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A web-based brain atlas of the vervet monkey, *Chlorocebus aethiops*

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ABSTRACT

Vervet monkeys are a frequently studied animal model in neuroscience research. Although equally distantly related to humans, the ancestors of vervets diverged from those of macaques and baboons more than 11 million years ago, antedating the divergence of the ancestors of humans, chimpanzees and gorillas. To facilitate anatomic localization in the vervet brain, two linked on-line electronic atlases are described, one based on registered MRI scans from hundreds of vervets (http://www.loni.ucla.edu/Research/Atlases/Data/vervet/vervetmratlas/vervetmratlas.html) and the other based on a high-resolution cryomacrotome study of a single vervet (http://www.loni.ucla.edu/Research/Atlases/Data/vervet/vervetatlas/vervetatlas.html). The averaged MRI atlas is also available as a volume in Neuroimaging Informatics Technology Initiative format. In the cryomacrotome atlas, various sulcal and subcortical structures have been anatomically labeled and surface rendered views are provided along the primary planes of section. Both atlases simultaneously provide views in all three primary planes of section, rapid navigation by clicking on the displayed images, and stereotaxic coordinates in the averaged MRI atlas space. Despite the extended time period since their divergence, the major sulcal and subcortical landmarks in vervets are highly conserved relative to those described in macaques.

Introduction

Chlorocebus aethiops, commonly referred to as the vervet monkey or the African green monkey, is an Old World monkey and a member of the Cercopithecinae subfamily. This subfamily also includes other terrestrial guenons, arboreal guenons, macaques, baboons, mangabeys and mandrills. The Cercopithecinae are thought to have diverged from the other Old World monkey subfamily, the Colobinae, approximately 14 million years ago (Stewart and Disotell, 1998) with guenons subsequently diverging from baboons, macaques, mangabeys and mandrills around 11.5 million years ago (Tosi et al., 2005). Members of the terrestrial guenon genus *Chlorocebus* were previously classified together with arboreal guenons as the single genus *Cercopithecus* (Grubb et al., 2003) but have recently been reclassified into their own separate genus (Groves, 2001; Tosi et al., 2003, 2005; Xing et al., 2007). Molecular studies indicate that the arboreal and terrestrial guenons diverged about 8 million years ago (Tosi et al., 2005). All Old World monkeys are equally distantly related to humans and apes, having diverged from a common ancestor approximately 30 million years ago (Steiper and Young, 2006). The relationships between vervets and other Old World monkeys, apes and humans are shown in Fig. 1.

Although some early monkey brain cytoarchitectonic work (e.g., that of Brodmann (1909) and of Vogt and Vogt (1919)) was based on guenons (most likely the arboreal guenon *Cercopithecus campbelli* according to von Bonin and Bailey (1947)), modern monkey brain atlases have typically been based on macaques. Aside from an anatomically labeled atlas published in 1981 by Contreras et al. and an electronic collection of mostly unlabeled Nissl stained slides

Abbreviations: AIR, Automated Image Registration; CIE, International Commission on Illumination; DICOM, Digital Imaging and Communications in Medicine file format; JPEG, Joint Photographic Experts Group file format; MRI, Magnetic Resonance Imaging; NIfTI, Neuroimaging Informatics Technology Initiative file format; PNG, Portable Network Graphic file format; ppm, portable pixmap file format; QTL, Quantitative Trait Loci; SVG, Scalable Vector Graphics; TE, excitation time; TI, inversion time; TR, repetition time; UCLA, University of California, Los Angeles; URL, Uniform Resource Locator; VA, Veterans Administration.

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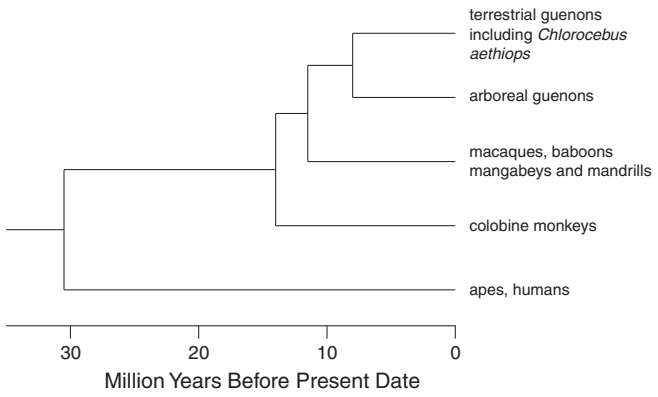

Fig. 1. Relationship of *Chlorocebus aethiops* to other Old World monkeys, apes and humans. Estimated divergence dates are represented along the *x*-axis.

described by Mikula et al. (2007) (accessible at http://brainmaps.org), we are unaware of any modern structural anatomic atlas of the genus *Chlorocebus* or any other arboreal guenon. The value of an anatomic brain atlas specific to this species is underscored by the fact that the vervet is a well established animal model (Carlsson, 2004) that has been used to study numerous brain disorders and traits. These include Parkinson's disease (Taylor et al., 1997; Campos-Romo et al., 2009), Alzheimer's disease (Lemere et al., 2004; Fainman et al., 2007), recovery from early brain injury (Burke et al., 2010), African sleeping sickness (Ouwe-Missi-Oukem-Boyer et al., 2006), aging related brain changes (Melega et al., 2007), fetal alcohol syndrome (Burke et al., 2009), alcoholism (Ervin et al., 1990; Mash et al., 1996), phencyclidine use (Jentsch et al., 1997), cocaine use (Jentsch et al., 2002), methamphetamine use (Melega et al., 2008), stress (Uno et al., 1989), eating disorders (Laćan et al., 2008), stereotypic behaviors (Hugo et al., 2003), impulsivity and aggression (Fairbanks et al., 2004b; James et al., 2007), novelty seeking (Bailey et al., 2007), separation anxiety (Marais et al., 2006), processing of vocalizations (Gil-da-Costa and Hauser, 2006), cerebrospinal fluid dopamine metabolite levels (Freimer et al., 2007) and brain size (Fears et al., 2009). Vervets are likely to account for an increasing proportion of non-human primate neuroscience studies in the future since macaques, the most commonly studied Old World monkey, are in short supply by virtue of their use in AIDS research (Carlsson et al., 2004). Vervets are abundant in Africa and on certain islands in the Caribbean as well as being available in breeding colonies in the United States and elsewhere. Relative to macaques, vervets pose less risk to humans as they are not infected with Cercopithecine herpesvirus 1, a herpes virus endemic in macaque colonies that has a 70% mortality rate when contracted by humans (Elmore and Eberle, 2008).

We have recently completed magnetic resonance imaging (MRI) of a large number of vervets from the UCLA-VA/Wake Forest Vervet Research Colony (Fears et al., 2009) and have assembled these scans into an averaged vervet MRI atlas. We have registered a very high resolution cryomacrotome anatomic data set collected from one member of this colony (Rubins et al., 1999) to this atlas and have labeled various sulcal and subcortical landmarks in this anatomic data set on all three primary viewing planes. To facilitate interpretation of the MRI images, the atlases have been incorporated into two interlinked Web-based viewer applications that simultaneously display transverse, coronal and sagittal sections with updating of sections whenever the user clicks on the images. Rendered surface views along the primary image axes are also included. Menu selections can be used to navigate directly to labeled structures. Stereotaxic coordinates of the current location are displayed. The images, labels and coordinate axes can be rescaled to any size in the viewer since the application is based on Scalable Vector Graphics (SVG) (http://www.w3.org/Graphics/SVG/), a scalable format viewable in most modern web browsers. To facilitate registration of other imaging data into this atlas framework, the data volume that was used to create the averaged MRI atlas is also available for download. We describe here the construction of this resource, which should be useful in interpretation of brain anatomic or imaging datasets collected from vervet monkeys. Due to strong conservation of brain anatomic features across all Old World monkey species, this electronic resource may be a useful supplement in interpreting such data from other monkey species as well.

Materials and methods

The Vervet Research Colony

The UCLA-VA/Wake Forest Vervet Research Colony was founded from 57 wild-caught animals trapped on the island of St. Kitts in the Caribbean between 1975 and 1985. Ancestors of these animals are believed to have been brought to St. Kitts from Africa in the 1600s. Morphometric and DNA evidence suggests that these animals originated in West Africa and that they are members of the subspecies *Chlorocebus aethiops sabaeus* (van der Kuyl et al., 1996). At UCLA, the animals were maintained in a naturalistic setting in matrilineal breeding groups. None of the animals studied had undergone any experimental manipulations expected to alter brain structure. At the time of this study, the colony was housed in the Los Angeles area; the colony has subsequently been relocated to Wake Forest University.

Data collection and processing

All MRI and cryomacrotome procedures were conducted in accordance with the UCLA Animal Research Committee and with the Animal Research Committee of the Department of Veterans Affairs Greater Los Angeles Healthcare System.

MRI data

Animals were scanned using a mobile 1.5 Tesla Siemens (Erlangen, Germany) Symphony unit located on the colony grounds. All available animals more than 2 years of age (357 in total) were scanned. The scanning procedure has been previously described in detail elsewhere (Fears et al., 2009). Briefly, animals were anesthetized with intramuscular ketamine (15 mg/kg) prior to insertion of an intravenous catheter. They were subsequently treated with atropine (0.027 mg/kg) to minimize secretions prior to endotracheal intubation to protect the airway. Anesthesia was maintained with intravenous ketamine and midazolam. Eight or nine T1-weighted scans (TR 1900 ms,TE 4.38 ms, TI 1100 ms, flip angle 15 degrees) were obtained from each animal using a multi-channel human knee coil (Invivo, Orlando) as a receiver. Image resolution was 0.5 mm in all three axes. All animals tolerated the procedure well.

MRI images were converted from DICOM format to 16-bit Analyze 7.5 format using in-house software. The MRI scans from each animal were coregistered to one another and averaged using a rigid-body spatial transformation model with the Automated Image Registration (AIR 5.2.6) package (Woods et al., 1998a). Non-brain structures were removed using a combination of manual and automated methods and the resulting brain-only images were registered to the images of one arbitrarily chosen animal using an affine spatial transformation model with AIR 5.2.6 (Woods et al., 1998b). Using the resulting spatial transformations, an average affine target space was defined (Woods, 2003a) and each animal's averaged MRI scan was resampled into this space and averaged to create a new target atlas. The registration and resampling processes were repeated iteratively until the resulting target atlas had converged to an atlas visually indistinguishable from its precursor. This final target atlas was adjusted to align the averaged