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Evolutionary Specializations of Human and Chimpanzee Cortical Organization

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Evolutionary Specializations of Human and Chimpanzee Cortical Organization

By

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MS, George Mason University, 2008

Advisor: Todd M. Preuss, PhD

An abstract of
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Abstract

Evolutionary Specializations of Human and Chimpanzee Cortical Organization

By Katherine L. Bryant

Human brains are notable for their large neocortex, both in absolute size and relative to body size. Large brains are common to the hominoid lineage, but even when compared to our closest relatives -- chimpanzees and bonobos -- human brain size is exceptional. One of the longstanding questions in evolutionary neuroscience is whether the human brain expanded uniformly, or whether some neocortical regions expanded to a greater degree than others (reviewed in Schoenemann 2006). In other words, is the human brain simply an enlarged primate brain, or has neocortical reorganization accompanied of human brain expansion? To address this broad research question, I examine cortical organization in three ways. In the first chapter, I review and discuss the structure and function of the primate temporal lobe from an evolutionary perspective. This chapter will pay special attention to visual striate and extrastriate modifications. The second chapter covers the methodologies employed to examine the evolutionary modifications to human and chimpanzee visual cortex. Here, I detail immunohistochemical and diffusion tensor imaging methods used to examine human, chimpanzee, and macaque cortex. The results of these studies, which suggest modifications to striate and extrastriate, and multimodal temporal cortices in humans and chimpanzees, are detailed in the third chapter. The final chapter discusses the implications of these findings for understanding the evolutionary modifications to the temporal lobe that have occurred in the hominid lineage as well as specializations that have appeared in the human lineage since our divergence from our common ancestor with chimpanzees approximately 6 mya.

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ABBREVIATIONS

AF	Arcuate Fasciculus
ATL	Anterior Temporal Lobe
CO	Cytochrome Oxidase
DAB	Diaminobenzidine
DTI	Diffusion Tensor Imaging
DW-MRI	Diffusion-Weighted MRI
FBA	Fusiform Body Area
FFA	Fusiform Face Area
FG	Fusiform Gyrus
fMRI	Functional MRI
FSL	FMRIB Software Library
FST	Fundal area of STS
HCP	Human Connectome Project
ILF	Inferior Longitudinal Fasciculus
IFOF	Inferior Fronto-Occipital Fasciculus
IPS	Intraparietal Sulcus
ITC	Inferotemporal Cortex
ITG	Inferior Temporal Gyrus
ITS	Inferior Temporal Sulcus
LGN	Lateral Geniculate Nucleus
LO	Lateral Occipital Area
MLF	Middle Longitudinal Fasciculus
MR(I)	Magnetic Resonance (Imaging)
MST	Medial Superior Temporal Area
MTG	Middle Temporal Gyrus
PMD	Post-Mortem Delay
PV	Parvalbumin
ROI	Region of Interest
SLF	Superior Longitudinal Fasciculus
STG	Superior Temporal Gyrus
STS	Superior Temporal Sulcus
MP-RAGE	Magnetization-Prepared Rapid Gradient Echo
MST	Medial Superior Temporal Area
MT	Middle Temporal Area/V5
MT+	Middle Temporal Complex
VGLUT1, 2	Vesicular Glutamate Transporter 1, 2
V1	Primary Visual Cortex/Striate Cortex
VIP	Ventral Intraparietal Cortex
VWFA	Visual Word Form Area
YNPRC	Yerkes National Primate Center

EVOLUTIONARY SPECIALIZATIONS OF HUMAN AND CHIMPANZEE CORTICAL ORGANIZATION

INTRODUCTION

INTRODUCTION

What makes humans unique? Although only separated from chimpanzees and bonobos, our closest relatives, by approximately 6-8 million years of evolution (Steiper and Young, 2006; Langergraber et al., 2012; comparable to the evolutionary distance between African and Asian elephant species; Rohland et al., 2007), humans display a behavioral repertoire that is distinctive among great apes. Human language and conceptual thought are arguably our most important distinguishing features: to our knowledge, no other species produces and comprehends such a complex web of semantic knowledge as is found in humans.

This work will examine several anatomical features unique to human brains. To effectively parse human-specific traits, a direct comparison between humans and our closest primate relatives, chimpanzees, is necessary (Preuss 2004; Preuss 2006; Preuss 2011). In addition, a primate out-group is required in order to disambiguate human specializations and chimpanzee specializations from traits common to the hominoid lineage broadly. Ideally, comparative neuroanatomical investigations are performed using identical methods, so as to minimize the possibility of methodological artefacts being mistaken for real species differences.

Learning about chimpanzee neuroanatomical specializations is of interest in its own right. The cognitive abilities of chimpanzees have been studied in depth for decades, and we now have a rich comparative literature on human and chimpanzee language abilities, tool use and tool-making skills, theory of mind, and other cognitive skills. These data can be used to guide hypotheses about chimpanzee brain structure and identify features that are unique to chimpanzees.

In Chapter 1, Historical Background, Part 1 examines the multiple threads of scientific inquiry that have led us to this particular moment and this particular dissertation. First, how did the notion of brain function-structure relationships come into being? Next, I will examine methodological legacies, and how they shaped both research questions and conclusions. For example, as histological methods for cortical mapping were being developed, debates began on the nature of cortex as a substrate for human thought. So-called "localizationists" and "anti-localizationists" battled as the field of neuroscience attempted to create cortical maps that accurately reflected both the functional specificity of primary/unimodal cortical regions as well as the structural variability and complex functionality found in association areas. Although the debate is not fully resolved, examining its origins can provide insight into current neuroimaging era in evolutionary neuroanatomy.

Association areas are important for understanding human brains and brain evolution for another reason – there are multiple lines of evidence suggesting that disproportionate expansion of these areas occurred in the human lineage. Association areas – cortical territories that receive inputs from multiple sensory modalities – have been of interest to evolutionary neuroanatomists since the turn of the 20th century – although the term "association" has evolved in meaning over time, but always in reference to primary areas which receive strong thalamic afferents (sometimes termed "projection cortex"). I will discuss the role of association cortex in the debate on cortical mapping.

It is not possible to understand the question of human brain uniqueness without another key piece of the puzzle -- the role of evolutionary theory in the development of brain mapping theories and applications. Part 1 also explores the role of Darwin's theory of

natural selection as the mechanism of human evolution on the early stages of human neuroanatomical research.

In Parts 2 and 3 of the first chapter, I outline the research questions of my dissertation. There are two interrelated questions that both examine human specializations of brain structure. Part 2 introduces the first research project, wherein I employed immunohistochemical techniques in order to identify similarities and differences in the laminar structure of primary visual cortex in human, great ape, and old world monkey species. Vesicular glutamate transporters are relevant to our understanding of the organization of primary areas because of their role in excitatory neurotransmission from thalamic afferents. Localizing these transporters with respect to cortical laminae permits us to infer which layers receive geniculocortical afferents. Evolutionary differences between primate primary cortical organization is of special note because primary cortex matures earlier than other cortical territories, and because of its presumed conserved structure.

The second research question is introduced in Part 3 of the Historical Background. Like the previous study, this work interrogates the cortical organization of humans and our primate relatives in a comparative manner. The second study focuses on areas of cortex that are candidates for important human specializations related to language and conceptual thought. These territories include lateral and inferior temporal cortex, which contain broad swathes of multimodal sensory association areas. Association areas, as later-maturing territories that have relatively expanded in Hominoid and human evolution, are important candidates for evolutionary modifications. Temporal association areas are especially notable because of their role in language comprehension, object recognition, and semantic memory.

Compared to frontal/prefrontal cortex, these areas are understudied as sites of human specialization and therefore ripe candidates for comparative neuroanatomical study.

Part 4 of the first Chapter provides an overview of more recent empirical data on association cortex in the temporal lobe and temporal lobe structure more generally in hominoids. Here, I discuss structural differences of the temporal lobe in humans compared to other hominoids with regard to cortical and fascicular organization. Possible behavioral and cognitive ramifications of these modifications – for example, language, tool use, semantic memory, etc. – are explored.

Chapter 2, the Methods section, covers the techniques used for the two studies in the dissertation. This dissertation's methods section is unique in that it involves techniques with a long neuroscientific history – architectonics – as well as imaging technologies that have come into use only in the past 10-15 years. This is perhaps appropriate given the recent resurgence of the field of brain mapping, a field whose heyday was arguably the turn of the 20th century – the time of Brodmann, the Dejerines, the Vogts, and other prominent neuroanatomists and histologists. Histology and structural MRI, in addition to both being well suited to cortical mapping, are also notable for their applicability across species. There are very few neuroscientific methods that can be used in humans, great apes, and macaques alike. Immunohistochemical methods used to examine the laminar distribution of vesicular glutamate transporters in humans and other anthropoid primate species are covered in the first section. The second section summarizes our neuroimaging methodologies, which include parameters for scanning and reconstructing diffusion tensor images and structural magnetic resonance images for human, chimpanzee, and macaque *in vivo* brains, as well as the multiple tractographic analyses used to reconstruct putative white matter pathways.

Results (Chapter 3) and Discussion (Chapter 4) will explore the findings from the 2012 vesicular glutamate transporter publication as well as the comparative diffusion tractography results. Here, I report on our findings of important differences in laminar organization of vesicular glutamate transporters between primate species. Our data from the diffusion tractography study of extrastriate and temporal cortex organization in hominoids and macaques will be covered in the second section of Chapter 3. Chapter 4 will cover the broader implications of our findings for understanding evolutionary pressures on humans and chimpanzees. In the VGLUT2 study, we identify modifications to layers IV and VI that appear to be unique to the Hominoids and humans in our study sample. In the diffusion tractography study, possible modifications to striate-extrastriate organization in the hominoid lineage are explored. First, the anterior portion of the middle temporal gyrus (aMTG), which evidence suggests is involved in language processing and comprehension. The second area of interest is the fusiform gyrus (FG), which plays an important role in face and object recognition. Face recognition in the fusiform facial area is a candidate human or Hominoid evolutionary specialization based on behavioral data from humans, great apes and rhesus macaques. The last area that is a candidate for evolutionary modifications is the anterior temporal lobe (ATL), which is expanded in surface area in humans and is likely a hub for conceptual processing, although the exact role of the ATL in human cognition continues to be a point of debate. Methodological limitations in both studies are examined in detail.

Part 3 of the discussion section expands upon Part 1 and 2 while weaving in contextual information from earlier discussions from Chapter 1 on temporal cortex. Within temporal association cortex, the three territories that have been identified in the diffusion tractography study putative sites upon which natural selection may have acted – aMTG, FG,

and ATL – are discussed in more detail. This includes a review of fMRI studies that have reported on functional activations in these areas and diffusion tractography data that have helped map fascicular projections in the temporal lobe. The relationship between multimodal areas, association cortex, and graph theory is explored in an attempt to shed light on the computational repercussions of cortical expansions in the aforementioned areas. Nodes, hubs, and "rich club" networks are included in this section.

The final section is a combination future directions section and Epilogue. Here I attempt to bridge the gap between classical empirical analysis and critical theory, based on my training in humanities during my time at Emory. Informed by post-colonial, feminist, and science and technology studies scholarship, I problematize some aspects of my dissertation research. What does it mean when humans study our own kind and ascribe values and utility judgements about our traits and attributes? How might gender, racial, and cultural biases influence the interpretations of our data, and even the initial formation of our research questions? Can critical theory tools like situated knowledges, standpoint theory, the animal-subaltern, and mixed modernity illuminate these issues?

Finally, although the work of the post-structuralist often ends with problematization that does not offer solutions to the questions it raises, I will attempt to offer some responses to these critiques based on my research experiences and offer space for future directions in evolutionary neuroanatomy research. Although it is extremely unlikely that neuroscientists and anthropologists will resolve the issues raised by these critiques, there may be a way forward that is at least conscious of these philosophical considerations and endeavors to respond to them where they can.

HISTORICAL BACKGROUND

HISTORICAL BACKGROUND

PART 1: HUMAN NEOCORTEX – A HISTORY OF SCIENCE PERSPECTIVE

Says Owen, you can see
The brain of Chimpanzee
Is always exceedingly small,
With the hindermost "horn"
Of extremity shorn,
And no "Hippocampus" at all.

Gorilla[1]
Excerpt from *Monkeyana,* Zoological Gardens, May 1851

The field of evolutionary neuroanatomy arguably finds its origins with a heated public scientific disagreement between anatomists Sir Richard Owen and Thomas Henry Huxley (the latter known as "Darwin's Bulldog"). Owen sparked controversy in the British scientific community by asserting that human brains were unique from other apes due to the presence of a several structures, most importantly the calcar avis, or "hippocampus minor" (Owen 1858), a small ridge found within the posterior horn of the lateral ventricles. The controversy unfolded at the time of the publication of Darwin's *On the Origin of Species* and was an important point of contention during the famous 1860 Huxley-Wilberforce debate on the merits of natural selection as the mechanism of evolution. Owen used the hippocampus minor as justification for a separation of *Homo sapiens* into a class distinct from the Primates, with the implication being that humans would retain their special place in nature in the face of the theoretical revolution that was *natural selection*.

[1] Probably Sir Philip Egerton, patron of Richard Owen (Darwin and Burkhardt 1993)

What was at stake was origin of humanity itself. Naturalists with theological leanings, like Owen, were concerned with maintaining man's dominion over the animals, which conflicted with Darwin's accounts of evolutionary gradualism. Darwin had suggestively indicated in the conclusion of *Origin* that an upcoming volume would explore the study of humans with the line, "Light will be thrown on the origin of man and his history" (Darwin 1859). The debate split the scientific community between Darwin supporters and attackers. Owen's claim of human uniqueness among animals relied on the absence of the hippocampus minor in apes, although the significance of this structure was unclear at the time[2] and now considered trivial (Gross 1993). Meanwhile, Huxley was performing a series of primate brain dissections, providing anatomical evidence for the presence of the hippocampus minor in non-human apes. Ultimately, through a combination of public debate, scientific demonstration, and publication of his scientific works, Huxley managed to sway majority opinion[3] on both the validity of natural selection as mechanism as well as the common ancestry of humans and apes (ibid). Huxley's opus, *Evidence for Man's Place in Nature* (Huxley 1863, revised and reprinted in 1896 as *Man's Place in Nature*) includes work from these lectures and letters, the key evidence coming from comparative anatomical studies of primate skulls and brains.

In addition to anatomical studies, Huxley produced a thorough summary of early Western European encounters with anthropoid apes. The earliest descriptions come from sailors working for the Portuguese in what was then known as the Kingdom of Congo.

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2 Owen's interest in ventricular structures may have been influenced by Ancient Greek beliefs about ventricles as the seat of human intelligence (Gross 1987, 1993).

3 In 1861, influential Dutch anatomists Jacobus Schroeder van der Kolk and Willem Vrolik publicly supported Huxley's observations at the Academy of Amsterdam after a demonstration of an orangutan brain dissection, stating, "la présence des parties contestees y a été universellement reconnue par les anatomistes présents à la séance. Le seul doute qui soit resté se rapporte au pes Hippocampi minor.... A l'état frais l'indice du petit pied d'Hippocampe était plus prononcé que maintenant" (as reported by Huxley, 1863). This quote suggests that preservation artifacts may have obscured the hippocampus minor in some primate specimens previously.

Huxley recounts a story from a 1613 book by an Englishman named "Purchas" of "a kinde of Great Apes, if they might so bee termed, of the height of a man, but twice as bigge in feature of their limmes, with strength proportionable, hairie all over, otherwise like men and women in their whole bodily shape. They lived on such wilde fruits as the trees and woods yielded, and in the night time lodged on the trees" (Huxley 1863). Later: "He differeth not from a man but in his legs; for they have no calfe […] They cannot speake, and have no understanding more than a beast" (Huxley ibid). Purchas distinguishes two types of Great Apes – "greater" and "lesser monsters" – probably referring to gorillas and chimpanzees, respectively.

Three centuries later, man's place among these "monsters" had become an active area of research, at least as far as the brain was concerned. The early 20th century featured a series of complete human cortical maps from a variety of European laboratories (Campbell 1905, Smith 1907, von Economo and Koskinas, 1925, Foerster, 1934, Sarkisov, 1949; reviewed in Zilles and Amunts 2010) but Korbinian Brodmann's cytoarchitectonic map (Brodmann 1909), composed from an unspecified number of human brains, horizontally sectioned and stained with cell-body stain (Zilles and Amunts 2010), gained the most currency and is still the standard reference for human cortical organization today. Influenced by Darwin, Brodmann became interested in evolutionary theory and produced a series of cortical maps of multiple primate species (Brodmann 1905), perhaps the first comprehensive study of comparative primate neuroanatomy.

Brodmann's engagement with evolutionary theory came on multiple fronts – first, his approach combined phylogeny with histology in an attempt to discern evolutionary novel cortical structures from earlier forms (Zilles and Amunts 2010). He also contradicted

Huxley's claims about the extent of similarities between humans and great apes (ibid). By now, natural selection was well accepted in the scientific community, and so the door was open for scientists to investigate the specializations of human brains without problematic implications for human origins. Accordingly, Brodmann's maps indicated important differences in the cytoarchitectonic arrangement of areas. Brodmann identifies 43 discrete areas onto human cortex, but finds that cercopithecoid monkeys (guenons) lack multiple human areas, including 36, 37, 38, 41, 42, and 52 in the temporal region. These areas include portions of the human fusiform gyrus (BA 37) and the anterior-most area of the temporal lobe (temporal pole/ATL; BA 38).

Although Brodmann published maps of an impressive array of primate and non-primate species over the course of a decade (Brodmann 1905, Brodmann 1909, Brodmann 1912), he did not give us a comparatively thorough map of the chimpanzee brain, or any other great ape. During roughly the same period, the Vogts (married couple Cécile and Oskar) also published works on comparative cytoarchitectonics and developed methods of staining myelin within cortical layers, termed myeloarchitectonics (Vogt and Vogt, 1919), while von Economo and Koskinas (1925) created one of the most comprehensive and high resolution cortical map to date. However, von Economo and Koskinas, Smith (Smith 1905), and Sarkisov (Sarkisov et al. 1949), restricted their cartography to human brains. Decades later, Von Bonin and Bailey decided to tackle the problem of understanding human brains in comparative perspective, and highlight the importance of examinations of human, ape, and monkey brains by the same observers (Bailey and von Bonin 1951). Performing these studies over the course of several years (macaque: von Bonin and Bailey 1947; chimpanzee: Bailey et al. 1950, human: Bailey and von Bonin 1951), these workers stressed consistency in

histological technique, with special attention paid to the laminar deformations due to gyrification.

Bailey and von Bonin's maps largely confirmed the parcellations of Brodmann for monkeys; however, important differences are to be found in their account of the human brain. Their 1951 map showed much fewer individual parcels in the cortical regions beyond the primary and secondary sensory and motor areas (regions which Oskar Vogt's mentor Paul Flechsig termed "association centers" (Flechsig 1901), suggesting these later developing regions consisted of a rather homogenous structure[4]. It is possible that artifacts of methodology led to differences between Brodmann and the Bailey/von Bonin maps, or this may be a result of motivated reasoning on either side. Le Gros Clark (1952) speculates that Brodmann was motivated to find more complex organization in humans as a result of our status as "higher primates"; Le Gros Clark himself agreed with this interpretation with a slight modification – he argued that architectonic differentiation becomes sharper as you move up the phylogenetic scale (see Preuss 1983). It is also possible that scientific and political trends in the 40s and 50s pushed von Bonin and Bailey to lump cortical areas together when there was ambiguity. Another possibility is that von Bonin and Bailey, in studying multiple brains unlike previous workers, may have encountered greater inter-individual variability in multimodal cortices and chose to resolve this issue by relaxing their criteria for defining cytoarchitectonic areas. Finally, differences in histological techniques result in different numbers of cortical subdivisions, with myeloarchitectonic techniques resolving a greater number of total cortical areas than Nissl stains (Nieuwenhuys 2013).

[4] Flechsig's study of stages of myelination during development showed his association centers to myelinate the latest of all neocortical regions. Flechsig postulated that association areas handled combinations of sensory information and were responsible for the production of mental imagery and what we might now call "semantic knowledge" (Flechsig 1900; translation in Clarke and O'Malley 1968).

Ultimately, architectonics is more qualitative in some respects than quantitative, and determining where borders begin and end, and indeed if a border is present, ultimately requires a degree of subjectivity. We shall see the issue of "lumping" versus "splitting" come up again, but it is important to note that here it had already become a point of contention in purely structural analyses.

Functional localization within the brain was hotly debated prior to the addition of evolutionary considerations. The phrenologists began to divide areas of the cortex into functional zones starting in the early 19th century, and continued into the early 20th century. Phrenological maps subdivided cranial areas into smaller and smaller subunits, culminating in what might be termed a "hyper-localizationist" approach, with hundreds of physiognomic designations (Wells 1866; reviewed in Finger 1994). French neuroscientist Marie-Jean-Pierre Flourens, on the other hand, used experimental lesions in animals to argue against cortical localization *in toto*. Although he found essential homeostatic functionality in the medulla, Flourens' lesion experiments indicated that birds could recover skills lost immediately after ablation. Further, after having removed both cerebral hemispheres from a pigeon and finding a total lack of sensory response, voluntary movement, or ability to learn, declared that the cerebral hemispheres must contain the functions of perception, volition, and memory. Flourens led the anti-localizationist camp, which supported equipotentiality of cerebral cortex, asserting "the faculty of sensation, perception, and volition is then the same faculty" (Flourens 1824).

It is possible that Flourens' reliance on birds and amphibians shaped his views on cortical localization. Contradicting the anti-localizationists, evidence for cortical localization of function began mounting from case studies of individuals with traumatic brain injury.

Case studies of patients with dramatic behavioral changes, particularly loss of fluent speech, garnered the most attention. One of the early pro-localization advocates was Jean-Baptiste Bouillaud (Bouillaud 1825); however, Bouillaud's explicit references to phrenologist Jean-Baptiste Gall[5] and poor anatomical knowledge worked against him (Head 1926; reviewed in Finger 1994). It is at this point that Paul Broca's study of Monsieur LeBorgne, independently confirming Bouillaud's claim[6] that aphasia was linked to damage in the frontal cortex ("lobes antérieurs," Broca 1861), provided important support for the localizationist camp. In particular, Broca highlights the importance of using gyral and sulcal landmarks ("circonvolutions"), as opposed to cranial lumps and bumps of the phrenologists, for identifying functional territories.

The battle between anti- and pro-localization is important for understanding the history of cortical mapping for several reasons. First, the problem of functional localization required neuroanatomical expertise. Second, the availability of brains of representative mammalian orders influenced conclusions about human brain organization. Lastly, the philosophical viewpoint of the researcher in question influenced the interpretation of the validity of cortical mapping. The rise of cytoarchitectonics at the moment of acceptance of Darwinian evolution lead to a prolific comparative cortical mapping era at the turn of the century. But when observations on structure and function do not neatly corroborate one

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5 Bouillaud's 1825 paper on neuroanatomical localization of language refers to Franz Joseph Gall, the founder of phrenology, directly in the title, which can be translated to: "Clinical research demonstrating that loss of language (*parole*) corresponds to a lesion of anterior brain lobules and confirming the opinion of Monsieur Gall on the seat of the organ of speech."

6 Broca refers to Bouillaud's paper multiple times in his 1861 monograph, while being careful to distance himself from the phrenologists. He does, however, give them credit for their hypothesis that language resides in a frontal area, and praises Bouillaud for both careful clinical and autopsy work as well as for recognizing an important distinction: language production and language comprehension (la faculté de langage articulé vs. la faculté générale du langage).

another, this forces a re-examination of the relationship between the two, and the implications for cortical mapping.

Neuroscientists in the post-Broca period who were interested in functional localization continued to struggle with inconsistent data on the role of lesions. An important point of contention was the role of association cortex in cognition and behavior. The work of Friedrich Goltz and his student Jacques Loeb on dogs with ablated association areas lead these neuroanatomists to conclude that these territories did not house specific cognitive functions, but rather worked in a holistic manner to coordinate behavior (reviewed in Finger, 1994). This intermediate form of localizationism, in which localization was accepted for sensory and motor areas but rejected for association territories, was expanded on by Karl Lashley in the early 20th century using behavioral and histological studies of rats (Lashley and Franz 1917). Part of Lashley's critique of strict localizationalism *sensu* Brodmann, interestingly, was the extraordinary amount of individual variation of cytoarchitectonic areal borders he and his colleague George Clark documented in a study of two *Ateles* specimens, along with a study of a macaque specimen that whose areal organization did not corroborate with previously published cytoarchitectonic maps (Lashley and Clark, 1946). Lashley was so impressed by the level of variability that he declared that for the purposes of functional localization, the '"ideal' architectonic chart is nearly worthless… the charting of areas in terms of poorly defined and variable characters… has contributed nothing to knowledge of cerebral organization" (Lashley and Clark, 1946). This problem of cytoarchitectonic localization lead Lashley to propose a theory of "mass action", in which association areas work in concert and are not divisible into discrete functional units (Lashley, 1929).

Although Lashley's interpretation of association areas and his theory of mass action were extremely influential, Jacobsen and colleagues were coming to quite different conclusions in their well-known study of the behavioral and cognitive abilities of two chimpanzees before and after a series of ablations to frontal association areas (Jacobsen et al., 1935). Jacobsen rejected Lashley's notion of equipotentiality of association areas, at least so far as it is applied to primates, because they observed the bilateral ablation of frontal areas produced specific deficits in short-term memory that were not reproduced with lesions in other parts of cortex. Further, unlike in rats, chimpanzees showed behavioral deficits after ablation, with little recovery of function (Jacobsen 1935).

Debates on the role of association areas in cognition and functional localization continue today. This problem is hard for several reasons. First, association areas, by their nature, synthesize and process inputs from multiple areas, making dissociation of discrete functions challenging. Second, different mammalian models of brain organization vary drastically in the proportion of association cortex to overall cortex size. It is arguable that studying the association cortex of the rat is a fundamentally different enterprise from studying the association areas of highly encephalized primates. Third, inter-individual variation in areal topography introduces noise into any dataset which attempts to produce universal maps of cortical function. Although I disagree with Lashley's assertion that individual variation means that areal organization of association cortices is irrelevant to understanding function, Lashley's frustration was prescient. Biological variation continues to pose problems for modern neuroimaging techniques that usually rely on averaging structural and functional data to produce interpretable scientific results.

Finally, this problem of functional localization in association cortex is a heated and longstanding debate, I believe, because of what is at stake. The ability to localize function has implications for neuroscientists, psychologists, and psychiatrists with regard to who has ultimate epistemological authority over human brains, behavior, and psychology. In the following sections of the introduction, I will introduce a series of research questions that interface with the history of cortical mapping and have implications for understanding the relationship between humans and our primate kin. Reflecting the complex history of the field of evolutionary neuroanatomy, these research questions span local laminar structure to long-range cortical connectivity. We ask: What organizational features of the human brain are responsible for uniquely human cognitive abilities? In order to identify candidate human specializations, we use comparative architectonics and diffusion tractography to interrogate primary and association cortex organization in humans, chimpanzees, and macaques.

HISTORICAL BACKGROUND

PART 2: EVIDENCE FOR APE AND HUMAN SPECIALIZATIONS IN GENICULOSTRIATE PROJECTIONS FROM VGLUT2 IMMUNOHISTOCHEMISTRY

The primary visual cortex (area V1; area 17, and striate cortex) receives its principal thalamic inputs from the lateral geniculate nucleus (LGN). The laminar distribution of LGN projections has been very well characterized in a variety of New and Old World monkeys by conventional tract-tracing studies [reviewed by Casagrande and Kaas, 1994; Preuss, 2004]. In all monkey species examined, the strongest projections are to layer 4C, including sublayer 4Cβ, which is the target of projections from the parvocellular LGN layers, and sublayer 4Cα, which receives input from the magnocellular LGN. Weaker projections from both magnocellular and parvocellular LGN layers target cortical layer 6 [Blasdel and Lund, 1983], while the koniocellular LGN layers project to the blobs in layers 2/3 [Casagrande, 1994; Callaway, 1998] and to layer 1 [Casagrande, 1994]. Also, with the sole exception of the New World owl monkey, *Aotus* [Kaas et al., 1976; Diamond et al., 1985], all the New and Old World monkey species examined to date show a projection from the parvocellular LGN to layer 4A, which in tissue sectioned through the thickness of the cortex appears as a thin, irregular band separate from the broad band of fiber terminals that spans layer 4C. In sections cut parallel or tangential to the cortical surface, this network has a 'honeycomb' appearance, consisting of bands of geniculostriate fibers and terminals surrounding fiber- and terminal-poor territories [Hendrickson, 1985].

In both New and Old World monkeys, the cortical layers targeted by LGN projections stain strongly for a mitochondrial enzyme, cytochrome oxidase (CO), high levels

of which are thought to reflect high levels of synaptic activity in geniculostriate terminals [Wong-Riley, 1979; Carroll and Wong-Riley, 1984; Wong-Riley, 1989, 1994]. Thus, in most monkey species, there is dense CO staining in layers 6, 4C, 4C, 4A, and 1, as well as staining of the periodic blobs in layers 2/3 [Horton and Hubel, 1981; Horton, 1984; Hevner and Wong-Riley, 1990]. Owl monkeys are an exception, again, showing a low level of CO staining in layer 4A, consistent with the lack of geniculate projections to 4A in owl monkeys [Condo and Casagrande, 1990]. These results suggest that CO staining is a useful proxy for localizing geniculostriate projections. However, its utility in this role is somewhat compromised by the fact that CO staining is quite diffuse in the layers it stains and does not label thalamocortical terminal fibers distinctly [Wong-Riley, 1989; Condo and Casagrande, 1990]. In addition, CO staining is reduced by fixation and by postmortem delay (PMD) [Jones et al., 1992; Wong-Riley et al., 1997], which can complicate the interpretation of the reduction or loss of labeling in comparative studies.

Despite its limitations, the value of having a molecular marker for geniculocortical projections is highlighted by studies of the primary visual cortex of the hominid (great ape-human) group of primates. In humans, CO stains layers 6, 4C, and 1, and the blobs in layers 2/3, but (as in owl monkeys) layer 4A does not stain prominently [Horton and Hedley-Whyte, 1984; Wong-Riley et al., 1993; Preuss et al., 1999]. A very similar pattern of staining was reported in a study of apes (9 chimpanzees and 1 orangutan), which specifically noted the lack of a CO-dense layer 4A band in these animals [Preuss et al., 1999]. The low level of CO staining in layer 4A in hominids prompted the suggestion that geniculate projections to layer 4A were reduced in density, or possibly lost, in hominid evolution [Horton and Hedley-Whyte, 1984; Wong-Riley et al., 1993; Preuss et al., 1999] (fig. 1). Great apes and humans also exhibit somewhat denser staining in layer 4B than do monkeys [Horton and Hedley-

Whyte, 1984; Preuss et al., 1999], raising the possibility that geniculate afferents target layer 4B in these species [Preuss and Coleman, 2002].

Evaluating possible differences in geniculostriate projections between monkeys and hominids poses considerable difficulties, because opportunities to directly examine the connectivity of ape and human cortex at the appropriate level of detail are few, owing to restrictions on invasive and terminal research in these species. There appear to be only two studies of connectivity that bear on the status of apes and humans. Tigges and Tigges [1979] used injections of tritiated amino acid to label the geniculostriate projection of a terminally ill chimpanzee, and reported labeling of layer 6 along with a single, broad band of label in layer 4, without a separate, more superficial band of labeling resembling layer 4A. Similarly, Miklossy [1992], examining degenerating axons and terminals in postmortem tissue from humans with lesions of the optic radiation, specifically noted an absence of degeneration in layer 4A.

Given the limitations on direct studies of connectivity in apes and humans, in which the invasive and terminal experimental procedures required for conventional tract-tracing are prohibited, and the fact that CO does not label geniculostriate fibers and terminals distinctly, it is useful to consider additional methods for labeling geniculostriate projections. One candidate is immunolabeling of parvalbumin (PV), which is localized in geniculate projection neurons [Jones and Hendry, 1989] and shows differences in its laminar distribution in humans and macaques similar to those observed with CO, as can be seen by com- paring figures 1 and 2 of Blümcke et al. [1990]. However, PV immunohistochemistry labels many processes and cell bodies intrinsic to V1, in addition to thalamocortical terminals [Blümcke

et al., 1990], complicating the interpretation of species differences in geniculostriate projections.

A more promising approach to revealing geniculostriate terminals is immunohistochemistry for vesicular glutamate transporter 2 (VGLUT2). VGLUTs are transporters that reuptake glutamate into synaptic vesicles. The distributions of two isoforms, VGLUT1 and VGLUT2, have recently been examined in the thalamus and cortex of mammalian species. Both are reported to be expressed in thalamic nuclei [Barroso-Chinea et al., 2007] and thalamocortical projection neurons [Graziano et al., 2008], but other reports indicate that VGLUT1 may be restricted to corticocortical and corticothalamic synapses [Gil et al., 1999; Kaneko and Fujiyama, 2002; Kaneko et al., 2002; Nahmani and Erisir, 2005]. By contrast, there is clear evidence that VGLUT2 is strongly expressed in the primary sensory nuclei of the thalamus, including the LGN, ventral posterior nucleus, and medial geniculate nucleus (ferret LGN [Kawasaki et al., 2004]; rat medial geniculate nucleus [Barrosa-Chinea et al., 2007], and mouse ventral posterior nucleus [Graziano et al., 2008]). Cortical labeling in these studies revealed coarse fibers with prominent en passant terminals located mainly in the middle cortical layers, consistent with the location and morphology of primary sensory thalamocortical fibers [Nahmani and Erisir, 2005; Graziano et al., 2008; Hackett and de la Mothe, 2009]. In a direct validation of VGLUT2 as a marker for geniculostriate projections, Nahmani and Erisir [2005] injected anterograde tracer in the LGN of ferrets and showed that labeled fibers in striate cortex were immunostained for VGLUT2. Further evidence for geniculostriate localization of VGLUT2 comes from studies of mRNA expression, showing VGLUT2 expression in thalamic nuclei (galago LGN [Balaram et al., 2011] and owl monkey medial geniculate nucleus and LGN [Hackett et al., 2011]), along with expression in the

corresponding primary sensory cortical areas (mouse [Graziano et al., 2008] and macaque [Hackett and de la Mothe, 2009]).

Given the strong evidence that immunohistochemistry for VGLUT2 selectively labels geniculostriate fibers, we compared the laminar distribution of VGLUT2 immunoreactivity of primary visual cortex in humans and a variety of nonhuman primate species. The hominid primates (humans and great apes) in our sample showed much less terminal-like labeling in layer 4A, consistent with previous work suggesting that the LGN projections to this layer were reduced or lost early in hominid evolution. This reduction or loss of projections to 4A appears to constitute a hominid specialization (apomorphy).

HISTORICAL BACKGROUND

PART 3: ORGANIZATION OF EXTRASTRIATE AREAS AND ADJACENT TEMPORAL CORTEX IN CHIMPANZEES COMPARED TO HUMANS AND MACAQUES

One of the longstanding questions in evolutionary neuroscience is whether human brain expansion has been uniform across neocortical regions, or whether expansion was accompanied by differential expansion of association areas (reviewed in Schoenemann 2006). Morphometric, cytoarchitectonic, and imaging studies suggest greater expansion of association areas relative to primary areas in humans, and to a lesser degree, chimpanzees, when compared to Old World monkeys (Schoenemann 1997; Glasser and Van Essen, 2011; Passingham et al., 2014; Rilling 2006; Rilling and Seligman, 2002; reviewed in Orban et al., 2004; and Preuss 2011). Less is known, however, about how association areas have been modified during this expansion. Comparable cortical maps of humans, chimpanzees, and Old World monkeys are necessary to understand what features of human brain organization are uniquely human, and which are shared with our great ape relatives. Assembling comparative cortical maps has been challenging because of the lack of neuroscientific methods that are applicable across species, and thus, directly comparable; currently, the most frequently cited cortical maps are over a century old (Brodmann, 1905). The advent of neuroimaging technologies, especially structural magnetic resonance (MR) imaging, including diffusion tensor imaging (DTI), permits direct comparison of cortical organization across humans, chimpanzees, and macaques for the first time.

Given the rich amount of data on visual cortical organization in macaques, and the rapidly expanding dataset in humans, it is reasonable to begin an examination of evolutionary

changes of cortical expansion on the visual areas and adjacent temporal cortices in chimpanzees. This will permit us to determine whether chimpanzees are human-like, macaque-like, something intermediate, or something quite different.

There are important differences in the organization of temporal cortex between hominoids and macaques. Two differences are due to modifications in cortical folding patterns - macaques possess only a single, well-developed temporal sulcus, whereas humans and chimpanzees possess both an inferior and superior temporal sulcus. Macaques also lack a fusiform gyrus, which is found on the ventral surface of the temporal lobe in chimpanzees and humans. There is also evidence for reorganization of the spatial relationships of visual cortical areas in the primate lineage. Of the extrastriate areas, area MT and its associated regions are of special interest because they have been well documented in macaques and humans (e.g., Allman and Kaas, 1971; Dubner and Zeki, 1971; Tootell and Taylor, 1995), and also because they show important inter-species differences in localization. Human MT+ has shifted posteriorly and inferiorly when compared to macaques (Ungerleider and Desimone, 1986; Watson et al., 1993), suggesting cortical expansion of higher-order association areas in humans may have relatively displaced MT+. In order to better understand human specializations, the location of chimpanzee MT+ has been regarded as crucial, as it can help us understand whether the expansion of multimodal association areas is disproportionately greater in humans or if both humans and chimpanzees share similar trends in multimodal cortex expansion.

Certain features of extrastriate organization are shared by humans and macaques, and have remained stable in the face of the posterior and inferior shifts in the location of striate and extrastriate cortex in humans (Orban et al., 2004). In both humans and macaques, a

band of foveal representation extends anteriorly from the foveal representation of V1, extending through V2, V3, V4, (and possibly the LO areas in humans), and finally into the MT complex (MT+), which consists of the middle temporal area (MT), the middle superior temporal area (MST), and the area of the fundus of the superior temporal sulcus (FST) (e.g., Zeki, 1978; Gatass and Gross, 1981; DeYoe et al., 1996; Tootell and Hadjikhani, 2001; Van Essen et al., 2001; Malach et al., 2002; Brewer et al., 2002; Amano et al., 2009; reviewed in Orban et al., 2004). This band of foveal representation, and the bands of lower and upper-field parafoveal representation that flank it, are among the key features that have been used to identify homologous visual areas across primates, including humans.

MT+ has several diagnostic characteristics which set it apart from neighboring cortical regions, including relatively dense myelination, as well as dual inputs from primary visual cortex and the ventral intraparietal cortex, specifically the ventral and/or lateral intraparietal sulcal areas (VIP/LIP; Ungerleider and Desimone 1986; Blatt et al., 1990; Maunsell and Van Essen 1983; Markov et al., 2012). Recent imaging-derived myeloarchitecture data from Glasser and colleagues (Glasser and Van Essen, 2011; Glasser et al., 2013a) suggests that chimpanzee MT+ is in a macaque-like position (fig. 2), although the connections of chimpanzee MT+ have yet to be examined.

Here, we use diffusion tractography to characterize the organization of chimpanzee and human extrastriate cortex. As a relatively new methodology for understanding brain connectivity, diffusion-based tractography has been examined in conjunction with more traditional histological methods in an effort to determine the precision and accuracy of diffusion tractography in reconstructing anatomical connections. These studies are essential

for validating conclusions drawn from our analyses, as well as for obtaining a reliable understanding of limitations of the technique and best practices for analysis.

Comparisons between neuron tracing data and diffusion tractography results have been performed in a number of species, including mouse (Chen et al., 2015; Keifer et al., 2015), macaque (Peled et al., 2005; Dauguet et al., 2007; Jbabdi et al., 2013), squirrel monkey (Gao et al., 2013), pig (Dyrby et al., 2007), and human (Sorenson et al., 2005; Seehaus et al., 2013). Histological stains have been compared to DTI data in owl monkey (Choe et al., 2012); rat (Leergaard et al., 2010) and humans (Hansen et al., 2010).

Histological staining techniques have provided validation for diffusion MRI in several species. Hansen and colleagues (2011) found an 89% correspondance between DTI tractography-derived tracts and Nissl and myelin stain-based histology in human spinal cord samples. In rats, fiber orientation distributions were quantified using ex vivo dMRI data, and compared to manual recordings of myelin stained fiber orientations (Leergaard et al., 2010). These authors observed that fiber orientation distributions, as estimated from dMRI, were accurate to myelin stain data, even in areas with crossing fibers. On a larger scale, Choe and colleagues (2012) also used myelin staining in an attempt to investigate the relationship between DTI tractography and white matter structure *in vivo*. These authors observed that agreement between myelin staining and tractography with regard to the major eigenvector of the tensor was especially accurate in areas of high fiber coherence (e.g., white matter bundles) in owl monkey.

In postmortem human tissue, DTI tractography replicated carbocyanine tracer data with sensitivity and specificity rates at 80% (Seehaus et al., 2013). In other words, DTI tracts replicated traditional tracer-defined pathways with regard to both true positives (sensitivity)

and true negatives (specificity) with 80% fidelity. These data provide validation for the use of diffusion tractography in humans, as well as important estimates of the upper and lower bounds of confidence for these imaging based reconstructions. The efficacy of diffusion-based tractography to reconstruct cortico-cortical pathways was examined using a "truth table" of known cortico-cortical connections in humans based on classical methods (Sorenson et al., 2005). Overall, streamline-based connectivity methods (4 were tested) successfully reproduced known cortico-cortical connections in humans, with the exception of divergent tracts.

Diffusion-based tractography has also been validated in new and old world monkey species. In macaques, diffusion-based tractography was compared to a 3D fiber pathway reconstruction based on tissue sectioned after WGA-HRP injections (Dauguet et al., 2006). The authors report that visually, diffusion-derived tracts were well corroborated by histology data. Discrepancies included a failure of DTI tracts to reach cortex reliably, as well as early termination of tracts when crossing fibers were encountered. A later study by Dauguet and co-workers (2007) observed limitations of DTI at remote locations from seeds in the macaque brain. The chosen level of threshold for FA values also played a role, with thresholds greater than 0.25 causing a decline in accuracy. Streamlines are forced to stop at the voxels which are at the FA threshold level or lower. More conservative restrictions, in this case, caused truncations to streamline pathways that were anatomically inaccurate.

The validity of deterministic and probabilistic tractography was evaluated by comparing these methods in *ex vivo* and *in vivo* macaque brains to WGA-HRP staining. Seeds from somatosensory cortex gray matter were tracked into white matter, and corroborated WGA-HRP staining. Gao and colleagues (2013) also examined the validity of both

deterministic and probabilistic tractography, this time in squirrel monkey using biotinylated dextram amine (BDA) tracer injections. They found both tractography methods to accurately reproduce BDA tracer pathways in primary motor cortex, however, correlations between the two techniques began to wane as cortical parcellations became finer.

Keifer and co-workers (2015) compared probabilistic tractography of mouse medial geniculate nucleus in postmortem brains to anterograde tracing. Probabilistic tractography successfully tracked major fasciculi known to contain MGN projections, including the internal capsule and superior cerebral peduncle, as well as projections to midbrain, thalamus, and hypothalamus, which are composed of less coherent mixtures of gray and white matter. The authors note that at lower thresholds, probabilistic tractography produced more diffuse projections to these areas than were identified with tracer methods, however, more stringent thresholds were able to ameliorate some, if not all of the erroneous connections. These data suggest that while DTI tractography may produce some false positives in territories where crossing fibers are present, that overall, this method effectively and reliably corroborates established tract tracing methods.

A connectome-level study, also in mice, provides support for diffusion tractography. The reliability of DTI for large-scale connectome mapping in mice by comparing a DTI tractography-based connectome with a meso-scale connectome constructed from neuron tracing data (Chen et al., 2013). These workers produced a similar conclusion comparing DTI tractography and neuron tracing in mouse brain connectome reconstruction – parcellation parameters affected validity. However, unlike Seehaus and colleagues (2012) these authors' findings suggest a trade-off between sensitivity and specificity. With optimized parameters based on tracer data, these authors were able to produce DTI tractography

results with 90% corroboration with tracer data. As in Dauguet et al. (2007), Chen and colleagues find tweaking the FA threshold to a lower level (0.1) produces the most accurate results. Like Gao and colleagues, parcellation size was also an important predictor of accuracy.

Another important variable for tractography validation is the type of tissue that the tracts are passing through. White matter, gray matter, and subcortical structures present with different FA values and may pose problems for diffusion tractography due to partial volume effects. Dyrby and co-workers (2007) investigated the ability of probabilistic tractography to track accurate cortico-cortical, corticonigral and corticothalamic fiber tracts in the porcine brain. When compared to BDA and paramagnetic contrast agent manganese, probabilistic tractography produced plausible fiber reconstructions. However, DTI tracts were observed to pass through subcortical structures in some cases, as opposed to terminating in them, as predicted by BDA injections. The authors suspect this may be due to partial volume effects, which could be potentially resolved with higher resolution (in this study, voxels = 0.7 mm). Strong corroboration of diffusion tractography for cortico-cortical connections with chemical tracers was also observed by Jbabdi et al. (2013). These data suggest diffusion tractography is an appropriate and reasonably accurate method for reconstructing cortico-cortical connectivity in humans, even those which split into multiple divergent paths.

Finally, a comprehensive comparison of in vivo diffusion weighted data in macaques with two macaque connectome datasets derived from collated tract-tracing experiments found robust agreement between the two methods (Van den Heuvel et al., 2015). This study focused on large-scale macroconnectomics, using the number of reconstructed fiber streamlines (NOS) as a metric of cortico-cortical connectivity. NOS from diffusion-based

tractography positively correlated with both macaque tract-tracing-derived datasets, strongly supporting the use of diffusion tractography as a proxy for tract-tracing in connectome studies.

In summary, traditional tract-tracing methods and histological approaches have consistently supported the validity of diffusion-based tractography. Across species, it has been observed that FA threshold, coarseness of parcellation, DW-MRI resolution, and lower FA values in gray matter are important variables to consider when setting tractography parameters. Low FA values may be a source of false negatives, while crossing fibers and low statistical thresholds in probabilistic tractography may be a source of false positives. Overall, diffusion-based tractography produces reasonable and reliable reconstructions of older neuron tracing and histological methods, when the risks for type 1 and type 2 errors are acknowledged.

The aim of this study is twofold: first, to determine whether DTI data can be effectively used to reliably track connections between cortical areas in humans and nonhuman primates; and second, to localize the major extrastriate visual areas in humans and chimpanzees. More detailed information on the organization of extrastriate areas in chimpanzees will provide insight into how chimpanzee and human cortical organization changed since our evolutionary divergence approximately 6-8 mya (fig. 3). Based mainly on the recent comparative myeloarchitectonic studies of Glasser et al. (2011, 2013; see fig. 2), we expect a more dramatic enlargement and reorganization of temporal cortex in humans than in chimpanzees, and thus predict that extrastriate visual areas in chimpanzees will reflect a more macaque-like organization, supporting multimodal association cortical expansion as a human-unique specialization.

HISTORICAL BACKGROUND

PART 4: TEMPORAL ASSOCIATION AREAS IN HOMINOIDS – STRUCTURE AND FUNCTION

Overview

There is evidence for structural features that are unique to the human temporal lobe. Humans and other great apes do share important similarities with regards to temporal lobe anatomy (lateralization of Wernicke's area in chimpanzees; Gannon et al., 1998) and differences (non-allometric scaling of human brain; Rilling, 2006; Schoenemann, 1997; specifically, a larger than predicted human temporal lobe (Semendeferi and Damasio, 2000; Rilling and Seligman, 2002).

Visual inspection of the temporal lobe across species reveals that macaques lack a deep inferior temporal sulcus and so lack the discrete middle temporal gyrus present in humans and chimpanzees. Further, the superior temporal sulcus is shallower in chimpanzees than in humans, suggesting a trend of expansion of the middle temporal cortex in the hominid lineage. Recent work has indicated that compared to macaques, humans display an expansion of anterior temporal cortex and a posterior displacement of higher-order visual areas (Orban et al., 2004), posterior displacement of area visual motion area MT (Ungerleider and Desimone, 1986; Watson et al., 1993; Glasser and Van Essen, 2011); expansion of intervening cortical areas between auditory core and area MT (Orban et al., 2004); and expansion of multimodal association cortex in the superior temporal cortex (Morosan et al., 2005). Compared to macaques, the primary auditory cortex of humans and chimpanzees appears to have been displaced posteriorly, and occupies a smaller proportion of cortical surface area in the superior temporal plane (Hackett et al., 2001). Moving to the

ventral aspect of the temporal lobe, he fusiform gyrus, which in humans, houses the fusiform facial area (FFA), is found in humans and chimpanzees but not macaques (Nasr et al., 2011; Weiner and Zilles, 2015). Taken together, these data strongly suggest that there are important differences in the structure of the temporal lobe in humans, chimpanzees, and macaques.

The anterior temporal lobe of chimpanzees and especially humans also shows less cortical myelin density than macaques, indicative of association cortex (Glasser et al., 2011), supporting the notion that hominid evolution has featured expansion of higher-order association cortex relative to sensory cortex (Preuss, 2011). Considering macaques as our outgroup, the evidence here suggests that the temporal lobe of humans has expanded and rewired over the course of evolution, and that the association regions within this lobe have disproportionately expanded with respect to sensory regions.

The significance of association cortices

Flechsig (1901) originated the term "association" to describe later-myelinating cortical regions; the term referring to the co-occurrence of projections from multiple primary sensory cortices. Morphometric, cytoarchitectonic, and imaging studies suggest greater expansion of association areas relative to primary areas in humans, and to a lesser degree, chimpanzees, when compared to Old World monkeys (Schoenemann 1997; Glasser et al., 2011; Passingham et al., 2014; Rilling 2006; Rilling and Seligman, 2002; reviewed in Orban et al., 2004 and Preuss 2011). Less is known, however, about how association areas have been modified during this expansion. Building comparative cortical maps has been challenging because of the lack of neuroscientific methods that are applicable across species, and thus, directly comparable; currently, the most frequently cited cortical maps are over a

century old (Brodmann, 1905). The advent of neuroimaging technologies, especially structural magnetic resonance (MR) imaging and diffusion tensor imaging (DTI) offers a new opportunity to compare cortical organization across humans, chimpanzees, and macaques. Comparable cortical maps of humans, chimpanzees, and Old World monkeys are necessary to understand what features of human brain organization are uniquely human, and which are shared with our great ape relatives.

Both structural and functional data suggest that humans are using the expanded cortical regions in the temporal lobe to perform novel, human-specific (or hominoid-specific) functions such as language, configural processing for object and face recognition, theory of mind tasks, and understanding the identity and functional properties of tools: broadly these may be referred to as "semantic representations". The construction of semantic or conceptual representations arises from the synthesis of information from multiple sensory modalities. This process of integration occurs in so-called association cortex. From a network perspective, association cortex is composed of nodes of convergence, or cortical "hubs" (Mesulam 1994, 1998). With regard to the processing of conceptual information, two candidate semantic hubs have been discussed in the literature: the anterior temporal lobe (Lambon Ralph et al., 2010; reviewed in Simmons and Martin, 2009) and the middle temporal gyrus (Turken and Dronkers, 2011; reviewed in Martin, 2007). In addition to forming semantic representations, these hubs may also serve as information gateways which gather local information and forward it across long-distance connections, thereby contributing to larger-scale cortical networks (Bassett and Bullmore, 2006). Consistent with this interpretation, macaque tract-tracing data indicate that association cortex is characterized by long-distance connections (Goldman-Rakic, 1988); and human resting state fMRI data suggest that hubs in association areas feature greater long-

distance connectivity and less local internodal connectivity, unlike primary sensory cortex (Achard et al., 2006; Sporns et al., 2007).

If changes to the structure of the temporal lobe occurred in human evolution, what roles might these changes play in function? Functional magnetic resonance imaging (fMRI) work and studies of individuals with localized atrophy or lesions have illuminated the functional properties of these expanded cortical regions. In the following section, I will examine three temporal association areas – middle temporal gyrus, fusiform gyrus, and anterior temporal lobe – and discuss their functional role in human cognition.

Middle Temporal Gyrus

A large portion of the literature on human MTG refers to the posterior half of the gyrus, which is well documented in humans as an important language center. Evidence has been mounting for the role of posterior MTG (pMTG) in mapping sounds to meanings (Hickok and Poeppel, 2004, 2007), perhaps being essential to semantic comprehension, based on data from patients with lesions in that region (Dronkers et al., 2004; Bates et al., 2003), potentially so crucial to language production and comprehension as to constitute a "semantic hub" (Turken and Dronkers 2011). Posterior MTG in humans has been implicated in naming and retrieving information about tools (Martin et al., 1996; Mummery et al., 1998; Chao et al., 1999; Martin and Chao, 2001), generating action words (Wise et al., 1991; Martin et al., 1995; Fiez et al., 1996) and further, has been suggested to be site of storing information about non-biological object motion more generally (Martin et al., 1996), including tools (Ramayya et al., 2010). Chao and colleagues (1999) have speculated that this is possibly related to its anatomical position, close to visual motion processing areas like the MT+ complex.

The anterior MTG (aMTG) is less well-studied, but available literature suggests that in humans, this territory is also part of a multimodal association area (Binder et al., 2009) involved in a semantic processing network (Copland et al., 2003, Schwartz et al., 2009; Butler et al., 2014). Human imaging studies have implicated aMTG in lexical decision-making, for example, reading words with atypical spelling-to-sound correspondences, or "exception words" (Wilson et al., 2012), visual word recognition (Pammer et al., 2004) and spoken word recognition (Roxbury et al., 2014). In one of the few studies examining the different role of anterior vs. posterior MTG, Vandenberghe et al. (1996) found aMTG had stronger activation in semantic tasks involving processing images of words rather than pictures when compared to pMTG; in contrast, Visser and co-workers (2012) found pMTG specialized for semantic processing of words, while aMTG responds equivalently to both words and pictures. Both findings are consistent with a recent meta-analysis suggesting the full anterior-posterior axis of the MTG acts as a multimodal convergence zone (Binder and Desai, 2011). However, unlike pMTG, there is less evidence for aMTG as handling semantic and action knowledge related to tools. Anterior MTG appears to be recruited for recognition of famous faces (Leveroni et al., 2000) and proper names of famous individuals (Gorno-Tempini et al., 1998), tasks that are may be considered as tapping into semantic "meaningfulness" (Binder et al., 2009). The latter two findings are similar to functions that have been localized in the ATL broadly, perhaps reflecting conflicting interpretations regarding the location and extent of the ATL as it encroaches posteriorly (reviewed in Bonner and Price, 2013).

Fusiform Gyrus

Of the face-responsive cortical areas in humans, the fusiform gyrus is the most robust in its face-specific activation (Kanwisher et al., 1997), with fMRI activations for faces over both

scenes (Epstein and Kanwisher, 1999) and objects (Allison et al., 1994; Kanwisher et al., 1999). The face-selective activation of the FG is more reliably observed in the right hemisphere of humans (Kanwisher et al., 1997; McCarthy et al., 1997). In both hemispheres, this territory, termed the fusiform face area (FFA) has been localized in the middle portion of FG (Allison et al., 1994, Saygin et al., 2012), just anterior to areas responsible for color perception (Clarke and Miklossy, 1990; Allison et al., 1993). Evidence for dissociation of whole face versus face component processing has been observed, with whole face processing correlated with activation in the right FG (Rhodes 1993; Hillger and Koenig, 1991), and left FG correlated with the processing of face components (Rossion et al., 2000).

The processing of face components as a "whole", whose recognition depends on the relative spatial relationship of component facial features, is termed configural face processing. Configural face processing has been argued to also be a part of chimpanzees' cognitive repertoire, but not macaques (Parr et al., 1998; Parr et al., 2006; Parr et al., 2008) and a chimpanzee homolog of FFA in the FG has been localized using PET (Parr et al., 2009). Face recognition in the FFA is dependent on expertise (Gauthier et al., 1999) and affective judgments (Pizzagalli et al., 2002).

Other territories within FG have been implicated in expertise in object recognition beyond face processing. Left FG, unlike the right hemisphere, is implicated in phonological decoding (Dietz et al., 2005). Grapheme to phoneme sound conversion, as occurs in reading, has been correlated with activation of a portion of FG posterior and medial to the visual word form area (Dietz et al., 2005). The left FG also houses the visual word form area (VWFA) in the middle portion of the gyrus, approximately at BA 37 (Cohen et al., 2000; McCandliss et al., 2003). VWFA has shown activation for both words and pictures. Unlike

the phonological decoding processing of left posterior FG, VWFA responds more specifically to the abstract, orthographic properties of words (Polk and Farah, 2003; Binder et al., 2006). Starrfelt and Gerlach (2007) propose the VWFA is specialized for letter and word recognition as a configural processing task. The exact nature of the function of the VWFA with regard to reading and word processing – i.e., is it operating at the lexical or pre-lexical level – is still up for debate (see Devlin et al., 2006). However, it seems clear that VWFA plays a role that interfaces with both auditory and visual sensory modalities, as well as abstracted or "supermodal" representations.

Within the FFA, it is possible that subregions may be distinguishable as imaging techniques become more sophisticated. Localization of the FFA with evoked potentials had previously demonstrated significant individual variation in the location of activation within the FG (Allison et al., 1994). A region of the right FG in a similar location to FFA which is selective for bodies has been identified (Schwarziose et al., 2005; Peelen and Downing, 2005). This "fusiform body area" (FBA) overlapped in territory in most individuals examined by Schwarziose and colleagues (2005), but was distinguishable as a cortical area in its own right, anterior and lateral to FFA. Saygin and colleagues (2012), using a novel structure-function connectivity fingerprint approach, found that for many subjects, two adjacent but discrete areas of face-selective activation were discernable within FG.

In summary, the fusiform gyrus houses the FFA, the VWFA, and the more recently observed FBA. The FFA is responsible for expertise-based recognition and configural face processing in humans, with the latter being right-lateralized. Evidence for configural face processing abilities in chimpanzees but not macaques, along with the lack of FG as a discrete

convolution in old world monkeys, suggests FG and functional area FFA may be hominoid evolutionary specializations.

Anterior Temporal Lobe

The ATL, a large swathe of cortex encompassing the temporal pole, is a multimodal association center that plays an important role in both semantic memory and affective cognition in humans. This encompasses language functions, including production and comprehension of spoken and written words and pictures (Coccia et al., 2004; Pobric et al., 2007), taste recognition (Small et al., 1997), olfactory memory (Rausch et al., 1977; Eskenazi et al., 1986) stimulus-invariant perception of emotional facial expressions (Schmolck and Squire, 2001; Cancelliere and Kertesz, 1990) generation of emotions in response to visual cues (Reiman et al., 1997), a storage site for unique, socially relevant entities, such as familiar people and landmarks (Damasio et al., 2004; Frith 2007; Kriegeskorte et al., 2007); comprehension of social concepts (Zahn et al., 2007; Zahn et al., 2009; Ross and Olson, 2010), emotional memory retrieval (Dolan et al., 2000) and coherent conceptual categorization of objects (Rogers et al., 2004; Lambon Ralph et al., 2010). The conceptual processing which occurs in the ATL has been argued to be transmodal, or perhaps amodal (Pobric et al., 2010), in that conceptual information is computed regardless of the sensory modality of the stimulus, as auditory, visual motion, olfactory, and gustatory processing streams converge at the temporal pole (Binder and Desai, 2011). On this view, the ATL constitutes a modality-invariant semantic hub (Lambon Ralph et al., 2010; Visser et al., 2012). Others have argued that the ATL binds multimodal inputs with visceral emotional responses while maintaining segregation of perceptual modalities (Olson et al., 2007). These sometimes conflicting reports can be categorized into three separate accounts of the role of

the ATL in semantic memory: 1) as a supramodal/transmodal/amodal semantic hub; 2) as a storage site for unique entities (e.g., famous names and faces); and 3) as a center for social conceptual knowledge (Simmons and Martin 2009; Simmons et al., 2009).

Critical data on the function of ATL in humans has come from the study of patients with semantic dementia or primary progressive aphasia, wherein progressive atrophy of the temporal poles bilaterally produces a unique deficit in core semantic knowledge that encompasses both receptive and expressive tasks (Lambon Ralph and Patterson, 2008). Lambon Ralph and Patterson (2008) observed undergeneralization and overgeneralization of concept in these patients, and suggest that the ATL plays a crucial role in binding perceptual features across stimulus categories to form modality-invariant conceptual information that links back to modality specific association cortices.

A direct comparison of ATL function and structure in humans and macaques is challenging, in that a lack of anatomical data makes it difficult to identify homologous territories. In a review of anatomical, lesion, and single-cell recording studies in macaques, Nakamura and Kubota (1996) argue for a TP homologue in anterior ventromedial temporal cortex (BA 38), with functions in object recognition and memory. Olson and colleagues (2007), in their review of neuroimaging studies of the temporal pole in macaques, argue that visual and auditory processing streams coexist in the pole but do not converge, as they do in humans. Instead, visual activations were concentrated in ventral TP, and auditory activations in dorsal TP. Although the TP and ATL are may be used nearly interchangeably in the human literature (e.g., Patterson et al., 2007), some authors have used the term ATL to encompass areas not traditionally included in the TP region, such as anterior portions of the MTG, STG, FG, and parahippocampal gyri (Bonner and Price, 2013).

Human ATL and TP have been implicated in the comprehension and expression of social knowledge, including theory of mind (Gallagher and Frith, 2003, but see Shaw et al., 2007). Imaging studies in humans support the role of TP in inferring deceit (Grezes et al., 2004), ethical decision-making (Heekeren et al., 2003), moral social judgements (Moll et al., 2001; Moll et al., 2002) Olson and colleagues (2012) propose, based partially on a review of human and non-human primate studies, that connectivity with the amygdala and orbitofrontal areas underpins this function, which is arguably a form of semantic or conceptual knowledge processing that privileges emotionally salient information. Another model, based on PET data in humans, includes ATL as part of an extensive neural network with other cortical regions, including medial and superior prefrontal cortices and cingulate cortices (Goel et al., 1995; Calarge et al., 2003). Evidence for vocal and facial identity discrimination extending into anterior portions of macaque STS and IT cortex (Perrett et al., 1992) suggests that a putative macaque TP homologue also plays a role in social knowledge.

The relevance of the specific portions of ATL to cognition is unclear, as few studies in humans have managed to subdivide the ATL into functional units. However, the superior ATL has been linked to processing of abstract social concepts (Zahn et al., 2007), in contrast to inferior ATL, which has been found to be a hotspot for semantic memory (Visser et al., 2010).

White Matter Fasciculi in the Human Temporal Lobe

Connectivity between distant association areas relies on fasciculi - large, coherent fiber bundles that travel long distances through white matter. These structures have been studied traditionally with blunt dissection and more recently via structural MR imaging, including diffusion tensor imaging and diffusion spectrum imaging. In the next section, I will

discuss the structure and known functions of fasciculi that traverse the temporal lobe in humans, with some discussion of differences with macaques.

Arcuate Fasciculus

The arcuate is unique among major fasciculi as having important connections across frontal, parietal, and temporal association cortices, as it arches around the Sylvian fissure. In humans, arcuate terminations reach STG, MTG, and ITG in the temporal lobe, linking them to Broca's area (BA 45 and BA44) as well as ventral premotor cortex and middle frontal gyrus (Glasser and Rilling, 2008; Powell et al., 2006). The current conception of the arcuate has been heavily influenced by Norman Geschwind's model (Geschwind, 1970; Dick and Tremblay, 2012), which localized the arcuate as the major connection between Broca and Wernicke's areas. Disruption of the left arcuate has been implicated in the classical conception of aphasia as a disconnection syndrome (Geschwind, 1970) resulting in conduction aphasia (impairment of repetition function; Damasio and Damasio, 1980; Catani and ffytche 2005; but see Bernal and Ardila 2009). Because of the importance of the arcuate in speech production (e.g., Marchina et al., 2011; Yeatman et al., 2011), it is sometimes termed the "phonological pathway" (Duffau, 2008). Leftward asymmetry of the arcuate in humans (Nucifora et al., 2005) supports the model of the arcuate as crucial for human language function. Less well studied, the right arcuate may play a role in processing music, particularly vocal-based music (Halwani et al., 2011).

The first descriptions of the arcuate/SLF describe a common bundle as either the arcuate (Meynert, 1885) or as the SLF/arcuate interchangeably (Dejerine, 1895; Wernicke 1897). Dejerine's locus of temporal terminations changed from 1895 to 1901, initially at the temporal pole; by 1901 he shortened the tract to terminate in Wernicke's area/posterior

STG, perhaps reflecting an increased attention to the role of Wernicke's area at the time (Dick and Tremblay 2012). Later work by Geschwind (1965, 1970) further emphasized a more posterior termination and a move from SLF terminology to "arcuate". Of the major fiber bundles in primates, the arcuate has arguably been studied the most rigorously in a comparative light, where the prominent temporal lobe projections of the arcuate were found in humans but not macaques or chimpanzees (Rilling et al., 2008). These data also suggest the chimpanzee arcuate may also have expansions into temporal lobe, to a lesser extent than in humans (Rilling et al., 2008).

The SLF/AF controversy is further complicated by the rather recent three-subcomponent model of SLF, derived mainly from work in macaques, and a fourth subcomponent, the AF (reviewed in Dick and Tremblay, 2012). Currently, there is no clear consensus on the status of the arcuate and the superior longitudinal fasciculus III. Turken and Dronkers (2011) recognize two distinct segments – the posterior segment, connecting temporal cortices with posterior parietal cortex, and the anterior segment, connecting prefrontal cortices with posterior parietal/occipitoparietal cortices.

Cingulum

The cingulum is a medial associative bundle that runs along the cingulate gyrus, medial to the corpus callosum, with the longest fibers extending from the orbitofrontal cortex to the anterior medial temporal lobe by way of the parahippocampal gyrus (Catani and Thiebaut de Schotten, 2008). Like the arcuate, it also bridges frontal, parietal, occipital, and temporal cortices, although perhaps less extensively than the arcuate.

The cingulum is implicated in emotional processing by way of its connectivity to the limbic system, and is involved in memory, emotions, and attention (Rudrauf et al., 2008; Catani, 2006).

Inferior Fronto-Occipital Fasciculus (IFOF)

The IFOF and the ILF have historically been difficult to disambiguate – and perhaps the two bundles are not fully separate. Early on, Curran (1909) located the IFOF superior to and distinct from the ILF. Later, Davis (1921) used blunt dissection to argue that no independent ILF system is present and that the ILF reported by Burdach (1822) and Sachs (1892) is actually the IFOF. Davis also preferred that the IFOF/ILF system be referred to as the FOF (which originally denoted non-canonical longitudinal pathways lateral to the corpus callosum in specimens with agenesis of the corpus callosum). Further, Davis' FOF system includes ventral connectivity to the frontal lobes, a fiber tract in close apposition to and medial/superior to the uncinate fasciculus. Davis' FOF ventral pathway is distinct from the external capsule. Further complicating things, some anatomists refer to the IFOF as the IOFF (Kier et al., 2004; Turken and Dronkers 2011).

Catani (2002, 2008) tracks the IFOF from two inputs, the posterior parietal and the occipital lobes, to the length of the temporal lobe and extending ventrally through the extreme/external capsule to both orbitofrontal and lateral prefrontal cortices, dorsal to the uncinate. Menjot de Champfleur et al. (2012) localize IFOF medial to ILF with an additional ventral extension. Schmahmann and Pandya (2007), however, argue that the IFOF is not a legitimate and distinct fiber bundle.

The function of the IFOF includes reading (Epelbaum et al., 2008; Catani and Mesulam, 2008) attention (Doricchi et al., 2008) and visual processing (Fox et al., 2008;

Rudrauf et al., 2008). DeWitt-Hamer et al. (2011) were able to elicit semantic paraphasias when stimulating the IFOF in patients during surgical procedures for glioma in the left dominant hemisphere. Catani (2007) has argued that the IFOF is unique to the human brain, which may explain some of the contention regarding its status as a distinct bundle. Given the expansion of parietal, prefrontal, and temporal association cortices in humans, it is reasonable to hypothesize that important anatomical modifications to long-distance connectivity have occurred.

Inferior Longitudinal Fasciculus (ILF)

The first description of the ILF comes from Burdach (1822), and included ventral projections via the uncinate and extreme capsule system. Sachs (1892) later described what became a more common description/conceptualization of the ILF, as a fiber bundle system that travels along the MTG and STG. Dejerine and Dejerine-Klumpke's (1895) description is similar to both Burdach and Sachs, in that it also continues ventrally, however Dejerine and Dejerine-Klumpke included the anterior commissure fibers as part of this system. Other concurrent descriptions of the ILF system describe it as a thalamocortical projection to the occipital lobe (Flechsig 1896; Niessl-Mayendorf 1903).

In humans, Catani and Thiebaut de Schotten (2008) describe the ILF as a ventral associative bundle connecting the occipital and temporal lobes, coursing through the middle temporal gyrus, with short fibers extending to the amygdala and hippocampus (Catani et al., 2003). Unlike older descriptions, Catani and Thiebaut de Schotten (2008) report no ventral projections in ILF, unlike the IFOF. These workers acknowledge the difficulty in distinguishing ILF with IFOF fibers in FA color map space. Menjot de Champfleur (2012) also localized ILF lateral to IFOF with no ventral extension in humans. Schmahmann et al.

(2007) recognize the ILF as coursing through the ITG in macaque, using a combination of diffusion spectrum imaging and autoradiography data.

The functional significance of the ILF in humans includes face recognition (Fox et al., 2008), visual perception (ffytche 2008; ffytche et al., 2010), reading (Epelbaum et al., 2008) and language (Catani and Mesulam 2008).

Middle/Medial Longitudinal Fasciculus (MdLF)

The MdLF is not universally recognized by neuroanatomists as a fasciculus discrete from IFOF and ILF, however, it has been recognized as a discrete fiber bundle passing through the STG in macaque (Schmahmann and Pandya, 2007). In humans, Menjot de Champfleur et al. (2012) argue that the MdLF is distinguishable from ILF using DTI tractography. Their model describes MdLF connecting between inferior parietal lobule/angular gyrus, with some occipital branching, to STG, while the ILF runs through MTG/ITG.

DeWitt-Hamer et al (2010) also describe the MdLF as beginning from the angular gyrus, but extending through the STG to the temporal pole. Makris et al. (2009) and Makris and Pandya (2009) chart the MdLF as superior to the IFOF and ILF, the latter which is found lateral to the IFOF. The MdLF is described as lateral and superior to the IFOF. The AF/SLF III is argued to be both superior and lateral to the MdLF. Other workers have proposed that the MdLF is constitutive of the vertical segment of the AF (Catani et al., 2005; Frey et al., 2008; Makris et al., 2009).

The MdLF's connectivity between the angular gyrus, which houses a recently localized part of the perisylvian language network called Geschwind's territory (Catani et al.,

2005), and the STG, containing Wernicke's territory, suggests a critical role for language comprehension. However, DeWitt-Hamer and colleagues' (2010) work on patients with resections of the STG in the left dominant hemisphere involving the MdLF show no semantic deficit; instead, these data suggest IFOF resection is more likely to elicit paraphasias.

Ventral Pathway/Extreme Capsule Pathway/External Capsule Pathway/Uncinate Fasciculus

A fiber bundle connecting Broca's area with STG, MTG, and Wernicke's area has been described in humans (Parker et al., 2004; Saur et al., 2008) and other primates (Kaas and Hackett, 1999; Romanski et al., 1999; Schmahmann et al., 2007). This pathway is problematic for a number of reasons; first, the terms ventral pathway, extreme capsule pathway, and ventral pathway are used interchangeably by some authors. Further, the uncinate is variously described as an independent pathway from the EmC/ExtC/Ventral pathway (e.g., Schmahmann et al., 2007), or as coursing through the extreme/external capsule (Anwander et al., 2007). Another interpretation involves the fascicular extensions of the IFOF or ILF through the Extreme/External capsule to the PFC. One way to deal with this confusion is to recognize three possible interpretations: 1) the ventral pathway as a white matter bundle in its own right which passes through either or both the extreme and external capsules (from OFC/lateral PFC to temporal pole) and the uncinate as a separate pathways; 2) the ventral pathway and uncinate as described in 1, except the ventral pathway is an extension of the IFOF or ILF fascicular bundle; or 3), the uncinate as a pathway which passes through the external and/or extreme capsule.

Catani and Thiebaut de Schotten (2008) localize the uncinate as distinct from the IFOF, passing through the external capsule ventrally to the IFOF. However, their atlas uses

the same IFOF termination mask in the temporal pole, which is suggestive that the IFOF and ventral pathways are not mutually exclusive but rather two segments along the same fasciculus. Other workers (Anwander et al., 2007) found evidence for separate ventral and uncinate pathways in some but not all of their subjects.

Using a combination of fMRI and DTI tractography, Saur and co-workers (2008) identify the ventral pathway as passing between ventrolateral prefrontal cortex through the extreme capsule to the temporal lobe. High angular resolution diffusion fiber tractography also supports the extreme capsule as part of the ventral pathway originating (Frey et al., 2008).

Functionally, the ventral pathway appears to be involved in comprehension of sentences rather than individual words (Saur et al., 2008), sound-to-word learning tasks (Wong et al, 2011), naming (Ueno et al., 2011), and the syntactic components of language (Weiller et al., 2011), although relatively little is known at this point in time (Friederici, 2009).

Special note on the anterior commissure: the anterior commissure is generally agreed to be distinct from the extreme/external capsule/ventral pathway system. Catani and Thiebaut de Schotten (2008) localize this tract medially and slightly posterior to the extreme/external capsule. Further, the anterior commissure connects the two temporal poles, and does not terminate in the prefrontal cortex. However, Dejerine and Dejerine-Klumpke (1895) described the anterior commissure as part of the ventral extension of the ILF, which is contested by most but was included in the original description of ILF by Burdach (1822). Based on FA color maps in humans from Catani and Thiebaut de Schotten (2008), it is plausible that the anterior commissure and the extreme/external capsule, as

localized by them, are branches from a common white matter bundle in the temporal pole, further complicating the our conceptualization of the ventral pathway system.

Temporal Lobe and Human Evolution

Association cortices have expanded in the human lineage. In the temporal lobe, association areas combine lower level unimodal perceptual inputs into multimodal and subsequently supermodal or amodal conceptual representations. Some of these cognitive functions include language comprehension, tool use, face, body, and object recognition, and semantic memory. Expansion of gray matter surface area and white matter volume are implicated in the functional modifications to the temporal lobe in humans. The next chapter will cover the two methodologies used to investigate structural differences in cerebral cortex between humans and our primate relatives.

METHODS

METHODS

PART 1: VGLUT2 IMMUNOHISTOCHEMISTRY

Subjects and Tissue

We examined occipital lobe tissue from anthropoid primates of six species, including humans (*Homo sapiens*; n = 5), chimpanzees (*Pan troglodytes*; n = 4), 1 orangutan (*Pongo pygmaeus*; n = 1), rhesus macaques (*Macaca mulatta*; n = 3), vervet monkeys (*Cercopithecus aethiops*; n = 3), and squirrel monkeys (*Saimiri sciureus*; n = 3; table 1). Four human specimens were obtained from the brain bank of the Northwestern University Alzheimer's Disease Center, and 1 was from Tulane University. Age at death ranged from 56 to 78 years (median 74 years). All 5 were rated by the supplying institution as normal control brains. Post-mortem delays (PMDs) ranged from 3 to 23 h (median 6 h); brains were fixed by immersion in 10% formalin or 4% paraformaldehyde. Chimpanzee and orangutan tissue came from the New Iberia Research Center at the University of Louisiana at Lafayette. Chimpanzee ages ranged from 19 to approximately 30 years; all died from natural causes or were euthanized for humane reasons. PMDs for chimpanzees were from 0 to 5.5 h (median 5 h); 3 brains were immersion fixed in paraformaldehyde solution, and 1 was perfusion fixed (table 1). The orangutan was a 33-year-old male; the brain was immersion fixed following a PMD of 2 h. Rhesus macaque brains were obtained from the Yerkes National Primate Research Center; with the exception of 1 rhesus macaque from the Vanderbilt University, ages ranged from 4 to 12 years (median 6 years). The macaque brains were perfusion fixed following PMDs from 0 to 1 h (median 0 h). Vervet monkey brains were obtained from the New Iberia Research Center; vervets ranged in age from 7 to 15 years (median 13) and were perfused with paraformaldehyde solution. Tissue from squirrel monkeys came from the New Iberia

Research Center. Age at death ranged from 18 months to 12 years (median 2 years). Three individuals were perfusion fixed with phosphate-buffered paraformaldehyde. All procedures involving nonhuman primates were carried out according to institutional animal welfare guidelines.

Following fixation, brain blocks were cryoprotected by successive immersion in sucrose solutions of increasing concentration (10, 20, and 30%) to prevent freezing artifacts, and then stored in ethylene glycol-based cryopreservative solution (Watson et al., 1986) at –20°C. Prior to sectioning, blocks were immersed in buffered 40% sucrose at 4°C for several days to remove cryopreservative. Tissue was cut on a freezing microtome in either 40- (humans) or 50-m (apes and monkeys) sections and stored in cryopreservative at –20°C before histological processing. Human brains were cut in coronal, horizontal or oblique longitudinal sections, chimpanzee brains in horizontal or coronal sections, and other species in coronal sections (table 1).

Immunohistochemistry

Purified mouse monoclonal antibody (clone 8G9.2; MAB5504), raised against recombinant rat VGLUT2, was obtained from Millipore (Temecula, Calif., USA). The epitope is unknown. This antibody has previously been used in studies of mammalian cortex (Hrabovszky et al., 2006; Sadakata et al., 2007; Hackett and de la Mothe, 2009; Wong and Kaas, 2009).

Tissue sections containing area V1 were first immersed with 3% hydrogen peroxide to block endogenous peroxidase and then blocked with horse serum. Sections were then incubated in primary antibody for 2 h at room temperature followed by biotinylated anti-mouse IgG secondary antibody for 1 h and then a solution of biotinylated peroxide + avidin

(Vector ABC reagent) for 1 h as part of the Vector Elite Kit (Vector Laboratories, Inc, Burlingame, Calif, USA). Sections were stained with diaminobenzidine (DAB) solution using the Vector DAB peroxidase substrate kit (Vector Laboratories).

Staining intensity varied across species and individuals, so a series of dilution trials were carried out to yield comparable levels of staining across cases. Final primary antibody dilutions, which ranged from 1:3,000 to 1:100,000, were chosen based on the optimal ratio of specific to nonspecific labeling. Samples were immunoreacted with antibody concentrations in the higher range, and additional trials were run until nonspecific DAB accumulation was low enough for the clear disambiguation of nonspecific and specific labeling. Optimal concentrations varied between species and individuals (table 1). Control sections were prepared and incubated in all experiments in an identical fashion to the experimental sections, except for the omission of the primary antibody during incubation.

No specific staining was observed in control sections. Sections were mounted on slides, dehydrated using graded alcohol solutions, and cleared with xylene. A Nissl counterstain with thionin was applied to selected sections in order to verify the laminar distribution of labeling. Slides were cover-slipped with mounting media (Cytoseal XYL; Richard-Allan Scientific, Kalamazoo, Mich, USA) to prepare for digital scanning.

Image Processing and Laminar Analysis

Digital images were acquired using a Scanscope digital slide scanner (Aperio, Vista, Calif., USA). Adobe Photoshop software (Adobe Systems, Mountain View, Calif., USA) was used to adjust contrast levels and, in the Nissl-counterstained sections, to separate the blue Nissl staining from the red-brown anti-VGLUT2/ DAB staining, by splitting color channels, as described by Preuss et al. (1999). DAB chromogen was visualized using the yellow

channel in CMYK color space or the blue channel in RGB space; thionin was visualized using the red channel in RGB color space. Area V1 cortical layers were identified and numbered according to the system of Brodmann (1909), as modified by Lund (1973). Some authorities (Casagrande et al., 2007) prefer the system of Hässler and Wagner (1965), whose layers 3B, 3C, 4, and 4 correspond to layers 4A, 4B, 4C, and 4C, respectively, of Lund (Billings-Gagliardi et al., 1974).

METHODS

PART 2: DIFFUSION TRACTOGRAPHY

Dataset

We examined *in vivo* T1-weighted and diffusion-weighted magnetic resonance (MR) scans from humans (*Homo sapiens*; n=10, age range 22-35 yrs, median range 26-30), chimpanzees (*Pan troglodytes*; n=15, 23 ± 12 yrs), and rhesus macaques (*Macaca mulatta*; n=10, 10 ± 7 yrs). All the individuals were female. Pre-processed human scans were obtained from the Human Connectome Project (HCP) 500 Subjects Release (Jenkinson et al., 2002; Andersson et al., 2003; Glasser and Van Essen, 2011; Andersson et al., 2012; Fischl 2012; Jenkinson et al., 2012; Van Essen et al., 2012; Glasser et al., 2013b). Chimpanzee and macaque scans were selected from larger scansets of both species collected as part of a comparative study on brain aging in females; these data have been used in previous studies (e.g., Chen et al., 2013; Autrey et al., 2014). Scans were selected for tractography analysis by K. Bryant based on criteria for high quality data, including strong grey matter/white matter contrast and lack of white matter lesions. All chimpanzees and macaques were housed at the Yerkes National Primate Research Center (YNPRC) in Atlanta, Georgia. All procedures were carried out in accordance with protocols approved by the YNPRC and the Emory University Institutional Animal Care and Use Committee (IACUC, approval # YER-2001206).

Nonhuman Primate Brain Imaging

Prior to MR scanning, chimpanzee and macaque subjects were immobilized with ketamine injections (2–6 mg/kg, i.m.), and then anesthetized with an intravenous

propofol drip (10 mg/kg/h), following standard YNPRC veterinary procedures. Subjects remained sedated for the duration of the scans as well as the time required for transport between their home cage and the scanner location. Upon scan completion, primates were housed in a single cage for 6–12 h to recover from the effects of anesthesia before being returned to their home cage and cage mates. The well being (activity and food intake) of the chimpanzees and macaques was evaluated twice daily after the scan for possible post-anesthesia distress by veterinary and research staff.

Anatomical MRI and DTI scans in chimpanzees were acquired on a Siemens 3T Trio scanner (Siemens Medical System, Malvern, PA, USA). A standard circularly polarized birdcage coil was used to accommodate the chimpanzee jaw, which is too large to fit into the standard phase-array coil designed for human subjects. Foam cushions and elastic straps were used to minimize head motion. For each diffusion direction, 2 diffusion-weighted images were acquired, each with 1 of the possible left–right phase-encoding directions and 8 averages, allowing for correction of susceptibility-related distortion (Andersson et al., 2003). For each average of diffusion-weighted images, 6 images without diffusion weighting ($b = 0$ s/mm^2) were also acquired with matching imaging parameters. High-resolution T1-weighted MRI images were acquired with a 3D magnetization-prepared rapid gradient echo (MP-RAGE) sequence for all subjects.

MR scanning in macaques was performed using the same Siemens 3T Trio scanner with a standard 8-channel human knee coil. Head motion was minimized with foam cushions, elastic straps, and a specially designed plastic holding device to secure subjects' ear canals. Diffusion MRI data were collected with a diffusion-weighted, single-shot, spin-echo echo-planar imaging (EPI) sequence. A dual spin-echo technique combined with bipolar

gradients was used to minimize eddy-current effects. Similar to chimpanzees, diffusion-weighted images were acquired with phase-encoding directions of opposite polarity (left–right), each with 4 averages, to correct for susceptibility-induced distortion. For each average of diffusion-weighted images, 5 images without diffusion weighting ($b = 0$ s/mm^2) were also acquired with matching imaging parameters. Detailed imaging parameters of the T1-weighted and diffusion MRI for chimpanzees and macaques are listed in Table 2.

Pre-processing

Anatomical and diffusion MR data were analyzed using tools from the software library of the Oxford Center for Functional Magnetic Resonance Imaging of the Brain (FSL, www.fmrib.ox.ac.uk/fsl/; Smith et al., 2004). T1-weighted images were skull-stripped using BET, with some manual correction (Smith 2002) for chimpanzee data, especially in the posterior occipital lobe. FAST (Zhang et al. 2001) and SUSAN (Smith and Brady, 1997) were used to correct for intensity bias and reduce noise, respectively. Diffusion-weighted MR data were corrected for eddy-current and susceptibility distortion using Matlab (Matlab7, Mathworks, Needham, MA). Following the method of Andersson and colleagues (2003), half of the data were collected with the opposite phase encoding direction compared to the other half, allowing for correction of susceptibility-related distortion using *topup*, as implemented in FSL.

HCP Pipeline Processing

Human, chimpanzee, and macaque scans were processed using the FreeSurfer 5.1 pipeline (Reuter et al., 2012), with additional HCP pre-processing steps (Van Essen et al., 2013), which reconstructs the pial surface and white-matter surface (i.e., the gray-white interface) from T1 and T2-weighted scans. Cortical myelin density was computed using the

method first described in Glasser and Van Essen (2011), and subsequently further refined (Glasser et al., 2013a, 2013b). Human scans were volumetrically registered to the HCP440 human atlas in MNI space using FLIRT and FNIRT (FSL); surfaces were registered using FreeSurfer to match cortical folding patterns (Reuter et al., 2012). For macaques and chimpanzees, averaged "templates" were produced for each dataset. In chimpanzees, the template was constructed from scans of 39 female individuals; in macaques, 15 female scans were used (details on the protocol and template generation are available in Li et al., 2011).

DTI Tractography

We used probabilistic diffusion tractography implemented in FSL's diffusion toolbox to track anatomical connections between ROIs in each hemisphere. We used a partial volume model with automatic relevance detection (ARD) (Behrens et al., 2007) for delineating subsidiary fibers in each voxel, as a recent study show that 63 — 90% white matter voxels contain crossing fibers (Jeurissen et al., 2013). Moreover, probabilistic fiber tracking (rather than deterministic fiber tracking) was employed for a quantified reproducibility in the tracking results (Behrens, Johansen-Berg et al. 2003, Behrens, Berg et al. 2007). The details used in our fiber-tracking process were as follows: Region of interest (ROI) masks were manually drawn on the white mater/gray matter interface in a pial projection view in HCP Workbench View. For each tract between any two ROIs (R1, R2), one ROI was first used as a seed mask and the other was used as a waypoint mask. The process was repeated with the seed mask and the waypoint mask reversed. The "probtrackx" in each individual tracking process gives the raw histogram for the spatial distribution of streamlines from the seed mask (R1) that pass through any given voxel x and the waypoint mask (R2) (i.e., fdt_paths(R1→x→R2)) and the waytotal, the total number of samples that

are not rejected by the tracking conditions (waypoint masks, exclusion masks, etc.). In order for the histogram to be comparable across subjects and hemisphere, the histogram for each subject must be normalized by its waytotal. So the probability p ([R1→x→R2] or [R2→x→R1]) that implies the probability of the path of the least hindrance to diffusion from the seed mask R1 (or R2) passes through x and the waypoint mask R2 (or R1) can be defined as:

$p([R1 \rightarrow x \rightarrow R2] \text{ or } [R2 \rightarrow x \rightarrow R1]) = p(R1 \rightarrow x \rightarrow R2) + p([R2 \rightarrow x \rightarrow R1]) - p([R1 \rightarrow x \rightarrow R2] \text{ and } [R2 \rightarrow x \rightarrow R1]) = fdt\_paths(R1 \rightarrow x \rightarrow R2)/ Wt_{(R1 \rightarrow R2)} + fdt\_paths(R2 \rightarrow x \rightarrow R1)/ Wt_{(R2 \rightarrow R1)} - [fdt\_paths(R1 \rightarrow x \rightarrow R2)/ Wt_{(R1 \rightarrow R2)}] * [fdt\_paths(R2 \rightarrow x \rightarrow R1)/ Wt_{(R2 \rightarrow R1)}].$

After the probability maps for each tract between an ROI pair in each hemisphere were derived, they were first thresholded by a series of values (0.5, 1, 1.5, $2 * 10^{-3}$) and then binarized, and averaged across subjects to form a probability map for the whole population. A value of 1 at the voxel x can be interpreted as that the path of the least hindrance to diffusion from either the mask R1 to R2 or from the mask R2 to R1 passes through the voxel x under that given threshold in all subjects. A value of 0 indicates that in no subject the path passes through the voxel between the two ROIs under the given threshold.

100,00 samples per vertex were started for each symmetrical tracking process. A curvature threshold of 0.2, and distance correction, were used. Maximally three crossing fibers were modeled. The pial gray matter surface without the medial wall was also used as the stop mask to prevent fibers jumping across gyri via CSF (Li, Hu et al. 2013). All other parameters were set as defaults. These final analyses for each individual produced a tractogram image in which each voxel on the pial surface contained a value which corresponds to the intensity of streamlines which passed through it. We used a conservative

normalization procedure, thresholding the bottom 99% of the robust range of the probability values for the tractogram in question. This produced a tractogram image composed of voxels representing the top 1% of successful streamlines.

Analysis of V1 and IPS Connectivity with Extrastriate and Temporal Cortex

Extrastriate and temporal lobe connectivity was examined using a series of ROI masks in macaques, chimpanzees, and humans. Cortical masks were drawn on each species template. A mask that covered the central V1 representation was created to reflect the portion of V1 most thoroughly described in macaque tracing studies; this includes the foveal plus parafoveal regions (fig. 4A). A set of masks that covered different retinotopic portions of V1 were created for each species (foveal, lower and upper parafoveal, and lower and upper peripheral V1; fig. 4B), Macaque retinotopic ROIs (foveal, parafoveal, peripheral, and central V1) were identified based on the composite parcellation in F99 space (Van Essen, 2002; Van Essen et al., 2012), which includes architectonic and retinotopic data from several sources (Brodmann, 1905; Von Bonin and Bailey, 1947; Seltzer and Pandya, 1978, 1980, 1986; Ungerleider and Desimone, 1986; Bayliss et al., 1987; Felleman and Van Essen, 1991; Preuss and Goldman-Rakic 1991; Lewis and Van Essen, 2000; Paxinos and Franklin, 2000; Lyon and Kaas, 2002; Kolster et al., 2009; Markov et al., 2011). Human retinotopic ROIs were identified based on the VGD11b parcellation map in HCP Workbench (Van Essen et al., 2011) compiled from multiple parcellation schemes (Ongur et al., 2003; Swisher et al., 2007; Pitzalis et al., 2007; Fischl et al., 2008; Burton et al., 2008). An IPS mask was created to serve as a control for the large V1c mask (fig. 4C). A temporal lobe mask was drawn to comprise most of the temporal cortex except for V1, the auditory core, and the majority of the parahippocampal gyrus (fig. 4D). Chimpanzee retinotopic ROIs were inferred from their

locations in macaques, taking into account the position of the lunate sulcus for the delineation of the V1-V2 border. Chimpanzee temporal lobe and IPS masks were drawn based on sulcal and gyral landmarks. Temporal mask medial edges in chimpanzees were informed by myeloarchitectonic information (Glasser and Van Essen, 2011).

For each species, 7 symmetric tractography runs were performed in the left hemisphere: one for each non-temporal lobe mask to the large temporal lobe mask. Individual tracking results were processed by thresholding as described in the DTI tractography section, then binarized. A mean for each species analysis was computed from individual tractograms, and this mean tractogram was transformed into a projection onto the Freesurfer cortical surface for each species. The final tractogram result was produced from a majority subset of individuals that varied from 70-90% of the total number of individuals. Results were assessed visually using Workbench View, part of the HCP Connectome Workbench software package (Marcus et al., 2011). The location of projected results on the cortical surface relative to known cortical areas in humans and macaques was estimated using data from HCP composite parcellations as described above (Van Essen et al., 2011; Van Essen et al., 2012) as well as additional retinotopic studies in humans (Wandell et al., 2005; Abdollahi et al., 2014).

MT+ Connectivity Analysis

For macaque and chimpanzee subjects, two sets of ROI masks each were drawn: first, a primary visual cortex (V1) mask and putative MT+ mask (fig. 5A & 6A), and second, an intraparietal sulcus (IPS) mask and a large extrastriate mask encompassing MT+ (fig. 5B & 6B). In humans, V1 and IPS masks were drawn similarly; however, a large extrastriate mask enclosing MT+ was used for both ROI pairs (fig. 7A & 7B). For each species, 2

symmetric tractography runs were performed in the left hemisphere: one run between the V1 and MT+ ROIs, and one between the IPS and MT+ ROIs. Averaged results were computed in the same manner as in the temporal lobe connectivity analysis.

RESULTS

RESULTS

PART 1: VGLUT2 IMMUNOHISTOCHEMISTRY

Immunostaining with anti-VGLUT2 yielded strong staining of area V1 in all species examined. Dense labeling was present throughout area V1, ending abruptly at the border of areas V1 and V2 (fig. 8). In all species, the densest label was present in layers 4 and 6, although some label was present in all layers (fig. 8–11). Fixation did not appear to affect VGLUT2 labeling, as evidenced by similar staining across all chimpanzee cases, which included both immersion- and perfusion-fixed tissue (fig. 9). Two types of staining were distinguishable: light-to-moderate diffuse staining of tissue, the appearance of which is consistent with nonspecific DAB accumulation, and darker staining of discrete, terminal-like processes (fig. 12). We focus here on the terminal-like staining and its laminar distribution across species.

All species examined exhibited dense terminal-like labeling in layer 4C, including both its deep (4Cβ) and superficial (4Cα) parts, although labeling was densest in layer 4C (fig. 8-11; 12a). In 4C of most species, labeling was concentrated in vertical stacks or arrays, although this was less apparent in squirrel monkeys than in other species (fig. 11). In 4C, by contrast, many of the terminal-like processes had oblique or horizontal orientations, as well as vertical (fig. 11).

Labeling of layer 4A varied markedly across species. In squirrel monkeys, macaques, and vervets, a thin band of labeling was observed at low magnification (fig. 8a; 10a, b; 11a–c). At higher magnification, this band could be seen to be composed of terminal-like staining (insets in fig. 11a–c; fig. 12b). The terminal-like fibers were distributed in all orientations, and in some sections, they appeared to be concentrated in clusters distributed parallel to the pial

surface. In some sections, sparse, small, labeled puncta could be observed in portions of 4A that appeared to represent individual en passant boutons (fig. 12b). In chimpanzees and humans, by contrast, very little labeling was observed in layer 4A, with only a few terminal-like processes observed at high magnification (fig. 11e, f, insets). Further, most of these processes were vertically oriented, suggesting that these consisted at least in part of fibers passing to the superficial layers. The single orangutan we studied (fig. 11d) had somewhat more terminal-like labeling of layer 4A than the chimpanzees and humans, although labeling was much sparser in the orangutan than in any of the monkeys.

Deep to layer 4, labeling was observed in layer 6, particularly in its upper part (layer 6A), but the strength of labeling varied between species and individuals. Overall, labeling of layer 6 was denser and more consistent in the monkeys than in the hominids (compare the squirrel monkey and human in fig. 8, and the monkeys in fig. 10a, b to the chimpanzee and human in fig. 10c, d). The orangutan also had weak labeling of layer 6 (fig. 12c). There was also substantial individual variation in labeling of layer 6 in both humans and chimpanzees, as illustrated by the moderate labeling of the human shown in figure 2b compared to the near absence of labeling in the human shown in figure 4d. Two of our 4 chimpanzee specimens showed a distinct band of labeling in layer 6 (e.g. N98-47, fig. 9b), 1 showed faint, patchy labeling (N99-11, fig. 10c), and 1 displayed little or no layer 6 labeling. Of the 5 humans, only 1 showed conspicuous labeling of layer 6 (N01-15, fig. 8b); in the other 4 cases, layer 6 labeling was either very sparse or absent (e.g. N99-9, fig. 10d). Terminal-like labeling in layer 6 was not uniformly distributed, but appeared to be clustered in the plane parallel to the pia.

In most cases, sparse labeling of terminal-like processes was observed in layer 3, with a preponderance of vertical and oblique orientations. In a few cases (squirrel monkeys N98-7 and N98-10, vervet monkeys N96-17 and N96-19), and chimpanzees, N96-30, N98-40, and N96-29; the latter pictured in fig. 13a, b), these processes appeared to form broad (100–200 μm wide), vertically extended clusters, which resemble blobs in both location and size. In some cases, we also observed terminal-like processes in layers 2 and 1, which in all instances consisted of sparse and sporadic labeling resembling en passant terminals (vervet monkeys N96-20, N96-19, and N96-17; orangutan N96-40; chimpanzees N99-11 and N96-30, and humans N98-32 and N99-13; N98-32 pictured in fig. 13c).

RESULTS

PART 2: DIFFUSION TRACTOGRAPHY

Central V1

We examined V1c connectivity with the temporal lobe in order to examine possible modifications to temporal association areas with respect to primary sensory information representation. In macaques, streamlines connected V1c with V2d, V2v, and V3d after thresholding (fig. 14A, dark arrows); human V1c streamlines reached the same visual areas, as well as V4v and V6d (fig. 14C, dark arrows). Chimpanzee V1c-temporal cortex connectivity included extrastriate areas consistent with foveal and parafoveal results, suggestive of connectivity with putative chimpanzee homologs of V2d and V2v, extending anteriorly into territories that arguably include V3 and V4, in the absence of chimpanzee cortical maps (fig. 14B, dark arrows). Beyond from these findings, V1c results diverge in important ways across species groups. Macaques do not show any significant streamline connectivity with V1c beyond V2 and V3 (fig. 14A). Chimpanzee and humans, on the other hand, in addition to connections with V2, V3, and other proximal visual cortex areas, show apparent major connectivity between V1c and anterior, lateral, and inferior temporal association regions (fig. 14B & 14C; 15B & 15C).

Streamline projections between V1c and temporal cortex in chimpanzees reached the anterior segment of MTG (white arrows, fig 14B), while the averaged human dataset displays apparent connectivity with MTG only in the anterior-most portions, adjacent to the temporal pole (white arrow, 14C). Projecting results on fully folded cortical surface maps (fig. 15) confirms anterior MTG connectivity in humans and chimpanzees, with some STS connectivity in chimpanzees, unlike humans (15B & 15C). Macaques, in contrast, show no

V1c connectivity with cortex anterior to visual areas V2 and V3 (fig. 14A & 15A). Streamline connectivity to V2 and V3 in macaques is obscured by cortical folding when projected on the fully folded macaque cortex (see transparent arrows; 15A).

Inferior temporal connections are also present in both chimpanzees and humans, including the inferior temporal gyrus (ITG) and fusiform gyrus (FG; black arrows; 15B & 15C). Compared with chimpanzees, humans show somewhat sparser V1c connectivity with FG (black arrows; 15C). Our macaque dataset show no streamlines reached the ventral surface of the temporal lobe, including ITG and surrounding territories (14A & 15A).

The final temporal association area with significant differences across species is the anterior temporal lobe (ATL). Macaque ATL showed no streamline connectivity with V1c; however both chimpanzees and humans display apparent major connectivity with this territory (gray arrows, fig. 15). Chimpanzee ATL results include anterior portions of the STG, STS, MTG, and ITS (gray arrow, 15B). V1c connectivity to ATL in humans covers a relatively larger surface area than chimpanzee (gray arrows, 15C), and is concentrated in the tip of the STG, with less MTG and ITG connectivity than in chimpanzee. Human results in the ATL region also extend medially (gray arrows, 15C), encompassing the major parts of the temporal pole.

To preclude the possibility that streamline connectivity represented general connectivity patterns common to large cortical seed masks, we ran a control condition in all three species wherein a large IPS seed mask (fig. 4C) run in a symmetric tractography analysis with the temporal cortex seed (4D) under identical conditions to the V1c-temporal cortex tractography. Here, we see similar sized areas of apparent major connectivity within each species comparison, however the spatial patterning of the temporal cortex connectivity

with the IPS seed mask is markedly different. IPS-temporal cortex connectivity spans the lateral aspect of the inferior parietal lobule in all three species (fig. 16A), unlike V1c-temporal cortex connectivity, which is concentrated in extrastriate regions bordering the lunate sulcus in macaques and chimpanzees (16B), and medial extrastriate cortices in humans (dark arrows, 15C). In chimpanzees, we see virtually no anterior temporal connectivity present in the IPS-temporal cortex condition (16A), unlike the V1c-temporal cortex condition (16B). The human IPS results show connectivity in anterior and inferior temporal lobe, unlike macaques and chimpanzees; however the pattern of connectivity differs from the V1c results, with stronger anterior temporal connectivity from the V1c seed (16A).

Retinotopy

We investigated whether the retinotopic organization of extrastriate cortex could be revealed with cortico-cortical tractographic analysis of V1 subdivisions with a large temporal lobe mask encompassing extrastriate areas and association areas. Streamlines from upper parafoveal seeds preferentially landed in the dorsal V2 in macaques, chimpanzees, and humans; similarly, lower parafoveal seeds showed the highest probability of connectivity with ventral V2 in all three species, after thresholding results to display 80% of the individuals sampled (8/10 macaques and humans; 12/15 chimpanzees; fig. 17A). Macaque and chimpanzee parafoveal connectivity was concentrated in the lateral part of V2, in contrast with peripheral connectivity in these species, which was concentrated in medial V2. In these averaged projections, macaque upper and lower parafoveal connectivity is limited to V2, while in the humans, in addition to V2 connections, we see hotspots of high probability connectivity to V3 with some extension into V6d in anterior temporal regions (fig. 17A). Chimpanzee streamline termination patterns further show more expansive connectivity

between upper parafoveal cortex and the anterior temporal lobe (ATL) than in humans, including anterior portions of the middle temporal gyrus and extending into the inferior temporal sulcus. Streamlines from the upper parafoveal field seed also reached territories along the fusiform gyrus in chimpanzees. Human upper parafoveal field connectivity to the anterior temporal lobe is sparser than macaque but areas of connectivity appear in anterior-most portions of the middle temporal gyrus. Some upper parafoveal streamlines also reached dorsal V2, although the majority of dorsal V2 connectivity arose from lower parafoveal field streamlines.

Peripheral connectivity to temporal cortices was restricted to superior and inferior extrastriate cortices in all three species. Peripheral data for macaques showed lighter successful streamline connectivity in macaques when compared to parafoveal and foveal data, so the number of individuals included in the averaged results was reduced to 7/10 individuals. In macaques, streamlines from upper peripheral and lower peripheral seeds reached dorsal and ventral extrastriate cortices, respectively. These extrastriate territories included medial V2v, V3v, and V4v for lower peripheral seed streamlines and V2d, V3d, and V4d for upper peripheral streamlines (fig. 17B). In humans, peripheral connectivity to extrastriate regions was slightly heavier than parafoveal areas; so averaged results were thresholded slightly lower by visualizing averaged results from 9/10, rather than 8/10 individuals. Human lower peripheral projections include medial V2v, V3v, and V6v; upper peripheral seeds tracked to V2d, V3d, and V6d. As with parafoveal data in humans, some "cross-contamination" of connectivity patterns is visible, with some lower peripheral streamlines connecting in dorsal extrastriate cortex and some upper peripheral with ventral extrastriate (fig 17B). Chimpanzee peripheral visual connectivity patterns were most similar to macaque results, although some lower peripheral connectivity appeared at the lingual and

fusiform gyri, which may encompass V4v. As expected based on known retinotopic projection patterns, peripheral connections are concentrated in medial extrastriate territories in all 3 species, and further anterior to parafoveal projections in humans (17B).

Tractography results between foveal seeds and the large temporal seeds were similar across species; with the strongest streamline connectivity restricted to lateral V2 in humans and macaques (17C). Chimpanzee results appear to be consistent with a primate-typical V2 localization (Rosa and Tweedale, 2005).

Weak tracking to MT+

In all 3 species, tractography between visual areas and a large temporal cortex mask revealed strong connections with extrastriate cortex, however, visual motion area MT+, which is known to possess strong connections with V1, showed surprisingly weak connectivity. We examined this phenomenon in more detail by drawing more circumscribed MT+ masks in all three species. Next, we tracked connections to these MT+ seeds from both V1c and IPS, both regions with strong connections to MT+. We expect streamlines from IPS and V1c to converge in area MT+ in all three species.

MT+ tractography results of V1 to extrastriate ROI masks and IPS to extrastriate ROI masks were averaged for each species (fig 18A & 18B). Results are consistent in their failure to show strong streamline connectivity at area MT+. Next, we examined individual tractography results in order to see the relationship between streamline connectivity and the location of myelin-rich area MT+.

Individual results for connectivity to both V1 with a circumscribed MT+ mask in macaques show poor fidelity to the MT+ cortical regions across subjects (fig. 5C). Macaque

RMY2 showed the strongest connectivity results with V1; however, these connections lacked specificity to the confines of the MT+ ROI. For the IPS-extrastriate tractographic analysis, we again see poor consistency and specificity to the MT+ region (fig. 5D), which contradicts our prediction that V1 and IPS seed masks would show strong connectivity with MT+. Chimpanzee tractographic results show a similar pattern to macaques. Streamlines from the V1 seed to the large putative MT+ ROI are inconsistent across individuals and frequently fail to reach the central portion of the myelin-rich parts of putative MT+ (fig. 6C). Results from the IPS-MT+ analysis are similar (fig. 6D). Closer inspection of the MT+ ROI show that results across individual chimpanzees are consistent in that streamline connectivity appears to be weakest in the most heavily myelinated central areas of putative MT+, producing producing connectivity patterns encircling MT+ which resemble lacunae (fig. 6E-F). Human MT+ results are also variable across individuals yet consistently fail to show strong connectivity within area MT+ (fig. 7C & 7D). As in chimpanzees, closer inspection of the MT+ ROIs demonstrates a failure of streamlines to reach heavily myelinated cortical territories, resulting in lacunae (fig. 7E-H).

DISCUSSION

DISCUSSION

PART 1: EVIDENCE FOR APE AND HUMAN SPECIALIZATIONS IN GENICULOSTRIATE PROJECTIONS FROM VGLUT2 IMMUNOHISTOCHEMISTRY

VGLUT2 Immunohistochemistry as a Tool for Labeling Geniculostriate Afferents in Postmortem Material

The distribution of VGLUT2 labeling of primary visual cortex documented in our study closely matches published accounts of the distribution of geniculostriate projects in several dimensions of organization. At high magnification, the elements that stain strongly for VGLUT2 appear to be fibers studded with thickenings resembling en passant synaptic boutons, an appearance consistent with the geniculostriate terminals labeled by tract-tracing studies in several species: the rhesus macaque (Blasdel and Lund, 1983); pigtail macaque (Freund et al., 1989); galago (Florence and Casagrande, 1987); cat (Ferster and Levay, 1978; Mason and Robson, 1979; Humphrey et al., 1985), and ferret (Nahmani and Erisir, 2005).

The study by Nahmani and Erisir (2005) is especially notable, because they found that the geniculostriate fibers and terminals labeled with anterograde tracer injections of the LGN were also strongly VGLUT2 immunopositive. Second, the dense VGLUT2 immunostaining found in area V1 ended abruptly at the V1/V2 border, and in primates, LGN is known to project very strongly to V1 but only minimally to V2 (reviewed by Preuss, 2007). Finally, as discussed in more detail below, the laminar and modular organization of VGLUT2 labeling within area V1 closely matches published descriptions of the tangential and radial distribution of geniculostriate projections. It is therefore highly likely that the terminal-like labeling we observed in striate cortex with VGLUT2 immunostaining included

predominantly geniculostriate fibers, although it remains possible that it does not represent exclusively geniculostriate fibers.

These results demonstrate the value of VGLUT2 immunohistochemistry as a proxy or marker for geniculate terminals in great apes and humans, species in which invasive tract-tracing studies cannot ordinarily be carried out. Furthermore, this technique would seem to provide less ambiguous evidence for changes in geniculostriate projections than is possible with CO histochemistry or with PV immunohistochemistry, both of which produce relatively diffuse labeling in contrast to the well-defined, terminal-like labeling observed with anti-VGLUT2 in area V1. The distribution of VGLUT2 immunoreactivity across the layers of area V1 corresponds closely to the distribution of CO and PV in the cortical layers that label with anti-VGLUT2, however, and thus results with anti-VGLUT2 reinforce interpretations of visual cortex organization and evolution obtained with CO and PV.

Laminar and Radial Distribution of VGLUT2 Immunoreactivity: Similarities and Differences across Species

The laminar distribution of terminal-like VGLUT2-immunopositive labeling of the primary visual area shared several characteristics across different groups of primates, and matched well the main targets of geniculostriate projections identified in tract-tracing studies (Blasdel and Lund, 1983; Casagrande, 1994; Casagrande and Kaas, 1994; Callaway, 1998; reviewed in Preuss, 2004, 2007). In the New and Old World monkeys, as well as in the hominids, the densest VGLUT2 labeling was present in layer 4C, spanning its lower (4Cbeta) and upper (4Calpha) strata, which are the targets of projections from the parvocellular and magnocellular LGN layers, respectively. Terminal-like labeling was also present in layer 6 in all groups, although the density of staining was variable: the monkeys consistently displayed

dense labeling in this layer, while the hominids were more lightly labeled overall and showed conspicuous inter-individual variability. Labeling of layer 4A showed even more striking differences across species: New and Old World monkeys had terminal-like labeling in a thin, irregular stratum, but labeling of this layer ranged from sparse to absent in apes or humans. Lastly, small numbers of terminal-like processes were observed in layers 1–3 in most cases. At high magnification, labeling often took the form of a series of thickenings strung along a fiber, suggesting en passant terminals (fig. 13c). In addition, large clusters of label in layer 3 were observed in some cases, resembling the blobs observable in tissue stained for CO (Horton and Hubel, 1981; Horton, 1984; Hevner and Wong-Riley 1990). It is known that the LGN projects directly to blobs in monkeys (Livingstone and Hubel, 1982; Fitzpatrick et al., 1983; Weber et al., 1983; Lachica and Casagrande, 1992; Ding and Casagrande, 1997). We note, however, that our material was not sectioned in the manner most useful for demonstrating blobs, i.e., in planes tangential or parallel to the surface of the cortex.

With regard to layer 4A, the present comparative results obtained with VGLUT2 immunohistochemistry mirror results obtained previously with CO histochemistry (Preuss et al., 1999); as with CO, staining for VGLUT2 revealed no obvious dense band of labeling in this layer, in contrast to the Old and New World monkeys. Thus, both the VGLUT2 and CO data support the hypothesis that parvocellular LGN projections to layer 4A were markedly reduced or lost in hominid evolution (Horton and Hedley-White, 1984; Wong-Riley et al., 1993; Preuss et al., 1999). Preuss et al. (1999) also indicated that CO staining of layer 4B might be stronger in hominids than in other anthropoid primates, suggesting that geniculate projections might extend into layer 4B in hominids, but the current results do not support this, as the hominids had no more labeling of layer 4B with anti-VGLUT2 than did

the other primates examined, with the possible exception of the single orangutan in our study.

The loss of the geniculate afferents to layer 4A in hominids could be taken as evidence that layer 4A itself was lost in hominid evolution, as suggested by Horton and Hedley-Whyte (1984) after noting the absence of a band of CO staining corresponding to layer 4A in humans. On current evidence, however, we prefer the hypothesis that layer 4A was modified, rather than lost, in human evolution. Layer 4A was originally identified by Brodmann (1909) in humans and other primates based on shared cytoarchitectonic characteristics. Moreover, loss of LGN afferents is just one of several changes that occurred in this stratum in hominid evolution, changes that involved the addition of features. Specifically, in humans and apes, but not in other primates, layer 4A contains a dense population of small neurons that express the calcium-binding protein, calbindin (Preuss and Coleman, 2002). In addition, Preuss et al. (1999) and Preuss and Coleman (2002) found that layer 4A in humans, but not other hominids or anthropoids, is enriched in molecules that have been associated with the magnocellular visual pathway, specifically aggrecan, the extracellular matrix proteoglycan labeled by the Cat-301 antibody (Fryer et al., 1992), non-phosphorylated neurofilament (which is labeled by antibody SMI-32), and microtubule-association protein 2 (MAP2). These human specializations could well indicate an enhancement or reorganization of magnocellular processing in human striate cortex, although the absence of VGLUT2 or CO staining in layer 4A makes it unlikely any such modification involved the evolution of a direct projection from the magnocellular LGN to that layer. Because V1 is the main source of visual information for higher-order areas, changes in V1 organization could affect higher levels of visual-system function (Preuss, 2004). Changes to area V1 in hominid evolution could be reflected in known increases in

motion sensitivity in human areas V3 and V3A (Tootell et al., 1997) and in human intraparietal areas (Vanduffel et al., 2002), compared to their macaque homologues, and in the selective responsiveness of human anterior inferior parietal cortex to the sight of tool actions, something not observed in macaques (Peeters et al., 2009).

DISCUSSION

PART 2: ORGANIZATION OF EXTRASTRIATE AREAS IN CHIMPANZEES COMPARED TO HUMANS AND MACAQUES

In this study, we used probabilistic diffusion tractography to investigate the organization of extrastriate cortex and adjacent temporal cortex in humans, chimpanzees, and macaques. Our results can be broken down into three findings: first, humans and chimpanzees show apparent major connectivity between V1c and temporal areas FG and ATL, unlike macaques; second, tractography reveals retinotopically organized streamline connectivity between V1 retinotopic subdivisions and extrastriate areas; and third, area MT+ presents special challenges for tractography.

Evolutionarily novel temporal connectivity in the hominoid lineage?

Our V1c-temporal cortex results in all three species are consistent with known primate extrastriate organizations, with strong macaque V1c connectivity in extrastriate areas V2 and V3 (Markov et al., 2011)(fig. 14A). In chimpanzees and humans, streamlines between the temporal ROIs and V1c are consistent with V2, V3, V4, and possible V6 connections (fig. 14B & 14C).

However, unlike macaques, our results provide evidence for connectivity from V1c to FG, anterior MTG, and ATL. The FG is a gyrus found in the ventral temporal cortex of humans and chimpanzees, medial to the inferior temporal gyrus, but not macaques. The MTG is a cortical convolution found in hominoids but not macaques, due to the presence of the inferior temporal sulcus, in addition to the STS common to both macaques and hominoids. The ATL is a large swathe of cortex in humans which encompasses the temporopolar cortex and anterior portions of the STG, MTG, and ITG. In macaques, the

anterior-most portion of the temporal lobe is referred to as temporal pole exclusively, and its homology with human ATL is unclear (Nakamura and Kobuta 1996; Olson et al., 2012).

Fusiform gyrus

In humans, the FG is known to house the fusiform face area (FFA), and two other visual recognition areas, the visual word form area (VWFA; Cohen et al., 2000; McCandliss et al., 2003) and the fusiform body area (FBA; Schwarziose et al., 2005; Peelen and Downing, 2005). Streamline connectivity between V1c and FG may represent V1c projections or, more generally, a portion of the ventral pathway reaching the fusiform face area (FFA). Macaques lack a discrete FG, however if we were to see similar connectivity patterns in macaques, we would expect to see streamlines reaching ventral temporal cortex. The lack of connectivity in macaques in the ventral portion of the temporal lobe is consistent with evidence that macaques lack an FFA. An FFA homolog in macaques, located in the anterior STS, has been proposed, based on fMRI data (Tsao et al., 2003; Tsao et al., 2006; Moeller et al., 2008; Pinsk et al., 2005; Pinsk et al., 2009), however, our data here did not reveal any significant streamline projections to this area in macaques. Moreover, it seems implausible that the face-sensitive zones in macaque STS could have been displaced so far in human evolution that they assume a location adjacent to parahippocampal cortex. Behavioral data support the interpretation that configural face processing is unique to humans and chimpanzees (Parr et al., 1998; Parr et al., 2006; Parr et al., 2008) and a chimpanzee homolog of FFA has been localized using PET (Parr et al., 2009). It is therefore not surprising that important differences in visual association areas were found between hominids and macaques. The V1-FG connections identified in humans and chimpanzees could be false positives. Given the lack of a tracer-based "ground truth" for humans and chimpanzees, it is

difficult to evaluate the status of connections revealed in humans and chimps with DTI that are not present in macaques. The same issue arises with other temporal connections discussed below.

Modified ATL connectivity in humans

Humans, and to a lesser extent chimpanzees, but not macaques, showed apparent major connectivity between V1c and the ATL (fig. 15). The ATL, a large swathe of cortex encompassing the temporal pole, is a multimodal association center that plays an important role in both semantic memory and affective cognition in humans. This encompasses language functions, including production and comprehension of spoken and written words and pictures (Coccia et al., 2004; Pobric et al., 2007), taste recognition (Small et al., 1997), olfactory memory (Rausch et al., 1977; Eskenazi et al., 1986) stimulus-invariant perception of emotional facial expressions (Schmolck and Squire, 2001; Cancelliere and Kertesz, 1990) generation of emotions in response to visual cues (Reiman et al., 1997), a storage site for unique, socially relevant entities, such as familiar people and landmarks (Damasio et al., 2004; Frith 2007; Kriegeskorte et al., 2007); comprehension of social concepts (Zahn et al., 2007; Zahn et al., 2009; Ross and Olson, 2010), emotional memory retrieval (Dolan et al., 2000) and coherent conceptual categorization of objects (Rogers et al., 2004; Lambon Ralph et al., 2010). The conceptual processing which occurs in the ATL has been argued to be transmodal, or perhaps amodal (Pobric et al., 2010), in that conceptual information is computed regardless of the sensory modality of the stimulus, constituting a modality-invariant semantic hub (Lambon Ralph et al., 2010; Visser et al., 2012). Others have argued that the ATL binds multimodal inputs with visceral emotional responses while maintaining segregation of perceptual modalities (Olson et al., 2007). These sometimes conflicting

reports can be categorized into three separate accounts of the role of the ATL in semantic memory: 1) as a supramodal/transmodal/amodal semantic hub; 2) as a storage site for unique entities (e.g., famous names and faces); and 3) as a center for social conceptual knowledge (Simmons and Martin 2009; Simmons et al., 2009).

Apparent major connectivity between V1c and ATL in chimpanzees extended from the ATL to the medial portion of the lateral temporal lobe, into the anterior MTG (aMTG; fig. 15). Human connectivity patterns were sparser and localized further anterior than in chimpanzees, concentrated in territories at the extreme anterior end of the temporal pole. It is important to note that although macaques do not possess a morphological MTG, we did not see connectivity in any portion of the temporal lobe anterior to unimodal extrastriate areas that might encompass putative homologs to hominoid MTG (fig. 14A & 15A).

Literature on MTG usually refers to the posterior half of the gyrus, which is well-documented in humans as an important language center (Bates et al., 2003; Dronkers et al., 2004; Hickok and Poeppel, 2004, 2007; Turken and Dronkers 2011). The anterior MTG (aMTG) is less well-studied, but available literature suggests that in humans, this territory is also part of a multimodal association area (Binder et al., 2009) involved in a semantic processing network (Copland et al., 2003, Schwartz et al., 2009; Butler et al., 2014). Human imaging studies have implicated aMTG in lexical decision-making, for example, exception word reading tasks (Wilson et al., 2012), visual word recognition (Pammer et al., 2004) and spoken word recognition (Roxbury et al., 2014). In one of the few studies examining the different role of anterior vs. posterior MTG, Vandenberghe et al. (1996) found aMTG had stronger activation in semantic tasks involving processing images of words rather than pictures when compared to pMTG; in contrast, Visser and co-workers (2012) found pMTG

specialized for semantic processing of words, while aMTG responds equivalently to both words and pictures. Both findings are consistent with a recent meta-analysis suggesting the full anterior-posterior axis of the MTG acts as a multimodal convergence zone (Binder and Desai, 2011). However, unlike pMTG, there is less evidence for aMTG as handling semantic and action knowledge related to tools. Anterior MTG appears to be recruited for recognition of famous faces (Leveroni et al., 2000) and proper names of famous individuals (Gorno-Tempini et al., 1998), tasks that may be considered as tapping into semantic "meaningfulness" (Binder et al., 2009). The latter two findings are similar to functions that have been localized in the ATL broadly, perhaps reflecting conflicting interpretations regarding the location and extent of the ATL as it encroaches posteriorly (reviewed in Bonner and Price, 2013).

In summary, chimpanzee and human FG, aMTG, and ATL show apparent major connectivity with V1c. Our FG data show apparent major connectivity between FG and V1c in humans and chimpanzees, suggesting important modifications to visual inputs to the ventral temporal lobe in the hominoid lineage. For MTG, the results in humans were restricted to anterior territories near the border of the ATL, while in chimpanzees the area extends to the middle portion of the MTG. In the ATL, we see strong streamline connectivity in both superior and middle temporal gyri in humans and chimpanzees, with heavier apparent connectivity in human superior and medial ATL. The lack of functional data in chimpanzees makes the differences in ATL results between the two hominoid species difficult to interpret.

Retinotopy revealed with cortico-cortical tractography

As predicted, selectively seeding portions of V1 yielded patterns of connectivity consistent with the known retinotopic organization of macaques and humans (e.g., Brewer et al., 2002). In all macaques and humans, we found foveal connections to lateral V2 immediately adjacent to V1, which is also consistent with known foveal representation in primates. Seeding of the upper parafoveal and peripheral representations of V1 in humans, chimpanzees, and macaques showed connectivity with ventral extrastriate areas, which represent the upper visual field; seeds in lower parafoveal and peripheral visual fields reached dorsal extrastriate areas (fig. 7A & 7B). Consistent with known patterns of visual field representation in primates, macaques present with parafoveal connectivity with V2 in the lateral occipital lobe, and peripheral seeds reached V2 on the medial surface. Human parafoveal and peripheral seeding both resulted in apparent connectivity with medial V2, which is consistent with known human visual field organization, wherein expansion of cortex has resulted in the movement of portions of unimodal visual cortices from lateral to the medial cortical surface. While the visual field organization of chimpanzee extrastriate areas has not been studied previously, our results in chimpanzees are generally congruent with our human and macaque results.

It is important to note that although streamlines from both parafoveal and peripheral masks in humans reached medial V2 territories, there is spatial differentiation between them. Streamlines from parafoveal seeds reached the posterior-most portion of V2, near the occipital pole, while those from peripheral seeds connected with anterior portions of medial V2 (17A & 17B). Also in the human dataset, we saw some overlap of upper and lower parafoveal and peripheral representations in V2. While the majority of streamlines from lower visual fields were confined to the expected ventral extrastriate, and upper visual field streamlines to dorsal extrastriate, there was some "cross-contamination" wherein upper

visual field seeds connected to ventral extrastriate and lower visual field seeds reached dorsal extrastriate, almost exclusively in the peripheral results (17B). There are several possible explanations: 1) some overreach of our original upper retinotopic seed mask into lower retinotopic territory, and of our lower retinotopic seed into the upper territory; 2) retinotopic representation of upper and lower peripheral fields are not completely spatially separated in the cortex in humans, but not in macaques or chimpanzees; or 3) noise in the dataset from inter-individual variability in the size and location of retinotopic areas, which could be related to the high degree of inter-human variability in visual cortex organization.

Retinotopic tracking between parafoveal ROIs and extrastriate areas reached higher-order visual areas and association areas in hominoids, including ATL in humans and ATL, aMTG, anterior STS, and inferior temporal cortex in chimpanzees, but not macaques. There are several possible explanations for this unpredicted, but not totally expected, result. First, it is possible that our upper parafoveal seed, which showed the most streamlines extending outside of unimodal cortex, may have been too generous, particularly in chimpanzees. Another possibility is that inter-individual variation of spatial location of retinotopic areas reduced the strength of high probability streamlines in the averaged tractogram results. In humans, V1 occupies a variable amount of cortical surface area, with differences in size between individuals ranging up to threefold (Stensaas et al., 1974; Andrews et al., 1997; Amunts et al., 2000; Dougherty et al., 2004). Secondly, the lack of temporal connectivity in macaques may be a false negative, given it is seen in both humans and chimpanzees but not macaques. Perhaps topographic and geometric differences due to the expansion of temporal cortex in apes facilitated tracking along the temporal lobe in those species. A final possibility is that these results reflect real differences in the parafoveal-temporal connectivity between hominoids and Old World Monkeys. This suggests that there may have been an expansion

of parafoveal representation in the ATL in humans and in both the ATL and ventral surface of the temporal lobe in chimpanzees. The implications of these differences will be explored in more detail in the section on temporal connectivity later in the discussion.

Troubleshooting cortico-cortical tractography: a case study in area MT+

In macaques and other non-human primates, traditional tract tracing methods have demonstrated that the MT complex is a major target of V1 connections. Our data showed poor fidelity to the MT+ region specifically when we targeted this territory using cortico-cortical tractographic methods. In macaques, visual motion area MT+ combines connections with primary visual cortex (V1) and the inferior parietal sulcus (IPS), which houses dorsal stream visual processing related to object location. Based on this well-established information, we ran tractographic runs from V1 and IPS to extrastriate ROIs encompassing the probable location of MT+ in all three species. This analysis failed to produce consistent streamline connections in the heavily myelinated MT+ territory. Magnifications of chimpanzee connectivity to IPS and V1c, and to a lesser extent human connectivity, reveal lacunae, or bare spots, which failed to receive streamline connections after thresholding (fig. 6E-H; 7E-H). These lacunae are bordered by areas of V1c and IPS connectivity where cortical myelin content is relatively lower.

Why does striate-extrastriate tractography succeed in producing some of the expected cortico-connections, but not those for MT+? Although one might conclude that a failure to track axonal projections to MT+ suggests a failure in the methodology to accurately localize cortico-cortical connections, repeated analyses using larger extrastriate masks and averaging across individuals (fig. 18) suggests probabilistic tractography may be particularly ill-suited for mapping connections in heavily myelinated territories. Perhaps

heavy myelin within gray matter introduces a "crossing fiber" type effect which obstructs streamlines. Another possibility is that areas which feature a steep gradient in myelin may bias streamlines towards adjacent gray matter. Another important variable to consider is the algorithm within the FreeSurfer package that interpolates the location of the gray matter-white matter border; since our ROI masks are drawn on this surface, any perturbation of the location of the border due to myelin content would impact the depth of the seed voxels, which in turn could cause problems with streamline integrity. Our results suggest that for area MT+ in primates, diffusion-weighted imaging produces artefacts of a methodological origin that interfere with cortico-cortical tractography.

Expansion of multimodal temporal cortices in humans

Taken together, these data suggest important modifications to temporal association areal organization in the hominoid lineage. Further, chimpanzee- and human-unique features of temporal organization are located in temporal areas that have expanded in hominid evolution. This supports the notion that human (and chimpanzee) brains are not simply large macaque brains, but rather that cortical reorganization accompanied cortical expansion. Functional magnetic resonance imaging (fMRI) work and studies of individuals with localized atrophy or lesions have illuminated the functional properties of these expanded cortical regions.

Here, it is important to note the differences in MTG connectivity we observed in humans and chimpanzees. Human V1c-aMTG streamline connectivity is concentrated very far anteriorly, closer to the temporal pole than the pMTG territory that has been associated with human language functions. Given the cortical expansion unique to humans among hominoids, it is reasonable to postulate that the visual-temporal connectivity may have

developed in the MTG in the hominoid lineage and was later modified with human cortical expansion to occupy cortical areas further anterior, perhaps displaced by the expansion of pMTG territories. This interpretation would mean that human and chimpanzee MTG areas with V1c apparent connectivity are homologous higher-order visual association areas. Another possible interpretation is that V1c-MTG connections were modified in different ways since the *Homo-Pan* split, with either chimpanzees expanding visual connectivity in middle temporal gyrus areas or humans losing these connectivity patterns. Without additional information from other hominoid species, it is not possible to disambiguate these three alternatives. These findings do, however, point to the aMTG as an important site for hominoid evolution, with likely ramifications for the evolutionary foundations of language and tool use.

Technical issues with imaging the temporal pole regions in humans have limited the number of studies finding functional activations and/or structural connectivity, due to inhomogeneities in the magnetic field at air-bone interfaces (Schmithorst et al., 2001; Weiskopf et al., 2006) resulting in distortions which demonstrably interfere with signal detection (Devlin et al., 2000). It is conceivable that the larger muzzles and greater sinus volume in chimpanzees may result in even greater levels of signal distortion than in humans. Thus, one possible interpretation of our data is that human and chimpanzees have similar anatomical patterns of apparent major connectivity between V1c and ATL, and that the sparser connectivity in the chimpanzee ATL is an artefact of signal noise (fig. 15B & 15C, gray arrows). On this view, humans and chimpanzees share V1c-ATL connectivity as an evolutionarily novel reorganization of temporal cortex. However, if we are to assume that technical issues that interfere with signal detection are similar between the two species, it is clear that humans have stronger apparent major connectivity between the ATL and V1c,

particularly in the superior portion of the ATL. Further, in humans, apparent connectivity extends medially to wrap around the temporal pole, reaching the border of entorhinal cortex (fig. 15C, gray arrows). This interpretation would suggest that while hominoids share ATL-V1c connectivity, modifications have occurred in the human lineage that have expanded V1c representation in the ATL, particularly in the medial and superior portions.

The relevance of the specific portions of ATL to cognition is unclear, as few studies in humans have managed to subdivide the ATL into discrete functional units. However, the superior ATL has been linked to processing of abstract social concepts (Zahn et al., 2007), in contrast to inferior ATL, which has been found to be a hotspot for semantic memory (Visser et al., 2010). Our results suggest modifications to V1c connectivity patterns with human ATL may be related to social cognition in humans.

Critical data on the function of ATL in humans has come from the study of patients with semantic dementia or primary progressive aphasia, wherein progressive atrophy of the temporal poles bilaterally produces a unique deficit in core semantic knowledge that encompasses both receptive and expressive tasks (Lambon Ralph and Patterson, 2008). Lambon Ralph and Patterson (ibid) observed undergeneralization and overgeneralization of concept in these patients, and suggest that the ATL plays a crucial role in binding perceptual features across stimulus categories to form modality-invariant conceptual information that links back to modality-specific association cortices. Our results in humans are consistent with this view, in that apparent connectivity patterns with primary visual areas is strong but does not cover the entire ATL territory. Further work is needed to support this interpretation, for example, diffusion tractography of connectivity patterns between the ATL and the auditory core and pyriform cortex, which house sensory modalities that have been

linked to semantic memory. Without these data, it is unclear whether chimpanzee V1c-ATL connectivity represents connections with a modality-invariant semantic hub or simply an expansion of higher order visual association cortex. Other features of human ATL organization which have been implicated in functional studies as being associated with the human-specific functions of the ATL, particularly theory of mind, involve the interconnection of ATL with medial prefrontal areas, retrosplenial and anterior cingulated cortices, and orbitofrontal areas. One possible method for determining the nature of the homology between humans and chimpanzees would be to identify an ATL structural connectivity "fingerprint" using tractography in humans, chimpanzees, and macaques.

Another important consistent finding in human ATL studies is the comprehension and expression of social knowledge. Olson and colleagues (2012) propose, based partially on a review of human and non-human primate studies, that connectivity with the amygdala and orbitofrontal areas underpins this function, which is arguably a form of semantic or conceptual knowledge processing that privileges emotionally salient information. Evidence for vocal and facial identity discrimination in macaque ATL (Rendall et al., 1996; Rendall et al., 1998; Perrett et al., 1992), combined with our lack of V1c-ATL apparent major connectivity in macaques, suggests that the ATL's function as a center for social cognition may be more ancient than its semantic component.

Many single-cell recording studies have found responsiveness of macaque neurons along the temporal lobe, including the anterior-most portions, to visual stimuli (e.g., Desimone and Gross, 1979). On first glance, this may seem to suggest our results are not reflective of "real" neuroanatomical connections. It is important to make two distinctions here: first, single cell responsiveness to stimuli is not an indicator of direct connectivity; it

merely reflects the sensitivity of a particular neuron to activation. One possible explanation for the discrepancy is that visually sensitive anterior temporal lobe neurons in macaques are being stimulated by connections from other visual association areas, and not directly from primary visual cortex. Perhaps macaque visual association areas are characterized by serial connectivity, and hominoid visual association areas, in contrast, contain multiple parallel processing streams from different levels of sensory processing.

A second important conflict with our results comes from previous histological studies. Anatomical connectivity between striate cortex and extrastriate areas in macaques has been examined in detail. Rockland and Pandya's (1981) retrograde and anterograde tract tracing study showed primary visual cortex connecting with extrastriate regions, including Brodmann areas 18 and 19, as well as the posterior third of the STS. Connections between V1 and the posterior portion of STS, particularly the posterior bank, have been well documented in both tract-tracing (Rockland and Pandya, 1979; Montero, 1980; Weller and Kaas, 1983; Maunsell and Van Essen, 1983) and lesion studies (Kuypers et al., 1965; Zeki, 1969, 1971,1976; Cragg and Ainsworth, 1969; Seltzer and Pandya, 1978; Ungerleider and Mishkin, 1979). These data are part of a larger literature on macaque extrastriate organization supporting a model in which V1 connections to MT+ constitute a major part of the dorsal visual pathway in primates (Mishkin et al., 1983). Problematically, our data do not resolve apparent connectivity between our striate ROI seeds and posterior STS in macaques. However, the lack of V1-MT+ and IPS-MT+ apparent connectivity across all three species in our study suggests imaging or methodological artefacts interfere with streamlines successfully reaching this cortical territory. Further work is needed to determine whether additional issues pertain to striate-extrastriate tracking that are unique in macaques or if our lack of extrastriate results beyond V3/V4 in macaques reflect real differences between

macaques and hominoids. However, the confirmation of known retinotopic organization of early visual areas in macaques and humans, along with the consistentcy of the MT+ lacunae finding across species, suggests diffusion tractography is an effective method for revealing extrastriate organization in primates.

One possible explanation of the differences between macaque and hominid striate-extrastriate apparent major connectivity may lie in modifications to fascicular organization as a direct result of evolutionary specializations or as a knock-on effect of cortical and white matter expansion in hominoids. Human inferior longitudinal fasciculus (ILF), a fiber bundle that travels along the temporal lobe, extends into visual cortex posteriorly and medially in humans, plausibly reaching V1 (Catani and Thiebaut de Schotten, 2008), while macaque ILF appears to terminate prior to the occipital pole (Schmahmann et al., 2007). It is possible that our heavy streamline termination in temporal areas in our V1c-temporal cortex results in hominoids are due to these ILF terminations. Conversely, the lack of ILF coherency in macaque occipital lobe may have limited the amount of streamlines that were able to travel long distances between V1c and temporal cortex in our macaque dataset.

In summary, our study has provided evidence for modifications to visual pathways within the temporal lobe in the hominoid lineage. FG, a higher order visual association area responsible for configural face processing in apes, shows patterns of apparent major connectivity with V1c in chimpanzees and humans, but not macaques. MTG, a higher-order visual and auditory association area, also shows apparent major connectivity with V1c in humans and chimpanzees, with some anterior displacement of V1c connectivity hotspots possibly occurring in the human lineage. Lastly, ATL, a multimodal association area and cognitive hub for semantic and social concepts, demonstrates apparent major connectivity

with V1c in chimpanzees and humans, with particularly robust results in the superior and medial ATL in humans. Given the important role of human MTG and ATL in language and conceptual processing, this work offers evidence for a neuroanatomical substrate of semantic cognition which may have arisen in the hominoid lineage, prior to the human-chimpanzee split.

DISCUSSION

PART 3: METHODOLOGICAL CONSIDERATIONS FOR CORTICAL MAPPING OF TEMPORAL ASSOCIATION AREAS IN THE HUMAN AND HOMINOID LINEAGE

Human temporal lobe structure is unique among primates in that it features a disproportionate expansion of association areas. It is reasonable to surmise that these expanded areas are crucial to human-unique abilities in manipulating conceptual representations. Language, abstract concepts, and the use and manufacture of tools are prominent examples of our ability to construct conceptual representations. Temporal cortex is responsible for forming these representations by combining sensory information from different modalities to create abstractions. In other words, the human temporal lobe produces meaning.

Multiple intellectual debates are directly related to the function of the temporal lobe in primates. First, the interplay between thought and language has been discussed extensively among psychologists and philosophers. Does language control thought, or is it the other way around? Is there some form of internal conceptual mediator between the two? Another debate is the relationship between conceptual representations in humans and non-human apes (especially chimpanzees). How are chimpanzees different than us in their understanding of how tools work? How about their conceptualization of their own minds, and other minds (theory of mind)? With regard to conceptual representations, are chimpanzees more like other primates, or more like us?

The role of evolutionary neuroanatomy

Work to characterize the differences in brain size and structure in the hominid lineage has been carried out in the field of biological anthropology, where study has focused on the study of endocasts from extinct hominids (sometimes termed paleoneurology). Data from these disciplines have supported the notion that human evolution is characterized by increases in petalial lateralization (Holloway and De La Coste-Lareymondie, 1982), and have helped pinpoint when gross morphological changes may have occurred in our ancestry (e.g., Falk et al., 2000). Brains do not fossilize, however, putting limits on the structural information we can infer from cranial impressions. The next best option for understanding the evolution of the human temporal lobe is the examination of extant primate species.

Knowledge about our closest relatives, the chimpanzees, is particularly critical to this line of inquiry. Although this has long been appreciated, there is, despite many years of intensive research, relatively little consensus in the field of comparative cognition about the cognitive abilities of chimpanzees vis à vis humans. If we focus on cognitive functions that are housed in the temporal lobe, a review of the literature shows cognitive researchers have both supported (Gardner and Gardner, 1969, 1975, 1980; Savage-Rumbaugh et al., 1977, 1985) and disputed (Terrace et al., 1979; Wallman, 1992; Rivas, 2005) the idea that apes possess language or language-like abilities. Also, there is also substantial disagreement on whether chimpanzees possess theory of mind (e.g., Povinelli and Preuss, 1995; Penn and Povinelli, 2007; Matsuzawa, 1996; De Waal, 1991; Whiten, 1996; Hare et al., 2001).

Where paleoneurology and chimpanzee cognitive research have stalled, comparative anatomical research may be able to provide insight into how human and chimpanzee brains differ. We know a good deal about the differences between humans and macaques temporal structure, but much less is known about chimpanzees. Understanding the cortical

modifications that occurred since our split with chimpanzees and bonobos is important for deducing what human specializations may underpin human conceptual processing. Did human evolution since our divergence from chimpanzees involve the selective expansion of certain association areas, or addition of new functional and structural territories unique to humans?

Evolutionary neuroanatomists first need a concrete plan for evaluating structural differences in the temporal lobe. First, homologous areas between humans and other primates need to be identified so that putative sites of expansion can be identified. But how do we identify a discrete cortical "area"?

Dividing up cortex

It is difficult to discuss areal organization without discussing the significance of the notion of modules. The module concept originated in observations about repeating, regular architecture in the brain. Scheibel and Scheibel's (1955; 1958) neuroanatomical descriptions of discrete units in the inferior olive were some of the earliest (Szentágothai 1978). Scheibel and Scheibel defined these units' boundaries by the interaction of excitatory and inhibitory neurons, with each architectural unit composed of internal excitatory networks surrounded by inter-unit inhibitory neurons. These concepts were successfully generalized to cerebellar nuclei and eventually cerebral cortex (Eccles et al. 1967; Szentágothai 1967). Szentágothai and Arbib (1974) later advanced a detailed structural-architectural model for modular organization. During this period, as evidence for the columnar arrangement of cortex grew, it bolstered the notion of repeating patterns of structural organization as a fundamental feature of cerebral cortex.

Szentágothai's "excitatory modules" are actually only a few dozens of microns wide,

and contain one single pyramidal cell with its surrounding spiny stellate cells and inhibitory neurons, and in fact are numerous within the columns themselves (micro-columns within columns), which tend to range from 200-300 microns wide. Already in this period, the importance of layer location for the termination of neurons in distant parts of the cortex (layer III neurons tend to synapse ipsilaterally, while cells in layers II-VI tend to synapse contralaterally) suggested that an important, inseparable feature of local, modular circuits is the organization of distant connections between them. Interestingly, Szentágothai's speculations about the relationship of these columns to one another feature language about networks, i.e., "nodal concentrations in diffuse connections" (Szentágothai 1978, p. 245) facilitated by overlapping arbors between modules.

Russian neuroanatomist L.S. Vygotsky also emphasized the network-like properties of module function, which he described as "dynamic systems" of inter-areal relations which can be modified over the course of development (Luria, 1965). Inspired by psychological approaches, which he wished to unite with structural observations, Vygotsky surmised that scientists will only be able to localize brain functions if they understand first that functional outputs are the result not of a specific, limited zone but as a "product of hierarchically organized functions of separate zones of the brain" (Vygotsky, 1965). Vygotsky's particular inter-disciplinary approach and attempt to reconcile functional and structural organization was prescient, as definitions of module began to diverge in the mid-80s, depending on the discipline of the definer.

Fodor's seminal interpretation of modules defined them as neural systems possessing the following features: fixed neural architecture, domain specificity, encapsulation, automaticity, inaccessibility to consciousness, speed, shallow outputs, fixed neural

localization, and characteristic breakdown patterns (Fodor, 1983). Fodor's model emphasizes the physical instantiation of modules in the brain; five of his nine features refer directly to structure (fixed neural architecture, domain specificity, encapsulation, shallow outputs, and fixed neural localization).

Other workers have identified modules based on functional properties. Modules that have been proposed primarily on the basis of function, rather than structure, include language (Chomsky, 1980), spatial orientation (Hermer and Spelke, 1996), number (McCloskey et al., 1990), emotion systems like fear and disgust (Öhman and Mineka, 2001; Rozin, Haidt, and McCauley, 1993), and face recognition (Duchaine et al., 2004; Kanwisher, 2000). Since many of these workers come from psychology and philosophy, it is not surprising that their interpretation of modularity focuses on behavioral characteristics. These approaches, however, bear little resemblance to the purely structural, often microanatomical, approaches described earlier.

Arbib and colleagues (1997) describe the search for functional modules in their book as a question of neuroanatomical localization. Modules are described in the same breath as local circuits, cortical laminae, and other architectonic features. As he did with Szentagothai several decades prior, Arbib and colleagues (and others; e.g., Herculano-Houzel et al., 2007) use the term "modules" to mean cortical columns. Our current state of understanding with regard to cortical columns is that they contain a common microcircuit that receives thalamic inputs to layer 4 and local interactions between areas within the column. Further, columns appear to be isolated from each other via inhibitory connections between each other. The classical example of a cortical column are the patchy groupings of visual inputs to the primary visual cortex, which form a checkerboard-like pattern of color sensitivity due to the

arrangement of cortical columns. The module, according to this paradigm, is the individual cortical column that receives and processes a particular color input (yellow, for example). Although the authors are explicitly interested in understanding the function of these modules, they describe the modules as structural units first, and treat the question of function as something to be understood after the neuranatomical groundwork has been laid down.

Bridging the gap between structural and functional approaches

At the beginning of Part 3 of the discussion, I argued that the temporal cortex in humans is the substrate for producing meaning. If the production of complex conceptual information, or meaning, is a human specialization, it follows that important modifications to the temporal cortex must have occurred in the human lineage in order to provide a substrate for these cognitive adaptations. In order to identify these modifications, we must find a way to join structural and functional approaches to brain mapping together.

Some candidate modules have bridged the structural/functional gap: Kanwisher has proposed the fusiform facial area (FFA), a cortical territory located on the underside of the anterior temporal lobe, as a locus for face identification. Theory of mind has been proposed as a specific module (Charman and Baron-Cohen, 1995; Leslie, 1994; Scholl and Leslie, 1999) that has been localized to the temporo-parietal junction (Saxe and Kanwisher, 2003). Turken and Dronkers (2011) used a combination of structural and functional data to identify an anteriormost portion of the pMTG in humans that has both the most extensive interconnectedness with AF, IFOF, and MdLF of all the pMTG territories, but also appears to lead to the most devastating language comprehension deficits in cases of lesion to the area. Although Turken and Dronkers do not use the term "module" in their paper, one

could argue that this territory is a candidate for a language comprehension module, both structurally and functionally.

An approach to understanding brain organization through the studying modules from both functional and structural perspectives can be applied to chimpanzees and other primates to create detailed comparative cortical maps of the temporal lobe. These structural/functional modules can provide manageable objects on which to apply evolutionary frameworks. A module can be thought of as the equivalent of a fossil bone or tooth for the anthropologist. For example, if we identify and define a module structurally, through diffusion tractography, and functionally, through fMRI or from behavioral changes in patients with lesions in the area of interest, we can turn our study to the brains of our primate relatives to look for structural homologues. Like a fossil bone or tooth, we know that structural homology may not imply identical function, but it can provide clues.

Structural connectivity is being probed with higher resolution and greater breadth than before with DTI. A more recent methodology, functional connectivity (fcMRI), use coincident activations across the brain to infer structural connectivity. The two fields appear to corroborate each other (Damoiseaux and Greicius, 2009), suggesting that the major white matter pathways which are trackable in DTI represent important functional groupings of cortical areas. For example, Greicius and colleagues (2009) found that bilateral cingulum bundles interconnected the posterior cingulate cortex (PCC), the medial temporal lobes (MTLs) and the medial prefrontal cortex (MPFC), regions known to activate as part of the default mode network. When followed up by an fcMRI analysis, the same functional connectivity appeared (albeit with an extra connection between the PCC and the MPFC which did not appear in the DTI analysis). As a side note, there are two possible

explanations here: first, the posterior cingulate cortex serves as a relay between MPFC and MTL; or second, the resolution of the DTI image is too coarse to detect a thin connection between the MPFC and MTL (which is possible, as DTI resolutions generally do not dip below 1 mm^3, much larger than a single axon or a bundle of axons).

This work has ramifications for the cognitive sciences and psychology in relation to understanding the brain as being composed of discrete functional units. Here we see support for the idea that a module may be physically constructed of a network of smaller areas that traverse rather large portions of cortex. One challenge of this approach is that the way that cortical territories are interconnected could become complex very quickly. For example, if we look at one territory, posterior cingulate cortex, and see that it as part of the default mode network, we must keep in mind this doesn't preclude PCC from participating in other large-scale networks. In Turken and Dronkers' study (2011), we find that the MTG has inputs from many fasciculi (among many, the IFOF, the AF, and the EmC pathway). This suggests that a single cortical territory (the pMTG, for example) participates in multiple functional networks.

Cortical networks

Understanding the organization of association cortex in humans may benefit from the network approach. In the network perspective in brain mapping, cortex is composed of nodes, each of which is interconnected with other nodes (no node is an island). Certain areas of cortex, particularly association cortices, contain nodes of convergence, or cortical *hubs* (Mesulam, 1998). In addition to synthesizing and coordinating inputs from multiple cortical nodes, these hubs may also serve as information gateways which gather local information and forward it across long-distance connections, thereby contributing to larger-

scale cortical networks (Bassett and Bullmore, 2006). Consistent with this interpretation, macaque tract-tracing data indicate that association cortex is characterized by long-distance connections (Goldman-Rakic, 1988), which Mountcastle (1997) viewed as strong evidence for the importance of understanding module function as part of long-range interconnected systems. Resting state fMRI data also provide corroborating evidence in humans, with hubs in association areas featuring greater long-distance connectivity and less local internodal connectivity, unlike primary sensory cortex (Achard et al., 2006; Sporns et al., 2007).

The problem of cortical mapping and the role of modular organization was considered by Mountcastle (1995) to be explicated by understanding "higher" cortical functions as part of what he called distributed systems. Many features of Mountcastle's distributed systems overlap with network models of cortical function. For example, Mountcastle lists as one of the fundamental properties of distributed systems as "they are not hierarchical, although some subsystems may have hierarchical properties". Could hubs be the nodes within distributed systems that operate with some hierarchical properties?

Hubs remedy some functional localization problems. First, they solve the issue of finding devoted cortical territories. We know some areas perform more than one function, but that is permissible in the network theory model. Each hub may have multiple functional networks tied to it, each of which has different (although probably often related) functions. Take the superior temporal sulcus, for example. It has been implicated in neuroimaging studies for being responsible for a plethora of processes: audiovisual integration, motion processing, speech processing, social perception, and theory of mind (reviewed in Hein and Knight, 2008). Hubs solve this problem by offering a unified portion of cortex that integrates information from multiple regions and forward this information to a larger

network, as the information pertains to a particular problem. Hubs can be the devoted cortical territory of interest, without being the only player in a particular function. Hubs and nodes explain why certain types of lesions (pMTG lesions, for example) can have devastating effects on function, while others have minor effects, even if the lesion is in a location that is known to activate during specific tasks. The pMTG is a language hub; if you lose it, you cannot compensate with redundant connectivity or move around it via another auxiliary connection. Other areas, like BA 46, while contributing to language function, produce mild deficits when lesioned. BA 44, part of Broca's area, produces moderate deficits that frequently ameliorate over time. On this view, neither Brodmann areas 44 or 46 are hubs in the language system and therefore not responsible for integrating the multiple inputs required for language comprehension.

The problem of homology

This leads to an important question: Can we identify homologous hubs across primate species? To investigate the function of a module of interest in a non-human primate, there are some important practical considerations. In macaques, it is possible to acquire fMRI data in some cases, but fMRI in chimpanzees is not currently possible. Another complication to chimpanzee research is the recent US federal mandate to retire the majority of research chimpanzees, meaning access to *in vivo* structural scans for chimpanzees may be coming to an end. Li et al. (2013) offer a solution – identify hubs from a structural perspective across primate species using diffusion tractography combined with graph theory. Here, putative hubs were found in association areas, including medial parietal cortex, inferior parietal cortex, insular cortex, medial prefrontal cortex, and ventrolateral prefrontal cortex in both macaques and chimpanzees, while humans showed differences in the location of

parietal hubs (one additional hub in the intraparietal sulcus and superior parietal cortex), as well as a novel hub in retrosplenial cortex. Detailed structural information about network organization of the temporal lobe is needed in chimpanzees in order for us to infer whether these networks are expansions of conserved hominoid cortical areas, or new forms of cortico-cortical organization.

Two temporal cortex hubs that have been proposed to exist in humans are the ATL and the pMTG. The ATL, a transmodal or amodal conceptual processing center (Pobric et al., 2010) has been proposed to be a modality-invariant semantic hub (Lambon Ralph et al., 2010; Visser et al., 2012) that combines auditory, visual motion, olfactory, and gustatory processing streams (Binder and Desai, 2011). Similar to the findings of Turken and Dronkers on the criticality of the pMTG for language comprehension, Lambon Ralph and Patterson (2008) report that patients with bilateral atrophy to the temporal poles (semantic dementia or primary progressive aphasia) present a unique deficit in core semantic knowledge that encompasses both receptive and expressive tasks (Lambon Ralph and Patterson, 2008). These patients initially undergeneralize during categorization tasks (i.e., fail to group together all the objects that belong to a category, instead breaking them into smaller subgroups) and later, as the atrophy progresses, tend to over generalize (lump objects that belong in different categories together), and suggest that the ATL plays a crucial role in binding perceptual features across stimulus categories to form modality-invariant conceptual information. This suggests that the ATL, in humans, operates as a semantic hub that links to modality-specific association cortices. Our diffusion tractography data suggest that temporopolar regions in chimpanzees and humans share organizational features related to visual inputs that macaques do not possess. One possible interpretation of our data, within

the network theory framework, is that the development of an amodal or super-modal conceptual processing hub in the temporal pole is a hominoid specialization.

Evidence has been mounting for the significance of pMTG in language comprehension (Hickok and Poeppel, 2004, 2007, Dronkers et al., 2004; Bates et al., 2003), potentially so crucial to language production and comprehension as to constitute another "semantic hub" (Turken and Dronkers 2011), in addition to ATL. Functional MRI and transcranial magnetic stimulation data in humans suggest this region functions as a hub connecting to "spokes" or distributed areas in the left inferior frontal gyrus and inferior parietal cortices (Jefferies 2013). Our data did not identify any human-unique organizational features of pMTG based on tractography from visual cortices; however, aMTG did have novel streamline connectivity in humans and chimpanzees. Whether the aMTG and ATL streamline connectivity in humans and chimpanzees are homologous is not clear, because we do not know how temporal cortex territories have shifted and/or expanded in human evolution. However, to explore the possibility that our results in aMTG in humans and chimpanzees are homologous, it is worth examining what functions this territory has in humans.

If the pMTG and ATL are human semantic hubs, what role might the aMTG play? The anterior MTG (aMTG) is another multimodal association area (Binder et al., 2009) involved in a semantic processing (Copland et al., 2003, Schwartz et al., 2009; Butler et al., 2014). The aMTG specializes in semantic tasks that involve reading (Wilson et al., 2012), and word recognition more broadly, both in the visual (Pammer et al., 2004) and auditory modalities (Roxbury et al., 2014). In comparison to the ATL and the pMTG, it is plausible that the aMTG, like the pMTG, plays a role in language comprehension, but that unlike the

pMTG, it recruits more heavily from visual inputs. aMTG equally responds to words and pictures, unlike pMTG, which is biased towards words (Visser et al., 2012). In this way, the aMTG is like the ATL; it is a fully multimodal territory that can process concepts regardless of perceptual modality. Like the ATL, aMTG is recruited in the recognition of famous faces (Leveroni et al., 2000) and proper names of famous individuals (Gorno-Tempini et al., 1998). Perhaps the aMTG, in sharing functions with both pMTG and ATL, serves as a multimodal node which connects two semantic hubs with different roles in the production of language and processing of semantic information. On this view, our data, showing streamline connectivity to aMTG in chimpanzees and humans, but further posterior (near central MTG) in chimpanzees, can provide clues on the evolutionary changes to this network. One possibility is that the development of language in humans caused visual representations, important for aMTG node functionality, to be pushed further anteriorly in the human temporal lobe. In our study, the left hemisphere was examined in all three species. Repeating our analysis on the right side may reveal whether similar modifications occurred to right aMTG in human evolution. Given the lateralization of the human brain in regard to language comprehension in production, we could hypothesize that the right aMTG might possess organizational features more similar to the chimpanzee left aMTG.

Intra-species variation

It is important to remember that there may be important structural variation between individuals. Saygin and co-workers (2012) probed this issue by developing a novel connectivity fingerprint approach that combined structural and functional neuroimaging. These authors report that for many subjects, instead of seeing a single area of face-selective activation in the FG, two adjacent but discrete areas of were observed. Creating individual

structural/functional maps is possible and indeed may be important for finer-grained cortical module mapping. Using "average" brains in neuroimaging studies is considered standard in the field, but this methodology does have flaws. One important problem with averaged brains is the distortion of scan data, which necessarily occurs during "warping" of individual brains to a brain "template". Each individual brain's volumetric and/or topological data is shifted to conform to the template, and as a result, noise is introduced. A second problem is the common practice of analyzing MR data at a population level. While boosting p-values, this method arguably obscures details of organization by blurring them into structural trends rather than individual maps. Work by Saygin and colleagues (2011) supports the notion that individual cortical organization in association areas varies, and further, that averaging brains obscures complexity of organization of higher order areas; in this case, two discrete "FFAs" were identified that had previously been collapsed and obscured into one single area in traditional group-based analyses.

In summary, several methodological challenges present themselves in the current and future endeavors to map the human brain. In order to understand the significance of human brain structure from an evolutionary perspective, it will be important to take into account the relationship between structure and function at the level of cortical organization; the inherent interconnectedness of cortical function, which will necessitate the consideration of the role of cortical areas in networks; the importance of highly interconnected hubs as part of association cortex organization; and the possible significance of inter-individual variation. Lastly, practical considerations require a methodological work-around when it comes to directly comparing humans with chimpanzees. Without chimpanzee functional neuroimaging data, it is necessary to examine human and macaque functional data in a comparative manner, in concert with structure, in order to infer the cognitive function of putative

homologs in the chimpanzee temporal lobe.

Future Directions

The next step is to determine how whether the ATL in chimpanzees is homologous as a hub in humans and chimpanzees. Data from this tractography study provides evidence that patterns of connectivity between the ATL and visual cortex evolved in the hominoid lineage. But we now need additional lines of evidence to evaluate these putative homologous hominoid hubs. To gather more evidence for structural homology, there are several options. First, since the ATL in humans is well documented as a sensory integration center, we might consider reproducing our study with tractography between auditory core and the temporal cortex in humans, chimpanzees, and macaques. We would expect to see streamline connectivity concentrated in the temporal pole in humans and chimpanzees, but not macaques, if the ATL is a site of convergence for these inputs. Other sensory modalities could be investigated as well – tracking from piriform cortex and anterior insula (which houses gustatory cortex in humans), for example.

Part of hub functionality is the participation of a hub in multiple small networks. We might expect the ATL hub in humans (and a putative ATL hubs in chimpanzees) to have long distance connections with prefrontal cortex, posterior temporal lobe, and parietal areas, as part of a language network. These connections could be investigated using graph-theoretic analyses of diffusion tractography, similar to those conducted by Li et al. (2013), or even more simply, by analyzing the global connectivity of the ATL by seeding a region of interest based on other data, for example, cortico-cortical tractography.

Another possible source of converging evidence would be a fasciculo-cortical tractographic analysis, similar to the work by Turken and Dronkers (2011) used to identify a

putative hub in human pMTG. Here, evidence for hub-like function (in the form of devastating loss of function after injury to the area) correlated with local strong interconnectivity with major fasciculi. The anterior expansion of arcuate fibers in humans, and to a lesser degree, chimpanzees (Rilling et al., 2008) suggests modifications to fascicular architecture may accompany the evolution of novel cortical hubs. In humans, we might expect to see greater fascicular connectivity to ATL as compared to neighboring regions – in addition to the AF, we might expect to see MdLF and IFOF, as in the pMTG (Turken and Dronkers, 2011). We might also expect to see stronger streamline connectivity with the ventral pathway, another fasciculus implicated in language function. Given the cingulum's role in emotional processing, and the possible role for human ATL in processing emotional saliency of semantic information, we might expect to see stronger streamline connectivity with this fiber bundle as well. The same analyses could be performed in chimpanzees and macaques to determine if similar hotspots of fasciculo-cortical connectivity appear.

Histology also offers an inroad for localizing territorial boundaries in a comparative fashion. Other possible techniques include the development of more detailed myeloarchitectonic maps. Another is the development of methods to correlate cortical thickness of disparate territories, which appears to correspond structural networks of connectivity (Chen et al., 2008). One could imagine a geographic information systems-type of methodology, where multiple layers, each containing a different type of information on cortical structure and organization, could be overlaid.

With regards to identifying the functional homology, we are limited by the lack of noninvasive techniques available for chimpanzees. Producing detailed comparative structural neuroanatomical maps, and examining these data alongside functional data in humans and

macaques, however, may permit us to develop a better understanding of how the temporal lobe was modified in hominoid evolution, and in turn, a better understanding of how the human temporal lobe was shaped by evolution to produce highly complex semantic and conceptual representations.

Meaning is crucial to the human experience. Knowledge about the structural uniqueness of the human temporal lobe cannot directly answer the question of what meaning is as a phenomenon, but is part of a larger project of comparative human brain mapping which has the potential to lay a foundation for understanding of the physical instantiation of meaning in the brain. Changes to ATL, FG, and aMTG organization with respect to primary visual inputs offer candidate areas for the substrate of human and chimpanzee functional specializations. Modifications to ATL organization observed in humans and chimpanzees provide candidate structures for both a novel cortical hub in hominoid evolution, and the substrate of meaning in humans.

EPILOGUE

EPILOGUE:

STARTING WITH THE PRIMATE IN THE MIRROR

Our relationship with chimpanzees sparks our imaginations because we share so many similarities, yet chimpanzees have important behavioral differences which beg the question as to the content of their minds. Ultimately, many of us want to know whether or not chimpanzees are our intellectual kin. If so, what features of mind do we require in order to grant this status? If not, in what ways are humans different? These questions have profound implications for animal rights and welfare debates, including questions about conservation and the status of apes in captivity.

Empirical documentation of chimpanzee cognition tends to focus on abilities that chimpanzees lack or possess in a lesser capacity than found in humans. As standpoint theory would predict, human experimenters are so influenced by their viewpoint that we create what is known in postmodern theory as "situated knowledges" – ways of knowing that reinforce notions of human superiority within the animal kingdom. Although we do not currently have access to chimpanzee situated knowledges, it is still important to acknowledge the legitimacy of learning and understanding chimpanzees for their own sake.

One of the surprising and striking features of the popular arm of primatology is the gesture to speak for "humanity": for all of us. As the byline of Frans de Waal's 2005 book *Our Inner Ape* promises: "A Leading Primatologist Explains Why We Are Who We Are". Who are we? And why are we that way? Primatologists often explicitly or implicitly embed these questions within their theoretical frameworks, interpretations of animal behavior, and

the research questions that guide the field. When implicit, we can use writings and illustrations to illuminate the assumptions, hopes, and yearnings of the primatologist and their popular science audience.

A 30-something white man in a business suit is on the cover of *Our Inner Ape*, reading a newspaper on a city park bench while holding a partially eaten banana. The message is clear: the white, educated, industrialized, rich, democratic (WEIRD; Henrich et al., 2010) man, dressed up in the trappings of "civilization", with his expensive-looking suit, his (overly) shiny shoes, and what looks suspiciously like the business section of the New York Times, cannot obscure his fundamental ape nature when it comes to his appetite for tropical fruit. His face, partially obscured by the newspaper, invites the reader to project him or herself onto him.

And indeed, de Waal returns frequently to the theme of projection, of mirroring, as a way to understand "ourselves". "Primates arouse a certain nervousness because they show us ourselves in a brutally honest light, reminding us […] that we are mere 'naked apes'. It's this honest light that we seek, or ought to seek, and the beauty is that now we know more about the bonobo, we can see ourselves reflected in two complementary mirrors" (p. 41, referring to the closest human relatives: chimpanzees and bonobos). Later, discussing the evolutionary path of humans (p. 250): "[The human species] is capable of unbelievable destruction of both its environment and its own kind, yet at the same time it possesses wells of empathy and love deeper than ever seen before. Since this animal has gained dominance over all others, it's all the more important that it takes an honest look in the mirror, so that it knows both the archenemy it faces and the ally that stands ready to help it build a better world." De Waal seems to argue for an evolutionary-based origins story - where looking (back) at the

chimpanzee and the bonobo will help give us clues to our "true" selves. Perhaps by looking in the mirror, we will see the ape within.

Will the ape give us what we seek, or is the chasm between our subjectivities too wide? Can a human scientist truly "know" her or his ape relative? In this Epilogue I will argue that the legacy of primatology is at risk of constructing gendered, hierarchical knowledges that reinforce preconceived notions of humanity or human nature. Further, I will argue that by engaging primatology with critical theory, particularly work from the field known as *science and technology studies*, primatologists and other scientists who use evolutionary biology to understand the human condition can avoid these pitfalls and construct expanded forms of scientific knowledge that are not restricted by colonialist legacies.

First, let us investigate these questions by observing what happens when we put the ape in front of the mirror.

The Ape-Object

"Primatology is simian Orientalism," argues Haraway in her book *Primate Visions*. The Western Subject's quest to search for itself within primatology often invokes the great ape as the Other – most frequently our closest genetic relatives, chimpanzees and bonobos – but also gorillas, and orangutans. This relationship (or lack of relationship) between Subject and object, and the desire on the part of the Subject to create the relationship such that it reinforces what the Subject feels it knows about itself, strikes me as much the same sentiment that permeates the field of primatology, especially work that deals with the differences between humans and great apes. Spivak's Subaltern framework (Spivak, 1995) suggests that the Subject will only receive and interpret communication from the Other

when it confirms the Subject's worldview – thus, the possibility of the Other speaking for him or herself is closed off from the get-go.

I want to make clear here that in discussing possible linkages between Spivak's notions of the subaltern with the field of primatology, it is not my intention to compare colonized/non-Western humans to non-human primates. However, there is possible utility of Spivak's conception of the Subaltern as a way to understand the relationship between Western human scientists and great apes. Spivak's Western subject and its relationship to the Subaltern possesses several characteristics which may be informative for understanding the motives and desires of primatologists. The utility of the animal-subaltern as a way to know human-animal relationships has been explored previously (Johnston 2008; Willett, 2014).

Projection

> "I […] envisioned a community of linguistic chimpanzees who would converse with one another in what I hoped would amount to some approximation of the Garden of Eden." (Terrace, Preface to *Nim*, 1985)
>
> "In my years in Borneo, I have learned much about orangutans and much about human nature. Humans and orangutans inhabit the same planet. But we experience different universes. Orangutans are not human; they move in a different realm." (Galdikas, p. 397)

Dr. Galdikas and Dr. Terrace are research contemporaries, having been especially active during the 1970s and 1980s – Galdikas in the forests of Borneo, and Terrace splitting time between his research lab at Columbia University and various upstate New York locales. Both of them had their objects of study – for Terrace, it was the single chimpanzee Nim (short for "Nim Chimpsky", an homage to Noam Chomsky, of course), who taken from his mother as an infant and trained in sign language from various graduate and undergraduate research assistants. Nim was socialized to wear clothes, use a toilet, and remove his jacket

and hang it up when entering a room. Terrace's research "subject" was arguably immersed in human culture in an attempt to see if he could perform "human-ness" in a way that Terrace would deem successful or unsuccessful. Little interest was paid to who Nim was, and what the subjectivity of Nim himself might entail or complicate for humans. Rather, Nim was asked to learn sign language on human terms – and he rapidly picked up individual signs. Yet because chimpanzees had already been demonstrated as having this capability, the goalposts had shifted for Terrace. He saw the ability to communicate with symbols as perhaps impressive but not transcendent – not human. What Terrace wanted Nim to do was use grammar in a human way.

Galdikas, on the other hand, went to Borneo under a missive from the eminent Louis Leakey (along with Dian Fossey and Jane Goodall, Galdikas was deemed one of "Leakey's Angels" by the press) to determine the relationship between humans and our ape relatives – but in a more open-ended way. Galdikas immersed *herself* in orangutan life, not the other way around, in attempt to understand the orangutan. One might compare her approach to that of a cultural anthropologist, while Terrace drew more from an experimental psychologist's tradition. Reflecting on her experience receiving news of Leakey's death while in Borneo, Galdikas writes, "As we mourned him, I was grateful that he had believed in me, and that his belief in me had been vindicated. I had contacted the orangutans". For Galdikas, contact was the first, crucial step to a lifelong study of orangutans as individuals and as a species.

Galdikas' "contact" with orangutans was met with much less fanfare than the "first contacts" of her predecessors. Images of Jane Goodall being groomed by a chimpanzee, or Dian Fossey touching hands with a gorilla, are arguably touchstones for popular

understanding of our relationship to our nearest kin. But orangutans live high up in the trees, and adults are solitary for the most part. All of this made for an even more "foreign" Other that seemed less interested in "speaking" to us. Galdikas describes her changing reactions to this apparent chasm between human and orangutan: "Orangutans are self-contained and self-sufficient. […] What I saw as rejection was in fact the deepest form of acceptance. Orangutans do not need to give, because they do not need to receive." (Galdikas, p.397-398)

The resistance to projecting oneself onto ones research "subject" posed different problems for different workers. Terrace did not appear to see a problem with projection, going so far as to call Nim his "son" to whom he would teach sign language. Nim was being asked to join human society or be left behind - as a father might cut off his shiftless son after putting him through college. After Project Nim loses funding and Terrace must send Nim to live in a primate center: "It was with real sadness that we drove away from the center. Nim was with Roger[7] outside his cage when we left. He did not appear to be particularly upset. It would probably take him a while to understand how profoundly his life had changed." (Terrace, p. 207). Although Terrace probably means here how profoundly his life was about to change now that he would be introduced to a chimpanzee society, we could read many other questions here – did Nim realize how profoundly it had changed since having been taken from his mother and more or less immersed in human culture? Since having been taught American Sign Language? And what is Terrace implying by the term

[7] Dr. Roger Fouts is a chimpanzee communication researcher whose work on chimpanzees' abilities to communicate with sign language was especially prominent in the 1970s (Fouts 1972, 1973, Fouts et al. 1976). Dr. Terrace's study was ostensibly an attempt to "replicate" Dr. Fouts findings that chimpanzees demonstrate the ability to understand and use some basic grammatical rules. Terrace's interpretation of Project Nim data was a refutation of Fouts' earlier research. I do not know of any scientific collaborations between the two; a search for Terrace + Fouts yields zero results on PubMed.

"profound"? Does he see Nim's move away from human society necessarily a move backwards?.

Galdikas' study was necessarily more observational, and required a certain form of acceptance of the Otherness of the orangutan. Yet the observation itself permitted personal reflection on human origins, with mythological and creation story overtones. "Looking into the calm, un-blinking eyes of an orangutan we see, as through a series of mirrors, not only the image of our own creation but also a reflection of our own souls and an Eden that was once ours." (Galdikas, p. 403). The urge to project human needs, emotions, and motives on our primate kin appears to be irrestible and independent of whether one attempts to purposefully avoid it or not.

Thus far we have examined the contrast between Galdikas and Terrace's approaches to the human subject – ape object problem. Terrace tries to teach his "son" human language and culture, and rejects the notion of sophisticated cognitive abilities when Nim fails to achieve certain human developmental milestones. Galdikas engages in somewhat more passive, immersive, observational research, which while still necessarily imposing herself in orangutan life, arguably gives the orangutan more room to be "him/herself". Yet the temptation to impose human moral and religious significance to orangutans – orangutans as a conduit to human salvation, arguably – clearly outlines the intertwined engagement required for primatological research. To reach out and engage with the other, the ape-object, requires a perturbation of the system. Even so, the desire to know the ape's essence can obscure this: "This book is about *gorillas*, not people. It is not even about me, and there is too much "me-itis" in it already as a result of editorial decisions. I would prefer there be no people in at all, good or bad, but I guess that's too much to ask." (from Dian Fossey's

diary, on a dispute with her publisher over her memoir *Gorillas in the Mist*, Mowat p. 281). As a director of research at her field station, Dr. Fossey employed local trackers, supervised American and British graduate students, foiled poachers, and negotiated with government officials, all while gaining the trust of several gorilla troops. Despite this, Fossey still attempted to create a story about the mountain gorillas of Karisoke with no human component. The writings and work of Galdikas, Terrace, and Fossey illustrate the need of the human/subject/scientist to know or understand apes on their own terms – and at the same time, paradoxically, demonstrates the impossibility of this endeavor.

Reflection

> "Recognition of one's own reflection would seem to require a rather advanced form of intellect; it is known, for example, that at least some mentally retarded children apparently do not have the capacity to recognize themselves in mirrors. Moreover, insofar as self-recognition of one's mirror image implies a concept of self, these data would seem to qualify as the first experimental demonstration of a self-concept in a subhuman form." (Gallup 1970).

We have seen that the status of the ape is a difficult problem for the primatologist. The primatologist must insert his or her own subjectivity into the exchange, despite the desire to know the ape on its own terms. But what happens when scientists explicitly turn to apes to know themselves? What happens when the scientist searches for himself? In other words, what happens when the scientist turns from *projection* to *reflection*?

Apes perform for us, about us. It's as if we desire to displace our own subjectivity onto the ape, and have the ape know himself as we feel we know ourselves. While given the developmental research on human infants and children, there is likely some useful

information in the study of apes' reaction to their own reflections, the prominence of the mirror self-recognition task (MSR) in the primatological literature, and the sustained nature of the conversation – spanning over 4 decades – suggests that the MSR test may be doing more for scientists and their popular audiences than what might appear at first glance. This double ramification – on the scientific community and on the popular community – highlights one of the ways that primatology shares features of Orientalism – it exists as both an academic field, and as a way for (primarily Western) popular culture to know itself.

The MSR was originally designed by Dr. Gordon Gallup to be a paradigm to test *self-recognition* in non-human animals (Gallup 1970). However, Gallup does not explain in his original publication how he arrived at that interpretation. In Gallup's test, an animal is sedated and a small visible mark (non-toxic paint, usually) is applied to a part of the animal's body in a location that is only visible to the animal in the mirror (in the control condition, an invisible "sham" mark is applied). A mirror is available to the animal when it recovers from sedation. Subjects that inspect the marked area significantly longer than other parts of their body are said to "pass" the test. Later, Gallup referred to his paradigm as diagnostic for *mind* (Gallup 1982). Other researchers have used terms such as *consciousness* (Keenan et al., 2003), and *empathy*[8] (de Waal, 2003) to describe the significance of an animal's ability to pass the test. I would argue that the shifting of names for the "thing" for which MSR is diagnostic reflects the scientists' understanding of their relationship with the ape. How "self-recognition" morphed into "mind" in approximately a decade is unclear, but the way different workers use the term, and how the use changes over time, depends on what they

[8] It is perhaps this move to empathy that prompted Marc Hauser (formerly of Harvard) to fabricate data suggesting cotton-top tamarins, his model organism of choice, pass the MSR. Given that his research focused on the evolutionary origins of morality, it is probable that he was motivated to produce empirical evidence for cotton-top tamarin empathy. After the raw video footage was examined by outside researchers following skepticism from Daniel Povinelli and others, the data were found wanting by an internal investigation and the publishing journal retracted the paper (The Boston Globe, August 10, 2010).

are searching from the ape. Further, the relationship of the scientist to the ape is defined by how the human individual defines him or herself. Whether we choose to see intellectual (mind), moral (empathy), or other, perhaps less tangible features (consciousness) as diagnostic for "human-ness" or not informs whether we allow the ape to step into this (human) space, or not. Thus while Gallup may see intellectual kinship, de Waal allows chimpanzees to occupy the same moral space as humans as a way to redemption: "The fact that the human moral sense goes so far back in evolutionary history that other species show signs of it plants morality firmly near the center of our much-maligned nature" (de Waal, p. 63).

Another example of human/subject/scientist relationship with the ape-object comes from the work of Daniel Povinelli, a primate cognition researcher at the University of Louisiana at Lafayette, carried out a series of precise and extensive empirical tests to interrogate how chimpanzees understand the physical world. For Povinelli, humans' "natural disposition for constructing an understanding of the self and other in explicitly mental (or psychological) terms" (p. 14) is crucial to the experience of being human. From here, he argues that humans are able to understand the difference between "self and other", to conceive of an "inherently private dimension". After demonstrating that the "folk physics" of the chimpanzee is fundamentally different from that of humans, Povinelli further argues that chimpanzee reactions and use of objects have ramifications for the interpretation of the positive MSR result. Povinelli's chimpanzee recognizes his physical being in the mirror, but cannot fathom the mind behind the physicality, what he might call the "unobservables". Povinelli's chimpanzee, thus, cannot recognize him or herself - at a level most fundamental to what some might consider "human". How can the

human/subject/scientist define the terms of the chimpanzee-object's own self-recognition, if we have placed the chimpanzee as the object in the first place?

Spivak does a reading of Foucault's "epistemic violence" in which she identifies the Western S/subject as de-legitimizing non-Western knowledge systems – and framing the comparison as a way to identify and reify "superior" features of the Western episteme. Povinelli's book *Folk Physics for Apes* might be re-titled as "Naïve Knowledges of the Ape" – whatever features of ape cognition that the animal cognition researcher might be able to discern or partially fathom will be relegated to a position lower on the hierarchy than that of humans. As Spivak asks, "What taxonomy can fix such a space?" – in other words, how can humans possibly conceive of a research question that will open up a space for ape cognitive subjectivity? And if this impossibility were possible, how would the scientist and his or her popular audience recognize it?

Beyond Reflection and Projection – Understanding the In-Between

> "Our departure from Eden allows us reflection – reflection on our origins and our relations to other creatures, reflection on good and evil, and ultimately, reflection on the possibility that we are engineering our own extinction. Never having left Eden, our innocent pongid kin are not burdened with this knowledge and the responsibility it entails. Looking into the calm, un-blinking eyes of an orangutan we see, as through a series of mirrors, not only the image of our own creation but also a reflection of our own souls and an Eden that was once ours. […] We are allowed to see the eyes of God." (Galdikas, p. 403)

How do scientists and (Western) popular audiences come to terms with the chasm that exists between themselves and the ape-other? While I have been critical of the

unexamined desires of primatologists to see the ape or to see themselves in the ape (or both), we can witness scientists grappling with the problem and recognizing the gulf on its own terms. The language that we use to characterize this space reveals an intertwining of evolutionary "creation stories" and Judeo-Christian themes.

"Between human language and the vocalizations of any animal lies a seemingly unbridgeable gulf. As has been clear since the time of Darwin, the mystery of human language origins is an *evolutionary* problem: how was this unbridgeable gulf nevertheless bridged?" asks Jared Diamond in his popular science book *The Third Chimpanzee*. Contrast this language with that of Galdikas and Terrace – who experience the difference between themselves and apes as a window to lost human origins. This interweaving of scientific theories – particularly evolution – which is often associated with "progress", and religious origin stories with moral undertones suggests Kavita Philip's concept of mixed modernity (Philip 2003) – in which science, culture, nature, and political force are co-constituted.

The alternating subjectivity and objectivity of the ape are recruited to explicate who "we" are – and the frequent jump from shared physical traits (opposable thumbs and large brains) to shared morality may point to a deep yearning within the primatologist to know him or herself. After early reports of brutal inter-chimpanzee violence (van Lawick-Goodall 1971, Goodall 1977), and dashed hopes of inter-species communication (Terrace 1979), apes are now being sought as our redeemers. We "subject" apes to testing and seek them to reveal our subjectivity to us. The subjectivity/objectivity of the ape is interrogated when we ask if we can communicate with non-human apes, when we ask what the nature of human morality is, when we look to apes for clues about human origins, and when we put apes in front of the mirror.

In a post-script of an edited volume titled *The Cognitive Animal*, which contains a series of expert scientific analyses of the ways different animals do and do not share cognitive features with humans, the volume editor asserts that the key difference between humans and non-human animals is the presence of "cognitive, subjective experiences" which supposedly undergird and distinguish all human experience as such. Is it a coincidence that cognitive difference implicates subjectivity? In other words, is it surprising that animal cognition researchers, after locating differences and inadequacy in their animal objects of study, use this cognitive difference to assert fundamental differences in subjectivity?

As primatologists search for themselves, using ever-changing experimental paradigms and phylogenetic tools, they must feel as if they are getting closer to the "truth" of the chasm, and thus the true nature of humans. But if we already see ourselves in the Subject position, in the experimenter position, or in the observer position, how can the ape assert his or her subjectivity under those conditions? And indeed, if an ape could, what would it mean for the entire primatological enterprise? Here we see the political force within mixed modernity come into play. Politically, it is unsustainable for primatologists to keep captive apes if they allow ape subjectivity. It is hard to imagine even less intrusive observational research – can an ape give consent? And how would we recognize it?

Perhaps primatology is fatally flawed as an enterprise in this way – overdetermined and overburdened by the subjectivity of primatologists and their audiences. For every inch we may give a great ape into our subjective space, we seem to find new ways to identify differences that allow us to continue to exploit them as objects of study. Temple Grandin, an animal sciences professor and outspoken "other mind", advocates for the concept of *neurodiversity*, as she attributes her successes in her work to the unique understanding her

experiences as a person with autism afford her. Grandin's otherness is also reflected in her approach to the question of our relationship to animals. She also avoids the obfuscating jargon of animal cognition research: "I hope we'll start to think more about what animals can do, and less about what they can't. It's important, because we've gotten too far away from the animals who should be our partners in life, not just pets or objects of study." (Grandin, p. 303) Is there hope for creating an interspecies partnership to forge what Sue Savage-Rumbaugh calls "Pan-homo culture" (Savage-Rumbaugh 2009), or Cynthia Willett's multispecies communitarian ethics (Willett, 2014)?

I have argued that the way that primatologists and their popular audiences relate to other great apes is determined by how they relate and conceive of themselves as human individuals – how they seem themselves in the mirror. Willett, Savage-Rumbaugh, and Grandin offer us a way forward – instead of placing ourselves in opposition to great apes, maybe we could consider placing ourselves alongside of great apes – asking questions like what can humans and non-human apes create together, and how can the new interactions illuminate things about apes, and ourselves, that we may not have been able to see before.

Ultimately, humans are interested in understanding themselves, other humans, and humanity in general. Understanding the minds of our closest relatives fascinates us because it allows us to gain purchase on these issues. If we want to understand the human condition, which is saturated with meaning-making, we need to learn as much as we can about our closest relatives. We can do this while simultaneously acknowledging that our comprehension of ape subjectivity is necessarily compromised as part of the endeavor to find and define ourselves.

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TABLES

Species	Case No.	Age years	Sex	Fix.	Plane/ thickness	PMD h	Cause of death	VGLUT2 conc.
H. sapiens	N98-32	78	M	I	Coro./40 μm	23	lung cancer	1:3,000
	N01-15	U	U	I	Long./40 μm	U	U	1:25,000
	N99-6	70	F	I	Coro./40 μm	3	cancer	1:10,000
	N99-13	56	F	I	Horiz./40 μm	6	pyelonephritis	1:30,000
	N99-9	78	F	I	Coro./40 μm	6	aortic aneurysm	1:80,000
P. troglodytes	N96-29	30	F	I	Coro./50 μm	5.5	U	1:10,000
	N96-30	20	M	P	Horiz./50 μm	0	euthanasia	1:20,000
	N98-47	25	F	I	Horiz./50 μm	1	peritonitis	1:20,000
	N99-11	19	M	I	Horiz./50 μm	5	pneumonia	1:5,000, 1:7,000
P. pygmaeus	N98-40	~33	M	I	Coro./50 μm	2	cardiac arrest	1:5,000
M. mulatta	N02-7	12 + 5 m	F	P	Coro./50 μm	0	sacrifice	1:25,000
	N98-23	4	F	P	Coro./50 μm	<1	sacrifice	1:20,000
	Y07-176	6	F	P	Coro./50 μm	0	euthanasia	1:10,000
C. aethiops	N96-17	15	F	P	U	0	sacrifice	1:100,000
	N96-19	7	F	P	U	0	sacrifice	1:5,000
	N96-20	13	F	P	U	0	sacrifice	1:3,000
S. sciureus	N98-7	1 + 6 m	M	P	Coro./50 μm	0	sacrifice	1:20,000
	N98-8	12	M	P	Coro./50 μm	0	sacrifice	1:20,000
	N98-10	2	M	P	Coro./50 μm	0	sacrifice	1:20,000

Fix. = Mode of fixation; P = perfusion fixed; I = immersion fixed; Coro. = coronal; Long. = longitudinal; Horiz. = horizontal; VGLUT2 conc. = optimal anti-VGLUT2 antibody concentration; U = unknown; m = months.

Table 1: Summary of cases examined in the VGLUT2 study.

MPRAGE									
Species	**iPAT**	**Flip angle**	**Slice thickness (mm)**	**Voxel size (mm^3)**	**TR/TI/TE (ms)**	**NEX**	**Matrix size**	**FOV**	**Scan time (min)**
chimpanzee	1	8	0.8	0.8×0.8×0.8	2600/900/3.06	2	256 × 256 × 192	205 × 205 × 154	16
macaque	2	8	0.5	0.5×0.5×0.5	2500/900/3.37	3	320 × 320 × 176	160 × 160 × 88	25
Double spin echo diffusion EPI									
Species	**iPAT**	**Partial Fourier**	**Slices**	**Voxel size (mm^3)**	**TR/TE (ms)**	**DWI/total b0s**	**Matrix size**	**FOV**	**Scan time (min)**
chimpanzee	1	5/8	41	1.8×1.8×1.8	5900/86	8/40	72×128	130×230	60
macaque	3	N/A	43	1.1×1.1 × 1.1	7000/108	10/50?	128×120	141×132	86

Table 2: Imaging parameters of the T1-weighted and diffusion MRI for chimpanzees and macaques. Notes: iPAT: GRAPPA parallel imaging factors; TR/TI/TE: repetition time/inversion time/echo time; NEX: number of excitations; FOV: field of view.

FIGURES

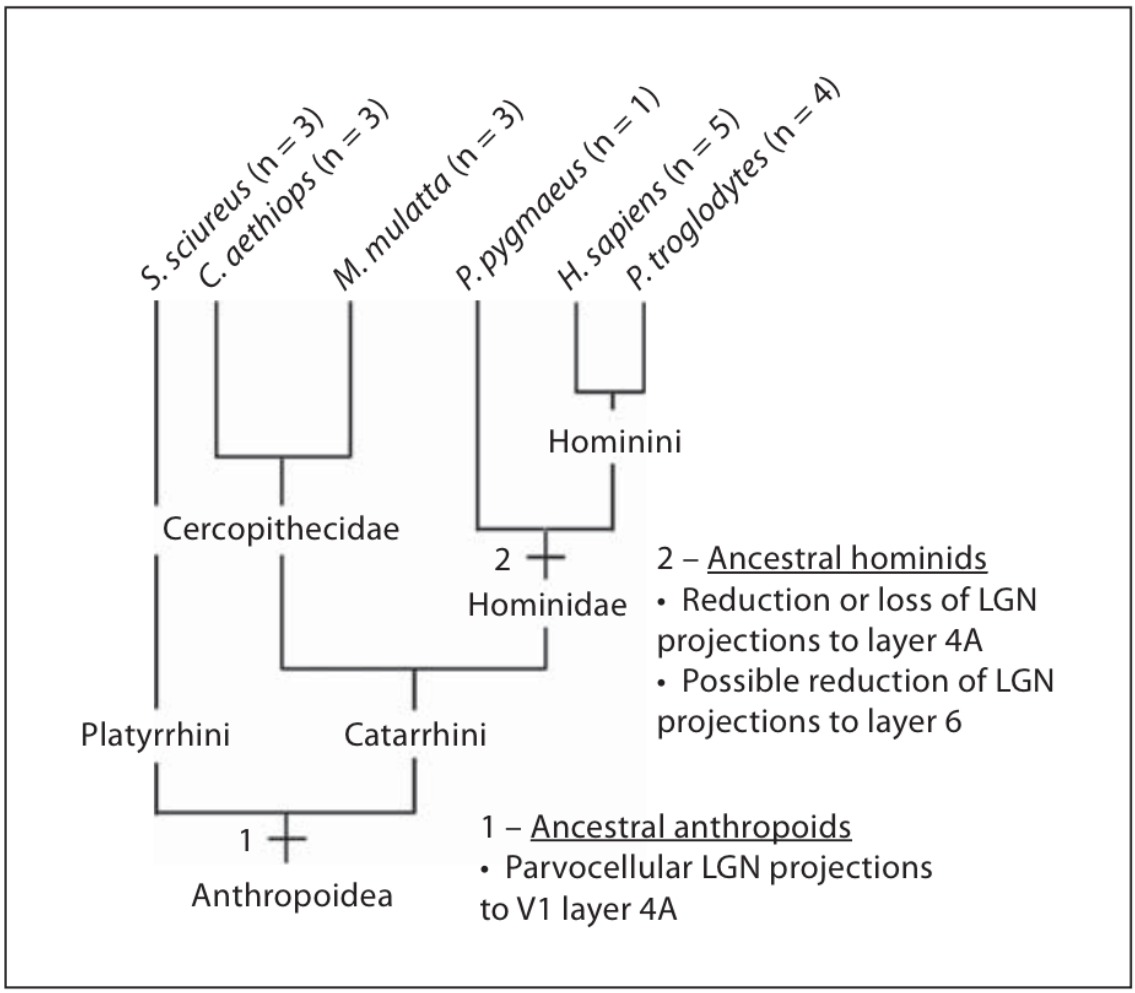

Figure 1: Phylogenetic tree showing the evolutionary relationships among the species examined in this study, sample sizes, and the distribution of character state changes in LGN projections inferred from previous research. The VGLUT2 study provides additional evidence to support state change 2, the reduction or loss of direct projections from the parvocellular LGN to layer 4A after the divergence of the Hominidae and Cercopithecidae.

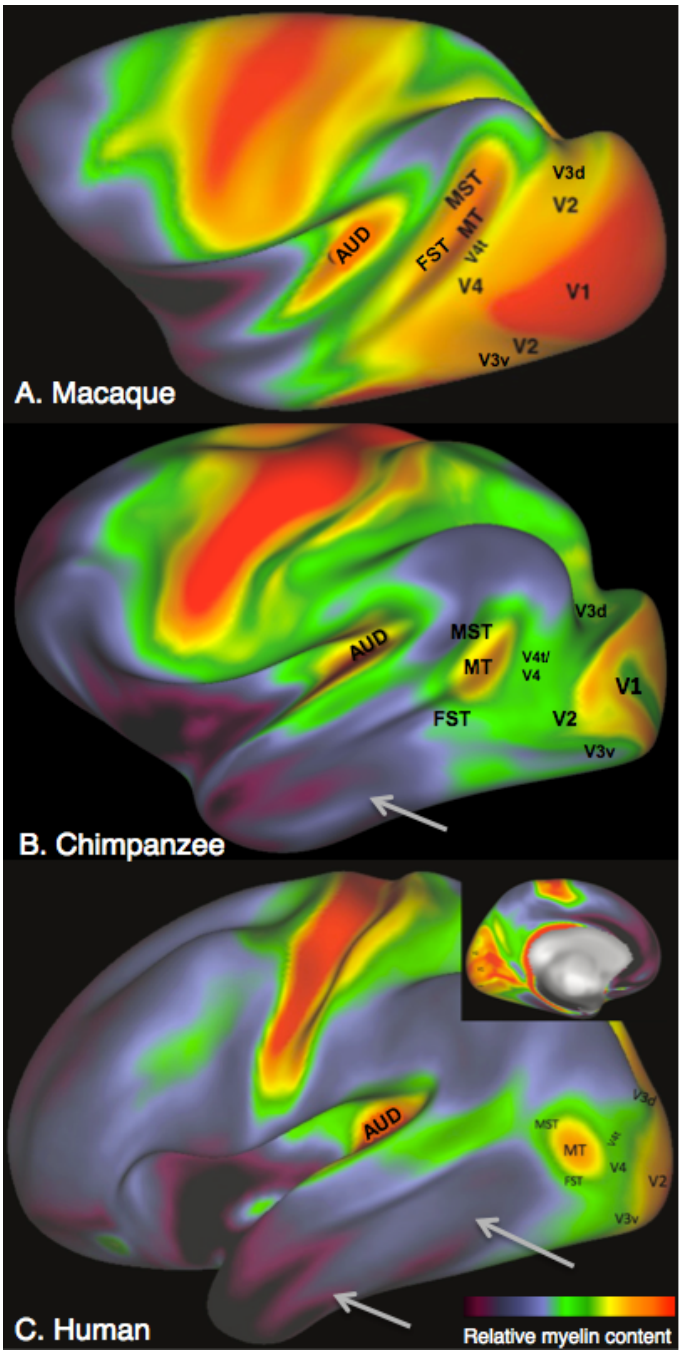

Figure 2: Cortical landmarks in (a) macaque, (b) chimpanzee, and (c) human cortical myelin maps (adapted from Glasser et al., 2011). Arrows highlight expansion and reorganization of extrastriate cortex in humans and chimpanzees relative to macaques. Visual area locations estimated for macaques from Markov et al., 2012 and humans from Abdollahi et al., 2014. Chimpanzee cortical area locations extrapolated from human and macaque data as well as cortical myelin maps.

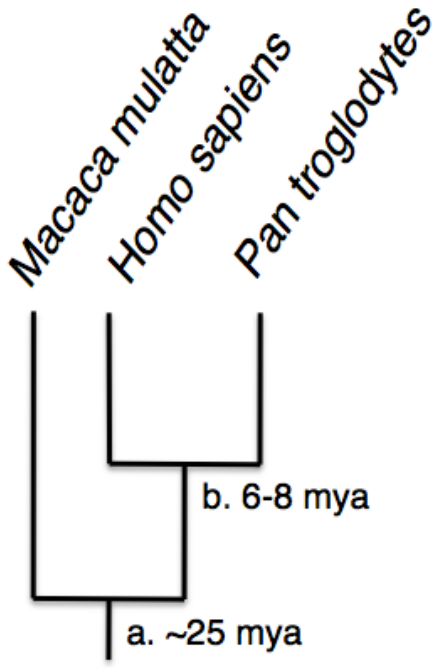

Figure 3: Divergence dates for the hominoid-cercopithecoid (a) and hominin (b) split. Hominoid-cercopithecoid split from Steiper and Young, 2006; hominin split from Langergraber et al., 2012; Chen and Li, 2001

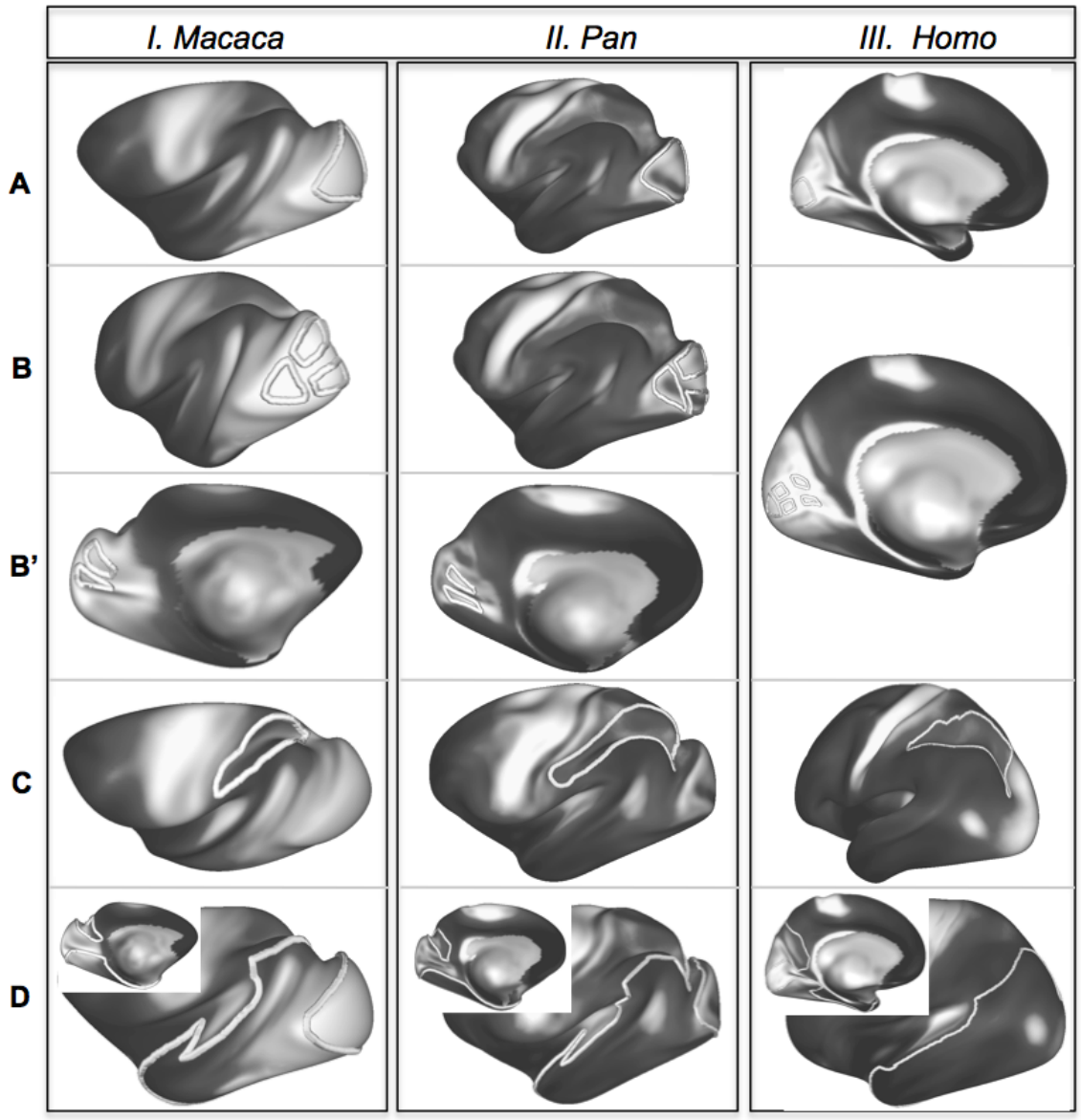

Figure 4: Location of experimental ROIs in macaques, chimpanzees, and humans. Central V1 ROIs (a), foveal and parafoveal ROIs (b), peripheral visual ROIs (b'), intraparietal sulcus (c), and temporal cortex (d).

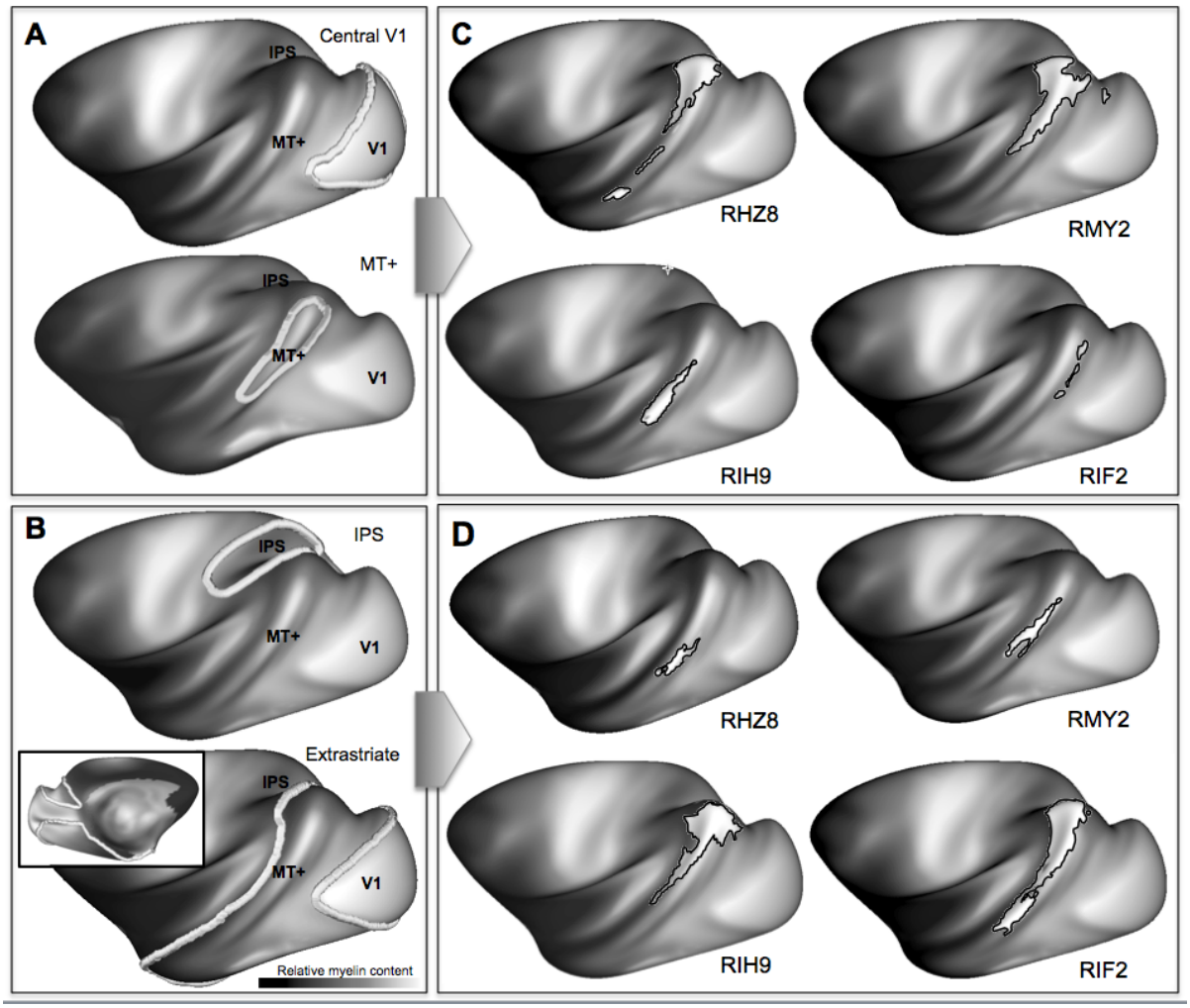

Figure 5: Macaque MT+ convergence results: A. Central V1 and Large MT+ masks; B. Intraparietal sulcus and Extrastriate masks; C. Representative subject results of central V1 connectivity to large MT+ mask; D: Representative subject results of IPS connectivity to extrastriate mask. Surface projection results are outlined in black to enhance visibility.

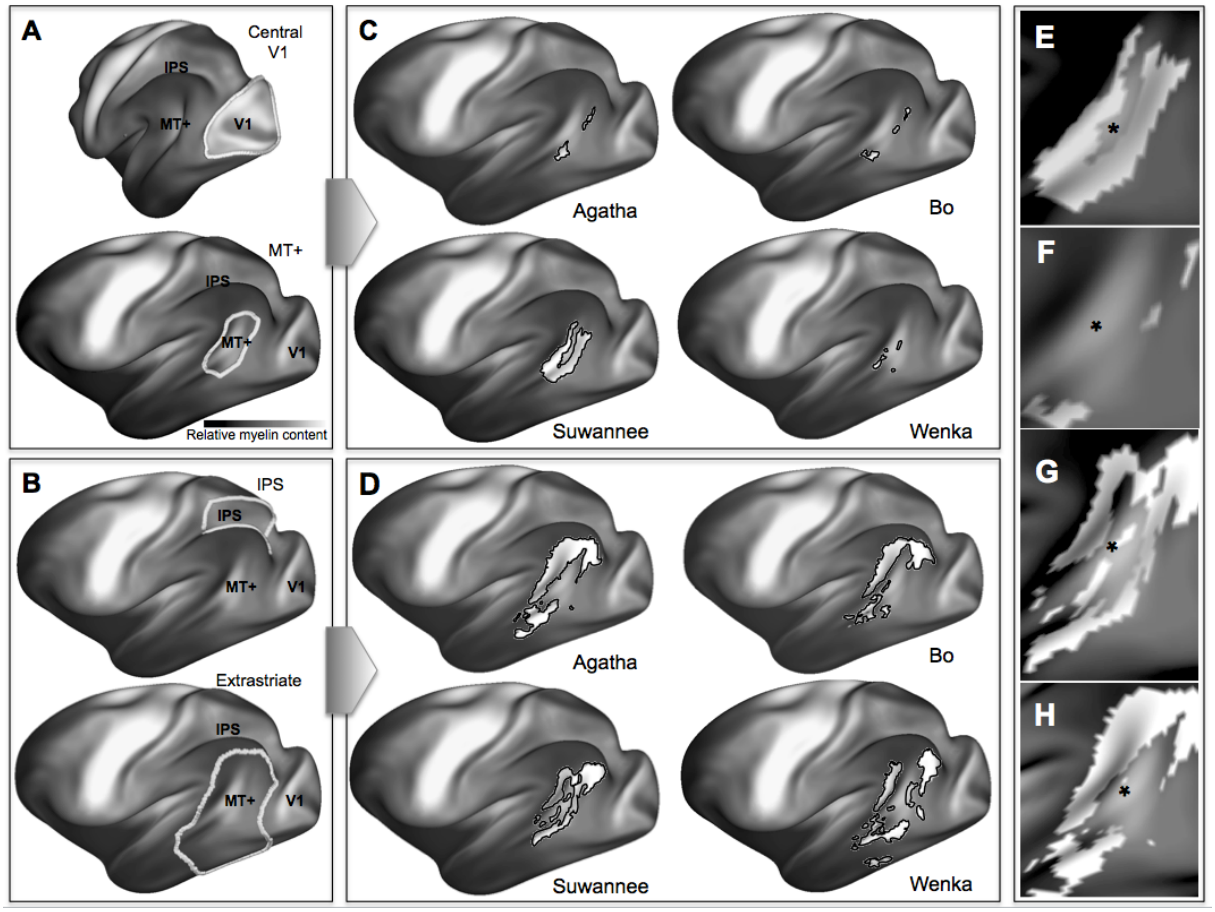

Figure 6: Chimpanzee MT+ convergence results: A. Central V1 and Large MT+ masks; B. Intraparietal sulcus and Extrastriate masks; C. Representative results of central V1 connectivity to large MT+ mask; D: Representative results of IPS connectivity to extrastriate mask. Results are thresholded at 99% for all subjects. IPS-Extrastriate results (D) further exclude the upper 15 percent. Surface projection results are outlined in black to enhance visibility. E: Detail of Suwannee V1-MT+ results. F: Detail of Bo V1-MT+ results. G:Detail of Suwannee IPS-Extrastriate results. H: Detail of Agatha IPS-Extrastriate results. Note lacunae-like distribution of connectivity encircling the densely myelinated center of area MT, indicated by an asterisk.

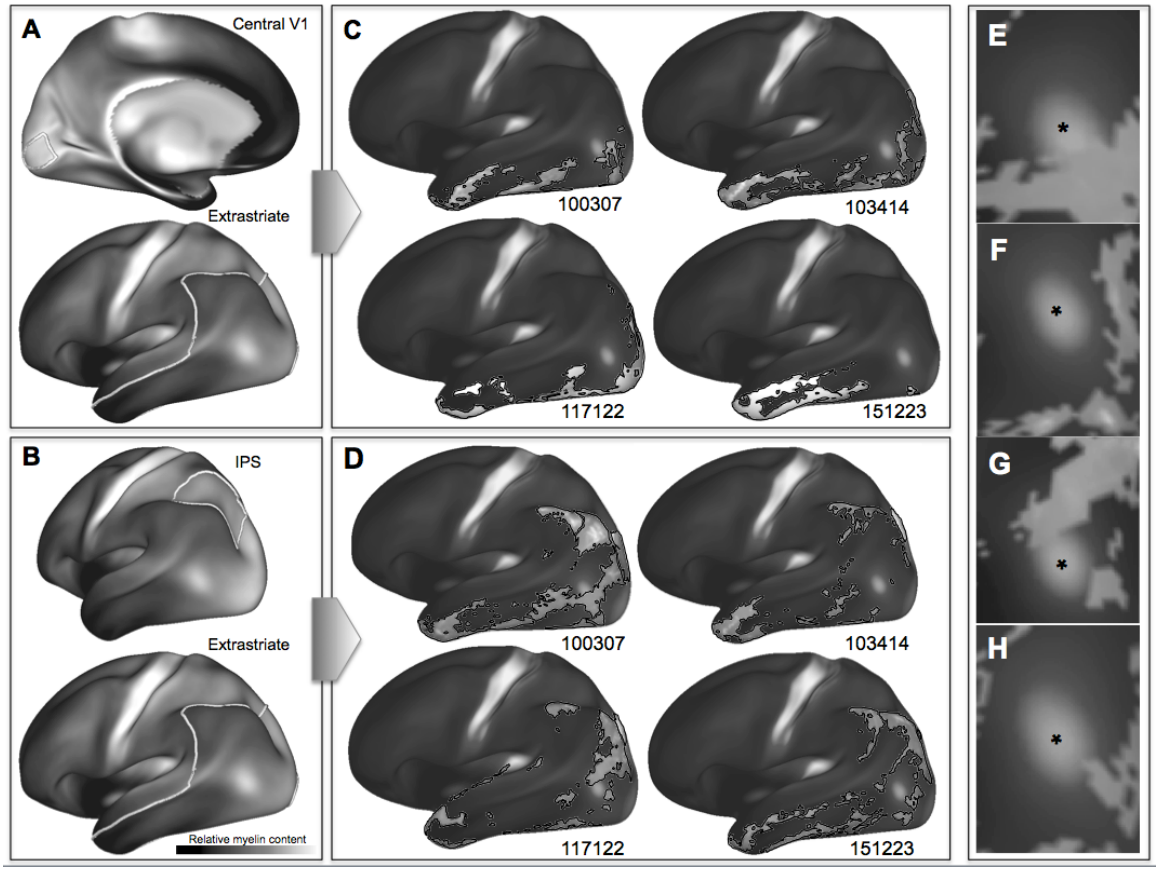

Figure 7: Human MT+ convergence results: A. Central V1 and Large MT+ masks; B. Intraparietal sulcus and Extrastriate masks; C. Representative results of central V1 connectivity to large MT+ mask; D: Representative results of IPS connectivity to extrastriate mask. Surface projection results are outlined in black to enhance visibility. E-H: Closeup of MT+ lacunae. E. V1c, subject 103414; F. V1c, subject 103414; G. IPS, subject 11712; H. IPS, subject 151223.

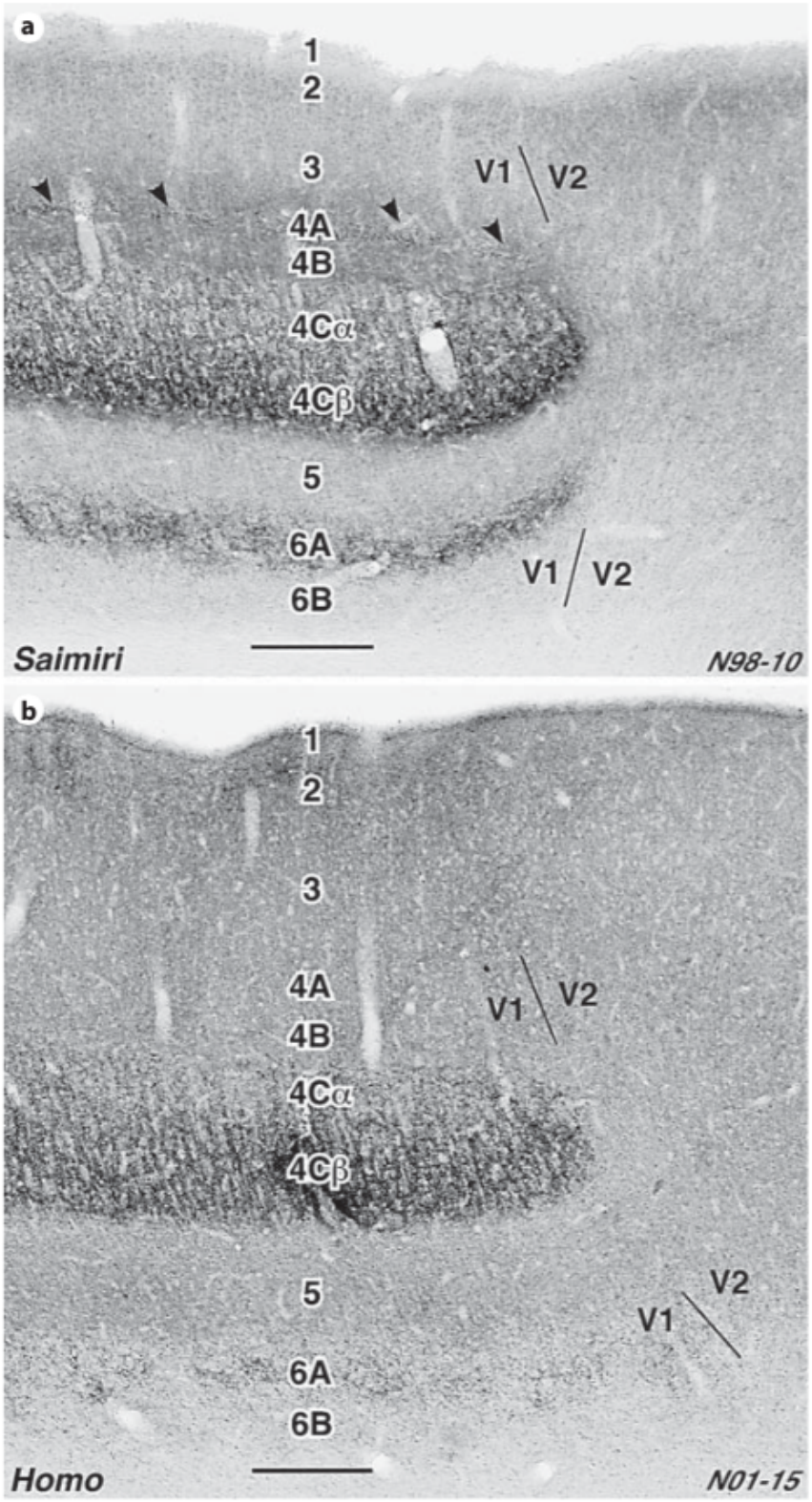

Figure 8: The marked reduction in VGLUT2 immunolabeling at the transition between areas V1 and V2 is illustrated in the squirrel monkey (*Saimiri*; **a**) and a human (**b**). Arrowheads mark the location of the layer 4A labeling band. Scale bars = 250 μm.

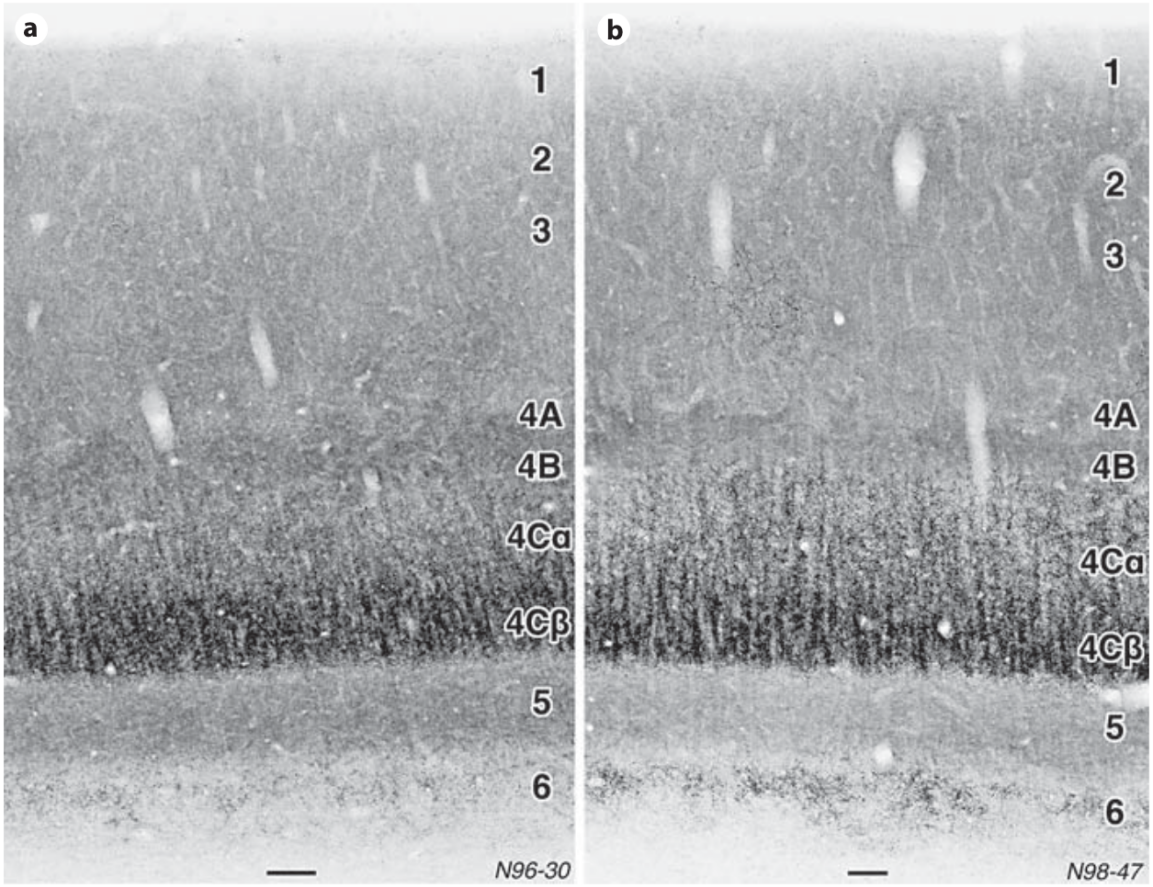

Figure 9: Anti-VGLUT2 DAB labeling of a perfusion-fixed chimpanzee (a) and an immersion-fixed chimpanzee (b). Scale bars = 100 μm.

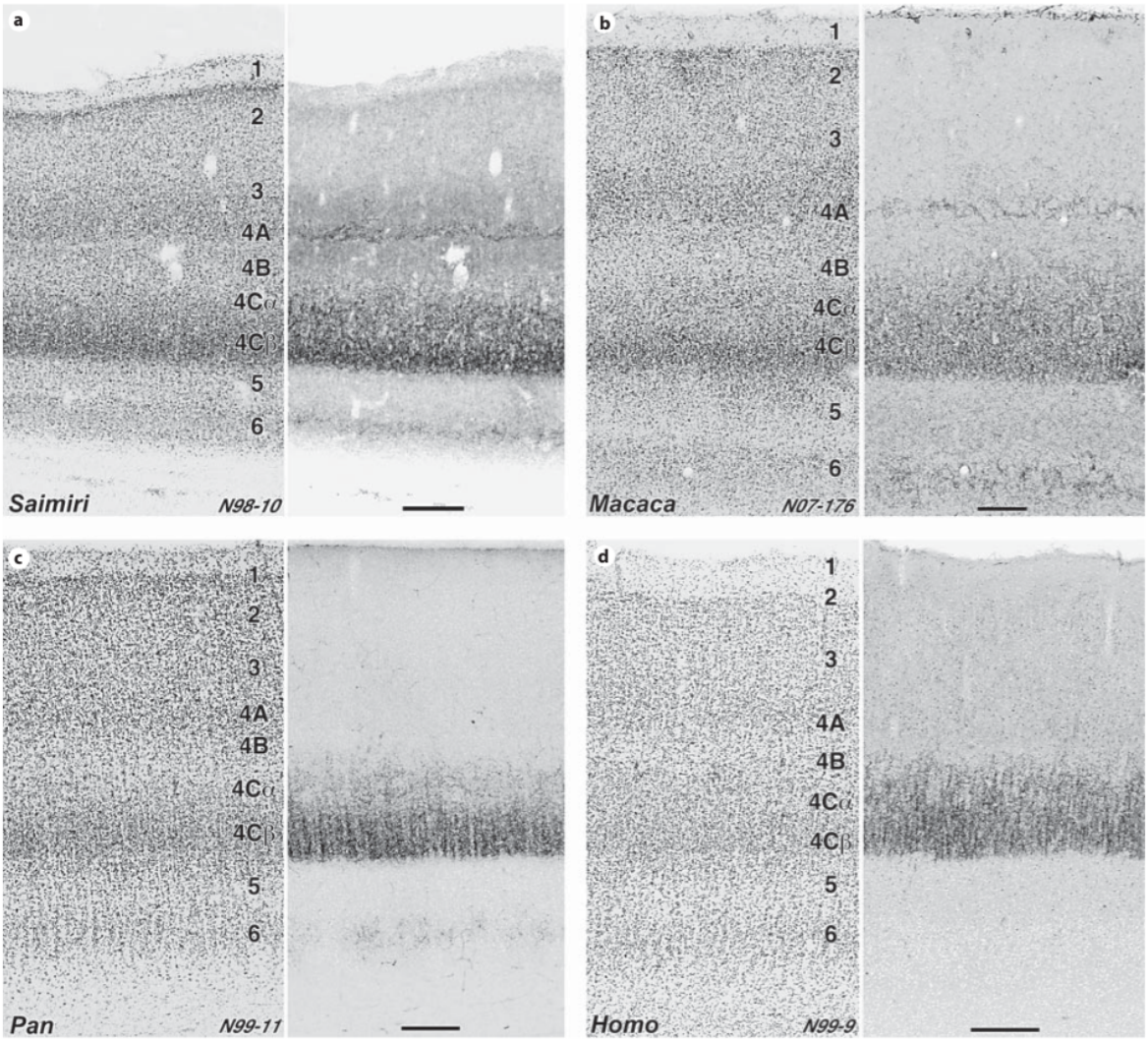

Figure 10: The laminar distributions of VGLUT2 immunolabeling in area V1 are depicted. **a** Squirrel monkey (Saimiri). **b** Rhesus macaque (Macaca). **c** Chimpanzee (Pan). **d** Human (Homo). Each figure pair represents a VGLUT2-immunostained section that was counterstained for Nissl with thionin. After scanning, the color channels were separated as described in the text to produce separate images of the blue Nissl staining (the left figure in each pair) and the red-brown VGLUT2 immunolabeling (the right figure in each pair). Note the lack of VGLUT2 labeling in layer 4A of the hominids (**c**, **d**) compared to the monkeys (**a**, **b**), as well as the weak labeling of layer 6 in the hominids compared to the monkeys. Scale bars = 250 μm.

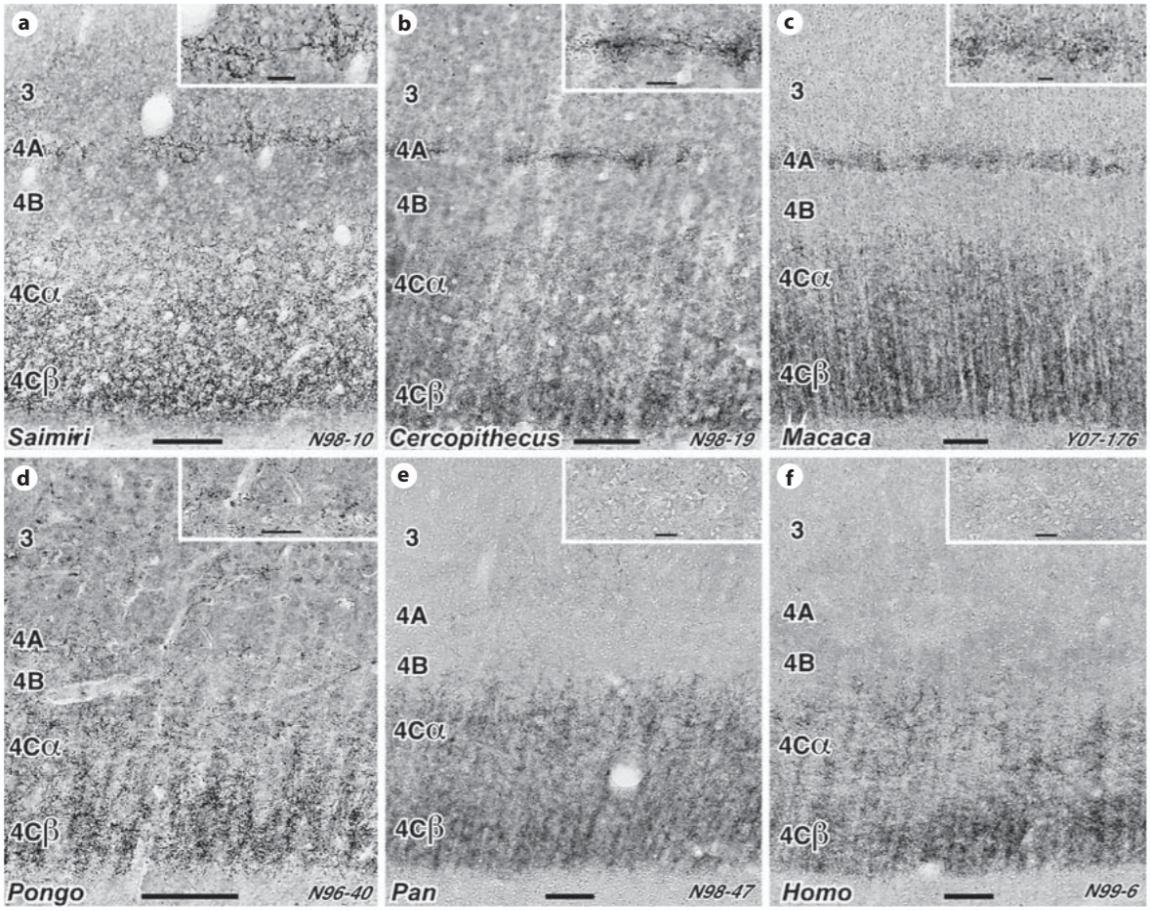

Figure 11: Detail of VGLUT2 labeling in layer 4. **a** Squirrel monkey (*S. sciureus*). **b** Vervet monkey (*C. aethiops*). **c** Rhesus macaque (*M. mulatta*). **d** Orangutan (*P. pygmaeus*). **e** Chimpanzee (*P. troglodytes*). **f** Human (*H. sapiens*). Higher magnification of 4A labeling shown in insets. Main scale bars = 100 μm, inset scale bars = 25 μm.

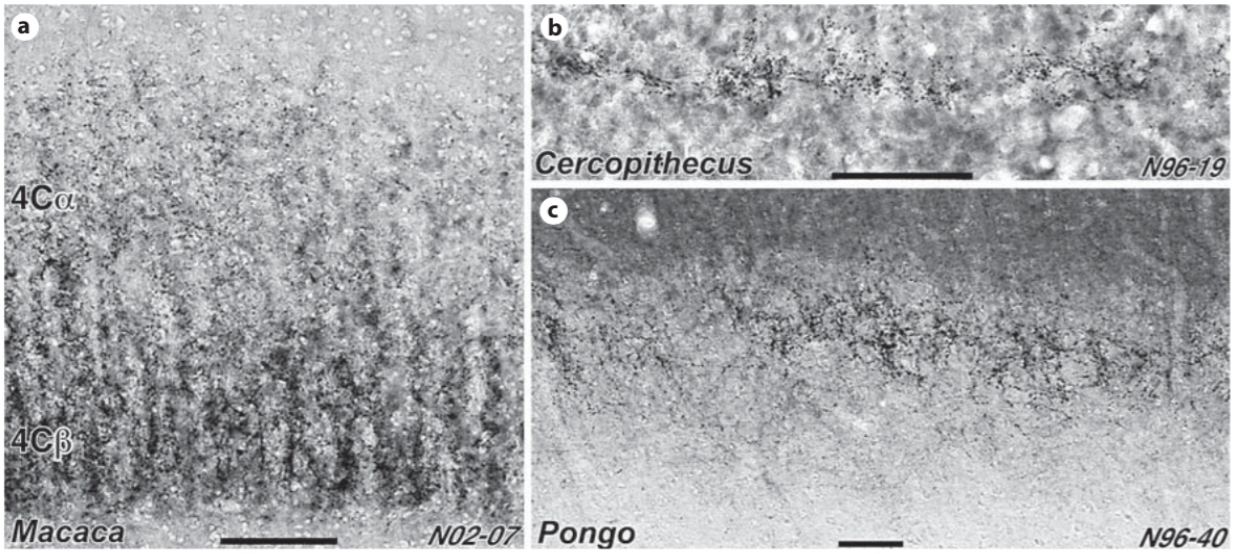

Figure 12: Detail of cortical layers with terminal-like labeling. **a** Layer 4C of rhesus macaque (*Macaca*). **b** Layer 4A of vervet monkey (*Cercopithecus*). **c** Layer 6 of orangutan (*Pongo*). Scale bars = 100 μm.

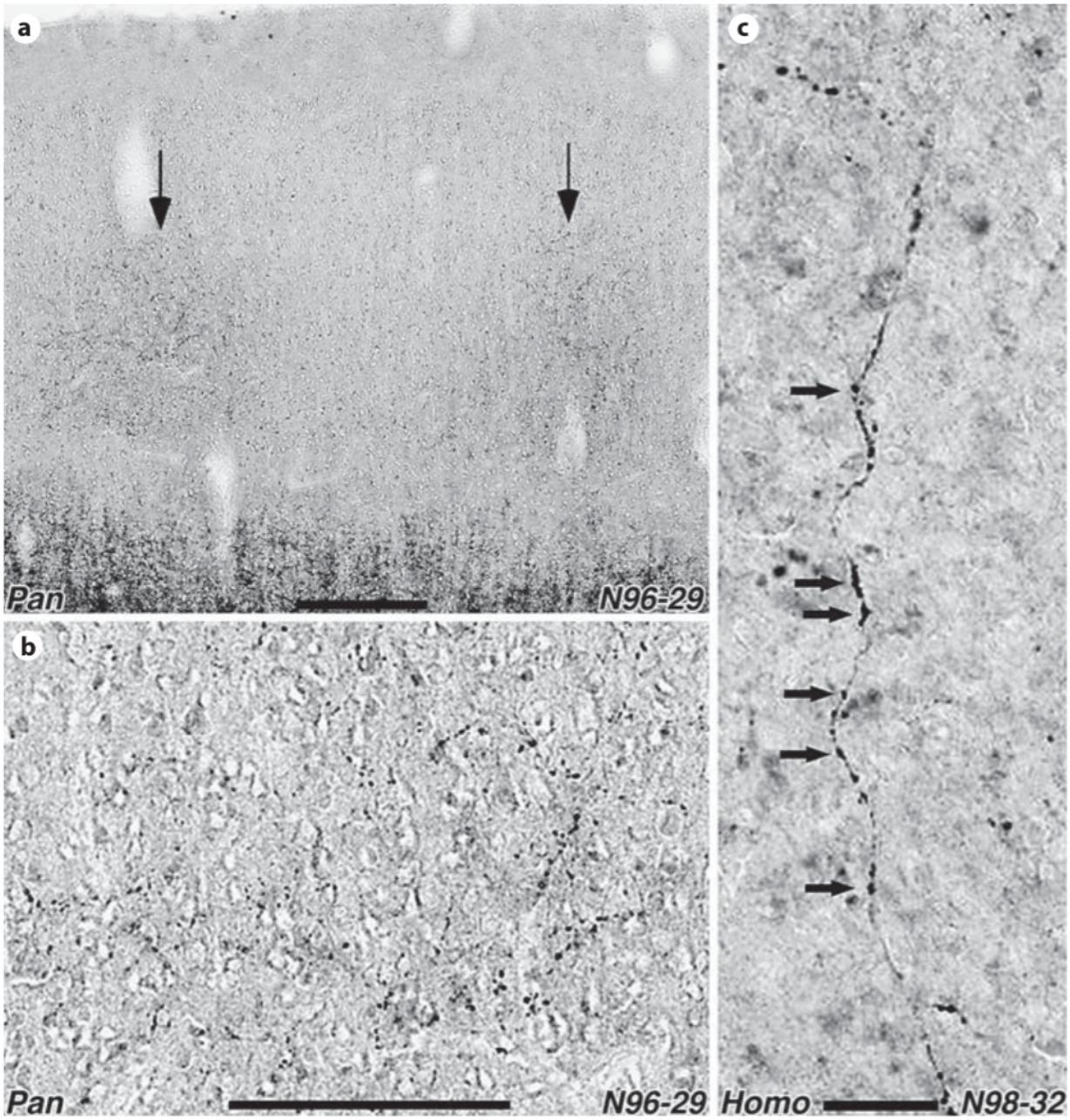

Figure 13: Detail of VGLUT2 immunolabeling in the superficial layers of area V1. **a** Arrows denote centers of blob-like labeling in layer 3 in a chimpanzee. **b** Higher magnification in a. **c** A labeled, vertically oriented fiber in layer 3 of a human showing apparent en passant terminal boutons. Scale bars = 250 (**a**), 125 (**b**), and 10 μm (**c**).

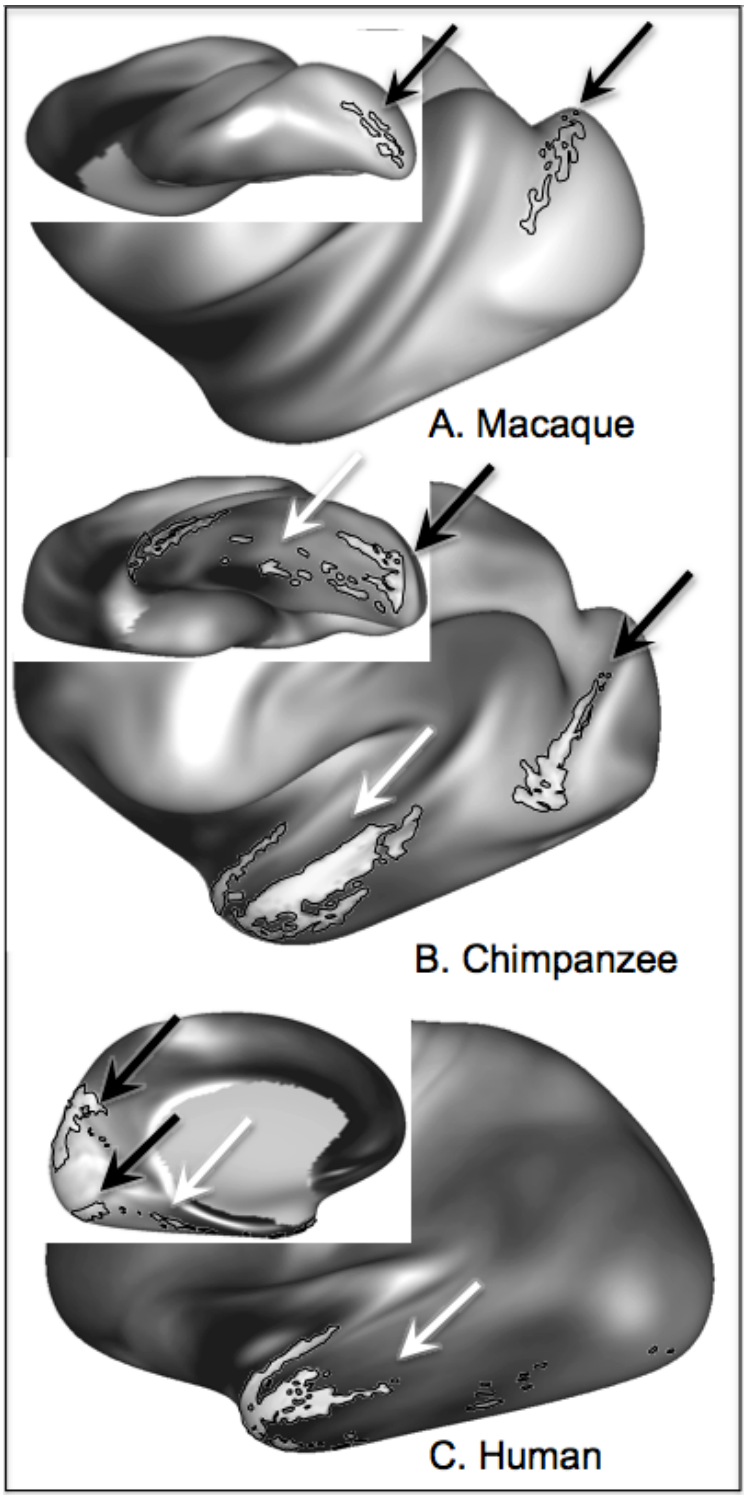

Fig 14: Averaged V1c->temporal cortex results in macaques (A), chimpanzees (B), and humans (C). Dark arrows point to streamline results in unimodal extrastriate territories. Light arrows indicate streamlines reaching higher order extrastriate and multimodal temporal cortex. Threshold for all subjects=0.8. Surface projection results are outlined in black to enhance visibility.

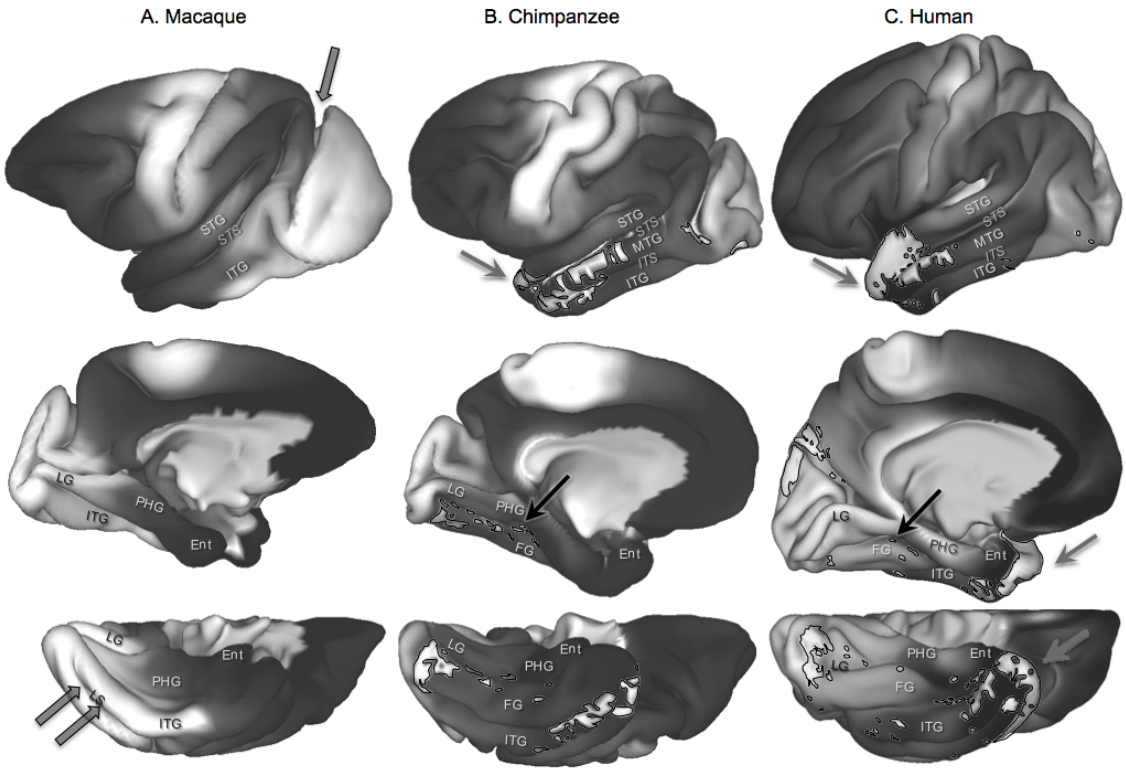

Figure 15: V1c thr=0.5, at 0.8. Projection of V1c results onto folded cortex in macaques, chimpanzees, and humans. Arrows point to middle temporal gyrus, anterior temporal lobe, and fusiform connectivity. Surface projection results are outlined in black to enhance visibility. STG: Superior Temporal Gyrus; STS: Superior Temporal Sulcus; MTG: Middle Temporal Gyrus; ITS: Inferior Temporal Sulcus; ITG: Inferior Temporal Gyrus; LS: Lunate Sulcus; FG: Fusiform Gyrus; LG: Lingual Gyrus; PHG: Parahippocampal Gyrus; EC: Entorhinal Cortex. Figure 16: Auditory core and central V1 to temporal lobe results.

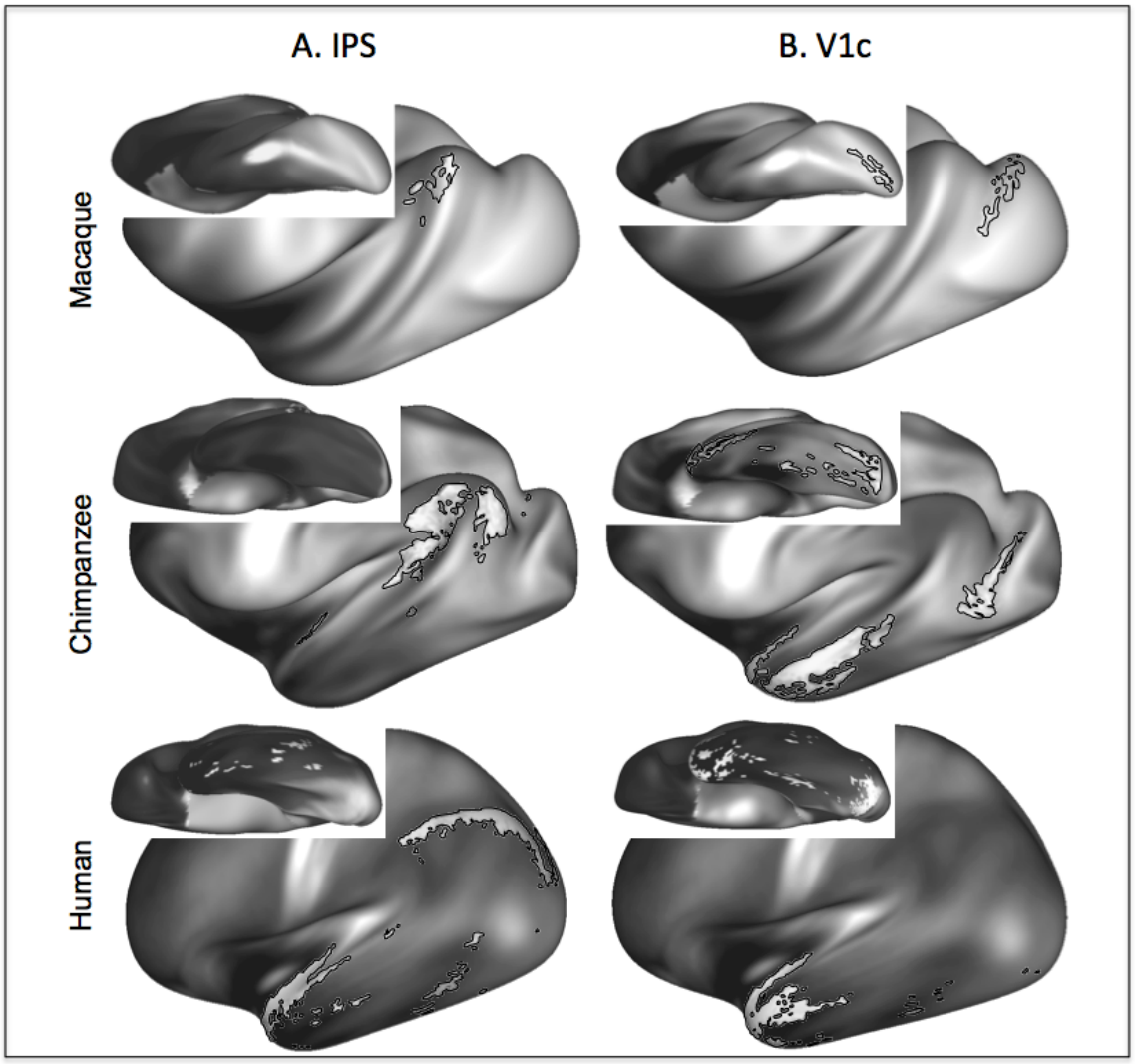

Figure 16: Comparison of V1c ->temporal cortex results with control ROI (IPS). Thr=0.8. Surface projection results are outlined in black to enhance visibility.

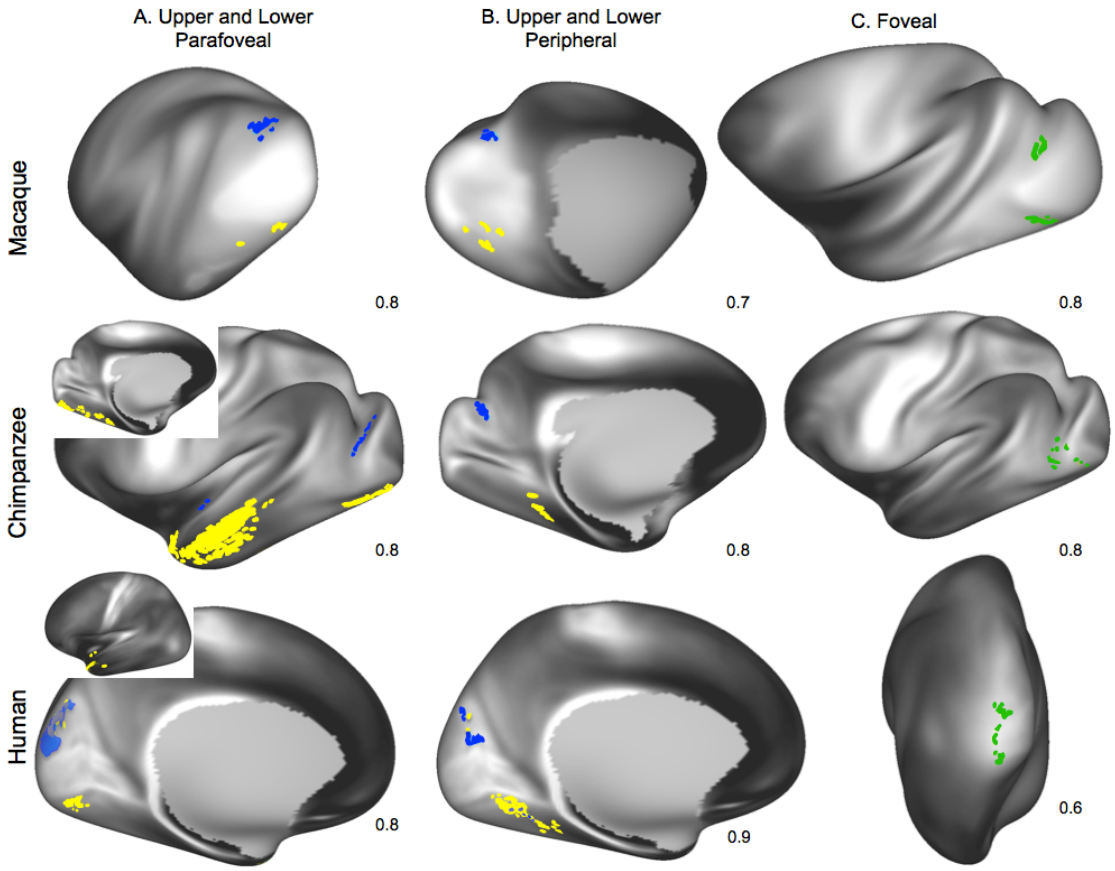

Figure 17: Averaged retinotopic tracking results in humans, chimpanzees, and macaques. Blue areas temporal seed voxels with apparent major connectivity to upper parafoveal (A) and peripheral (B) V1 ROIs; yellow areas represent apparent major connectivity to lower parafoveal (A) and peripheral (B) V1 ROIs. Green areas in 7C represent results from central foveal ROIs. Numbers in lower right corner of each map indicate the percentage of individual results included to produce the final averaged result. Human peripheral and parafoveal results are thresholded at 0.25; all others are thresholded to 0.05.

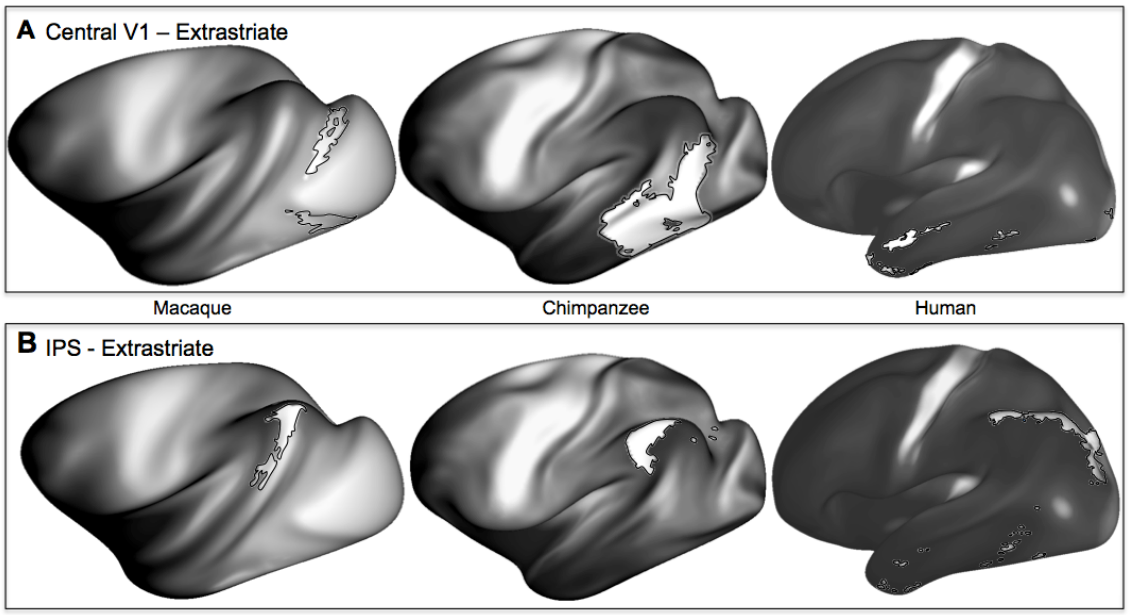

Figure 18: Averaged MT+ convergence results for central V1 connectivity to large MT+ mask (A: macaque; B: chimpanzee; C: human) and IPS connectivity to extrastriate mask (D: macaque; E: chimpanzee. Macaques: 10 subjects; 8/10 subjects; Chimps: 15 subjects; 12/15 subjects; Humans (V1c): 10 subjects; 8/10 subjects; (IPS): 9 subjects, 7/9 subjects. Surface projection results are outlined in black to enhance visibility.