also extends to considerations of the well-being of other individuals. The size of the dendritic arborizations and the number of synapses are greater in area 10 pyramidal neurons than in any other cortical area, which suggests the integrative role of this area (Jacobs and others 2001). In summary, the activity of the anterior cingulate cortex brings about the awareness of discrepancies between the current state and desired states for the individual and initiates behavior to improve his or her state. Area 10 compares the current state with past experience, calculates reward probabilities, formulates strategies, and makes choices based on these calculations.

#### Brain Specializations and the Economy of Human Extended Families

One of the key behavioral specializations in humans is the extended family (Allman 2000). Human infants develop very slowly and depend for a very long time on the support of their families. We propose that the enlargement of area 10 and the increased size and density of spindle cells in the anterior cingulate cortex in humans were part of a suite of adaptations related to the

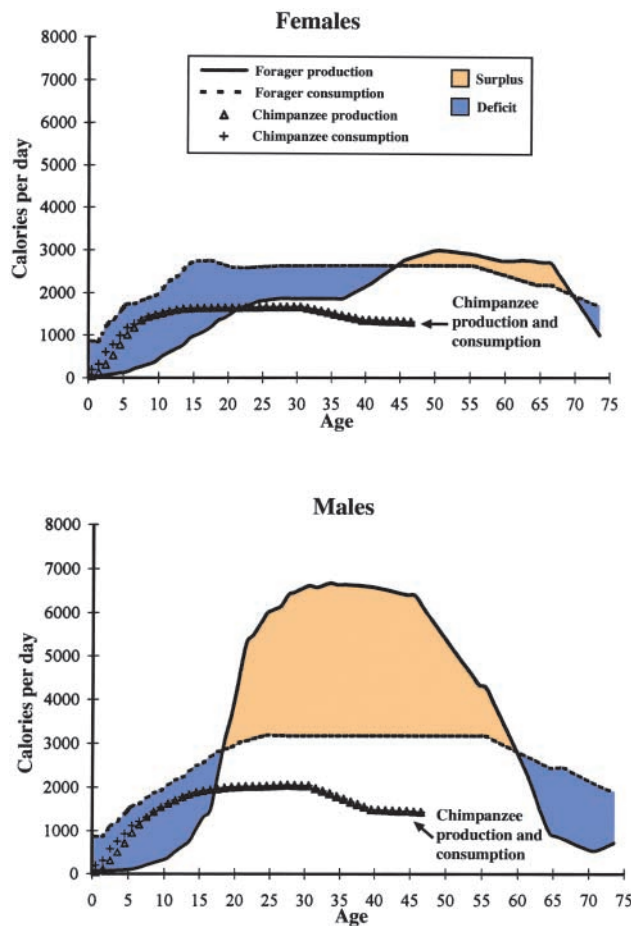


**Fig. 10.** (A) Sites of activation in area 10 produced by verbal and nonverbal episodic memory tasks from 10 separate brain imaging studies reviewed by Buckner (1996). (B) Activation in the ventral part of area 10 by choosing between small, likely rewards and large, unlikely rewards in a PET imaging study by Rogers and others (1999). (C) Activation in medial area 10 by emotionally charged moral judgments from Greene and others (2001). (D) Activation of anterior and medial area 10 during the formulation of a successful bidding strategy in an auction from an ongoing fMRI study by Daniel Rowe, David Grether, Charles Plott, and John Allman. The map was generated by subtracting the block of trials before the subject arrived at the optimal strategy from the block of trials during which she arrived at the optimal strategy. The scale is in differences in  $t$  values between the first block and the successful block of trials. The auction involved actual monetary rewards for the subject.

special economic needs of human extended families. Quantitative studies of foraging production and food consumption in chimpanzee and human hunter-gatherer populations indicate that young apes are able to provide nearly all their sustenance through their own foraging activities; however, young humans do not (see Fig. 11) (Kaplan and others 2000). Human males do not acquire through their own efforts as many calories as they consume until about age 17 in hunter-gatherer populations. Human females, because they are engaged in childbearing and rearing, do not acquire through their own forag-

ing as many calories as they consume until about age 45. The economy of the human extended family is based on transfers of food resources from fathers, grandfathers, and grandmothers to their children and grandchildren. Much of the food acquired by men is obtained by hunting; much of the food acquired by women is obtained through the extractive foraging of resources that are difficult to harvest; both activities require many years of hard-won expertise to be performed efficiently (Kaplan and others 2000). Effective food acquisition requires intense focus and monitoring of the outcome in terms of





**Fig. 11.** The mean daily energy production and consumption by individuals of each sex as a function of age in chimpanzees and humans from several hunter-gatherer populations (Kaplan and others 2000).

size and quality of nutritional reward. The anterior cingulate is clearly involved in these functions, and we suggest that the spindle cells may participate in the relay of these assessments to other parts of the brain. Effective food acquisition also requires changing to more rewarding activities in the face of decreasing reward, which also activates neurons in the anterior cingulate cortex (Shima and Tanji 1998). Effective hunting and foraging requires knowledge and appropriate application of specialized techniques, which require the retrieval of episodic memory and probability assessment that activate both the anterior cingulate cortex and area 10. For example, it might involve childhood memories of how a parent or grandparent captured or foraged for a particular type of food. It also requires choices among different possible foraging strategies in terms of their likely payoff and links these choices to concerns for the well-being of dependent family members. These last two functions are related to the activation of area 10 in formulating an optimal economic strategy and decision making in the face of emotionally charged moral judgments, both of which activate area 10.

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