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THE HUMAN BRAIN EVOLVING:

Paleoneurological Studies in Honor of Ralph L. Holloway

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FRONT COVER CAPTIONS

Center: Portrait of Ralph L. Holloway.
Upper left: A modern human brain.
Upper right: Ralph measuring landmarks on an endocast ca. 1976.
Lower right: Homo habilis cranium KNM-ER-1813 from Koobi Fora, Kenya (photo by Holloway).
Lower left: Ralph with an endocast of the Flores "hobbit" cranium.

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CHAPTER 13

The Evolution of Cortical Neurotransmitter Systems Among Primates and Their Relevance to Cognition

Mary Ann Raghanti, Patrick R. Hof and Chet C. Sherwood

Abstract

The neurotransmitters dopamine, serotonin, and acetylcholine are known to exert modulatory effects on prefrontal cognitive functions, such as learning and memory processes, by regulating neuronal activity. In addition, all three neurotransmitters are implicated in neurodegenerative processes to which humans appear to be uniquely susceptible. Taken together, these facts suggest that neuromodulatory supply to the prefrontal cortex may have been modified during human evolution to support human-specific cognitive and behavioral specializations. This chapter reviews recent molecular, genetic, anatomical, and behavioral evidence concerning the contributions of neuromodulatory transmitter systems to the evolution of human and nonhuman primate brains.

Introduction

One of the most compelling and complicated questions yet to be answered in the study of human evolution involves identifying the neuroanatomical bases of human behavior and cognition. One hallmark of the modern human condition is an enlarged brain. However, while expansion of the brain in the course of human evolution has certainly made an important contribution to our species' intelligence, total brain size alone may not fully explain the origin of human-specific cognitive abilities. Indeed, despite its expanse, the human brain matches up on a macroscopic level, nearly part for part, to that of a macaque monkey, with similar nuclei, neocortical areas, and axon pathways (e.g., Petrides and Pandya, 1994; Preuss and Goldman-Rakic, 1989). What, then, underlies our species' elaborated capacity for reason and symbolic thinking?

As Ralph Holloway put it in 1968, "This preoccupation [with overall brain size] led to the use of these mass aspects as explanations *in themselves* of behavioral differences of quite specific natures, such as 'memory', 'insight', 'forethought', 'symbolization' etc. It should be obvious that such correlations are not causal analyses, and that a parameter such as brain weight in grams, or volume in ml, or area in sq. mm. cannot explain the differences in behavior which are observed" (Holloway, 1968). Throughout his career, Ralph Holloway championed the notion that "reorganization" is equally as important as encephalization in understanding the evolution of the human brain. The evidence that he marshaled in favor of this proposal concerned both macro- and microanatomical changes (Holloway, 1996). Some aspects of gross structural reorganization can be seen in the fossil record, including redistribution of neocortical area volumes as indicated by sulcal positions and the asymmetry of cerebral hemispheres (e.g., Holloway, 1985; Holloway and De La Costelareymondie, 1982). Other structural changes, however, are not recorded in paleontological remains because they are at the microscopic or molecular level. Such evolutionary modifications to neuroanatomy, nonetheless, can comprise a very significant mechanism for encoding behavioral variation within and between species.

Recent comparative research into the neuroanatomical microstructure of primates has begun to yield tantalizing clues regarding uniquely human specializations (Buxhoeveden et al., 2001; Dorus et al., 2004; Hof et al., 2001; Nimchinsky et al., 1999; Preuss and Coleman, 2002; Sherwood et al., 2007). It is becoming clear that

a real understanding of human evolution requires that we supplement traditional volumetric neuroanatomical studies with comparative data on the infinitesimal aspects of our species' brain histology, connectivity, and gene expression patters in order to see how they differ from those of our closest living relatives (i.e., apes and monkeys; see, e.g., Preuss, 2000; Preuss, 2006). Several researchers have noted that the human brain is not merely an enlarged chimpanzee brain (Penn et al., in press; Premack, 2007) and Ralph Holloway made the prescient statement more than 40 years ago that "One c.c. of chimpanzee cortex is not equivalent to one c.c. of human cortex" (Holloway, 1966, p. 108).

This conclusion is supported by numerous findings indicating that the histology and molecular composition of the modern human neocortex differs from that of other primates, including chimpanzees. For example, humans demonstrate histological differences from other apes in having a distinctive patterned arrangement of dendrites and interneurons in layer IVA of primary visual cortex, possibly translating into functional differences in how the visual pathway processes motion-related cues (Preuss and Coleman, 2002). There is also a unique neuronal subtype, the Von Economo neurons (VENs), found in great apes and humans with a restricted cortical distribution within anterior cingulate and frontoinsular cortex (Nimchinsky et al., 1999; Nimchinsky et al., 1995). Human VENs differ from those of great apes in being more numerous and having larger somata. These spindle-shaped neurons are projection neurons that are enriched with dopaminergic D3 and serotonergic 2b receptors (Allman et al., 2005). The unique localization and biochemical phenotype of VENs indicate that they may have played a critical role in mediating intuitive processes that synthesize a homeostatic representation of the self with social information, a key component of the capacity to attribute mental states to others and to envision oneself projected into alternative scenarios (Allman et al., 2005). Humans may also be distinguished from nonhuman primate species in having increased population-level asymmetry of neuropil across several cortical areas, including area Tpt and the primary motor cortex representation of the hand (Buxhoeveden et al., 2001; Sherwood et al., 2007). Other studies have identified potential species differences in the functional biochemistry of the cortex using genomic and molecular approaches. For example, adaptations for increased neuronal activity and energy production appear to have occurred in human evolution through the evolution and upregulation of genes involved in the aerobic metabolic pathway (Cáceres et al., 2003; Uddin et al., 2004) and proliferation of glial cells (Sherwood et al., 2006).

Additional compelling candidates for microscopic modifications during human evolution include the serotonergic, cholinergic, and dopaminergic systems of the brain. These neurotransmitters are key components of higher cognitive functions, including learning and memory processes, language comprehension, and overall intelligence (Azmitia, 1999; Goldman-Rakic, 1998; Hasselmo, 1995; Herremans et al., 1995; Previc, 1999; Sarter and Bruno, 1997). Moreover, these systems are selectively compromised in human-specific neuropathological conditions that result in devastating cognitive deficits, including Alzheimer's disease, Parkinson's disease, and schizophrenia (Akil et al., 1999; Mega, 2000; Naughton et al., 2000; Roth et al., 2004; Venator et al., 1999; Whitehouse, 1992). Finally, the innervation patterns of these neurotransmitters are regionally distinct (i.e., different cortical areas receive variant levels of input), with the primate neocortex receiving denser and more complex patterns of innervation relative to other mammals (e.g., Berger et al., 1991; Berger et al., 1988). The evidence of neurotransmitter regional heterogeneity, their roles in higher cognitive functions, and their deficits in human neurodegenerative diseases all collectively raise the question of how human neuromodulator systems differ from those of other primates. Is it possible that an increased reliance on neuromodulators has contributed to human-specific intellectual advances, and that this in turn has rendered humans uniquely susceptible to neurodegenerative diseases? This chapter will explore this question by reviewing the properties and effects of dopaminergic, serotonergic, and cholinergic systems with a concentration on their roles in cognitive functions mediated by the prefrontal cortex (PFC). In addition, we summarize the results of our recent comparative studies of the innervation pattern of these neuromodulators across the frontal cortex of macaque monkeys, chimpanzees and humans.

The PFC lies rostral to the premotor and primary motor regions of the frontal lobes (Uylings and van Eden, 1990) and is involved in many of our higher order functions, including personality, working memory, attentional processing, mental state attribution (also known as "theory of mind"), behavioral inhibition, and planning and executing actions (Fuster, 1997; Goldberg, 2001). Humans and great apes together share an enlarged frontal cortex relative to other primate species (Semendeferi et al., 2002). Further, human PFC appears to be disproportionately larger compared to great apes, as primary motor (area 4) and premotor cortex (area 6) occupy a smaller proportion of the frontal lobe when compared with other species (Deacon, 1997; Preuss, 2004; Rilling, 2006). The PFC is comprised of a network of many cytoarchitecturally and functionally distinct regions that send and receive projections from virtually all other cortical regions as well as subcortical structures (Brodmann, 1909; Fuster, 1997). Through these extensive connections, the PFC synthesizes information from motor, sensory, and limbic areas of the brain, thus integrating the functions of all other brain regions, leading Goldberg (2001) to liken this brain region to the conductor of an orchestra.

What is a Neuromodulator?

Neurotransmitters regulate neuronal communication through actions mediated by various receptor subtypes; depending on the effect at the postsynaptic target, neurotransmitters may also act as neuromodulators. Classically defined, neurotransmitters have effects that are immediate and short-term, usually engaging an ion channel to allow for the influx or efflux of charged ions. In these instances, the neurotransmitter receptors form ion channels, with no associated downstream metabolic consequences (Gu, 2002; von Bohlen und Halbach and Dermietzel, 2006). In contrast, neuromodulatory actions are slower, of longer duration, and are more spatially diffuse (Hasselmo, 1995). Receptors mediating the neuromodulatory actions of neurotransmitters belong to the family of G-protein linked receptors that, once activated, may signal multiple signal transduction pathways. In this way, neurotransmitters have long-term effects on the processing characteristics of cortical networks by influencing synaptic transmission and pyramidal cell adaptation (Dreher and Burnod, 2002; Goldman-Rakic, 1998; Hasselmo, 1995).

The separate neuromodulatory transmitter systems share several defining characteristics (e.g., Gu, 2002). First, the cortical neuromodulator systems that target the cerebral cortex are derived from discrete subcortical neuron populations that have long projection axons. The effects of neuromodulators may be either excitatory or inhibitory in nature, depending upon the postsynaptic receptor complex, and neuromodulators further have the capacity to mediate their own release via autoreceptors located at the presynaptic site. In addition to the ascending projection axons that innervate neurons of the PFC, there are also reciprocal connections between the PFC and the subcortical neuronal populations that modulate neurotransmitter systems through descending projections. Further, the separate systems also interact with one another to fine-tune cellular excitability (for a review, see Briand et al., 2007). It is likely that multiple systems act in concert with one another, rather than being recruited separately, to support cognition. However, as will be discussed further below, while acting synergistically, each of the transmitter system functions to support discrete components of cognition. For example, Robbins and Roberts (2007) recently reviewed the differential contributions of DA, ACh, 5HT and norepinephrine within the PFC in the performance of attentional set-shifting tasks that assess cognitive flexibility and perseverative deficits, highlighting the distinct and separate components of the task supported by each transmitter system. In this task, it was shown that DA supports set formation, 5HT mediates reversal learning, and ACh is necessary for serial reversal learning (Robbins and Roberts, 2007). This evidence illustrates the highly orchestrated organization of neuromodulatory transmitter systems in regulating cognitive processing, and highlights the importance of understanding each system's contribution to the evolution of human intellectual abilities.

Dopamine (DA)

Dopaminergic systems originate in the midbrain and include the mesostriatal system that sends projections to many subcortical areas (e.g., striatum, nucleus accumbens), and the mesocortical system that innervates the frontal, piriform, and entorhinal cortices (Fuster, 1997; Squire et al., 2003). It is the mesocortical DAergic system that innervates the PFC, sending out long projection axons from cell bodies located in the nucleus parabrachialis pigmentosus of the ventral tegmental area (VTA) (Goldman-Rakic et al., 1989; Smiley et al., 1999). DA does not act as an excitatory or inhibitory neurotransmitter in the PFC (e.g., González-Burgos et al., 2002). Rather, DA acts as a neuromodulator, targeting its G-protein linked receptors on apical and basal dendritic shafts and spines of pyramidal glutamatergic cells (Benavides-Piccione et al., 2005; Goldman-Rakic et al., 1989; Seamans and Yang, 2004) and on the dendrites of parvalbumin-containing GABAergic interneurons involved in inhibitory processes (Goldman-Rakic et al., 1989; Sesack et al., 1995; Sesack et al., 1998). Thus, DA is capable of moderating the signal-to-noise ratio within the PFC by preventing interruptions in the active maintenance of information (Dreher and Burnod, 2002; Kulisevsky, 2000; Winterer and Weinberger, 2004).

At least five known receptor subtypes interact with DA (D1 - D5), each being functionally distinct (Seamans and Yang, 2004). The five receptor subtypes are classified into two groups, D1-like (D1 and D5) and D2-like (D2, D3, and D4) (von Bohlen und Halbach and Dermietzel, 2006), with D1-like receptors activating (G_s) and the D2 group inhibiting (G_i) adenylate cyclase. D1 and D2 receptors mediate DAergic actions within the PFC and exhibit lamina- and region-specific distributions, with D1 receptors concentrated in supragranular layers and D2 receptors preferentially located in layer V in macaques and humans (Goldman-Rakic et al., 1990; Goldman-Rakic et al., 1992; Lidow et al., 1989). Further, D1 and D2 receptors have differential binding affinities for DA, with D2 receptors demonstrating an increased sensitivity to low concentrations of DA compared to D1 receptor binding affinity (Grace, 2000).

Through its neuromodulatory actions in the PFC, DA is well known for regulating working memory, the capacity to hold a finite amount of information "on-line" in order to comprehend and plan actions (Abi-Dargham, 2004; Goldman-Rakic, 1998; Kulisevsky, 2000). Blocking the actions of DA impairs performance on working memory tasks (Brozoski et al., 1979; Cools et al., 2002; González-Burgos et al., 2002; Robbins, 2000; Sawaguchi and Goldman-Rakic, 1991), and agonists are associated with improved performance (Akil et al., 1999; Brozoski et al., 1979). In addition, the extent of cortical DAergic innervation correlates with behaviors involved in planning voluntary actions that invoke working memory functions, indicating that an increase in DAergic afferents allows for these functional capacities (Nieoullon, 2002). Additional executive functions that rely on DAe-

rgic input to the PFC include language comprehension, reasoning, and overall intelligence (Arnsten et al., 1995; Boshes and Arbit, 1970; Dreher and Burnod, 2002; Goldman-Rakic, 1998; Sawaguchi and Goldman-Rakic, 1991).

Available evidence indicates that there are phylogenetic differences in cortical DA innervation. Berger et al. (1991) qualitatively compared cortical DA innervation, as measured by tyrosine hydroxyase-immunoreactive (TH-ir) axon density, in rodents (rats) and primates (rhesus macaques, long-tailed macaques, and humans) and found that the primates exhibited denser and more extensive DAergic innervation within the cerebral cortex. In fact, humans and other primates receive DAergic input to all cortical areas. This is in contrast to rodents who have little or no DAergic innervation in the motor, premotor, and supplementary motor areas, or to the parietal, temporal, and posterior cingulate cortex. There are also differences in laminar distribution, with widespread dense innervation of layer I in primates, whereas in rodents, dense innervation of the superficial layers occurs only in a few select areas, such as the anterior cingulate cortex and entorhinal cortex (Berger et al., 1991). Humans and other primates demonstrate different regional patterns, with TH-containing fibers in all cortical layers of agranular cortices, and a bilaminar pattern, with the densest innervation in layers I and V-VI, in granular somatosensory and association cortex (Berger et al., 1991; Gaspar et al., 1989; Lewis et al., 2001). The differences between primates and rodents in both the organization of the frontal cortex and in DAergic innervation of this area are striking and suggest evolutionary changes that paralleled increases in both the size and functional differentiation of the cerebral cortex (Berger et al., 1991; Gaspar et al., 1989; Lewis et al., 2001; Preuss, 1995; Sesack et al., 1995; van Eden et al., 1987; Williams and Goldman-Rakic, 1998).

A broader view of phylogenetic differences was provided by Hof and colleagues in an analysis of cortical TH-ir axon distribution in the harbor porpoise and pilot whale (Hof et al., 1995). Their findings revealed a different pattern of innervation of cetacean auditory and visual cortex compared to that of other mammals. Most other mammals share in common a sparser DAergic innervation in primary sensory cortex relative to all other cortical areas. This is particularly true of the primary visual cortex, where DAergic axons are rarely evident in rodents, and present only in layer I of human and nonhuman primates. In contrast, the cetacean primary visual cortex is innervated throughout all layers and is more densely innervated than the auditory cortex, whereas the reverse is true for other mammals. Such phylogenetic differences strongly suggest a potent role for this neurotransmitter in brain evolution.

Additional lines of evidence suggest that DAergic systems may have been further altered during human evolution. DAergic system dysfunction plays an important role in a number of neuropsychiatric disorders presenting with cognitive deficits that appear to be exclusive to humans (Akil et al., 1999; Ciliax et al., 1999; Sutoo et al., 2001; Venator et al., 1999; Winterer and Weinberger, 2004). In fact, Previc (1999) has argued that an expansion of DAergic innervation in the human cerebral cortex is singularly responsible for the origin of human intelligence.

Raghanti et al. (submitted) recently tested the hypothesis that humans have an increased DAergic input to prefrontal cortical areas relative to chimpanzees and macaque monkeys. In this study, dorsolateral prefrontal area 9 (involved in inductive reasoning and specific components of working memory) and medial prefrontal area 32 (involved in "theory of mind") were examined, with primary motor cortex (area 4) serving as a control region, as it is not associated with higher cognitive functions (Figure 1). TH-ir axon length density to neuron density (i.e., innervation per neuron) was quantitatively assessed in layers I, II, III, and V/VI of each cortical area using computer-assisted stereology (MBF Biosciences, Williston, VT). Species differences were not detected in the primary motor cortex, but several differences were detected in the prefrontal areas. Humans exhibited a sublaminar pattern of innervation in layer I of areas 9 and 32, meaning that DA-containing axons were restricted to the bottom of layer I rather than being distributed evenly through the layer, as observed in other species. This pattern of sublaminar innervation of the molecular layer has been reported in agranular cortices of long-tailed macaques (Berger et al., 1988), but may have been extended in humans to include both agranular and granular cortices, a pattern that has been suggested to have evolutionary implications (Gaspar et al., 1989). Humans and chimpanzees together deviated from macaques in having an increased density of DAergic afferents in layers III and V/VI of the prefrontal cortical areas. This is particularly interesting in light of the lamina-specific decrease in TH-ir axons in layer VI of area 9 reported for schizophrenic subjects (Akil et al., 1999), a deficit that may potentially underlie the working memory deficits associated with this disease (Abi-Dargham, 2004; Akil et al., 1999). It is conceivable that an increase in DAergic innervation to the PFC infragranular layers is critical to the integrity of executive functions governed by these brain regions, and this may be a point of vulnerability for the progression of neuropathological processes.

In addition, morphological specializations in the form of TH-ir axon coils (Figure 2), were found in human and chimpanzee cortex, to the exclusion of macaques. Although TH-ir coils were previously described in humans, the functional significance of these structures is unknown (Benavides-Piccione and DeFelipe, 2003; Gaspar et al., 1989). However, analogous axonal configurations have been reported in human cortex immunostained for cholinergic axons, with the suggestion that they may represent local events of cortical plasticity or local circuit alterations (Mesulam et al., 1992), as will be discussed further below.

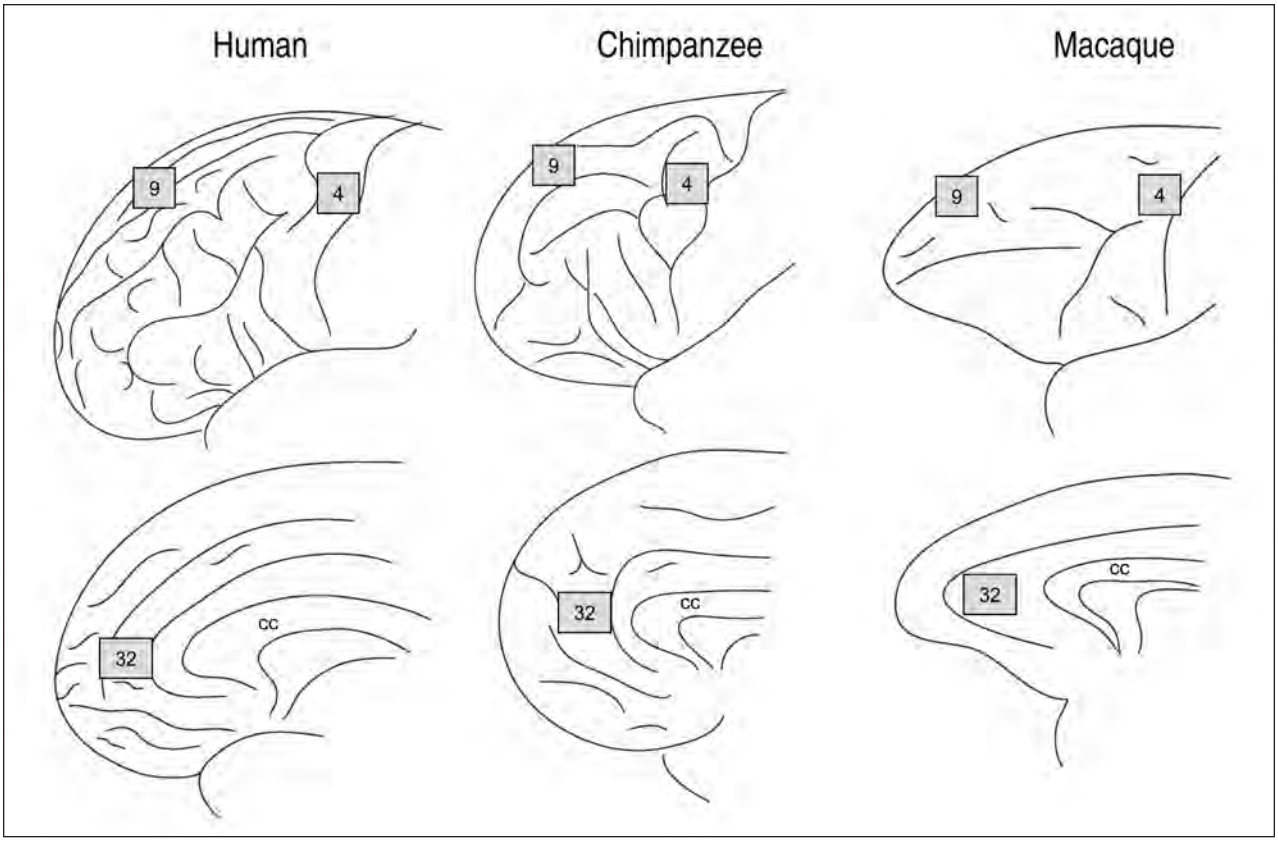

Figure 1. Lateral (upper) and medial (lower) views of human, chimpanzee, and macaque brains. The cortical regions sampled are labeled with their respective numerical designations.

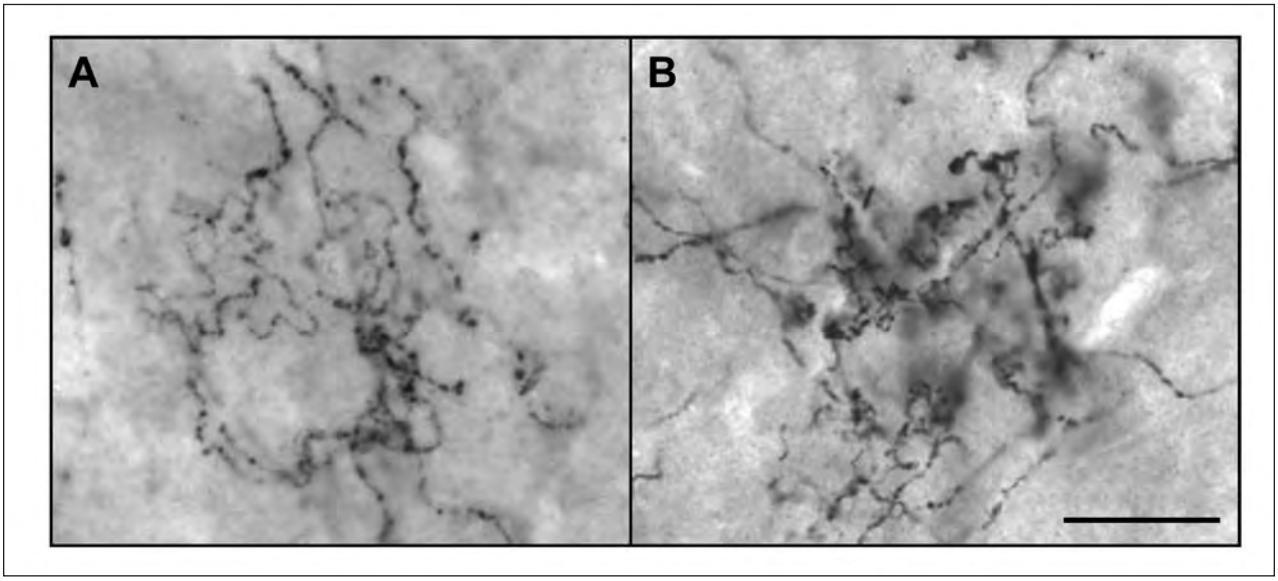

Figure 2. TH-ir axon coils in human (A) and chimpanzee (B). Scale bar = 25 µm.

The presence of TH-ir neurons in the neocortex has been noted in several vertebrate species (for review see Smeets and González, 2000). These cortical neurons have been classified as aspiny non-pyramidal cells (Benavides-Piccione and DeFelipe, 2003) and demonstrate considerable species-specific variation in their location and distribution within the cortical mantle. For example, TH-ir neurons were noted in the lower portion of layer I in two cetacean species (Hof et al., 1995), whereas rats express TH-ir cells in all layers of the cortex, with the highest density occurring in layers II and III (Kosaka et al., 1987). We noted the presence of TH-ir cells in lower layer VI and in the white matter immediately adjacent to layer VI in all frontal cortical fields of the Moor macaque (*Macaca maura;* unpublished data). In the human neocortex, TH-ir interneurons are found almost exclusively

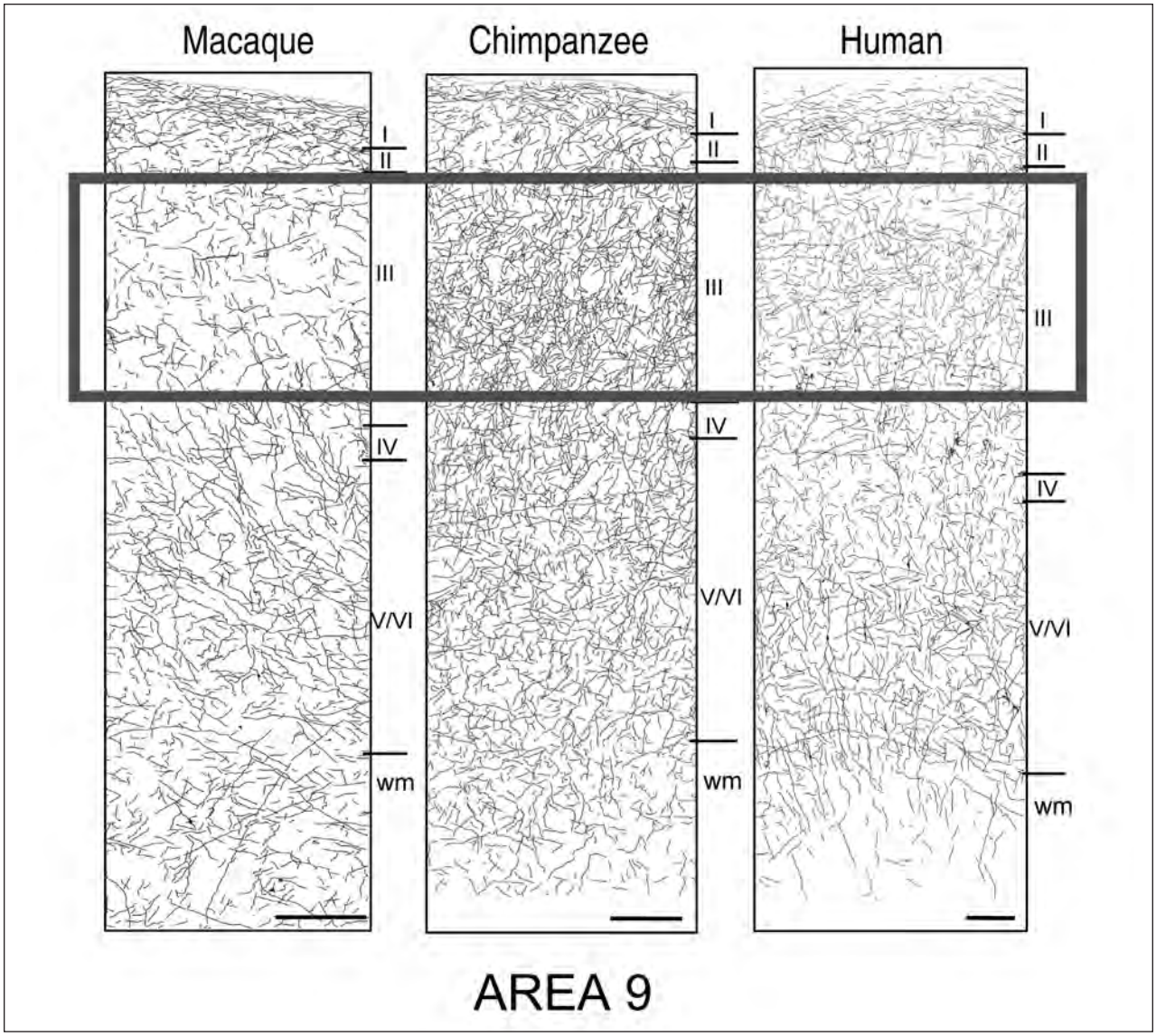

Figure 3. TH-ir axon tracings in PFC area 9 for macaque, chimpanzee, and human. Scale bar = 250 µm, 'wm' = white matter.

in the infragranular layers and subjacent white matter (Benavides-Piccione and DeFelipe, 2003; Gaspar et al., 1987; Hornung et al., 1989), and humans are the only species to express these cells in all cortical areas examined (Benavides-Piccione and DeFelipe, 2007).

Although these neurons have been noted in several species, little is known regarding their function. However, recent studies have illustrated a significant decrease in cortical TH-ir neuron numbers in individuals afflicted by dementia with Lewy bodies (Marui et al., 2003) and in individuals with Parkinson's disease (Fukuda et al., 1999). Benavides-Piccione and DeFelipe (2007) recently assessed the density and distribution of TH-ir neurons across eleven cortical areas in humans. They reported significant regional differences in TH-ir neuron density, and have proposed an event in human evolution that involved the utilization of this intrinsic source of cortical DA to support function-specific cortical circuits.

In humans, we have also observed TH-ir neurons mostly in layers V/VI, and rarely in layer III of cortical areas 9, 32, and 4 (unpublished data). Interestingly, we have not observed TH-ir neurons within any neocortical region of great apes, including chimpanzee, bonobo, gorilla, and orangutan. This is intriguing given that the TH-ir axon length density to neuron density ratio in layer III of chimpanzee areas 9 and 32 was twice that of humans or macaques (Raghanti et al., submitted) (Figure 3). Perhaps the DAergic afferent input to layer III increased in chimpanzees and other great apes to compensate for the loss of TH-ir cells within the cortical mantle.

Serotonin

Serotonergic neurons are located in the dorsal and median raphe nuclei of the brainstem and their projections are widely distributed throughout the brain (Azmi-

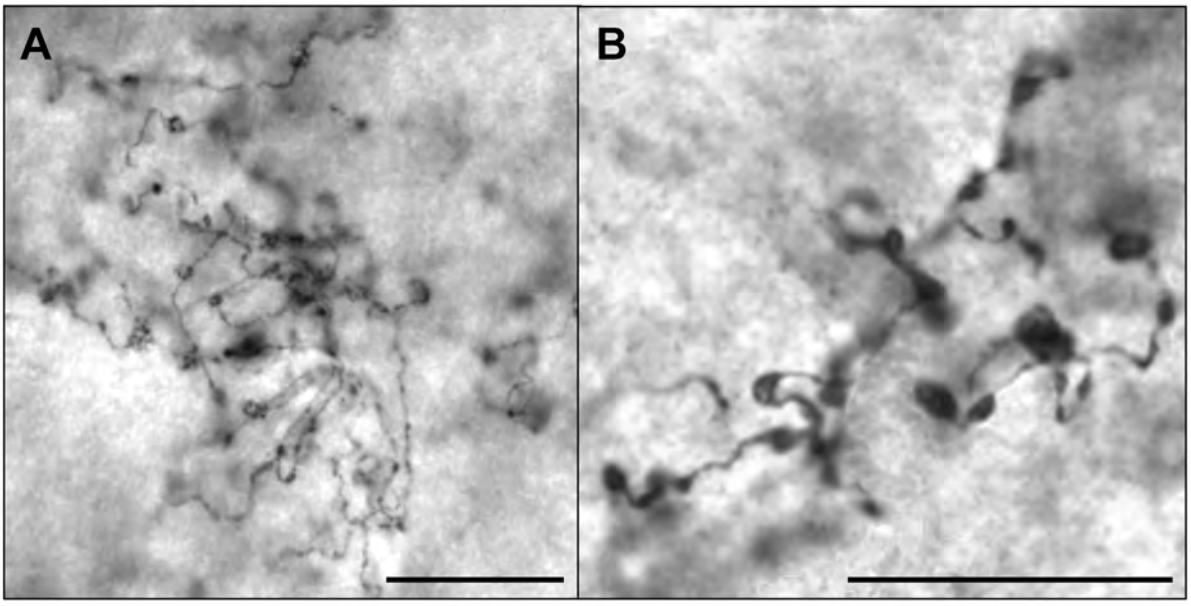

Figure 4. SERT-ir axon coils in human (A) and chimpanzee (B). Scale bar = 25 µm

tia, 1999; Bradshaw, 2003; Kandel et al., 1995). There exists a duality of serotonergic innervation within the mammalian cerebral cortex, with type 1 axons (thin with small ovoid varicosities) originating from the dorsal raphe nuclei and type 2 axons (thin with large spherical varicosities) arising from the median raphe nuclei (Hornung et al., 1990; Kosofsky and Molliver, 1987; Miner et al., 2000; Mulligan and Törk, 1988; Trottier et al., 1996; Wilson and Molliver, 1991). This duality of innervation and the variations observed in the local patterns of cortical serotonergic afferents suggests that the separate classes of axons target different populations of cortical neurons, thereby selectively affecting specific elements of cortical networks (Hornung et al., 1990; Wilson and Molliver, 1991).

Serotonin is known to interact with many different receptor types and subtypes, many of which are still incompletely understood (Bradshaw, 2003; Buhot, 1997). Currently, there are at least fourteen different 5HTergic G-protein linked receptors recognized within the central nervous system, classified according to their second-messenger system, location, and binding affinity (Buhot, 1997; von Bohlen und Halbach and Dermietzel, 2006). There is also one ligand-gated ion channel receptor ($5HT_3$) (Jakab and Goldman-Rakic, 2000). The diverse array of 5HT receptors may support cell- and circuit-specific postsynaptic effects, allowing 5HT to modulate many different functions at once (Briand et al., 2007; von Bohlen und Halbach and Dermietzel, 2006). The effect of 5HT on cortical neurons may yield either enhanced or inhibited activity, depending on the post-synaptic receptor type (Buhot, 1997).

The localization of 5HT receptors in the PFC facilitates 5HT's contributions to memory and cognition (Azmitia, 1999; Buhot, 1997; Marek and Aghajanian, 1998). 5HT is also involved in behavioral inhibition, and its action may be to moderate the influences of synapses from intrinsic local circuits in comparison to extrinsic sources, allowing for learning (Buhot, 1997; Harrison et al., 1999). 5HT acts as a neuromodulator, targeting its receptors on dendritic shafts and the perisomatic region of pyramidal cells as well as several subclasses of inhibitory interneurons (Buhot, 1997; Jakab and Goldman-Rakic, 2000). Thus, 5HT is able to alter directly the excitability of pyramidal cells by targeting their dendrites or indirectly through inhibitory interneurons (Jakab and Goldman-Rakic, 2000).

Several lines of evidence illustrate the role of 5HT in cognitive functions. For example, 5HT levels are positively correlated with accuracy of performance on an attention task in rats (Puumala and Sirviö, 1998). Moreover, drugs that increase central 5HT concentrations, such as 5HT uptake blockers, improve attention, visual and verbal memory, working memory, and processing speed in intact, healthy rodents as well as in macaques and patients with schizophrenia (Buchanan et al., 2003; Meneses and Hong, 1995; Williams et al., 2002). Also, prefrontal depletion of 5HT in marmosets results in impaired performance on serial discrimination reversal tasks and decreased cognitive flexibility (Clarke et al., 2004; Clarke et al., 2005). Dysfunction of 5HTergic systems contribute to the cognitive disturbances associated with depression and suicide, obsessive-compulsive disorder, anxiety disorders, and impulse-control disorders (Austin et al., 2002; Bradshaw, 2003; Noguchi et al., 2001). In addition, cortical depletion of 5HT has been noted in human neurodegenerative diseases including schizophrenia, Parkinson's disease, and Alzheimer's

disease (e.g., Naughton et al., 2000; Vergé and Calas, 2000). For example, Thomas et al. (2006) reported a 47% decrease in serotonin transporter (SERT) density in the PFC of Alzheimer's disease patients regardless of depressive symptoms.

Reports on the distribution of serotonergic afferents within the primate frontal cortex have been published for marmosets (*Callithrix jacchus*) (Hornung et al., 1990), long-tailed macaques (*Macaca fascicularis*) (Azmitia and Gannon, 1986; Berger et al., 1988; Wilson and Molliver, 1991), rhesus macaques (*Macaca mulatta*) (Smiley and Goldman-Rakic, 1996; Wilson and Molliver, 1991), vervets (*Chlorocebus aethiops*), and humans (Trottier et al., 1996; Varnäs et al., 2004). Recent comparative research indicates that the cortical 5HTergic system has been substantially reorganized in humans and chimpanzees relative to macaques (Raghanti et al., 2007). As with DA, coils of 5HTergic axons were found in humans and chimpanzees but were absent in macaques (Raghanti et al., 2007) (Figure 4). Additionally, humans and chimpanzees together deviated from macaques in having denser 5HTergic input in layers V/VI of cognitive prefrontal areas 9 and 32, with no species differences detected in the primary motor cortex (Raghanti et al., 2007). Of interest in this context, Hornung et al. (1990) noted that the only consistent difference between earlier macaque studies and their analysis of the marmoset cerebral cortex was a weaker 5HT innervation of the infragranular layers in marmosets. Although one cannot assume that a single species represents a larger phylogenetic clade, it is tempting to speculate that within the order Primates there might be a shift across New World monkeys, Old World monkeys, and hominoids towards increasing innervation of cortical output layers within the PFC. Additionally, the infragranular layers of rats are sparsely innervated relative to the layers I-IV of cats (DeFelipe et al., 1991). Although carnivores are only distantly related to primates, these findings raise the possibility that primates diverged from other mammalian species in having an increased reliance on 5HTergic afferents in cortical output functions. The fact that humans and chimpanzees have emphasized this difference is particularly notable when considering that Austin et al. (2002) found a specific reduction in 5HT transporter density in layer VI (but not in layers II or IV) of dorsolateral prefrontal cortical area 46 in depressed subjects who committed suicide. This layer-specific deficit in 5HT transmission may contribute to the cognitive deficits, such as the disruption of working memory processes, that are characteristic of major depression (Pelosi et al., 2000).

An additional species differences in cortical serotonergic input includes the presence of pericellular arrays (or 'baskets') formed by type 2 axons and surrounding nonpyramidal neurons in the supragranular layers. Pericellular arrays have been reported in cats (DeFelipe et al., 1991; Mulligan and Törk, 1987), marmosets (Hornung et al., 1990), rhesus, long-tailed, and Moor macaques (Foote and Morrison, 1984; Raghanti et al., 2007; Smiley and Goldman-Rakic, 1996; Wilson et al., 1989), and chimpanzees (Raghanti et al., 2007). However, no such morphologies were observed in the human neocortex (Raghanti et al., 2007). Interestingly, both morphological specializations, pericellular arrays in cats and nonhuman primates and axon coils in humans and chimpanzees, are comprised of type 2 serotonergic axons that originate from the median raphe nuclei. There is evidence of a greater number of 5HTergic neurons in the median raphe of cats and primates relative to that of rodents (Azmitia and Gannon, 1986; Jacobs et al., 1984). This putative increase in cell number may be correlated with the incidence of pericellular baskets, as this feature has not been detected in rodents (Audet et al., 1989). It has been suggested that axons arising from the dorsal raphe nuclei (type 1 axons) play a specific role in prefrontal cognitive control because this is the most abundant axon type found in the PFC (Briand et al., 2007). However, albeit type 2 axons are not as abundant within the PFC as type 1 axons, this axon type does form morphological specializations and therefore may play a critical role in supporting cognitive flexibility and learning capabilities.

As noted, 5HT has a role in regulating behavioral inhibition (Soubrié, 1986), and differences in the capacity for behavioral inhibition have been reported among primate species. Chimpanzees and humans share the capacity to demonstrate self-control in delay-maintenance tasks in order to maximize rewards (Beran and Evans, 2006; Evans and Beran, 2007a). In contrast, rhesus macaques fail to demonstrate a consistent ability for similar self-control (Evans and Beran, 2007b). Cools et al. (2007) recently posited that 5HT actions within the orbital PFC mediate emotional processing and behavioral output by facilitating descending projections, presumably originating within the infragranular layers (i.e., layers V/VI). While quantitative comparative data have not been reported for regions of the orbital PFC, it is likely that, similar to areas 9 and 32, humans and chimpanzees share an increased serotonergic innervation in the infragranular layers of orbital PFC regions. If this is the case, then the increased density of serotonergic afferents within infragranular layers of human and chimpanzee orbital PFC may facilitate their enhanced behavioral inhibition capacities in delay of gratification tasks.

Acetylcholine

Cholinergic axons originate from the magnocellular neurons of the nucleus basalis of Meynert of the basal forebrain and project to all regions of the cerebral cortex, with a substantial degree of regional heterogeneity (Ichikawa and Hirata, 1986; Lehmann et al., 1984; Lewis, 1991; Lysakowski et al., 1986; Mesulam and Geula, 1991; Mesulam, 2004; Mesulam et al., 1992; Mesulam et al., 1986). Additionally, subpopulations of cholinergic cells within the nucleus basalis preferentially project to specific areas within the PFC (Ghashghaei and Barbas, 2001). Although cortical cholinergic input is ubiquitous,

the existence of regional differences in cholinergic innervation of cortical areas and distinct laminar preferences support the concept that cholinergic systems have specific local circuit processing properties. Cholinergic axons (as measured by ChAT-immunoreactive axons) synapse on glutamatergic pyramidal neurons as well as on layer-specific populations of GABAergic interneurons (Chadhuri et al., 2005; Mesulam, 2004; Mrzljak et al., 1995).

The actions of ACh are mediated either by nicotinic or muscarinic receptors. Nicotinic receptors are ligand-gated ion channels that have immediate excitatory effects with no associated second messenger systems (Gu, 2002; von Bohlen und Halbach and Dermietzel, 2006). There are five genes for muscarinic receptors (M1-M5), each belonging to the class of G-protein linked receptors (Bonner et al., 1987). As with the other G-protein linked receptors discussed, muscarinic receptors may have excitatory or inhibitory effects depending on the postsynaptic complex and each receptor subtype appears to have region- and layer-specific concentrations within the cortical mantle (Bozkurt et al., 2005; Mrzljak et al., 1998; Mrzljak et al., 1993; Rasmusson, 2000).

The role of ACh in cognition was initially demonstrated in studies using ACh receptor antagonists in humans and rats (Deutsch, 1971; Drachman, 1977). ACh projections to the PFC act to enhance input processing in attentional contexts and to facilitate memory encoding (Blokland, 1996; Harder et al., 1998; Levin and Simon, 1998; Sarter and Parikh, 2005). ACh accomplishes this by amplifying the influence of synapses from outside the cortex relative to those from other cortical pyramidal cells (Hasselmo, 1995). The input provided by ACh to the PFC is critical to the learning process (Levin and Simon, 1998; Sarter and Parikh, 2005; Steckler and Sahgal, 1995) and is also important in cognitive flexibility and working memory (Levin and Simon, 1998; Sarter and Parikh, 2005; Steckler and Sahgal, 1995). The administration of scopolamine, a cholinergic antagonist, eliminates the capacity to form episodic memories and diminishes the ability to analyze information or acquire semantic knowledge in macaque monkeys (Harder et al., 1998). Furthermore, lesions or drugs that deplete ACh cortical innervation in primates and rodents impair learning and memory in the acquisition and performance on discrimination tasks that challenge attentional processes (Fine et al., 1997; Harder et al., 1998; Irle and Markowitsch, 1987; Levin and Simon, 1998; McGaughy et al., 2000; Sarter and Parikh, 2005), and learning and memory deficits are ameliorated with ACh agonists (Levin and Simon, 1998; Wu et al., 2000).

Cortical ACh has been suggested as a potential marker for intelligence due to its fundamental role in attentional processes, learning, and memory (Gray and Thompson, 2004). Interindividual variation in cortical cholinergic innervation in the hippocampus, caudate nucleus, and frontoparietal cortex was positively correlated with performance on learning tasks in mice (Durkin et al., 1977), and it has been suggested that variations in cholinergic innervation of human and nonhuman primates would reflect individual differences in learning abilities (Mesulam et al., 1986). Several researchers have found that neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and schizophrenia demonstrate reduced ACh activity in prefrontal cortical areas implicated in learning and memory (Mega, 2000; Sarter and Parikh, 2005; Whitehouse, 1992), as measured by ChAT-immunoreactive (ChAT-ir) fibers (Katzman et al., 1988; Mechawar et al., 2000; Mega, 2000; Sigle et al., 2003). For example, Beach et al. (1997) reported significant decreases in cholinergic fiber densities in both the entorhinal cortex and inferior temporal gyrus associated with the preclinical stage of Alzheimer's disease. Furthermore, Ikonomovic et al. (2007) demonstrated a loss of both cholinergic fiber and varicosity densities in prefrontal cortical area 9 in mild to moderate Alzheimer's disease that correlated with impaired cognitive function. Recent evidence also indicates an accelerated rate of protein evolution in primates relative to rodents for three cholinergic receptor subtypes (Dorus et al., 2004), suggesting that natural selection has modified the postsynaptic function of this system along the lineage leading to humans.

A comparative study of cortical ACh input involved measuring the amount of potassium-induced ChAT activity in mouse versus human neocortical slices (Sigle et al., 2003). Relative to mice, only a very low concentration of potassium was required to induce ChAT activity in humans. Several studies have analyzed cortical cholinergic afferents in different mammalian species, and comparisons across species can be made using these data. ChAT-ir axons are present in all cortical areas and layers of rat neocortex (Ichikawa and Hirata, 1986; Lysakowski et al., 1986; Mechawar et al., 2000) with the frontal cortex receiving the densest complement of fibers and layer I having the highest laminar density (Mechawar et al., 2000). In contrast, Old World primates exhibit a rostrocaudal gradient of innervation, with the most rostral areas of the frontal cortex demonstrating fewer fibers than the caudal motor and premotor areas (Lewis, 1991; Mesulam et al., 1992; Mesulam et al., 1986).

Our recent quantitative comparative analysis of ChAT-ir axons in the frontal cortex found that humans and chimpanzees together demonstrated a pattern of innervation that emphasized cholinergic input to layers III and V/VI of prefrontal cortical areas 9 and 32 relative to macaques, whereas no species differences were detected in the primary motor cortex (Raghanti et al., 2008). Further, clusters (or coils) of cholinergic fibers were present in humans and chimpanzees, but not in macaques (Figure 5). Differences among primates have also been reported for the localization of galanin relative to cholinergic neurons in the basal forebrain (Benzing et al., 1993; Kordower et al., 1992). Galanin is an inhibitory modulator of ACh in rats (Elvander and Ögren, 2005; Laplante et al., 2004) and galanin-ir fibers are hyper-

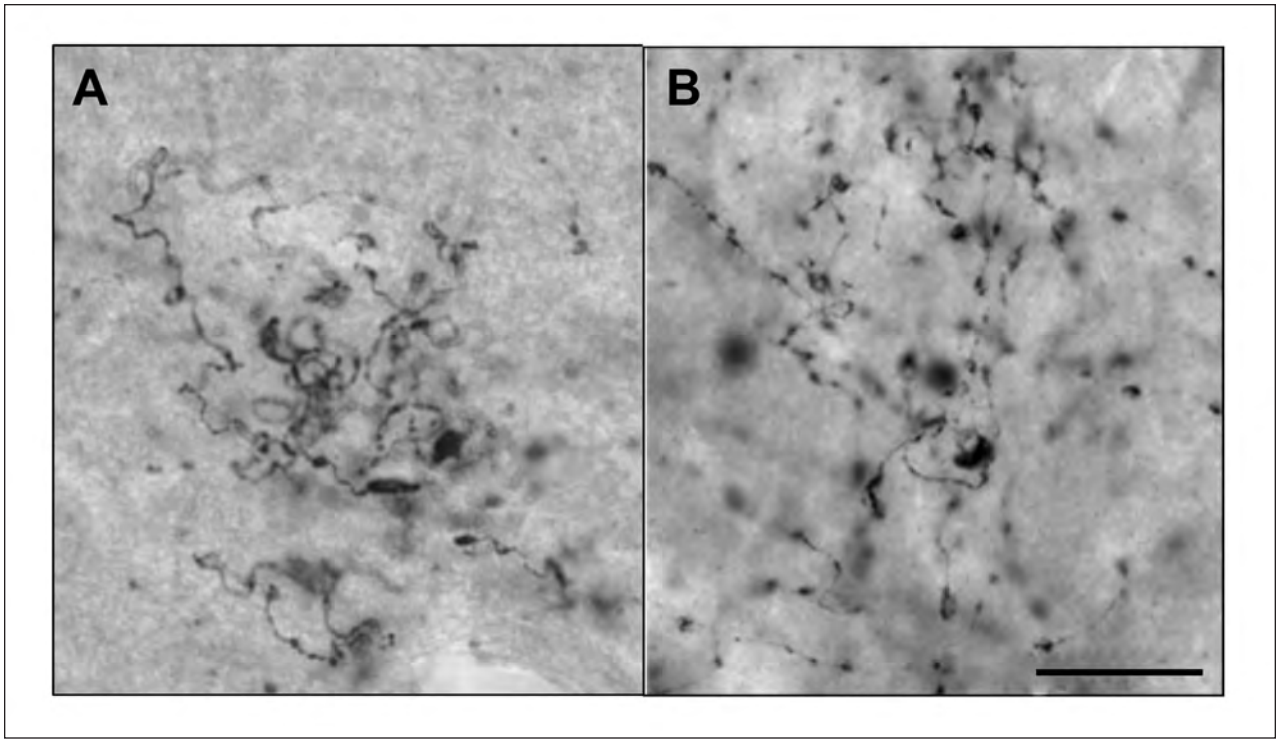

Figure 5. ChAT-ir axon coils in human (A) and chimpanzee (B). Scale bar = 25 µm

trophied in Alzheimer's disease (Mufson et al., 2000). Galanin hyperfunction is associated with cholinergic hypofunction and likely contributes to the associated learning and memory deficits characteristic of Alzheimer's patients (Chan-Palay, 1988). Among primates, hominoids (gibbons, chimpanzees, and gorillas) displayed a distinctively different localization of galanin immunoreactivity relative to monkeys (brown capuchins, rhesus macaques, and baboons) (Benzing et al., 1993). Taken together, it appears that both cholinergic innervation and the modulation thereof were altered in the evolution of apes and humans.

Neuromodulatory Transmitter Summary

As discussed, the DAergic, 5HTergic, and cholinergic neuromodulatory systems play important roles in the regulation of specific cognitive functions. It is likely that these neuromodulator systems do not act exclusively, but several neuromodulator systems may have evolved in concert with one another to support higher cognitive specializations in humans, including language. Previous research revealed that phylogenetic differences exist among humans and other primate species in neuromodulator axon length density relative to neuron density (DA, 5HT, and ACh) in prefrontal cortical areas involved in cognition (areas 9 and 32), but not in primary motor cortex (Raghanti et al., 2007; Raghanti et al., 2008; Raghanti et al., submitted). Additionally, the unique morphological appearance of coils, highly varicose axons surrounding specific cells, is suggestive of a distinct functional specialization. This morphological specialization of neuromodulatory axons is seen only in humans and great apes. Neuromodulatory transmitters have well described functions in cortical plasticity, modifying cortical neuron response properties as mediated by numerous receptor subtypes for each neuromodulator (Gu, 2002; von Bohlen und Halbach and Dermietzel, 2006). Specific effects include long-term potentiation and long-term inhibition, depending on the properties of the post-synaptic element involved. Both long-term potentiation and inhibition alter the response properties of neurons, characteristic of cortical plasticity. The distinctive morphology of coils indicates that they may be involved in cortical plasticity events or local circuit rearrangement (Mesulam et al., 1992). If this is indeed true, coils of neuromodulatory system axons in prefrontal cortical areas may contribute to the increased cognitive and behavioral flexibility shared by humans and great apes and may represent a special neuroanatomical substrate for supporting advanced learning capacities. These neural adaptations might relate to some of the shared cognitive abilities displayed by humans and great apes, such as the diffusion of social learning through regional traditions, a capacity for self-awareness, enhanced attention to the gaze of others, increased social tolerance, and the ability to manufacture tools (Boesch, 1993; Heyes, 1994; Keller, 2004; Povinelli and Bering, 2002; Povinelli and Preuss, 1995; Suddendorf and Whiten, 2001).

Human Brain Evolution: Advantages and Afflictions

The human capacity for reasoning, behavioral and cognitive flexibility, and language, just to name a few, is unparalleled among other species (Neill, 2007; Premack, 2007). However, the evolution of these abilities and the neuroanatomical substrates that support them is not without cost. Humans are also uniquely susceptible to neuropathological and neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and schizophrenia. Each is characterized by some common cognitive manifestations that are indicative of diminished cortical function. In addition, their incidence among human populations is universal and at a relatively high percentage (e.g., approximately 1% of human populations are schizophrenic and 5% of individuals over 65 years of age are diagnosed with Alzheimer's disease) (Molnar, 2006). Most hypotheses regarding the etiology of these diseases involve the disruption of PFC functioning via dysregulation of one or more of the neuromodulatory systems described in this review (Briand et al., 2007). It is conceivable that these neuropathological processes may represent a byproduct resulting from the evolution of human intellect. A further possibility is that human cognitive advances rely on specialized neuromodulatory moderation of neuronal communication and that this increase in functional responsibility has made a significant contribution to our vulnerability to neurodegenerative processes.

Early researchers of schizophrenia, including Emil Kraepelin, believed that this pathology was intimately linked to the acquisition of higher intellectual functions of humans (Goldberg, 2001). More recently, researchers have described schizophrenia as a byproduct of human brain evolution, particularly as a consequence of language acquisition and/or complex social relations (Burns, 2006a; Crow, 2000; Kuttner et al., 1967; Randall, 1998). Genetic studies are now providing some support for these hypotheses. Although schizophrenia is likely a complex, polygenic disorder, many genes have been identified that appear to moderate its incidence and progression. It has been shown that some of the genes or gene combinations that contribute to the development of schizophrenia have undergone positive selection during human evolution, hence accounting for the high incidence of this disease in human populations. Crespi et al. (2007) reported that 28 of 76 genes underlying schizophrenia were subjected to positive selection during human evolution. DA receptor (D4), ACh receptor (muscarinic) and SERT genes are included among these candidate genes (Bustamante et al., 2005; Crespi et al., 2007; Dorus et al., 2004). The negative symptoms and cognitive deficits associated with schizophrenia are linked to DAergic hypofunction within the cortex while a subcortical excess of DA has been implicated in the positive symptoms (Abi-Dargham, 2004). Additionally, disruptions of the cortical 5HTergic and cholinergic systems make further contributions to the cognitive disturbances associated with schizophrenia, with therapeutic recommendations to include appropriate agonists/antagonists for effective treatment (Roth et al., 2004; Stip et al., 2005).

Here, we suggest that not only is schizophrenia a possible side-effect of human encephalization, but other neurodegenerative diseases, including Alzheimer's and Parkinson's diseases, may be as well. Whereas this claim in and of itself is not novel (e.g., Burns, 2006b; Seeley et al., 2007), we suggest one possible neuroanatomical basis for this postulate. Neuromodulatory systems regulate communication within cortical circuits, and their roles in higher cognitive functions and cognitive pathologies are well documented. Our recent research has revealed significant alterations in neuromodulatory transmitter systems within the cortex of the lineage leading to humans, including chimpanzees (Raghanti et al., 2007; Raghanti et al., 2008; Raghanti et al., submitted). While an increased dependence upon these systems may have contributed to cognitive specializations in humans, a trade-off with neurodegenerative pathologies may have taken place.

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