Comparative anatomy of the macaque and the human frontal oculomotor domain

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Abstract:	In non-human primates, at the junction of the prefrontal with the premotor cortex, there is a sector designated as frontal eye field (FEF), involved in controlling oculomotor behavior and spatial attention. Evidence for at least two FEFs in humans is at the basis of the still open issue of the possible homologies between the macaque and the human frontal oculomotor system. In this review article we address this issue suggesting a new view solidly grounded on evidence from the last decade showing that, in macaques, the FEF is at the core of an oculomotor domain in which several distinct areas, including areas 45A and 45B, provide the substrate for parallel processing of different aspects of oculomotor behavior. Based on comparative considerations, we will propose a correspondence between some of the macaque and the human oculomotor fields, thus suggesting sharing of neural substrate for oculomotor control, gaze processing, and orienting attention in space. Accordingly, this article could contribute to settle some aspects of the so-called “enigma” of the human FEF anatomy.
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Response to Reviewers:	

Cover Letter

Dear Dr. Lee,

We are submitting to you a new version of the manuscript revised according to the suggestions of the Reviewers. We were glad about the favorable comments of the reviewers and we hope that now the manuscript could be considered acceptable for publication in Neuroscience and Biobehavioral Reviews.

Sincerely,

Elena Borra

Responses to the Reviewers

We sincerely thank the Reviewers for taking their time in reviewing our manuscript and for their favourable comments. Their suggestions have been all considered and implemented in the revised version of the manuscript.
The following is the detailed description of the way in which the comments of the Reviewers have been addressed.

Reviewer 1

Comment

The only comment is that the legend at the bottom of figure 5 indicates the skeleto-motor fields with 6-10, but it should be A-E.

Response

Sorry for the inconvenience, the figure has been changed accordingly.

Reviewer 2

Comment

At the end of the Abstract, the so called "enigma" of FEF anatomy is referring to the monkey, or to the humans, or both in the sense of the correspondence between the two? Please specify.

Response

The term “enigma” has been used in the past to refer to some still unsolved issue about the anatomical location of the human FEF compared to that of the macaque FEF. We made some changes to the text in order to make this clearer.

Comment

I found in particular the chapter "2.2 Connectional and functional features of the frontal oculomotor domain areas" in the first half of the manuscript, quite heavy. This chapter is related to the description of the cortical and subcortical circuits and the functional properties of FEF areas in non-human primates. The different sections each of which focused on a specific sub-area of oculomotor domain are rich in details but only one illustration is presented. Figure 2, composed by 5 different panels, results too much crowded making the little details (for example the location of anterograde labelling in the basal ganglia) low visible. I suggest to subdivide Figure 2 at least into two different figures and possibly add colors instead of the total black/white style to help in outstanding some peculiar aspects.

Response

As suggested by the reviewer, we have split the presentation of the cortical and subcortical connectivity of the frontal oculomotor areas in two separate figures (Figure 2 and 3). The subcortical connectivity is now presented in a more schematic way and similarly for all the structures.

Comment

Second, the authors describe together with the connectional data also functional properties, but this last aspect is not illustrated. I suggest to schematically represent in a figurative way also the functional role of the different oculomotor fields.

Response

As suggested by the reviewer, we have added a table showing a summary view of the main functional features, which characterize the areas under the focus of this review as oculomotor-related areas.

Comment

Finally, in Figure 3 as a summary view, I suggest to add also a summary view of subcortical contributions making for example a cumulative map like it was presented for example in Gerbella et al. 2015, Cereb Cortex.

Response

As the new Figure 3 now provides an overall view of all the subcortical connections we think that a further presentation of these data, albeit in a different format, would result somewhat redundant. We hope that the reviewer will agree.

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Highlights

In macaques a caudal prefrontal field – the frontal eye field (FEF) – plays a crucial role in oculomotor control and spatial attention

In humans, functional imaging studies show that oculomotor and spatial attention tasks activate two frontal sectors (dorsal and ventral hFEF)

The definition of the possible macaque homologs of the two hFEFs is still matter of debate

Recent evidence shows that in macaques the FEF is surrounded rostrally by several distinct eye-related areas, including areas 45B, and 45A

Based on comparative considerations, a homology of the dorsal and ventral hFEF with the macaque FEF and area 45B, respectively, is suggested

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Abstract

In non-human primates, at the junction of the prefrontal with the premotor cortex, there is a sector designated as frontal eye field (FEF), involved in controlling oculomotor behavior and spatial attention. Evidence for at least two FEFs in humans is at the basis of the still open issue of the possible homologies between the macaque and the human frontal oculomotor system. In this review article we address this issue suggesting a new view solidly grounded on evidence from the last decade showing that, in macaques, the FEF is at the core of an oculomotor domain in which several distinct areas, including areas 45A and 45B, provide the substrate for parallel processing of different aspects of oculomotor behavior. Based on comparative considerations, we will propose a correspondence between some of the macaque and the human oculomotor fields, thus suggesting sharing of neural substrate for oculomotor control, gaze processing, and orienting attention in space. Accordingly, this article could contribute to settle some aspects of the so-called "enigma" of the human FEF anatomy.

Comparative anatomy of the macaque and the human frontal oculomotor domain

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Abstract

In non-human primates, at the junction of the prefrontal with the premotor cortex, there is a sector designated as frontal eye field (FEF), involved in controlling oculomotor behavior and spatial attention. Evidence for at least two FEFs in humans is at the basis of the still open issue of the possible homologies between the macaque and the human frontal oculomotor system. In this review article we address this issue suggesting a new view solidly grounded on evidence from the last decade showing that, in macaques, the FEF is at the core of an oculomotor domain in which several distinct areas, including areas 45A and 45B, provide the substrate for parallel processing of different aspects of oculomotor behavior. Based on comparative considerations, we will propose a correspondence between some of the macaque and the human oculomotor fields, thus suggesting sharing of neural substrate for oculomotor control, gaze processing, and orienting attention in space. Accordingly, this article could contribute to settle some aspects of the so-called "enigma" of the human FEF anatomy.

Keywords

Frontal eye field; saccades; spatial attention; oculomotor control; area 8; area 45; monkey; human

1. Introduction

In the primate brain, at the junction of the prefrontal with the premotor cortex, there are cortical sectors that play an essential role in the control of oculomotor behavior. In macaques, an oculomotor cortical sector extending over the prearcuate gyrus was first identified by Ferrier (1874) using cortical surface electrical stimulation. Förster (1926), using a similar approach in patients, identified an oculomotor field in the middle frontal gyrus just rostral to the precentral sulcus, which was referred to as "frontal eye field" (FEF). However, the location and boundary of this oculomotor field largely varies in primates, according to the criteria used for its definition. In macaques, at the present time, it is unanimously agreed to define the FEF as the sector from which saccadic eye movements can be evoked with intracortical microstimulation at low current thresholds (see Schall et al., 2017). Based on this criterion, the macaque FEF occupies a restricted sector of the rostral bank of the arcuate sulcus (Bruce et al., 1985; Stanton et al., 1989). In humans, oculomotor fields are mostly defined using functional magnetic resonance imaging (fMRI) as those sectors that activate during the execution of saccadic eye movements. Based on this criterion, most studies provided evidence for two distinct human FEFs (hFEFs), located at different dorso-ventral levels in the superior and in the inferior precentral sulcus, respectively, both located within the limits of area 6 of the Brodmann's architectonic map (1905). These findings raised the question of which of these two fields is the possible homolog of the macaque FEF (located within the prefrontal cortex) and, thus, which is the possible macaque counterpart of the other field. Two main views have been put forward in which the macaque FEF would be the homologue of either the dorsal hFEF, or the ventral hFEF and the other hFEF would correspond to a macaque oculomotor ventral (PMv) or dorsal (PMd) premotor field, respectively. This issue is still debated and is part of the so-called "enigma" of the human FEF anatomy (Tehovnik, 2000; see also Percheron et al., 2015; Schall et al., 2017; Petit and Pouget, 2019), which emerges from comparative anatomical considerations.

The main aim of this review article is to address this issue suggesting for consideration a new position solidly grounded on anatomical and functional evidence of the last ten years. Indeed, it seems quite clear today that, in macaques, the FEF is at the core of a frontal oculomotor domain in which several distinct areas provide the substrate for parallel processing of different aspect of oculomotor behavior. Specifically, we will argue that two caudal ventrolateral prefrontal (VLPF) areas -45A and 45B- are integral part of the frontal oculomotor domain and thus must be considered when attempting to establish homologies between the macaque and the human frontal oculomotor system.

Accordingly, in the next sections we will first describe in detail the anatomical and functional organization of the macaque frontal oculomotor domain. The picture emerging from these data will be then used for comparative considerations on the organization of the corresponding domain of the human brain. Noteworthy, the macaque frontal oculomotor domain, as defined in the present review article, does not include the oculomotor field located in the rostral part of the PMd and referred to as “supplementary eye field” (SEF).

2. The macaque frontal oculomotor domain

2.1 Architecture of the macaque caudal prefrontal cortex

One fundamental requirement for understanding the organization of a cortical region is a reliable anatomic frame of reference for the attribution of data from different experimental approaches to specific cortical entities and, in case, for distinguishing connectionally and functionally distinct areas.

In the macaque brain, the prearcuate gyrus was considered by Brodmann (1905) as a single architectonic area designated as area 8. Subsequent architectonic studies of this region have resulted in markedly different parcellation schemes, in which both the number and the extent of the identified areas vary, raising conflicting interpretations on the architectonic definition of functionally different fields. For example, in most cytoarchitectonic studies of this region (Walker, 1940; Barbas and Pandya, 1989; Petrides and Pandya, 1994) the prearcuate gyrus was subdivided into a dorsal and a ventral subdivision. Thus, the FEF, if defined based on intracortical microstimulation (Bruce et al., 1985), would not have an architectonic counterpart, as it would correspond to a sector of the anterior bank of the arcuate sulcus straddling over the caudalmost part of both the dorsal and the ventral prearcuate area, architectonically defined. However, this question was settled by Stanton et al. (1989), which showed that the FEF, as functionally defined, has indeed an architectonic counterpart, which can be clearly identified based on the presence of relatively large layer V pyramids.

The issue of the architectonic organization of the macaque prearcuate gyrus was re-addressed by Gerbella et al. (2007) in a multimodal architectonic study, based on analysis of cyto-and myelo-architecture and the distribution of specific populations of pyramidal, or non-pyramidal neurons. In full agreement with Stanton et al. (1989), Gerbella et al. (2007) provided multimodal evidence for the architectonic counterpart of the FEF, which was designated as area 8-FEF (Fig. 1). Area 8-FEF can be clearly identified based on the presence of large layer V pyramids, which are also positive for SMI-32 immunoreactivity (ir), heavy myelinization, and a relatively low content of calbindin (CB) immunopositive non-pyramidal neurons.

Rostral to area 8-FEF, Gerbella et al. (2007) identified a distinct architectonic area extending over the prearcuate convexity cortex, as far as the caudal tip of the principal sulcus, which was designated as area 8r (Fig. 1). This area appears to correspond to the myeloarchitectonic area 8Ar defined by Preuss and Goldmann-Rakic (1991). Area 8r is characterized, in general, by a relatively small overall thickness, a relatively thin layer III, a dense and homogeneous layer IV and a layer V populated by densely packed small pyramids. This area is also much less myelinizated and shows a weaker overall SMI-32ir than area 8-FEF.

The cortical sector located ventral to areas 8-FEF and 8r corresponds to a cortical region designated by Petrides and Pandya (1994; 2002) as area 45. This area extends from the ventral part of the anterior bank of the arcuate sulcus to the adjacent prearcuate convexity cortex as far as the inferior frontal sulcus when present. The caudal part of this area, buried within the arcuate sulcus, and the rostral part were designated as areas 45B and 45A, respectively (Fig. 1). Gerbella et al. (2007) found several criteria for considering these two sectors as two distinct architectonic areas. The major identifying cytoarchitectonic feature of area 45B is the presence of large outstanding sparse pyramids in the lower part of layer III, which are also very evident in SMI-32ir. The lack of large pyramids in layer V and a lower myelin content clearly distinguish this area from area 8-FEF. The major identifying architectonic features of area 45A are an evident increase in cell size from the upper to the lower part of layer III - which lacks, however, the outstanding layer III pyramids typical of area 45B - and evident outer and inner Baillarger bands in myelin stained sections. Furthermore, SMI-32 immunopositive pyramids and CB immunopositive non-pyramidal neurons in layer III are significantly denser than in area 45B. Based on some general cytoarchitectonic features, Petrides and Pandya (1994; 2002) proposed that this region, as a whole, is the macaque putative homolog of the corresponding language-related area 45 of the human brain. However, as it will be argued below, both areas 45B and 45A are more likely two distinct eye-related areas, integral part of the frontal oculomotor domain.

Rostral to area 8r, along and within almost the entire extent of the principal sulcus, there is area 46 (Fig. 1). This area has been the object of several architectonic studies (Preuss and Goldmann-Ralkic 1991; Petrides and Pandya 2002) resulting in different parcellation schemes, which, however, always distinguish the dorsal from the ventral part. Finally, rostral to area 45A there is area 12r, which according to Carmichael and Price (1994) occupies most of the rostrocaudal extent of the VLPF ventral to area 46 (Fig. 1). As it will be argued below, the caudal part of dorsal and ventral 46 and of area 12r should be included in the frontal oculomotor domain.

2.2 Connectional and functional features of the frontal oculomotor domain areas

2.2.1 Area 8-FEF

Area 8-FEF is one of the most studied areas of the macaque brain. Its key role in generating saccadic eye movements and modulating attention in space is widely acknowledged and has been the object of comprehensive reviews (e.g., Lynch and Tian, 2006; Schall, 2009; Vernet et al., 2014). Here, we will just highlight some major functional and connectional features of this area, especially those that characterize it as an oculomotor area and could be then used as a benchmark for the assignment of other areas to the frontal oculomotor system. Table 1 provides a summary view of the distribution of some major characterizing functional features within the frontal oculomotor domain. Summary views of the cortical and subcortical connectivity of areas 8/FEF, 45B, 45A and 8r are shown in Figures 2 and 3, respectively.

As noted above, area 8-FEFcorresponds to the cortical sector in which intracortical microstimulation evoke saccades at stimulus currents less than 50 µA (Bruce et al., 1985; Stanton et al. 1989). This area hosts neurons that activate just before the initiation of saccadic eye movements or during fixation. Neurons in this area may have visual receptive fields, some have a combination of both movement-related and visual activity, and others have sustained, memory-related activity (Lynch and Tian, 2006; Schall, 2009). Visually responsive neurons may show shape selectivity (Peng et al., 2008). Functional investigations of this area also showed a gradient in which the amplitude of saccadic eye movements evoked by intracortical microstimulation or coded by individual neurons increases from the ventral to the dorsal part of this area. Area 8-FEF neurons also contribute to selecting the target and shifting attention in space before gaze shifts, even when the target location is signaled by a manual response, reflecting a role of this area in spatial attention (see Schall, 2009). According to the “premotor theory of attention”, spatial attention results from an activation of the same circuits that program eye movements (Rizzolatti et al., 1987). In line with electrophysiological data, fMRI in awake macaques showed that this area activates for visual motion processing (Vanduffel et al., 2001), when executing visually guided saccades (Koyama et al., 2004; Baker et al., 2006; Premereur et al., 2015), memory guided saccades (Kagan et al., 2010), antisaccade tasks (Ford et al., 2009), visual search tasks (Wardak et al., 2010), and when shifting attention in space (Caspari et al., 2015).

The results of connectional studies in which neural tracers were placed selectively in area 8-FEF are summarized in Figures 2 and 3. These studies consistently showed that the ventral to dorsal functional gradient is paralleled by a connectional gradient (Huerta et al. 1987; Stanton et al. 1993;

Schall et al. 1995; Stanton et al. 1995; Gerbella et al. 2010). Specifically, area 8-FEF, as a whole, directly connects to all its neighbor caudal prefrontal areas, including areas 8r, 45B, 45A and the caudal part of areas 46 (dorsal and ventral 46) and 12r. However, areas 45B and caudal 12r appear to be preferentially connected to the ventral part of area 8-FEF, whereas area 45A preferentially to the dorsal part. The dorsal part of area 8-FEF is also connected to a rostral sector of dorsal area 46 (46d). Other frontal connections involve the SEF, located in the rostral part of the PMd, which cooperates with the FEF in the generation of saccadic eye movements and contribute to some higher order aspects of oculomotor behavior (see Lynch and Tian, 2006; Schall 2015). In the parietal cortex, area 8-FEF is tightly connected to the oculomotor lateral intraparietal (LIP) area located in the lateral bank of the intraparietal sulcus, mostly in its ventral part. These connections play a crucial role in the cortical oculomotor network in mediating visuomotor transformations for controlling saccadic eye movements and in the orientation of spatial attention (see Lynch and Tian, 2006; Wardak et al., 2011). In the temporal cortex, the ventral part of area 8-FEF is preferentially connected to inferotemporal sectors of the ventral bank of the superior temporal sulcus (STS) located at higher levels of the ventral visual stream and corresponding to area TEa/m. These sectors are involved in 3D object and action processing (Denys et al., 2004; Nelissen et al., 2011) and activate during the execution of visually guided eye movements (Ward, et al., 2015). Other connections involve more caudal temporal (FST, MST, and TEO) and even extrastriate visual areas (V2, V3, V4, V4t, and V5/MT). In contrast, the dorsal part of area 8-FEF is preferentially connected to superior temporal areas, especially the superior temporal polysensory area (STP), located in the upper bank of the STS, a higher-order multisensory area integrating information within and across modalities (Baylis et al., 1987; Bruce et al., 1981).

A further characterizing connectional feature of area 8-FEF is the projection from the multiform part of the mediodorsal thalamic nucleus (MDmf), which is by far the major source of thalamic input to this area (Huerta et al., 1986; Stanton et al., 1988a; Contini et al., 2010). Indeed, MDmf is a target of dense projections from the superior colliculus (SC) and the reticular part of the substantia nigra (Harting et al., 1980; Ilinsky et al., 1985), hosts neurons displaying presaccadic activity (Sommer and Wurtz, 2004) and is thought a key node in the “oculomotor” basal ganglia circuit (Alexander et al., 1986). A further robust thalamic input originates from a central zone of the medial pulvinar nucleus (Huerta et al., 1986; Stanton et al., 1988a; Contini et al., 2010).

Area 8-FEF is also a source of descending projections to several preoculomotor brainstem structures (Huerta et al. 1986; Stanton et al. 1988a, 1988b; Borra et al., 2013). These projections involve the SC, mostly the superficial and intermediate layers, the pretectum, the nucleus of Darkschewitsch, the ventral periaqueductal gray above the oculomotor (III) and trochlear (IV) nuclei, the mesencephalic reticular formation (MRF) near the interstitial nucleus of Cajal, the pontine reticular formation (PnO), the pontine raphe, the region around the abducens (VI) nucleus, and the nucleus prepositus hypoglossi.

Finally, area 8-FEF is a source of corticostriatal and corticopontine projections providing this area with an access to the basal ganglia and cerebellar oculomotor loops. Striatal projections of area 8-FEF involve a sector of the caudate body hosting neurons displaying saccade-related activity (Hikosaka et al. 1989; 2000) and considered to be the striatal region engaged in the oculomotor basal ganglia circuit. Area 8-FEF also projects to the ventral and caudal part of the subthalamic nucleus where saccade-related neurons were recorded (Matsumura et al. 1992; Isoda and Hikosaka 2008), suggesting engagement in the oculomotor basal ganglia circuits also through the "hyperdirect" basal ganglia pathway (Nambu et al. 1996). Cortico-pontine projections from area 8-FEF involve the dorsomedial and dorsolateral parts of the pontine nuclei, hosting saccade-related neurons and projecting to oculomotor regions of the cerebellar cortex (see, e.g., May 2006; Thier and Möck 2006).

2.2.2 Area 45B

Area 45B corresponds to the sector of the anterior bank of the arcuate sulcus just ventral to the FEF, from which intracortical microstimulation is not effective in evoking saccadic eye movements (at least at stimulus currents less than 50 µA). For this reason, and all the more so considering the proposed homology of this area, together with the adjacent area 45A, with the corresponding language area of the human brain (Petrides and Pandya, 1994; 2002), it is not surprising that area 45B has been virtually neglected by studies of the frontal oculomotor system.

Petrides and Pandya (2002) provided the first description of the cortical connectivity of area 45 based on relatively large tracer injections, involving both areas 45A and 45B considered, all together as a single area. Based on multimodal architectonic evidence for the distinctiveness of areas 45B and 45A, Gerbella et al. (2010) carried out a connectional study specifically aiming to distinguish between the connectivity of these two areas. This study clearly showed that area 45B displays a connectivity pattern distinct from but sharing several characterizing features with area 8-FEF and summarized in Figure 2. Indeed, area 45B is tightly connected to area 8-FEF, mostly the ventral part, with areas 45A and 8r, the caudal part of areas 12r and 46v, and the SEF. Differently from area 8-FEF, area 45B is also connected to more rostral prefrontal sectors and orbitofrontal areas. Area 45B also displays parietal connections, which, as for area 8-FEF, are virtually limited to area LIP, although in its dorsal part, and temporal connections involving the same inferotemporal area TEa/m sector connected to area 8-FEF. Differently from area 8-FEF, area 45B is not connected to more caudal temporal and extrastriate visual areas.

Thalamic afferents to area 45B originate mostly from different subdivisions of nucleus MD, including a robust projection from MDmf and from a zone of the medial pulvinar like that projecting to area 8-FEF (Contini et al., 2010). Furthermore, this area richly projects to the SC, involving the intermediate, but also the superficial layers, and to other brainstem preoculomotor regions such as the rostral MRF, including the region around the III and IV nuclei, the ventrally adjacent PnO and the pontine raphe (Borra et al., 2015). As for area 8-FEF, area 45B also projects to the oculomotor dorsomedial and dorsolateral parts of the pontine nuclei and to the oculomotor sectors of the caudate body and subthalamic nucleus. Area 45B also projects to the caudate tail, possibly in a sector target of projections from the temporal cortex (Van Hoesen et al. 1981), hosting neurons involved in guiding saccades based on “what” and “where” object-related visual information (Yamamoto et al. 2012). Finally, area 45B is a target of robust projections from the amygdala (Gerbella et al. 2014).

Electrophysiological studies have been so far limited to the sensory properties of area 45B neurons. Janssen and colleagues (Theys et al 2012; Caprara et al., 2018; Caprara and Janssen, 2020) have specifically studied the visual properties of these neurons and provided evidence for 2D and 3D shapes selective neurons, suggesting a role in guiding saccades and in object processing. 2D shape selective neurons in the location of area 45B were also found by Peng et al. (2008). Furthermore, fMRI data have revealed area 45B activation for the observation of objects, faces, and actions (Denys et al., 2004; Nelissen, et al, 2005; Tsao et al., 2008). All together, these sensory properties of area 45B appear to reflect both dorsal and ventral visual stream input. The possible role of area 45B neurons in oculomotor control has not been so far looked for in electrophysiological studies. However, Premereur et al. (2015) using fMRI very clearly showed that area 45B activates during the execution of saccades. An activation in the location of area 45B during the execution of saccades has been observed in the fMRI study of Baker et al (2006) and 2-deoxyglucose data have shown that the prearcuate sector activated by the execution of saccadic eye movements extends ventrally to the FEF, in the location of area 45B (Moschovakis et al. 2004).Other fMRI studies have shown that area 45B together with area 8-FEF activates during memory guided saccade tasks (Kagan et al., 2010), visual search tasks (Wardak et al., 2010), and when shifting attention in space (Caspari et al., 2015).

All together, these data seriously challenge the proposed homology of the macaque area 45B with at least part of the corresponding language-related area of the human brain and strongly suggest that this area is in all respects an oculomotor area connectionally and functionally similar to the ventral part of area 8-FEF. Specifically, area 45B could be viewed as a “preoculomotor” area, in which rostral prefrontal, orbitofrontal, inferotemporal, and amygdalar inputs guide the exploration of visual scenes for the perception of objects, actions, and faces (Gerbella et al. 2010; Gerbella, et al. 2014) and contribute to eye-hand coordination (Caprara et al 2020).

2.2.3 Area 45A

Until its identification as a distinct area (Petrides and Pandya 1994), most of the cortical sector corresponding to area 45A was commonly considered as part of a larger region, mostly overlapping with Walker’s area 12, involved in object and faces encoding in working memory (Levy and Goldman-Rakic 2000) or in conditional learning based on object identity (Passingham et al. 2000). Studies carried out over the last fifteen years, however, have pointed out connectional and functional features, which clearly distinguish this area from all the other VLPF areas. Indeed, as summarized in Figure 2, tracer injections selectively placed in area 45A (Gerbella et al., 2010; Saleem et al., 2014) show that this area is robustly connected to area 8-FEF, the adjacent areas 45B, 8r, caudal 46 and 12r, and the SEF. Differently from area 45B, connections with area 8-FEF primarily involve the dorsal part of this area. Other rich connections involve more rostral areas including the frontopolar area 10 and the rostral part of dorsal area 46, which is also connected to the dorsal area 8-FEF. Area 45A displays relatively weak connections with the parietal cortex but is unique among all the various VLPF areas in being a target of temporal input from regions of the superior temporal gyrus involving area STP and rostral and caudal auditory parabelt areas.

Thalamic afferents from MDmf are relatively weak, but those from the central zone of the medial pulvinar, which projects also to areas 45B and 8-FEF, are robust (Contini et al., 2010). As for areas 8-FEF and 45B, area 45A is a source of projections to the SC, involving the intermediate, but also the superficial layers, and to other brainstem preoculomotor regions including the rostral MRF, also involving the parabigeminal nucleus and the ventrally adjacent PnO (Borra et al., 2015). Additional projections to the brainstem involve the oculomotor dorsomedial and dorsolateral parts of the pontine nuclei. As for areas 8-FEFand 45B, area 45A projects to the oculomotor sectors of the caudate body and subthalamic nucleus and, as area 45B, to the oculomotor zone of the caudate tail. Finally, as area 45B, area 45A is a target of a robust amygdalar input (Gerbella et al., 2014).

Electrophysiological studies of Romanski and colleagues (see Romanski 2004; 2007; Romanski and Averbeck, 2009) showed that in the correspondence of area 45A, there are neurons responsive to auditory, visual, or combined auditory and visual communication stimuli, likely reflecting the input from auditory-related temporal areas and the higher-order multisensory area STP, hosting visual neurons coding different types of biological motions (see, e.g., Oram and Perrett 1994;

Barraclough et al. 2005). Furthermore, fMRI data showed that area 45A activates for the observation of faces (Tsao et al. 2008) and for the observation of actions made by others (Nelissen et al. 2005), an aspect of visual information of behavioral relevance in animals with a complex social life, such as primates. These functional data suggest a role in communication behavior for area 45A, in apparent agreement with the proposed homology of this area with the corresponding language-related area of the human brain. However, the above-reviewed connectivity pattern of area 45A shows a tight linkage of this area with frontal and subcortical oculomotor centers. Indeed, though the motor properties of area 45A neurons have not been so far investigated in detail, fMRI studies show that this area (Baker et al., 2006; Premereur et al 2015) activates together with areas 8-FEF and 45B during the execution of saccades. Area 45A also activates as areas 8-FEF and 45B during visual search tasks (Wardak et al., 2010) and when shifting attention in space (Caspari et al., 2015). Indeed, area STP, one major source of input to area 45A, is involved in processing various forms of biological motion, including the direction of gaze and head, which may be relevant in understanding where the conspecifics are fixating (Carey et al., 1997; Jellema et al., 2000; Mistlin and Perrett, 1990) and is involved in the integration of audiovisual communication signals (Barraclough et al., 2005; Chandrasekaran and Ghazanfar, 2008; Dahl, et al., 2009). Furthermore, reversible inactivation of the posterior STP severely disrupts gaze-following behavior (Roy et al., 2014).

All together, these data indicate that area 45A, as area 45B, is integral part of the frontal oculomotor domain. Specifically, connections with area STP, the dorsal part of area 8-FEFand the amygdala could represent the neural substrate for a role in communication behavior of gaze direction, an important communicative signal in social interactions (e.g., Emery 2000; Ghazanfar et al. 2006).

2.2.4 Area 8r

Cytoarchitectonic area 8r, basically corresponding to myeloarchitectonic area 8Ar of Preuss and Golmann-Rakic (1991), still today is hardly recognized as a distinct prefrontal area, as in most studies this sector has been considered together with the FEF or the caudal periprincipal cortex. However, there is clear connectional evidence, summarized in Figure 2, for the distinctiveness of this area from both areas 8-FEFand 46 (Gerbella et al 2010; Borra et al., 2017). This area has a very high prefrontal connectivity, mostly with area 8-FEF and is also connected to the SEF. Unlike the adjacent areas 8-FEF, 45B, and 45A, it possesses quite a low temporal connectivity, limited to areas STP, MT, FST, and V4. The only robust extrafrontal connection is with the dorsal and the ventral part of LIP, differently from area 8-FEF, which is preferentially connected to ventral area LIP (Medalla and Barbas, 2006; Gerbella et al 2010; Borra et al., 2017).

Area 8r is a target of thalamic projections from MDmf and medial pulvinar (Barbas et al., 1991) and a source of descending projections to the SC, involving the intermediate, but also the superficial layers, and to other brainstem preoculomotor regions including the rostral MRF, also involving the parabigeminal nucleus and the ventrally adjacent PnO (Borra et al., 2015). Additional projections involve the oculomotor dorsomedial and dorsolateral part of the pontine nuclei and the oculomotor sector of the caudate body (Fig. 3).

Very few electrophysiological studies have so far attempted to describe the functional properties of area 8r neurons, so that the exact role of this area in oculomotor control remains to be fully assessed. Early studies showed that in this cortical sector there are visually responsive neurons with visual receptive fields whose eccentricity tends to increase from the ventral to the dorsal part (Suzuki and Azuma, 1983) and, in the dorsal part, auditory responsive neurons (Azuma and Suzuki, 1984). A recent study showed that in this area there are neurons with pre-saccadic activity and that visual responses to some extent resemble those of areas MT and V4 (Bullock et at al., 2017). Other studies showed that this area hosts neurons involved in vergence and ocular accommodation and in the sensorimotor transformations required for these eye movements (Gamlin and Yoon 2000) and neurons modulated by shift of attention in space (Kodaka et al., 1997). Area 8r also hosts a class of direction selective visually responsive neurons, which appear to play a role during the execution of a delayed memory direction discrimination task (Zaksas and Pasternak 2006).

As expected from electrophysiological data, fMRI studies showed that this cortical sector activates during the execution of saccadic eye movements (Baker et al., 2006; Premereur et al., 2015), also when memory guided (Kagan et al., 2010) and visual search tasks (Wardak et al., 2010). Furthermore, area 8r appears to be part of the frontal cortical region activated when shifting attention in space (Caspari et al., 2015).

These data suggest that area 8r represents a further independent field of the frontal oculomotor domain, architectonically, connectionally, and functionally distinct from the FEF and the caudal part of area 46.

2.2.5 Caudal area 46

Architectonic area 46, as originally defined by Walker (1940), is a functionally and connectionally heterogeneous region extending over almost the entire rostro-caudal extent of the principal sulcus (PS) and the immediately adjacent convexity cortex and is involved in several aspects of executive control of behavior (Tanji and Hoshi 2008). Connectional studies first of all suggest a subdivision of this area into a dorsal part (46d) primarily connected with superior and medial parietal and dorsal premotor areas and a ventral part (46v) primarily connected to inferior and opercular parietal and ventral premotor areas (for review, see Tanji and Hoshi, 2008).

Recent data provided evidence for rostrocaudal connectional gradients in both 46d and 46v (Gerbella et al., 2013; Borra et al., 2017). In both these subdivisions, the rostral half primarily connects to other prefrontal areas, with additional connections of 46v with inferotemporal areas and 46d with area STP. The middle part is characterized by connections to parietal and frontal arm/hand-related areas, and the caudal part to frontal and parietal oculomotor areas. Specifically, caudal 46d and 46v connect to areas 8-FEF (mostly the dorsal and the ventral part, respectively), 8r, and the SEF. Caudal 46v also connects to areas 45B and caudal 12r. In the parietal cortex, both caudal 46d and 46v are connected to area LIP, but 46d displays additional connections with area V6A (mostly the ventral part) and the medial parietal area PGm. Additional connections of area 46v involve inferotemporal areas and areas FST and MT.

Caudal area 46 is a target of thalamic projections from MDmf and medial pulvinar (Barbas et al., 1991) and is a source of projections to the brainstem involving the SC, the MRF and the PnO (Borra et al., 2015). Other projections involve the oculomotor zone of the pontine nuclei and of the caudate body.

These connectivity patterns suggest an affiliation of caudal 46d and 46v with the frontal oculomotor system. Indeed, this caudal part of area 46 has been designated as “prefrontal eye field” (PFEF) by Lynch and Tian (2006).

Neurons in caudal 46 are active in tasks requiring oculomotor responses (e.g., Boch and Goldberg 1989; Averbeck et al. 2006; Ichihara-Takeda and Funahashi 2007). Furthermore, they show pre-saccadic activity (Funahashi et al., 1991), code visual cue location or saccade direction in spatial working memory tasks (Funahashi et al., 1990; Takeda and Funahashi, 2002), are active during delayed anti-saccade tasks (Funahashi et al., 1993), and interact with area LIP during the performance of an oculomotor delayed response (Chafee and Goldman-Rakic 2000). Finally, they appear to contribute to the known role of area 8-FEF in top-down control of spatial attention based on knowledge and goals, crucial for stimulus selection and voluntary orientation of spatial attention (Thompson and Bichot 2005; Ibos et al. 2013).

As expected from these data, fMRI studies showed that caudal 46 is part of the cortical region that activates during the execution of saccadic eye movements (Baker et al., 2006; Premereur et al., 2015), also when memory guided (Kagan et al., 2010), visual search tasks (Wardak et al., 2010) and shifting attention in space (Caspari et al., 2015).

2.2.6 Caudal area 12r

Area 12r, is a well-known target of projections from higher-order ventral visual stream areas of the inferotemporal cortex (Webster et al., 1994) and is considered to play an important role in higher-order aspects of nonspatial information processing (Levy and Goldman-Rakic, 2000; Passingham et al., 2000; Tanji and Hoshi, 2008).

Connectional studies of this area provided evidence for a rostrocaudal connectional gradient similar to that observed in area 46 (Gerbella et al., 2010; Borra et al., 2011; Saleem et al., 2014). The rostral 12r displays predominant connections with other prefrontal and orbitofrontal areas and additional ones with the fundus and the upper bank of the STS. The middle part is connected to other prefrontal and orbitofrontal areas, to inferior and opercular parietal and ventral premotor hand-related areas and to inferotemporal areas; the caudal part to frontal oculomotor and inferotemporal areas. Specifically, caudal 12r displays connections with neighbor areas caudal 46v and 45A, with areas 8r and 45B and with area 8-FEF (mostly the ventral part). Weak connections also involve the SEF. The only significant extrafrontal connections involve inferotemporal area TEa/m sectors overlapping with those projecting to areas 8-FEF and 45B. Furthermore, caudal 12r also projects to superficial and intermediate layers of the SC, to the MRF and the PnO and to the oculomotor zones of the pontine nuclei and of the caudate body (Borra et al., 2015).

Accordingly, these data suggest for caudal area 12r a role in nonspatial information processing related to oculomotor control.

2.3 Summary view

Data reviewed above, provide strong evidence for a picture of the frontal oculomotor domain in which the FEF is surrounded rostrally by several distinct oculomotor areas. These areas connect with one another, to the FEF and the SEF, and are sources of descending projections to brainstem oculomotor structures. This picture to some extent resembles that of the frontal skeletomotor cortex in which a primary motor area is surrounded rostrally by a series of interconnected premotor areas, which are sources of descending motor projections to the spinal cord (see, e.g., Rizzolatti and Luppino, 2001; Picard and Strick, 2001). Thus, as for the skeletomotor system, the organization of the frontal oculomotor system provides the neural substrate for a parallel processing of different aspects of oculomotor behavior.

Indeed, connectional and functional data suggest a preferential involvement of some areas of this domain in different, partially segregated, functionally specialized large-scale cortical networks (Fig. 4; see Borra and Luppino, 2019). Specifically, the ventral part of area 8-FEF, together with area

45B and likely caudal 12r, appears to be preferentially involved in a large-scale temporo-parieto-frontal network also involving areas LIP and caudal TEa/m, in which visuospatial dorsal visual stream information and ventral visual stream information on objects and actions could be used for guiding small-amplitude saccades. Furthermore, the dorsal part of area 8-FEF, together with area 45A, appears to be preferentially involved in a large-scale temporo-parieto-frontal network, involving also areas LIP and STP and a rostral sector of area 46d, which could provide the substrate the role of gaze position and eye movements in social behavior (Ghazanfar et al., 2006; Shepherd, 2010).

In the context of the present review article, it is noteworthy that the involvement of the macaque areas 45B and 45A in the frontal oculomotor domain raises the issue, which will be addressed in the next section, of which are the possible counterparts of these areas in the human brain.

3 Comparative anatomy of the frontal oculomotor domain

3.1 FEFs in the human brain

Localization and functions of frontal oculomotor fields in humans have been mostly studied using fMRI during the execution of different types of oculomotor tasks. In most of these studies (for reviews, see Gosbras et al., 2005; Amiez and Petrides, 2009; Vernet et al., 2014; Schall et al., 2017; Petit and Pouget, 2019) preparation and execution of saccadic eye movements activate two cortical sectors located at the junction of the prefrontal with the premotor cortex. One is located more dorsally in the superior precentral sulcus, close to the intersection with the superior frontal sulcus, the other is located more ventrally in the dorsal ramus of the inferior precentral sulcus (Fig. 5). Both these two oculomotor fields activate during the execution of either smaller or larger amplitude saccades (Grosbras, 2016) and also activate during tasks requiring covert attentional shift suggesting their involvement not only in saccades generation but also in spatial attention, as expected from the premotor theory of attention (Rizzolatti et al., 1987).

Thus, at least as far as we can learn from fMRI studies, the dorsal and the ventral hFEF appear functionally quite similar with one another and to the macaque FEF. These similarities, as well as the location of both these fields within the limits of Brodmann's area 6 are at the origin of the still debated issue of which of them is the counterpart of the macaque FEF (see for review and discussion of this issue, Amiez and Petrides, 2009; Schall et al., 2017; Petit and Pouget, 2019). Most studies in this field have favored the hypothesis that the dorsal hFEF is the human counterpart of the macaque FEF. However, it has been proposed to consider also the possibility of a homology of the ventral hFEF with the macaque FEF. Both these positions share the hypothesis that the other hFEF is the counterpart of an oculomotor field located in either the ventral, or the dorsal postarcuate premotor cortex of the macaque brain.

As it will be argued in the next section, the possibility that the macaque postarcuate premotor cortex hosts a pure oculomotor field, functionally and connectionally similar to the FEF, so that it could represent the possible counterpart of one of the two hFEFs, appears quite unlikely.

3.2 Is there any macaque postarcuate premotor eye field akin to the FEF?

The idea that the macaque premotor cortex hosts a FEF homolog to one of the two hFEFs is non-univocal and, in our opinion, mistakes the real functional organization of this region.

Evidence for this idea has been developed based mostly on the observations of Fuji et al. (1998; 2000), which found two relatively restricted zones in the premotor cortex in which intracortical microstimulation evoked saccadic eye movements, one located in the PMv on the gyral convexity cortex, the other in the PMd, close to the superior arcuate sulcus. Saccadic eye movements evoked by intracortical microstimulation were also observed by Neromyliotis and Moschovakis (2017) in the posterior bank of the inferior arcuate sulcus, in the dorsalmost part of the PMv. It is noteworthy that saccadic eye movements evoked in PMv were goal-directed (Fuji et al., 1998), those evoked in the postarcuate bank were ipsiversive (Neromyliotis and Moschovakis, 2017) and those evoked in the PMd were contraversive (Fuji et al., 2000). In all these fields there are neurons showing saccade-related activity (Fujii et al., 1998; 2000; Neromyliotis and Moschovakis 2018). Furthermore, using fMRI, Koyama et al. (2004) found that the frontal region activated by the execution of saccadic eye movements extends from the FEF caudally, involving the depth of the spur of the arcuate sulcus and Savaki et al (2015), using metabolic autoradiographic methods, observed activation of the entire extent of the posterior bank of the arcuate sulcus for saccadic eye movement execution. Baker et al (2006) using fMRI observed in one out of two subjects an activation of the PMd cortex close to the arcuate sulcus during the execution of saccadic eye movements, in a subject in which there was an activation also of the primary motor cortex, suggesting that the PMd activation reflected an associated somatomotor behavior. Finally, it is noteworthy that there also studies in which saccades execution (Premereur et al 2015) or visual search (Wardak et al, 2010) activated prearcuate oculomotor, but not postarcuate premotor areas.

All together, these data suggest that in the macaque premotor cortex oculomotor activity is quite distributed and heterogeneous rather than localized to a specific field functionally akin to the FEF.

Actually, electrophysiological evidence since the eighties of the last century has clearly shown that the primate premotor cortex, except for the SEF, is primarily involved in skeletomotor control (see, e.g., Rizzolatti and Luppino 2001; Picard and Strick, 2001). Specifically, in the PMv, the gyral convexity cortex corresponding to area F4 is involved in controlling arm, neck and oro-facial movements, the posterior bank of the inferior arcuate sulcus corresponding to area F5 is primarily involved in controlling hand actions, and the PMd sector close to the superior arcuate sulcus (F2vr and F7) is involved in controlling reaching and reaching-grasping movements. Indeed, Fujii et al. (2000) and Neromyliotis and Moschovakis (2018) reported that premotor neurons displaying saccade-related activity are either intermingled with arm-related neurons or show also arm-related activity.

Furthermore, connectional studies show that these above-mentioned premotor fields could be directly connected to the primary motor cortex and to somatomotor posterior parietal areas of the superior and inferior parietal lobule and are all not connected with the FEF and area LIP (see, e.g., Rizzolatti and Luppino 2001; Caminiti et al., 2017). F5 and F2vr are also sources of projections to the cervical spinal cord (Borra et al., 2010; Morecraft et al., 2019). Thus, the connectivity patterns of these fields are clearly unrelated to the cortical oculomotor networks centered on the 8-FEF/LIP circuit.

In this context, it should be noted that arm-related activity of PMd and PMv neurons can be modulated by gaze direction suggesting combination of retinal and eye position signals for target localization and a role of these neurons in the neural mechanisms underlying eye-hand coordination. These neuronal properties have been observed in areas F4 (Mushiake et al., 1997), F5 (Lehmann and Scherberger, 2013), and F2 (Boussaoud and Bremer, 1999; Jouffrais and Boussaoud, 1999), as well as in connected posterior parietal areas including areas V6A (Gamberini et al., 2020), PG and Opt (Battaglia-Meyer et al., 2007) and AIP (Lehmann and Scherberger, 2013). Furthermore, the described projections from PMd and PMv to the SC (Borra et al., 2014; Distler and Hofmann, 2015) could convey signals used for controlling orienting behavior to the targets of object-oriented actions and for the eye-hand coordination necessary for appropriate hand-object interactions.

In sum, gaze or eye movement-related activity in the premotor cortex appears to be fully integrated with visual, somatosensory and motor signals for the eye-arm coordination required to reach for visual targets, which was the original interpretation given even by the authors of the studies on which the idea of a “premotor FEF” has been based (Fujii et al., 1998; 2000; Neromyliotis and Moschovakis 2017). Hence, the possibility that one of the two hFEF is equivalent to a macaque premotor eye field seems quite unlikely. This appears even truer if it is considered that in humans gaze orientation modulates brain activity during planning and execution of hand movements in a hPMd sector, but not in the hFEFs (Baker et al. 1999), suggesting homologies of the macaque PMd with the hPMd and not with one of the two hFEF. Furthermore, fMRI data in humans (Makino et al., 2004) showed that visual search activates both the hFEFs, but not the premotor cortex, similarly to what observed in macaques (Wardak et al., 2010).

3.3 A new proposal

The lack in the macaque premotor cortex of an equivalent of one of the two hFEFs leaves open the questions of whether and where in the macaque frontal lobe there are counterparts of both the hFEFs. In this section we will address this issue based on anatomical and functional evidence for an oculomotor frontal domain in the macaque.

In the view proposed in Figure 6 the possible human homologue of the macaque FEF is the dorsal hFEF. Several topological considerations point to this direction. First, Amiez et al. (2006) using fMRI found that a visuomotor hand conditional task activates a dorsal premotor sector localized in the dorsal branch of the superior precentral sulcus, near the caudal end of the superior frontal sulcus, close but distinct from the dorsal hFEF, suggesting homology of this premotor sector with the macaque PMd. This study also showed that the dorsal hFEF, as the macaque FEF, is at about the same horizontal level of the hand representation of the primary motor cortex. Furthermore, Fornia et al. (2018) using surface cortical electrical stimulation provided evidence for a ventral premotor hand field located in the precentral gyrus caudal to the location of the dorsal hFEF and rostral to the hand field of the primary motor area. Based on these and other data of the same group (Fornia et al., 2020; Simone et al., 2020), it has been suggested that this premotor hand field is the possible homolog of the macaque PMv hand field of area F5, which is located just caudal to the FEF and at a similar dorsoventral level of the hand field of the primary motor area F1. Finally, Alvarez et al. (2010) showed that the execution of vergence eye movements activates a sector located rostral to the dorsal hFEF and Petit et al. (1997) showed that smooth pursuit eye movements activate a relatively small sector located ventral and lateral to the dorsal hFEF. The first sector could be equivalent, at least in part, to the macaque area 8r, which hosts neurons that activate during the execution of vergence eye movements and is located just rostral to the FEF, whereas the second one could be the equivalent of the smooth pursuit eye field (SEM) ventrally and caudally adjacent to the FEF (see Lynch and Tian 2006). Against this view, it has been argued that the anterior bank of the superior precentral sulcus, where the dorsal hFEF is located, is within the limits of Brodmann’s area 6. However, Rosano et al. (2003) showed that this sector is granular and displays distinctive chemoarchitectonic features, such as large SMI-32 immunopositive neurons in layer V and dense CB immunopositive neurons in layers II and upper III, whereas more rostrally CB immunopositive neurons are dense over the entire extent of layer III. These features are quite similar to those observed in the macaque FEF (Gerbella et al., 2007).

As far as the ventral hFEF is concerned, we suggest a possible homology of this field with the macaque area 45B. As reviewed above, this area appears to be functionally and connectionally quite similar to the FEF, which is a prerequisite for the candidacy of this field for being the possible equivalent of the ventral hFEF. Furthermore, the ventral hFEF is located below the dorsal hFEF and just rostral to a PMv zone where both hand and oro-facial movements are represented (Fornia et al 2018). Indeed, the macaque area 45B is located just ventral to the FEF and rostral to the hand and face-mouth representation of the PMv area F5. Thus, in the human precentral sulcus eye movement related zones are just rostral and distinct from hand-related ones, exactly as in the macaque inferior arcuate sulcus (Premereur et al., 2015)

Against this view is that fMRI studies usually localize the dorsal and the ventral hFEF as two separated distinct fields, whereas in macaque area 45B is adjacent to the FEF. However, in these studies the localization of activation foci is usually indicated with the coordinates of the local maxima with reference to a template brain and, thus, does not reflect its precise location and effective extent in each subject. Furthermore, activation foci observed for a specific task do not necessarily involve the entire extent of a given area. Finally, there are studies in which group analysis of changes in BOLD signals during the execution of saccadic eye movements (Heide et al., 2001; Petit et al 2009; Hagler et al., 2007; Gosbras et al., 2005) or shifting attention in space (Ikkai and Curtis, 2008) shows a single precentral activated sector extending over the location of both the dorsal and the ventral hFEF. As for the dorsal hFEF, also the ventral hFEF is located within Brodmann’s area 6. The architecture of this cortical sector has not been so far studied in detail. However, the caudalmost part of the middle frontal gyrus was found architectonically distinct from the precentral cortex in other classical architectonic studies (Von Economo and Koskinas, 1925; Sarkissov et al., 1955) and in more recent multimodal chemoarchitectonic studies (Rosano et al., 2003). It is thus possible that, as for the dorsal hFEF, the ventral hFEF has an architectonic counterpart.

If the ventral hFEF, located in the inferior precentral sulcus, is the possible counterpart of the macaque area 45B, then it could be expected that cortical sectors located rostral to the ventral hFEF are the counterpart of the macaque area 45A. Different lines of evidence suggest that the cortex buried in the caudal part of the inferior frontal sulcus and at its junction with the inferior precentral sulcus (inferior frontal junction) hosts cortical sectors corresponding to the macaque area 45A.

First, Ikkai and Curtis (2008) have reported that attentional shifts with or without eye movements (overt or covert) activate a cortical sector involving the superior and the inferior precentral sulcus and extending also in the caudal part of the inferior frontal sulcus. Furthermore, Bristow et al. (2007) and Hooker et al (2003) observed activation at the inferior frontal junction or in the inferior frontal gyrus for gaze perception and attentional shifts guided by changes in gaze direction (see also Grosbras et al., 2005, Nummenmaa and Calder, 2009). Finally, Ishai et al. (2005) and Tsao et al. (2008) found that face perception activates cortical sectors in the caudal part of the right inferior frontal sulcus. Interestingly, Chan and Downing (2011) found that the activation in the inferior frontal junction during faces observations significantly decreases when the eyes are masked.

One possible objection to this proposed equivalence is that activation foci within the inferior frontal sulcus have been in some cases attributed to Brodmann's area 44 and 45, usually considered to correspond to the language-related Broca's region. However, it is noteworthy that as also argued above, Brodmann's map appears today not adequate for explaining the complex anatomical and functional organization of the human cerebral cortex. Indeed, Amunts et al. (2010) provided evidence for a much more complex subdivision of the Broca's region in which there are at least four distinct architectonic areas located in the caudal part of the inferior frontal sulcus and at the inferior frontal junction. Thus, the human cortical sectors possibly equivalent to the macaque area 45A could be very well distinct from language-related cortical sectors.

4. Concluding remarks

It is largely agreed in comparative neuroscience that primates share common principles of cortical organization, which have been likely conserved along the various lineages that have differentiated during primate evolution. Indeed, primates display similar layouts of homologous sensory, motor, and association areas organized in similar sensorimotor domains, which, to a large extent, can be identified even in prosimians (Kaas and Stepniewska, 2016).

In line with this view, in the present article we have reviewed data providing evidence for a caudal prefrontal domain of distinct oculomotor areas in the macaque brain and based on comparative considerations we have suggested the existence of a corresponding domain in the human brain.

Obviously, the proposal of the organizational homologies between the macaque and the human frontal oculomotor domain shown in Figure 6 does not necessarily imply that these two domains host the same number of areas. Indeed, in the evolution of the lineage leading to *Homo sapiens*, there have been substantial changes in brain size and organization, which represent the neural substrate for the increase in complexity of the structural and functional organization of the human cerebral cortex and the emergence of higher order, human specific cognitive functions. Accordingly, humans and non-human primates appear to share neural circuits and mechanisms for basic gaze-following behavior, which, in humans, could have been the foundation for more sophisticated social skills, such as mutual awareness of shared mental states (Shepherd, 2010).

In this context, there is evidence for other frontal sectors that activate together with the hFEFs in a variety of attentional tasks which could represent the counterpart of other prefrontal areas of the macaque, such as caudal areas 46 and 12r, or evolutionarily new human-specific zones, which could have differentiated from phylogenetically older eye-related areas. For example, when subjects detected a previously memorized target image, Patel et al. (2015) observed in addition to the dorsal hFEF and the inferior precentral sulcus an activation in a relatively anterior part of the IFS and suggested an equivalence of this sector with the macaque area 46. Furthermore, Michalka et al (2015) found that an auditory attentional task activates two frontal sectors, one located in between the dorsal and the ventral hFEF, the other in the caudal IFS. It is possible that the former sector corresponds to auditory-responsive dorsal prearcuate sectors of the macaque (Azuma and Suzuki, 1984) and the latter coincides with the gaze- and face-responsive IFS sector, or is a new sector differentiated from the macaque area 45A.

Thus, it appears clear today that if we want to go deeper in these kind of comparative anatomy issues it is necessary to exploit the potential of multimodal architectonic approaches in providing fine-scale anatomical subdivisions for more precise anatomo-functional correlations. Indeed, this approach has been useful for the definition of the anatomical correlate of the dorsal hFEF (Rosano et al 2003) and could be then useful in the future for the definition of the anatomical correlate of the various human frontal oculomotor fields.

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Figure legends

Figure 1. Upper part: architectonic subdivision of the macaque caudal prefrontal cortex based on the studies of Preuss and Goldmann-Rakic (1991), Carmichael and Price (1994), and Gerbella et al (2007). Lower part: photomicrographs of representative fields from Nissl-stained (upper row), myelin-stained (middle row), and SMI-32 immunoreacted (lower row) sections showing architectonic features of areas 8-FEF, 8r, 45B, and 45A. Scale bar shown in the photomicrographs of area 8-FEF = 500 µm and applies to all photomicrographs in the same row. Abbreviations: C = central sulcus; IA = inferior arcuate sulcus; iB = inner Baillarger band; IF = inferior frontal sulcus; IP = intraparietal sulcus; L = lateral sulcus; Lu = lunate sulcus; oB = outer Baillarger band; P = principal sulcus; SA = superior arcuate sulcus; SF = superior frontal sulcus; ST = superior temporal sulcus.

Figure 2. Summary view of the cortical connections of the dorsal and the ventral part of area 8-FEF, 8r, 45B, and 45A, shown in drawing of the hemisphere in which the arcuate, intraparietal, and superior temporal sulci are unfolded. Abbreviations as in Figure 1.

Figure 3. Summary view of the subcortical connections of the dorsal and the ventral part of area 8-FEF, 8r, 45B, and 45A. AC = anterior commissure; MD = mediodorsal thalamic nucleus; SGI = stratum griseum intermediale; SGS = stratum griseum superficiale; SO = stratum opticum.

Figure 4. Lateral view of a hemisphere of the macaque brain showing a simplified view of the large-scale cortical networks involving the dorsal (dashed lines) and ventral (continuous lines) part of area 8-FEF. The SEF, which is connected to both parts of area 8-FEF and with all the other oculomotor frontal areas in not shown. Areas ventral and dorsal 46 and 8r are connected to both the dorsal and ventral part of area 8-FEF. Abbreviations as in Figure 1.

Figure 5. Location of the dorsal and the ventral hFEF shown on an enlarged view of the precentral and middle frontal gyrus of the left hemisphere of the MNI Colin-27 brain taken from the Julich-Brain Cytoarchitectonic Atlas (https://jubrain.fz-juelich.de/apps/cytoviewer2/cytoviewer-main.php#). The ventral hFEF, usually observed in fMRI studies within the inferior precentral sulcus (iPrC) is indicated by an arrow. sPrC = superior precentral sulcus. Other abbreviations as in Figure 1.

Figure 6. Comparative view of the macaque and human frontal oculomotor domain and of the nearby skeletomotor fields. Possibly corresponding oculomotor fields and possibly corresponding skeletomotor fields are indicated in both the macaque and the human brain with the same number and the same letter, respectively. Fields buried within sulci are indicated by arrows.

Table 1. Summary view of the main functional features that characterize areas 8-FEF, 45B, 45A, 8r, and caudal 46 as components of the macaque frontal oculomotor domain.

		8-FEF	**45B**	**45A**	**8r**	**caudal 46**
Single unit recording	Eye movement-related	+ [1]	**?**	**?**	+ [2]	+ [4]
	Shift of attention in space	+ [1]	**?**	**?**	+ [3]	+ [5]
fMRI	Saccades	+ [6]	+ [6]	+ [6]	+ [6]	+ [6]
	Memory guided saccades	+ [7]	+ [7]	**?**	+ [7]	+ [7]
	Visual search	+ [8]	+ [8]	+ [8]	+ [8]	+ [8]
	Spatial attention	+ [9]	+ [9]	+ [9]	+ [9]	+ [9]

? = to be determined; 1= see refs. in Shall (2009); 2 = e.g., Gamlin and Yoon (2000); 3 = Kodaka et al. (1997); 4 = e.g., Boch and Goldberg (1989); 5 = e.g., Funahashi et al. (1990); 6 = e.g., Premereur et al. (2015); 7 = Kagan et al (2010); 8 = Wardak et al. (2010); 9 = Caspari et al. (2015)

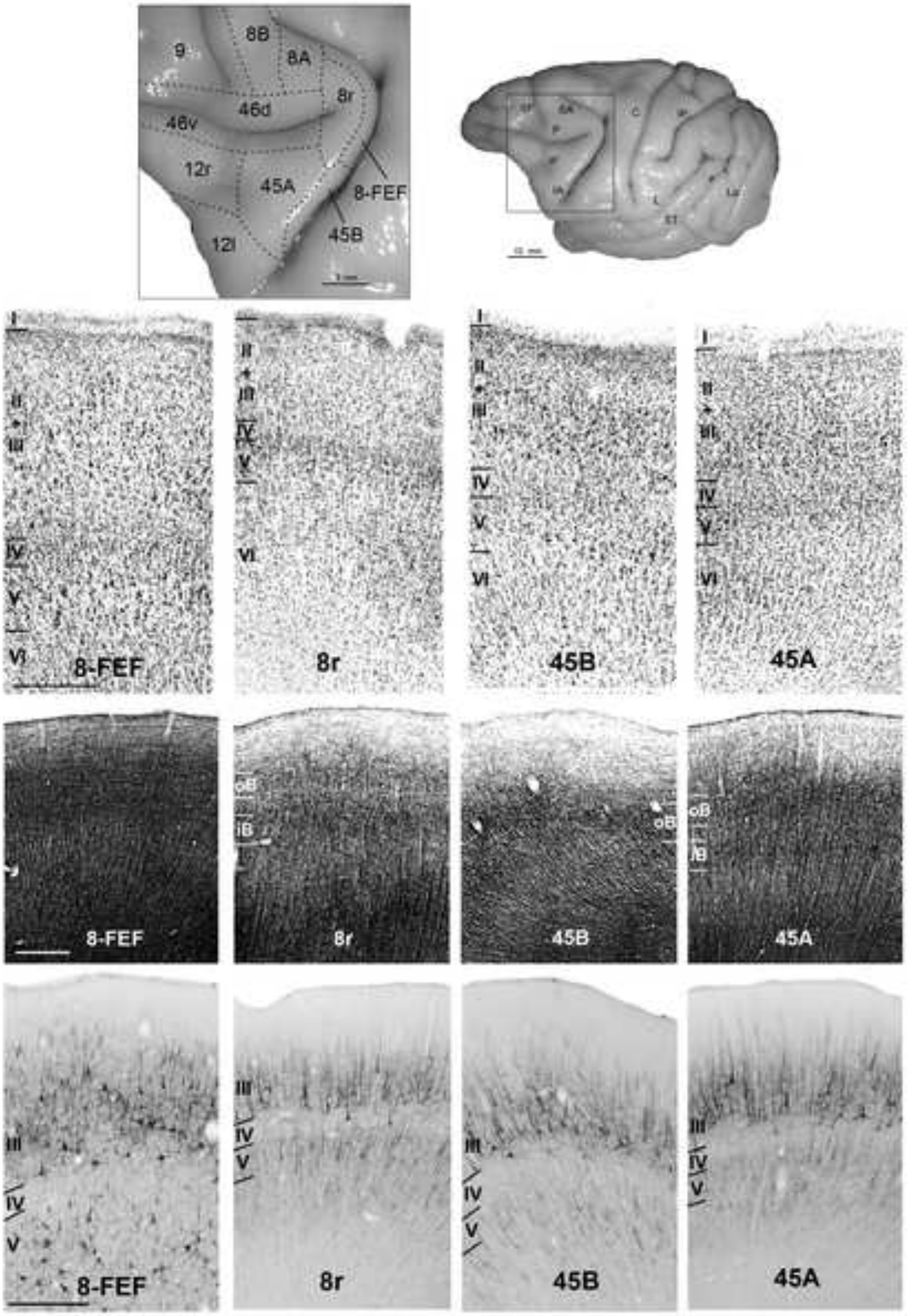

9
8B
8A
8r
46d
46v
12r
45A
8-FEF
45B
12l
C
L
ST
I
II
III
IV
V
VI
8-FEF
8r
45B
45A
oB
iB
8-FEF
8r
45B
45A
III
IV
V
8-FEF
8r
45B
45A

Figure 2

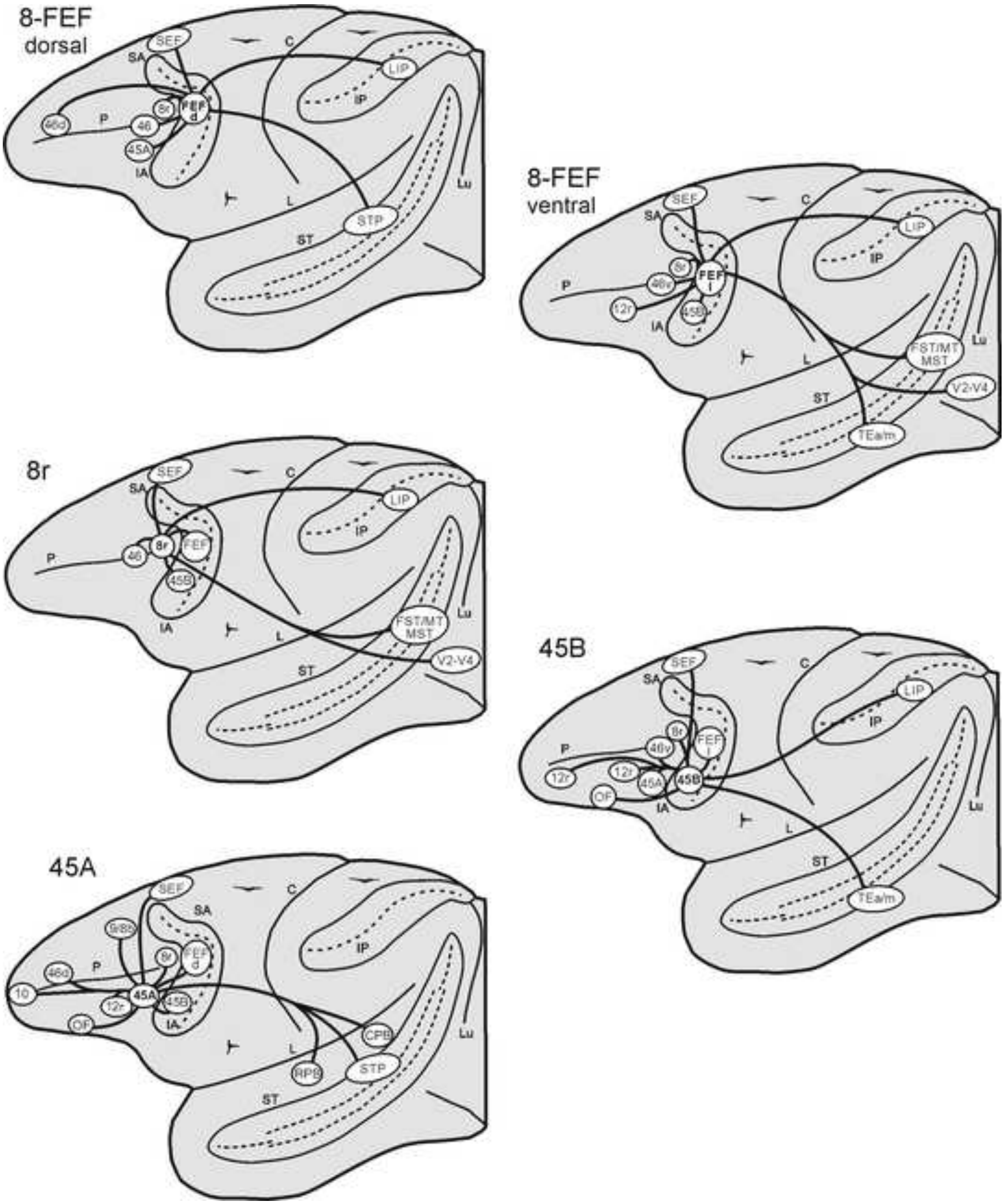
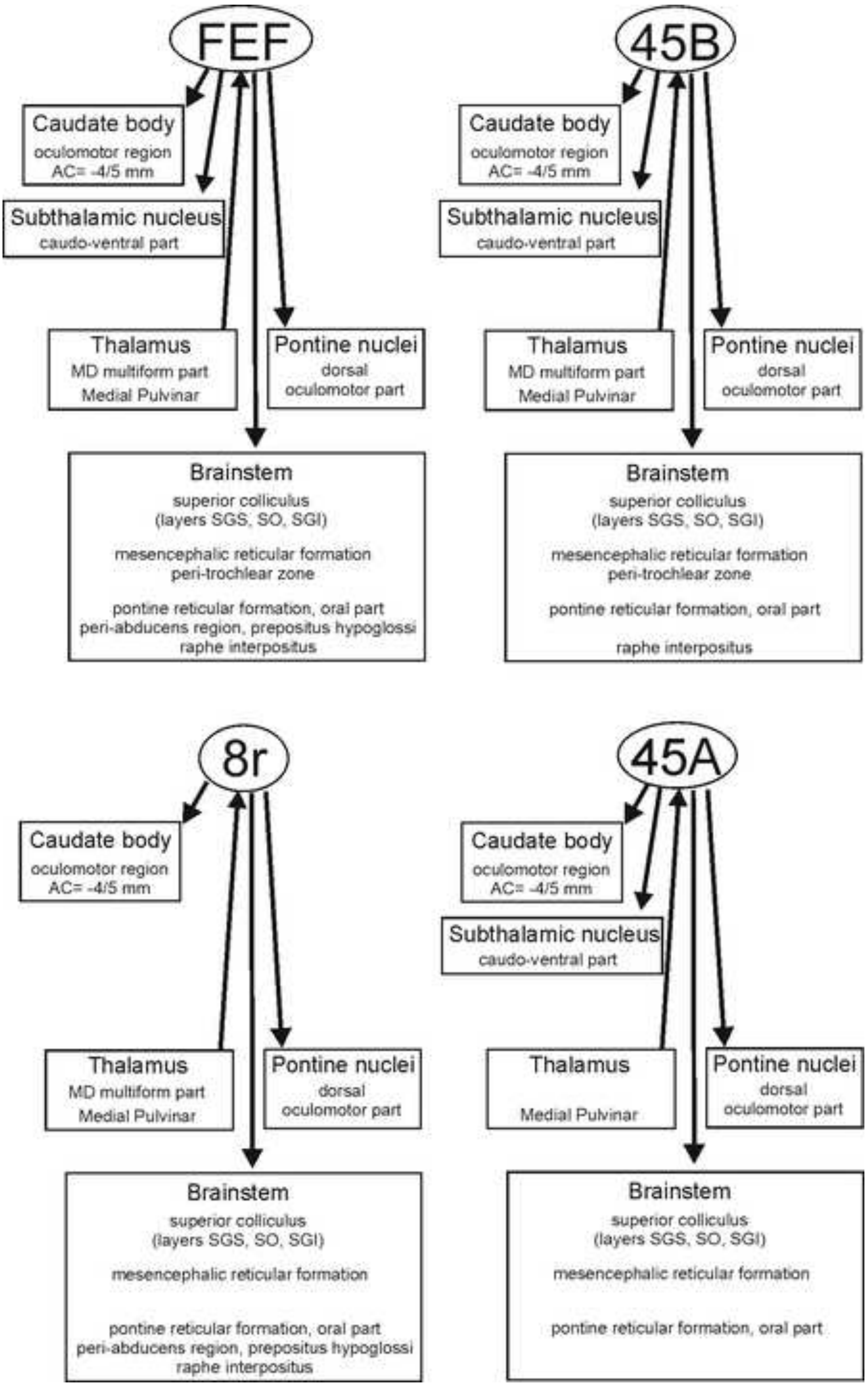

8-FEF
dorsal
SEF
SA
C
LIP
IP
8r
FEF
d
46d
P
46
45A
IA
L
Lu
STP
ST
8-FEF
ventral
SEF
SA
C
LIP
IP
8r
FEF
l
P
46v
12r
45B
IA
L
FST/MT
MST
Lu
V2-V4
ST
TEa/m
8r
SEF
SA
C
LIP
IP
P
46
8r
FEF
45B
IA
L
FST/MT
MST
Lu
V2-V4
ST
45B
SEF
SA
C
LIP
IP
8r
P
46v
FEF
l
12r
12r
45A
45B
OF
IA
L
Lu
ST
TEa/m
45A
SEF
SA
C
9/8B
8r
FEF
d
IP
46d
P
10
45A
12r
45B
OF
IA
L
CPB
Lu
RPB
STP
ST

Figure 3


FEF
Caudate body
oculomotor region
AC= -4/5 mm
Subthalamic nucleus
caudo-ventral part
Thalamus
MD multiform part
Medial Pulvinar
Pontine nuclei
dorsal
oculomotor part
Brainstem
superior colliculus
(layers SGS, SO, SGI)
mesencephalic reticular formation
peri-trochlear zone
pontine reticular formation, oral part
peri-abducens region, prepositus hypoglossi
raphe interpositus
45B
Caudate body
oculomotor region
AC= -4/5 mm
Subthalamic nucleus
caudo-ventral part
Thalamus
MD multiform part
Medial Pulvinar
Pontine nuclei
dorsal
oculomotor part
Brainstem
superior colliculus
(layers SGS, SO, SGI)
mesencephalic reticular formation
peri-trochlear zone
pontine reticular formation, oral part
raphe interpositus
8r
Caudate body
oculomotor region
AC= -4/5 mm
Thalamus
MD multiform part
Medial Pulvinar
Pontine nuclei
dorsal
oculomotor part
Brainstem
superior colliculus
(layers SGS, SO, SGI)
mesencephalic reticular formation
pontine reticular formation, oral part
peri-abducens region, prepositus hypoglossi
raphe interpositus
45A
Caudate body
oculomotor region
AC= -4/5 mm
Subthalamic nucleus
caudo-ventral part
Thalamus
Medial Pulvinar
Pontine nuclei
dorsal
oculomotor part
Brainstem
superior colliculus
(layers SGS, SO, SGI)
mesencephalic reticular formation
pontine reticular formation, oral part

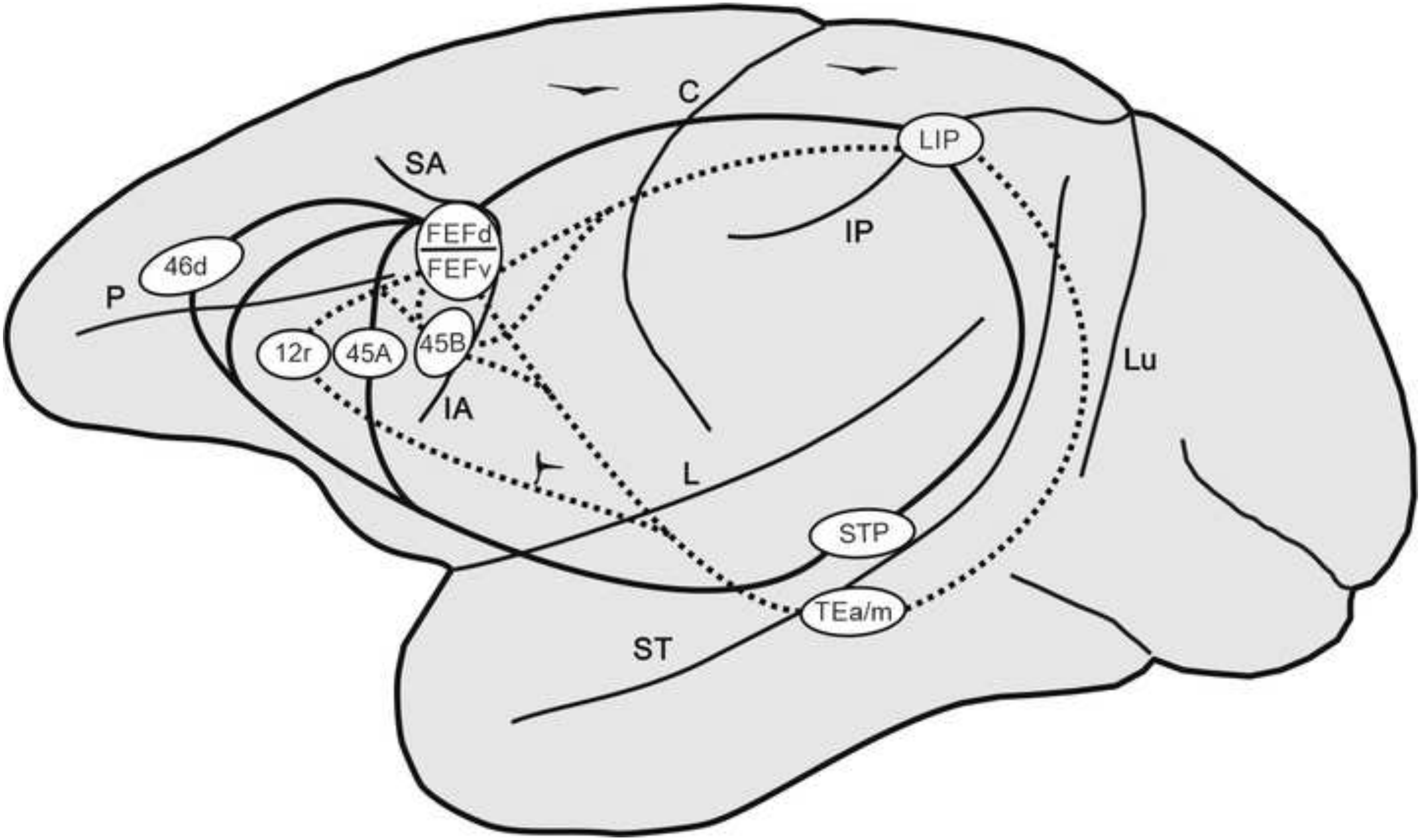

C
SA
LIP
FEFd
FEFv
46d
P
IP
12r
45A
45B
IA
Lu
L
STP
TEa/m
ST

Figure 5

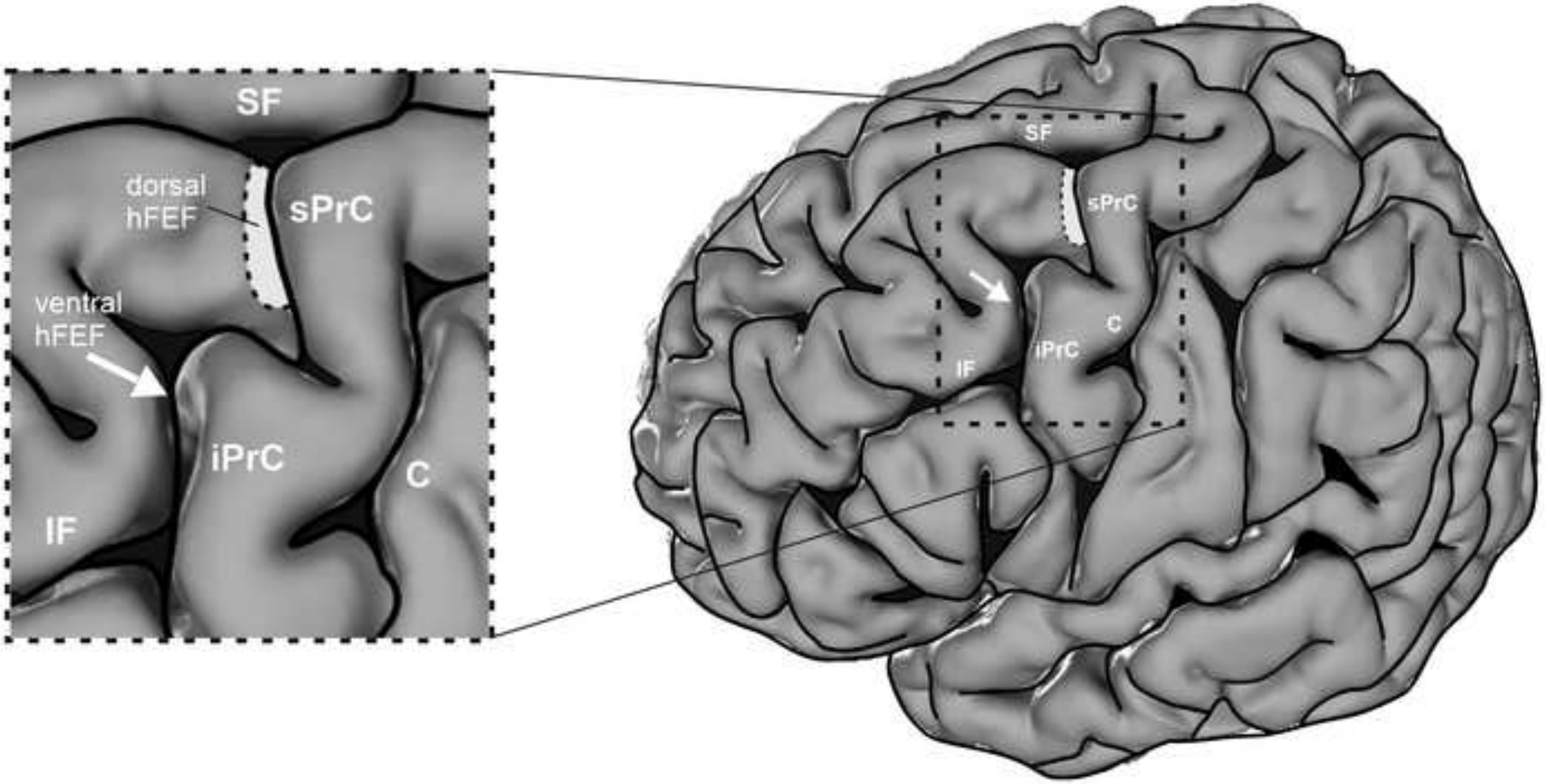
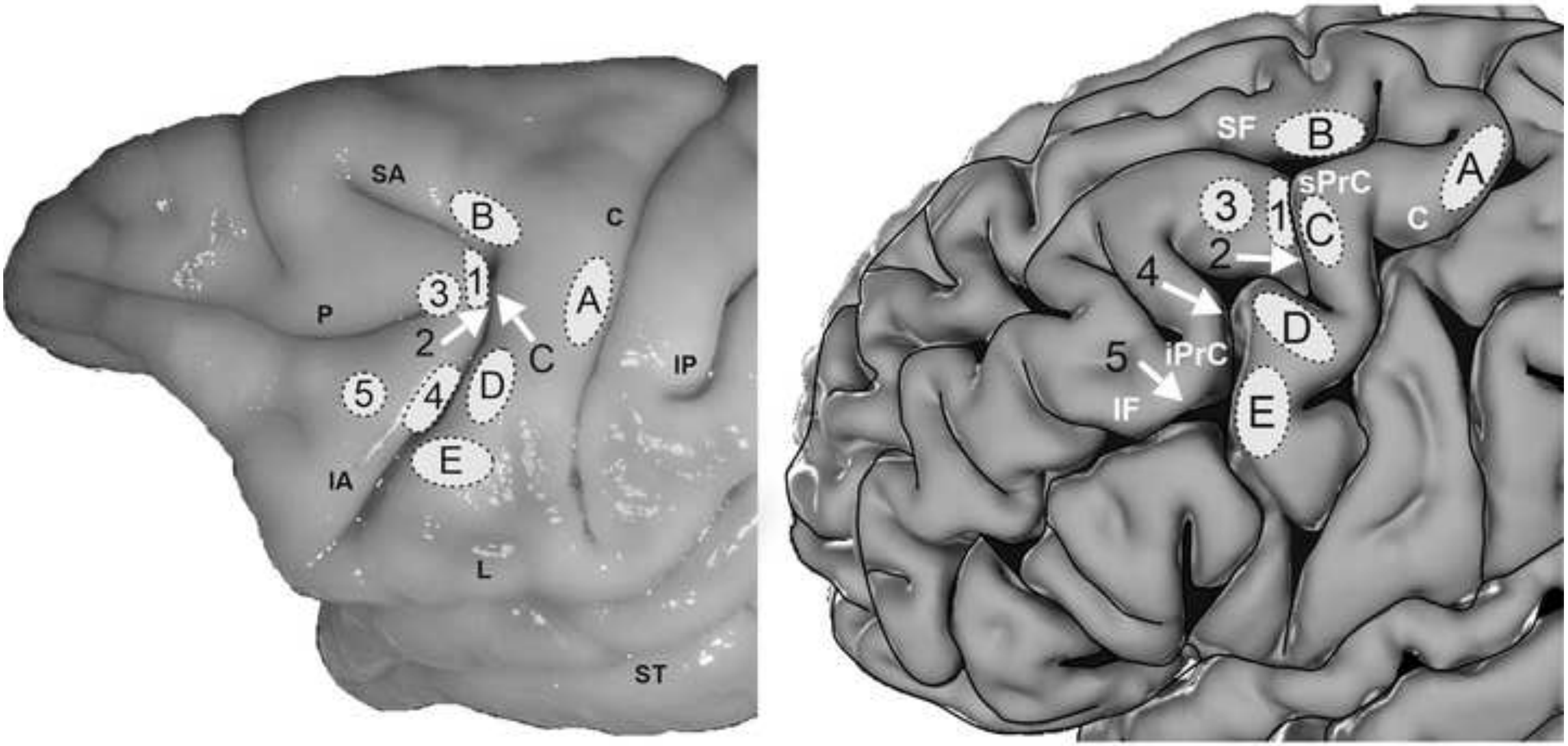


Figure 6



1 FEF - dorsal hFEF
2 SEM - pursuit FEF
3 8r - vergence hFEF
4 45B - ventral hFEF
5 45A - IFJ-IFS

A F1 hand - M1 hand
B F2 arm/hand - hPMd hand
C F5 hand - hPMv hand
D F5 hand/mouth - hPMv oro-hand
E F5 face/mouth - hPMv oro-facial