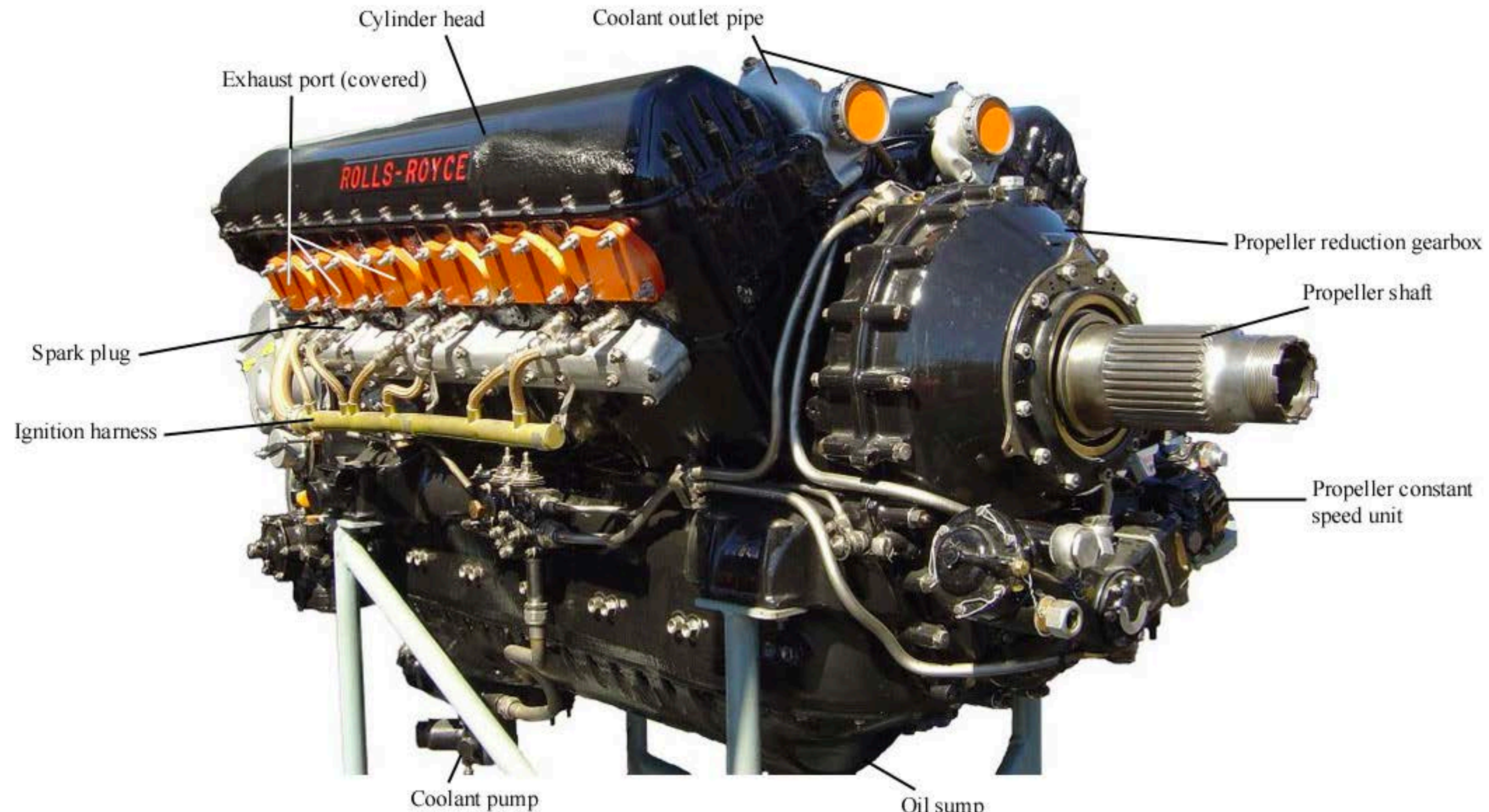


More than just a “Motor”: Recent surprises from the frontal cortex

Christian L. Ebbesen, PhD



Rolls-Royce *Merlin* V-12 Aircraft Engine, 1933

More than just a “Motor”: Recent surprises from the frontal cortex

1:30 PM - 1:35 PM. **180.01 - Introduction**

C. L. Ebbesen; Chair. Skirball Inst. of Biomol. Med., New York University School of Medicine, New York, NY.

1:35 PM - 1:55 PM **180.02 - The role of rat frontal orienting fields in decision commitment**

C. D. Kopec; Princeton Neuroscience Institute, Princeton University, Princeton, NJ.

1:55 PM - 2:15 PM **180.03 - Movement suppression and socio-sensory signals in vibrissa motor cortex**

C. L. Ebbesen; Skirball Inst. of Biomol. Med., New York University School of Medicine, New York, NY.

2:15 PM - 2:35 PM **180.04 - Neural substrates of action timing decisions**

M. Murakami; Champalimaud Research, University of Yamanashi, Chuo-shi, JAPAN.

2:35 PM - 2:55 PM **180.05 - Nominally non-responsive frontal cortical cells encode behavioral variables via ensemble consensus-building**

M. Insanally; New York University, NY, NY.

2:55 PM - 3:15 PM **180.06 - In vivo spiking dynamics and encoding of forelimb movements in rat M1/M2**

A. Saiki; Neurobiology, Northwestern University, Evanston, IL.

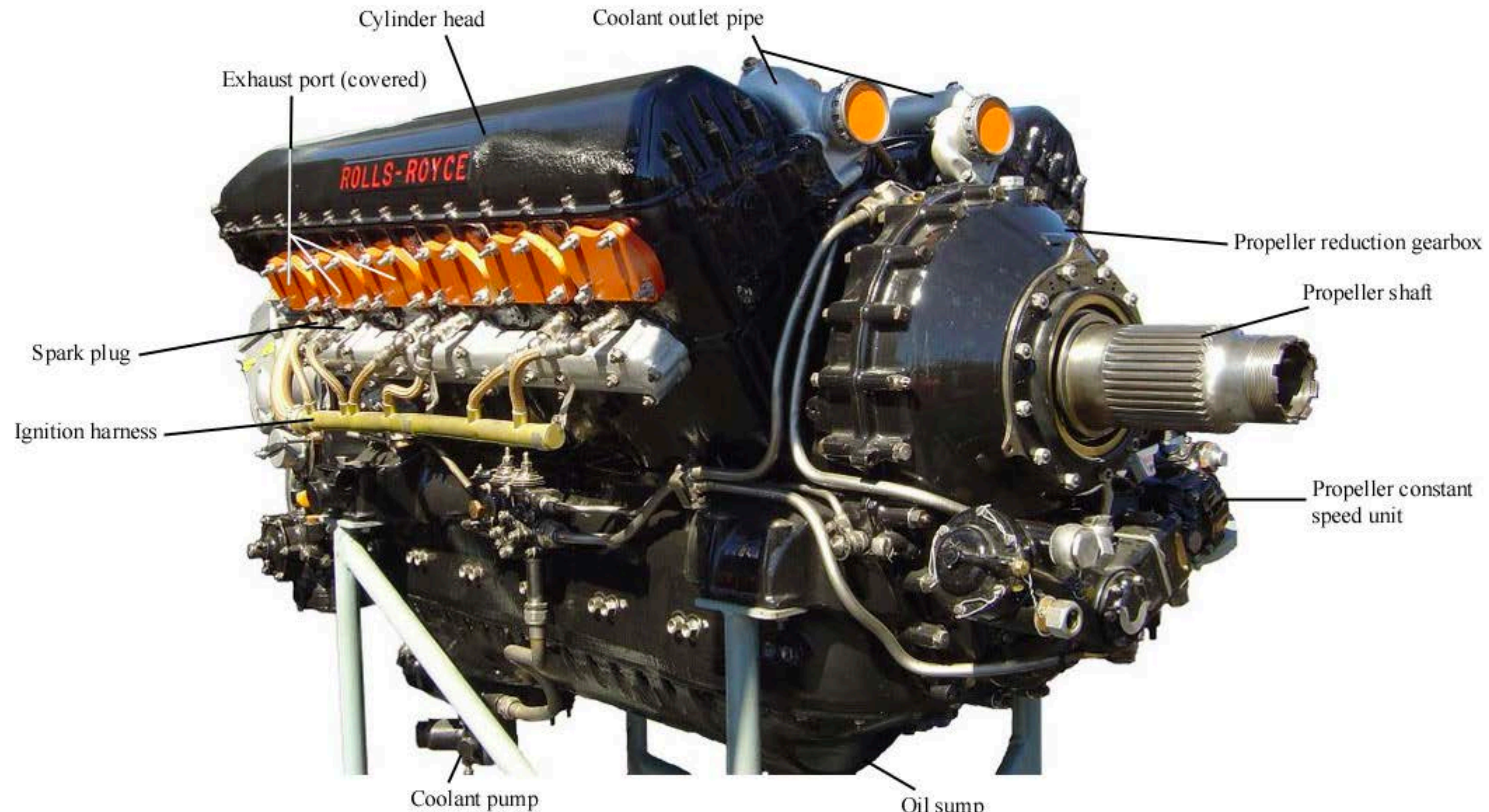
3:15 PM - 3:35 PM **180.07 - Spatio-temporal receptive fields in the rodent frontal orienting field**

J. C. Erlich; Institute of Brain and Cognitive Science, NYU Shanghai, Shanghai, CHINA.

3:35 PM - 4:00 PM **180.08 - Closing Remarks**

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Human M1

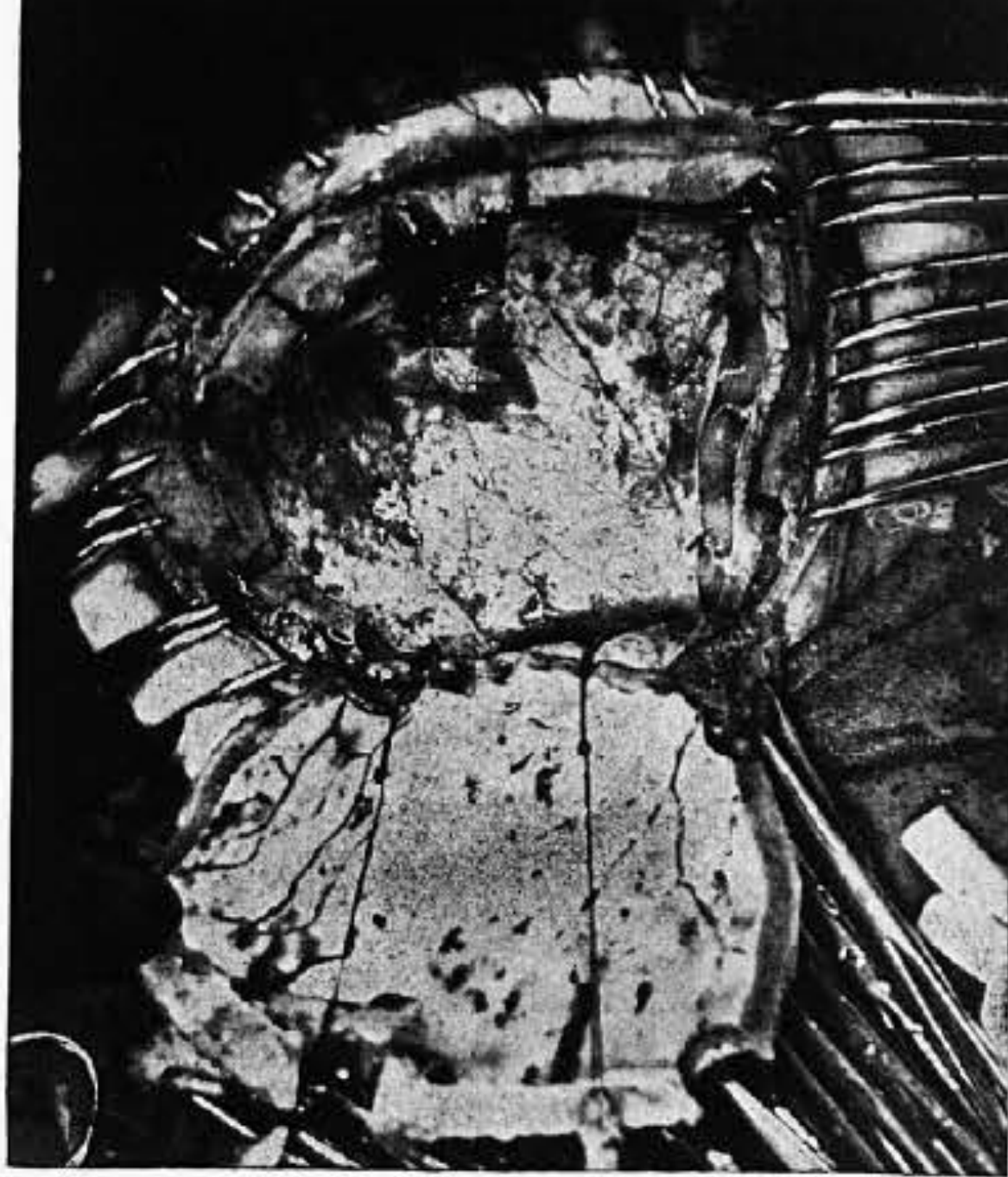


Fig. 2. CASE G.C. Osteoplastic bone flap turned down on its attachment of temporal muscle.

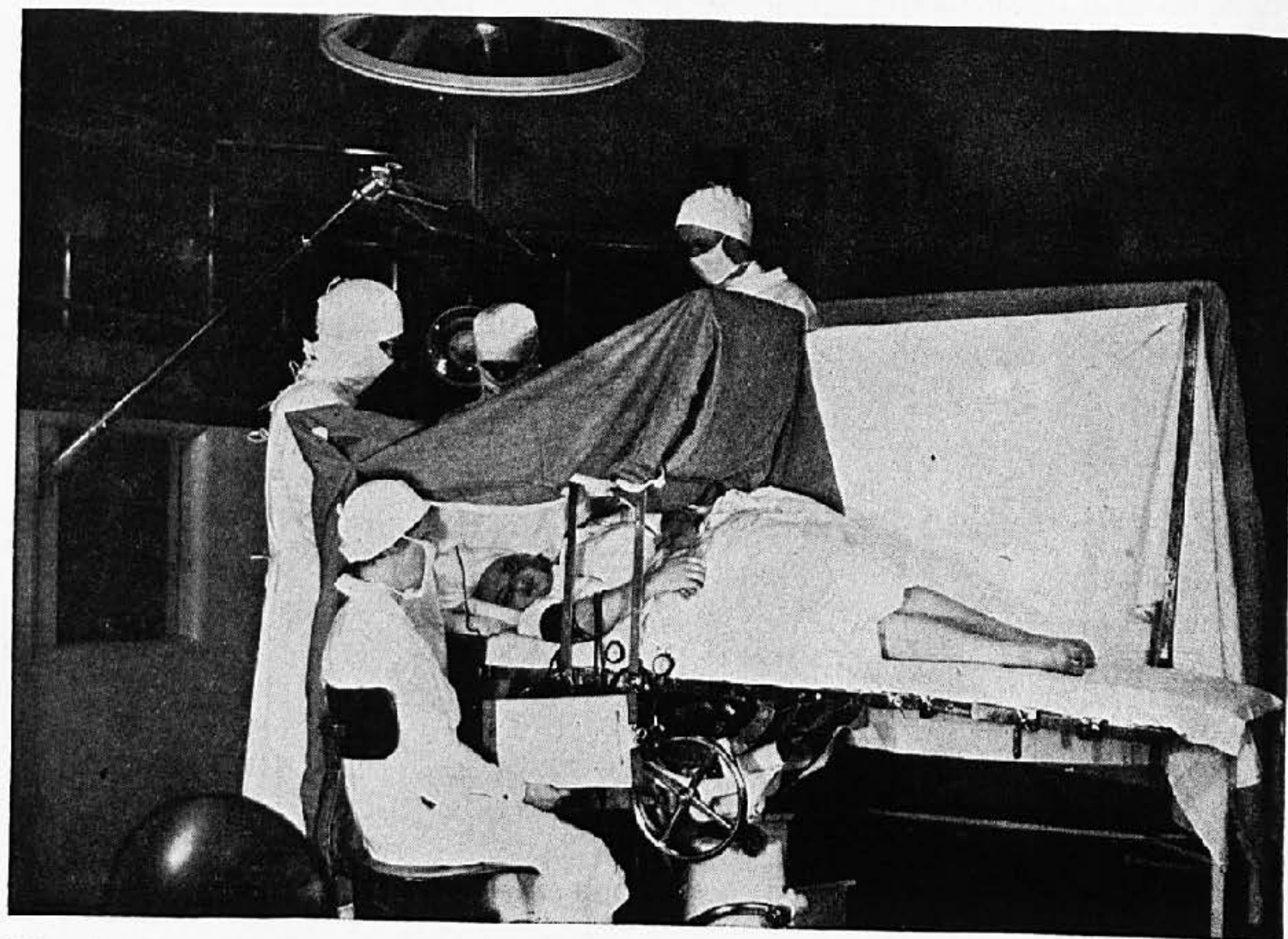
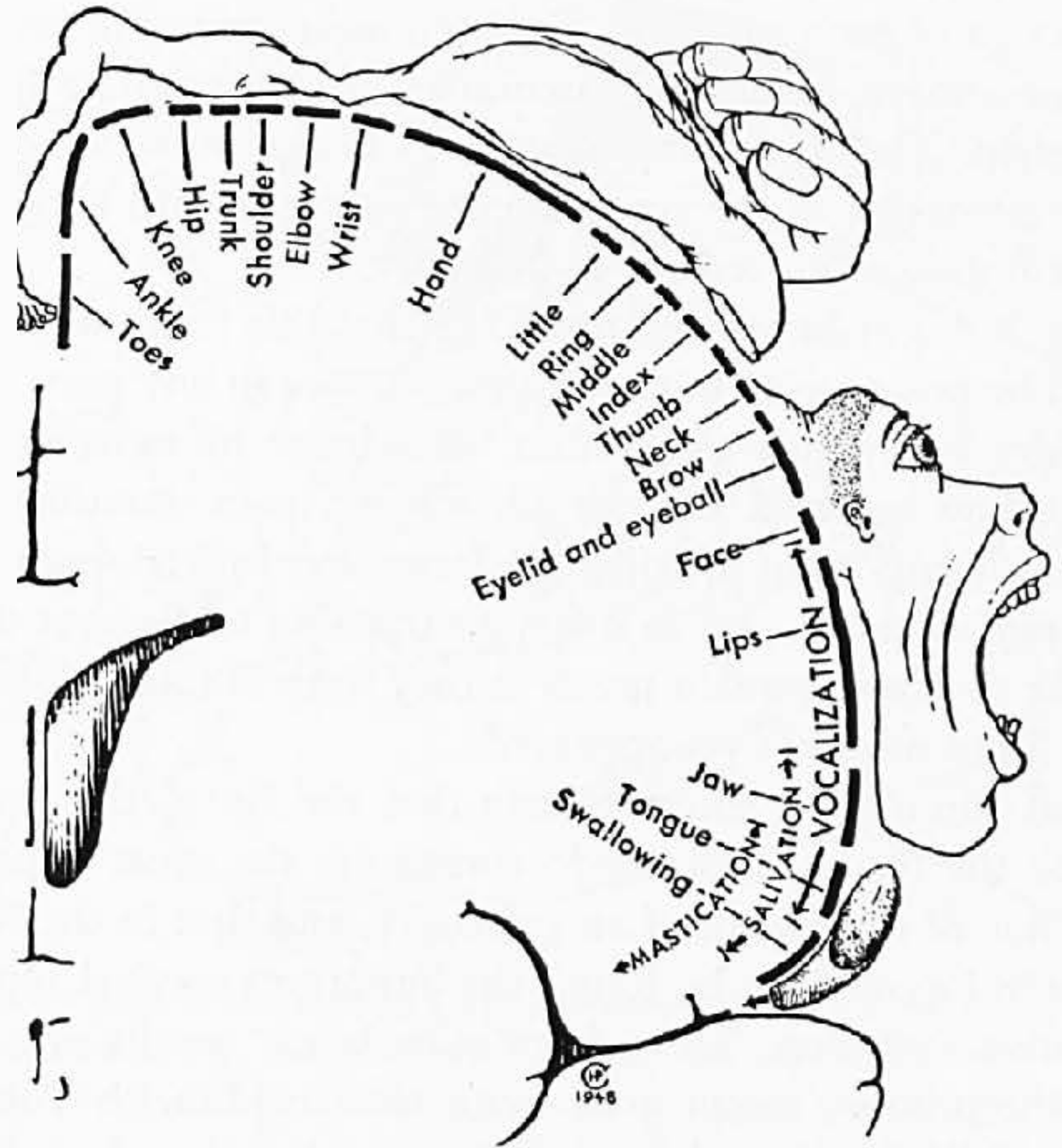
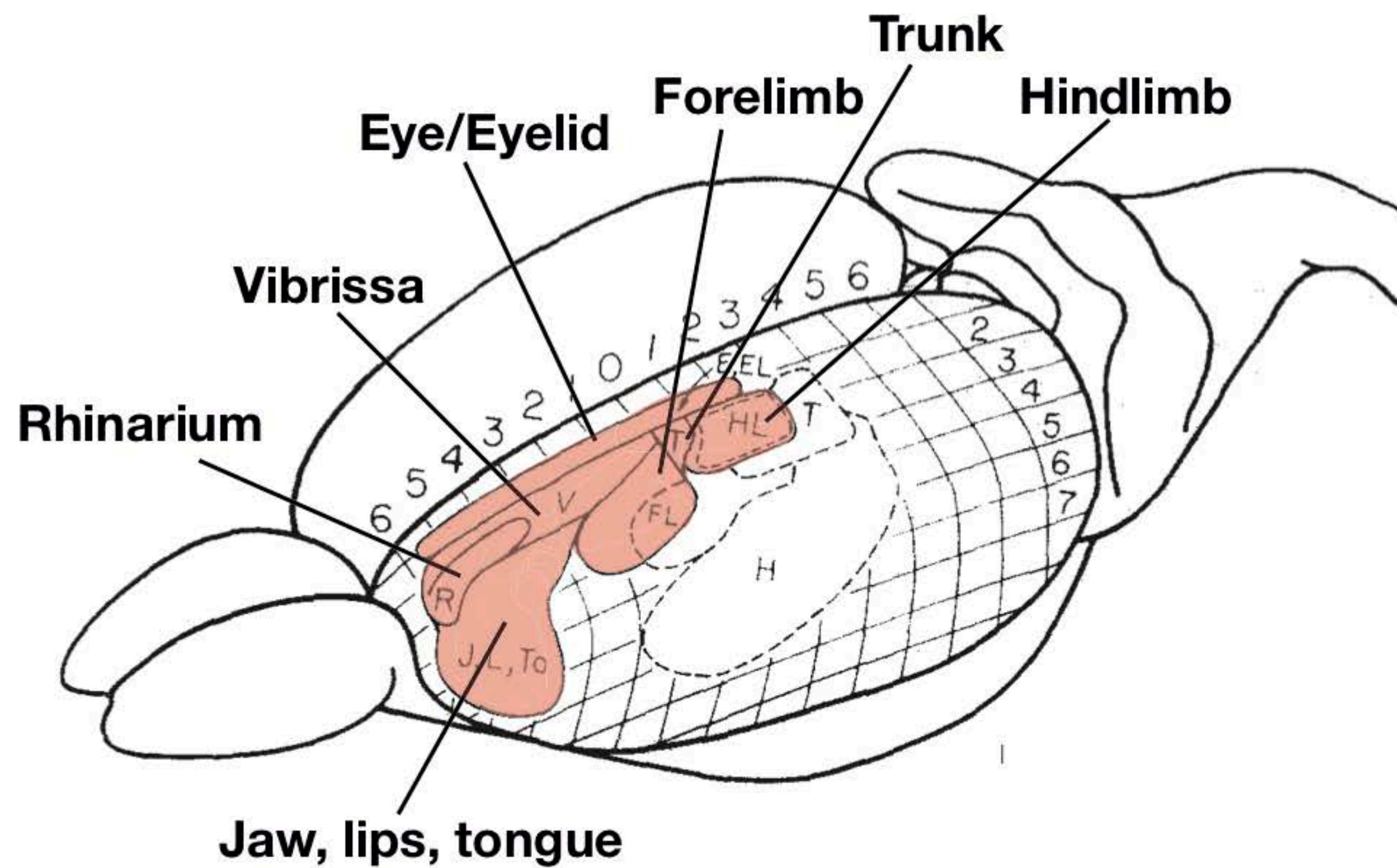
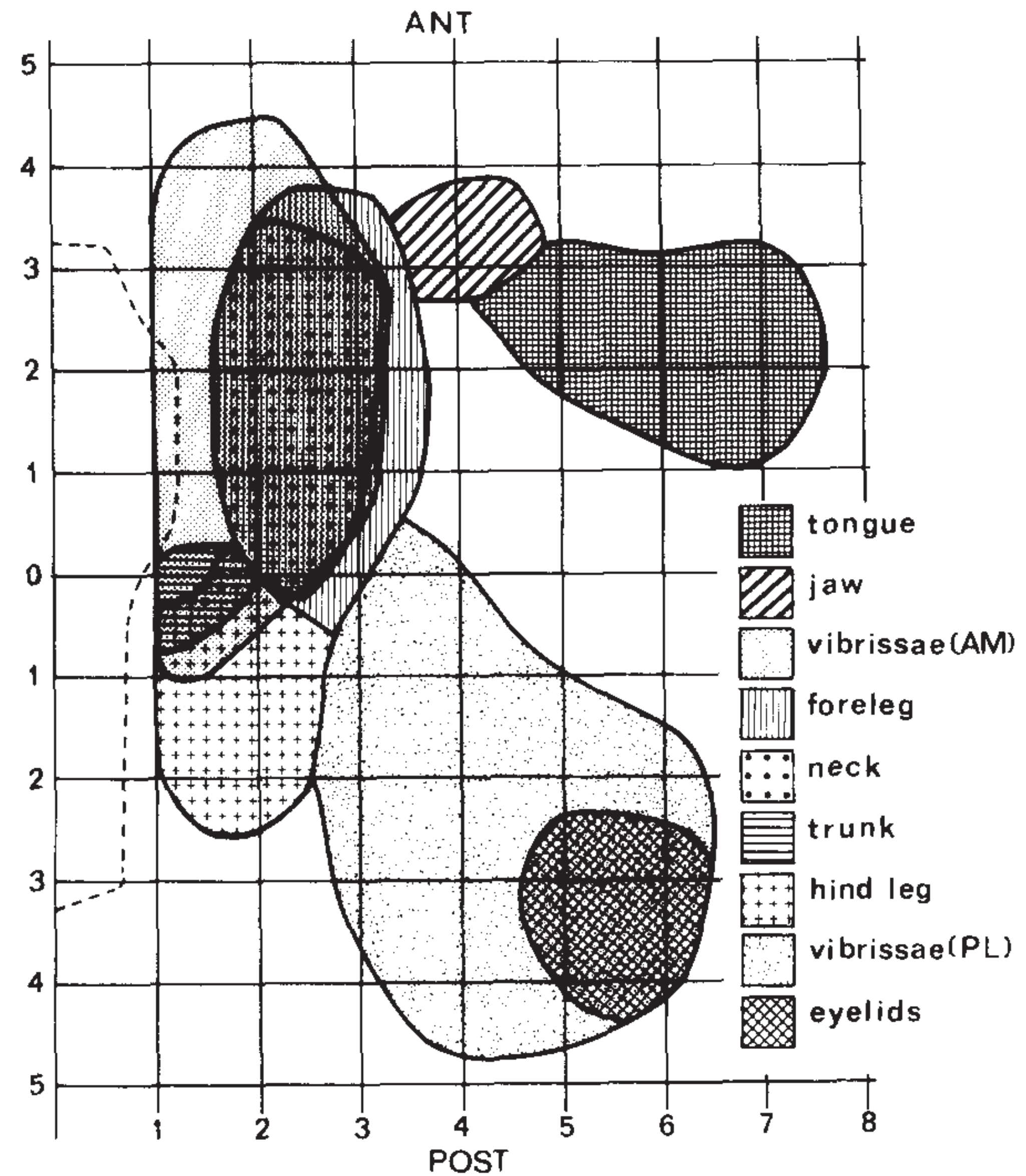


Fig. 4. Position of patient and observer during operation under local anesthesia. The photographer's camera is located outside window behind the surgeon and is focused on the brain through the mirror above.

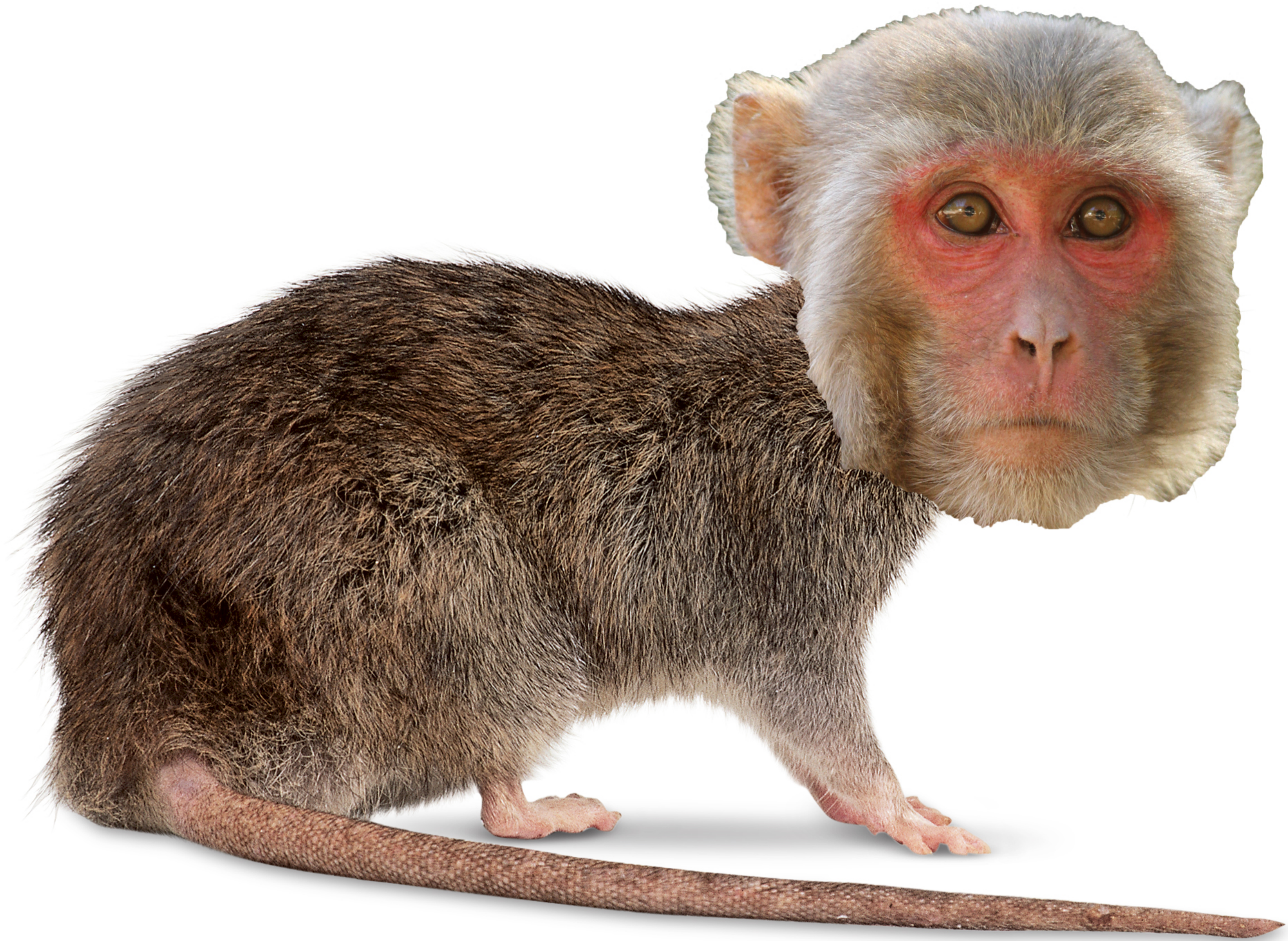


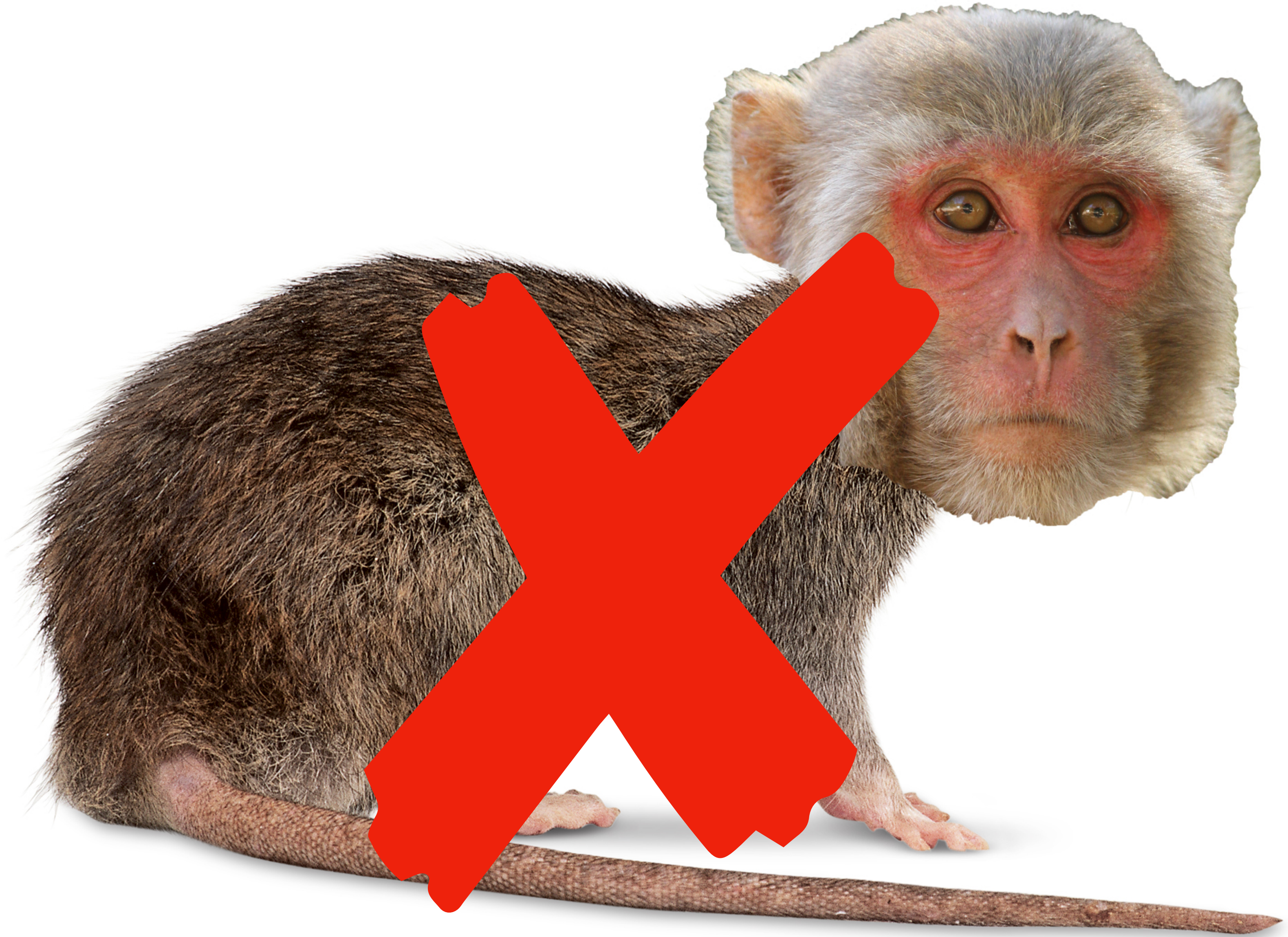


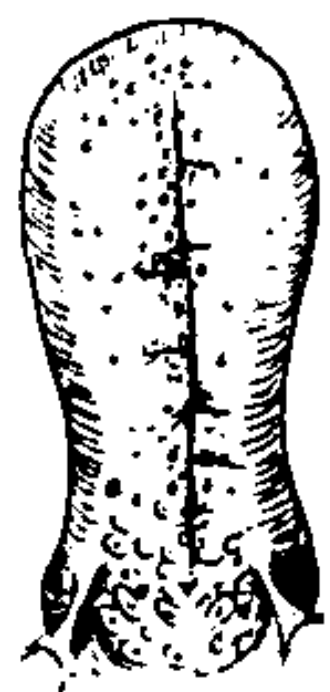
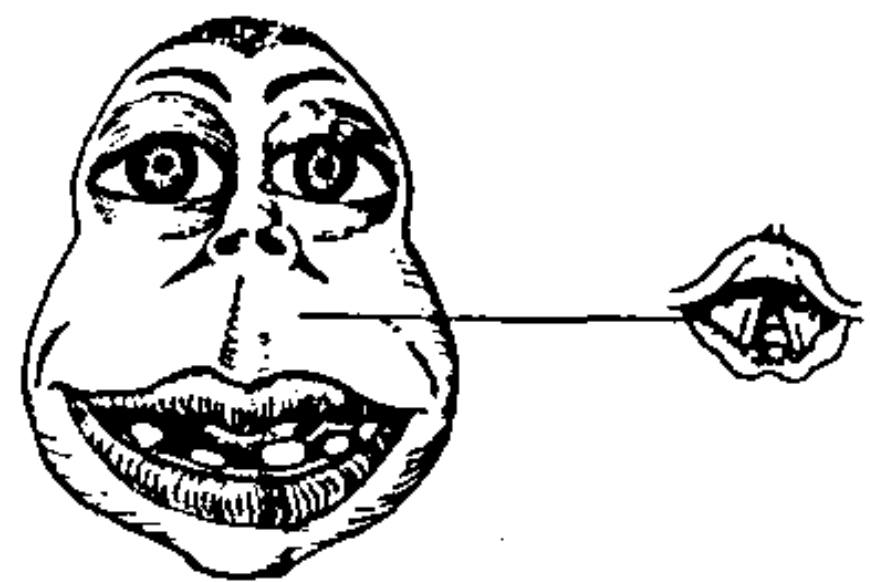
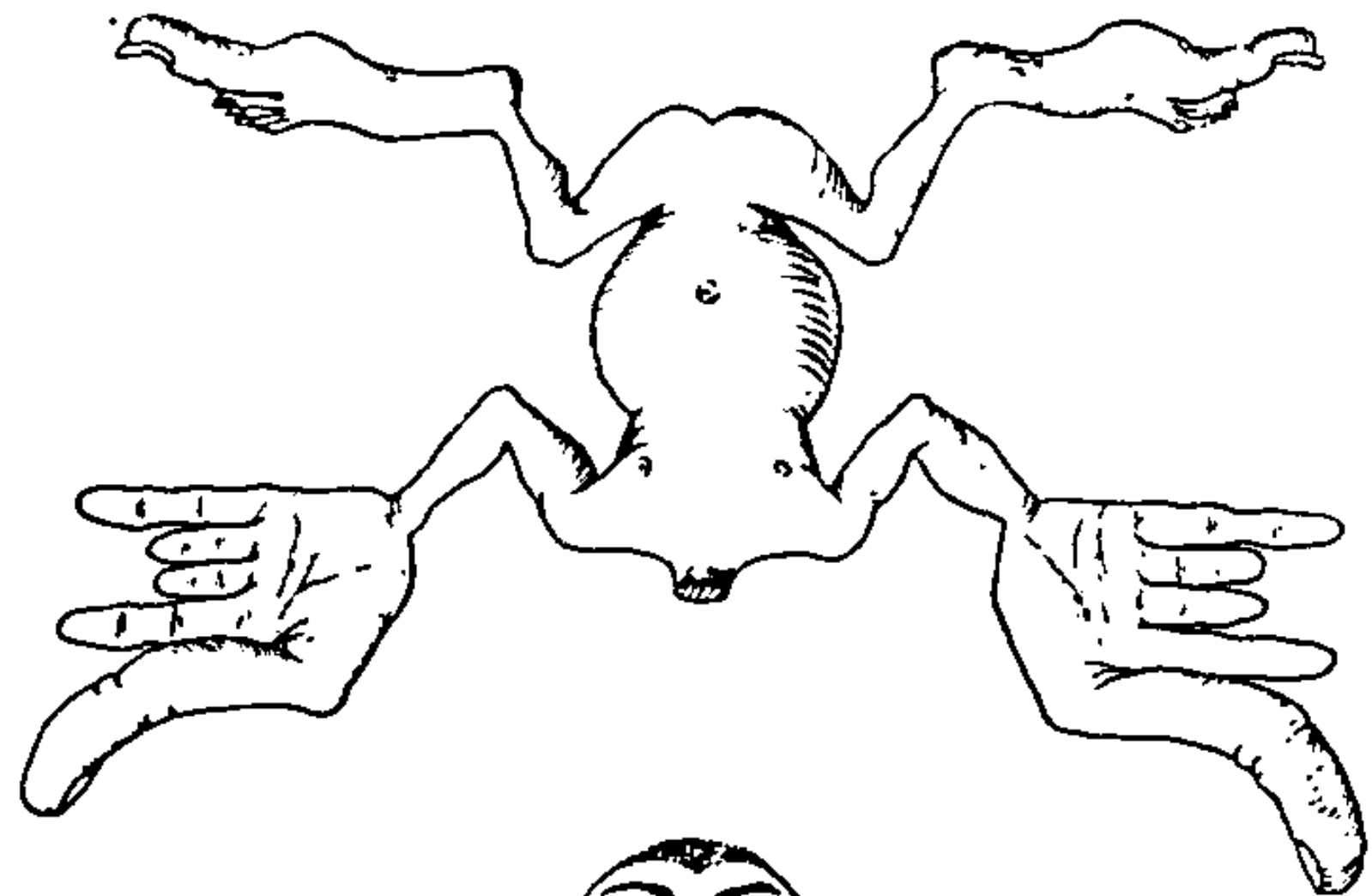
Hall & Lindholm, *Brain Res.* 1974



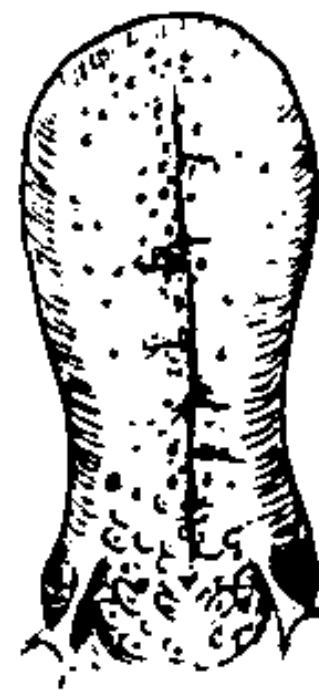
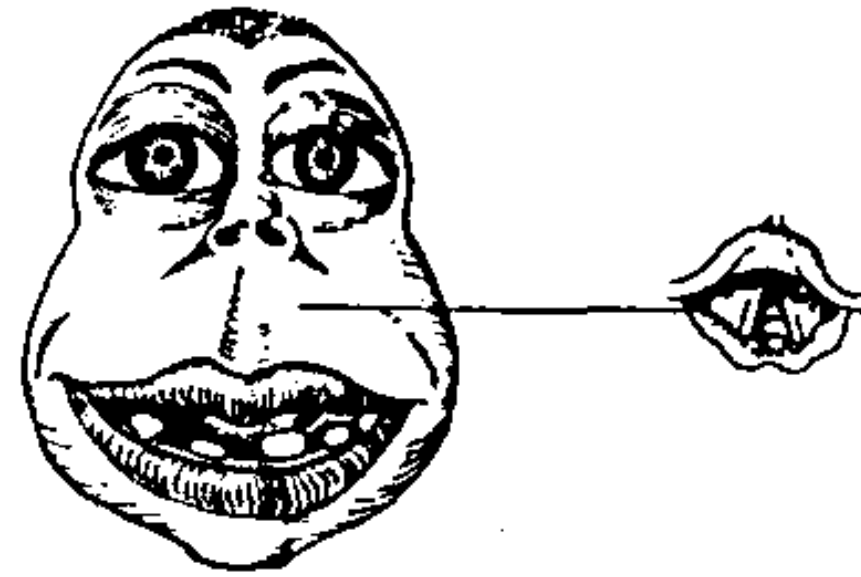
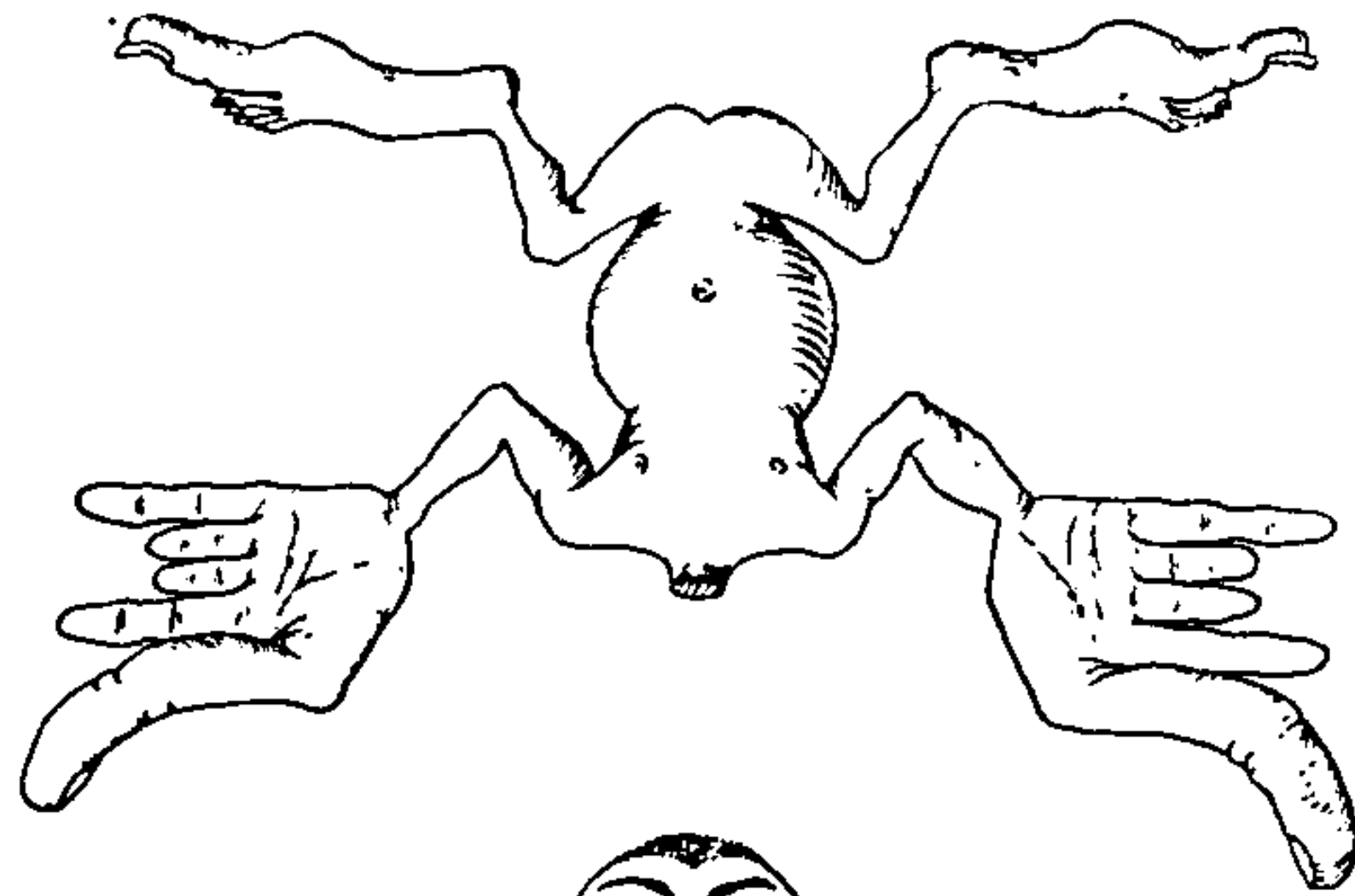
Gioanni & Lamarche, *Brain Res.* 1985



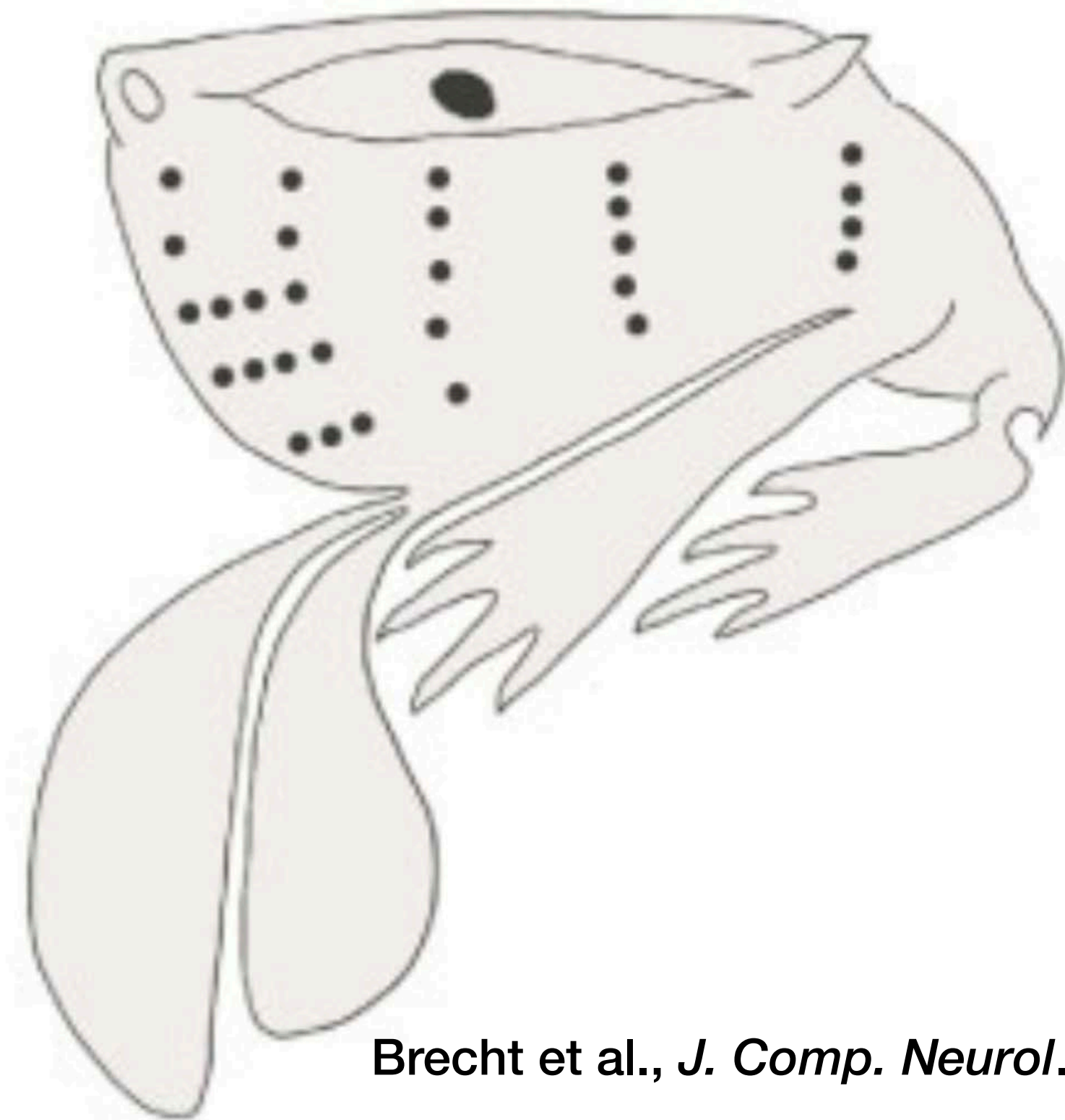




Penfield and Boldrey (1937). *Brain* 60, 389-443.

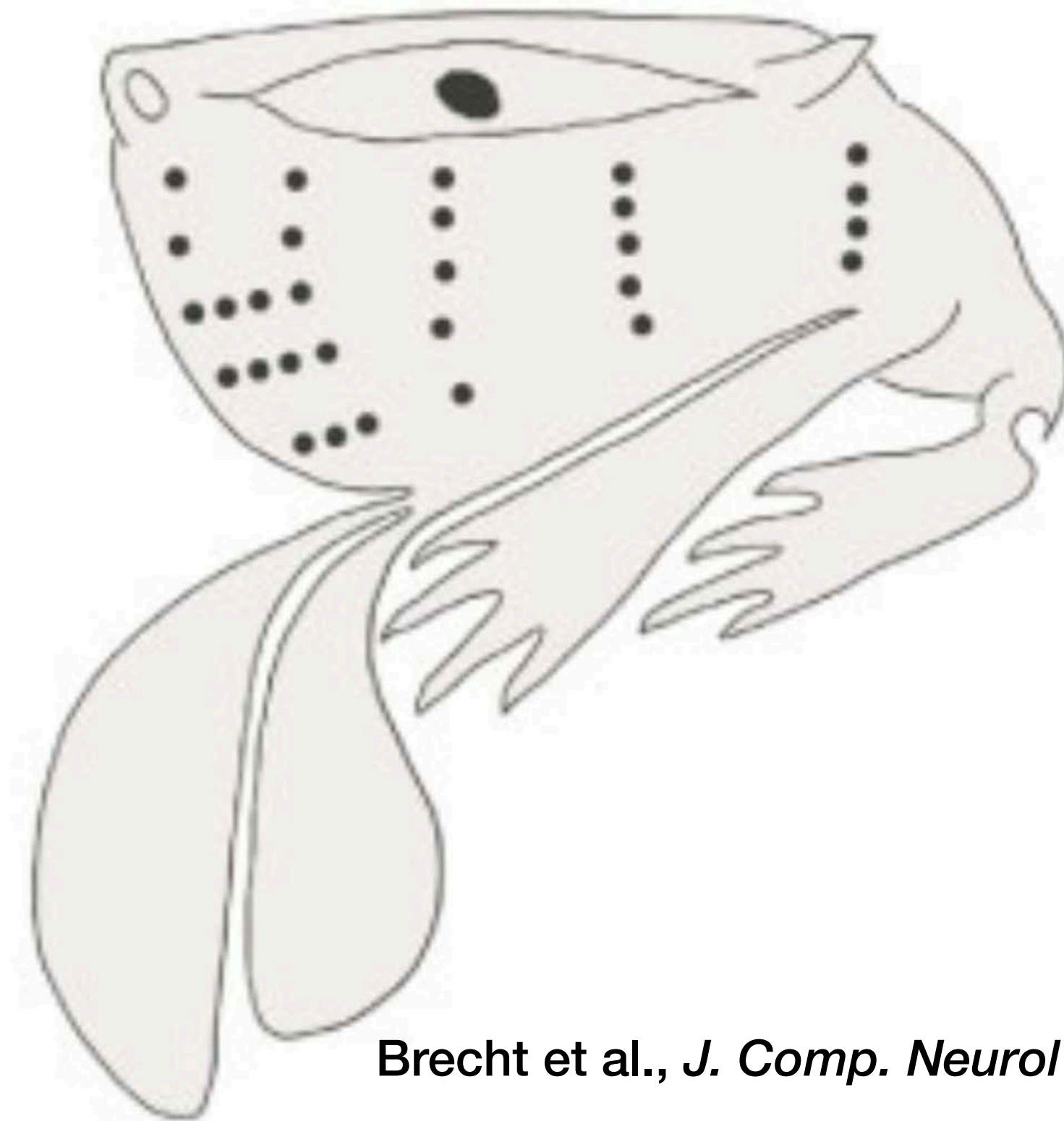


Penfield and Boldrey (1937). *Brain* 60, 389–443.



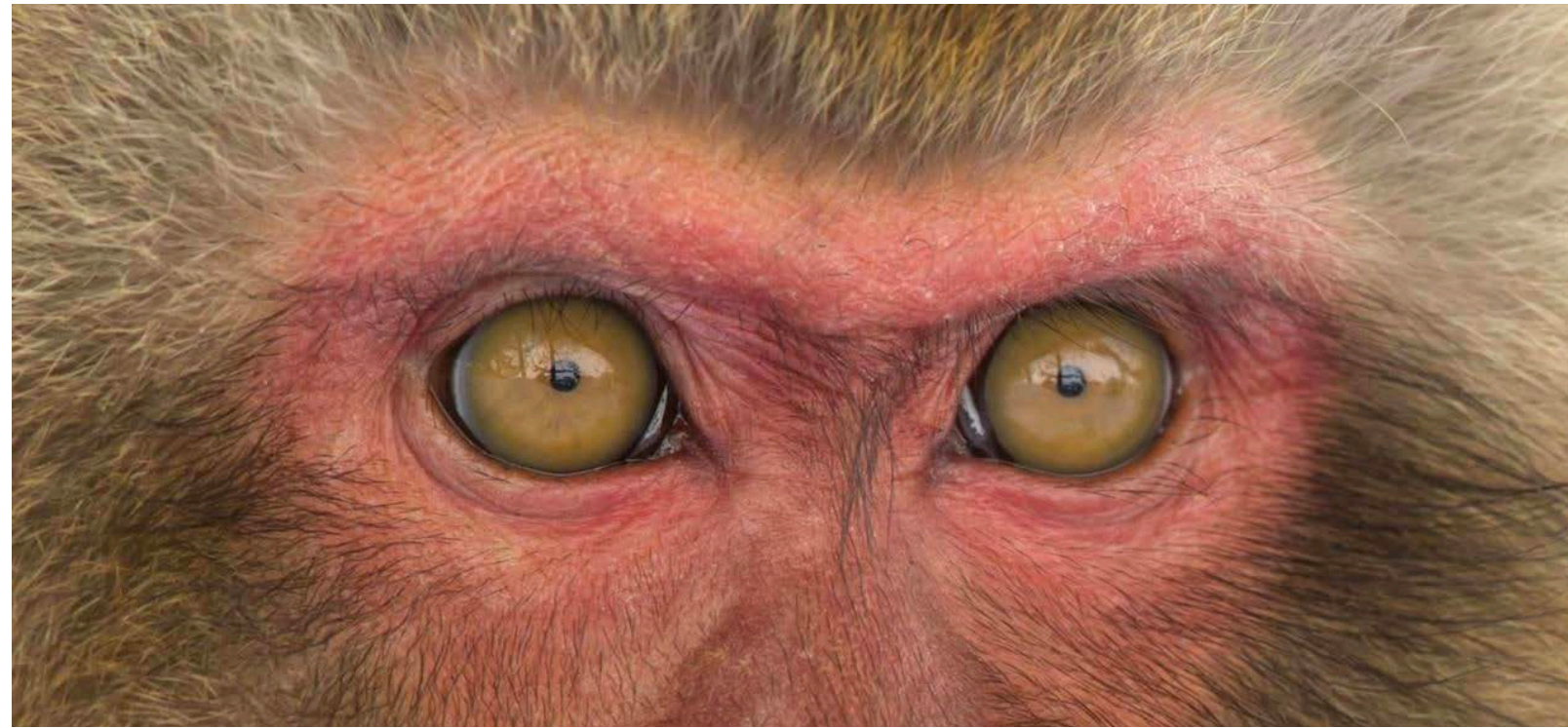
Brecht et al., *J. Comp. Neurol.* 2004

Different specializations

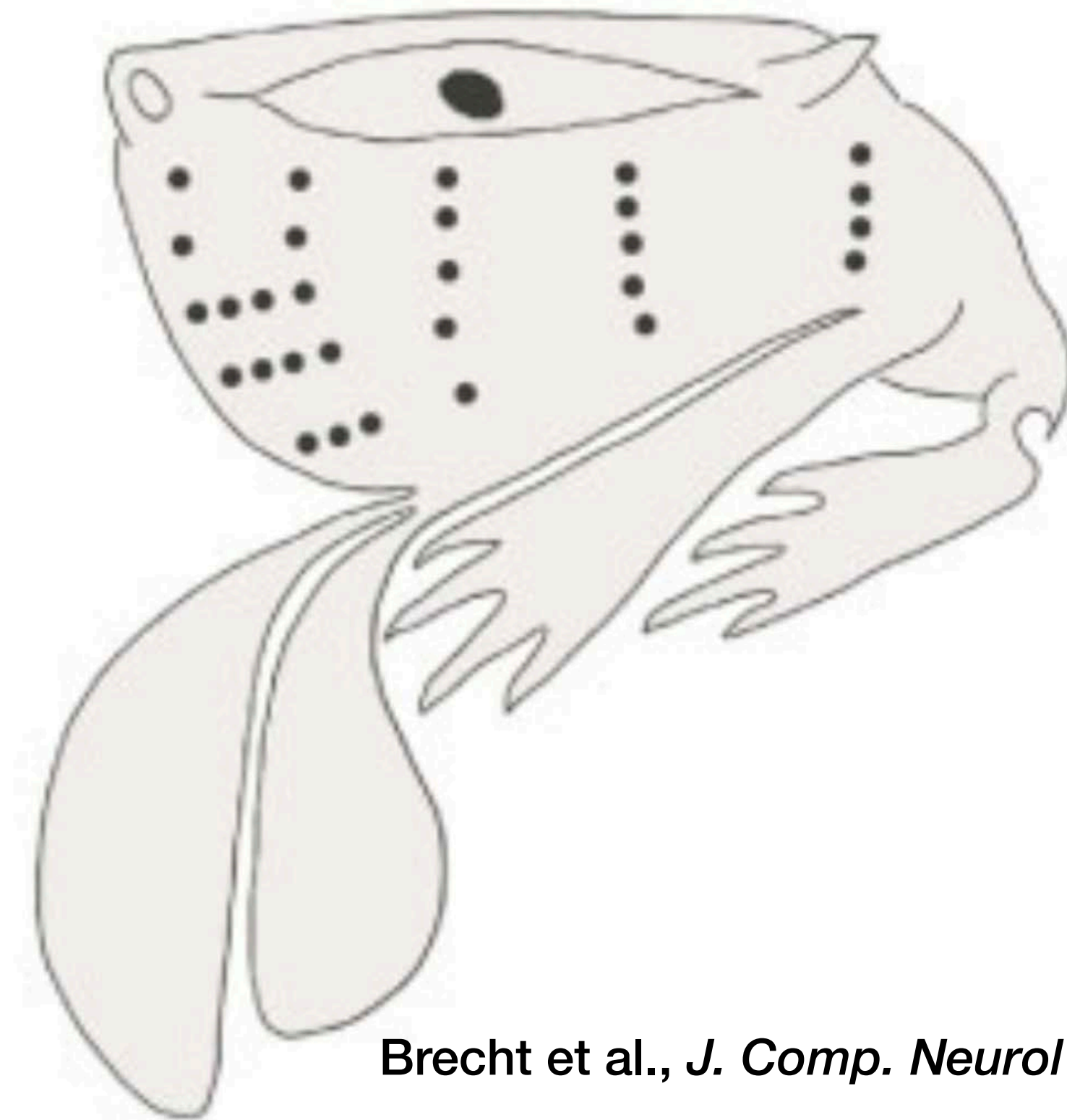


Brecht et al., *J. Comp. Neurol.* 2004

Different specializations

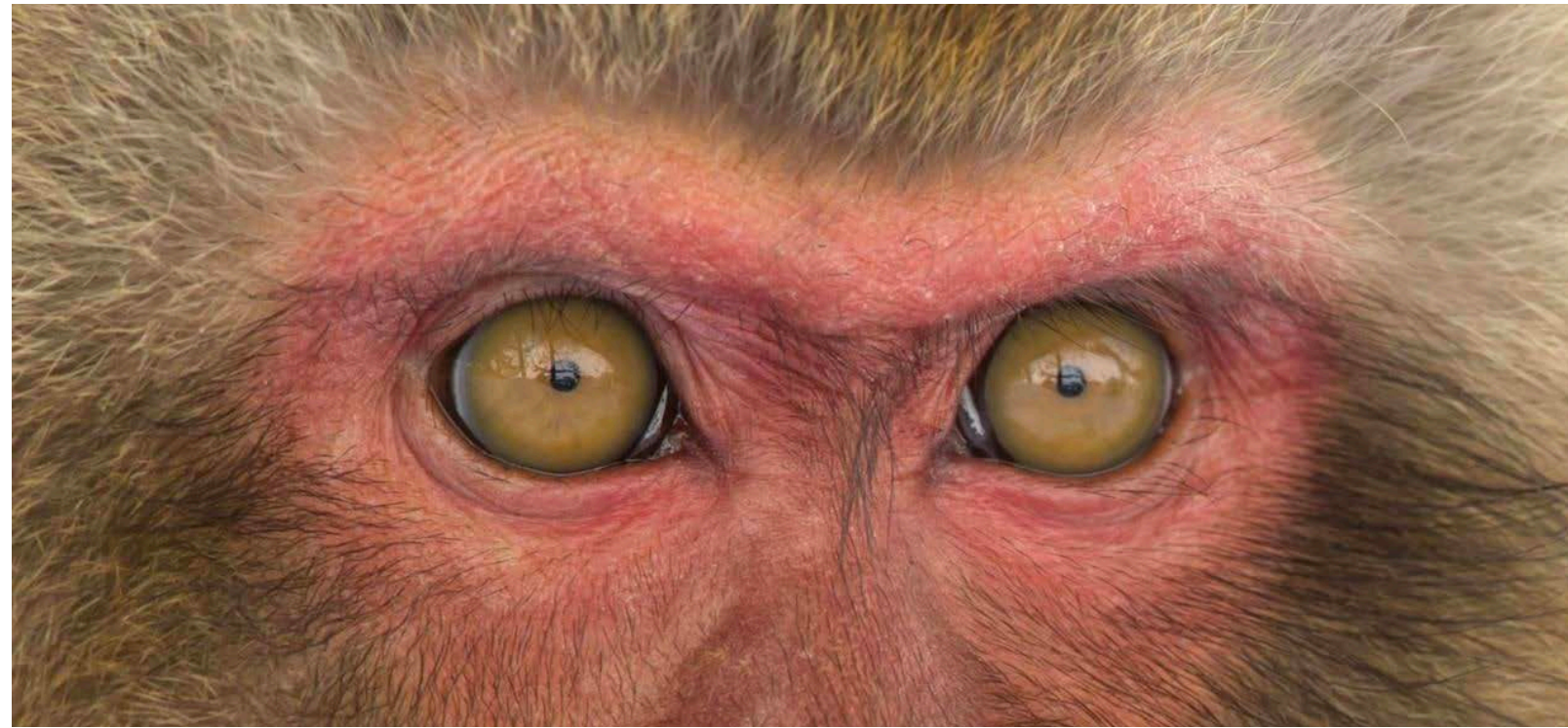


Vision



Brecht et al., *J. Comp. Neurol.* 2004

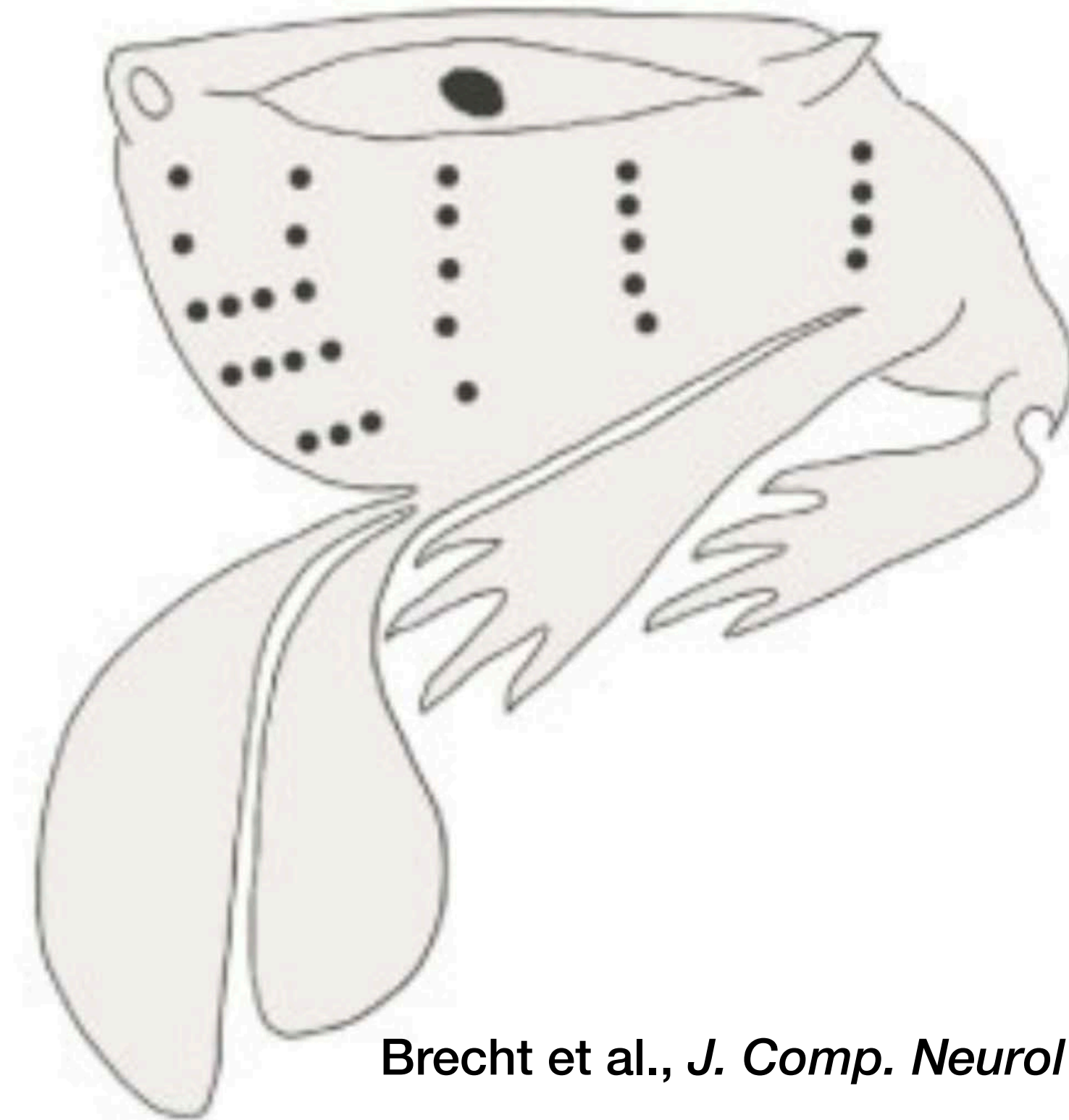
Different specializations



Vision



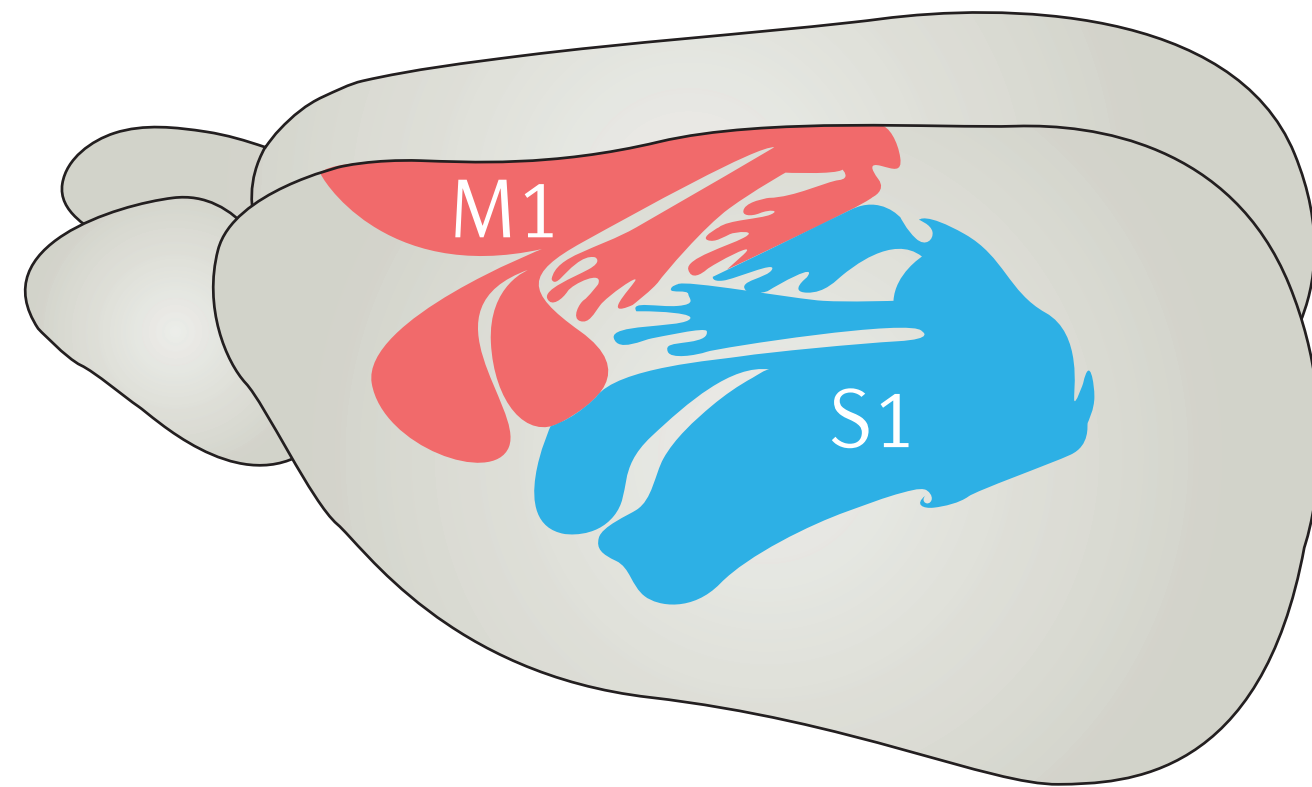
Whisker touch



Brecht et al., *J. Comp. Neurol.* 2004



Rat

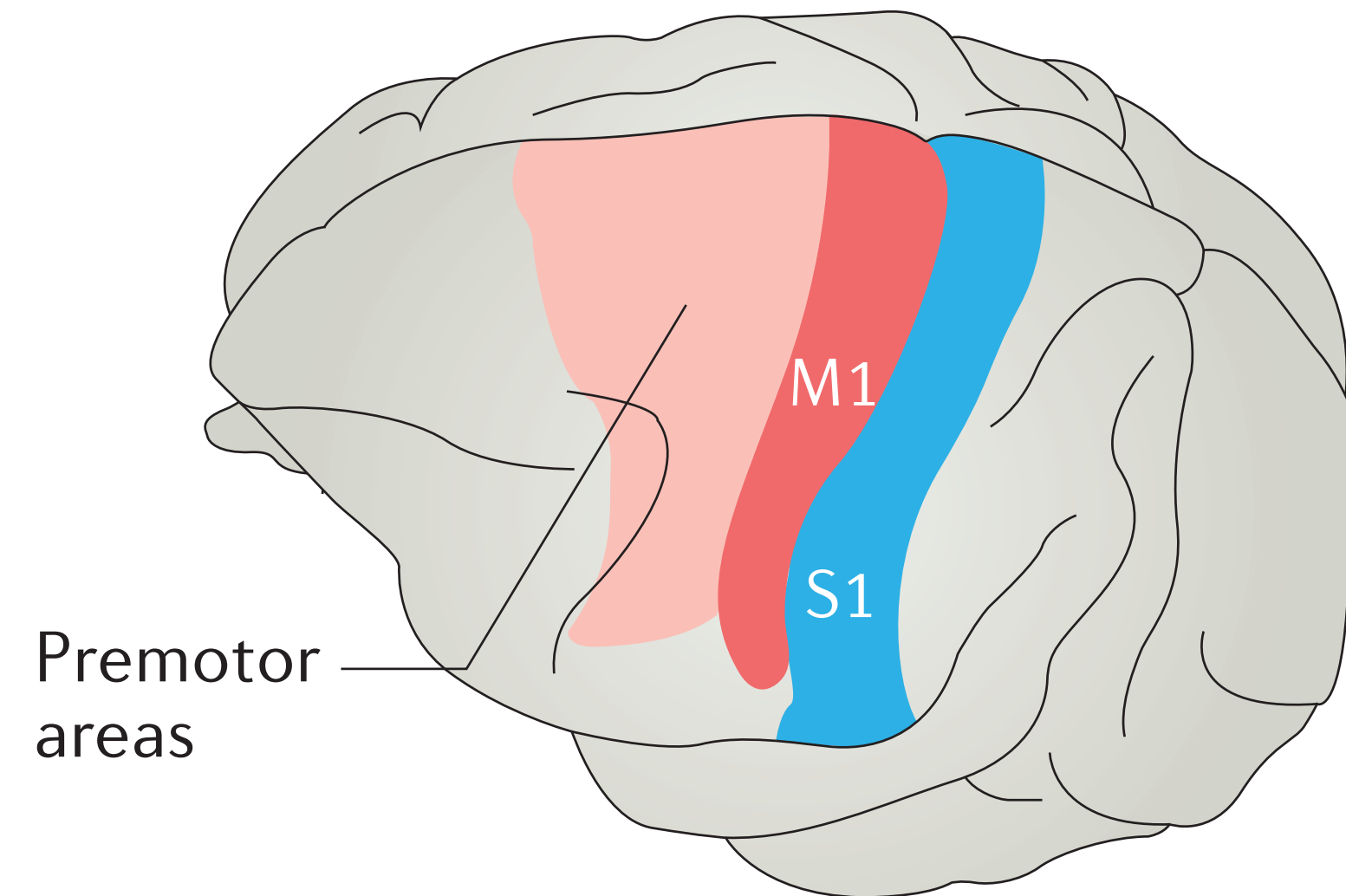


Rodents

Large motor cortex taking up most of the frontal cortex



Macaque

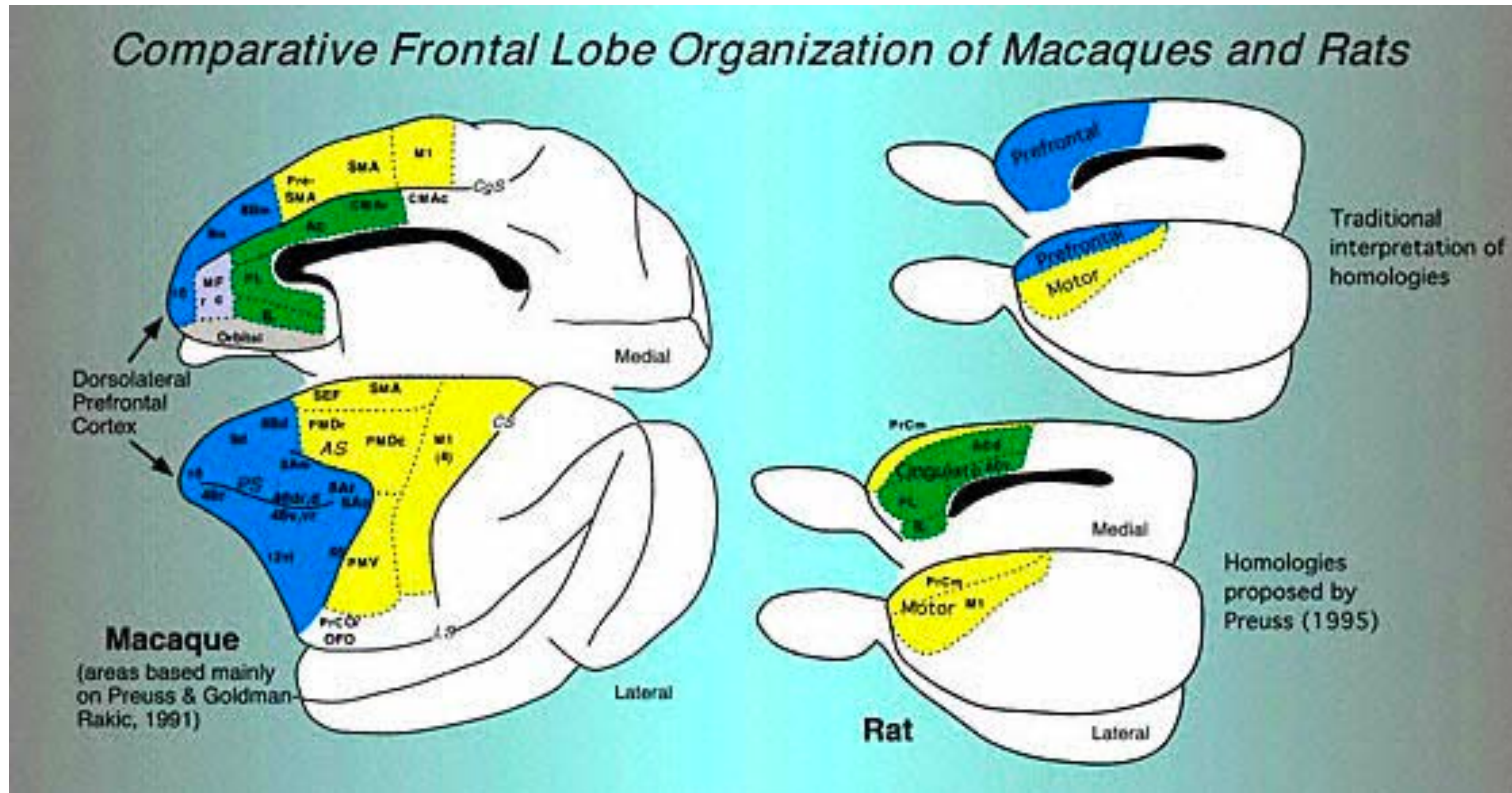


Primates

Small motor cortex, but large frontal and premotor areas

Do Rats Have Prefrontal Cortex? The Rose–Woolsey–Akert Program Reconsidered

Todd M. Preuss
Vanderbilt University



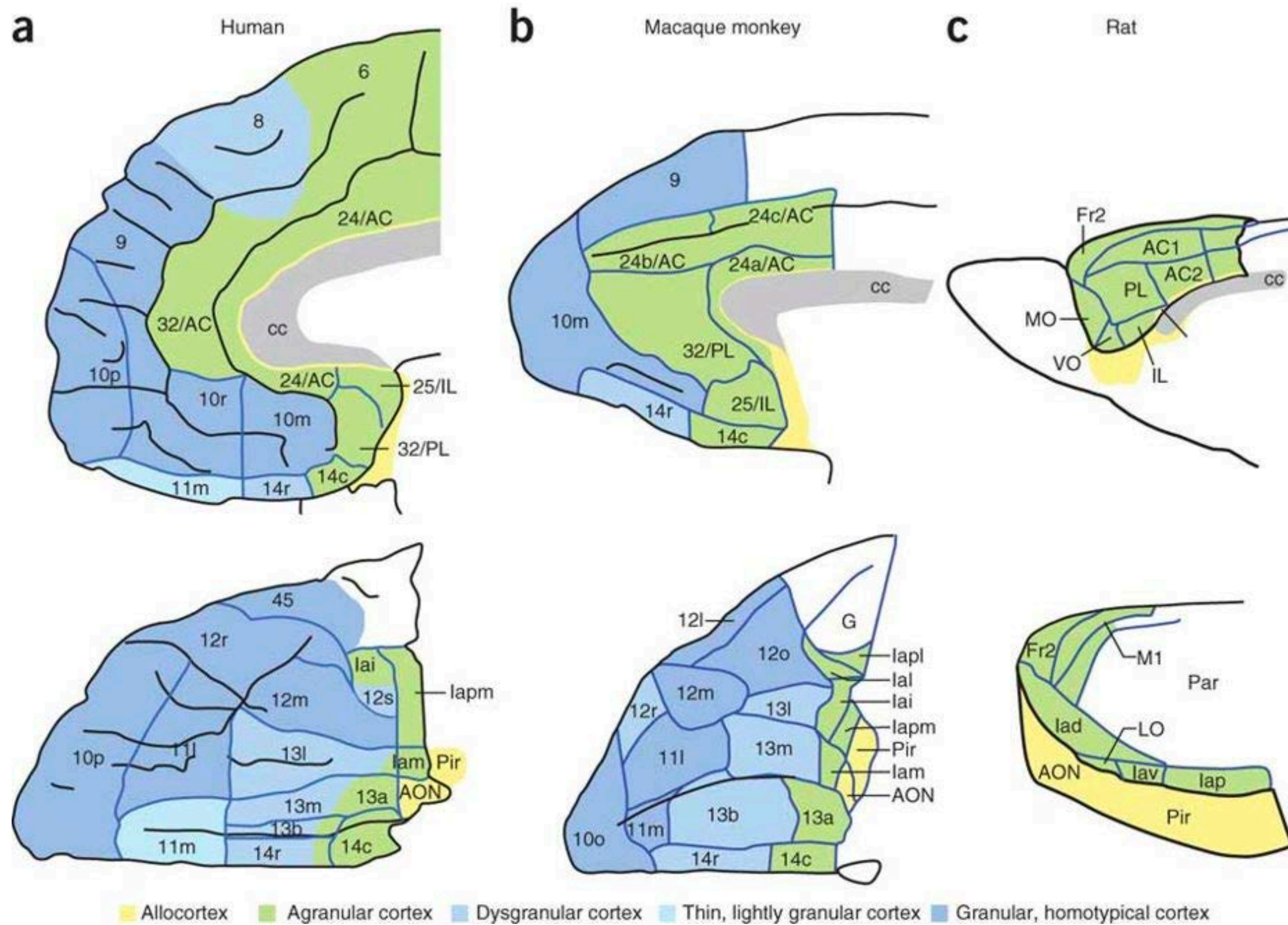
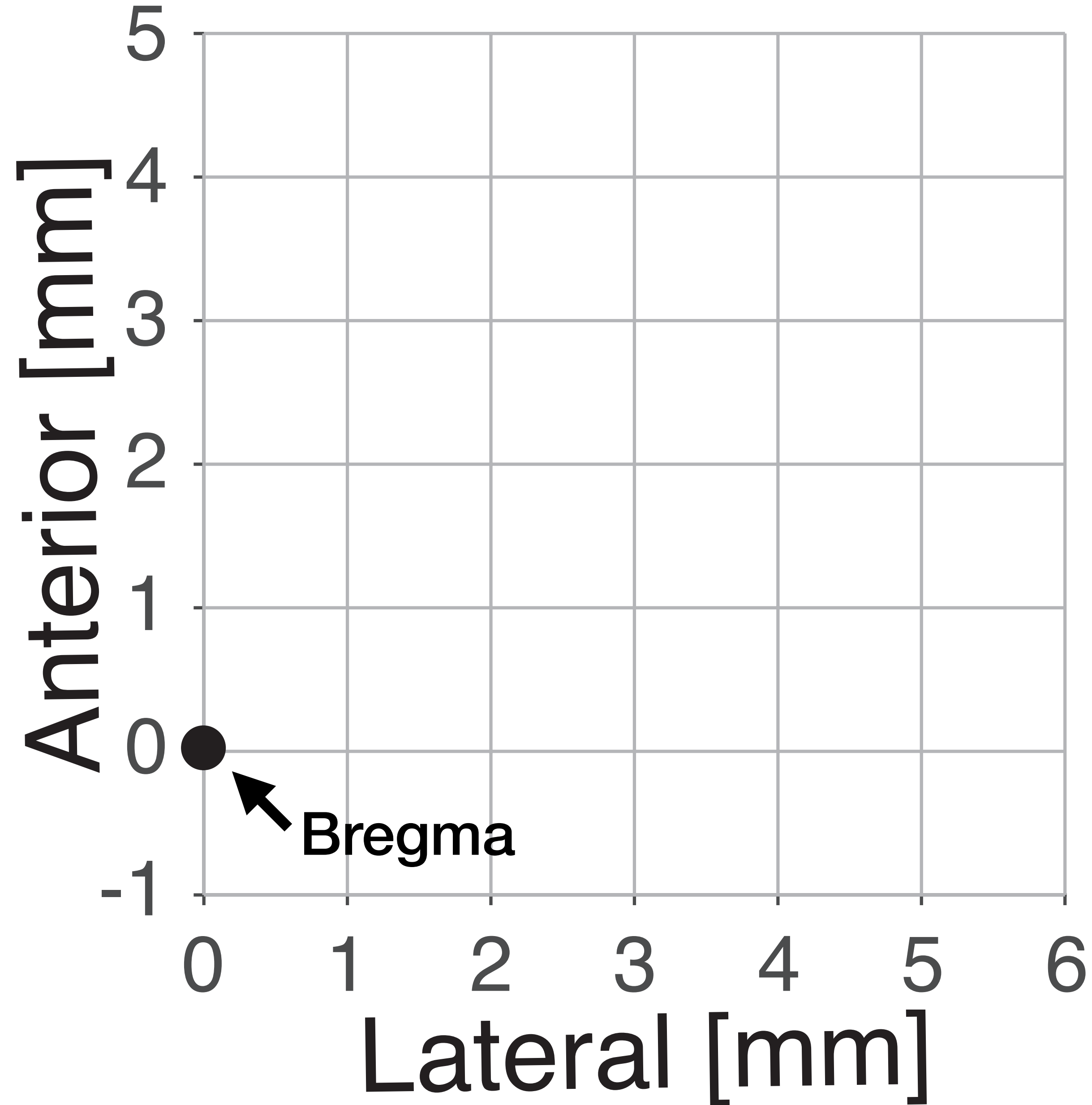
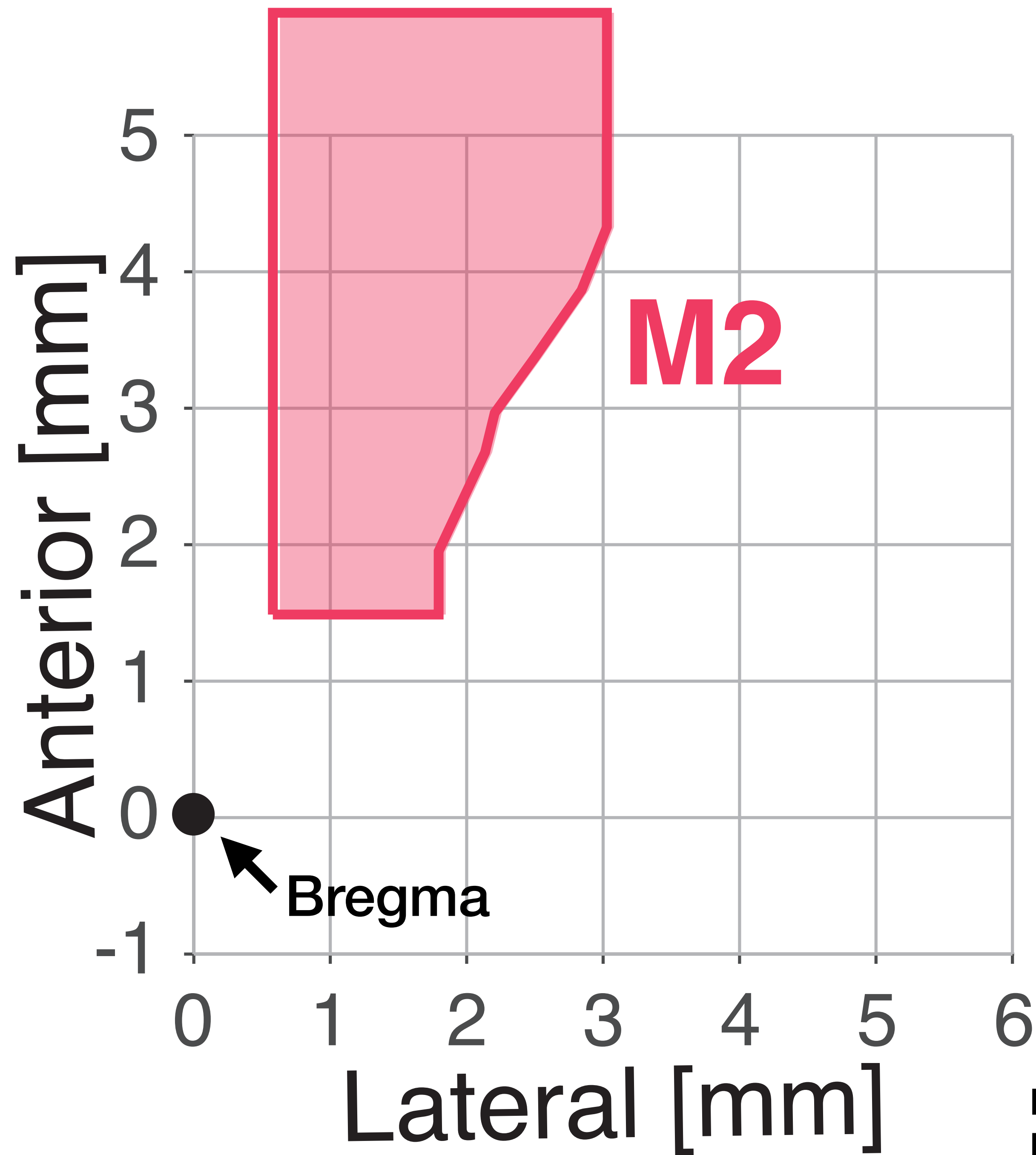
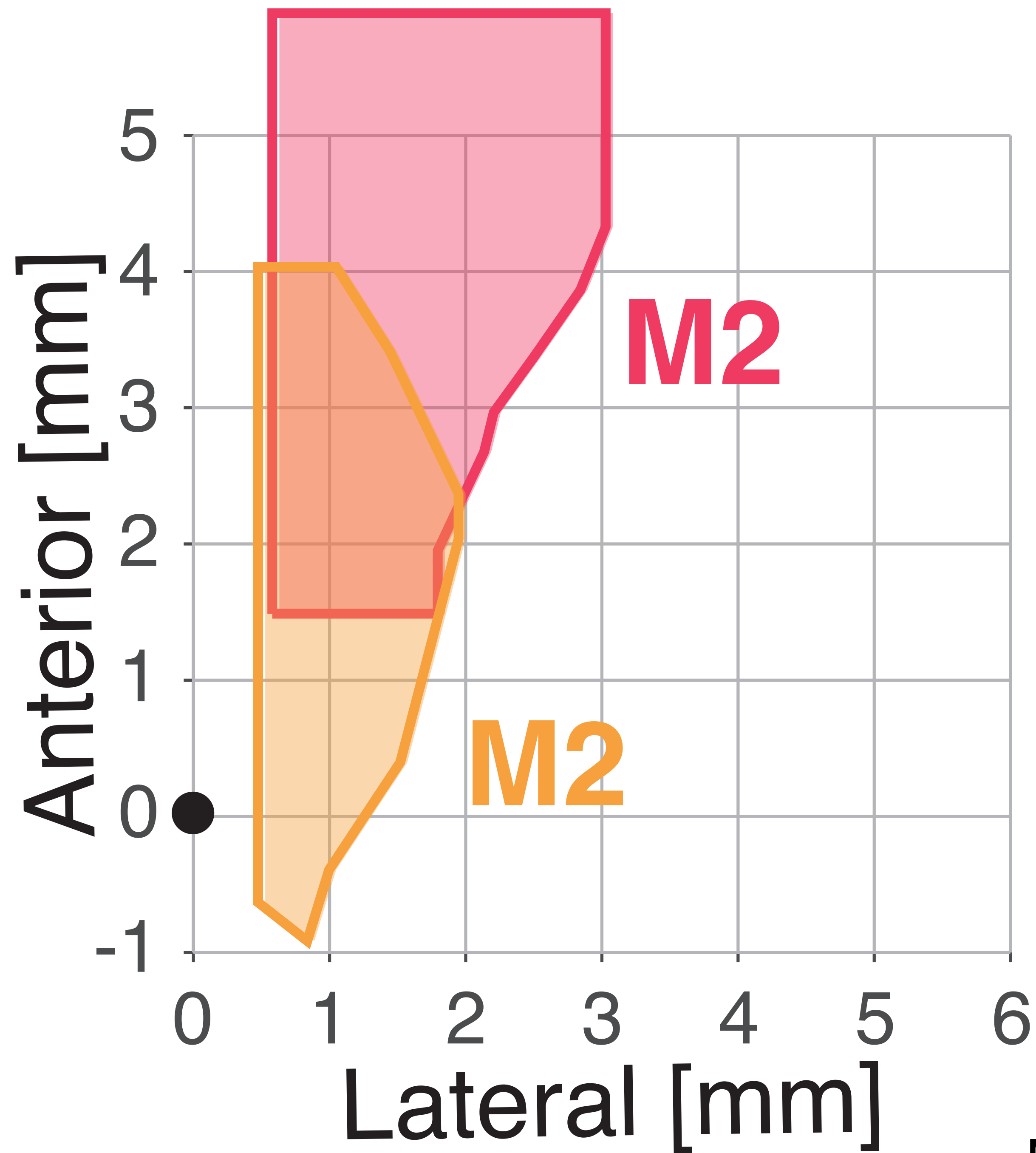


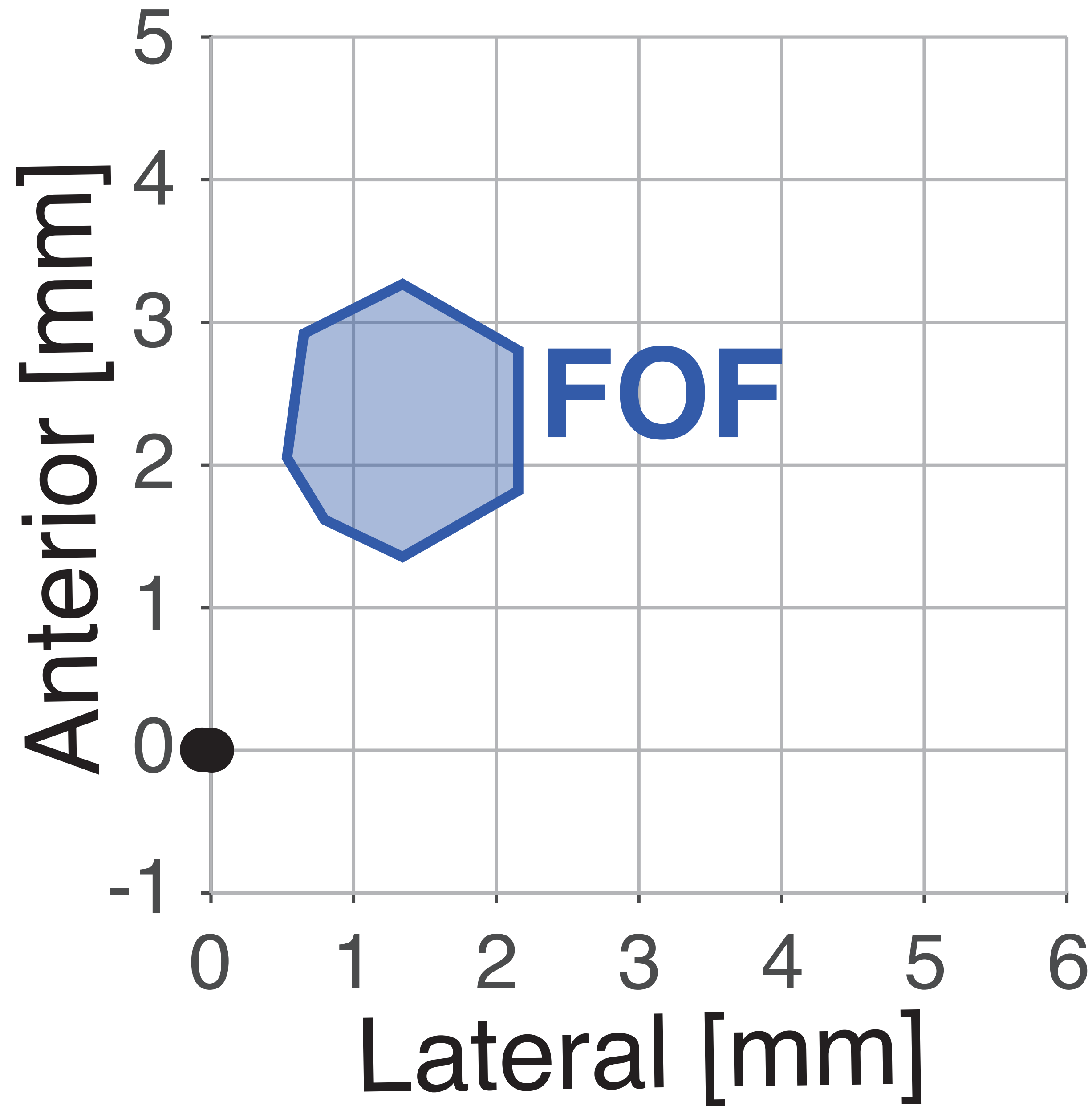
Figure 1 Comparative anatomy of the human, monkey and rat frontal cortex.

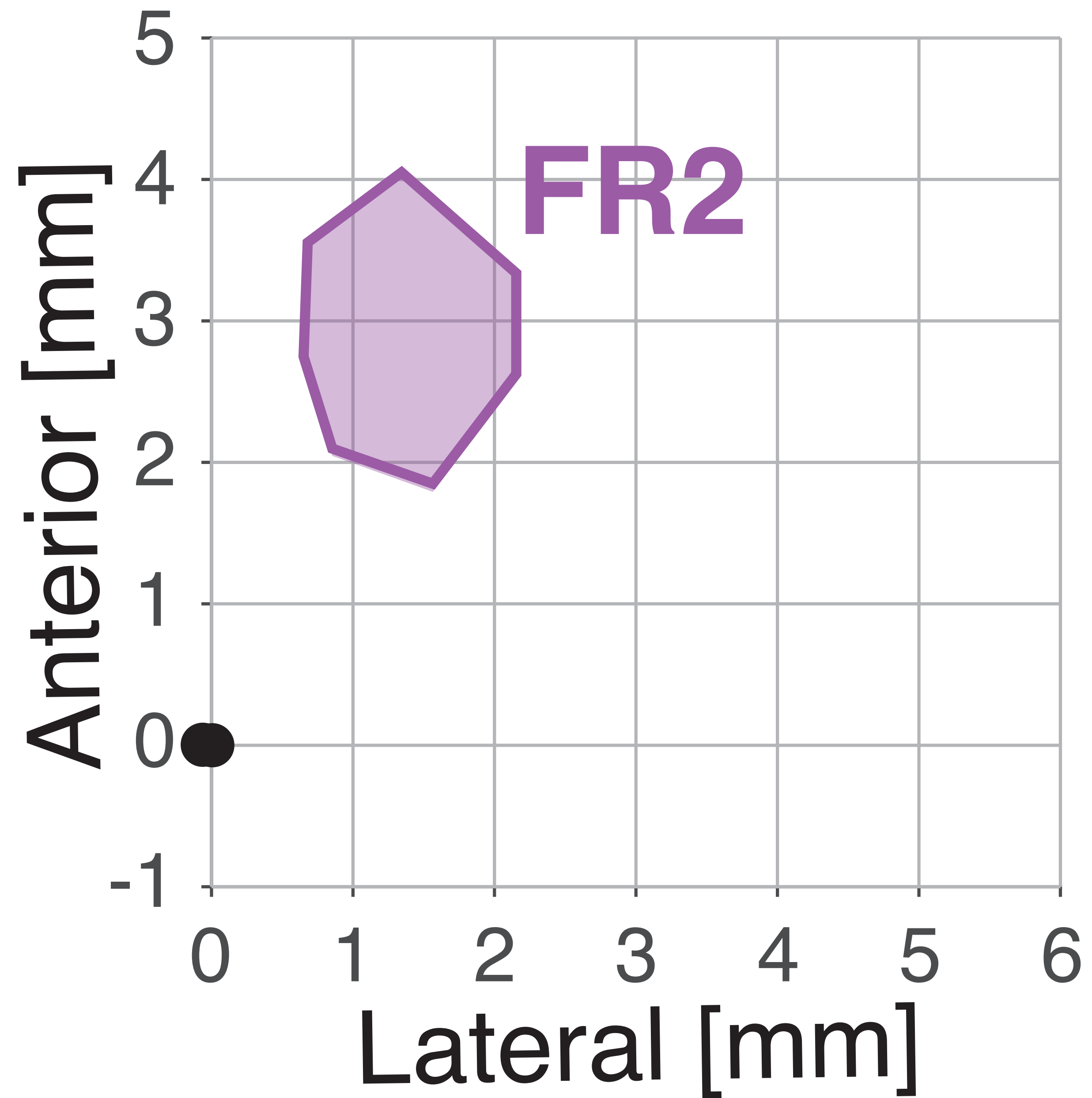
Maps of rat frontal cortex

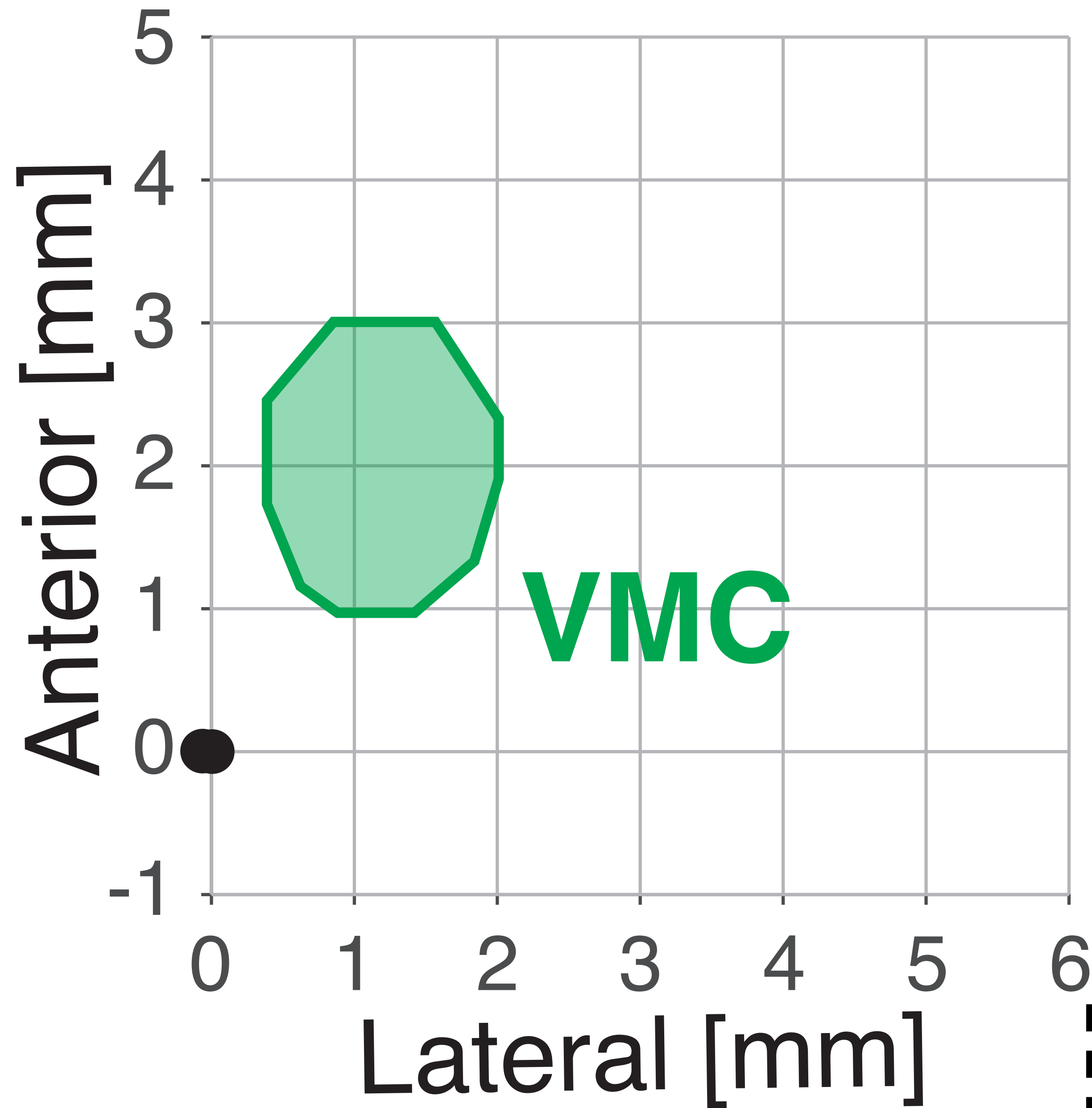




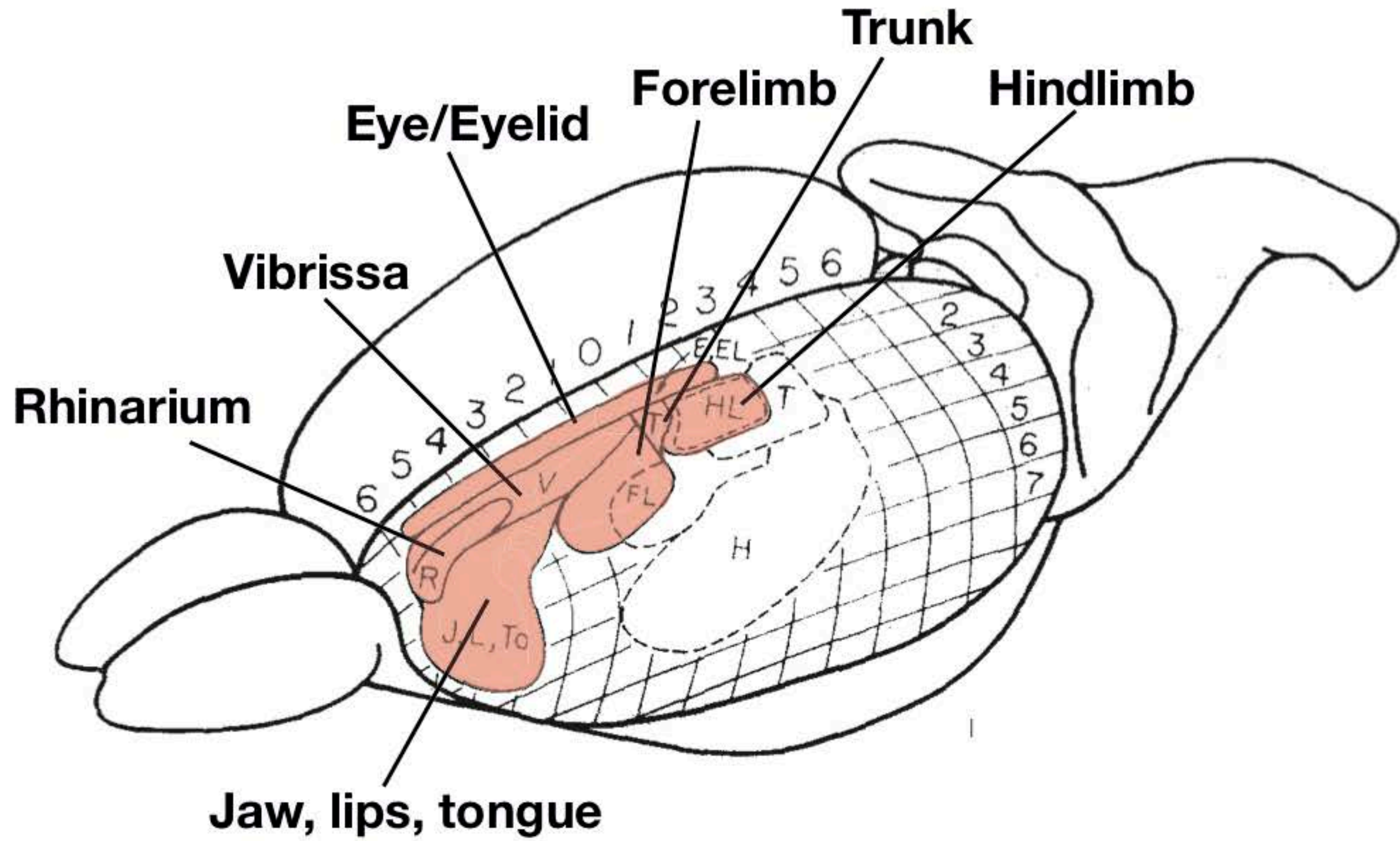


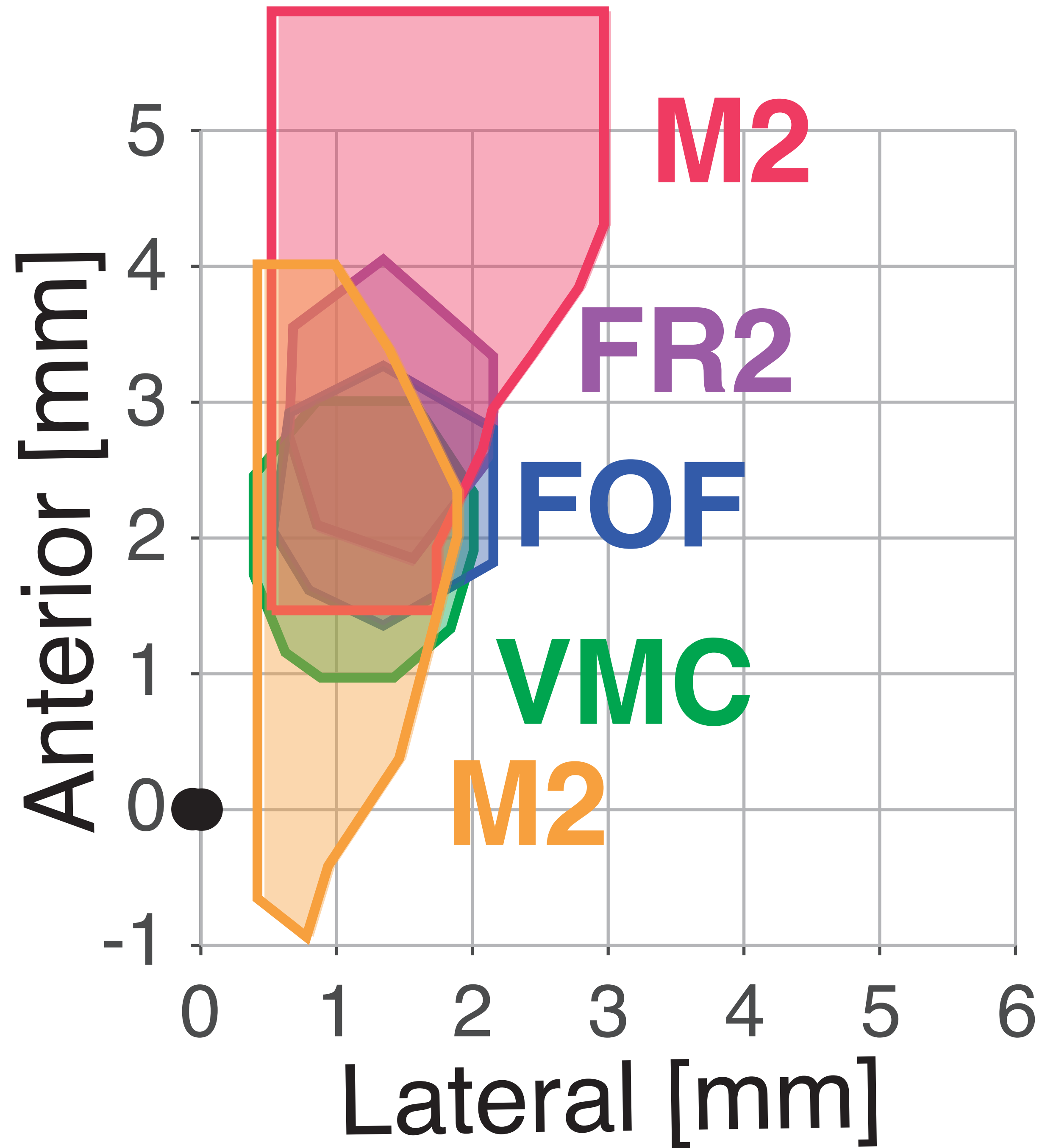




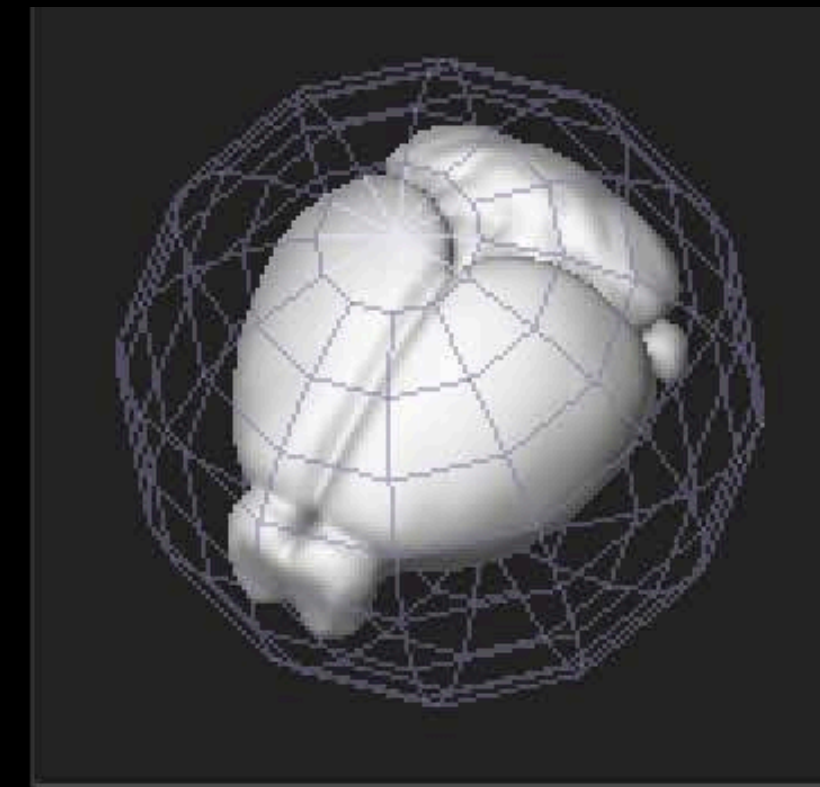


Ebbesen et al. Nat.Neurosci. 2017
Hill et al. Neuron 2011
Brecht et al. Nature 2004
Berg & Kleinfeld J.Neurophys. 2003

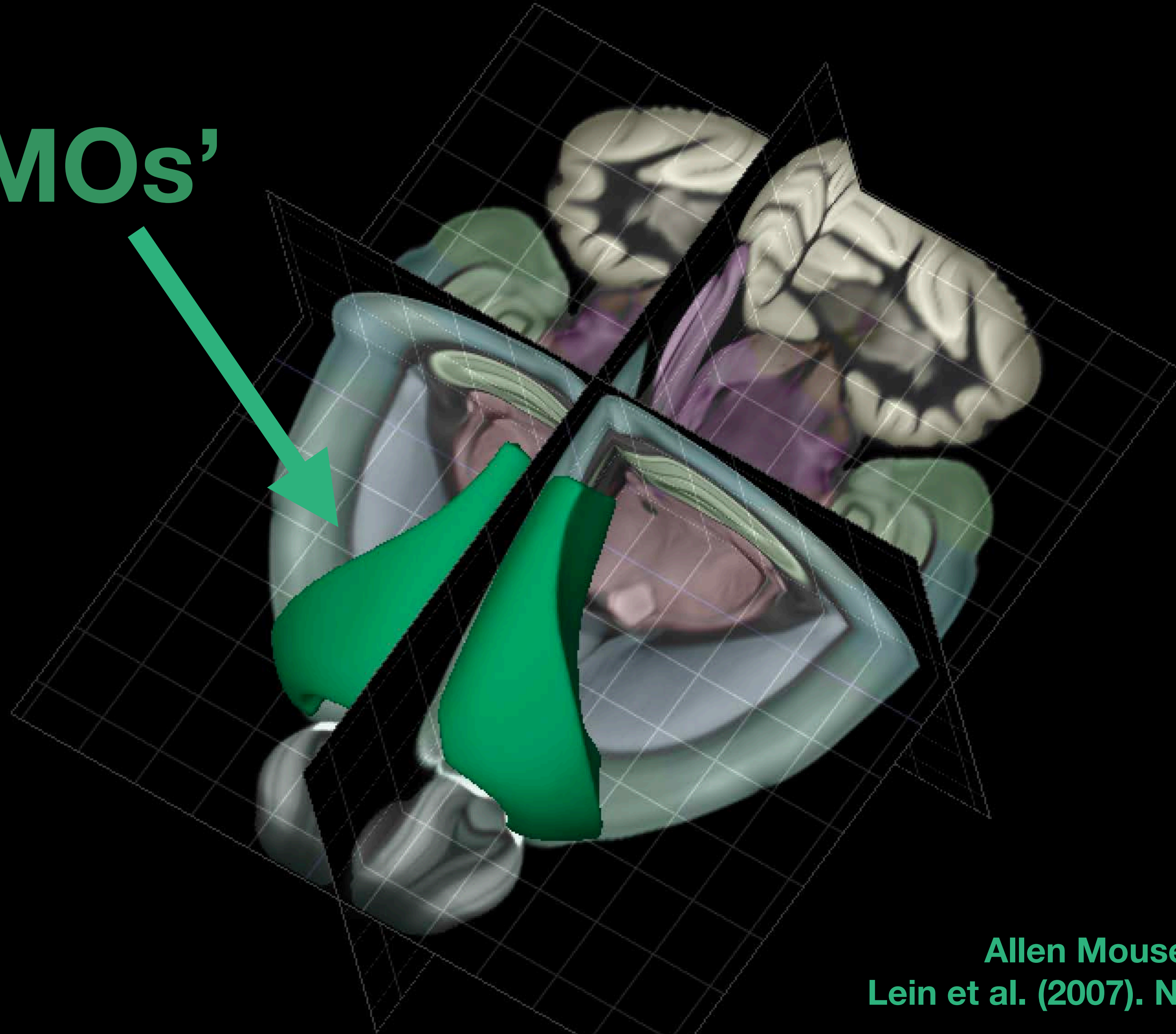
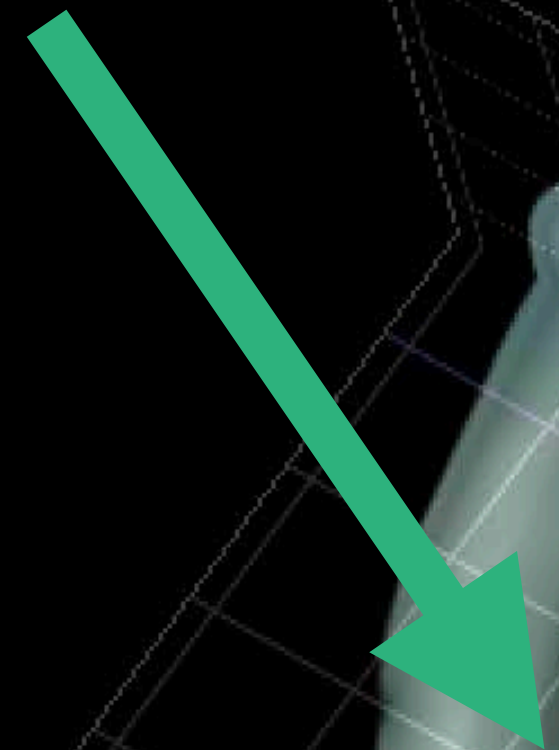




Secondary motor area

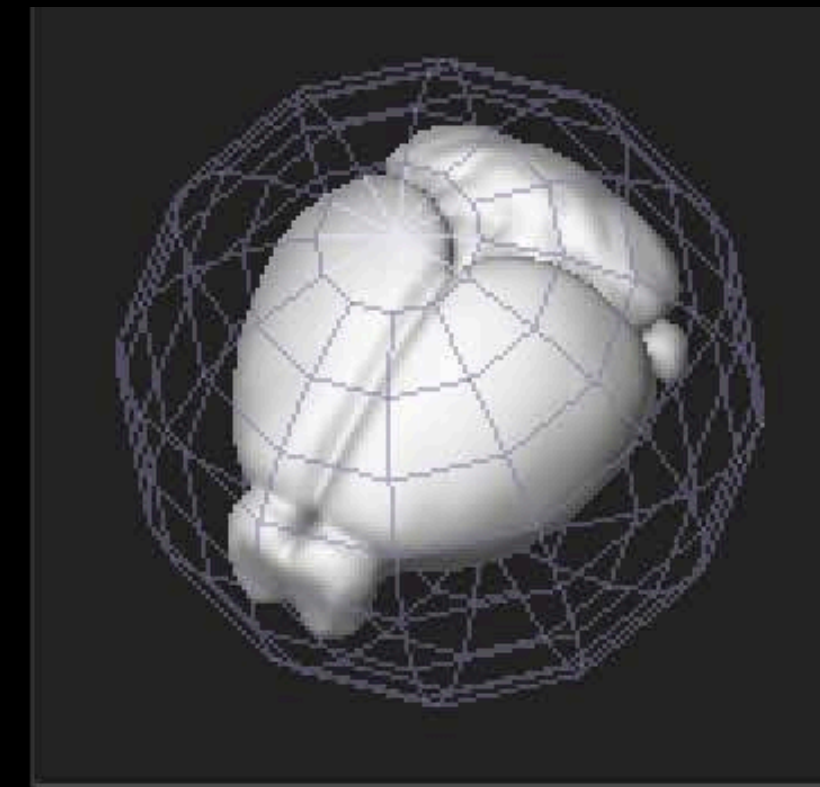


'MOs'

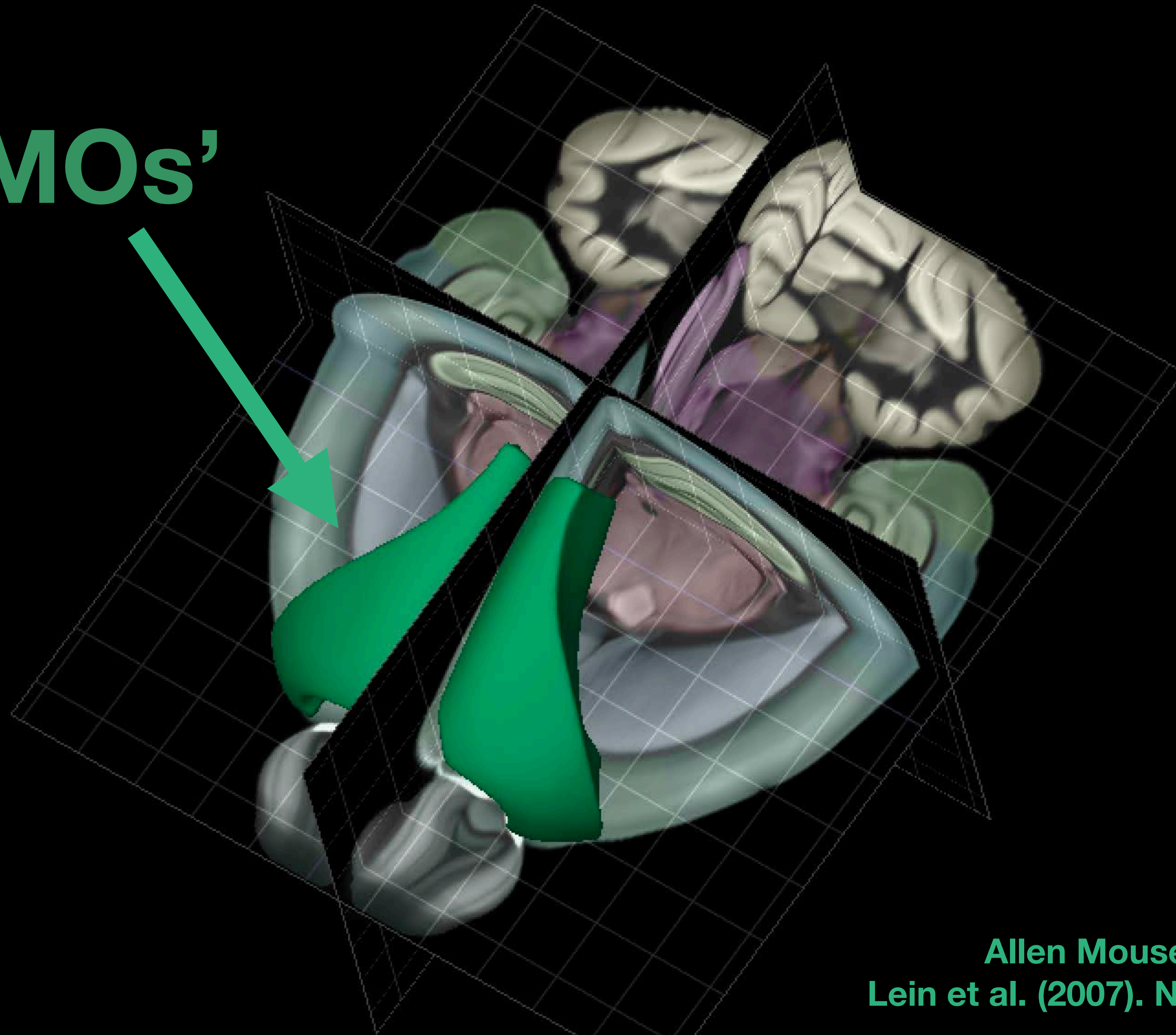
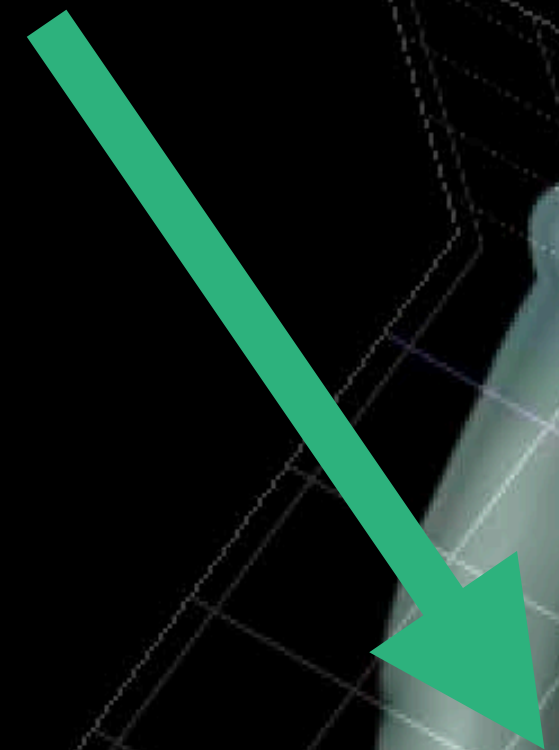


Allen Mouse Brain Atlas
Lein et al. (2007). Nature 445, 168–176.

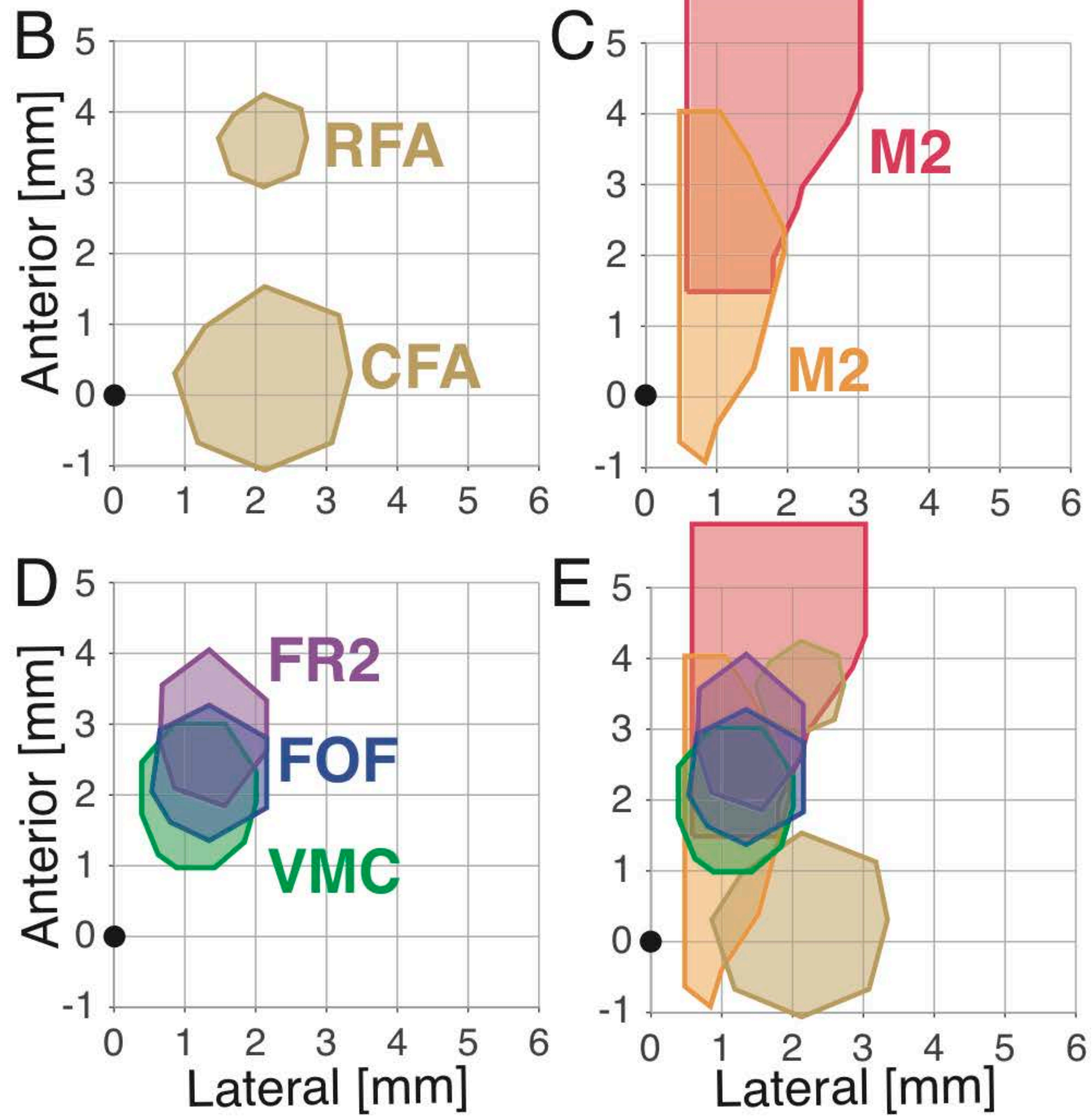
Secondary motor area

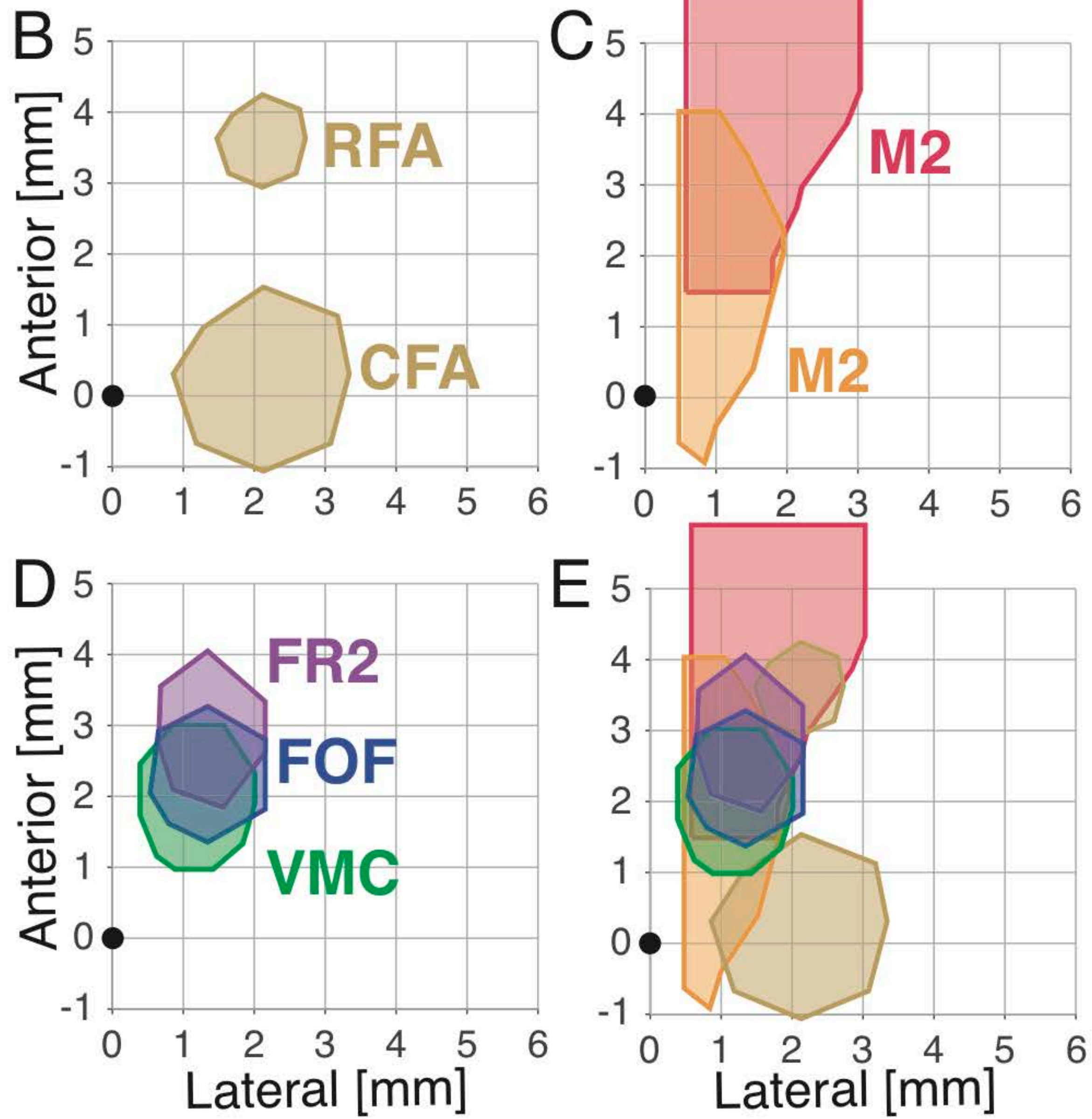


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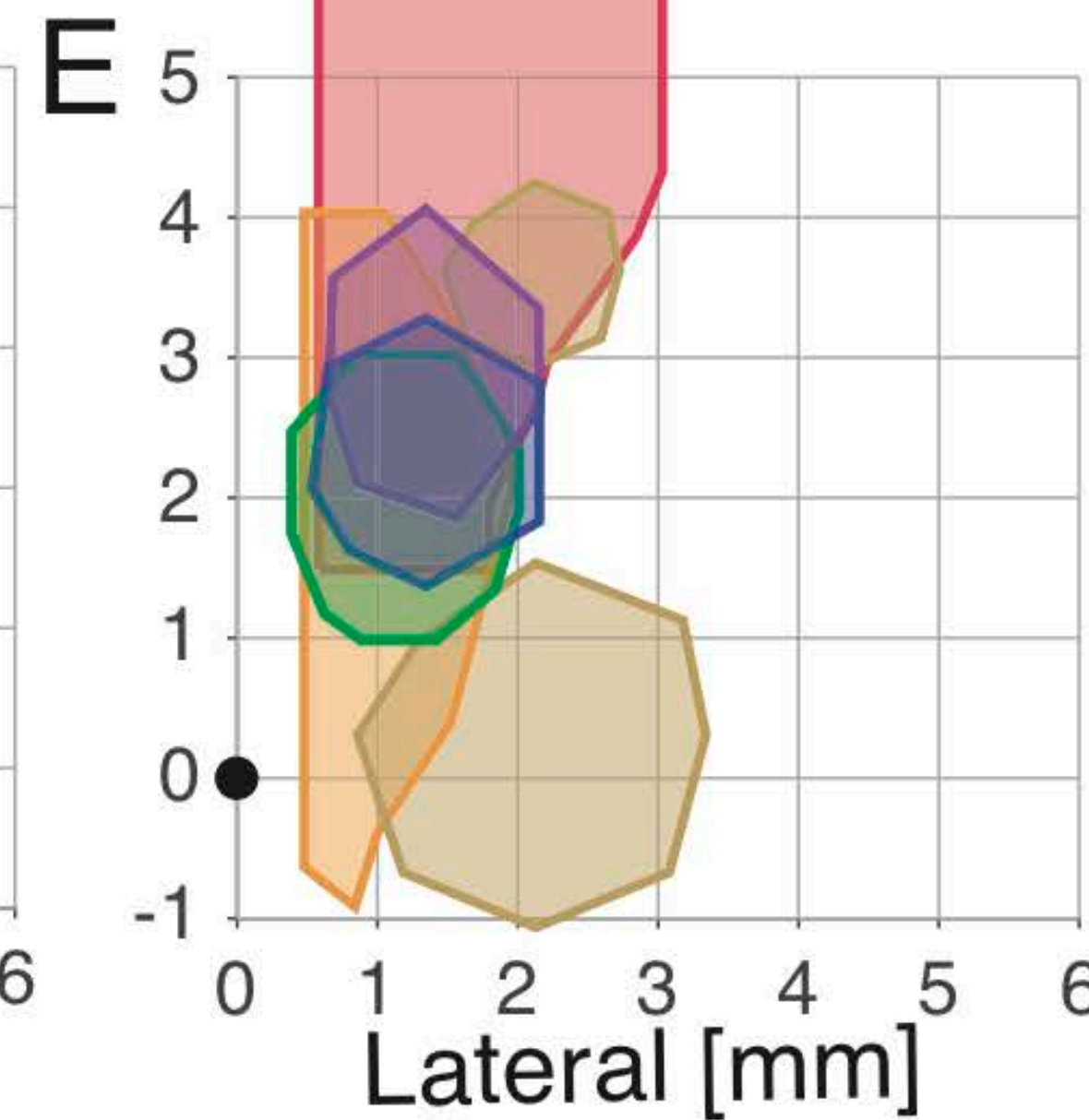
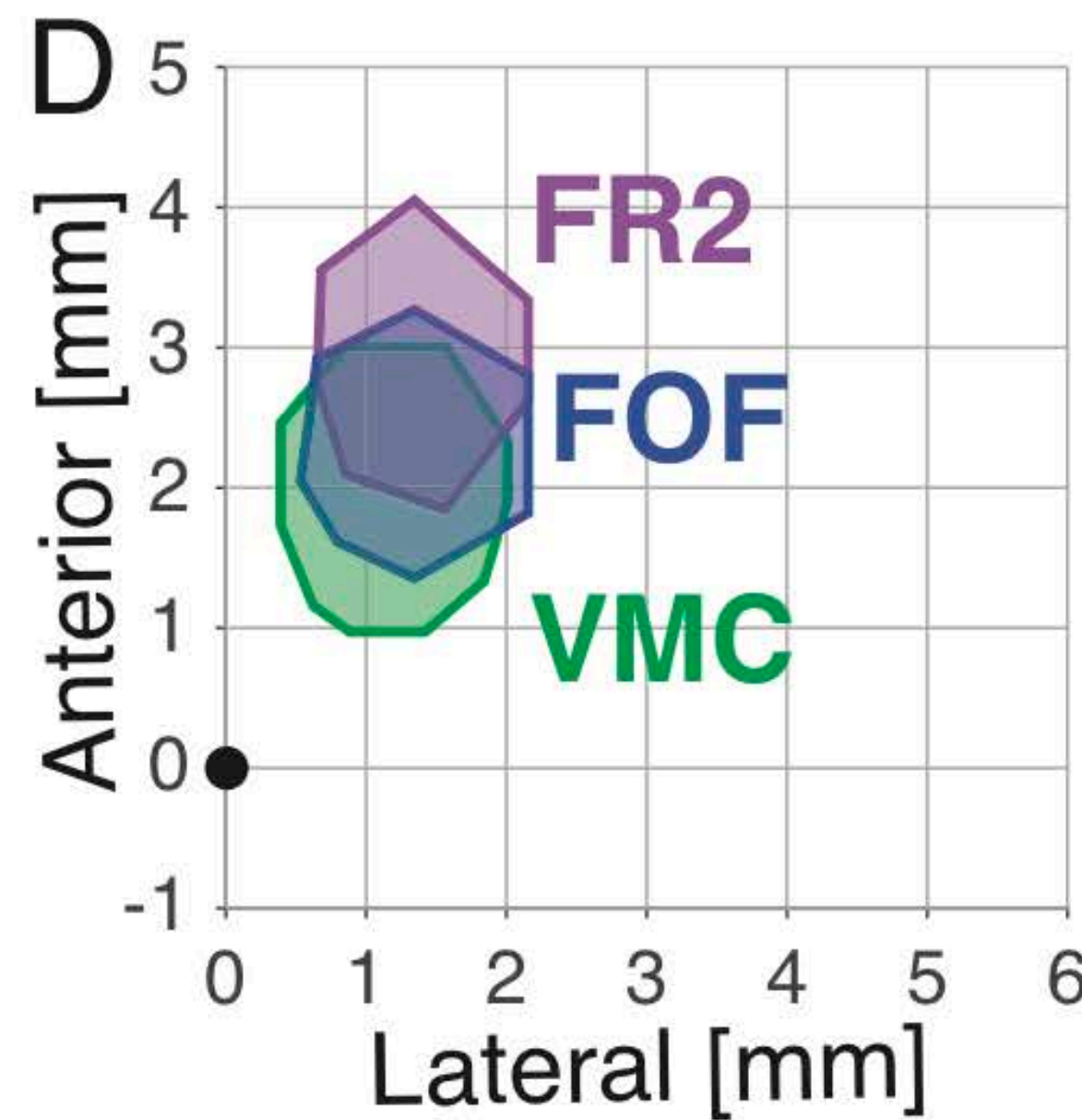
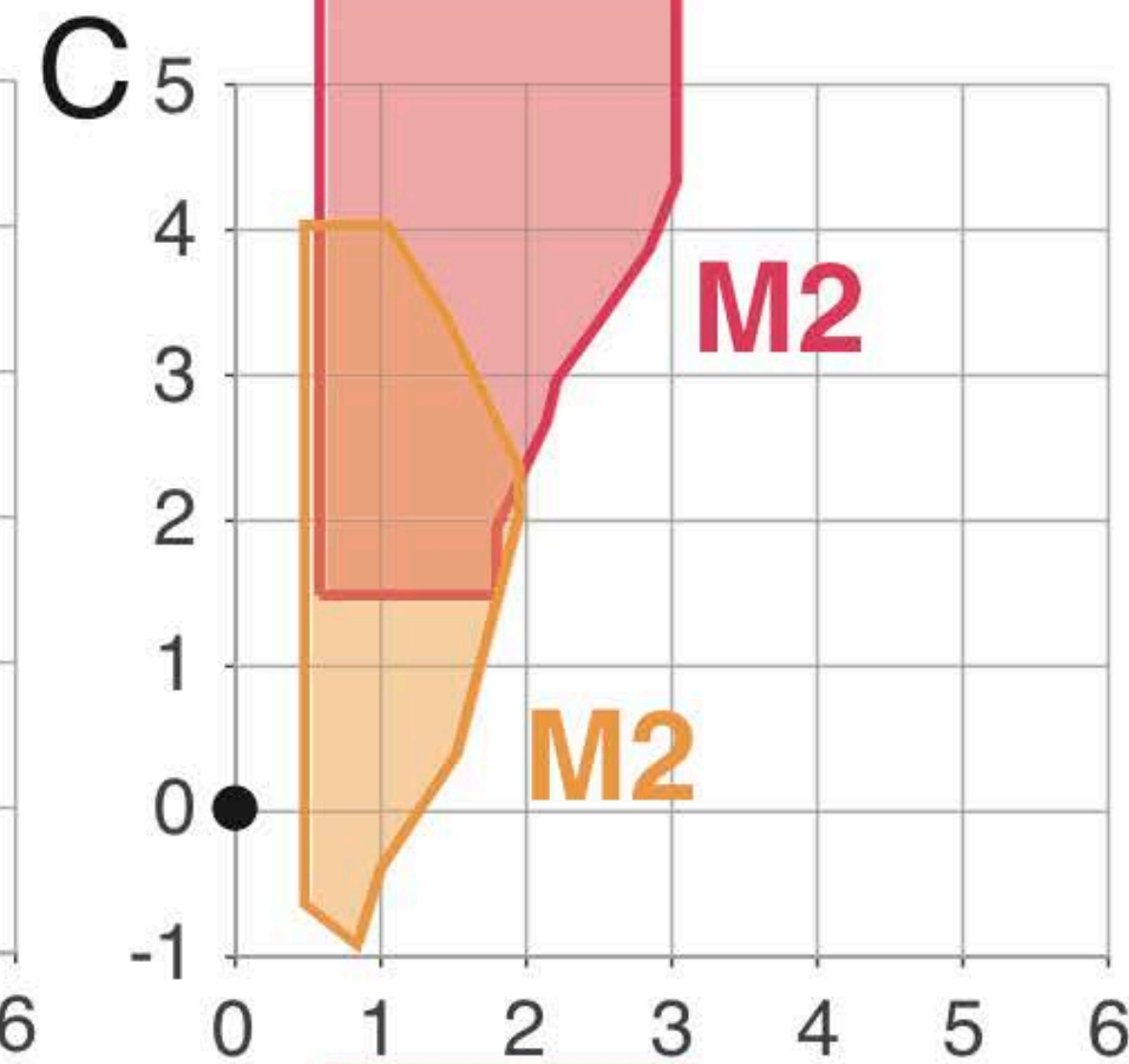
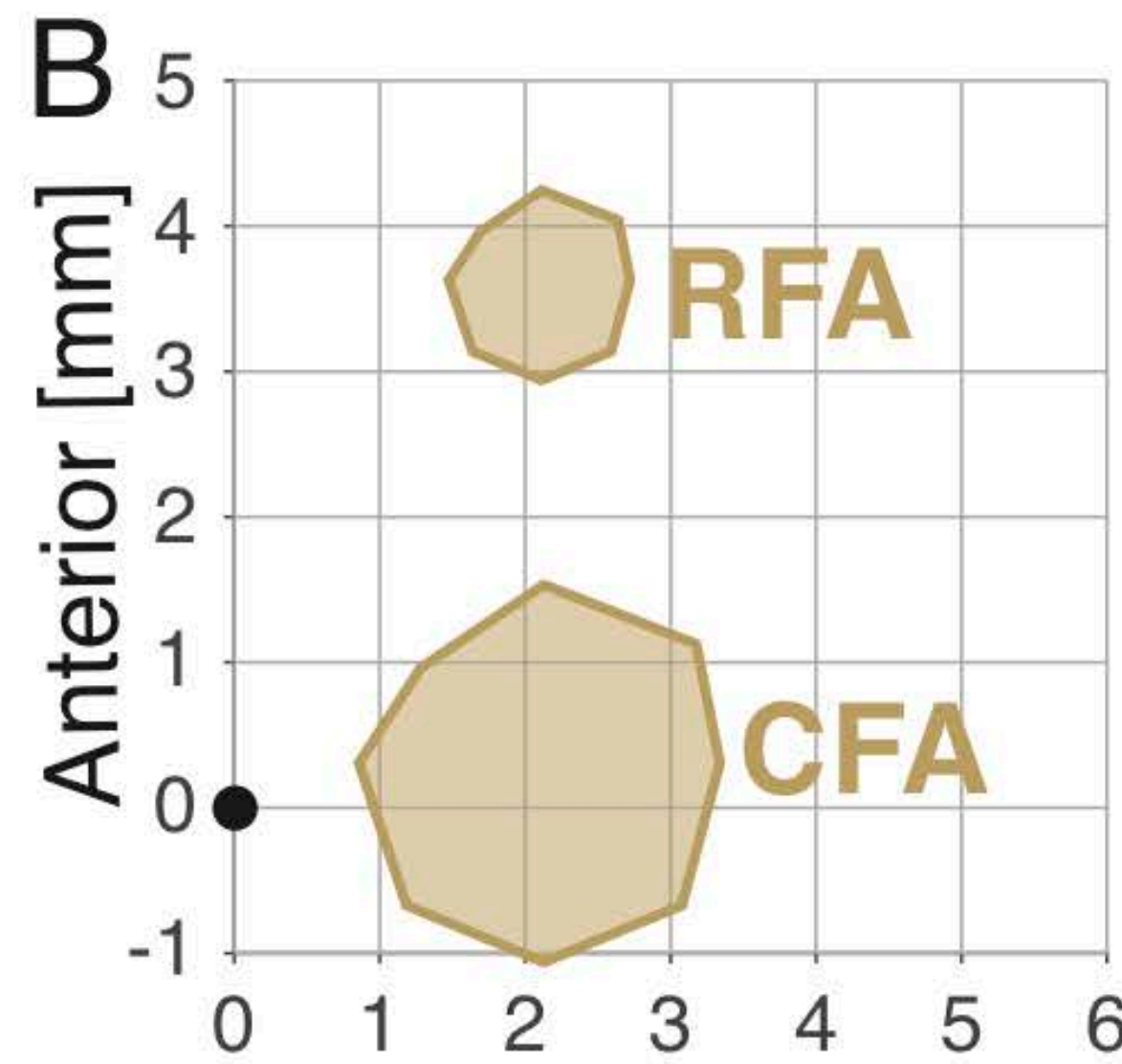


Also know as:
**'AGm',
'vFMCx',
'fMR', 'MOs',
'vM1/wM1'**





Ebbesen, Insanally, Kopec, Murakami, Saiki & Erlich, *J.Neurosci.* 2018



Mini-Symposium

More than Just a “Motor”: Recent Surprises from the Frontal Cortex

Christian L. Ebbesen,^{1,2} Michele N. Insanally,^{1,2} Charles D. Kopec,⁴ Masayoshi Murakami,⁴ Akiko Saiki,^{5,6} and Jeffrey C. Erlich^{1,3}

¹Skidell Institute for Biomolecular Medicine, New York University School of Medicine, New York, New York 10016, ²Center for Neural Science, New York University, New York, New York 10003, ³Princeton Neuroscience Institute, Princeton University, Princeton, New Jersey 08544, ⁴Department of Neurophysiology, Division of Medicine, University of Yamaguchi, Yamaguchi 753-8588, Japan, ⁵Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, 734-8553, Japan, ⁶Department of Neurobiology, Northwestern University, Evanston, Illinois 60208, ⁷New York University Shanghai, Shanghai, China 200122, ⁸NYU-ECNU Institute for Brain and Cognitive Science at NYU Shanghai, Shanghai, China 200062, and ⁹Shanghai Key Laboratory of Brain Functional Genomics (Ministry of Education), East China Normal University, Shanghai, China 200062

Motor and premotor cortices are crucial for the control of movements. However, we still know little about how these areas contribute to higher-order motor control, such as deciding which movements to make and when to make them. Here we focus on rodent studies and review recent findings, which suggest that—in addition to motor control—neurons in motor cortices play a role in sensory integration, behavioral strategizing, working memory, and decision-making. We suggest that these seemingly disparate functions may subserve an evolutionarily conserved role in sensorimotor cognition and that further study of rodent motor cortices could make a major contribution to our understanding of the evolution and function of the mammalian frontal cortex.

Key words: motor control; active sensing; action selection; action timing; decision-making; frontal cortex

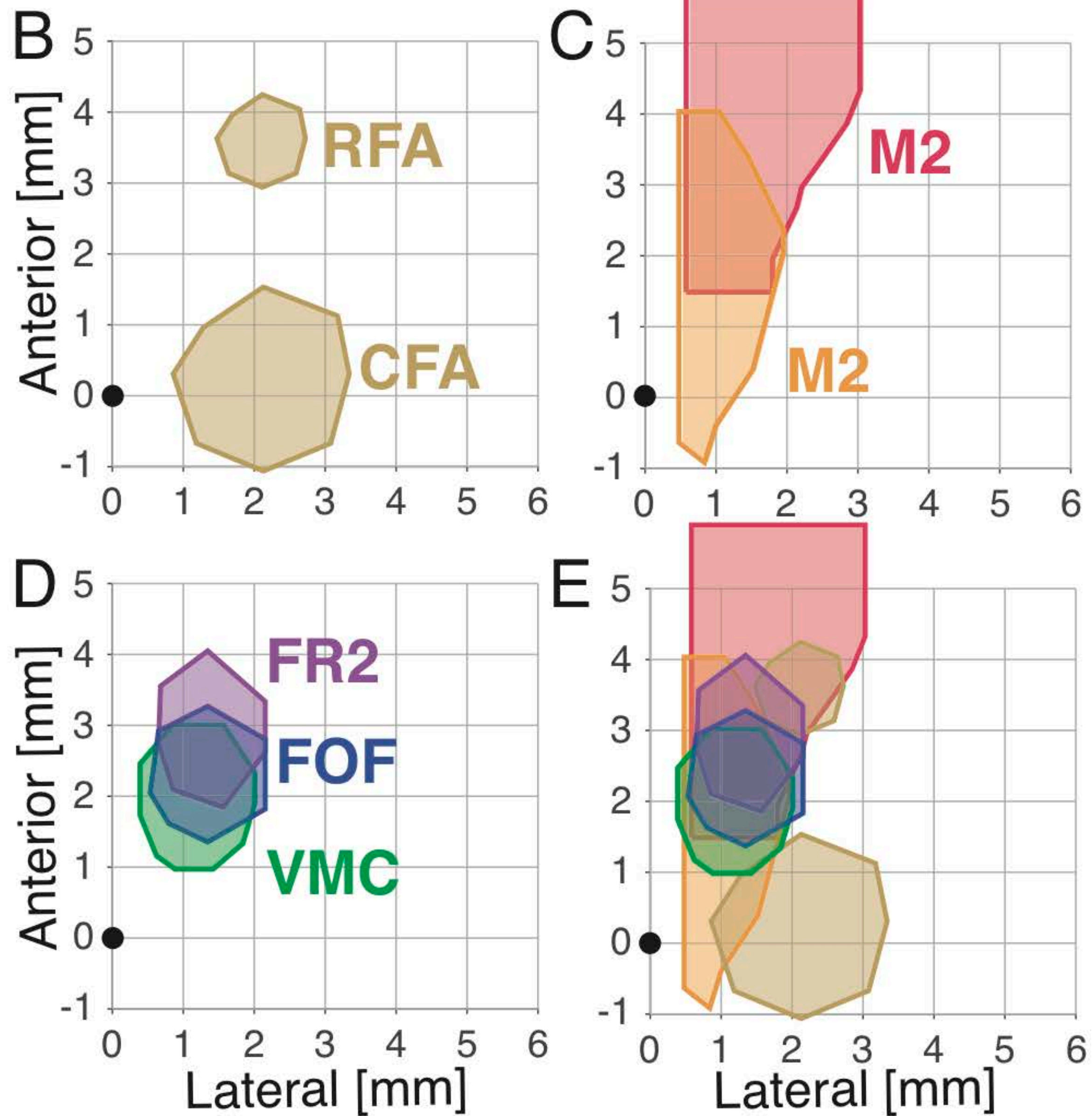
Introduction

Primate motor and premotor cortices are some of the most intensely studied structures in all of neuroscience. Despite our sizeable knowledge, several major conceptual questions remain open. For example, the classic controversy over whether motor cortex acts mainly as a musculotopic map of the body, organizing low-level features of movements (e.g., force; Evarts, 1968; Asanuma, 1975) or mainly represents high-level movement kinematics (Fetz, 1992; Omrani et al., 2017) has recently been further complicated by the observation that motor cortex appears to be organized both somatotopically and according to behavioral categories (Graziano et al., 2002; Graziano, 2016). Second, it is still an open question whether population activity sums to generate motor output (Georgopoulos et al., 1982, 1986), or whether preparatory activity, for example (Tanji and Evarts, 1976) is better understood as acting to configure the state of a dynamical system (Shenoy et al., 2013). Third, in a sense, motor control is decision-making (Wolpert and Landy, 2012), but we still know little about

how motor cortices contribute to actually deciding how and when to act (or not to act; Ebbesen and Brecht, 2017), beyond simply managing the execution of the selected motor plans (Gold and Shadlen, 2007; Thura and Cisek, 2014; Remington et al., 2018). Finally, the discovery of mirror neuron responses in premotor (di Pellegrino et al., 1992), but also in proper M1 (Klacz et al., 2007; Dushanova and Donoghue, 2010) and corticospinal M1 neurons (Vigneswaran et al., 2013; Kraskov et al., 2014) raises intriguing questions about how motor cortices contribute to motor imagery, action understanding, social meta-cognition and cognition more generally (Kilner and Lemon, 2013).

A comparative study of forebrain motor control in rodents in addition to primates (and other species; Ocaña et al., 2015), could be a powerful way to advance our understanding of the evolution and function of the mammalian frontal cortex. In recent years, there has been massive advances in tools for monitoring and manipulating neural activity of awake, behaving rodents with cellular and subcellular resolution, beyond what is currently practical in primates. For example, there are currently abundantly available transgenic lines and viral tools (Heidt and Ressler, 2009; Witten et al., 2011; Harris et al., 2014), optogenetics (Deisseroth, 2015; Kim et al., 2017), DREADDs (Whissell et al., 2016), *in vivo* multiphoton imaging of various sensors (Brossard et al., 2014; Tang and Yuste, 2017), high-density electrophysiology (Buzsáki et al., 2015; Jun et al., 2017) and genome editing tools (Heidenreich and Zhang, 2016). Further, as we will outline in this review, it is possible to train rats to solve complex and demanding motor-cognitive tasks and precisely quantify (for example by high-speed videography, Rigosa et al., 2017; Nischaat et al., 2017) the kinematics of limb and whisker movements to

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Correspondence should be addressed to Dr. Christian Ebbesen, New York University, 540 First Avenue, New York, NY 10016. E-mail: ebbsesen@nyu.edu.
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Mini-Symposium

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¹Skidell Institute for Biomolecular Medicine, New York University School of Medicine, New York, New York 10016, ²Center for Neural Science, New York University, New York, New York 10003, ³Princeton Neuroscience Institute, Princeton University, Princeton, New Jersey 08544, ⁴Department of Neurophysiology, Division of Medicine, University of Yamaguchi, Yamaguchi 753-8588, Japan, ⁵Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, 734-8553, Japan, ⁶Department of Neurobiology, Northwestern University, Evanston, Illinois 60208, ⁷New York University Shanghai, Shanghai, China 200122, ⁸NYU-ECNU Institute for Brain and Cognitive Science at NYU Shanghai, Shanghai, China 200062, and ⁹Shanghai Key Laboratory of Brain Functional Genomics (Ministry of Education), East China Normal University, Shanghai, China 200062

Motor and primate higher-order motor review recent findings behaviorally strategic evolutionarily conserved to our understanding

Key words: motor

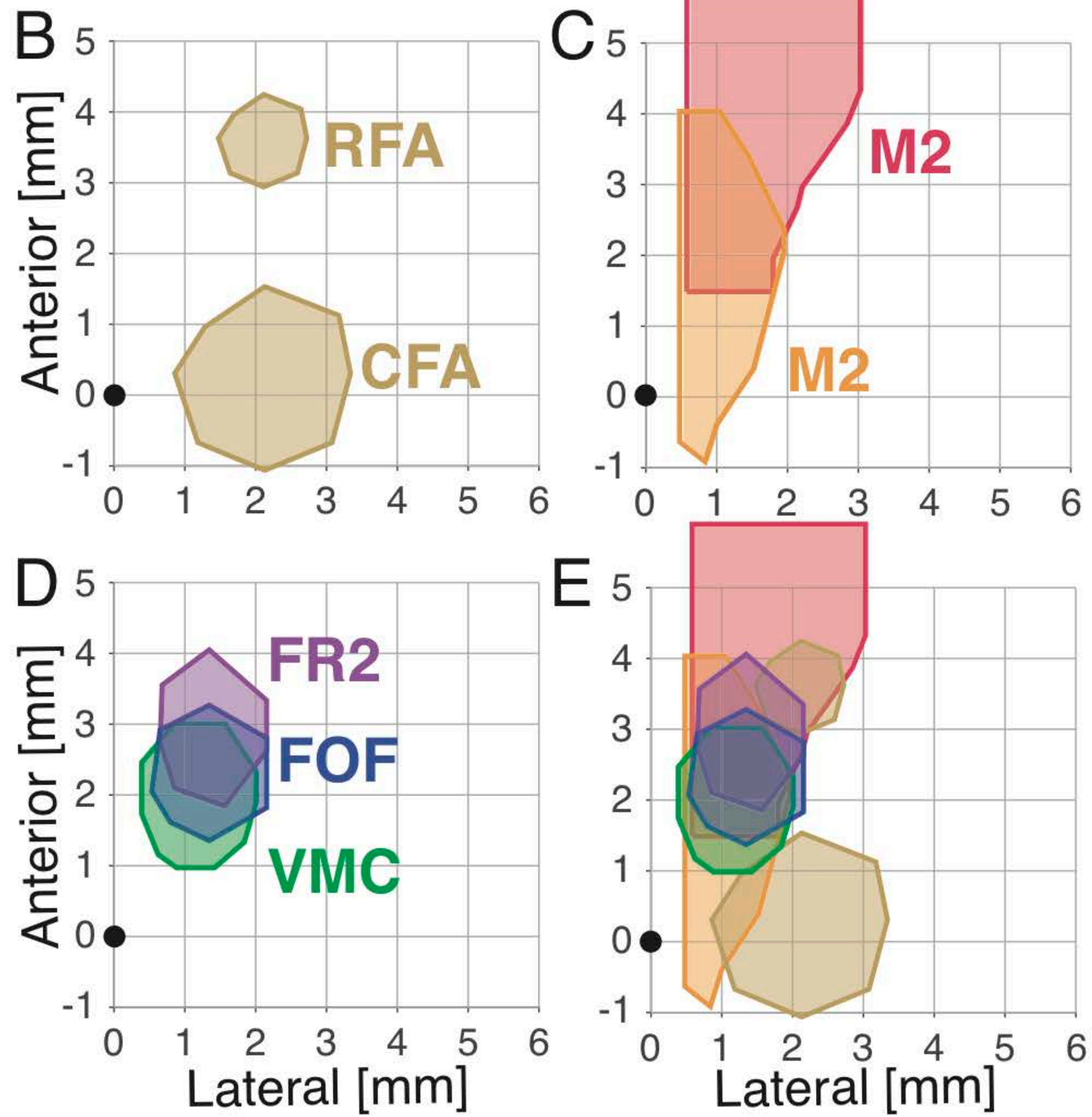
Introduction
Primate motor a tensely studied stable knowledge open. For example cortex acts main low-level feature Asanuma, 1975) matics (Fetz, 1999 complicated by organized both s egories (Graziano an open question motor output (G paratory activity understood as ac (Shenoy et al., 20 making (Wolper

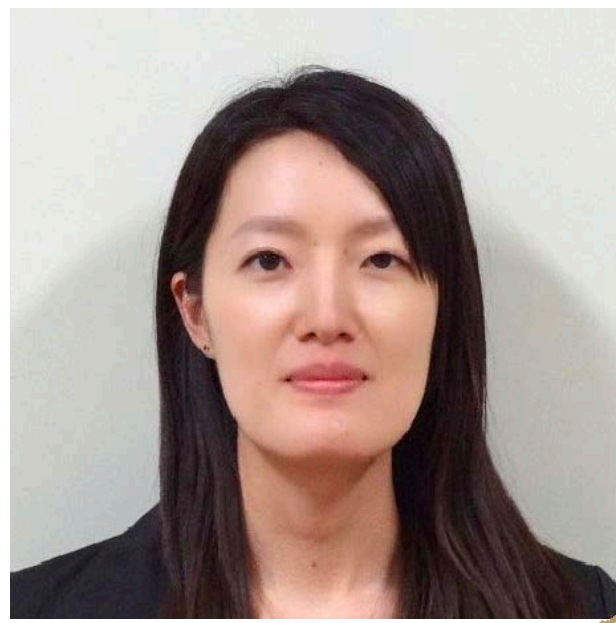
Received Aug. 1, 2018; revised Sept. 10, 2018; accepted Oct. 1, 2018. This work supported by NIH (R01NS087490) and the Skidell Institute for Biomolecular Medicine. We thank Dr. Jeffrey C. Erlich for his helpful comments on this manuscript. Correspondence should be addressed to Jeffrey C. Erlich, Skidell Institute for Biomolecular Medicine, 550 First Avenue, New York, NY 10016. E-mail: jcerlich@nyu.edu. DOI: 10.1523/JNEUROSCI.4511-18.2018

Figure 1. Maps of rat frontal cortex. **A**, Delineation of rat frontal cortex by intracortical microstimulation suggests a large, somatotopically organized primary motor representation (a ratunculus, indicated by shaded area; dashed lines indicate primary somatosensory cortex adapted with permission from Hall and Lindholm, 1974). **B**, Forelimb movements can be evoked by stimulation of a posterior zone (CFA) and an anterior zone (RFA; regions indicated by dot Nealey and Sievert, 1982; Rouiller et al., 1993). **C**, Some publications consider an anterior region of rat frontal cortex as M2 (a putative homolog of primate supplementary motor area, red; Murakami et al., 2014, 2017). Other publications assign M2 to a much more posterior region (orange; Minicic et al., 2018). **D**, The regions of rat frontal cortex referred to in the literature as primary VMC (Berg and Kleinfeld, 2003; Brecht et al., 2004a,b; Hill et al., 2011; Ebbesen et al., 2017), FOF (a putative homolog of the primate FEF; Erlich et al., 2011; Hanks et al., 2015; Kopec et al., 2015) and FR2 (Insanally et al., 2018) overlap. **E**, Overlay of all the above regions.

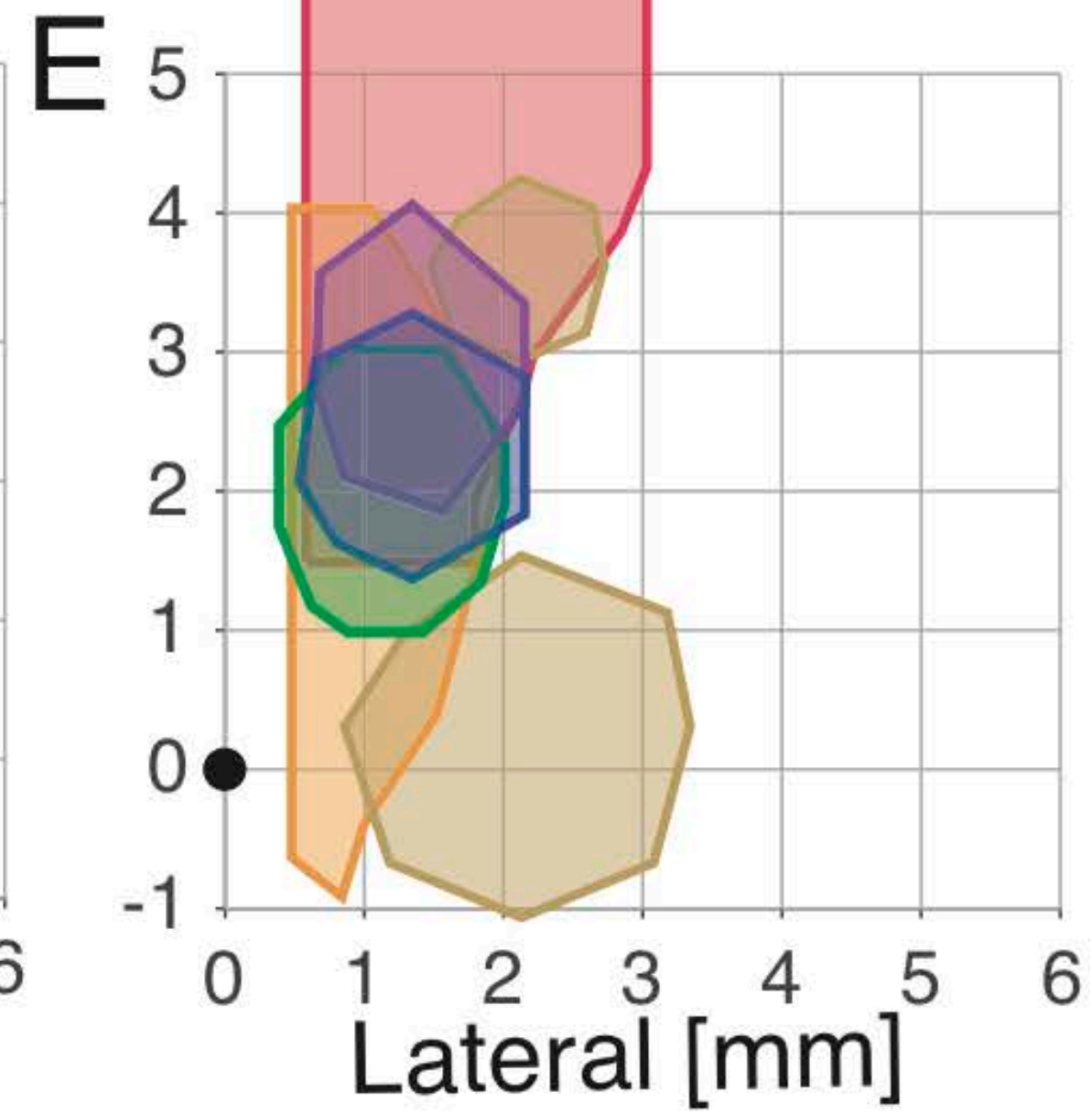
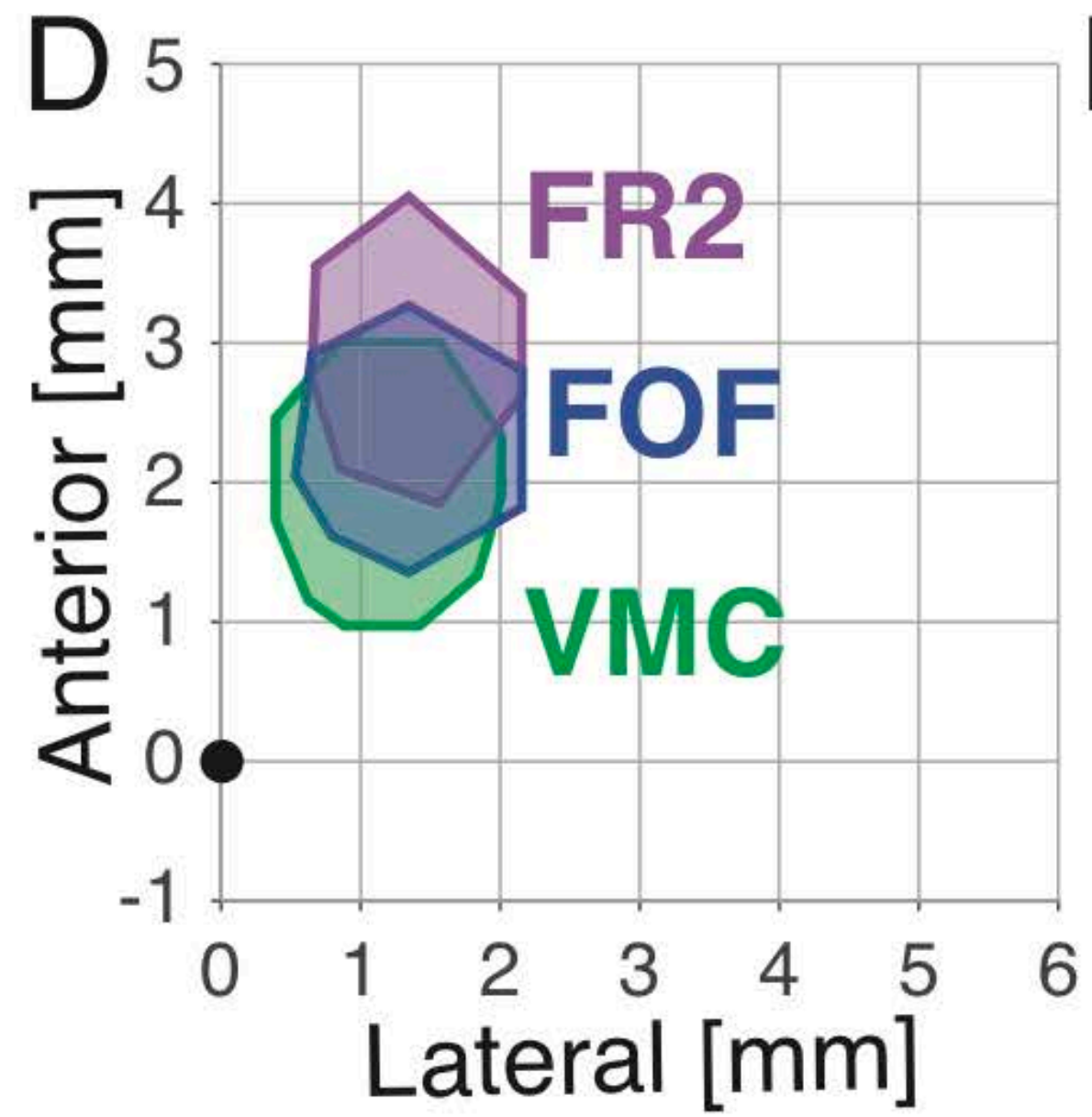
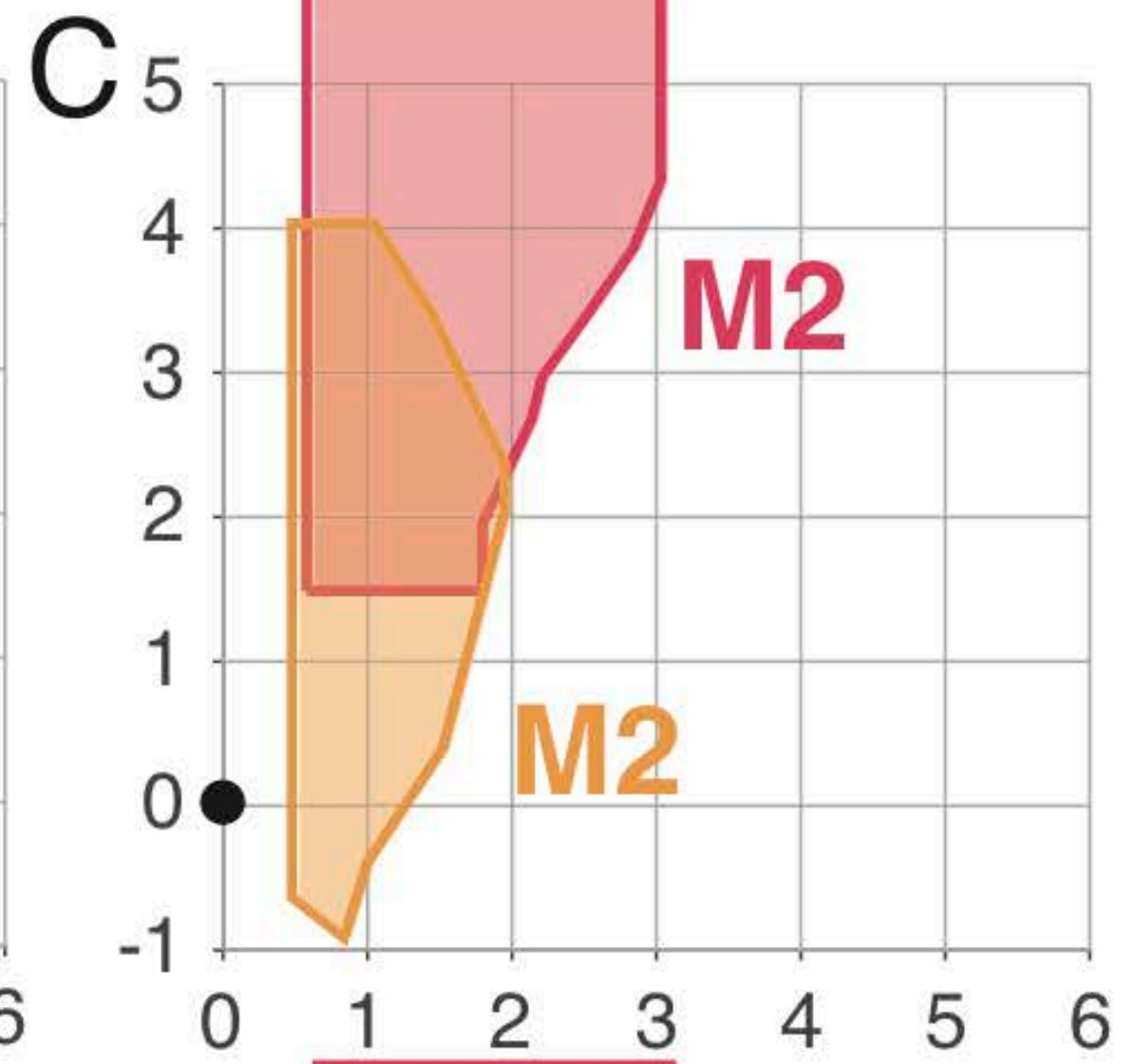
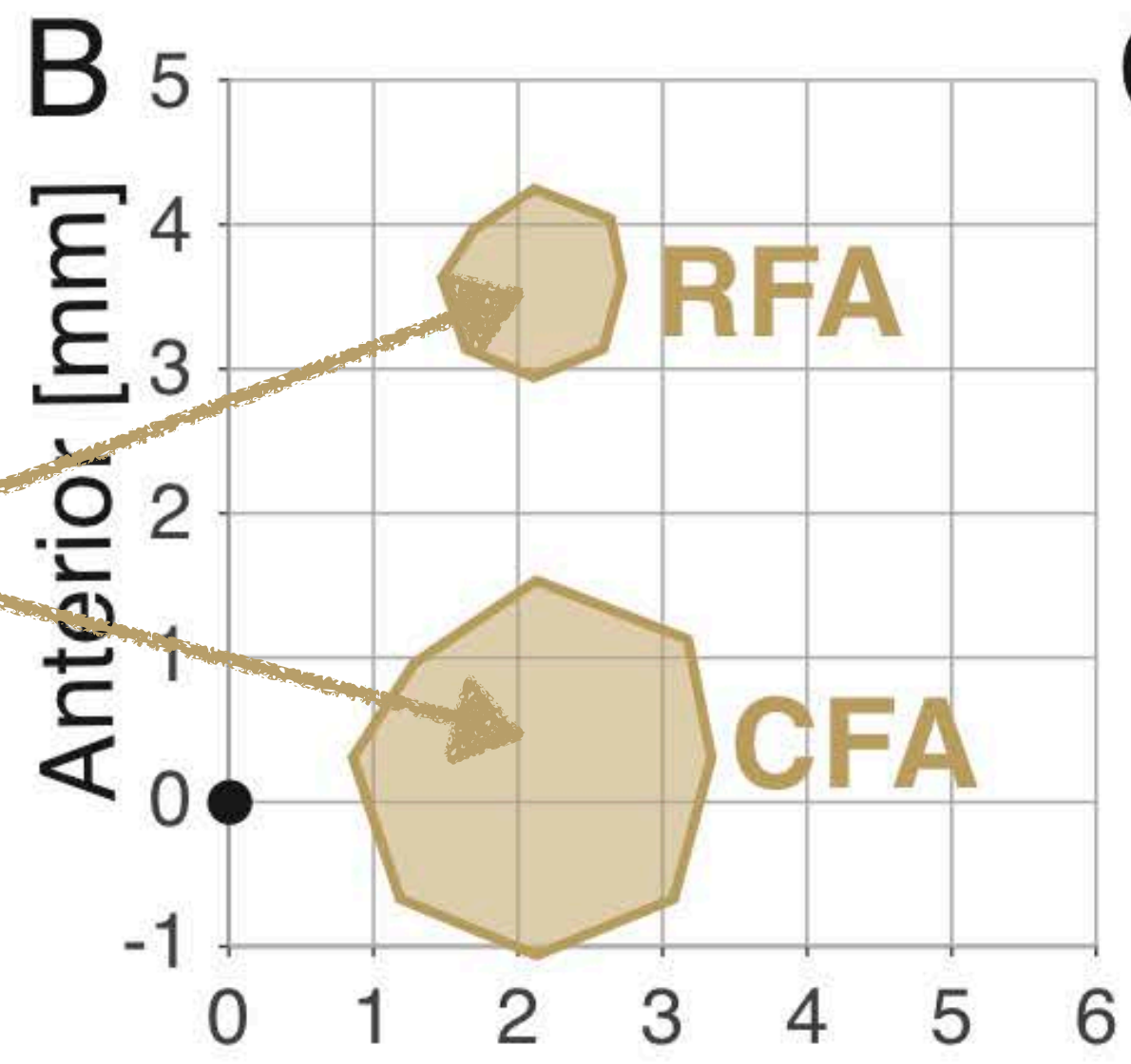
Real picture is more complex and stimulation and anatomical tracing suggests, for example, are controlled by two, spatially segregated regions (caudal and rostral forelimb areas; Nealey and Sievert, 1982; Rouiller et al., 1993; Fig. 1B). Nomenclature, that relies on comparative anatomy to name motor structures in the rat brain after their putative corresponding primate homologues, often suggest conflicting naming schemes. Thus, the same region of rat frontal cortex is referred to in the literature as primary vibrissa motor cortex (VMC; whisker M1; Brecht et al., 2004a,b; Berg and Kleinfeld, 2003; Hill et al., 2011; Ebbesen et al., 2017), secondary motor cortex (M2; a putative homolog of primate supplementary motor areas; Paxinos and Watson, 1982; Murakami et al., 2014, 2017; Minicic et al., 2018), the frontal orientational field (FOF; a putative homolog of the primate frontal eye field; Erlich et al., 2011; Hanks et al., 2015), frontal area 2 (FR2; Insanally et al., 2018), ventral frontal motor cortex (vFMC; Lee et al., 2008) and medial agranular cortex (AGM; Smith and Alloway, 2013; Fig. 1C–E). In the mouse, the terminology is comparably varied and the same region also goes under several names, such as vibrissa/whisker motor cortex (vMI; Huber et al., 2012; wMI; Matyas et al., 2010; Sreenivasan et al., 2015, 2016), secondary motor cortex (M2; Schneider et al., 2014; Nelson and Mooney, 2016; Simischke et al., 2016), medial agranular motor cortex (also M2; Nelson et al., 2013), frontal motor cortex (MR; Goard et al., 2016), and secondary motor area (MOs; Allen Mouse Brain Atlas, Lein et al., 2007; Zingg et al., 2014). This variety of terminology is confusing and can hamper discovery and exchange both between primate and rodent researchers and within the rodent community. Fortunately, the inconsistency in nomenclature has been beneficial in some ways. Because it is unclear which primate motor structures the various regions of rodent frontal cortex correspond to, this neuronal population has been investigated from very divergent vantage points, something that is actually rare in neuroscience, and implicated in a surprising variety of functions. Here, we review recent studies, which have investigated the role of rodent frontal cortex, in classic motor control of whisker and limb movements, in processing sensory stimuli, and in higher-order functions, such as motor decision-making, both in self-initiated action and in tasks, that require integration of sensory information over time. We conclude by highlighting major open questions and future directions.

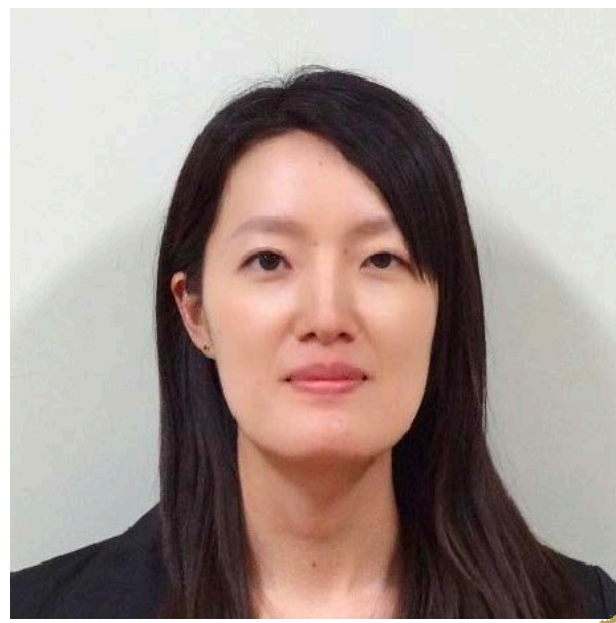
Frontal control of whisker movements
A relatively large portion of rodent motor cortex is involved in whisker control. Active vibrissal touch is a major sensing strategy of rats and mice, small nocturnal mammals who live in dark tunnels. These animals have evolved highly specialized neural circuitry for expert control of whisker movements. Rats move their whiskers individually during active touch sensing (Welker, 1964; Sachdev et al., 2002; O’Connor et al., 2010; Zuo et al., 2011; Voigts et al., 2015), in anticipation of head turning (Towal and Hartmann, 2006) and during social interactions (Wolfe et al., 2011). The fine motor control for active vibrissal touch mirrors the fine motor control of primate and human fingertips (Diamond, 2010; Prescott et al., 2011). Analogous to the enlarged representation of digital movements in the primate and human motor homunculus (Leyton and Sherrington, 1917; Penfield and Boldrey, 1937), the vibrissa motor representation in frontal cortex (as assessed by intracortical microstimulation) is huge, taking up ~6.5% of the whole cortical sheet (Hall and Lindholm, 1974; Giovanni and Lamarche, 1985; Nealey et al., 1986; Zilles and Wree, 1995; Brecht et al., 2004a).



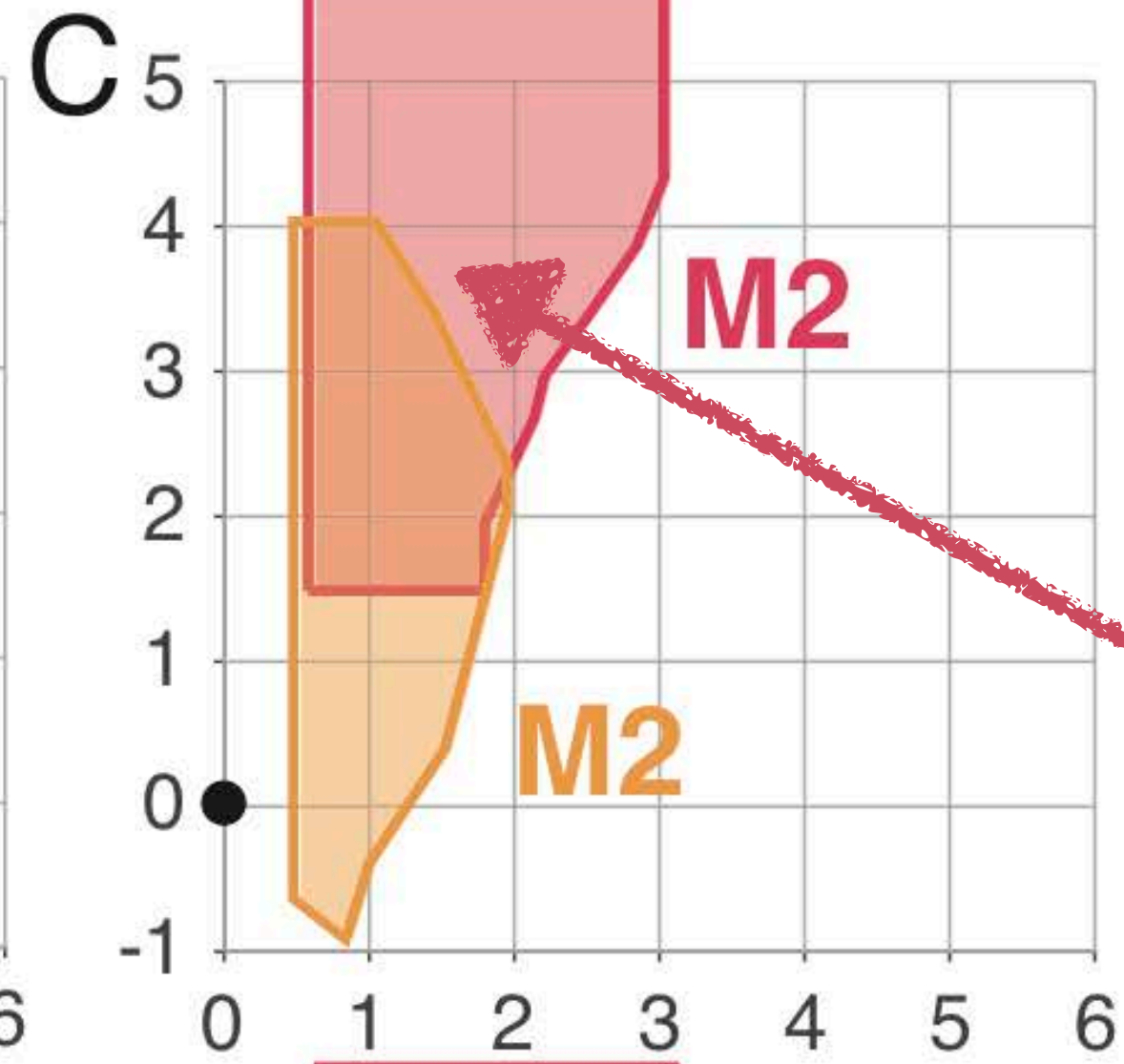
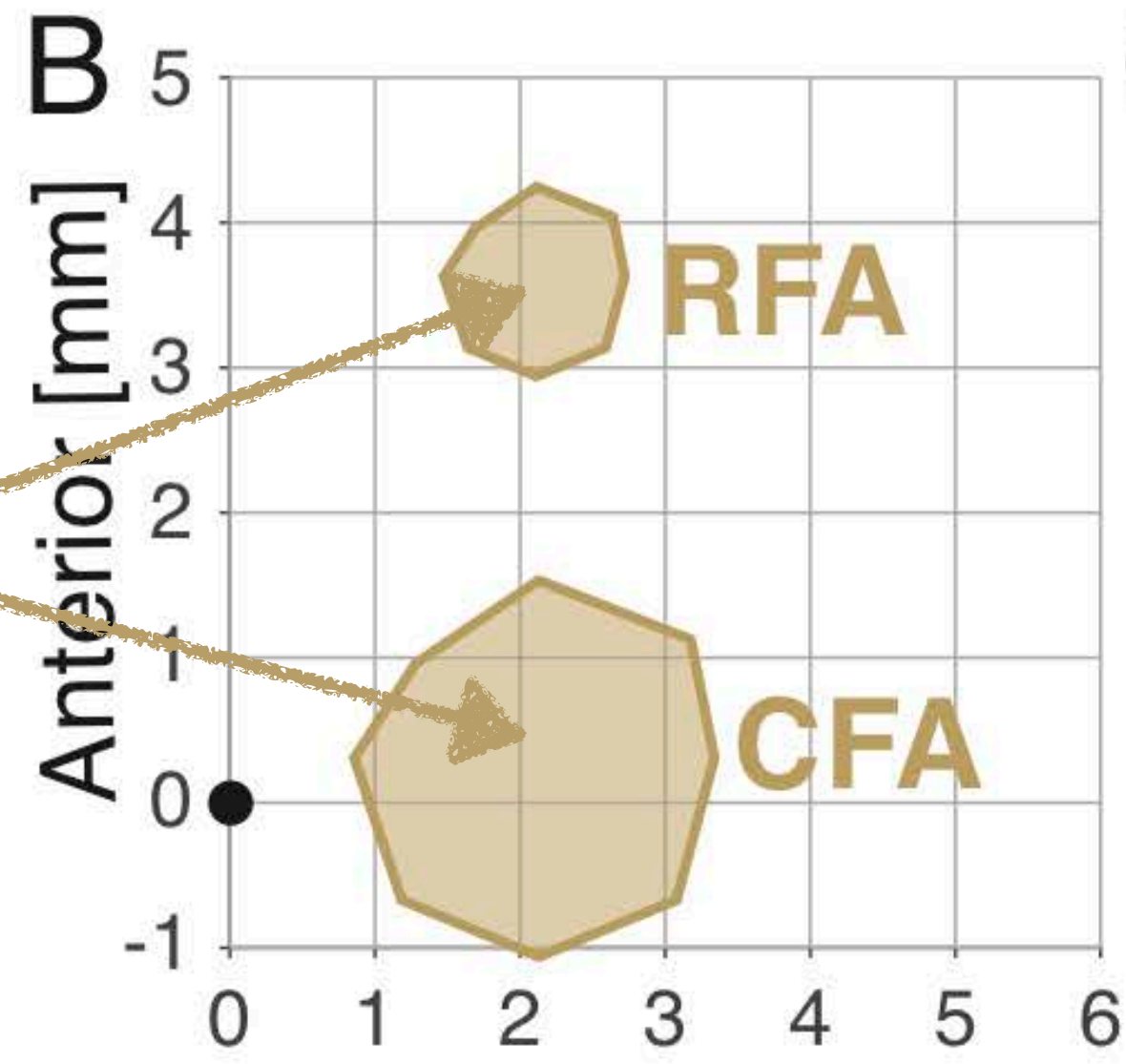


Akiko Saiki
Isomura Lab
Tamawaga

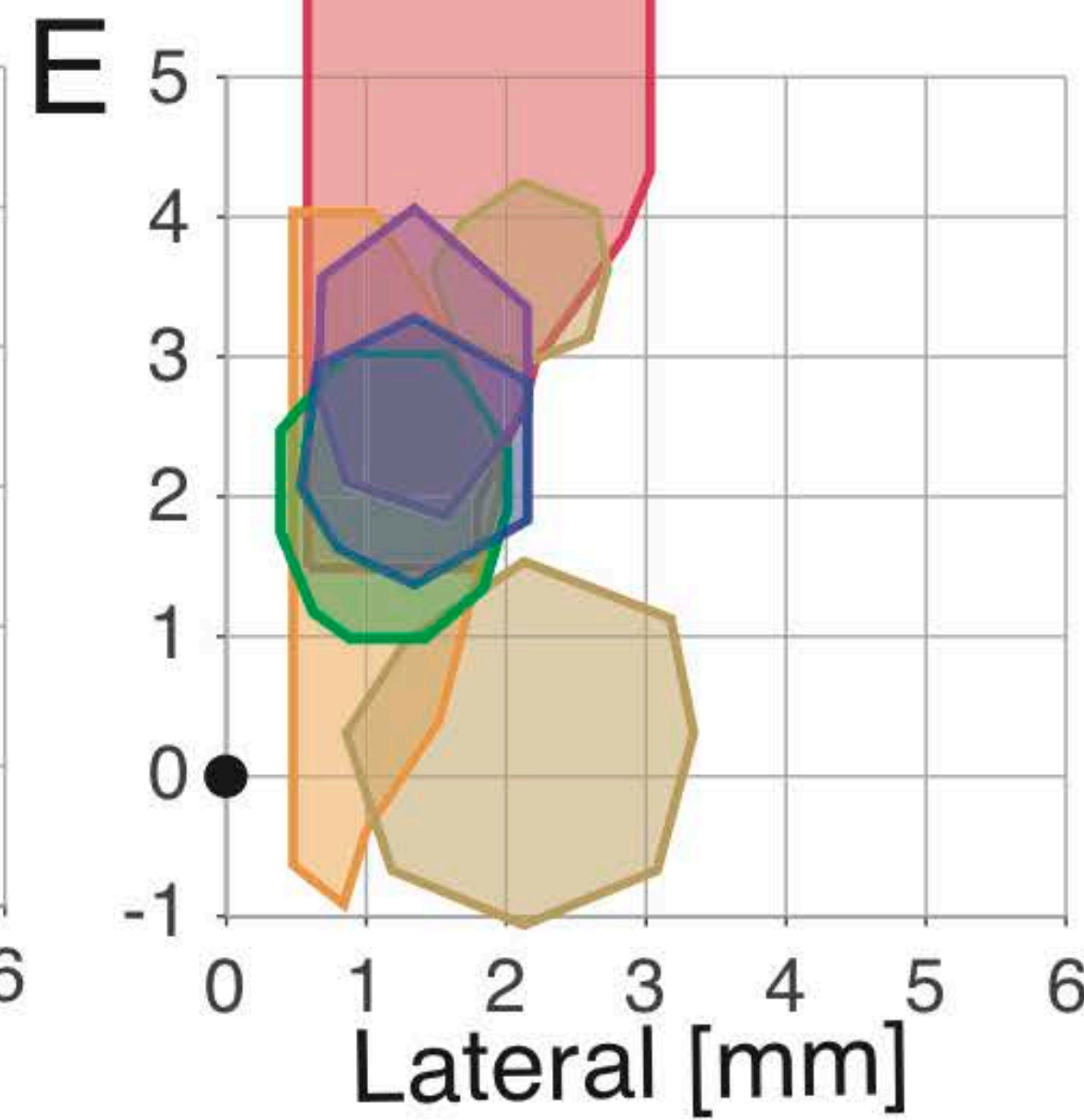
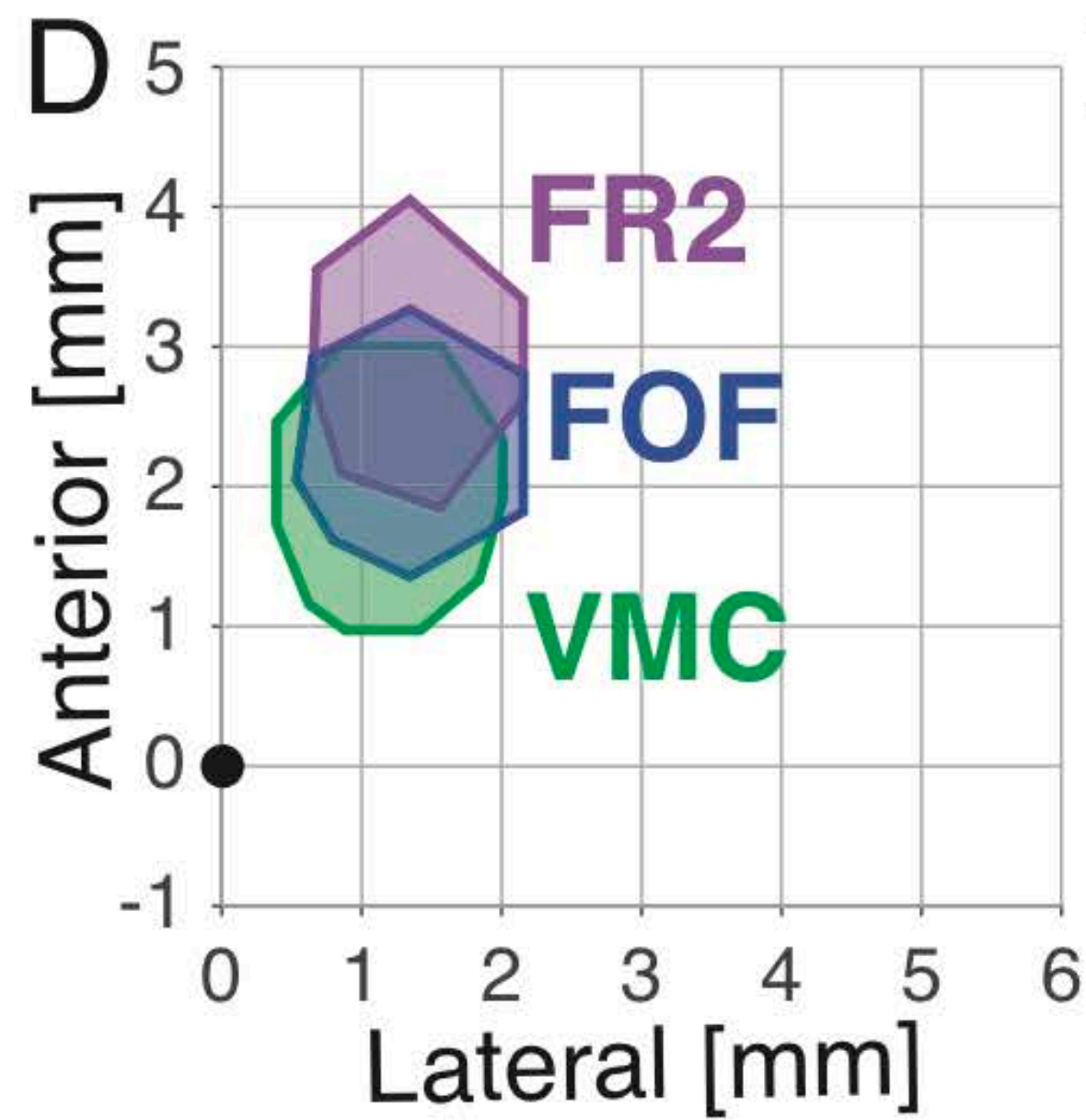


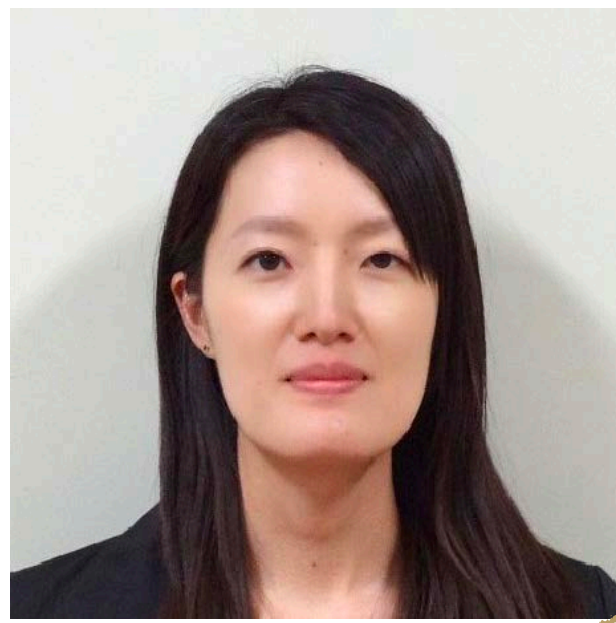


Akiko Saiki
Isomura Lab
Tamawaga



Masa Murakami
Mainen Lab
Champalimaud

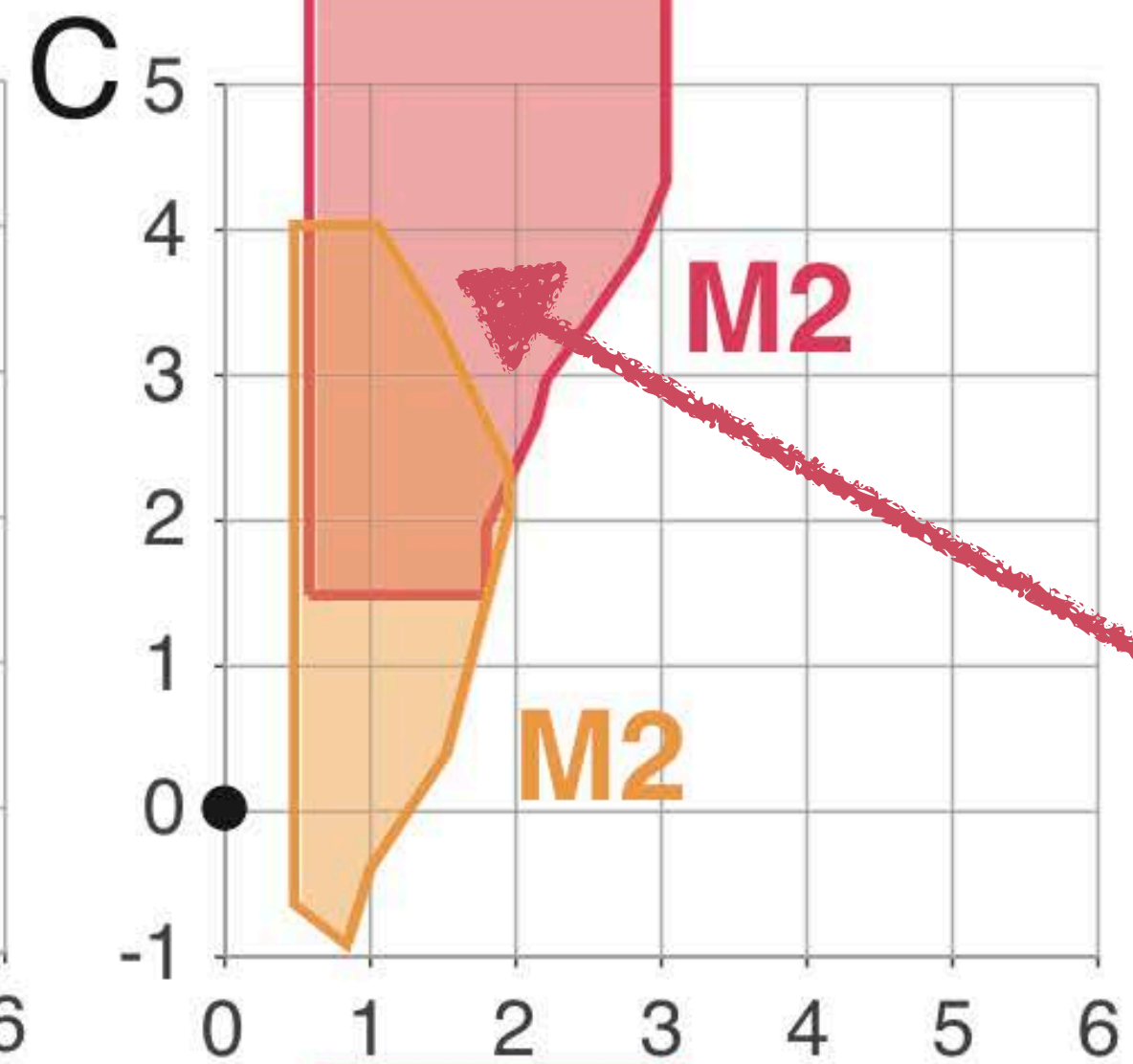
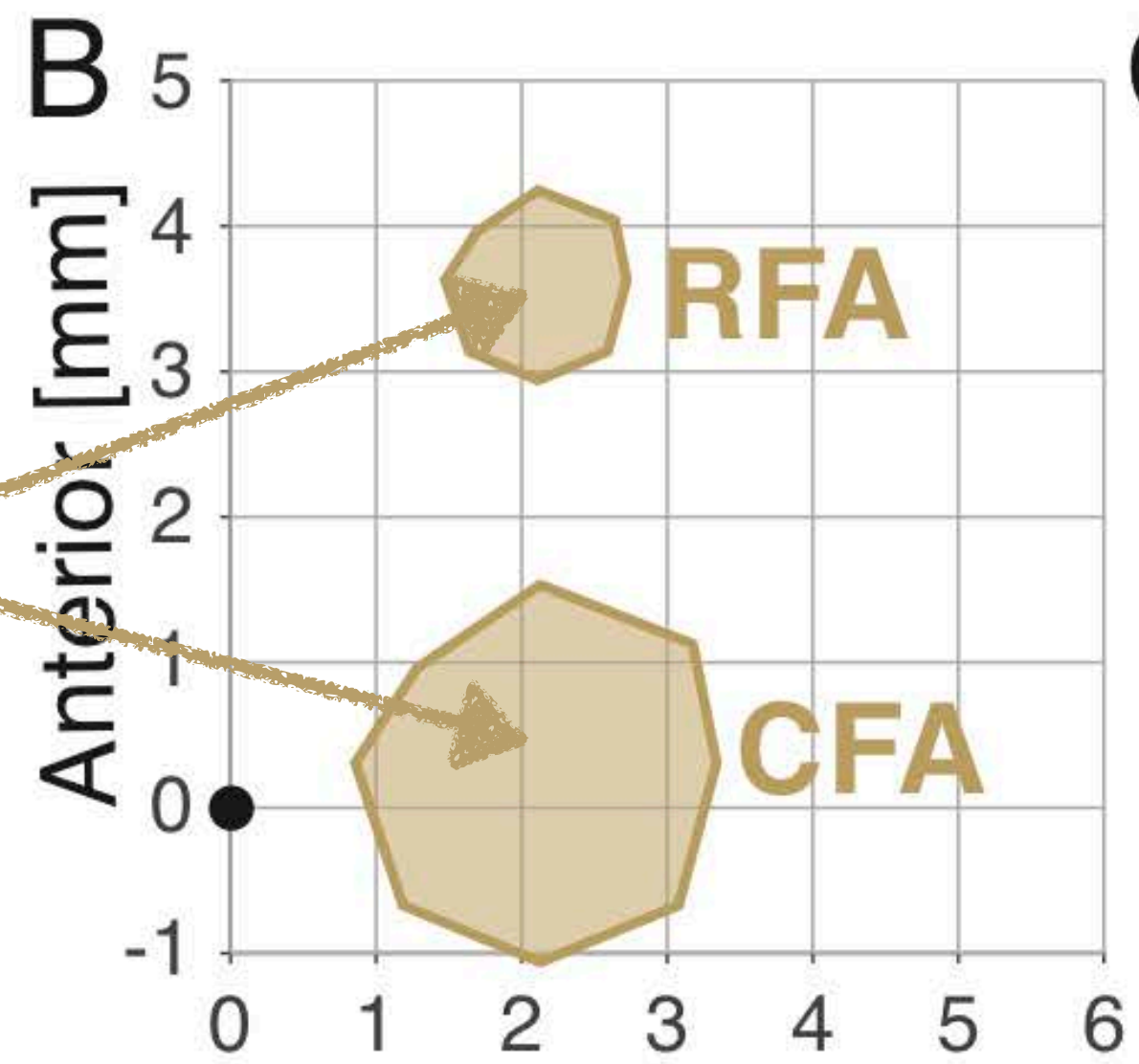




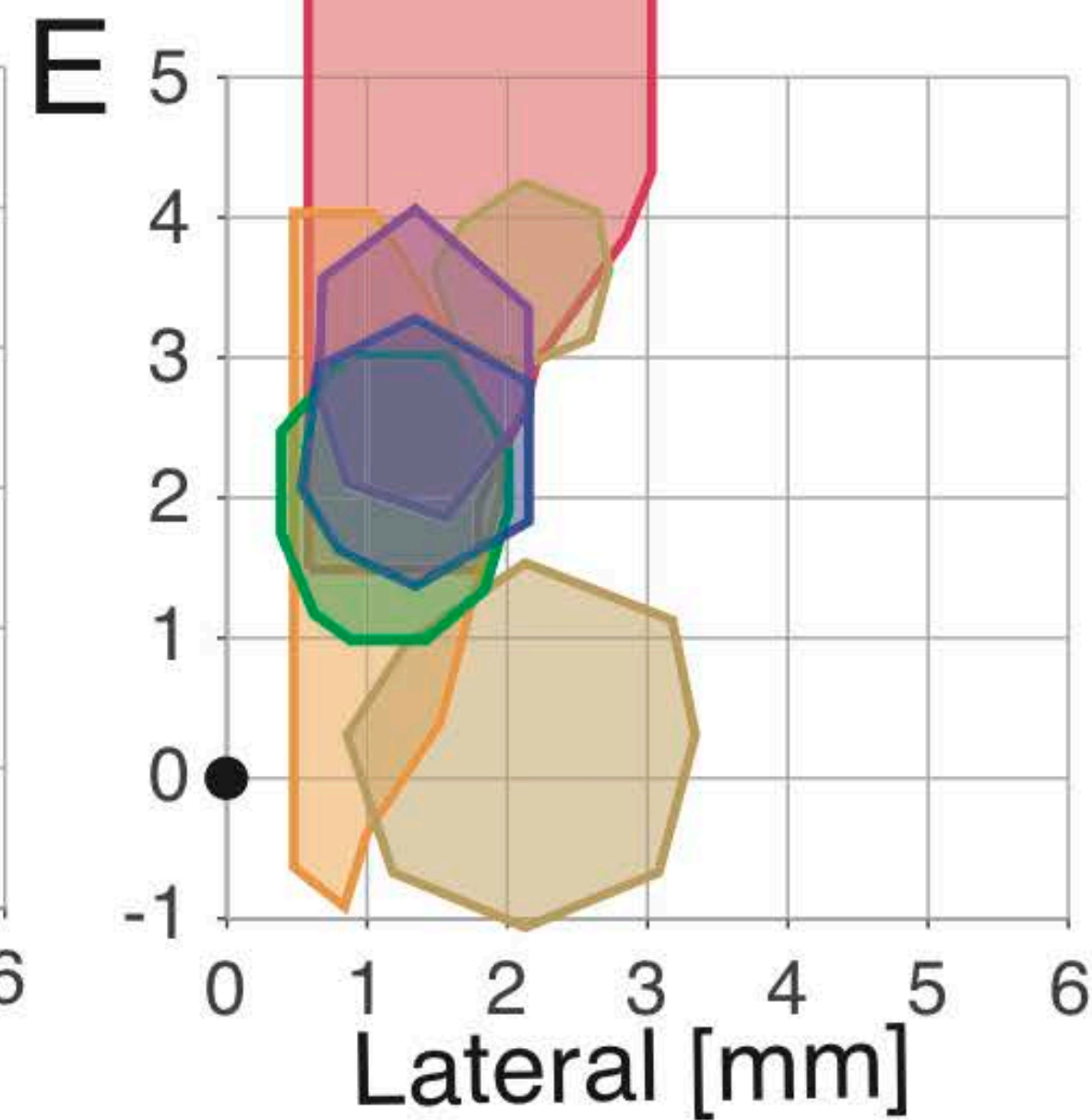
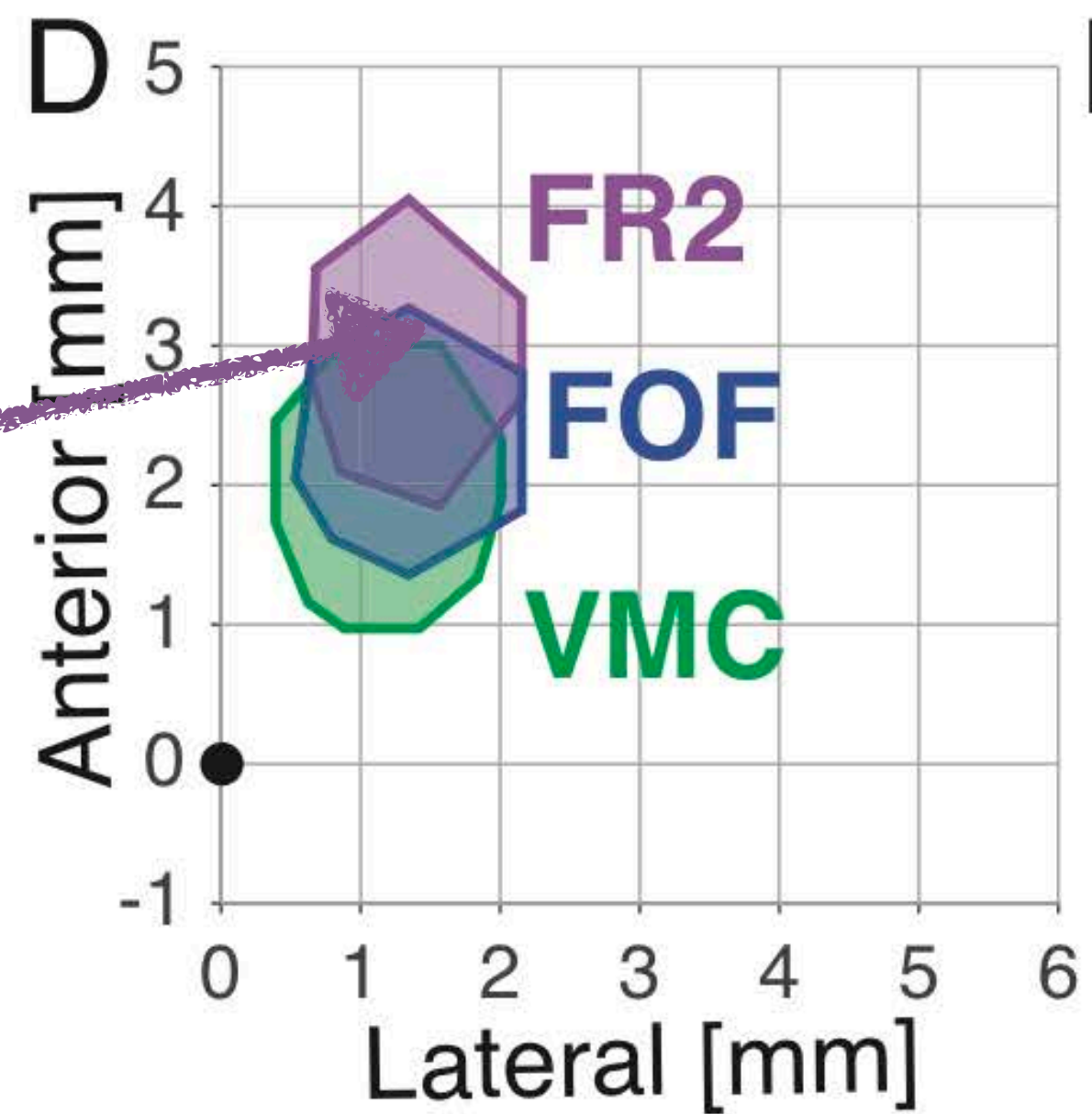
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Isomura Lab
Tamawaga

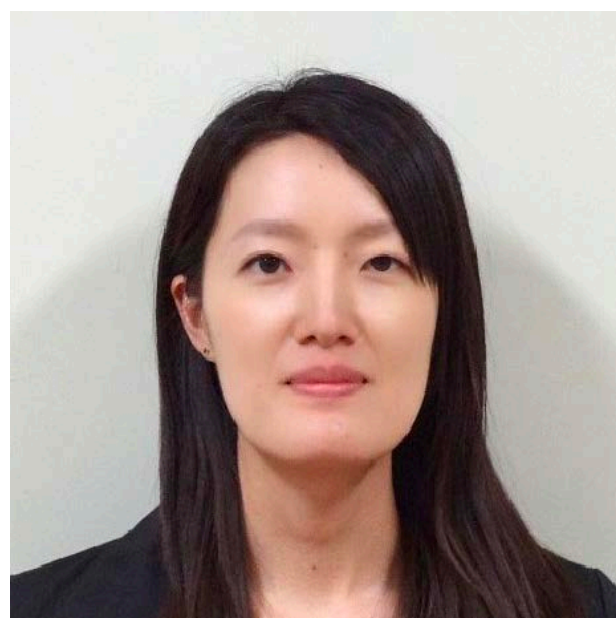


Michele Insanally
Froemke Lab
NYU



Masa Murakami
Mainen Lab
Champalimaud

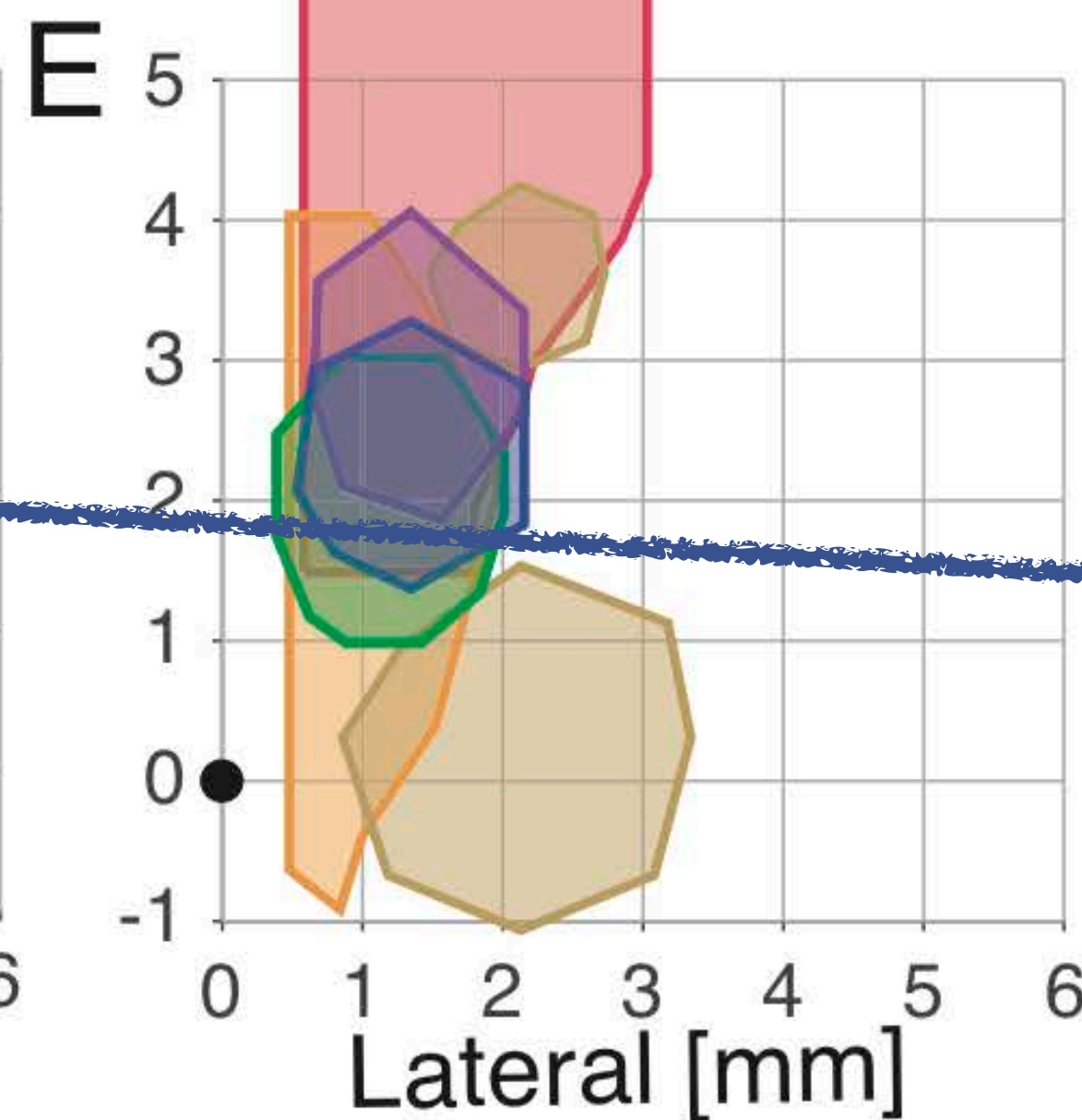
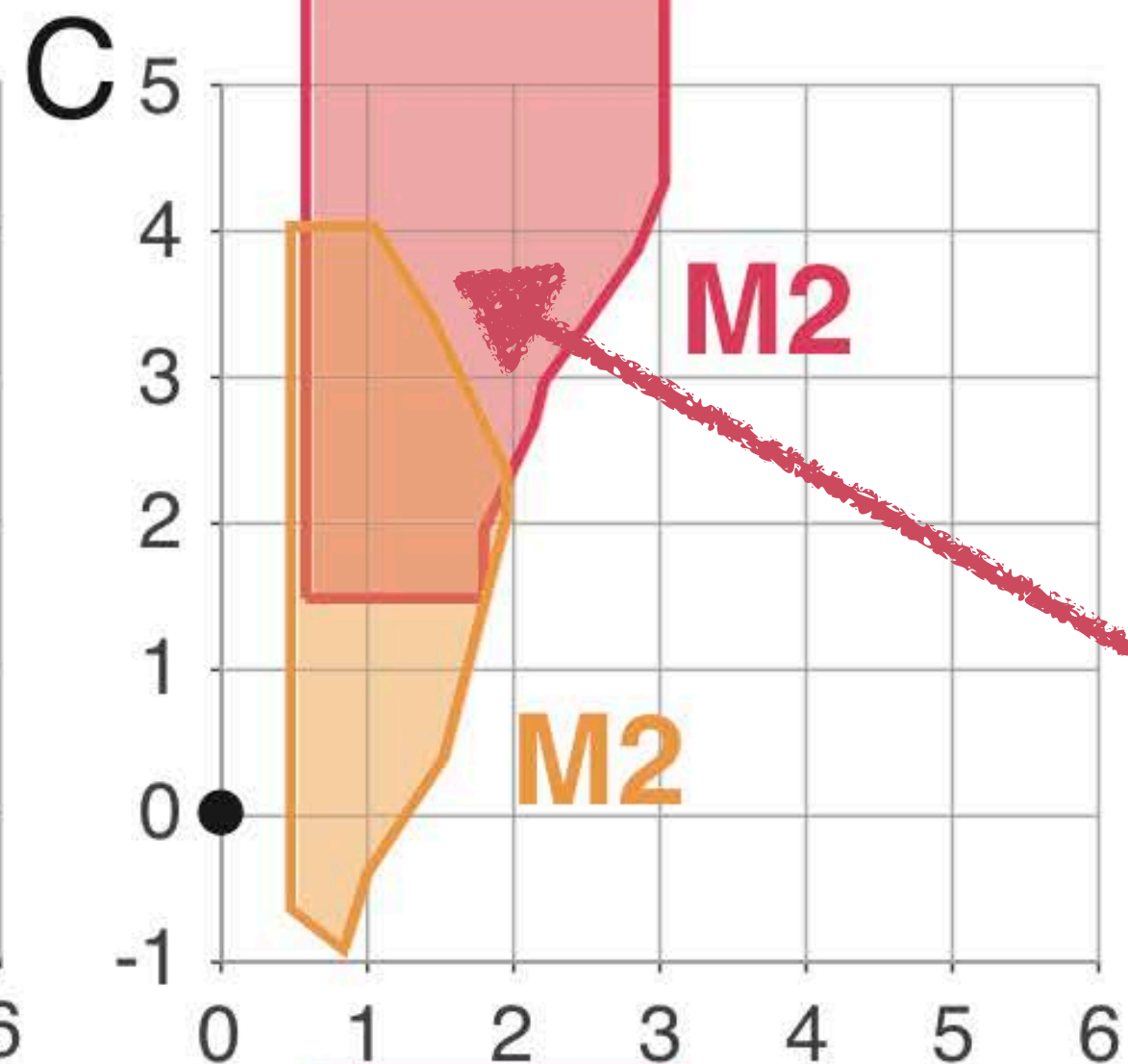
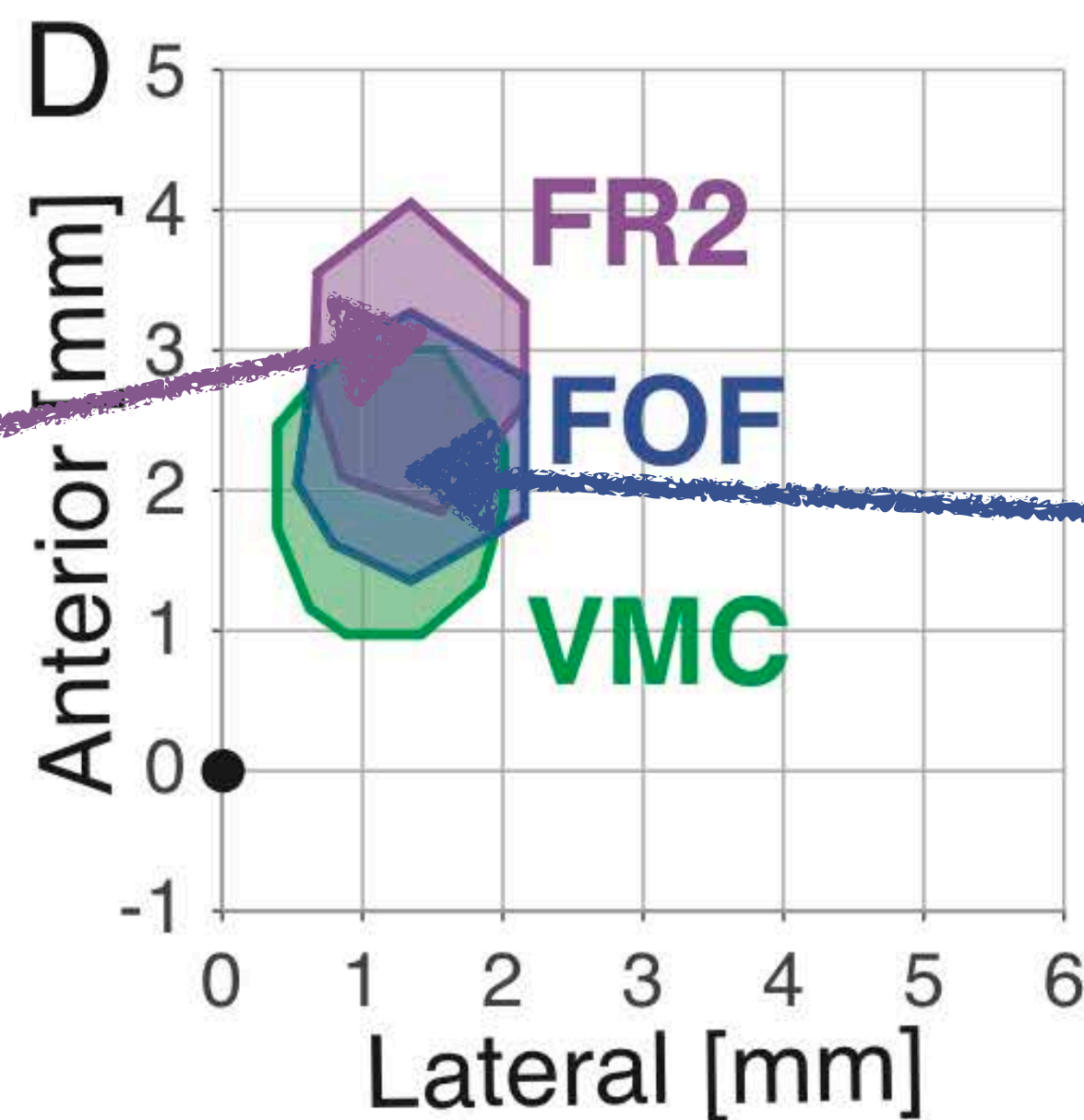
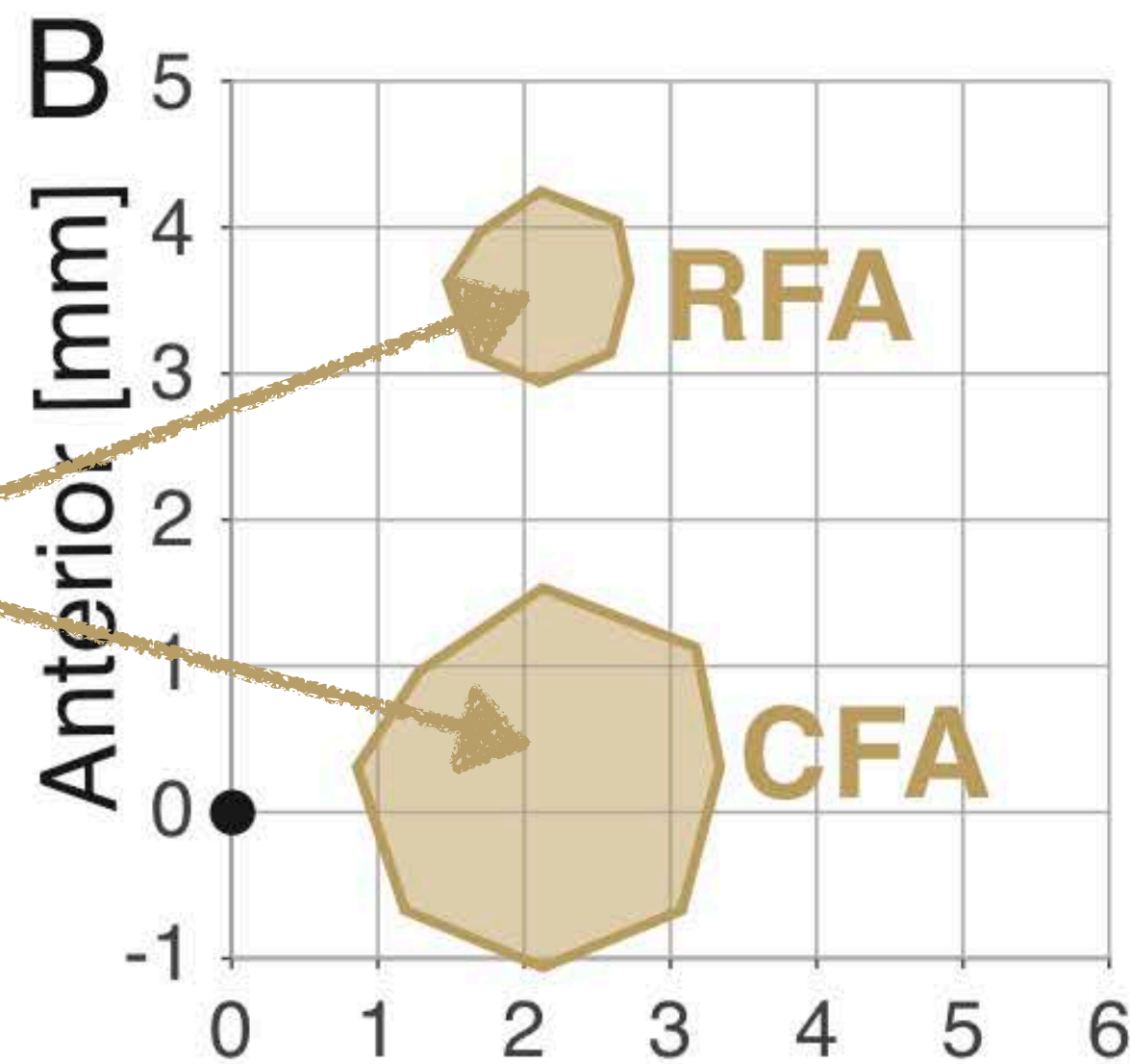




Akiko Saiki
Isomura Lab
Tamawaga



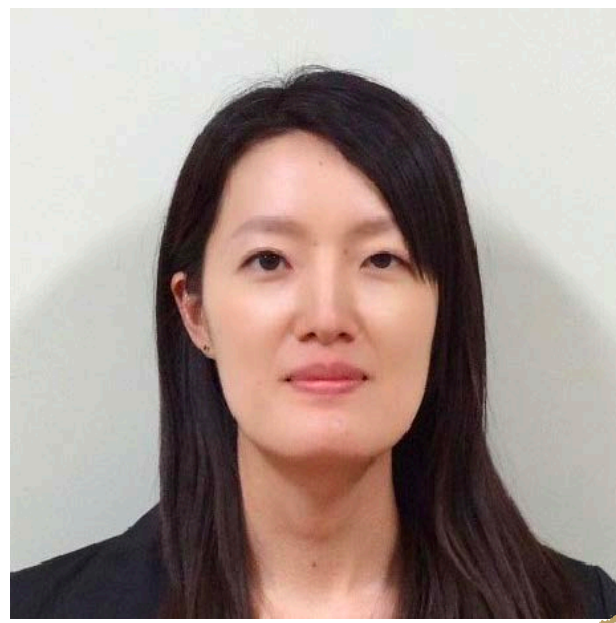
Michele Insanally
Froemke Lab
NYU



Masa Murakami
Mainen Lab
Champalimaud



Chuck Kopec
Brody Lab
Princeton



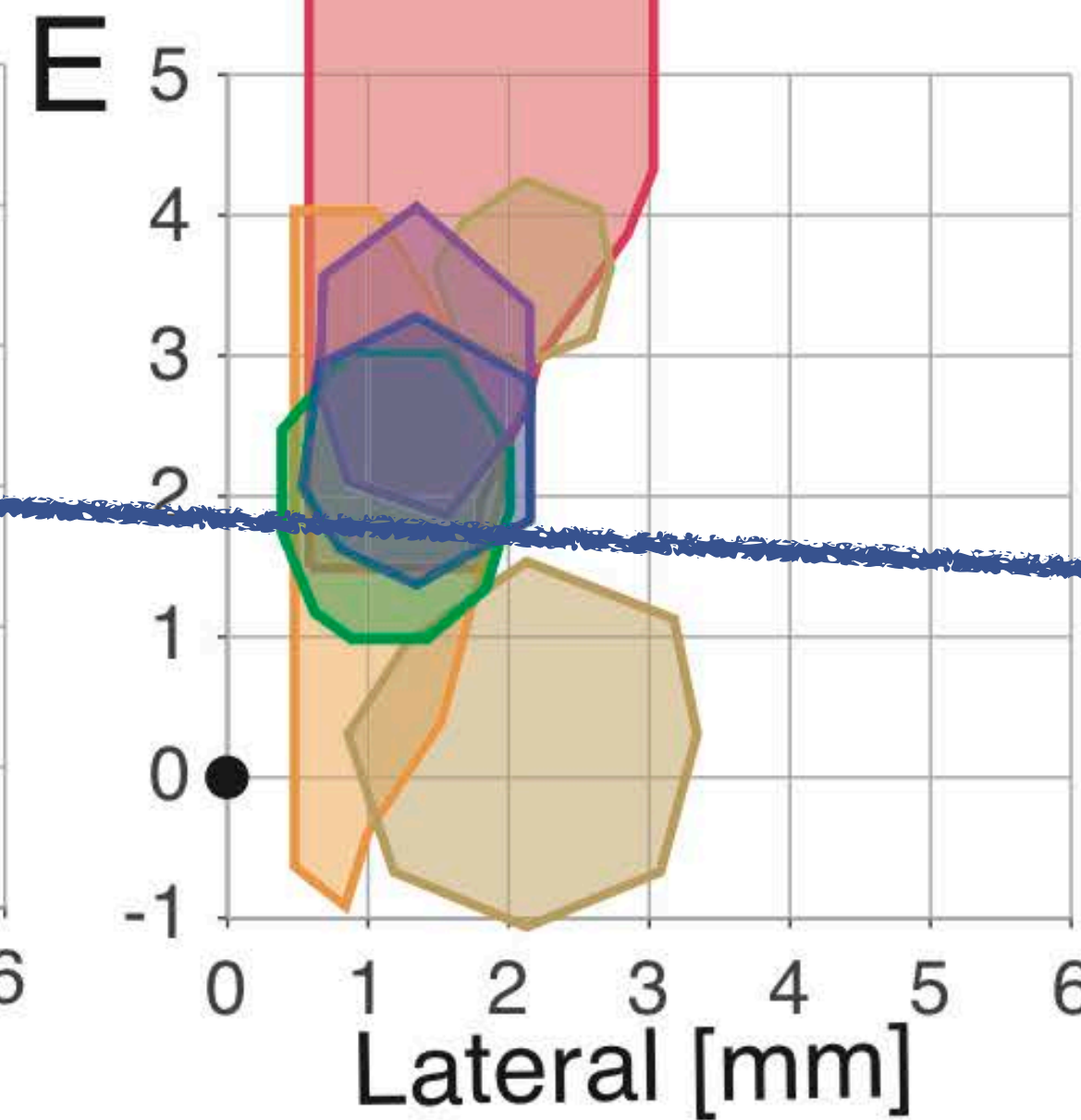
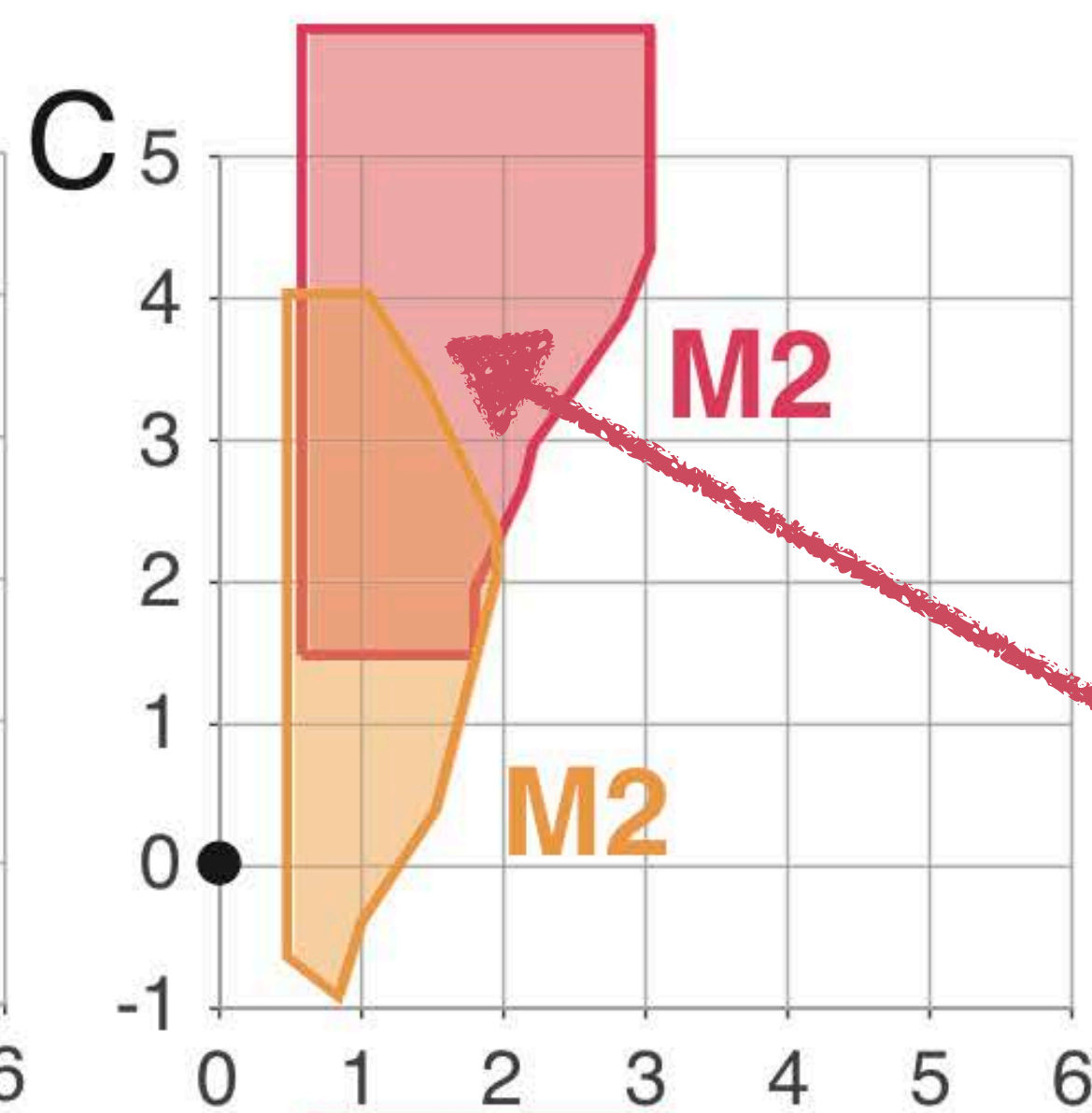
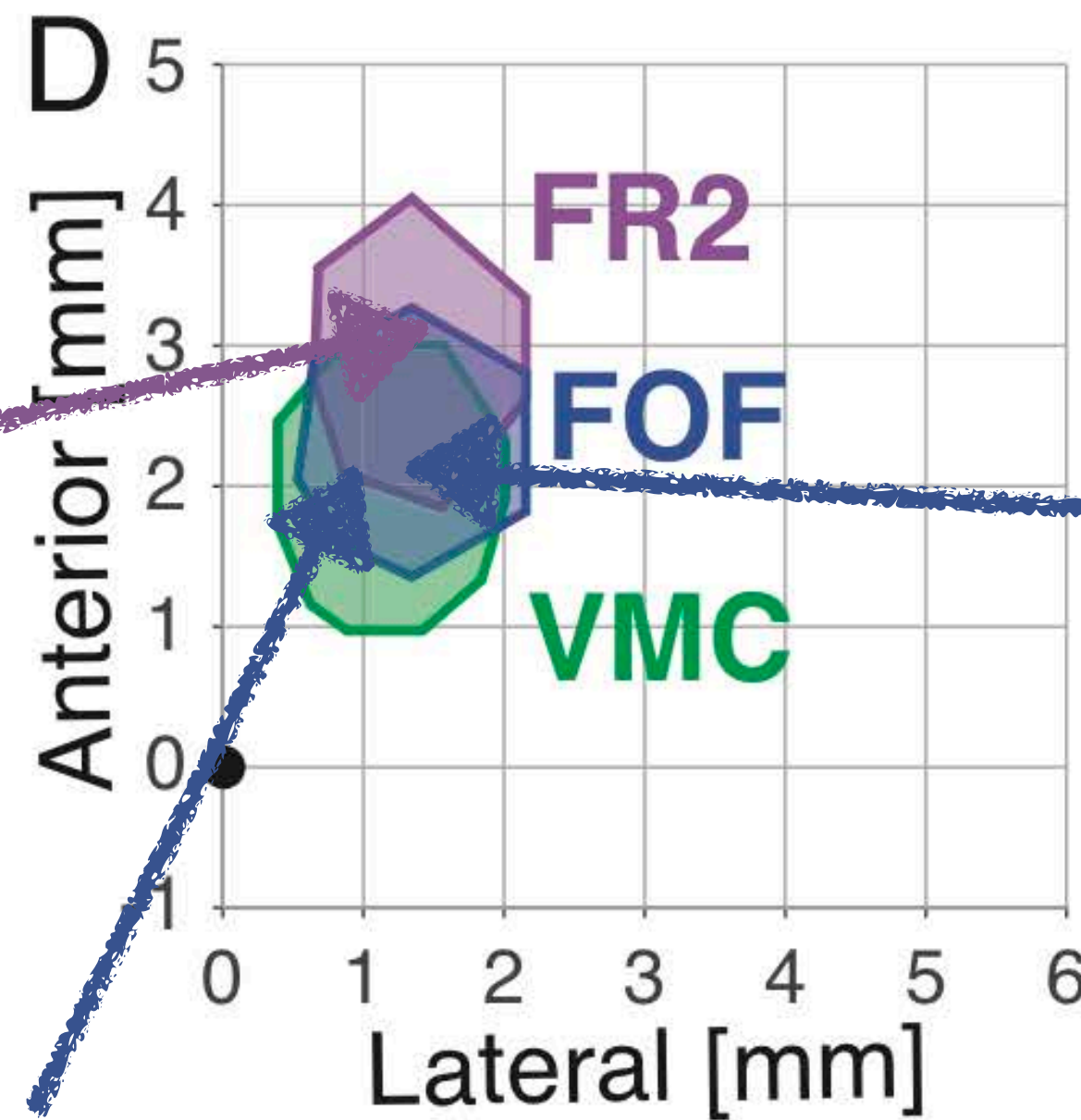
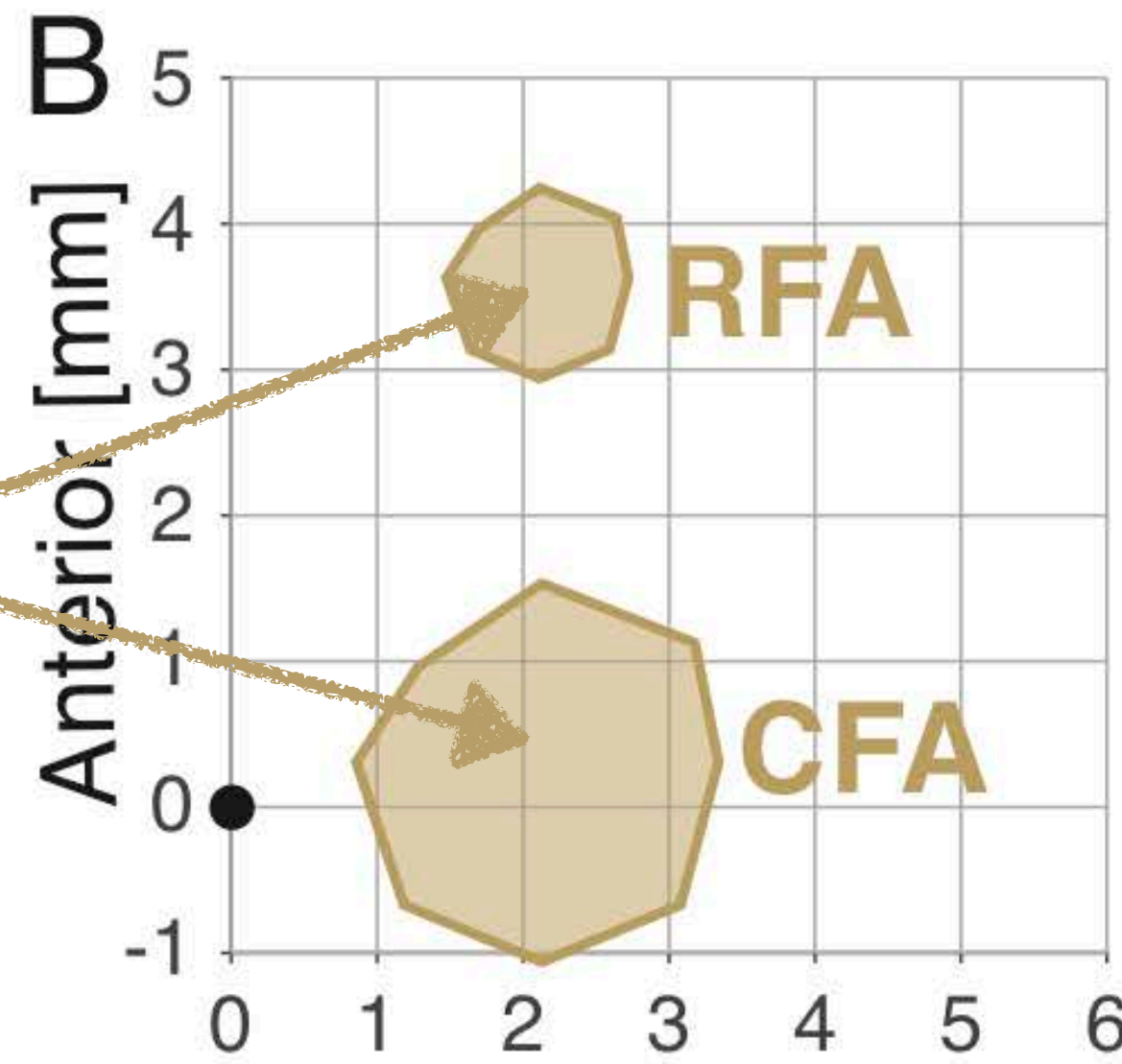
Akiko Saiki
Isomura Lab
Tamawaga



Michele Insanally
Froemke Lab
NYU



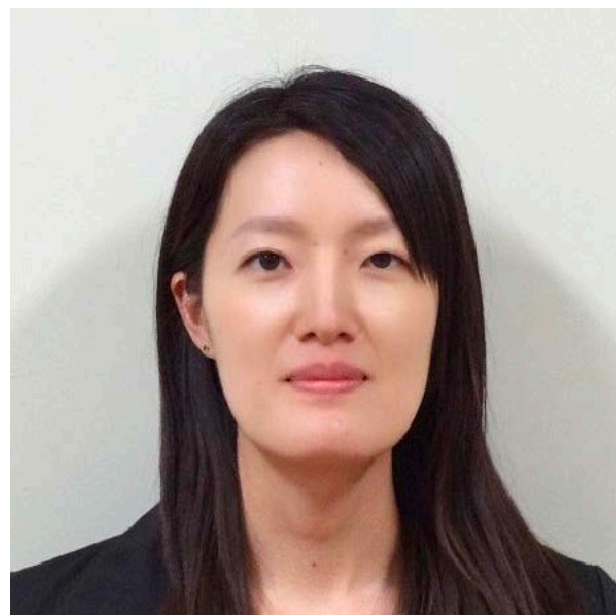
Jeff Erlich
Erlich Lab
NYU Shanghai



Masa Murakami
Mainen Lab
Champalimaud



Chuck Kopec
Brody Lab
Princeton



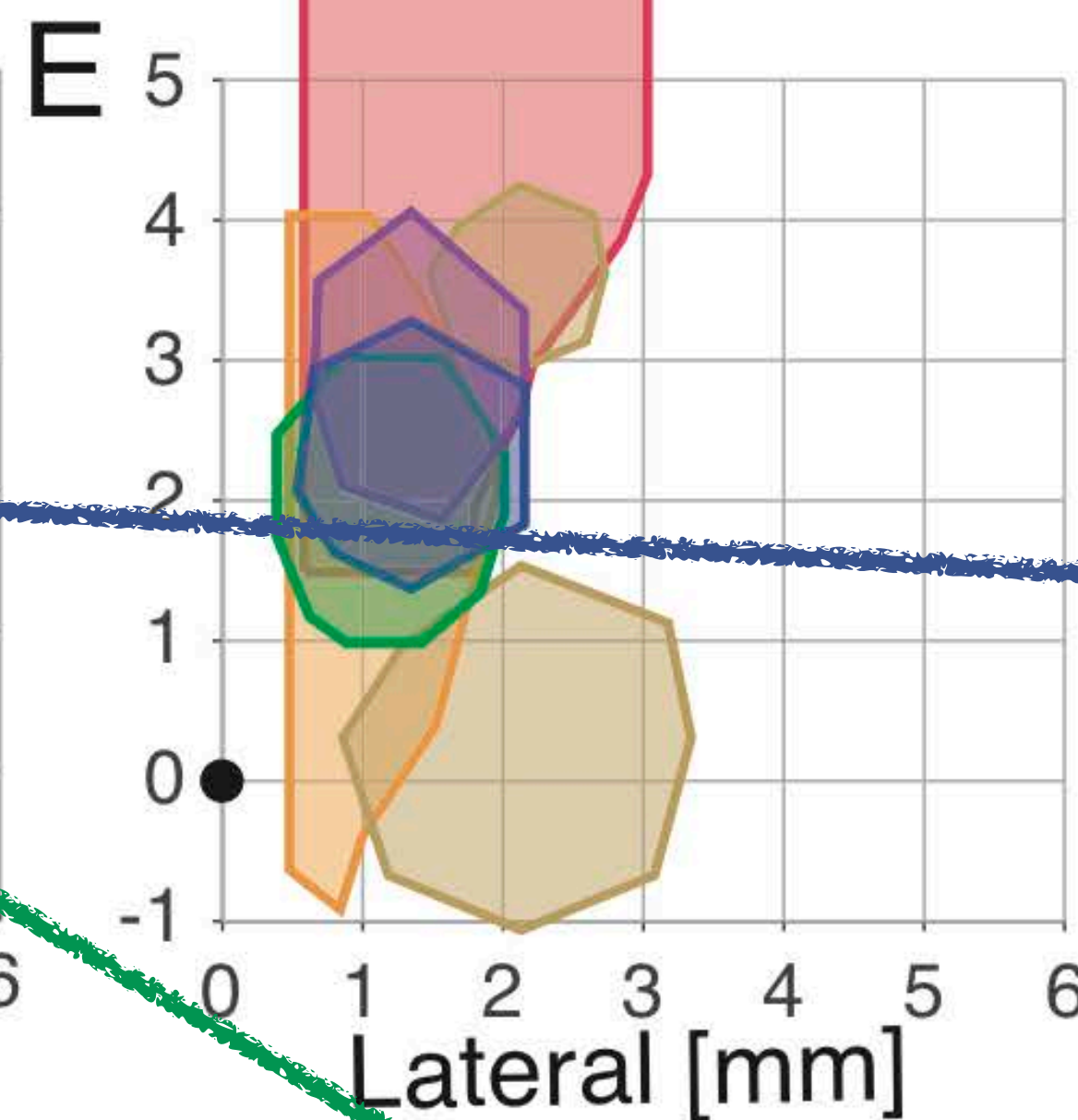
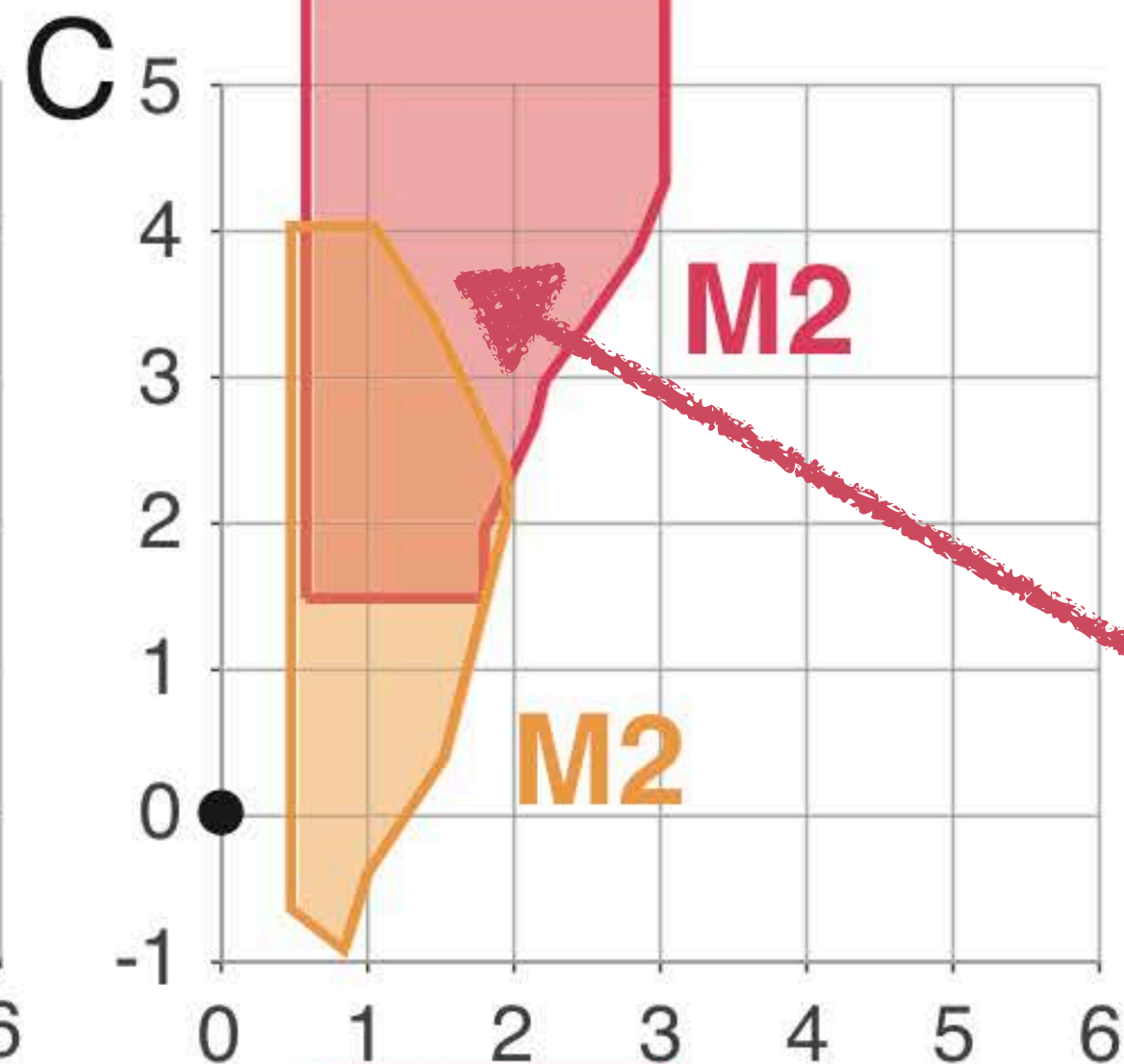
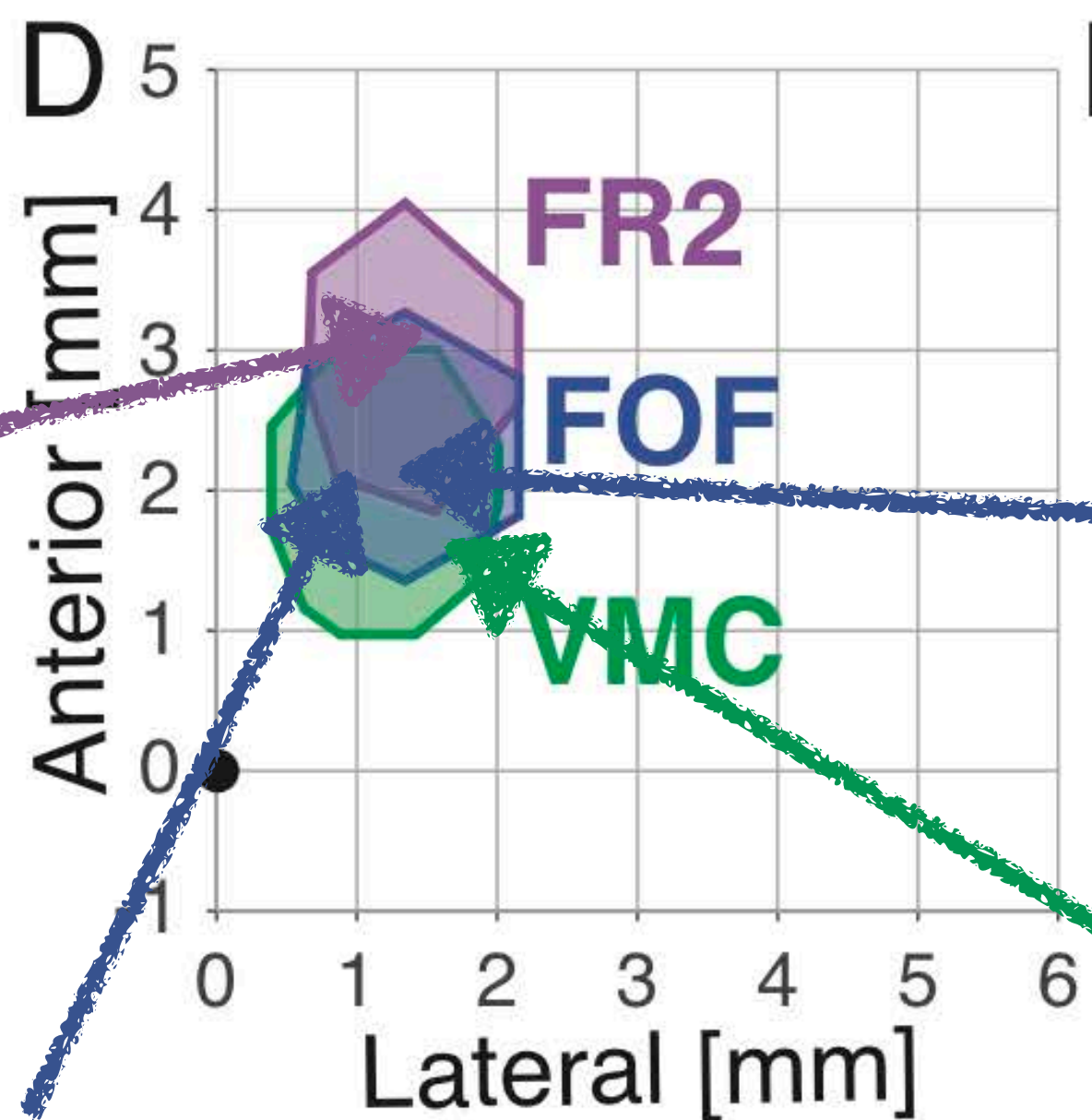
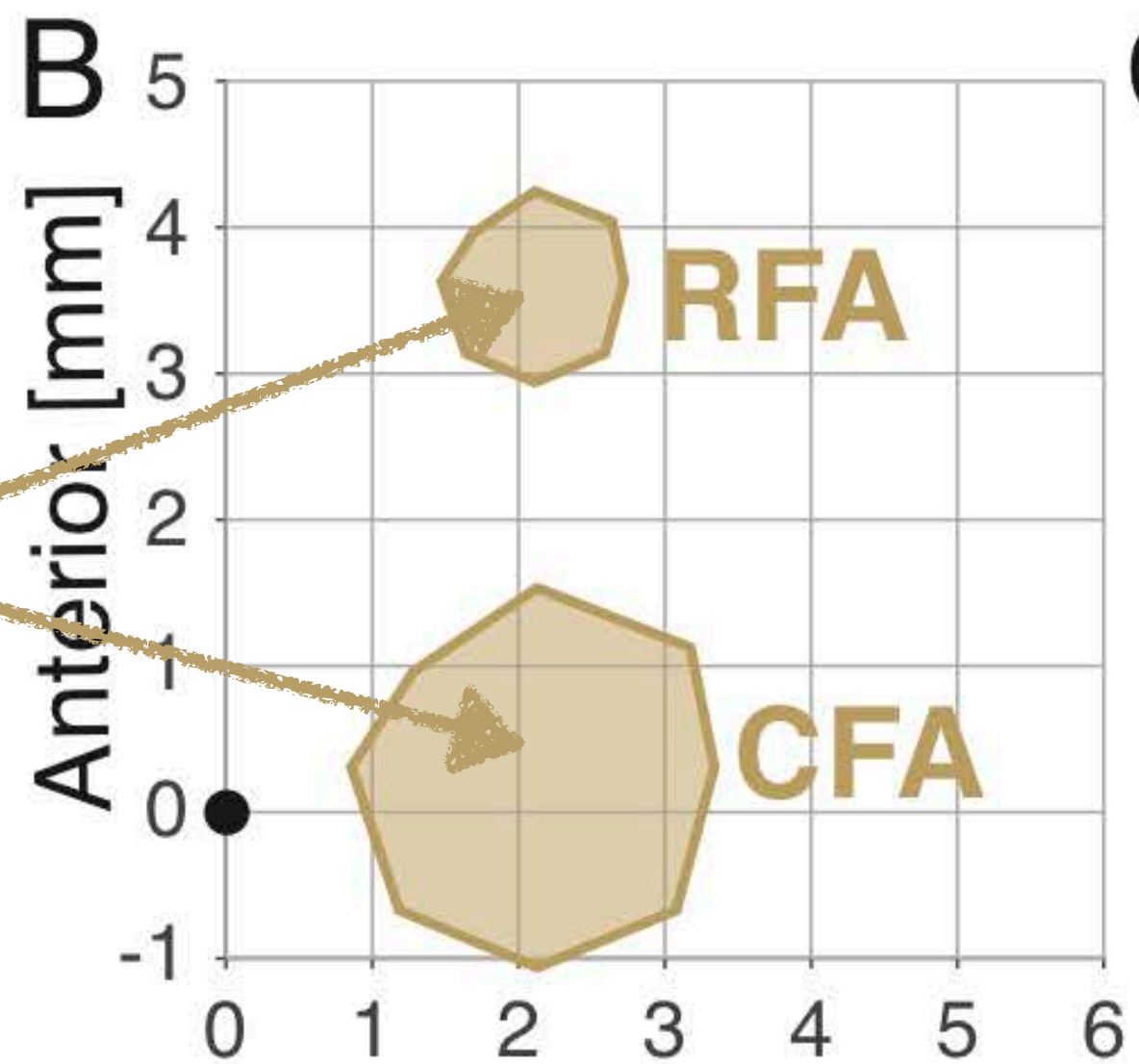
Akiko Saiki
Isomura Lab
Tamawaga



Michele Insanally
Froemke Lab
NYU



Jeff Erlich
Erlich Lab
NYU Shanghai



Masa Murakami
Mainen Lab
Champalimaud



Chuck Kopec
Brody Lab
Princeton



Christian Ebbesen
Brecht Lab
HU Berlin

More than just a “Motor”: Recent surprises from the frontal cortex

1:30 PM - 1:35 PM. **180.01 - Introduction**

C. L. Ebbesen; Chair. Skirball Inst. of Biomol. Med., New York University School of Medicine, New York, NY.

1:35 PM - 1:55 PM **180.02 - The role of rat frontal orienting fields in decision commitment**

C. D. Kopec; Princeton Neuroscience Institute, Princeton University, Princeton, NJ.

1:55 PM - 2:15 PM **180.03 - Movement suppression and socio-sensory signals in vibrissa motor cortex**

C. L. Ebbesen; Skirball Inst. of Biomol. Med., New York University School of Medicine, New York, NY.

2:15 PM - 2:35 PM **180.04 - Neural substrates of action timing decisions**

M. Murakami; Champalimaud Research, University of Yamanashi, Chuo-shi, JAPAN.

2:35 PM - 2:55 PM **180.05 - Nominally non-responsive frontal cortical cells encode behavioral variables via ensemble consensus-building**

M. Insanally; New York University, NY, NY.

2:55 PM - 3:15 PM **180.06 - In vivo spiking dynamics and encoding of forelimb movements in rat M1/M2**

A. Saiki; Neurobiology, Northwestern University, Evanston, IL.

3:15 PM - 3:35 PM **180.07 - Spatio-temporal receptive fields in the rodent frontal orienting field**

J. C. Erlich; Institute of Brain and Cognitive Science, NYU Shanghai, Shanghai, CHINA.

3:35 PM - 4:00 PM **180.08 - Closing Remarks**