Brain & Language 131 (2014) 36–55

Contents lists available at ScienceDirect

Brain & Language

journal homepage: www.elsevier.com/locate/b&l

Cortico-cortical connections of areas 44 and 45B in the macaque monkey

Stephen Frey *, Scott Mackey, Michael Petrides

Montreal Neurological Institute, McGill University, 3801 University Street, Montreal, Quebec H3A 2B4, Canada

ARTICLE INFO

Article history:
Available online 30 October 2013

Keywords:
Broca's
Wernicke's
Arcuate fasciculus
Temporo-frontal extreme capsule fiber system
Language
Frontal
Temporal
Parietal
Auditory

ABSTRACT

In the human brain, areas 44 and 45 constitute Broca's region, the ventrolateral frontal region critical for language production. The homologues of these areas in the macaque monkey brain have been established by direct cytoarchitectonic comparison with the human brain. The cortical areas that project monosynaptically to areas 44 and 45B in the macaque monkey brain require clarification. Fluorescent retrograde tracers were placed in cytoarchitectonic areas 44 and 45B of the macaque monkey, as well as in the anterior part of the inferior parietal lobule and the superior temporal gyrus. The results demonstrate that ipsilateral afferent connections of area 44 arise from local frontal areas, including rostral premotor cortical area 6, from secondary somatosensory cortex, the caudal insula, and the cingulate motor region. Area 44 is strongly linked with the anterior inferior parietal lobule (particularly area PFG and the adjacent anterior intraparietal sulcus). Input from the temporal lobe is limited to the fundus of the superior temporal sulcus extending caudal to the central sulcus. There is also input from the sulcal part of area Tpt in the upper bank of the superior temporal sulcus. Area 45B shares some of the connections of area 44, but can be distinguished from area 44 by input from the caudal inferior parietal lobule (area PG) and significant input from the part of the superior temporal sulcus that extends anterior to the central sulcus. Area 45B also receives input from visual association cortex that is not observed in area 44. The results have provided a clarification of the relative connections of areas 44 and 45B of the ventrolateral frontal region which, in the human brain, subserves certain aspects of language processing.

1. Introduction

In the human brain, cytoarchitectonic areas 44 and 45 make up Broca's region (Amunts et al., 1999) which is thought to be critical for certain aspects of language production (Geschwind, 1970; Grodzinsky & Amunts, 2006). Although the homologues of Broca's region, areas 44 and 45, in the macaque monkey have been established by comparative architectonic studies and electrophysiological recording (Petrides, Cadoret, & Mackey, 2005; Petrides & Pandya, 1994, 2002a, 2009) and their connections from the inferior parietal lobule and the superior temporal region have been examined (Petrides & Pandya, 2009), several aspects of their cortico-cortical connectivity require clarification. In the monkey brain, area 44 is buried deep in the fundus of the inferior ramus of the arcuate sulcus and is bounded, anteriorly, by area 45B and, posteriorly, by area 6VR (Fig. 1). Dorsally areas 44 and 45B are replaced by area 8Av. Anteriorly, area 45B is replaced by area 45A which continues on the ventrolateral frontal cortex as far as the infraprincipal dimple (Fig. 2). The agranular premotor area 6VR adjoins, caudally, dysgranular area 44 in which the granular layer IV begins to emerge. By contrast, area 45 is typical prefrontal granular cortex in which layer IV is well developed (Petrides & Pandya, 1994, 2002a; Petrides et al., 2005).

Petrides and Pandya (1984, 2009), using the autoradiographic method, demonstrated that distinct axonal connections originating in the inferior parietal lobule terminate in the ventrolateral frontal region of the macaque monkey and the projections to the homologues of areas 44, 45B and 45A have been shown to course via branches II and III of the superior longitudinal fasciculus (SLF II, SLF III). Axons originating from the mid-lateral part of the superior temporal gyrus and the adjacent superior temporal sulcus course as part of the extreme capsule to terminate in the ventrolateral frontal region and these form the temporo-frontal extreme capsule fasciculus (TFECF) (Petrides & Pandya, 1988, 2009). Fibers originating from the caudal part of the supero-lateral temporal lobe form the arcuate fasciculus (Petrides & Pandya, 2009). Data consistent with these findings were also demonstrated in the human brain using diffusion weighted magnetic resonance imaging (Frey, Campbell, Pike, & Petrides, 2008) and, more recently, with resting state connectivity (Kelly et al., 2010).

The present investigation aimed to refine further our understanding of the cortico-cortical connections of areas 44 and 45B of the macaque monkey by injecting retrograde fluorescent tracers in these areas in order to establish the entire set of neurons that send axons to terminate in these two areas. Additional injections

* Corresponding author. Fax: +1 514 398 1338.
E-mail address: steve@rogue-research.com (S. Frey).

0093-934X/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bandl.2013.05.005

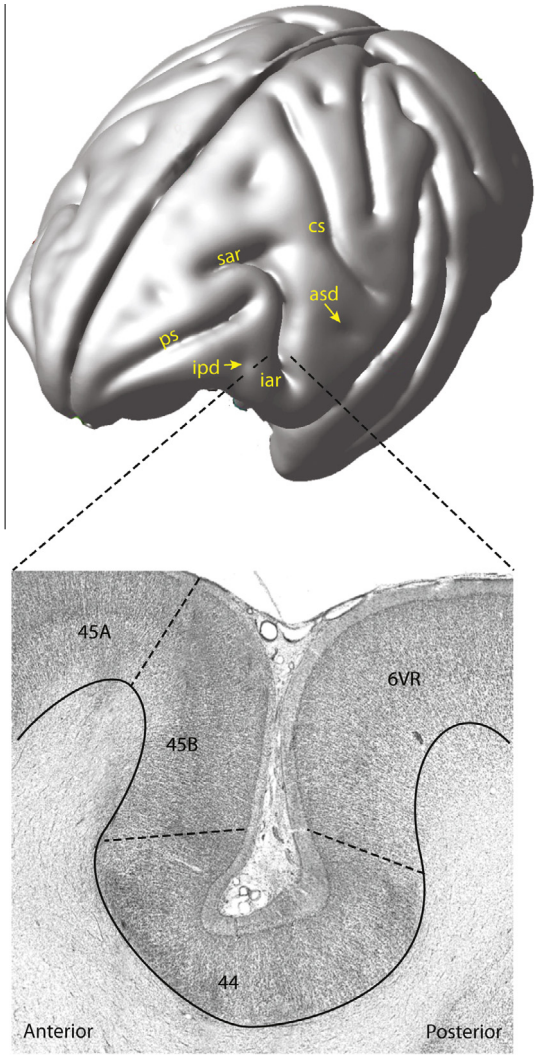

Fig. 1. The location of areas 44 and 45B within the inferior ramus of the arcuate sulcus demonstrated on a magnetic resonance imaging surface reconstruction of the average macaque monkey brain. A cross section from the inferior ramus of the arcuate sulcus shows the location of architectonic areas 44, 45A, 45B and 6VR within the arcuate sulcus. For Abbreviations, see List of Abbreviations.

into the anterior part of the inferior parietal lobule and the mid-temporal region of the superior temporal gyrus were used to examine further the bi-directionality of connections of the ventro-lateral frontal region with these posterior regions of the cortex.

2. Material and methods

2.1. Subjects

The subjects were seven adult macaque monkeys (1 female and 5 male Macaca fascicularis and 1 male Macaca mulatta), 3.7–10 kg (average 6.2 kg) at the time of surgery. The study was approved by the Montreal Neurological Institute Animal Ethics Committee and conformed to the Canadian Council of Animal Care guidelines for humane care of laboratory animals.

2.2. Anesthesia and surgery

All surgical procedures were performed under strict aseptic conditions. Fifteen minutes prior to anesthesia, the animal was administered an initial dose of glycopyrrolate (0.005 I.M., Sandoz, Canada) to reduce salivary, tracheobronchial and pharyngeal secretions (re-administration every 2.5–3 h). This was followed by a cocktail injection of ketamine hydrochloride (15 mg/kg I.M., Ketaset®, Wyeth, Canada) and Diazepam (1 mg/kg, Sandoz, Canada). Deep anesthesia was produced with isofluorane (3–4% at induction and 0.8–2%, AErrane®, Baxter, Canada). The same anesthetic procedures were carried out for the implantation of the fiducial markers, the magnetic resonance imaging (MRI) scan, and the injection of the anatomical tracers. At the end of surgery for fiducial post implantation or the injections of tracers, the animal was administered prophylactic antibiotics (1 mg/kg Dexamethasone sodium phosphate, I.M., Dexamethasone 5, Vétoquinol, Canada), as well as postsurgical analgesics (0.032 ml/kg, I.M., buprenorphine, Buprenex®, Schering-Plough, UK) for a period of 48 h. Antibiotics were also administered after the surgical procedures (cefovecin sodium, Convenia®, 8 mg/kg I.M., Pfizer, Canada).

2.3. Fiducial implantation

Prior to the MRI scan, the monkey was anesthetized and fitted with an MR compatible post that attaches a hub of 6 fiducial MR markers (Rogue Research Inc., Qc, Canada). This post is surgically implanted on the skull with 6 ceramic screws and together with the fiducial markers is used to increase the accuracy of reaching anatomical targets in combination with a frameless neuronavigation system (Brainsight™ Vet, Rogue Research Inc., Qc, Canada). This procedure is a modification to an existing technique that is described elsewhere (Frey, Comeau, Hynes, Mackey, & Petrides, 2004).

2.4. MRI scanning session

Following the implant of the fiducial post, the monkey was re-anesthetized and a high- resolution T1-weighted 3D anatomical image was acquired from a 3T Siemens Trio scanner (Siemens Medical Systems, Germany) (TR = 2300 ms, TE = 3.44 ms, flip angle = 9°, FOV = 256 mm, 0.6 × 0.6 × 0.6 mm voxels, coronal slices, 4 averages, 48 min: 19 s). The monkey was fitted with an 8-channel custom phased array coil and was placed in the magnet in the supine position (no frame was used). Throughout the scan, the monkey's oxygen saturation levels (SPO2) and heart rate were monitored using pulse oximetry with an infrared sensor that was clipped to the animal's hallux.

2.5. Injection of tracer

Injections of the fluorescent retrograde anatomical tracers Fast Blue (FB, Polysciences Inc., Warrington, PA, USA) were placed in area 44 or area 45B within the lower branch of the inferior arcuate sulcus, and in the inferior parietal lobule and the superior temporal gyrus. The placement of each injection was based on known anatomical landmarks as seen in each animal's T1 weighted MRI scan (cases 1–4, 6 and 8; Figs. 3–10, 12, 13 and 15–17). In addition, a fluorescent bi-directional tracer, Mini-ruby (dextran, tetramethylrhodamine and biotin; 10,000 MW, lysine fixable, D-3312, Invitrogen, Canada), was placed into the rostral bank of the inferior arcuate sulcus where area 45B is located (case 5, Figs. 10 and 11). The dextran amine, Mini-ruby, is generally thought of as an anterograde tracer but can also yield very sensitive retrograde labeling, and can be used in combination with other tracers (for review, see Reiner et al., 2000). In the present experiment, we focused only on retrograde post-processing histology for case 5. In addition, a fluorescent retrograde anatomical tracer, Diamidino Yellow dihydrochloride (DY, Sigma–Aldrich Inc., Canada), was placed in the rostral part