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THE HUMAN BRAIN EVOLVING:

Paleoneurological Studies in Honor of Ralph L. Holloway

Editors

Douglas Broadfield
Florida Atlantic University

Michael Yuan
Columbia University

Kathy Schick
Stone Age Institute & Indiana University

Nicholas Toth
Stone Age Institute & Indiana University

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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 10

SEARCHING FOR HUMAN BRAIN SPECIALIZATIONS WITH STRUCTURAL AND FUNCTIONAL NEUROIMAGING

JAMES K. RILLING

ABSTRACT

The comparative study of living primate brains is one method for elucidating the neurobiological changes that evolved to support human cognitive specializations. We have been using non-invasive neuroimaging to compare brain structure and function in humans, chimpanzees and rhesus macaques. Specifically, we have used diffusion tensor imaging (DTI) to compare the size and trajectory of the arcuate fasciculus fiber tract to provide insights into the evolution of the neural substrates supporting human language. Results suggest that the human arcuate fasiculus is considerably larger and has more widespread projections to both temporal and frontal cortex than the arcuate fasiculus of either chimpanzees or macaques. We have also used [^{18}F]-fluorodeoxyglucose Positron Emission Tomography (PET) imaging to compare resting brain glucose metabolism in humans and chimpanzees in order to shed light on resting state cognition in the two species. Results show that like humans, chimpanzees show high levels of activity in a network of areas implicated in mental self-projection. Humans, but not chimpanzees, also show strongly left-lateralized activity in cortical areas involved in language and conceptual processing. These results imply both similarity and difference in resting state cognition between the two species. Comparative primate neuroimaging is one of many available tools that will help us to flesh out the specifics of Professor Holloway's early recognition that brain reorganization was a critical component of the evolution of the human brain and mind.

INTRODUCTION

Ralph Holloway was instrumental in demonstrating that hominin cranial capacity approximately tripled in size over the past 3 million years (Holloway 1970; Holloway 1973; Holloway 2000; Holloway et al. 2008). This fact is undoubtedly of importance in explaining the evolution of human intelligence. However, from very early in his career, Holloway emphasized that human evolution was also characterized by fundamental reorganization of the brain (Holloway 1968). That is, the human brain is not just a scaled up version of an ape brain, rather it is qualitatively different. To support this claim, he pointed to evidence that human microcephalics with chimpanzee sized brains were capable of behavior patterns that were often more human-like than pongid-like. He also famously observed that the anterior border of primary visual cortex (as estimated by the lunate sulcus) was in a human-like as opposed to a chimpanzee-like position in early australopithecine endocasts that had cranial capacities comparable to living chimpanzees (Holloway 1983; Holloway 1985; Holloway et al. 2003; Holloway and Kimbel 1986). Thus, reorganization appeared to have preceeded large scale encephalization in the hominin lineage. Finally, he turned to the comparative study of human and living non-human primate brains for indirect evidence of brain reorganization. For example, he showed that human primary visual cortex is significantly smaller than one would expect for a typical primate of human brain size (Holloway 1992). This raised the possibility that the adjacent posterior parietal association cortex enlarged disproportionately in human evolution, a prediction that has received support in subsequent research (Orban et al. 2006; Orban et al.

2004). The comparative study of living brains enables researchers to investigate the evolution of a wide variety of neurobiological traits that are not preserved in the fossil record, and has the potential to dramatically expand our knowledge of human brain evolution.

In our own work, we are using non-invasive neuroimaging techniques to compare brain structure and function in humans and non-human primates. We particularly emphasize the human-chimpanzee comparison, given that chimpanzees are our closest living primate relative and that, without chimpanzee data, it is not possible to make inferences about human brain specializations or human brain evolution. In this paper, we will discuss two of our most recent comparative neuroimaging studies. The first uses diffusion tensor imaging (DTI) to investigate the evolution of the neural substrates supporting language by comparing white matter fiber tracts involved in human language with their homologues in chimpanzees and rhesus macaques. The second uses Positron Emission Tomography (PET) imaging to investigate the evolution of resting-state cognition by comparing resting state brain activity in humans and chimpanzees.

Evolution of the neural substrates supporting language

Among the most distinguishing features of the human species is our capacity for language. How and why language evolved in humans is one of the greatest mysteries in anthropology. The human brain must have been significantly modified to support this highly specialized and complex skill.

How does the human brain process and produce language? The classic model, as summarized by Geschwind (Geschwind 1970), postulates that there is a region of cerebral cortex in the left posterior superior temporal gyrus, Wernicke's area, that is responsible for speech comprehension, and a region in the left inferior frontal cortex, Broca's area, that is responsible for speech production (figure 1). Broca's area encompasses two gyri, pars opercularis (BA 44) posteriorly and pars triangularis (BA 45) anteriorly. The model further postulates that Wernicke's and Broca's areas are linked by a white matter fiber tract known as the arcuate fasciculus that originates in Wernicke's area and curves around the sylvian fissure to project to Broca's area. The putative function of this tract is to convey information from Wernicke's to Broca's area, for example during the repetition of spoken language.

However, recent evidence from functional neuroimaging studies as well as from brain damaged patients suggests that cortical areas involved in language extend well beyond Wernicke's and Broca's areas. For example, virtually the entire surface of the left temporal lobe is involved in either phonetic or lexical-semantic processing (Damasio et al. 1996; Hickok and Poeppel 2004; Price 2000; Sakai 2005; Vigneau et al. 2006). Still, Wernicke's and Broca's areas remain critical nodes in the network supporting language, so we might ask whether there is evidence that homologues of these brain regions exist in non-human primates. Indeed, based on location, cytoarchitecture and shared non-linguistic functional properties, putative homologues to Wernicke's and Broca's areas have been identified in macaques (Preuss 2004) (figure 2). But are Wernicke's and Broca's homologues connected in non-human primates as they are in humans? Studies using neuronal tracer injections suggest that the arcuate fasciculus of macaque monkeys links posterior STG (Wernicke's area homologue) with posterior dorsolateral prefrontal cortex, rather than Broca's area homologue in the inferior frontal cortex (Petrides and Pandya 2002) (figure 3). These findings suggest that there may be differences in the trajectory of the arcuate fasciculus between humans and macaques. However, the arcuate fasciculus has not yet been compared in humans and nonhuman primates using the same method. Moreover, the it has not been explored in our closest living primate relative, the chimpanzee.

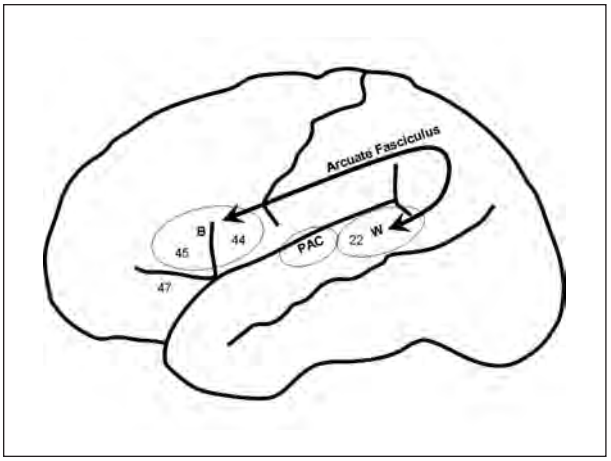

Figure 1: Classic model of human brain language processing as proposed by Geschwind (1970). PAC = primary auditory cortex, W = Wernicke's area, B = Broca's area.

The recent advent of diffusion tensor imaging (DTI), which can track white-matter pathways noninvasively, makes it possible to compare patterns of connectivity in humans and non-human primates. Although standard MRI protocols can image white matter, they do not permit identification of specific fiber tracts within white matter. DTI, however, enables tracking and identification of fiber pathways (Basser and Jones 2002; Mori and Van Zijl 2002). DTI measures the direction and magnitude of water diffusion in brain tissue. Within white matter, water will preferentially diffuse parallel to axons that compose fiber tracts because the myelin that coats the axons is hydrophobic and restricts diffusion perpendicular to the direction of the axon. Thus, in white matter, water diffusion is highly directional. On the other hand, in gray matter, diffusion is less restricted. For each

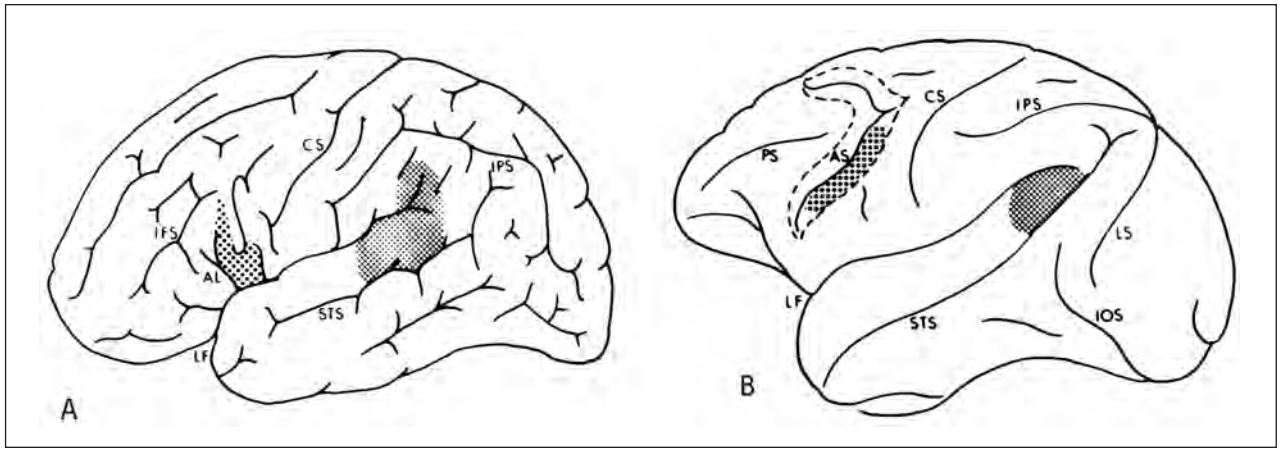

Figure 2: Wernicke's and Broca's areas in humans (left) and their putative homologues in macaques (right). From figure 5 (p.212) in: Galabdura AM, and Pandya DN. 1982. Role of architectonics and connections in the study of primate brain evolution. In: Falk EAaD, editor. Primate Brain Evolution: Methods and Concepts. New York: Plenum Press. p 203-216.

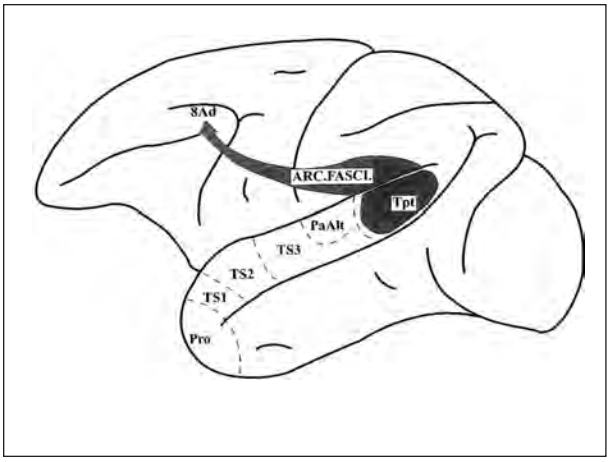

Figure 3: Trajectory of macaque arcuate fasciculus based on neuronal tracer study. From figure 3-8 (p.38) in: Petrides M, and Pandya DN. 2002. Association pathways of the prefrontal cortex and functional observations. In: Stuss DT, and Knight RT, editors. Principles of Frontal Lobe Function. New York: Oxford University Press. p 31-50.

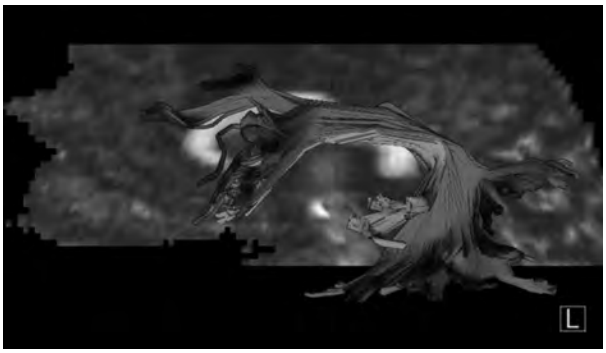

Figure 4: Reconstruction of arcuate fasciculus in human brain using diffusion tensor imaging (DTI) and a deterministic tractography algorithm. Green portion of the tract terminates in the superior temporal gyrus. The red portion terminates in the middle and inferior temporal gyri, as well as the angular gyrus. A mid-sagittal non diffusion-weighted image is shown in the background.

brain voxel of an image, a diffusion tensor can be calculated that describes the direction and magnitude of water diffusion. Tractography algorithms can then use the information from these diffusion tensors to reconstruct fiber tracts in the brain (figure 4) (Basser and Jones 2002; Behrens et al. 2003; Mori and Van Zijl 2002).

We acquired DTI brain scans from human, chimpanzee and rhesus macaque brains in order to compare the size and trajectory of the arcuate fasciculus across these three species using the same method (Rilling et al. 2008). Specifically, scans were acquired from ten live human subjects, three postmortem chimpanzee brains, one live chimpanzee subject, two postmortem macaque brains and one live macaque subject. Protocol parameters for each scan are listed in table 1.

The principal direction of water diffusion in each voxel of a diffusion tensor image can be represented with colors (figure 5). Typically, red, green and blue are used to represent diffusion in the x (medial-lateral), y (anterior-posterior) and z (superior-inferior) directions, respectively. Therefore, for example, voxels in the corpus callosum that carry fibers passing from one cerebral hemisphere to the other through the midline of the brain, are colored red. On the other hand, voxels in the posterior limb of the internal capsule, that carry fibers projecting from motor cortex to the spinal cord, are colored blue. The arcuate fasiculus is one of the largest fiber tracts in the human brain and can be easily visualized in parasagittal sections of a principle diffusion direction color map. The dorsal portion of the arcuate, which

travels in an anterior-posterior direction, as indicated by its green color, transitions into blue where the pathway descends into the temporal lobe, and turns green again as it moves anteriorly in the temporal lobe. This is the situation in the human brain. However, in chimpanzees, a small region of red (medio-laterally directed fibers) interrupts the transition from green to blue in the hook of the arcuate. In macaques, the red area is considerably expanded, and the color map in the region of the arcuate bears little resemblance to human or chimpanzee color maps. Thus, only in the human brain is a continuous uninterrupted arcuate pathway evident in the color map of the principal diffusion direction. It is possible, however, that in chimpanzees, at least, the arcuate actually does pass into the temporal lobe, but that this pathway is not the dominant pathway in the region of the hook of the arcuate. Standard tractography algorithms, which consider only the principal diffusion direction, cannot follow it through a region where it intermingles with a larger, medio-laterally oriented pathway. For this reason, we utilized a newly developed algorithm designed to track through crossing fibers by also considering the secondary diffusion direction (Behrens et al. 2007).

We used this technique to track the arcuate fasciculus along with two additional pathways that convey fibers between frontal and parietal-temporal cortex, the superior longitudinal fasciculus and the extreme capsule. These pathways can be clearly identified in a coronal section through the color map at the level of the precentral sulcus (figure 6a). In all three species, we tracked between a coronal region of interest (ROI) that encompassed these three pathways and an ROI in the white matter underlying the superior, middle and inferior temporal gyri, as well as the inferior parietal lobule (figure 6b).

Below, we first describe the tractography results, and then interpret them and discuss their significance.

Tractography Results (see figure 7 and 8)

Macaque tractography revealed posterior terminations in posterior superior temporal gyrus (STG, 22) and anterior inferior parietal cortex (area 7a). Anteriorly, terminations were found in the frontal operculum, insular cortex and the inferolateral margin of the frontal lobe (area 6), including the extreme ventral aspects of areas 44 and 45 in the arcuate sulcus (figure 7). The pathway of highest probability ran deep to the insula in the vicinity of the extreme capsule and projects most strongly to area 45. Weaker pathways ran both dorsal and lateral to the insula (figure 8). The dorsal pathway was in the location of SLFII and the arcuate fasciculus, and the lateral pathway was in the location of SLFIII (Petrides and Pandya 2006). Thus, these DTI results are compatible with tracer studies that found extreme capsule projections from posterior superior temporal gyrus to area 45 and SLFIII projections from area PF to area 44 (Petrides and Pandya 2002), as well as a DTI study showing that the extreme capsule and SLF pathways projected with highest probability to areas 45 and 44, respectively (Croxson et al. 2005). Tractography also revealed projections to dorsolateral prefrontal cortex (DLPFC), but terminations are only observed with lower thresholds (see methods).

Chimpanzee tractography revealed posterior terminations in the posterior superior temporal gyrus (STG, 22), the supramarginal gyrus (SMG, 40) and the angular gyrus (AG, 39), with minimal connectivity to the superior temporal sulcus and the middle temporal gyrus (MTG). Anteriorly, the pathway projected with high probability to the inferolateral margin of the frontal lobe (ventral 6, 44), extending into the ventral most aspect of pars opercularis (possible 44) and the cortex just rostral to the fronto-orbital sulcus (possible 44 or 45) (Sherwood et al. 2003). Connections also reached dorsolateral prefrontal and dorsal premotor cortex, specifically the superior (6) and middle frontal gyri (8, 46) (figure 7). Terminations were also found in insular cortex as well as the frontal operculum. In contrast to macaques, the pathway that runs dorsal to the insula is stronger than the extreme capsule pathway running deep to the insula (figure 8). In chimpanzees, this dorsal pathway was dominated by connections with the inferior parietal lobe, including both SMG and AG.

In humans, tractography results revealed posterior terminations in posterior superior temporal gyrus (STG, BA 22), middle temporal gyrus (MTG, BA 21 and 37), inferior temporal gyrus (ITG, BA 20), as well as the angular (BA 39) and supramarginal gyri (BA 40) of the parietal lobe. Anteriorly, the pathways reached the insular cortex, frontal operculum, pars opercularis (BA 44), pars triangularis (BA 45), pars orbitalis (BA 47) and the inferior frontal gyrus (BA 46 and 10) rostral to pars triangularis (figure 7). There was also a small projection to dorsolateral prefrontal cortex, dorsal to the inferior frontal sulcus. As with chimps, the dorsal pathway is dominant to the extreme capsule pathway, but in humans the temporal projections from the arcuate fasciculus make a much greater contribution to the dorsal pathway (figure 8).

Two noteworthy asymmetries were observed in humans. Angular gyrus terminations were stronger in the right hemisphere, whereas temporal lobe terminations were stronger and more widespread in the left hemisphere, particularly within the middle temporal gyrus (figure 7). Limited sample sizes in chimpanzees and macaques preclude conclusions about the presence or absence of asymmetries in these species.

Our results show that in macaques, the strongest link between auditory cortex in the STG and frontal cortex is via the more ventral extreme capsule pathway. This pathway has been implicated in auditory object recognition, analogous to the role of the ventral visual stream in visual object recognition (Petrides and Pandya 2002; Romanski et al. 1999). Thus, the pathway may be involved in processing the identity of an object based on its sound, and it is particularly relevant that cells in area 45, where the pathway terminates, respond to monkey vocalizations (Romanski et al. 2005). This pathway may

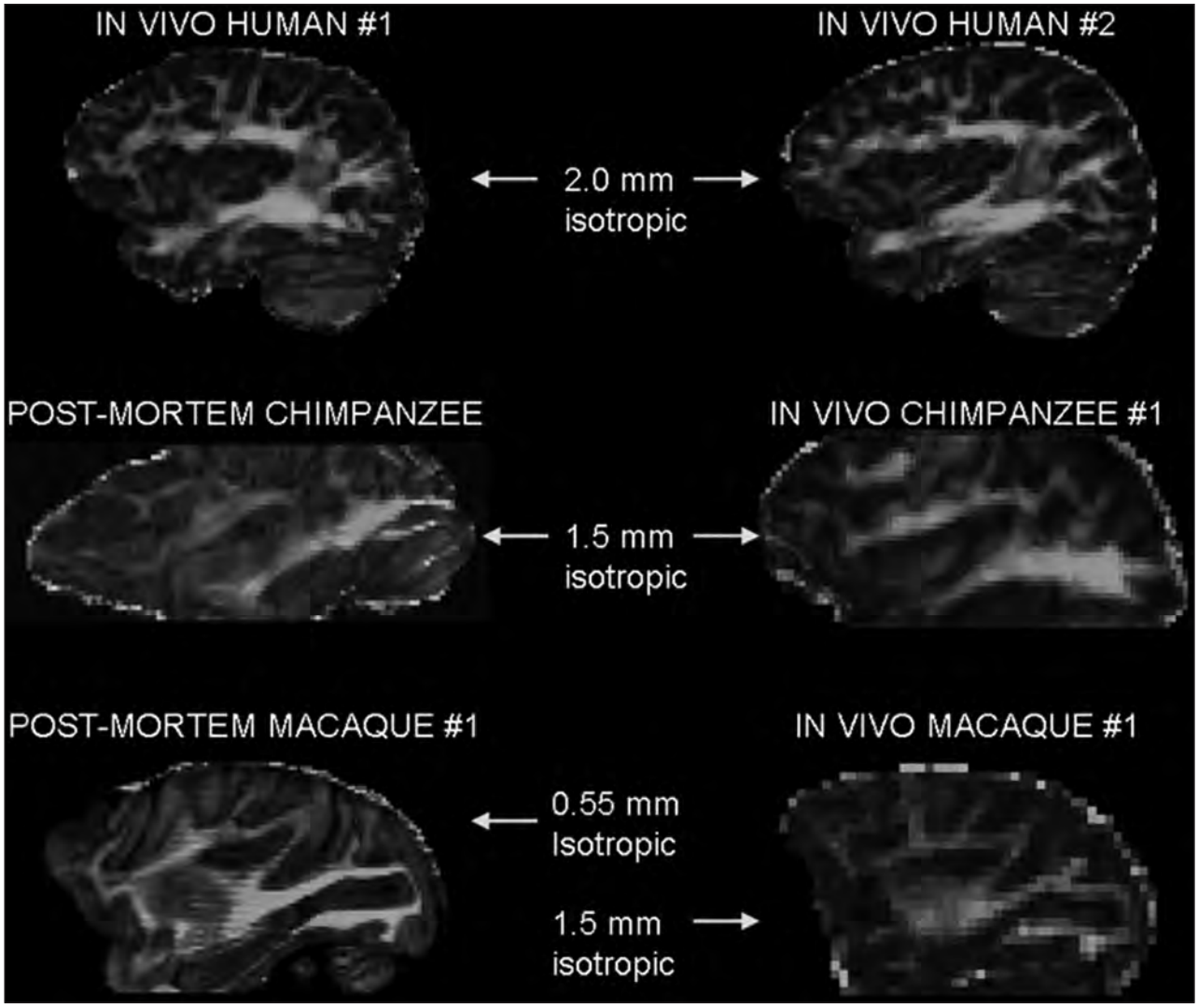

Figure 5: DTI color maps of the principle diffusion direction in humans, chimpanzees and rhesus macaques. Parasagittal sections through the arcuate fasciculus are shown for all three species.

be involved in identifying a caller.

Relative to macaques, chimpanzees have a much stronger dorsal pathway that projects with high probability to the inferior parietal lobe. This pathway likely includes SLFII and SLFIII. Although the function of this pathway has not been investigated in chimpanzees, it is of interest that in humans, a network consisting of inferior parietal and inferior frontal cortices is involved in self-recognition and self-awareness, as well as action understanding through simulation (Uddin et al. 2005). The strong dorsal pathway of chimpanzees could therefore provide part of the substrate of mirror self-recognition, a capacity they share with humans but not macaques(Gallup 1970; Povinelli et al. 1997). Given the pathway's role in understanding the actions of others, perhaps via simulation, it might also help to explain the greater sophistication of chimpanzee social cognition compared with macaques.

Humans differ from chimpanzees and macaques in having much stronger terminations posteriorly in the middle temporal gyrus, as well as stronger terminations anteriorly in pars opercularis and pars triangularis, particularly in their more dorsal aspects. Also, in humans terminations extend further anteriorly into BA 46 and even area 10. Humans also differ in having terminations in pars orbitalis (BA 47). What are the specific functions of these regions of expanded connectivity in humans? Substantial evidence indicates that the middle temporal and angular gyri are involved in lexical-semantic processing (Price 2000), and that pars triangularis (BA 45) and pars orbitalis (BA 47) are involved in syntactic processes of sentence comprehension (Sakai 2005). To explore whether these two regions involved in higher aspects of linguistic processing were specifically connected with one another, we quantified the probability of connectivity between MTG/AG and pars opercularis (BA 44) on the one hand, and between MTG/AG and pars triangularis and orbitalis combined (BA 45 and 47)

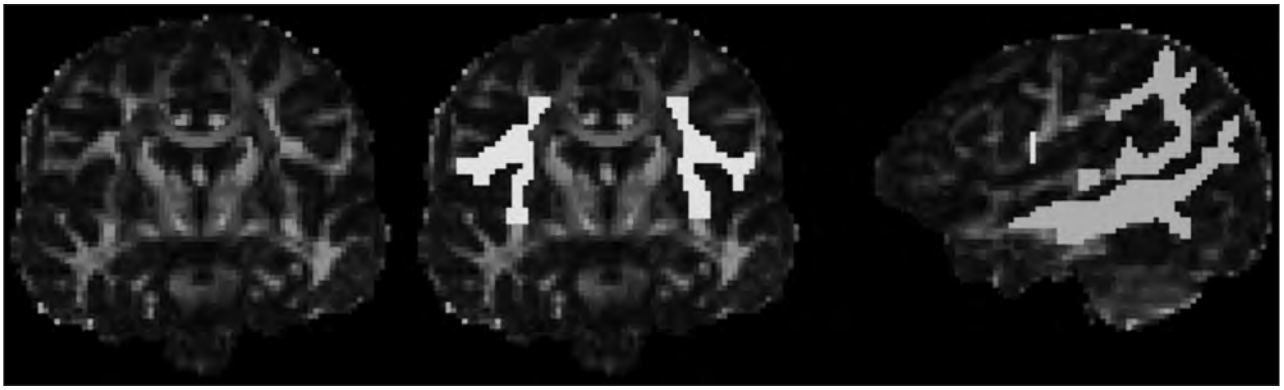

Figure 6: Tractography method for a human brain, illustrating a) anterior coronal ROI, with (right) and without (left) mask, b) parasagittal section showing posterior ROI in white matter of temporal and parietal lobes (blue), along with anterior ROI (yellow). Probabilistic tractography was used to track between these two ROIs in each scan for each species.

Species	Status	sequence	b value	diff. directions	# averages	duration	voxel size
Human	in vivo	EPI	1000	60	3	45 minutes	2.0 isotropic
Chimpanzee	in vivo	segmented EPI	1000	60	5	115 minutes	1.5 isotropic
Chimpanzee	post-mortem	spin echo	4500	60	2	24 hours	1.5 isotropic
Macaque	in vivo	segmented EPI	1000	30	4	32 minutes	1.5 isotropic
Macaque	post-mortem	spin echo	2000	60	3	72 hours	0.55 isotropic

Table 1

on the other hand. In both hemispheres, MTG/AG had a higher probability of connectivity with pars triangularis and pars orbitalis, suggesting that the expanded pathway in humans supports the transmission of lexical-semantic information stored in MTG/AG to pars triangularis for sentence comprehension. Thus, in contrast to macaques in which the predominant pathway from auditory responsive cortex in the temporal lobes to the frontal lobe travels ventrally and conveys information about object identity, in humans the predominant pathway travels dorsally via the arcuate fasciculus and conveys information about the conceptual and semantic meaning of what is heard.

This observation of an expanded projection from MTG/AG to lateral inferior frontal cortex in humans is consistent with other comparative evidence. Human temporal lobes are significantly larger than predicted for a primate of human brain size, and the difference is most pronounced within the white matter of the temporal lobes (Rilling and Seligman 2002), particularly the gyral white matter as opposed to the core white matter (Schenker et al. 2005). Furthermore, visual cortical areas in humans are in a more posterior and ventral location compared with visual cortical areas in macaques, perhaps to accommodate expansion of language cortex on the lateral surface of the left temporal lobe (Orban et al. 2004; Preuss 2004; Ungerleider et al. 1998). Although there is some debate, considerable evidence also suggests that prefrontal cortex is disproportionately large in humans (Avants et al. 2006; Brodmann 1912; Deacon 1997; Passingham 1973; Preuss 2004; Rilling and Insel 1999; Schoenemann et al. 2005; Semendeferi et al. 2002; Sherwood et al. 2005), again particularly in the gyral white matter (Schenker et al. 2005).

In humans, angular gyrus terminations were found to be stronger in the right hemisphere, an asymmetry that could relate to right hemispheric specialization for self-recognition (Uddin et al. 2005), theory of mind (Saxe and Wexler 2005), or visuospatial attention (Mort et al. 2003). Humans also exhibited a leftward asymmetry in the connection probability and spatial extent of terminations in the middle temporal gyrus. This result is consistent with functional imaging evidence suggesting that lexical-semantic processing is lateralized to the left middle temporal and angular gyri (Price 2000), and with previous studies reporting leftward asymmetries in the human arcuate fasciculus as a whole (Glasser and Rilling 2008; Nucifora et al. 2005; Powell et al. 2006).

Thus, we observe human-specific differences within brain regions involved in the two domains of language believed to distinguish humans from non-human primates: symbolic(Deacon 1997) and syntactic (Hauser et al. 2002; Pinker 2000) processing. These significant modifications within language-related cortex challenge earlier suggestions that human language evolved as an incidental by-product of selection for general brain size enlargement (Gould 1991), instead suggesting that lexical-semantic and syntactic processing were specific

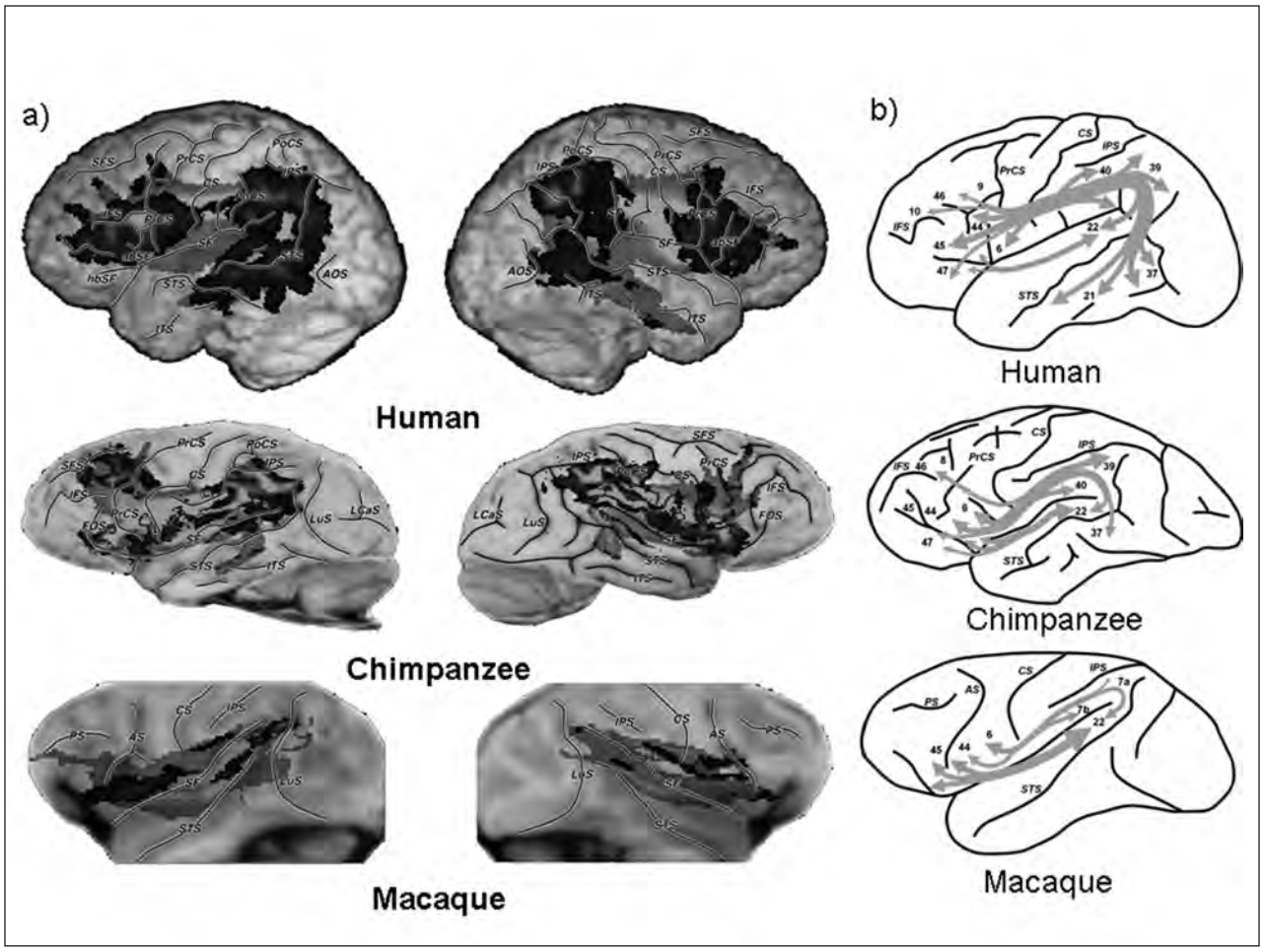

Figure 7: Tractography results. a) Average results for humans, chimpanzees and rhesus macaques, b) schematic summary of results. abSF, ascending branch of the Sylvian fissure; AOS, anterior occipital sulcus; AS, arcuate sulcus; CS, central sulcus; FOS, fronto-orbital sulcus; hbSF, horizontal branch of the Sylvian fissure; IFS, inferior frontal sulcus; IPS, intraparietal sulcus; ITS, inferior temporal sulcus; LCaS, lateral calcarine sulcus; LuS, lunate sulcus; PoCS, postcentral sulcus; PrCS, precentral sulcus; PS, principal sulcus; SF, Sylvian fissure; SFS, superior frontal sulcus; STS, superior temporal sulcus. From figure 2 in Rilling JK, Glasser MF, Preuss TM, Ma X, Zhao T, Hu X, and Behrens TE. 2008. The evolution of the arcuate fasciculus revealed with comparative DTI. Nat Neurosci 11(4):426-428.

targets of natural selection.

Comparison of resting state brain activity in humans and chimpanzees

One of the remarkable aspects of human cognition is our ability to mentally project ourselves into other times and places so that we are not limited to thinking about the immediate here and now (Buckner and Carroll 2007; Tulving 2005). In other words, we can simulate alternative worlds that are separate from the one being directly experienced. We can project ourselves into the past to remember things that have happened to us, into the future to formulate and rehearse plans, and even into the mind of others to understand their mental states (Buckner and Carroll 2007). How do they feel? What do they know?

Experimental evidence suggests that chimpanzees may also be capable of some degree of mental self-projection. For example, a capacity to project into the future is suggested by the fact that they will transport tools for future use (Mulcahy and Call 2006). However, others have argued that the ability to mentally travel into the past and future is unique to humans (Suddendorf and Corballis 1997; Tulving 2005). There has also been considerable debate as to whether chimpanzees can understand the mental states of others. Anecdotal evidence of deception in field studies raises the possibility that they can (Byrne and Whiten 1992); however, this has been difficult to definitively demonstrate in experimentally controlled laboratory studies (compare, e.g., (Hare et al. 2006; Povinelli et al. 2000)).

In humans, each of these forms of self-projection, remembering, prospection and theory of mind, seems to rely on a common neural network, consisting of medial prefrontal cortex as well as medial and lateral parietal cortex, and in many cases the hippocampus (figure 8). Interestingly, a very similar network, known as the default mode network, is tonically active at rest, that is,

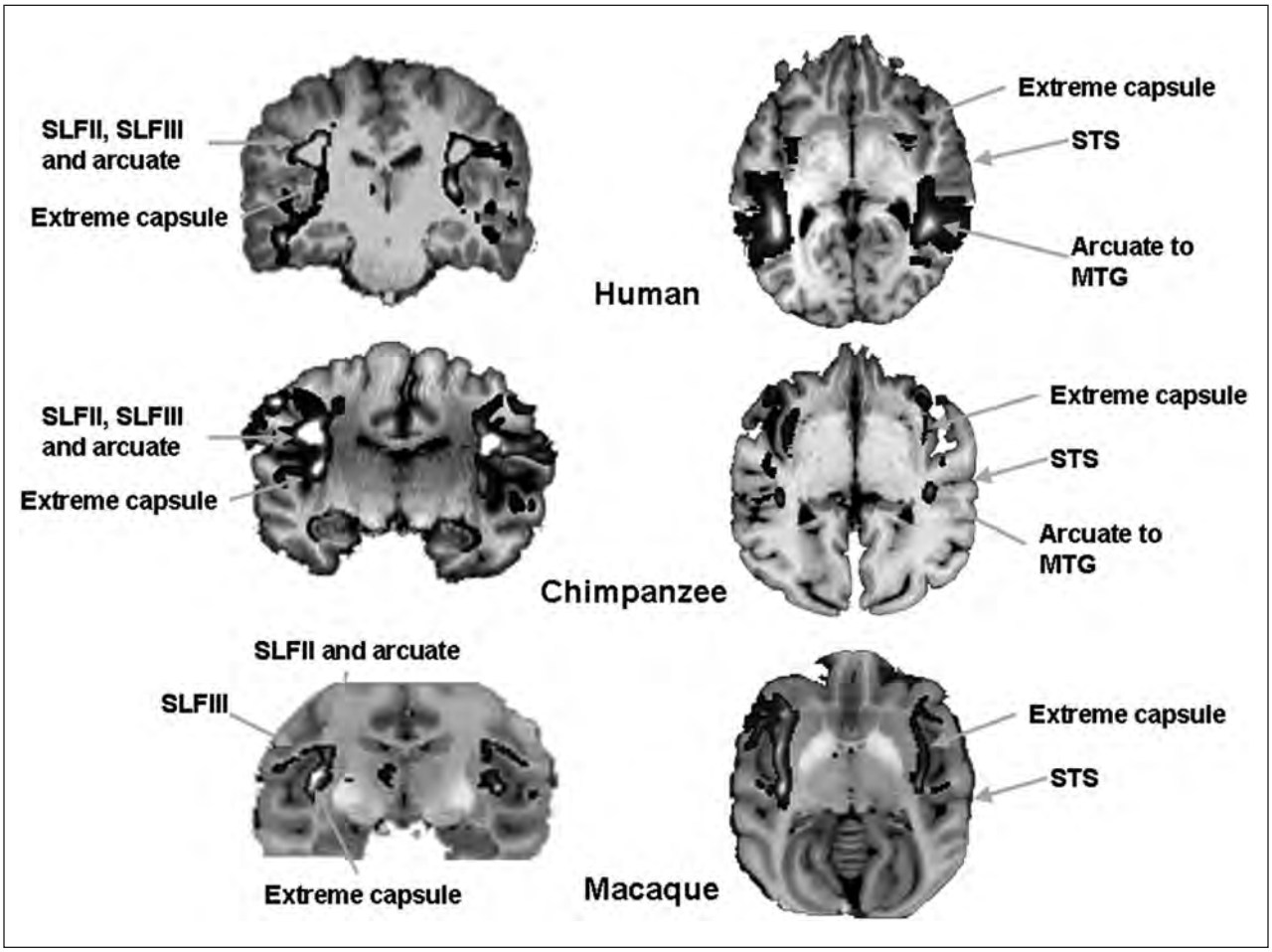

Figure 8: Two-dimensional tractography results. Coronal (a) and axial (b) sections from an individual human, chimpanzee and macaque, illustrating the relative strength of the dorsal and ventral pathways. SLFII and SLFIII, superior longitudinal fasciculus II and III. From figure 3 in Rilling JK, Glasser MF, Preuss TM, Ma X, Zhao T, Hu X, and Behrens TE. 2008. The evolution of the arcuate fasciculus revealed with comparative DTI. Nat Neurosci 11(4):426-428.

when subjects are lying awake in the scanner, but are not engaged in an attention demanding tasks. This observation suggests that people may engage in mental self-projection when resting (Buckner and Carroll 2007). Consistent with this hypothesis, subject self-reports suggest that much of this time is spent reflecting on past social interactions and planning or rehearsing future social interactions (Andreasen et al. 1995; Christoff et al. 2004; Ingvar 1979). These mental exercises may prove useful in clarifying the meaning of past interactions and practicing pending future interactions so they can be exercised more skillfully. Planning in the non-social domain would be similarly adaptive, for example, planning to save or store currently available food and water so that it can be used to survive a future drought. These abilities may be fundamental to the current and past success of our species.

To shed light on the question of whether chimpanzees are capable of mental self-projection, we used functional neuroimaging to define resting state brain activity in chimpanzees, and we compare these results with those of a human sample.

For this study, we used [^{18}F]-fluorodeoxyglucose PET ([^{18}F]-FDG PET) imaging, which makes it possible to image resting state brain activity in awake subjects outside the scanner. Adult humans (n=8) and adult chimpanzees (n=5) received a dose of [^{18}F]-FDG, a radioactively-labeled, chemically modified glucose molecule. After entering the bloodstream, [^{18}F]-FDG accumulates and becomes trapped in neurons at a rate proportional to their glucose metabolic rate (Phelps and Mazziotta 1985). During this extended period of cellular [^{18}F]-FDG uptake (~45 minutes in humans and 75 minutes in chimpanzees), human subjects rested quietly by themselves in a private room adjacent to the PET scanner, and chimpanzee subjects rested quietly in their home cages. Chimpanzee subjects were dosed in the late morning hours when they typically interact minimally with either their cagemates or the animal care staff. After the uptake period, subjects received a PET scan to image the distribution of [^{18}F]-FDG in the brain. Variation across the brain in the resulting image results from regional differences in glucose metabolism during the period of [^{18}F]-FDG uptake. Human subjects were scanned awake, whereas

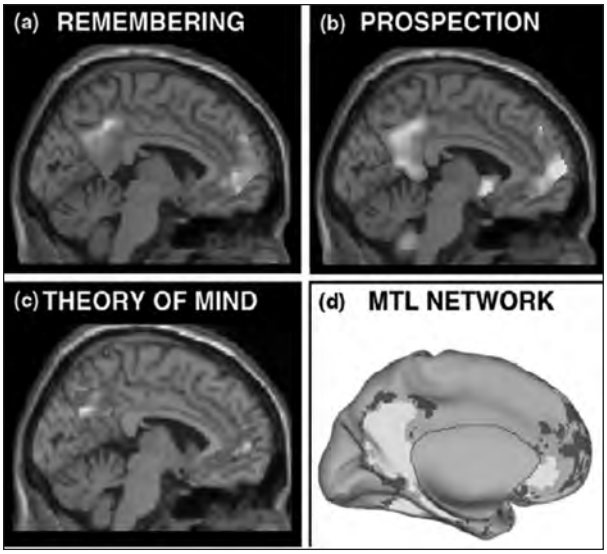

Figure 9: Common neural network activated during different types of mental self-projection, including remembering, prospection and theory of mind. Reproduced from: Figure 2 in Buckner RL, Carroll DC (2007): Self-projection and the brain. Trends Cogn Sci 11:49-57.

chimpanzee subjects were sedated and scanned in the anesthetized state. It is important to recognize, however, that since [^{18}F]-FDG uptake is largely complete prior to sedation, and since it leaves cells at a very slow rate, the resulting images reflect brain metabolism during the uptake period when the animal was awake, and not real-time activity in the anesthetized state.

Although the homologies of chimpanzee and human cortical areas have in some cases not been definitively established, we reasoned that if the chimpanzee pattern of resting brain activity differs substantially from that found in humans, it is unlikely that they are engaged in the same mental processes as humans are at rest. On the other hand, if chimpanzee and human patterns of activation are similar, one possible explanation is that there are similarities in their resting-state cognition.

Behavioral Results

Chimpanzee subjects were videotaped during the [^{18}F]-FDG uptake period to verify that we had attained a reasonable "resting state". An ethogram was used to quantify each subject's behavior during the uptake period. None of the five chimpanzees spent any time in physical contact with their cagemate during the uptake period. Subjects spent the overwhelming majority of their time lying down or sitting in what we characterized as a "neutral" state of attention, as opposed to "alert", "watching" or "moving" (see (Rilling et al. 2007) for further details).

Imaging Results

In both humans and chimpanzees, we identified the 5% most metabolically active voxels (figure 9). In humans, this included the classic default-mode regions, including dorsomedial prefrontal cortex, and medial and lateral parietal cortex. Humans also showed strongly left-laterlalized activity in lateral frontal, temporal and parietal cortices, as well as in several subcortical structures, including the striatum and thalamus. Finally, there was activity in visual cortex, as expected given that our subjects rested with their eyes open during the uptake period.

The lateralized activity we observed in left posterior temporal and inferior parietal areas is consistent with previous studies reporting this area to be more active at rest compared with various active task conditions (Binder et al. 1999; Shulman et al. 1997). In combination with left frontal lobe activity, these areas may form a conceptual processing network that is involved in semantic memory retrieval and its manipulation in working memory for the purposes of planning, organization and problem solving (Binder et al. 1999; Christoff et al. 2004; Shulman et al. 1997). The left-lateralized cortical activity overlaps extensively with the human brain language network (as discussed above), raising the prospect that, even in the resting state, humans can't help but think with words. Language is essential to human thought.

In sum, the pattern of brain activity observed in our human subjects is similar to that reported in previous resting state studies, and this pattern of activity is consistent with a resting state involving mental self-projection, conceptual and semantic processing, and inner speech.

Like humans, chimpanzees exhibited high levels of activity in default mode areas, including medial prefrontal cortex, as well as medial and lateral parietal cortex. If these regions have a similar function in humans and chimpanzees, then our results are consistent with the possibility that chimpanzees engage in mental self-projection in the resting state.

There were also some subtle differences between humans and chimpanzees in activity within the default mode network. Within medial prefrontal cortex, humans showed the highest level of activity in more dorsal areas, whereas chimpanzees showed more widespread activity, including activity in more ventral areas. Recently, it has been suggested that different subdivisions of medial prefrontal cortex are related to different aspects of mentalizing (Amodio and Frith 2006; Frith and Frith 2006; Mitchell et al. 2006), with more dorsal regions being involved with thinking about others' thoughts as well as person knowledge, and more ventral regions being involved with monitoring emotion in self and others or emotional processing more generally. Thus, it is possible that the chimpanzee resting state is imbued with a stronger emotional tone than the human resting state, perhaps including greater reflection on emotional states as opposed to thoughts. However, given that other studies have found high levels of activity within ventromedial PFC in human subjects (Raichle et al. 2001), it is possible that the lack of high levels of activity in this area in our human sample relates to differences in the exact

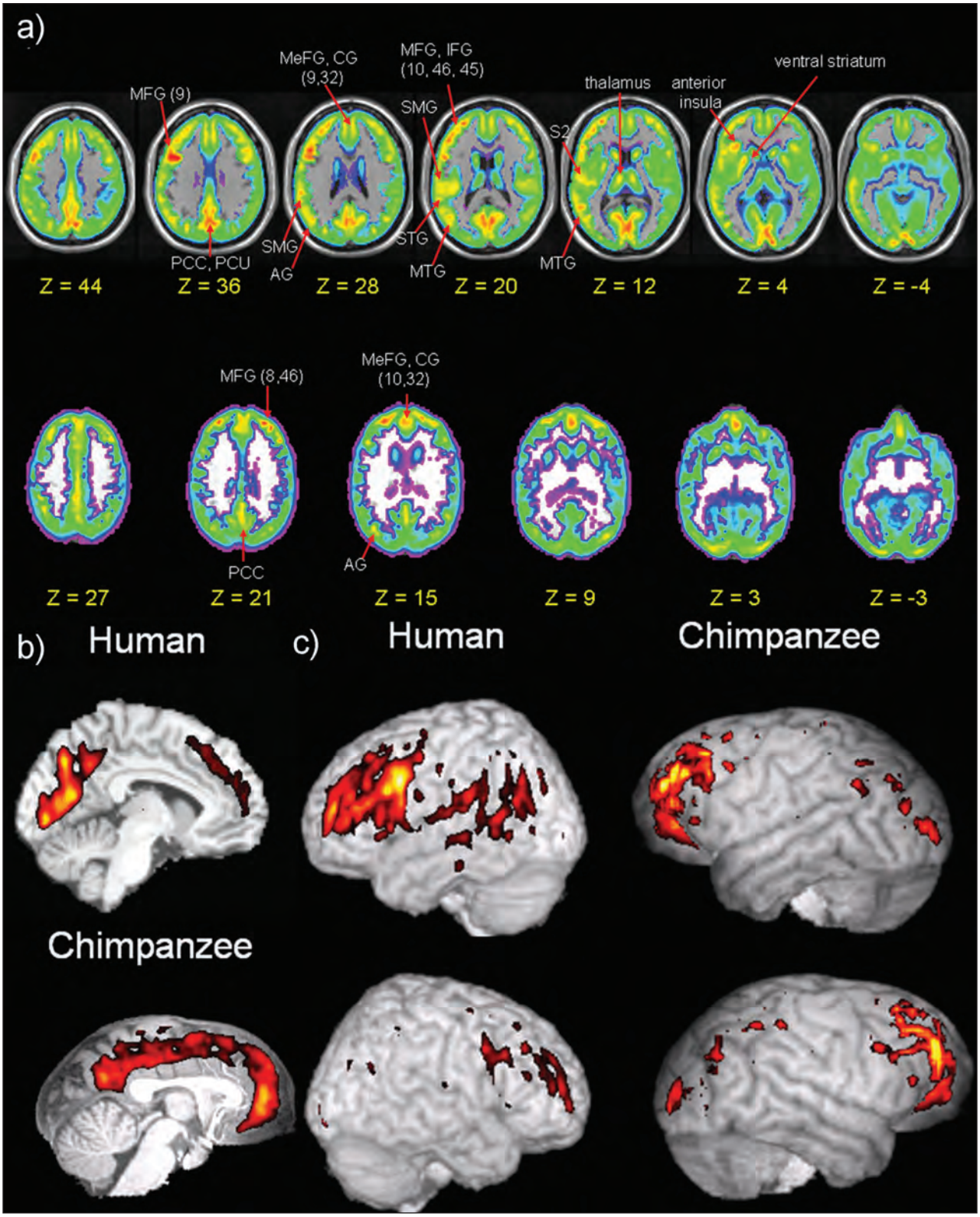

Figure 10: Resting-state brain activity in humans and chimpanzees. a) Average human (n=8) and chimpanzee (n=5) PET images in horizontal section. Regions of highest metabolic activity are colored yellow to red. The five percent most active voxels in each species are shown in b) midsagittal and c) lateral views. Modified from figures 1 and 2 in Rilling JK, Barks SK, Parr LA, Preuss TM, Faber TL, Pagnoni G, Bremner JD, and Votaw JR. 2007. A comparison of resting-state brain activity in humans and chimpanzees. Proc Natl Acad Sci U S A 104(43):17146-17151.

nature of the resting state condition rather than genuine species differences. For example, thinking about familiar and unfamiliar others has been localized to ventral and dorsal aspects of MPFC, respectively (Mitchell et al. 2006). The fact that chimpanzees, unlike the humans, were surrounded by familiar others during the [^{18}F]-FDG PET uptake period could explain the higher levels of activity ventrally in chimpanzee images.

Unlike humans, chimpanzees did not show left lateralized activity in frontal, temporal and parietal regions involved in language and conceptual processing. These results suggest that one major difference between humans and chimpanzees is that human resting state cognition is linked with language. The left lateralized areas that are active in humans but not chimpanzees have also been implicated more generally in conceptual processing involving semantic knowledge retrieval, representation in awareness, and directed manipulation of represented knowledge for organization, problem-solving and planning (Binder et al. 1999). Thus, organization, planning and problem-solving may be other aspects of resting state cognition that differentiate humans from chimpanzees.

In conclusion, our results imply some degree of commonality in resting state cognition between humans and chimpanzees, possibly including a tendency to mentally project oneself into other times, places or mental perspectives. However, left lateralized activity in humans that is absent in chimpanzees, may mean that humans are engaged in a greater degree of conceptual processing than chimpanzees at rest, and that humans think with words when in a resting state.

Overall Conclusion

With the new methods of neuroimaging, we can begin to non-invasively compare both the structure and function of human and non-human primate brains, in the quest to identify the unique features of the human brain that evolved since we shared a last common ancestor with chimpanzees. These techniques will help us to flesh out the specifics of Professor Holloway's early recognition that reorganization was a critical component of the evolution of human brain and mind.

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