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# Anatomo-functional organization of adaptive manual, orofacial and vocal control in the human frontal cortex

Kep Kee Loh

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**Anatomo-fonctionnelle organisation of  
adaptive manual, orofacial and vocal  
control in the human frontal cortex**

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**Kep Kee LOH**

Devant le jury composé de :

Pr. MACALUSO, Emiliano	Université Lyon 1	Président
Dr. BURLE, Boris	CNRS Marseille	Rapporteur
Dr. GROSBAS, Marie-Helene	CNRS Marseille	Rapporteuse
Dr. COUTUREAU, Etienne	CNRS Bordeaux	Examinateur
Dr. ROY, Alice	CNRS Lyon	Examinatrice
Dr. AMIEZ, Celine	CNRS Lyon	Directrice de thèse

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## **Abstracts**

### **Abstract (English)**

This thesis examines how the human frontal cortex is organised to learn and use conditional rules linking contextual stimuli with manual, vocal and orofacial actions. My first study demonstrated that in humans: 1) the posterior lateral frontal cortex (pLFC) is organized along a dorso-ventral gradient, where the dorsal premotor cortex (PMd) and the ventral prefrontal cortex (BA 44) are involved in manual, and vocal-orofacial conditional associations respectively, and 2) the anterior cingulate motor area (RCZa) within the mid-cingulate cortex (MCC), contributes to auditory feedback evaluation during the trial-and-error learning of these associations. My second study revealed that in the MCC, the three CMAs are functionally coupled with the lateral frontal cortex along a rostral-caudal gradient where more rostral regions are implicated in more abstracted levels of behavioral control. These findings provide important insights to current theories about frontal cortical organization for behavioural control. Via an extensive review, I showed that, within the pLFC-MCC network, BA 44 and RCZa are part of a homologous brain network that might play a similar role in cognitive vocal/orofacial control across primates - the adaptive control of vocal/orofacial actions based on auditory feedback monitoring. This hypothesis was validated in humans in my first study. As such, this thesis has established an important neural network for the study of how speech control evolved across primate evolution. Finally, I presented preliminary findings that resting-state connectivity profile matching is a promising approach for inter-species brain comparisons.

Keywords; prefrontal cortex, cognitive control, adaptation, vocal control, mid-cingulate cortex, broca's area, speech evolution, primate brain.

### **Abstract (French)**

Ce travail de thèse explore l'organisation fonctionnelle du cortex frontal chez l'homme lors de l'apprentissage et l'utilisation de règles conditionnelles associées à des stimuli contextuels et demandant la réalisation d'actions manuelles, vocales et orofaciales. Ma première étude a démontré chez l'homme que : **1)** le cortex frontal latéral postérieur (pLFC) est organisé selon un gradient dorso-ventral, où le cortex prémoteur dorsal (PMd) et le cortex préfrontal dorsal (BA 44) sont impliqués respectivement dans les associations conditionnelles manuelles et vocal-orofaciales, et **2)** que l'aire motrice cingulaire antérieure (RCZa) au sein du cortex cingulaire moyen (MCC), contribue à l'évaluation des feedback auditifs durant l'apprentissage par essai-erreur de ces associations. Ma seconde étude a révélé qu'au sein du MCC, les trois CMAs sont fonctionnellement couplées avec le cortex préfrontal latéral le long du gradient rostro-caudal où les régions les plus rostrales sont impliqués dans un contrôle comportemental de plus haut niveau. Ces résultats apportent de nouveaux éclaircissements aux théories actuelles concernant l'organisation cortico-frontal du contrôle comportemental. En réalisant une revue de la littérature, j'ai montré qu'au sein du réseau pLFD-MCC les aires BA 44 et RCZa font partie d'un réseau cérébral homologue qui pourrait jouer un rôle similaire dans le contrôle cognitif vocal/orofacial chez les primates – le contrôle adaptatif des actions vocales/orofaciales basés sur l'évaluation des feedback auditifs. Cette hypothèse a été validé chez l'homme dans ma première étude. Cette thèse a mis en évidence un important réseau neural aidant

à comprendre comment le contrôle du langage a évolué au cours de l'évolution des primates. Pour finir, j'ai présenté des résultats préliminaires qui montre que la correspondance des profils de connectivité en état de repos est une approche prometteuse pour comparer l'organisation fonctionnelle cérébrale inter-espèces.

Mots clés : cortex préfrontal, contrôle cognitif, adaptation, contrôle vocal, cortex cingulaire moyen, aire de Broca, évolution du langage, cerveau de primate

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## General Introduction

We encounter a myriad of complex situations and environments in our everyday lives. In order to achieve our goals, it is necessary for us to constantly adapt our behaviours according to variations in our immediate surroundings. Central to this adaptability are stimulus-response behavioural contingencies which dictate the appropriate responses given a particular contextual stimulus. For example, at a traffic junction, based on whether a red or green light is indicated, we know to either stop or continue driving our cars respectively. Since these contingencies involve arbitrary pairings between certain meaningful contextual stimuli (e.g. green light) and behavioural responses (e.g. continue driving) that are implicitly unrelated, they have to be explicitly learnt, and typically, via trial-and-error. For instance, imagine a scenario where you first encounter a traffic light with blue and yellow signals instead of the usual colours. With no prior experience, you will have to first try a response (e.g. stopping) to the first yellow signal you encounter, and to subsequently evaluate the outcome of this action (e.g. furious honking by the cars behind you), in order to learn the correct stimulus-response pairings (yellow-go, blue-stop).

The ability to acquire arbitrary stimulus-response pairings via trial-and-error learning, also known as conditional associative learning, is present not only in humans, but across other primate species. As such, the neural mechanisms underlying conditional associative learning have been extensively studied in both human and non-human primates (NHPs) since they constitute a common basis for more complex adaptive behaviours in primates. However, in comparison with NHPs, humans can flexibly acquire a wider range of conditional associations across multiple response modalities.

In particular, the capacity to adaptively control vocal responses, relative to orofacial and manual responses, is much more expanded in humans than in NHPs. Secondly, relative to NHPs, we are also able to learn and use more abstract and complex context-behavioural rules to guide our actions. The increased capacities to acquire and perform sensory-vocal conditional associations and to implement adaptive behavioural control via more abstract and complex rules might have contributed to the emergence of human vocal communicative abilities that require the higher-order flexible adaptation of vocal responses. The present doctoral dissertation is conceived to examine this proposition via three main research questions:

1. How is the human frontal cortex, in particular, the posterior lateral frontal cortex (pLFC) and the mid-cingulate cortex (MCC), anatomically and functionally organized to acquire and execute multimodal visuo-motor conditional associations involving manual, orofacial and vocal actions?
2. How are the various frontal regions within the lateral frontal cortex and the MCC functionally coupled to enable more abstracted levels of adaptive behavioural control?
3. How might the pLFC-MCC network has changed from NHPs to humans to enable increased flexibility in adapting vocal behaviours?

## Overview

Chapter 1 aims to provide a comprehensive literature review relevant to the main research questions: Firstly, we define and describe the main regions in the primate frontal cortex that are implicated in adaptive behavioural control and that are of central interest to the thesis. Here, we provide an overview of the main anatomical features and functions of these frontal regions in behavioural control. Secondly, we summarize existing models about the functional organization of the primate frontal cortex in behavioural control. Thirdly, reviewing existing work in human and non-human primates, we show that the posterior lateral frontal cortex (pLFC) and the mid-cingulate cortex (MCC) are important structures involved in sensory-motor conditional associative learning. Here, we further elucidate the bases of our hypotheses about the anatomical-functional organization of the pLFC and MCC during conditional associative learning. Additionally, we briefly discuss the literature suggesting that, within the primate pLFC-MCC network, Broca's area and the anterior cingulate motor area (called rostral cingulate motor zone RCZa) are implicated in cognitive vocal control across humans and NHPs. Finally, we summarize existing evidence to support the importance of sulci-based landmarks in the anatomical localization of cognitive functions in the human brain.

In Chapter 2, in line with the first research question, we present a human fMRI study that investigated the anatomo-functional organization in the human pLFC and MCC during the acquisition and performance of visuo-manual, vocal, verbal and orofacial conditional associations based on auditory feedback. We showed that: 1) in the pLFC, the learning and execution of visuo-manual, visuo-vocal, and visuo-orofacial

conditional associations follow a dorsoventral gradient: while conditional visuo-manual associations involve the dorsal premotor area (PMd) in the dorsal pLFC, conditional visuo-orofacial/vocal associations involve the ventral Broca's area 44 in the ventral pLFC; and 2) in the MCC, adaptive auditory feedback processing is achieved in RCZa. This work also provides important insights into how the human Broca area 44-MCC network functions in the cognitive control of vocal, orofacial and speech production.

In Chapter 3, in line with the second research question, we present an article where we investigated the functional connectivity between lateral frontal regions with the various CMAs within the MCC. The main findings revealed that RCZa is more strongly coupled with progressively anterior lateral frontal regions that are involved in higher-order cognitive control, while RCZp and CCZ are more strongly coupled with progressively posterior lateral frontal regions that are associated with more basic motor control. This suggested that the three CMAs within the MCC are organized along a rostro-caudal cognitive-motor organization in parallel with the lateral frontal regions. The observed rostro-caudal pattern of medio-lateral coupling in the frontal cortex could likely contribute to different levels of adaptive behavioural control.

In Chapter 4, in line with the third objective, we present a review article that brings together evidence that area 44 and the anterior MCC are crucial nodes within a homologous primate ventrolateral-dorsomedial prefrontal network that is involved in top-down vocal control in both humans and NHPs. We further argued that the involvements of area 44 and the aMCC in cognitive vocal control, as revealed in Chapter 2, are similar across human and non-human primates. Lastly, the review article discusses how area 44 and the aMCC, along with the other regions in the

prefrontal vocal control network, could have changed across primate evolution to enable complex speech abilities in humans.

In Chapter 5, we present preliminary results from the application of the connectivity profile matching technique to determine the functional homologue of the human area anterior cingulate motor area in the monkey brain. We discuss the advantages and potential applications of this technique to identify the functional homologues of the human vocal control network in the monkey for further comparative analyses.

In Chapter 6, I present an overall discussion of the results, their implications and perspective directions.

## Chapter 1: Literature Review

1. Overview of the anatomy and functions of the main primate frontal cortical regions in adaptive behavioural control.

The primate frontal cortex can be physiologically and anatomically defined as the part of the neocortex directly anterior to the central fissure and dorsal to the sylvian fissure (Fuster, 2001) and has been historically regarded as having a major role in the adaptive regulation of cognition and behaviour (e.g. Duncan & Owen, 2000; Goldman-Rakic, 1996; Luria, 1969; Petrides, 1996; Stuss et al., 1986). This part of the brain is highly heterogeneous in terms of its cytoarchitectonic divisions (Brodmann, 1909; Petrides & Pandya, 1994; A. E. Walker, 1940), anatomical connectivity patterns with other cortical and subcortical regions (Petrides & Pandya, 1999; 2002), and functions in executive behavioural control (Stuss & Alexander, 2000). As such, there are often inconsistencies in the nomenclature and definition of the various frontal cortical regions. In this section, we aim to define, and describe the anatomy and functions of the main frontal regions in the human and monkey that are implicated in adaptive behavioural control and which are of central interest to the thesis. These include the primary motor cortex and premotor areas, the lateral and medial prefrontal cortices and the frontopolar cortex.

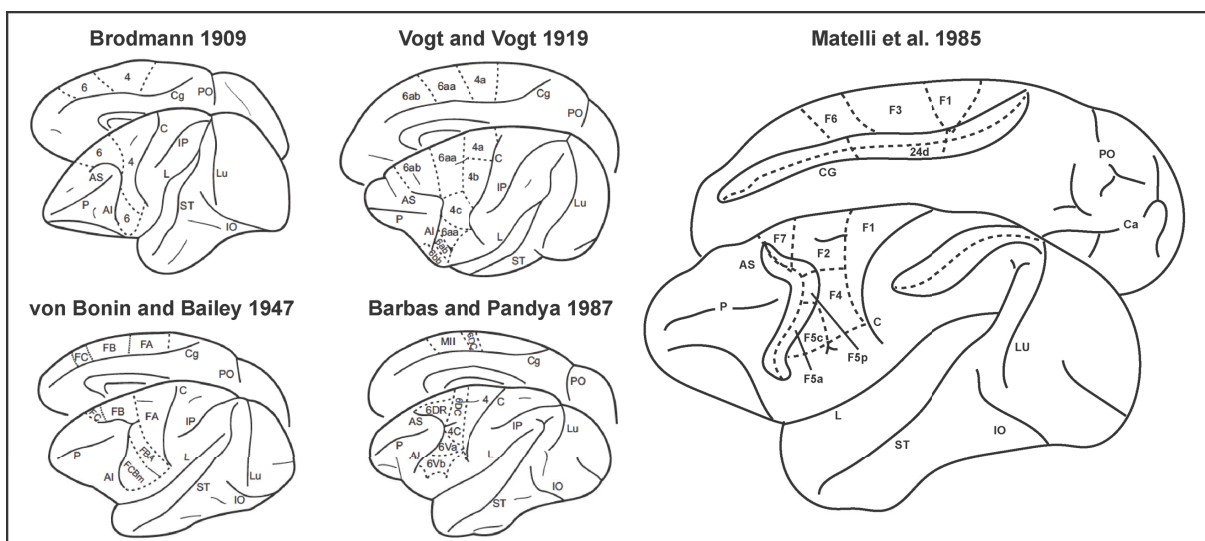
### 1.1 Primary motor cortex

The final output of any goal-directed behavioural control mechanism, simple or complex, is the execution, or non-execution, of an action or movement. Seated at the

most caudal end of the frontal lobe, the primary motor cortex plays a key role in the volitional execution of motor responses.

## Macaque

The macaque primary motor cortex typically refers to the Brodmann's agranular area 4 (Brodmann, 1909) that is located between the fundus of the central sulcus and of the arcuate sulcus (Fig 1). This area generally corresponds macaque area F1 based on a modern parcellation of the agranular cortex via its cytoarchitectural and histochemical properties (Matelli, Luppino, & Rizzolatti, 1985; 1991a) and also to area FA in Von Bonin and Bailey (Bonin & Bailey, 1947). While Brodmann's area 4's anterior border is set to the arcuate sulcus, Matelli et al. and Von Bonin and Bailey respectively localised the anterior limit of F1 and FA to be slightly caudal as both group of researchers had identified a dysgranular area that is located between the arcuate sulcus and their designated primary motor areas (F1 and FA respectively). In the present thesis, we adopted Matelli's F1 to define the macaque primary motor cortex.



**Figure 1. Motor areas in the macaque frontal cortex.** Adapted from Rizzolatti et al. (2014).



Cyto-architecturally, the primary hand motor area is characterized by the occurrence of giant pyramidal (Betz) cells and a lack of granular area IV. It has direct corticospinal projections that terminate in the intermediate region of the spinal cord (laminae VI, VII, and VIII) and lamina IX (where motor neurons are located) (He, Dum, & Strick, 1993; 1995). In contrast, other frontal motor areas project only into the intermediate region (Porter & Lemon, 1993). As such, Luppino and Rizzolatti (2000) suggested that the primary motor cortex, with direct access to the motor neurons, is able to determine the fine morphology of movements; whereas other frontal motor areas, which connect to the motor neurons via the primary motor areas, are involved in more global tuning of movements. Within the cortex, apart from the other motor areas, the primary motor cortex is strongly connected with area PE (area 5) and the primary somatosensory area (S1) in the parietal cortex, which provide proprioceptive and sensory inputs necessary for movement control (Rizzolatti, Luppino, & Matelli, 1998). Tract-tracing experiments had revealed that prefrontal-primary motor area connections predominantly pass through the lateral premotor areas (J. F. Bates & Goldman-Rakic, 1993; Luppino, Rozzi, Calzavara, & Matelli, 2003; Morecraft & Van Hoesen, 1993; Takada et al., 2004). This indicated that prefrontal influence on the primary motor area was likely exercised through the premotor areas.

The existence of somatotopic motor maps in the primary motor cortex was first revealed by David Ferrier's work involving the application of low-current electrical stimulation to the central fissure region in the macaque monkey (Ferrier, 1875; 1876). He demonstrated that, along a dorsal-ventral axis, stimulations evoked simple and complex movements of the leg, arms and hands, and finally tongue and mouth. More recently, Graziano and colleagues (2002) proposed that the primate motor cortex is

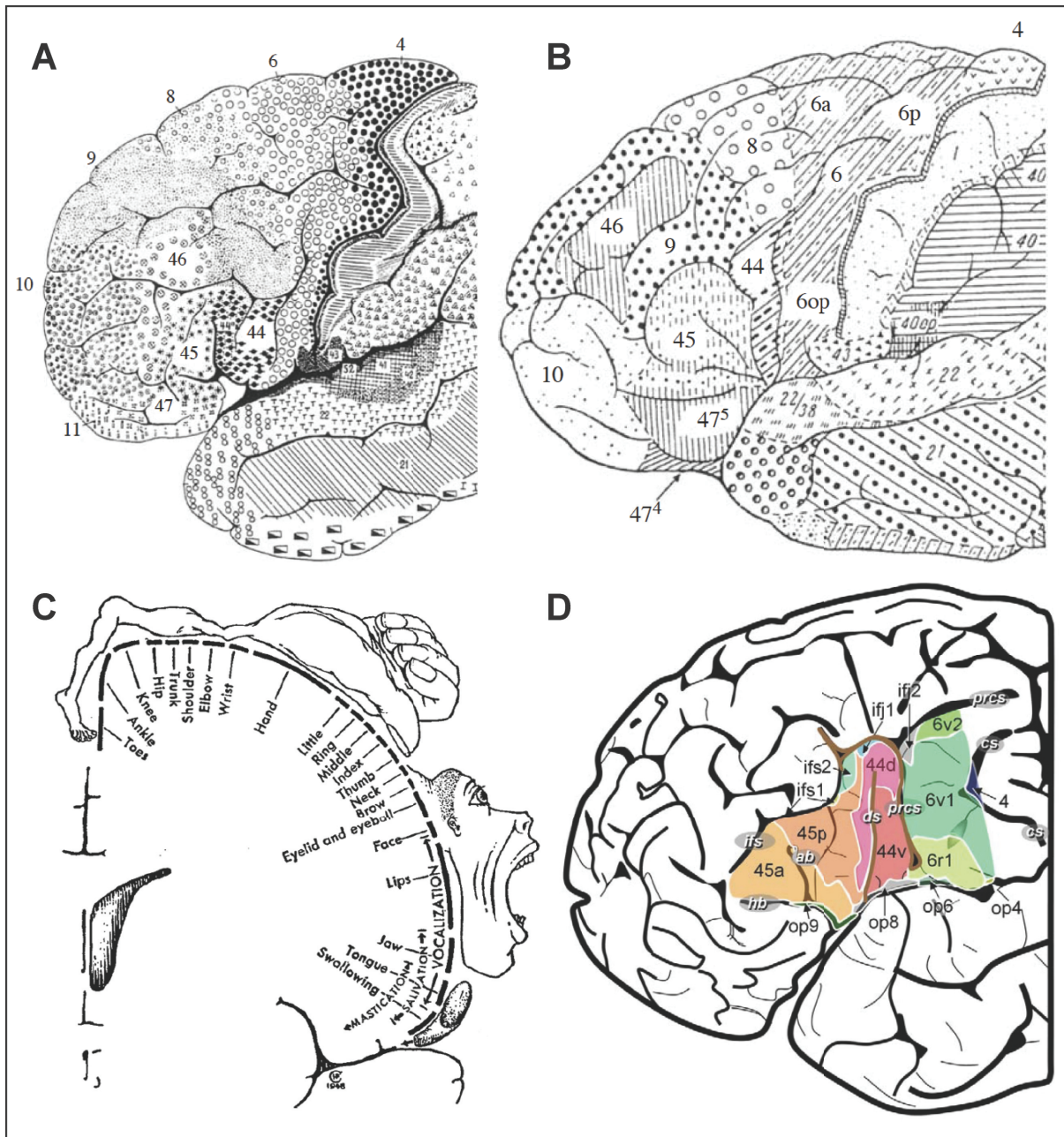
organized with functional maps corresponding to specific actions from the animal's natural repertoire, such as defensive and feeding movements. By extending the duration of macaque precentral stimulations to 500ms, Graziano and colleagues (2002; 2005) evoked chewing and licking movements (ventral stimulations), arm and hand movements that resembled object manipulations (middle stimulations), and complex movements that brought the arm and hand towards the ground (dorsal stimulations). The same actions can be reliably evoked from the same zone. These findings were subsequently replicated in other monkey species (review in Graziano, 2016). Graziano (2016) further noted that this new ethological action mapping in the motor cortex was still generally coherent with the original somatotopic mapping in terms of the effectors involved.

## Human

Like the macaque, the human primary motor cortex (Fig. 2) is usually defined by Brodmann's cytoarchitectonic area 4 (Brodmann, 1909) that is characterized by the occurrence of giant pyramidal (Betz) cells and a lack of a granular layer IV. This area is located on the anterior wall of the central sulcus and extends partly onto the precentral gyrus.

In the current thesis, the term 'M1' is used to denote the human primary motor cortex subtended by the cytoarchitectonic area 4. This nomenclature follows the school of thought (Brodmann, 1909; Campbell, 1905; Foerster, 1936; Fulton, 1935; C. Vogt & Vogt, 1919) that lateral cytoarchitectonic areas 4 and 6 constitute functionally distinct motor areas (i.e. the primary motor and premotor areas, respectively). However,

notably, some researchers (Penfield & Boldrey, 1937; Woolsey et al., 1952) have also used 'M1' to collectively refer to both the lateral areas 4 and 6, and 'M2' to refer to the supplementary motor areas in medial area 6.



**Figure 2. Motor areas in the human frontal cortex.** (A) Cytoarchitectonic map of the lateral frontal cortex by Brodmann's (1909). (B) Cytoarchitectonic map of the lateral frontal cortex by Sarkissov et al. (1995). (C) Human homunculus by Penfield and Rasmussen (1949). (D) Cytoarchitectonic parcellation of the ventral lateral frontal cortex by Amunts et al. (2010)

Penfield and colleagues provided a highly-detailed confirmation of the somatotopy in the human motor cortex via direct cortical stimulations in awake patients (Penfield, 1958; Penfield & Boldrey, 1937; Penfield & Jasper, 1954; Penfield & Rasmussen, 1949). Their work revealed the famous motor homunculus that detailed the relative positions and extents of the various body maps within the human motor cortex. Based on this map, the toes are represented at the most dorsal part of the primary motor cortex, followed by the legs, hips, trunk, neck, head, arms, hands, fingers and subsequently the face and mouth representations at the most ventral end. This mapping is also generally consistent with that obtained via functional neuroimaging studies in which subjects voluntarily performed various movements corresponding to different effectors (e.g. Lotze et al., 2000; S. M. Rao et al., 1995).

#### The primary orofacial area in macaque and humans

Here, we provide a focused discussion on the primate primary orofacial motor area given its implication in vocal actions. As mentioned earlier, the orofacial part of the primary motor cortex is ventrally located in the precentral gyrus. In NHPs, there are direct projections from this area to the various orofacial motor nuclei controlling jaw, lips and tongue movements (Kuypers, 1958b). Kuypers noted that these corticobulbar projections are almost non-existent the cat and are denser in the chimpanzee than in the monkey. This indicated that the neocortical control of orofacial musculature is more elaborated in primates than other mammals, and appears to increase across primate evolution (Sherwood et al., 2005; Sherwood, Holloway, Erwin, & Hof, 2004). In humans, apart from the orofacial motor nuclei, the primary orofacial area additionally projects to the nucleus ambiguus that is involved in laryngeal control (Kuypers, 1958a;

Simonyan & Horwitz, 2011). These projections are sparse in the chimpanzee and almost absent in the monkey (Kuypers, 1958b). This increased direct access to laryngeal control in the human primary orofacial cortex could have provided the fine motor coordination of both articulatory and laryngeal muscles that was necessary in human verbalizations (Simonyan, 2014). Consistent with this, electrical stimulation in the NHP orofacial area consistently yielded lips, jaw, tongue, vocal fold movements, but not vocalizations (Jürgens, 2002). In humans, orofacial movements and vocalizations could be evoked via primary orofacial area stimulations (Breshears, Molinaro, & Chang, 2015; Penfield & Rasmussen, 1949). Confirming its critical involvement in human speech production but not NHP calls, lesions of the primary orofacial area resulted in the loss of voluntary speech production in humans while monkeys with comparable lesions could still vocalize voluntarily (Kirzinger & Jürgens, 1982).

## 1.2 Premotor areas in the frontal cortex

Immediately rostral to the primary motor cortex, distinct premotor areas have been identified. Electrical stimulations of these areas evoke movements and they display direct projections to the spinal cord (Dum & Strick, 2002). These areas include the lateral dorsal (PMd) and ventral premotor areas (PMv), and the medially located supplementary (SMA), pre-supplementary motor areas (pre-SMA) and cingulate motor areas (CMAs). Note that the CMAs are not discussed in the current section but as part of the mid-cingulate cortex (MCC) in section 1.4 and in detail in Chapter 3.

### 1.2.1 PMd

## Macaque

The dorsal premotor cortex (PMd) refers to dorsal part of Brodmann area 6 on the lateral surface on the frontal cortex (Fig. 1). Cytoarchitecturally, it can be distinguished from the primary hand motor area by the absence or sparse presence of giant pyramidal cells, and from the granular prefrontal cortex by the absence of a well-defined layer IV (dysgranular). Classic architectonic and recent histological analyses have revealed that this area contains at least two distinct areas (Barbas & Pandya, 1987; Bonin & Bailey, 1947; Matelli et al., 1985; C. Vogt & Vogt, 1919). The PMd can be further sub-divided into a rostral and caudal part (Barbas & Pandya, 1987; Dum & Strick, 1991; He et al., 1993): Architectonically, the caudal PMd contains dispersed large pyramidal cells in layer V, whereas rostral PMd lacks such cells (Barbas & Pandya, 1987). Within the PMd, only the caudal PMd contains direct corticospinal projections and have somatotopically organized connections with the primary motor cortex (He et al., 1993). In contrast, the rostral PMd is predominantly connected with the directly adjacent prefrontal areas (Barbas & Pandya, 1987; M. T. Lu, Preston, & Strick, 1994). Nomenclature-wise, the above-mentioned caudal and rostral PMd roughly corresponds to Matelli's (1991a) area F2 and the caudal non-SEF part of area F7 (Luppino et al., 2003). In this dissertation, we adopt Barbas and Pandya's (1987) delineation of the rostral and caudal PMd areas.

Functionally, the PMd is involved in both the preparation and execution of actions (di Pellegrino & Wise, 1993a; Wise, 1985). PMd neurons reflect increased activity once an upcoming movement is instructed (e.g. via a visual cue) and continue until the movement is executed. The PMd is also implicated in the integrating multiple aspects

about the upcoming movement (e.g. amplitude and direction of movement, action target, type of motor effector) to construct and execute the final motor plan (Hoshi & Tanji, 2000; 2002; 2006; Kurata, 1993). Nakayama et al. (2016) investigated the functional dissociation between the rostral and caudal PMd via a conditional visual goal task where subjects had to first determine the behavioural goal (selecting target in the left or right relative position) based on a visual cue, and subsequently, in transforming the goal to action (hand-reaching to the correct target) once the choice cue were presented, and finally, preparing and executing the action. Neural recordings indicated that the rostral and caudal PMd regions were involved in determining of the behavioural goal as well as in specifying the action based on the goal. As the preparation and the execution of the action approaches, caudal PMd and primary motor neurons shows an increasing and major involvement as the rostral PMd activity decayed. Given its role in forming sensory-motor action plans, the rostral PMd is shown to be crucial in the learning and performing of visuo-hand conditional associations (Halsband & Passingham, 1982; Petrides, 1982; 1987). Monkeys with peri-arcuate lesions in dorsal area 6 (rostral PMd) were unable to perform previously learnt if-then relationships between two visual stimuli and two hand actions (Petrides, 1982).

## Human

As in the macaque, the human PMd occupies the dorsal lateral part of Brodmann area 6 (Fig. 2). Cytoarchitectonic studies have proposed a rostral and caudal division within the PMd (e.g. areas 6a and 6p respectively based on Sarkissov, Filimonoff, Kononowa, Preobraschenskaja, & Kukeuw, 1955).

The delineation into rostral and caudal PMd in the human have been largely driven by functional neuroimaging work. Boussaoud (2001) scanned subjects as they performed an attentional and intentional paradigm that respectively involved the spatial attention and motor preparation aspects of associated with a directed action. Their findings, in parallel with the results obtained from the same task in monkeys, revealed that the rostral and caudal PMds are associated with the spatial attention and motor preparation aspects of actions. Based on a meta-analyses of human imaging protocols, Picard and Strick (2001) found that tasks involving movement performance versus higher-order cognitive tasks led to more caudal activations in the PMd. In line with Petrides (1982)'s finding that the monkey rostral PMd is critically involved in visuo-hand conditional associations, Amiez et al. (2012a; Amiez, Kostopoulos, Champod, & Petrides, 2006) showed that the human rostral PMd was involved in the learning and selection of competing hand actions based on conditional visuomotor rules. Importantly, the peak activations associated with conditional visuo-hand selections could be reliably localised on the dorsal branch of the superior precentral sulcus in individual subjects (Amiez et al., 2006).

### 1.2.2 PMv

#### Macaque

The ventral premotor cortex (PMv) is situated in the ventral extent of Brodmann's area 6 (Fig. 1). Distinguishing it from the PMd, the PMv has an emerging granular layer 4 (Barbas & Pandya, 1987). In terms of anatomical connectivity, the PMv is connected



with the inferior parietal cortex and ventral prefrontal cortex. In contrast, the PMd is connected to the superior parietal cortex, dorsal prefrontal cortex, and cingulate cortex (Rizzolatti, Cattaneo, Fabbri-Destro, & Rozzi, 2014). Like the PMd, this area can be sub-divided into a rostral and caudal parts based on cytoarchitectural, connectivity and functional distinctions. Based on Matelli's (1985; Matelli, Luppino, & Rizzolatti, 1991b) parcellation scheme, the caudal area F4 is directly anterior to the primary motor cortex and succeeded rostrally by area F5. The two areas are cytoarchitecturally distinct: area F4 is characterized by low overall cell densities and with increasing pyramid sizes from superficial to deep layer III. Large pyramidal cells can be found scattered in layer V towards the dorsal extent of F4. Area F5, in contrast, has more closely packed cells and is clearly laminated. It can be further subdivided into F5p, F5a and F5c areas. Connectivity-wise, caudal PMv regions (F4, F5p and F5c) are more strongly linked with the parietal cortex while the rostral-most F5a area is strongly linked with the ventral prefrontal cortex (reviewed in Rizzolatti et al., 2014). Critically, F5a presents transitional architectonic features, such as the sparse presence of a granular area IV, that places it between the agranular premotor and fully granular prefrontal cortex. Based on this property and its involvement in orofacial motor control, Petrides et al. (2005) have classified this area, which resides on the posterior bank of the inferior arcuate sulcus, as the homolog of the human area 44 in the macaque. Whether Matelli's area F5a and Petrides' area 44 refer to the same region remains to be investigated. In this thesis, we broadly refer to Matelli's areas F4, F5a, F5c and F5p as PMv.

Functionally, stimulations in the PMv produce arm, neck, face and mouth movements (Fogassi et al., 1996; Gentilucci et al., 1988; Godschalk, Lemon, Nijs, & Kuypers, 1981;

Petrides, Cadoret, & Mackey, 2005a; Rizzolatti et al., 1988). Neurons in the caudal PMv (F4) show increased activity during simple movements and the execution of actions directed towards the mouth, body or particular space locations (Hoshi & Tanji, 2007; Rizzolatti et al., 2014). The rostral PMv (F5) is associated with the encoding of object-related actions, such as grasping, holding, tearing and object manipulations (Luppino & Rizzolatti, 2000). Notably, F5 neurons do not encode the individual movements that constitute these actions (Rizzolatti et al., 1988). Neurons in this area show increased firing to the execution of object-manipulation actions, the visual presentation of objects, and the observation of actions performed by others (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti et al., 2014). Rizzolatti and colleagues (2014) further suggested that this area is crucial in the internal representation of actions that enables the recognition and reproduction, or “mirroring”, of the same actions by others.

With regards to PMv’s involvement in voluntary orofacial and vocal control, stimulations in this region evoke orofacial movements in NHPs (Jürgens, 2002; Loh, Petrides, Hopkins, Procyk, & Amiez, 2017b). Neurons in this area showed increased activity with the conditioned production of calls in macaques (Coudé et al., 2011; Hage & Nieder, 2013) and the production of attention-getting calls in chimpanzees (Tagliabattola, Russell, Schaeffer, & Hopkins, 2008; 2011). Critically, lesions in the monkey area 44/PMv spare the ability to produce conditioned calls (Aitken, 1981; Sutton, Larson, & Lindeman, 1974), suggesting that it is not a critical region for NHP voluntary vocalizations.

Human

The human PMv is generally located at the ventral part of Brodmann area 6 (Fig. 2). In terms of connectivity, the human PMv can be differentiated from the PMd based on its stronger connections with the inferior parietal lobule and ventral prefrontal cortex (Schubotz, Anwander, Knösche, Cramon, & Tittgemeyer, 2010; Tomassini et al., 2007). A recent parcellation of the human ventrolateral frontal cortex based on receptor distribution revealed that the PMv contained 3 subdivisions: 6v1, 6v2 and 6r1 (Amunts et al., 2010). The authors suggested that amongst these regions, 6r1 could be the homolog to monkey area F5a given that both are located at the border to area 44 and possess a transitional dysgranular cytoarchitecture. Indeed, this homology was further supported by the work of Neubert and colleagues (2014) who showed similarities between the resting-state connectivity profiles of monkey area F5a and the 6r1 (named 6r in Neubert et al., 2014). It was revealed that both areas are functionally linked with the anterior parietal area (AIP), pre-SMA and the ventral prefrontal cortex.

Functionally, stimulations in the human PMv produce arm, orofacial and vocalizations (Penfield & Rasmussen, 1949). Imaging experiments also confirmed the presence of forelimb and orofacial fields in the rostral and caudal parts of the PMv (Schubotz et al., 2010). Notably, the arm and orofacial representations are located dorsally and ventrally in the PMv respectively. Geyer and colleagues (2000) suggested that, as in the monkey F4 and F5 areas, the caudal and rostral parts of the human PMv are involved in distal (fingers, hands) versus proximal (arms) movement representations. Also, showing a distal-vs-proximal dissociation between the rostral and caudal PMv regions, Schubotz and colleagues (2010) further showed that the observation of grasping (distal movement) and pointing (proximal movement) lead to increased

activity in the rostral and caudal PMv respectively. As such, as in the monkey, the human rostral and caudal PMv areas are involved in both the observation and performance of distal versus proximal actions respectively. Lastly, the human PMv appears to have an expanded role in human speech control as compared to NHPs. As mentioned earlier, PMv stimulations in humans, but not NHPs evoke vocalizations. Crucially, while the PMv has a crucial role in human speech productions (C. J. Price, 2012), PMv lesions in NHPs spare the ability to volitionally produce calls (Aitken, 1981; Sutton et al., 1974).

### 1.2.3 Pre-SMA and SMA

#### Macaque

The pre-SMA and SMA regions are located on the dorsomedial parts of Brodmann cytoarchitectonic area 6 (Fig. 3). Based on Matelli's (Matelli, Luppino, & Rizzolatti, 1991b) notation, the pre-SMA and SMA corresponds to macaque areas F3 and F6 respectively. Cytoarchitectonically, F3 is characterised by poor lamination, and increased cellular densities in lower layer III and layer Va, while F6 is clearly laminated, and has a prominent layer V. The pre-SMA receives strong inputs from PMv and the dorsolateral and ventrolateral prefrontal cortex but has relatively weaker connections with the primary motor cortex and PMd. SMA, on the other hand, is more strongly linked with the primary motor area and PMd, and weakly linked with the lateral prefrontal regions (Luppino, Matelli, Camarda, & Rizzolatti, 1993a). This reflects a dissociation between pre-SMA and SMA for more cognitive and motor control functions respectively.

Functionally, electrical stimulations in the SMA reveal a complete motor map including a leg representation at the most caudal end, followed by a hand and finally an orofacial representation at the border between the pre-SMA and SMA (Luppino, Matelli, Camarda, Gallese, & Rizzolatti, 1991; Mitz & Wise, 1987). While face and upper limb movements can be elicited from the pre-SMA, these were less consistent and involved longer stimulus trains (Luppino et al., 1991). SMA neurons show increased effector-specific activity prior to movement onset (Brinkman & Porter, 1979; Tanji & Kurata, 1982). Thaler and colleagues (Thaler, Chen, Nixon, Stern, & Passingham, 1995) further revealed that monkeys with SMA lesions were no longer able to self-initiate actions to obtain rewards but were able to perform the previously trained movement based on an auditory cue. This suggested that the SMA was involved in the internal, and not external triggering of actions. Evident of their role in action sequencing, pre-SMA/SMA neurons encode specific movements within sequences (Shima & Tanji, 2000; Tanji & Shima, 1994) and even reflect the relative ranks of actions within a sequence (Clower & Alexander, 1998). Dissociating between the pre-SMA and SMA, Nakamura and colleagues (1998) showed that muscimol inactivations of the pre-SMA, but not the SMA, resulted in monkeys being unable to learn new motor sequences but were unimpaired on previously acquired sequences. This indicated that the pre-SMA was crucial for acquiring novel combinations of action and movement sequences, whereas the SMA was more involved in the execution of acquired movement sequences.

With regards to vocal control, the pre-SMA/anterior SMA region in NHPs produces orofacial movements but no vocalizations (Mitz & Wise, 1987). Lesions invading the

pre-SMA, but not SMA, led to increased latencies of spontaneous and conditioned calls (Kirzinger & Jürgens, 1982). As such, in NHPs, the pre-SMA/anterior SMA, but not the posterior SMA region, appears to contribute to voluntary call initiation.

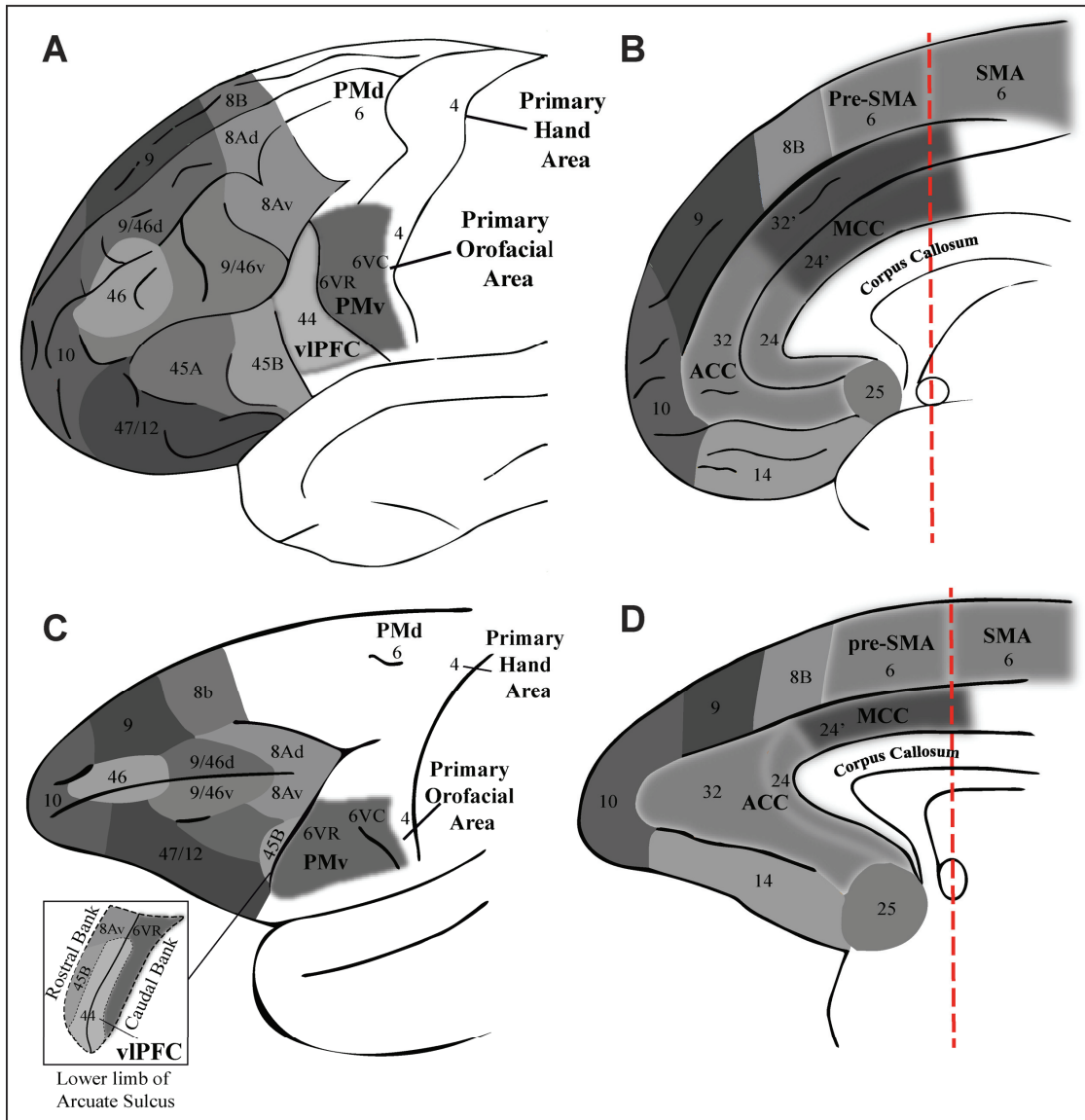
## Human

In the human brain, the pre-SMA and SMA are defined by areas 6a and 6b respectively (C. Vogt & Vogt, 1919). It is generally agreed that the vertical line drawn from the anterior commissure serves as the border between the two regions (Johansen-Berg et al., 2004). Using diffusion weighted tractography, Johansen-Berg and colleagues (2004) showed that, the human SMA and pre-SMA can be differentiated based on their connectivity profiles. In particular, while the SMA is more connected with motor areas (corticospinal tract, precentral gyrus), the pre-SMA was more linked to the superior frontal gyrus, medial parietal cortex and the inferior frontal cortex.

As in the macaque, the human SMA contains somatotopic mapping of the leg, hand and an orofacial representation in a caudal-to-rostral direction. Notably, stimulations around the anterior SMA/pre-SMA border evokes speech-like vocalizations in humans (Fried et al., 1991; Penfield & Welch, 1951). The human pre-SMA and SMA regions are generally associated with the voluntary and internal initiation of actions. Lau and colleagues (2004) found increased SMA activity as subjects freely determined their actions and when they focused on their conscious intentions. Cunnington and colleagues (Cunnington, Windischberger, Deecke, & Moser, 2002) further showed that while SMA activity increased prior to both internally and externally driven actions, pre-

SMA activity increased more for internally versus externally driven actions. Dissociating the pre-SMA from the SMA, the former is also more consistently involved in the learning of context-action associations than the latter (Hikosaka et al., 1996; Sakai et al., 1999). As subjects learnt and performed button press sequences that was guided by visual information, Hikosaka and colleagues (1996) revealed that the pre-SMA was more active during the learning of the association between the visual cue and the motor sequence, while the SMA was more active during the performance of the associations. Sakai and colleagues (1999) further confirmed via an fMRI study that the pre-SMA contributed specifically to the learning of context-motor sequence associations rather than the learning of the motor sequences themselves, which is typically linked with the SMA.

In contrast with monkeys, stimulations in the human pre-SMA/anterior SMA area have been associated with both orofacial movements and speech-like vocalizations (Fried et al., 1991; Penfield & Welch, 1951). Pre-SMA/SMA lesioned patients show a great reduction in spontaneous, but not externally-cued (e.g. reading a passage aloud or responding to questions) speech production (reviewed in Brown, 1988). Functional imaging studies of human speech production have also converged on the involvement of the pre-SMA and SMA in the volitional initiation and production of verbalizations (C. J. Price, 2010; 2012). Alario and colleagues (2006) suggested a dissociation between the pre-SMA and SMA for the higher-level cognitive planning and lower-level motor control aspects of volitional vocal behaviours. Thus, in humans, both the pre-SMA/anterior SMA and the SMA regions are implicated in voluntary speech control.



**Figure 3. Human and macaque prefrontal areas based on Petrides and Pandya's (1994) comparative parcellation maps. (A) Human lateral frontal cortex. (B) Human medial frontal cortex. (C) Macaque lateral frontal cortex. (D) Macaque medial frontal cortex. Figure adapted from Loh et al. (2017b, Figure 2).**



### 1.3 Lateral prefrontal cortex

The primate lateral prefrontal cortex (Fig. 3) consists of dorsal areas 8Ad, 8Av, 9/46, 46 and 9 (dorsolateral prefrontal cortex; DLPFC), and ventral areas 44, 45 and 47/12 (ventrolateral prefrontal cortex VLPFC), based on a comparative parcellation of the human and macaque brain by Petrides and Pandya (1999; 2002). Overall, the lateral prefrontal cortex has diverse connections with: 1) the association cortices, the limbic cortex and subcortical structures, which provide a range of sensory and motivational-emotional inputs; and 2) the premotor areas, basal ganglia, and the cerebellum, which provide motor control outputs. This pattern reveals the general role of the lateral prefrontal cortex in the integration of multiple sources of information to exert control over motor behaviours (reviewed in Tanji & Hoshi, 2008). Within the lateral prefrontal cortex, the VLPFC and DLPFC are associated with distinct origins of architectonic differentiation, distinct anatomical networks and different levels of behavioural control (Barbas & Pandya, 1987; Petrides, Tomaiuolo, Yeterian, & Pandya, 2012; Tanji & Hoshi, 2008).

#### 1.3.1 DLPFC

##### Macaque

Within the DLPFC (Fig. 3), areas 9, 46 and 9/46 all receive inputs from the multimodal temporal areas (superior temporal sulcus, rostral superior temporal gyrus) and paralimbic areas (anterior and posterior cingulate and retrosplenial cortices). Differentiating area 9 from the other two regions is the absence of incoming projections

from the lateral and medial parietal cortex (Andersen, Asanuma, Essick, & Siegel, 1990; Cavada & Goldman-Rakic, 1989; Petrides & Pandya, 1999). The caudal dorsolateral areas 8Ad and 8Av are primarily linked with the parietal and posterior temporal areas, and are distinguishable from the more rostral dorsolateral areas by a lack of connections with the retrosplenial cortex (Andersen et al., 1990; Barbas & Mesulam, 1981; Petrides & Pandya, 1999). DLPFC regions are also linked with the premotor regions – PMd, rostral cingulate motor area, pre-SMA and supplementary eye-fields (Tanji & Hoshi, 2008). Based on this connectivity profile, the DLPFC has access to multimodal and processed sensory inputs from the temporal and parietal cortices, spatial memory systems via the retrosplenial cortex, and motor outputs via the premotor areas. This corroborates the generally accepted role of the DLPFC in the active monitoring, manipulation and integrating of information for behaviour planning (Goldman-Rakic, 1996; Petrides, 2005; Tanji & Hoshi, 2008).

Functionally, the DLPFC has been implicated in the active processing of spatial-related information in working memory (Goldman-Rakic, 1988). Neurons in area 46 reflected sustained increases in activity across the delay period of a delayed-response task when monkeys had to recall a visual stimulus presented at the start of trial (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster & Alexander, 1971). Lesions confined to area 46 in and around the principal sulcus severely impair performance on spatial working memory tasks, such as oculomotor spatial delayed response task where subjects had to perform saccade in a particular direction informed by a spatial cue presented earlier in time (Goldman & Rosvold, 1970; Goldman, Rosvold, Vest, & Galkin, 1971; Levy & Goldman-Rakic, 1999). However, the lesioned monkeys were still able to perform tasks that involved object identity information (e.g. matching object

representations on a delayed match-to-sample task; Bachevalier & Mishkin, 1986; Mishkin, 1978; Passingham, 1975). These findings led to the proposal that the DLPFC was specifically involved in the active processing of spatial but not object-related information (Goldman-Rakic, 1988). This view, however, can be challenged by findings of DLPFC neurons that respond not only to spatial processing, but also object-related or both object-related and spatial information processing (Rainer, Asaad, & Miller, 1998; S. C. Rao, Rainer, & Miller, 1997).

Based on a series of lesion experiments, Petrides (Petrides, 1991a; 1991b) proposed that the DLPFC is involved in monitoring and manipulating retrieved information for behavioural planning and execution. Monkeys with lesions of area 46 and 9/46 were specifically impaired in the ability to track previously selected objects, which involved the active retrieval and tracking of past actions (Petrides, 1991b). Crucially, the same monkeys were able to successfully select objects based on whether they had been presented before – which indicated that the failure to select previously selected objects was not due to a failure of recognition memory. Hoshi and Tanji (2004) also revealed that the DLPFC was preferentially associated with the retrieval of processed task-relevant information, and the integration of this information during behavioural planning, as opposed to the lower-level detection and extraction of behavioural meaning from the visuo-spatial task cues.

## Human

Petrides and Pandya (1999) established homologies between the macaque and human dorsolateral prefrontal areas 9, 9/46 and 46 based on comparative analyses of

the connectivity and architectonic properties (Fig. 3). Sallet and colleagues (2013) performed a diffusion-weighted tractography-based parcellation of the human DLPFC, and subsequently examined the functional connectivity profiles of the various DLPFC region. Their results revealed that the resting-state connectivity profiles of the human DLPFC areas (area 9, 9/46, 46) were comparable to that of the macaque. In particular, these regions were strongly linked with the PMd, anterior and posterior cingulate areas, the VLPFC and VMPFC, and inferior parietal cortex.

Contrary to monkey studies that demonstrated the critical involvement of DLPFC neurons in the goal-directed maintenance of visuo-spatial information across task delays (e.g. Funahashi et al., 1989), neuroimaging studies in humans typically find sustained neural activity in a more caudal location in the precentral sulcus (Courtney, Petit, Haxby, & Ungerleider, 1998; Srimal & Curtis, 2008). More recently, Mackey and colleagues (2016) showed that subjects with DLPFC lesions sparing the human precentral sulcus area were unimpaired on a memory-guided saccade task. Only subjects with lesions invading the precentral sulcus area showed reduced accuracy on the task. The authors suggested that the DLPFC was involved in executive operations on spatial working memory rather than in maintaining the working memory representation which involves a network of regions. Along the same vein, Petrides and colleagues (e.g. Owen, Evans, & Petrides, 1996; Petrides, 1994) suggested that the DLPFC was involved in the executive monitoring and manipulation of information in working memory. Notably, Owen and colleagues (Owen et al., 1998) further demonstrated that when memory demands were controlled for, the active monitoring and manipulation of both spatial and non-spatial task information implicated the DLPFC. This provided further evidence that the DLPFC is involved in the executive

control over the information in working memory rather than representing the information itself (Petrides, 2005).

### 1.3.2 VLPFC

#### Macaque

Based on Petrides and Pandya's (2002) parcellation, the VLPFC includes area 44, 45, and 47/12 (Fig. 3). Directly anterior to the PMv, transitional area 44 is characterized by the presence of scattered patches of small neurons between layer III and V that resembles an emerging granular layer IV. Area 45 is situated immediately rostral to area 44. It has a well-defined layer IV and is considered a prefrontal region (Amunts et al., 1999; Petrides, 2006; Petrides & Pandya, 1994). Differentiating area 45 from the other prefrontal areas is the presence of large, deeply stained pyramidal cells in deep layer III. Finally, area 47/12 is located on the pars orbitalis rostral to area 45. This area constitutes the caudal part of Brodmann's area 47 and also area 12 based on Walker's (1940) maps. In this thesis, we refer to prefrontal granular areas 45 and 47/12 as the mid-VLPFC region and dysgranular area 44 as the transitional area 44. Virtue of its anatomical connectivity, the mid-VLPFC receives a wide range of sensory inputs, including visual (inferior temporal cortex), auditory (superior temporal cortex), somatosensory (second somatosensory area SII), gustatory (gustatory cortex), and olfactory (olfactory cortex) and projects to premotor areas, such as the anterior cingulate motor area, pre-SMA, 8A, supplementary eye fields, and distinguishing it from the DLPFC, the ventral premotor cortex. This connectivity profile suggests that the mid-VLPFC has a crucial role in receiving and integrating multiple sensory signals

necessary for driving behaviours (Petrides, 2005; Petrides & Pandya, 2002; Tanji & Hoshi, 2008).

In contrast with the DLPFC, Goldman-Rakic (1988) proposed that the VLPFC is involved in the processing of non-spatial, object feature information to drive behaviours. Revealing a double dissociation with the DLPFC, VLPFC lesions impair performance on tasks requiring the processing of object-related information, such as delayed match-to-sample task, but not on tasks involving spatial information processing (Mishkin, 1978; Passingham, 1975; M. Wang, Zhang, & Li, 2000). Hoshi and Tanji (2004) demonstrated that VLPFC neurons showed increased activity during the detection and encoding of visuospatial information for subsequent use, rather than the retrieval and integration of processed task-related information for action planning which was associated with increased DLPFC activity.

In the macaque, a dysgranular area 44 has been identified in the fundus of the inferior arcuate sulcus (Petrides & Pandya, 2002; Petrides, Cadoret, & Mackey, 2005a). The transitional area 44 has rich connections with prefrontal regions 45 and 9/46, and premotor regions, such as the PMv, cingulate and supplementary motor areas (Frey, Mackey, & Petrides, 2014). It also receives multisensory inputs from the parietal operculum, insula and the inferior parietal lobule. Located between higher-order cognitive, multimodal sensory and premotor regions, area 44 is well-positioned to exert executive sensorimotor control over vocal and orofacial responses (Petrides, 2006). Indeed, transitional area 44 is associated with voluntary vocal control across primates. In NHPs, stimulations in area 44 induces orofacial movements but not call productions (Petrides, Cadoret, & Mackey, 2005a). The conditioned production of

vocal signals is also associated with increased neuronal activity in area 44 (Coudé et al., 2011; Hage & Nieder, 2013). Importantly, area 44/PMv lesions in monkeys do not abolish their ability to produce calls in operant contexts (Aitken, 1981; Sutton et al., 1974), indicating that this region is not critical for voluntary call productions in NHPs.

## Human

For the human VLPFC (Fig. 2D, 3), we also adopted the naming conventions by Petrides and Pandya (1994; 2002). Human area 44 is generally situated on the pars opercularis, anterior to the ventral premotor area 6; and rostral to prefrontal area 45 which is found on the pars triangularis (Amunts et al., 1999; Petrides, 2014). Cytoarchitecturally, area 44 is characterized by an emerging granular layer IV and is thus commonly referred to as a dysgranular or transitional area 44 (Petrides & Pandya, 1994; 2002; Petrides, Cadoret, & Mackey, 2005a). As in the macaque, human areas 45 and 47/12 are granular frontal areas that constitute the mid-VLPFC. The two areas can be differentiated via the presence of large neurons in layer III of area 45.

Within the mid-VLPFC, the human area 45 has strong links with the auditory and multisensory association areas in the lateral temporal cortex (Frey et al., 2008) and the angular gyrus, which is associated with semantic processing (Binder, Desai, Graves, & Conant, 2009; Segal & Petrides, 2013a). It is also strongly linked with the dorsolateral prefrontal areas (46, 9/46 and 8) that are involved in executive monitoring and attentional control, as well as the pre-SMA and the medial superior frontal gyrus (areas 8, 9). Based on this connectivity profile, Petrides (2014) suggested that area 45 played a critical role in interfacing between the prefrontal control functions and the

higher order processing of language information.

Petrides (2002) proposed that the mid-VLPFC actively encodes and retrieves the relevant sensory information for further manipulation and processing to support goal-directed behaviours. Petrides (2002) devised a task where subjects were presented with two abstract visual stimuli to which they had to either: 1) select any of the two stimuli to proceed to the next trial (control condition); or 2) select the stimuli that was previously presented (familiarity condition); or 3) first determine if the pair of stimuli had been presented previously, and subsequently select the stimuli that was not previously selected (monitoring condition). On this task, the familiarity condition required the active retrieval of previously encoded stimuli to be compared with the presented stimuli that was hypothesized to be associated with the mid-VLPFC. Indeed, using PET imaging, Petrides and colleagues (2002) demonstrated that making familiarity judgements, relative to the control condition, led to increased activity in the mid-VLPFC but not in the mid-DLPFC. The monitoring condition involved both the active retrieval of previous stimuli (to determine if they recurred) and additionally the active tracking of previously selected stimuli. Providing a dissociation from the mid-VLPFC, the comparison between the monitoring and familiarity condition evoked increased activity in the mid-DLPFC. In the context of language functions, the mid-VLPFC (area 45) has been associated with the active retrieval of verbal information (Petrides, Alivisatos, & Evans, 1995), words (Amunts et al., 2004; Poldrack et al., 1999) synonyms, (Klein, Milner, Zatorre, Meyer, & Evans, 1995) and semantic processing (Saur et al., 2008).

Compared to area 45, transitional area 44 is more strongly connected with the



supramarginal gyrus in the caudal part of the inferior parietal lobule (Margulies & Petrides, 2013; Petrides, 2014), which is implicated in phonological processing (Saur et al., 2008). It is also linked with the intraparietal sulcus – a multimodal cortical region which contains an integrated representation of the body, as well as the auditory and multimodal temporal cortex. Area 44 has also rich access to orofacial motor representations in the various premotor areas, i.e. the anterior SMA/pre-SMA area, the rostral cingulate area, and the PMv. Lastly, it is also strongly connected to prefrontal areas 9/46 and 45 (Petrides, 2014). This connectivity pattern suggests that area 44 has a crucial involvement in the higher-order sensorimotor control of orofacial/vocal movements (Petrides, 2006).

Indeed, within the VLPFC, area 44 is part of the classical Broca's area that plays a critical role in speech production (Broca, 1861; Friederici, 2011; Geschwind, 1970; Grodzinsky, 2000). In humans, area 44 stimulations evoke orofacial movements and speech arrests (Breshears et al., 2015; Penfield & Rasmussen, 1949). Functional neuroimaging experiments demonstrate that the human area 44 is involved in the both processing of articulatory/phonological information and production of verbalizations (Poldrack et al., 1999; C. J. Price, 2000; 2012). Besides its role in the higher-order motor control of orofacial and vocal actions, area 44 has also been implicated in a language-related cognitive processes including the processing of syntax (Novick, Trueswell, & Thompson-Schill, 2005) and the construction of syntactic relationships during speech production (Grodzinsky, 2000; 2006). It is also associated with non-linguistic processes such as action recognition (Fadiga et al., 2006; Fazio et al., 2009; Lotze et al., 2006), action sequencing (Ardila & Bernal, 2007), motor imagery (Grèzes & Decety, 2002), action imitation (Iacoboni et al., 1999) and verbal working memory

(Chein, Fissell, Jacobs, & Fiez, 2002).

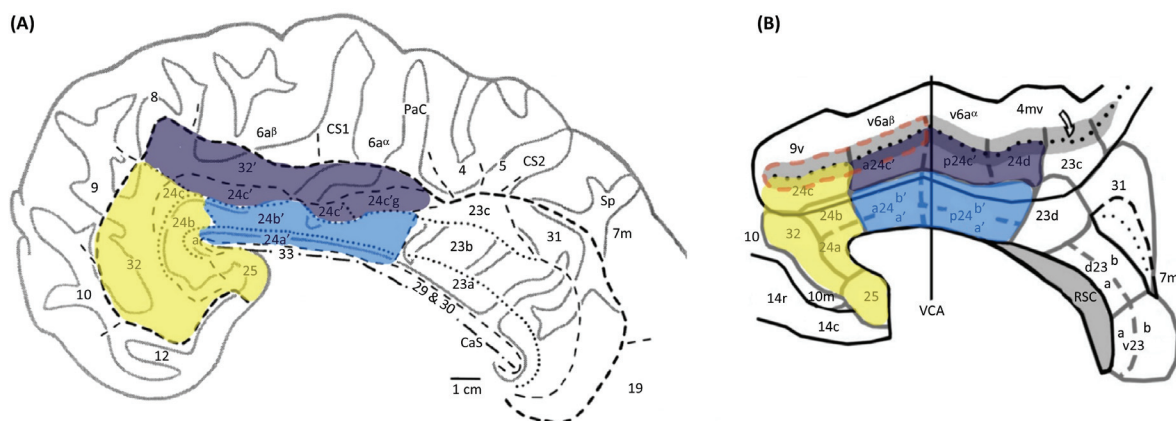
#### 1.4 Medial prefrontal cortex

The primate medial prefrontal cortex (Fig. 3) consists of the dorsomedial area 9, the cingulate areas 24, 25 and 32 (Passingham & Wise, 2012). The medial prefrontal cortex has dense reciprocal connections with the hippocampus and subiculum, and the amygdala (Carmichael & Price, 1995a; Insausti & Muñoz, 2001; Morecraft et al., 2007). It has access to the adjacent medial premotor areas, such as the anterior cingulate motor areas, the pre-SMA and SMA, and projects directly to the hypothalamus (Rempel-Clower & Barbas, 1998) and brainstem reticular nuclei (Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003). Finally, the medial prefrontal cortex is also characterized by a scarcity of visual inputs from the inferior temporal cortex (Carmichael & Price, 1995b). This pattern of connectivity suggests that the medial prefrontal cortex has strong access to memories of past events and outcomes via the hippocampus and amygdala, is associated with the medial premotor areas that are linked to internally driven actions, has limited access to environmental sensory inputs (unlike the lateral prefrontal cortex), and has influence over the autonomic nervous system. As such, the primate medial prefrontal cortex is typically associated with the driving of adaptive actions via an “internal” evaluation of past action outcomes, as opposed to the lateral prefrontal cortex which drives adaptive actions based on “external” contextual information (Passingham, Bengtsson, & Lau, 2010). Here, we focus our discussion exclusively on the mid-cingulate cortex (MCC; B. A. Vogt, 2016) given its crucial role in adaptive action selection and vocal control.

### 1.4.1 MCC

#### Macaque

Based on Vogt and colleagues's (2005) 4-region model of the macaque cingulate cortex (Fig. 4), the MCC consists of area 24c' and area 24d. Vogt et al.'s model depicts the fundus of the cingulate sulcus as the superior limit of the MCC, but other neuroanatomical studies have observed that the MCC might extend to the dorsal bank of the sulcus (Matelli, Luppino, & Rizzolatti, 1991a; Petrides & Pandya, 1994; Sallet et al., 2011).



**Figure 4. Parcellations of the human and macaque cingulate cortex by Vogt et al. (1995, 2005, 2016).** (A) Human cingulate cortex. (B) Macaque cingulate cortex. Yellow shaded areas refer to the anterior cingulate cortex (ACC). Blue areas refer to the mid-cingulate cortex (Dark blue – gyral regions, Light blue – sulcal regions). Adapted from Mansouri et al. (2017a).

Three cingulate motor areas (CMAs) have been identified in the monkey cingulate cortex via intracortical stimulation and anatomical connectivity studies (Dum & Strick, 1991; e.g. 1993; He et al., 1995). The 3 areas are somatotopically organised and contain arm, legs and face representations (Cléry et al., 2017; Luppino et al., 1991;

Morecraft, Schroeder, & Keifer, 1996; Shima et al., 1991; Y. Wang, Shima, Sawamura, & Tanji, 2001): the anterior-most CMA (CMAr) and a slightly posterior CMA on the ventral bank (CMAv) both contains a hand, foot and face motor representation each; while the dorsal CMA (CMA<sub>d</sub>) contains two hands and a leg representation. The CMAr, relative to the caudal CMAs, has denser connectivity with the lateral prefrontal cortex and pre-SMA, but weaker connections with the primary cortex, spinal cord and SMA (Dum & Strick, 1991; M. T. Lu et al., 1994; Luppino, Matelli, Camarda, & Rizzolatti, 1993a). Consistent with this connectivity profile, stimulations in the CMAr evoke movements less consistently than in the caudal CMAs (Dum & Strick, 1991; He et al., 1995). However, CMAr neurons show strong correlated activity with movement initiations and often fire prior to movement onsets (Shima et al., 1991). This indicated that the anterior-most CMA is more involved in the higher-order initiation and preparation of motor actions, whereas the caudal areas are more involved in motor execution.

Accumulating evidence is suggesting that the MCC is involved in the monitoring of action outcomes for driving behavioural adaptations (Procyk, Tanaka, & Joseph, 2000; Procyk et al., 2016; Quilodran, Rothé, & Procyk, 2008; Rushworth, Walton, Kennerley, & Bannerman, 2003; Shima & Tanji, 1998). In a problem-solving task where monkeys had to first discover the rewarded response out of 4 possible responses via trial-and-error (search phase), and subsequently repeat that response to obtain rewards (repeat phase), MCC neurons showed increased firing in response to all incorrect feedbacks and the first correct feedback during the search phase, compared to correct feedbacks in the repeat phase. Crucially, both incorrect and the first correct feedback during the learning phase are both indicative of a need for behavioural change: while incorrect

feedback informs the monkey to try a different response on the next trial, the first correct feedback informs the monkey to switch from an exploratory strategy to an exploitative one when he can repeat the same response to obtain rewards. In other words, MCC activity reflected the tracking of action outcomes that are relevant for behavioural adaptations. Procyk and colleagues (2016) performed a meta-analysis on the relative locations of juice feedback-related activity and the motor representations in the CMAr in macaques. Their findings reveal that the location of juice-related feedback processing coincided with the face motor representation in the CMAr. As such, Procyk et al. hypothesized that behavioural feedback processing in the MCC proceeded in an embodied manner where feedback of a particular modality (e.g. hand tactile) is evaluated in the corresponding CMAr body map (hand representation).

## Human

Based on the recent parcellation of the cingulate cortex by Palomero-Gallagher and colleagues (2009), 'MCC' refers to the cingulate region dorsal and posterior to the genu of the corpus callosum, while 'ACC' refers to the region anterior and ventral to the genu (Fig. 4). The MCC comprises the cytoarchitectonic areas 24a', 24b', 24c', 24d, 33', and 32'. Notably, areas 33' and 32' appear to be present only in humans but not in monkeys. In humans, the relative locations of areas 24c' and 32' vary according to the sulci morphology on the medial wall. While all humans possess a cingulate sulcus (cgs) in both hemispheres, some might present a second cingulate sulcus – the para-cingulate sulcus (pcgs) situated dorsal to the cgs (Petrides, 2012). The pcgs is present in around 70% of subjects in at least one hemisphere (Fornito et al., 2008; Paus et al., 1996; B. A. Vogt, Nimchinsky, Vogt, & Hof, 1995). Importantly, when a

pcgs is absent, areas 24c' and 32' will occupy the ventral and dorsal banks of the cgs; when a pcgs is present, area 32' will occupy the paracingulate gyrus and the pcgs, and area 24c' will cover both banks of the cgs (B. A. Vogt et al., 1995). In other words, the relative locations of area 32' can vastly differ in hemispheres with or without pcgs. This underscores the importance of taking into account individual cingulate morphology when averaging activations in this region (Amiez & Petrides, 2014; Shackman et al., 2011).

The human cingulate motor areas were first identified by Picard and Strick (1996) based on a meta-analysis of existing PET imaging studies involving motor execution, response selection, motor learning and planning. They located the anterior and posterior rostral cingulate zones (RCZa and RCZp) and a caudal cingulate zone (CCZ). Extending their work, Amiez and Petrides (2014) more precisely mapped the CMA regions as well as their individual motor maps via fMRI as subjects performed voluntary eye, tongue, arm and foot movements. Their work revealed the presence of 3 distinct human cingulate zones with a set of arm, face, and foot representations in each of the two rostral cingulate zones (RCZa and RCZp), and two arms, and one foot representations in the caudalmost CCZ. Importantly, the location of the RCZa face representation varied according to whether a pcgs was present: when a pcgs was present or absent, the RCZa face representation would be found in the pcgs or cgs respectively. As such, the displacement of the RCZa face representation depending on the presence of a pcgs appeared to be similar to that of area 32'. The connectivity of the human CMAs had been studied via diffusion-based and resting-state functional imaging techniques (M. Beckmann, Johansen-Berg, & Rushworth, 2009; Habas, 2010; Loh, Hadj-Bouziane, Petrides, Procyk, & Amiez, 2017a). Using diffusion-based

imaging, Beckmann and colleagues (2009) investigated the connectivity associated with 3 seed clusters (cluster 4-6) that likely corresponded to the 3 CMAs. All 3 CMAs showed strong connectivity with the dorsal striatum, the premotor cortex, precentral gyrus and the DLPFC. Between CMAs, the rostral-most cluster showed stronger connectivity with the DLPFC while the caudal-most cluster showed stronger connectivity with the premotor, motor and parietal cortex. This pattern of increasingly rostral (caudal) CMAs showing increasingly stronger (weaker) connections with prefrontal (motor) areas was also observed in studies that investigated the resting-state functional connectivity associated with the CMAs (Habas, 2010; Loh, Hadj-Bouziane, Petrides, Procyk, & Amiez, 2017a).

As in the macaque, the human anterior MCC is associated with the monitoring of behavioural outcomes and feedback to adapt future behaviours (Procyk et al., 2016) (Procyk et al., 2016). Accordingly, Amiez et al. (2013) found increased BOLD activity in the anterior MCC as subjects were evaluating the juice feedback to guide their trial-and-error learning. Procyk et al. (2016) further showed that the activation peaks associated with adaptive processing of juice feedback in Amiez et al. (2013) overlapped with those associated with the performance of orofacial movements from Amiez and Petrides (2014). This suggested that the orofacial motor representation in the anterior CMA could likely also be involved in the evaluation of juice feedback for behavioral adaptation. Procyk and colleagues (2016) further proposed that the monitoring of behavioural outcomes in the MCC could be embodied in the various motor maps in the anterior CMA.

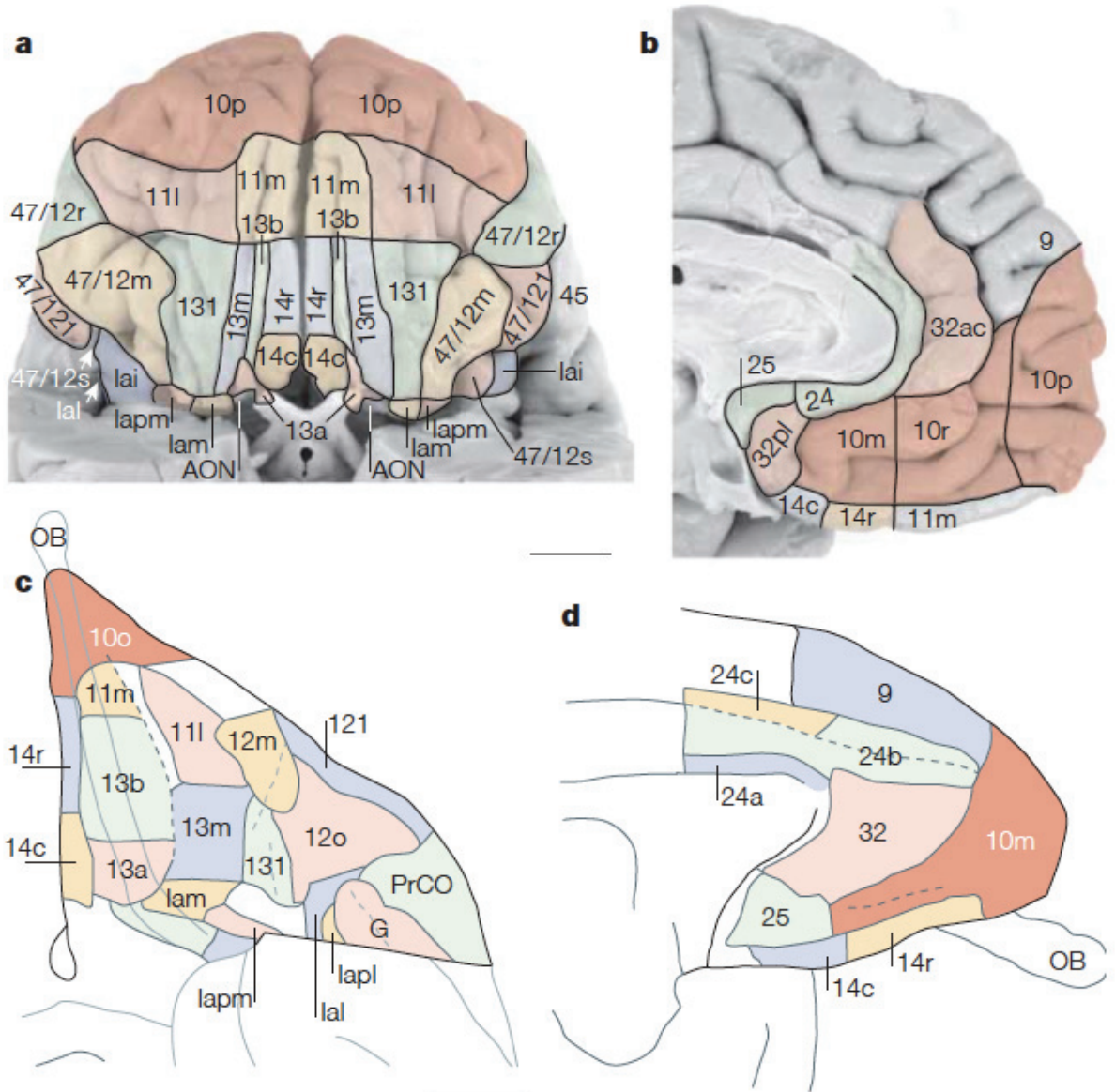
Role of MCC in primate vocalizations

In primates, a cingulate vocalization area exists around the border between the anterior MCC and the ACC (Jürgens & Ploog, 1970; Paus, Petrides, & Evans, 1993). This region has direct projections to the facial motor nuclei and the periaqueductal gray (PAG) region that provide direct access to species-typical facial movements and calls respectively (An, Bandler, Ongür, & Price, 1998; Morecraft et al., 1996). With rich connections with the amygdala, spinothalamic system and the striatum, this region appears to play a general role in emotional vocal and orofacial expressions in primates (Shackman et al., 2011). In NHPs, stimulations in this area result in the production of innate affective calls (Jürgens & Ploog, 1970; Robinson, 1967). Revealing its critical role in NHP voluntary vocal control, lesions of the ACC/MCC region result in decreased spontaneous calling and the ability to voluntarily produce calls (Aitken, 1981; MacLean & Newman, 1988; Sutton et al., 1974). In humans, stimulations of the same region can evoke orofacial movements and emotional vocalisations, like laughter (Caruana et al., 2015; Sperli, Spinelli, Pollo, & Seeck, 2006; Talairach et al., 1973). ACC/MCC lesions in human patients result in akinetic mutism, which is associated with a lack of will to speak or move (Ackermann & Ziegler, 1995; Brown, 1988). Notably, they could still respond to questions when probed. Chapados and Petrides (2013) further revealed that lesions to a critical region in the left-hemispheric dorsomedial prefrontal cortex, including the supplementary motor areas and the mid-cingulate areas, result in major impairments on the verbal fluency task. Lastly, Brotis and colleagues (2009) reported that patients with cingulate resections could generally recover their verbal abilities and social functioning in time. As such, in humans, the ACC/MCC area contributes to motivational-emotional aspects of vocal control like in NHPs, but are not critical for voluntary verbalizations.



## 1.5 Frontopolar cortex

The frontopolar cortex corresponds to the rostral-most prefrontal area 10 in both macaque and humans. This region exists only in primates and appears to be greatly expanded in humans relative to other NHPs (Semendeferi, Armstrong, Schleicher, Zilles, & van Hoesen, 2001). Area 10 can be distinguished from the other prefrontal areas based on its unique connectivity profile: It is predominantly inter-connected with higher-order multimodal association areas in the prefrontal, anterior temporal and the cingulate cortices, and has minimal down-stream projections to sensory and motor areas like other prefrontal regions (Ramnani & Owen, 2004). Area 10 also matures later than other prefrontal regions postnatally, providing an extended time window for experiential-based structural changes that could be important for the development of higher cognitive abilities (Dumontheil, 2014; D. J. Miller et al., 2012; Sowell et al., 2004). As such, area 10 is often seen as the apex of behavioural control and a key region contributing to the complex cognitive abilities unique to humans (Boorman, Behrens, Woolrich, & Rushworth, 2009; Boorman, Behrens, & Rushworth, 2011; Koechlin, 2016; Mansouri, Koechlin, Rosa, & Buckley, 2017b; Ramnani & Owen, 2004).



**Figure 5. Parcellations of the human and macaque orbital and medial cortex adapted from (Ongür, Ferry, & Price, 2003).** (A) Human orbitofrontal cortex. (B) Human mediofrontal cortex. (C) Macaque orbitofrontal cortex. (D) Macaque mediofrontal cortex.

## Macaque

In the macaque, the highly granular prefrontal area 10 based on Brodmann's (Brodmann, 1909) classification was subsequently divided into areas 10m and 10o by Carmichael and Price (1994) (Fig. 5). Area 10m is generally homogeneous in terms of cytoarchitecture, but connectivity investigations (An et al., 1998; Carmichael & Price, 1996; Ongür, An, & Price, 1998) have suggested that it can be sub-divided into a rostral part near the frontal pole, and a caudal part along the medial wall. These regions correspond to the human areas 10r and 10m respectively. Area 10o occupies the rostral-orbital region in the prefrontal cortex. Ongur and colleagues (2003) had suggested that macaque area 10o had expanded greatly in human into the human area 10p. Connectivity-wise, the macaque area 10 is predominantly interconnected with the prefrontal cortex (Bachevalier, Meunier, Lu, & Ungerleider, 1997; Barbas & Pandya, 1989; Petrides & Pandya, 1999), the anterior temporal cortex (Amaral & Price, 1984) and the cingulate cortex (Arikuni, Sako, & Murata, 1994; Bachevalier et al., 1997; Morecraft & Van Hoesen, 1993), and has minimal down-stream projections to sensory and motor areas like other prefrontal regions (Ramnani & Owen, 2004). This connectivity profile suggests that area 10 is mainly involved in the integration and processing of higher-order and abstract inputs and less in lower-level cognitive-motor processes.

Functionally, area 10 has been associated with deliberating between the exploitation of a current task/goal and exploration of alternatives, by monitoring the relative values of current versus alternative task/goals and reallocating cognitive resources to the better option (Mansouri et al., 2017b). In a landmark study by Mansouri et al. (2015),

monkeys with area 10 lesions performed a classical, and three variants of the Wisconsin Card Sorting Task (WCST). In the classical WCST, subjects are required to determine the sorting rule (i.e. by color or shape), via trial-and-error, in order to select the correct target to the presented cue. Interestingly, monkeys with area 10 lesions are not impaired on the task. In contrast, monkeys with lesions in other prefrontal areas (i.e. DLPFC, orbitofrontal cortex and the ACC) were impaired on the same task (Buckley et al., 2009), revealing a dissociation between area 10 and the other prefrontal areas. In a variant of the WCST, monkeys were presented trials with high or low conflict between rules. In high conflict trials, monkeys were presented with one test item that matched the sample in color, another that matched in shape, and a last one that did not match in neither color nor shape. As such, monkeys faced a conflict between two rules in order to select the correct test item. In low conflict trials, monkeys were presented with one test item that matched the sample in both shape and color, and another two items that did not match in both shape nor color. As such, there was no conflict in the rules to select the right item since both rules led to the same correct item. Area-10 lesioned monkeys showed the comparable effects of conflict cost on performance (better performance in low versus high conflict trials) as controls, but enhanced effects of conflict adaptation (improved performance in a low conflict trial after a high conflict trial) compared to controls. Mansouri et al. (2015) argued that area 10-lesioned monkeys showed an enhanced conflict adaptation effect as they were unable to consider alternative tasks and goals and were thus more focused on the current task. Providing support for this hypothesis, Mansouri and colleagues further showed, via two other variants of the WCST involving a distractor task and free rewards, respectively, that performance on the main task were less affected by the secondary task and free rewards in area 10-lesioned monkeys versus

controls. These results could also be explained by the idea that without area 10, monkeys are unable to consider alternatives when distractor trials were presented and consequently, could stay focused on the main task.

## Human

The human Brodmann area 10 can be sub-divided into 3 parts: area 10p that occupies the frontal pole, and areas 10r and 10m that, respectively, occupy the rostral and caudal parts of the ventromedial prefrontal cortex (Ongür et al., 2003) (Fig. 5). Based on cytoarchitectonic features, Ongur and colleagues further proposed that human area 10p corresponds to the macaque area 10o, whereas human areas 10r and 10m correspond respectively to the rostral and caudal parts of macaque area 10m. Neubert and colleagues (2014) compared the functional connectivity between the lateral and medial parts of the human area 10, and with the macaque area 10. Overall, both human medial and lateral area 10 show predominant coupling with the prefrontal cortex. Distinguishing between the medial and lateral areas, the latter has increased coupling with the parietal cortex, whereas the former has increased coupling with the temporal cortex. As such, the lateral area 10, in contrast with its medial counterpart, has a connectivity profile that was more similar to area 46. Importantly, the human medial area 10, but not the lateral area 10, had a matching connectivity profile with the macaque area 10. As such, Neubert et al. (2014) suggested that the lateral area 10 was unique to the human brain.

The precise function of the frontopolar cortex in cognition is currently still being debated as it has been implicated across a myriad of cognitive tasks and experimental

paradigms (Burgess, Gilbert, & Dumontheil, 2007; Koechlin, 2011; Ramnani & Owen, 2004). However, neuropsychological studies have provided evidence that area 10 has distinct roles in cognition compared to other prefrontal areas (Burgess et al., 2007; Dreher, Koechlin, Tierney, & Grafman, 2008; Hoffmann & Bar-On, 2012; Ramnani & Owen, 2004): Area 10 lesions do not significantly disrupt general intelligence, language abilities, basic sensory-motor functions and executive control tasks are typically compromised via lesions in the more caudal prefrontal areas. Notably, area 10 lesions appear to specifically impact the ability to manage and organize everyday activities that involve open-ended and novel situations (Shallice & Burgess, 1991). Based on a review of recent experimental findings from human and NHP work, Mansouri and colleagues (2017b) proposed that the primate frontopolar cortex is involved in deliberating between the exploitation of a current task/goal and exploration of alternatives, by monitoring the relative values of current versus alternative task/goals and reallocating cognitive resources to the better option. Via computational modelling, Donoso et al. (2014) revealed that the medial area 10 in humans, like macaque area 10 was implicated in the reallocation of cognitive resources between the current goal/task and other potential alternatives. In particular, they proposed that the existence of an additional mechanism, in human lateral area 10, that was involved in reallocating resources between the current goal/task and a few possible alternatives that was previously used. Critically, this region appears to be present only in humans and not macaques (Neubert et al., 2014). This ability to contemplate previously reliable alternatives as we are engaged in a current goal or task could explain our expanded capacities in cognitive branching, multitasking, abstract reasoning and problem-solving (Mansouri et al., 2017b).

## **2 Functional organization of the primate frontal cortex for behavioural control.**

### 2.1 Dorso-ventral organization in the mid-prefrontal cortex.

#### 2.1.1 Anatomical distinctions between the dorsal and ventral prefrontal cortex.

The dorsal and ventral parts of the lateral prefrontal cortex are associated with distinct origins of architectonic differentiation (Barbas & Pandya, 1989): the dorsal part arises via a mediodorsal trend from the corpus callosum, to the medial areas 24, 25, 32, dorsal-medial areas 9, 10, 14, lateral areas 10, 9 and rostradorsal 46, and finally to the caudal ends of dorsal areas 46 and 8; the ventral part arises via a basoventral trend from the caudal orbitofrontal region, to medial area 13, orbital areas 12, 11, 14, area 10, rostroventral area 46 and finally the caudal part of ventral area 46 and 8. Congruent with these trends, the dorsal and ventral LPFC are also interconnected with regions along their architectonic origins: while the dorsal LPFC is more connected with the medial prefrontal cortex, the ventral LPFC is more connected with the orbitofrontal cortex (Barbas & Pandya, 1989). Apart from having different architectonic origins, the dorsal and ventral LPFC are anatomically linked with distinct networks within the PFC (Barbas & Pandya, 1987; Tanji & Hoshi, 2008). The ventral LPFC receives a range of direct sensory inputs, including visual (area PF in the parietal cortex), auditory (inferior temporal cortex), somatosensory (S2), olfactory (olfactory cortex) inputs etc. In contrast, the dorsal LPFC receives mainly highly processed inputs from multimodal areas in the temporal cortex and auditory areas in the superior temporal gyrus. This suggested that while the VLPFC is involved in retrieving and integrating multiple direct

sensory information, the DLPFC is involved in retrieving and integrating processed and multimodal inputs (Tanji & Hoshi, 2008).

### 2.1.2 Domain-specific model

Goldman-Rakic (1996) proposed that the dorsal and ventral LPFC are involved in processing information from different domains. While the DLPFC is involved in spatial information processing, the VLPFC is implicated in processing object-related information. This distinction was supported by the differential connectivity profiles of the dorsal and ventral LPFC areas: while the DLPFC receives its main inputs from the posterior parietal cortex (the final area in the dorsal visual 'where' pathway), the VLPFC receives strong projections from the inferior temporal cortex and the ventral visual 'what' pathway (Cavada & Goldman-Rakic, 1989; Constantinidis & Procyk, 2004; Petrides & Pandya, 1984; Selemon & Goldman-Rakic, 1988). As reviewed in section 1.3, DLPFC neurons show sustained activity increases across the delay period when monkeys had to retain information from a spatial cue presented at the start of trial (Funahashi et al., 1989; Fuster & Alexander, 1971). Area 46 lesions severely impair performance on spatial working memory tasks (Goldman et al., 1971; Goldman & Rosvold, 1970; Levy & Goldman-Rakic, 1999), but not tasks that involved the matching of object identity information (Bachevalier & Mishkin, 1986; Mishkin, 1978; Passingham, 1975). Revealing a double dissociation, VLPFC lesions impair performance on tasks requiring the processing of object-related information, such as delayed match-to-sample task, but not on tasks involving spatial information processing (Mishkin, 1978; Passingham, 1975; M. Wang et al., 2000). These findings led to the proposal that the DLPFC was specifically involved in the active processing



of spatial but not object-related information (Goldman-Rakic, 1988). This hypothesis was also supported in some early human studies (Ungerleider & Haxby, 1994; Ungerleider, Courtney, & Haxby, 1998). However, in the recent years, contradictory evidence is accumulating against the domain-specific theory. Firstly, it has been found that DLPFC neurons responded not only to spatial processing, but also object-related or both object-related and spatial information processing (Rainer et al., 1998; S. C. Rao et al., 1997). Importantly, Owen and colleagues (Owen et al., 1998) demonstrated that the active monitoring and manipulation of both spatial and non-spatial task information implicated the DLPFC. This suggested that the functioning of DLPFC in working memory was not specific to the information domain but to the cognitive process (i.e. active monitoring and manipulation) exerted on the information.

### 2.1.3 Process-specific model

Petrides (2005) proposed that the dorsal and ventral LPFC are functionally differentiated based on the executive process they perform on working memory representations rather than the type of information they operate on. While the DLPFC is implicated in the monitoring and manipulation of information for planning and executing behaviours, the VLPFC is involved in the encoding and retrieval of specific sensory information from the various sensory association areas for active selection and manipulation. Supporting this distinction, monkeys with DLPFC lesions were specifically impaired in the ability to track previously selected objects, which involved the active retrieval and tracking of past actions (Petrides, 1991b). Crucially, the same monkeys were able to successfully select objects based on whether they had been presented before – which indicated that the failure to select previously selected objects

was not due to a failure of recognition memory. In humans, Petrides (2002) devised a task where subjects had to select a previously presented object (familiarity) or an object that was not previously selected (monitoring). The familiarity condition involved the active retrieval of previously encoded stimuli for comparison. On the other hand, the monitoring condition involved both the active retrieval of previously encoded information, and additionally, the active tracking of past selections. Using PET imaging, Petrides and colleagues (2002) demonstrated that making familiarity judgements led to increased activity in the mid-VLPFC but not in the mid-DLPFC. Providing a dissociation from the mid-VLPFC, the comparison between the monitoring and familiarity condition evoked increased activity in the mid-DLPFC.

## 2.2 Rostro-caudal functional organization in the frontal cortex

Behavioural control can be implemented at various abstraction levels. Behaviours can be regulated at more abstracted levels via higher-order action plans or goals (e.g. to score a goal during a football game), that are temporally further from the final actions, or at more concrete levels via specific motor implementations (e.g. kicking the ball in a particular direction), that are temporally nearer to the final actions. The view that the primate frontal cortex reflects a rostro-caudal functional organization in behavioural control was first proposed by Fuster (2001). Fuster's influential "perceptual-action cycle" theory suggested that there are two inter-linked anterior-posterior hierarchies in the brain corresponding to increasingly abstract action and perception representations:

- 1) From the primary motor cortex to the lateral premotor and prefrontal cortices, brain regions progressively specify less concrete/more abstract action plans by integrating information over longer temporal delays.
- 2) From the primary sensory cortex to the

multimodal association areas, brain regions progressively specify less concrete/more abstract perceptual representations. Currently, there is a general consensus in the field that primate frontal cortical areas are organized along a rostro-caudal axis with progressively rostral areas carrying out more abstract and higher-order levels of behavioural control (Badre & D'Esposito, 2009a; Fuster, 2001; Koechlin, 2003). In this section, we summarize the main evidence pointing to a rostro-caudal organization of behavioural control in the primate frontal cortex.

Firstly, the inter-connectivity of frontal regions reflects a hierarchical control structure with more rostral/caudal regions occupying more superordinate/subordinate levels (Badre & D'Esposito, 2009a): 1) The rostral-most area 10 projects caudally to all other lateral prefrontal areas (Petrides & Pandya, 2007); 2) the mid-DLPFC area is reciprocally connected with area 10 rostrally, and PMd caudally (Schmahmann & Pandya, 2006); 3) the PMd is rostrally connected only with mid-DLPFC but not area 10 (Barbas & Pandya, 1987). This pattern of inter-connections is suggestive that at the rostral end, area 10 occupies the apex of the hierarchy within the frontal lobe since it has influence over all other subordinate levels. On the caudal end, PMd occupies the lowest hierarchy amongst the 3 regions since it can only influence the immediately rostral mid-DLPFC, but not area 10 due to a lack of efferents. The mid-DLPFC region likely occupies an intermediate level since it has reciprocal connections with both area 10 and PMd. Next, in terms of extrinsic connections, more rostral frontal areas (areas 10 and 9) do not project to the parietal, inferotemporal nor the occipital cortices that provide visual sensory inputs, whereas more caudal areas (9/46, 8, 45) are richly inter-connected with these areas (Petrides & Pandya, 2007). This suggested that along a rostro-to-caudal axis, frontal areas interact more strongly with more concrete sensory

information and less with more abstract sensory representations that are more integrated and highly-processed.

Experimental evidence from both human and monkey work has also revealed that increasingly abstract behavioural rules are being implemented in more rostral frontal areas (Badre & D'Esposito, 2009b). At the most caudal end, the PMd shows increased neural activity associated with simple conditional stimulus-action rules (e.g. if tone A, then left saccade) (Brasted & Wise, 2004; di Pellegrino & Wise, 1993b; Hadj-Bouziane, Meunier, & Boussaoud, 2003). Lesion experiments have also indicated the PMd is necessary for both the learning and performance of conditional visuo-motor associations (Petrides, 2005). Human fMRI work has also corroborated the involvement of the PMd in conditional visuo-manual associations (Amiez et al., 2006; Amiez, Hadj-Bouziane, & Petrides, 2012a). Immediately rostral to the PMd, mid-lateral prefrontal (mid-LPFC) areas are involved in more abstract rule representations. Showing a dissociation with the PMd, mid-LPFC lesions do not impair the performance of learnt simple stimulus-action rules (Petrides, 1985). It has been shown that mid-LPFC neurons selectively increase their firing rates to win-stay, lose-shift strategies (a more abstract rule to guide action selections) but not to the performance of specific responses (Genovesio, Brasted, Mitz, & Wise, 2005) and that lesions prevent the application of these strategies (Bussey, Wise, & Murray, 2001). Mid-LPFC activity is also associated with the maintenance of more abstract sequential movement plans (e.g. responding to a particular category of movement sequences) as opposed to individual movements that are maintained in the caudal-LPFC regions (Averbeck & Lee, 2007; Tanji & Hoshi, 2008). At the most rostral part of the frontal cortex, area 10 is implicated in monitoring the current task goals or strategies implemented in the more

caudal frontal areas and to switch to alternatives as the current ones become unreliable (Mansouri et al., 2017b). As such, area 10 contributes to the more abstracted level of behavioural control over the task goal and strategy representations in the mid-LPFC.

A landmark study by Koechlin and colleagues (Koechlin, 2003) provided direct evidence of a caudal-to-rostral gradient in the lateral frontal cortex that implemented progressively abstract and temporally extended levels of behavioural control. Based on the 'cascade model' proposed by the authors, the lowest level of control, "sensory control", involved the selection of a particular motor response based on a sensory input (e.g. selection between two button presses based on a colored cue). The next higher level of control, "contextual control" involved the selection of an action based on an environmental context cue (e.g. selection between two tasks that involved distinct stimulus-response mappings based on a secondary cue). At a higher level of abstraction, episodic control involved the selection between context-stimulus-response mappings across different temporal episodes. Via a computational model, Koechlin and colleagues revealed that the PMd, posterior DLPFC, and anterior DLPFC were involved in sensory, contextual and episodic control respectively. In a separate experiment, Koechlin and colleagues (1999) showed that as the performance on a main task was interrupted by a sub-task, the rostralmost area 10 was activated. The selection between main and sub-tasks /goals constituted "branching control", that was considered the most abstract level of control since its further displaced in time from the final action than episodic control.

How are the medial frontal regions involved in the rostro-caudal hierarchy of behavioural control demonstrated in the lateral frontal cortex? In a recent human fMRI study, Kounieher and colleagues (2009) have demonstrated that posterior-to-anterior medial frontal regions contribute to the processing of increasingly abstract motivational information to drive increasingly abstract levels of cognitive control along the lateral frontal cortex. Specifically, the processing of lower-order cues (which indicate the relative outcomes associated with single trials) led to increased activity in the pre-SMA (along with caudal LPFC regions); whereas the processing of higher-order cues (which indicate the relative outcomes associated with groups of trials, regardless of the status of single trials) led to increased activity in the more rostrally-located MCC region (along with the mid-DLPFC). Critically, effective connectivity analyses revealed that at the two abstraction levels, the activity in the medial frontal regions (i.e. pre-SMA and MCC) was driving activity in the lateral frontal regions (i.e. caudal LPFC and mid-DLPFC, respectively). The authors concluded that caudal-to-rostral medial frontal regions compute motivation signals to support behavioural control at increasingly levels of abstraction implemented by the LPFC.

Interestingly, a rostral-caudal gradient appears to be present within the MCC itself. Amongst the three cingulate motor areas, the most anterior CMA (CMAr) has strong inter-connections with the prefrontal cortex and pre-SMA and weak links with the premotor and motor areas, whereas the posterior CMAs show reversed pattern with stronger connections with motor-related and weaker links with prefrontal areas (Dum & Strick, 1991; Hatanaka et al., 2003; He et al., 1995; Luppino, Matelli, Camarda, & Rizzolatti, 1993a; Morecraft, Cipolloni, Stilwell-Morecraft, Gedney, & Pandya, 2004; Morecraft et al., 2012; Petrides & Pandya, 2006). This was indicative that in a caudal-

rostral axis, CMAs are increasingly involved in more abstract cognitive processing in tandem with the prefrontal cortex as opposed to more concrete motor processing with the motor areas. Corroborating this view, stimulations in caudal CMAs evoke movements more consistently than in rostral CMAs – indicating that caudal CMAs are more involved in motor control (Dum & Strick, 1991; He et al., 1995), and the CMAr is often associated with higher order cognitive functions, such as performance monitoring and error detection (Botvinick, Cohen, & Carter, 2004; Procyk et al., 2016; Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007). Currently, the functional connectivity between the 3 CMAs and the lateral frontal cortex has not been precisely investigated in humans. To address this gap, in Chapter 3, we investigated the connectivity between the 3 human CMAs and posterior-to-anterior lateral frontal regions to further elucidate the functional interactions between the MCC and lateral frontal cortex to support increasing behavioural control along a caudal-to-rostral axis. In this work, we precisely mapped the 3 human CMAs and their individual somatotopic representations based on a motor mapping protocol and subsequently examined their functional connectivity with lateral frontal regions via resting-state fMRI.

### **3. Anatomic-functional organization of the pLFC and MCC in conditional associative learning.**

#### 3.1 Hypothesis 1: Area 44 is involved in the visuomotor selection of vocal and orofacial responses.

In the present dissertation, the posterior lateral frontal cortex (pLFC) refers to the rostral premotor and caudal prefrontal cortical areas that are immediately anterior to the primary motor areas. As discussed in the earlier sections, this part of the frontal cortex is implicated in the selection of actions via stimulus-response associations (Amiez & Petrides, 2018; Amiez, Hadj-Bouziane, & Petrides, 2012a; Koechlin, 2003; Petrides, 2005; Tanji & Hoshi, 2008; Wise, di Pellegrino, & Boussaoud, 1996). Based on a series of experiments involving selective lesions in the macaque frontal cortex, Petrides (2005) proposed that the pLFC is involved in the selection between sensory information or motor actions on the basis of conditional operations. Petrides (Petrides, 1982; 1985) demonstrated that the anterior area 8 and the posterior rostral PMd (area 6) are necessary for the learning and performance of conditional associations between visual stimuli, and between visual stimuli and hand motor actions respectively. Notably, area 8 is closely associated with brain regions involved in oculomotor and visuo-spatial processing, whereas the pPMDr is closely associated with the parietal and motor systems. As such, Petrides (2005) suggested that different pLFC regions are involved in the selection between competing sensory stimuli or motor actions on the basis of the information they have access to. In line with this idea, a series of human functional neuroimaging experiments (Amiez et al., 2006; Amiez & Petrides, 2009; 2018; Amiez, Hadj-Bouziane, & Petrides, 2012a) have shown that that the pLFC is organized along



a functional gradient where areas involved in the conditional selection of a particular motor action (e.g. hand or saccadic movements) are located immediately rostral to the premotor/motor areas controlling the corresponding effector (PMD or FEF). By the same reasoning, one could expect that the ventral pLFC region (i.e. area 44), which is immediately anterior to the ventral premotor area that is strongly associated with orofacial/vocal motor control, could play an important role in the adaptive selection of orofacial/vocal responses (Loh, Petrides, Hopkins, Procyk, & Amiez, 2017b; Petrides, 2006). Indeed, area 44 in both humans and NHPs have been associated with the voluntary control of vocal and orofacial productions (Loh, Petrides, Hopkins, Procyk, & Amiez, 2017b). This hypothesis is investigated and validated via a human fMRI experiment that is reported in Chapter 2.

3.2 Hypothesis 2: 'Face' representation in the anterior-most CMA is involved in the evaluation of auditory vocal/verbal feedback.

As discussed earlier in Section 1.4.1., the primate MCC is implicated in the evaluation of previous action outcomes to drive adaptive behaviours (Amiez, Sallet, Procyk, & Petrides, 2012b; Procyk et al., 2016; Quilodran et al., 2008; Rushworth et al., 2003; Shima & Tanji, 1998). Critically, indicating a role in conditional associative learning, Amiez et al. (Amiez, Hadj-Bouziane, & Petrides, 2012a) found increased feedback-related activity in the MCC during the trial-and-error learning of conditional visuo-hand associations. In a review of the locations of feedback processing activity and motor stimulation sites in the monkey and human MCC, Procyk and colleagues (2016) reported an overlap between the locations for the evaluation of juice-rewarded behavioural outcomes and the face motor representation in the monkey rostral-most

CMA (CMAr). This led to the proposal that adaptive feedback processing in the MCC proceeded via an embodied manner where feedback corresponding to a particular modality is processed by the corresponding motor representation in the CMAr. In realistic situations, it is highly likely that the conditional associative learning associated with vocal actions is driven by feedback in the auditory modality (e.g. vocal signals from the communicating partner). However, how adaptive auditory feedback is processed in the MCC remains unknown. Based on the theory of embodied feedback processing in the MCC, we hypothesized that auditory feedback could be processed in the 'face' motor representation in the CMAr. This hypothesis is investigated and validated via a human fMRI experiment that is reported in Chapter 2.

### 3.3 Involvement of area 44 and MCC in cognitive vocal control across human and non-human primates.

The cortical control of primate vocalizations is achieved via two distinct pathways (Jürgens, 2002): 1) a more primitive "cingulate vocalization pathway", which descends from the MCC, down to the periaqueductal gray (PAG), which has access to the innate and affective vocal patterns; and 2) a "neocortical vocalization pathway", which descends from area 44, to the ventral premotor area, and finally the orofacial representation on the primary motor cortex which has direct projections to the orofacial and/or laryngeal motor nuclei. Seated at the top of their respective vocal control pathways, area 44 and MCC are involved in the voluntary control of vocalizations in both humans and NHPs: In NHPs, stimulations in the ACC/MCC evokes the production of species-typical calls, and ACC/MCC lesions result in decreased spontaneous calling and abolish the ability to initiate calls via discriminative cues

(Aitken, 1981; Jürgens & Ploog, 1970; MacLean & Newman, 1988; Robinson, 1967; Sutton et al., 1974). Stimulations in area 44 induces orofacial movements but not vocalizations (Petrides, Cadoret, & Mackey, 2005a). Critically, neurons in area 44 showed increased firing as monkeys voluntarily initiated calls based on discriminative cues (Coudé et al., 2011; Hage & Nieder, 2013). In humans, ACC/MCC stimulations evoke both orofacial movement and emotional vocalizations (Caruana et al., 2015; Sperli et al., 2006; Talairach et al., 1973). ACC/MCC lesions result in akinetic mutism, which is associated with a lack of will to speak or move (Ackermann & Ziegler, 1995; Brown, 1988). In humans, stimulations in area 44 evoke orofacial movements and speech arrests (Breshears et al., 2015; Penfield & Rasmussen, 1949). In addition, functional neuroimaging studies have consistently implicated that area 44 is involved in the both the processing and production of speech (Poldrack et al., 1999; C. J. Price, 2010; 2012). Importantly, Flinker and colleagues (2015) revealed via electrocorticographic (ECoG) recordings that prior to word productions that are cued via a spoken or non-spoken word, area 44/45 is involved in the transformation of the sensory representation associated with the word cue in the temporal cortex to articulatory motor patterns in the motor cortex. As such, across humans and NHPs, the MCC appears to be involved in the motivational and emotional initiation of vocalizations, while area 44 seems to be involved in the sensorimotor driving of vocal actions. These propositions are congruent with our hypothesized functions of the two regions in adaptive behavioural control detailed in Sections 3.1 and 3.2. We had suggested that the primate area 44 is involved in the conditional selection of vocal responses based on sensori-motor mapping, while the RCZa/CMAr (situated at the anterior MCC) is involved in processing of auditory feedback to adapt subsequent vocal actions. In Chapter 4, based on a comprehensive review of the neural correlates

of cognitive vocal control in both humans and NHPs, we argued that the above roles of area 44 and RCZa/CMAr in cognitive vocal control is common across primates. We further proposed how this common area 44- RCZa/CMAr network might have changed across primate evolution to enable human speech.

#### **4. Sulci-based localization of cognitive functions in the human brain**

Relative to other mammals or primates, the human brain exhibits a disproportionately high degree of gyrification, or folding (Zilles, Palomero-Gallagher, & Amunts, 2013). The complex patterning of sulci and gyri observed in individual human brains is not arbitrary, but carries important information about its anatomo-functional organization (Tomaiuolo & Giordano, 2016). Indeed, recent work has demonstrated that reliable and precise functional localizations can be achieved based on individual sulci-based anatomical landmarks in the frontal (i.e. dorsal premotor cortex (Amiez & Petrides, 2009; 2018), inferior frontal junction (Derrfuss, Brass, Cramon, Lohmann, & Amunts, 2009; Derrfuss, Vogt, Fiebach, Cramon, & Tittgemeyer, 2012), orbitofrontal cortex (Y. Li, Sescousse, Amiez, & Dreher, 2015) and cingulate cortex (Amiez et al., 2013; Amiez & Petrides, 2014; 2018)) and parietal brain regions (i.e. somatomotor cortex (Zlatkina, Amiez, & Petrides, 2015a) and angular cortex (Segal & Petrides, 2013b)). Importantly, these sulci-based anatomo-functional relationships can only be revealed via a single-subject analysis approach (pioneered by Amiez et al., 2006; Amiez & Petrides, 2009) that involved the investigation of task-related functional activations in individual subjects. The precise correspondences between sulcal patterning and functional localizations in individual brains underscore the importance of taking individual anatomy into account during the localization of brain functions. The common practice of averaging brain activations across subjects with different brain anatomy in stereotaxic space can lead to imprecise localization of functional activity. Critically, the precise anatomo-functional relationships revealed by sulci-based functional localizations have important utility for efficient brain navigation during open-brain neurosurgery (Tomaiuolo & Giordano, 2016). Currently, all the occurring sulci in the

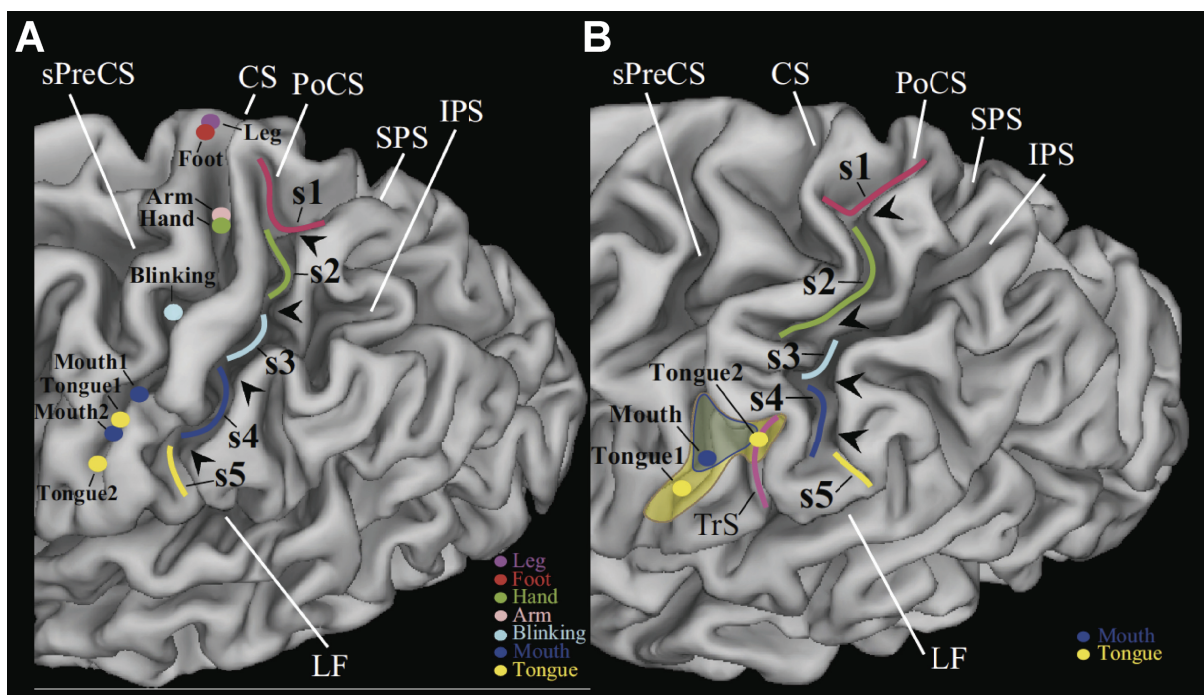
human brain have been labelled and named (see Petrides, 2012). In this section, we summarize existing findings about sulci-based functional localizations in the main frontal brain regions that are of interest to the current dissertation.

#### 4.1 Sensorimotor cortex

The sensorimotor cortex broadly includes the lateral cortical region peripheral to the central sulcus (CS) that is bounded anteriorly by the pre-central sulcus (PreCS), and posteriorly by the post-central sulcus (PoCS). Investigating the morphology of the pocs, Zlatina and Petrides (2010) revealed that it can be separated into segments via submerged gyral bridges ('plis de passage') that link the anterior and posterior sulcal banks. In all of their subjects, Zlatina and Petrides (2015a) consistently identified four plis de passages, which led to 5 different segments along the dorsal-ventral extent of the PoCS (namely, s1-s5 along the dorsal-ventral order). In addition, a short transverse postcentral sulcus (TrS) can be also present or absent in the ventral postcentral gyrus (Fig. 6). When a TrS is absent (Fig. 6B), the most ventral branch of the postcentral sulcus (s5) extends more ventrally towards the lateral fissure.

A series of electrical stimulation experiments by Penfield and colleagues has established a general dorsal-to-ventral organization of motor and somatosensory body maps in the pre- and post-central gyri of the human brain, respectively: going ventrally along the peri-central sulcus gyri, one will find the toes and feet, followed by the legs, trunk, arm, hand, and finally, the orofacial representation (Penfield & Boldrey, 1937; Penfield & Rasmussen, 1949). To determine if there is a correspondence between the dorsal-ventral organization of the somatosensory-motor maps and of the various

segments along the pocs, Zlatkina and Petrides (2015a) examined the locations of activation peaks associated with foot, leg, hand, mouth, tongue and eye movements in relation to individual sulcal anatomy in the PoCS. Their results demonstrated that the relative positions of the sensory-motor maps in the pre-/post-central gyrus could be predicted from the locations of the PoCS segments: the foot and leg representations are typically located anterior to s1, the arm and hand representations are found anterior to s2, blinking activity peaks are located anterior to s3, and finally the mouth and tongue representations are typically localized anterior to s4 and s5 (Fig. 6). Interestingly, when a TrS was present (20% of the hemispheres in (Zlatkina, Amiez, & Petrides, 2015b)), the tongue and mouth representation was anterior to the TrS; when it was absent, the representations were instead located anterior to s5.

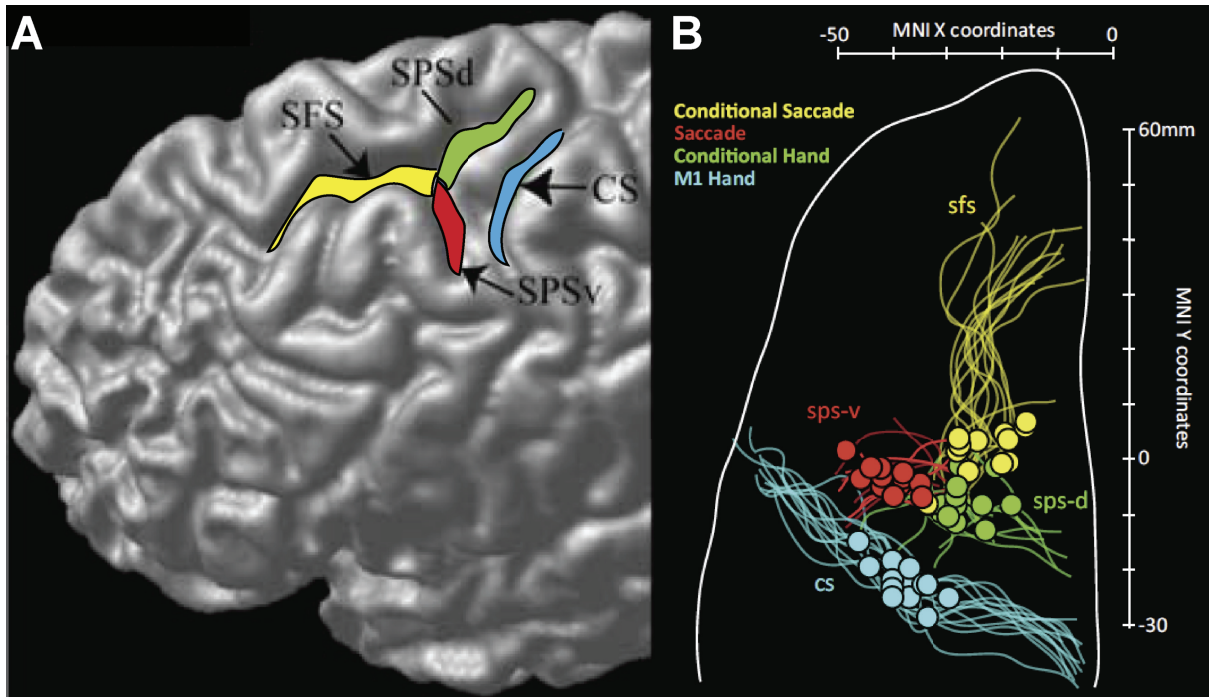


**Figure 6. Sulcal-based anatomo-functional relationships in the sensorimotor cortex. Adapted from (Zlatkina, Amiez, & Petrides, 2015a).** (A) Hemisphere without a TrS. (B) Hemisphere with a TrS. Abbreviations: CS, central sulcus, PoCS, post-central sulcus, LF, lateral fissure, sPreCS, superior precentral sulcus, SPS, superior parietal sulcus, IPS, inferior parietal sulcus.

## 4.2 Posterior lateral frontal cortex

The posterior part of the lateral frontal cortex (pLFC) includes the typically dysgranular caudal prefrontal and rostral premotor areas that are situated immediately adjacent to the agranular premotor and motor areas. As reviewed in section 3.1, the pLFC is implicated in the selection between competing stimuli and motor responses based on conditional operations (Petrides, 2005). Through a series of neuroimaging experiments, Amiez and colleagues (2006; 2009; 2018) have demonstrated that in the dorsal pLFC, the precise anatomical locations associated with the conditional visuomotor selection of hand and saccadic movements can be reliably predicted on the basis of individual sulcal morphology. Providing evidence of a rostral-caudal gradient between the dorsal pLFC and the more caudally located premotor/motor areas, Amiez and Petrides (2018) further demonstrated that the activation peaks associated with the basic hand and saccadic movements are located immediately caudal to the pLFC areas recruited for conditional operations involving the same effectors. Importantly, these basic movement peaks can also be precisely localised on the basis of individual sulcal anatomy. In this section, we summarize the sulcal morphology in the dorsal pLFC and its relation to the conditional visuomotor selection and basic performance of hand and saccadic responses.





**Figure 7. Sulcal-based anatomo-functional relationships in the dorsal posterior lateral frontal cortex.** (A) Sulcal morphology in the dorsal posterior lateral frontal cortex (Amiez et al., 2006). (B) Single-subject activation peaks corresponding to conditional visuo-saccadic associations (yellow), conditional visuo-hand associations (green), saccadic movements (red), hand movements (blue). Adapted from (Amiez & Petrides, 2018). Abbreviations: CS, central sulcus, SFS, superior frontal sulcus, SPSd, dorsal superior precentral sulcus, SPSv, ventral superior precentral sulcus.

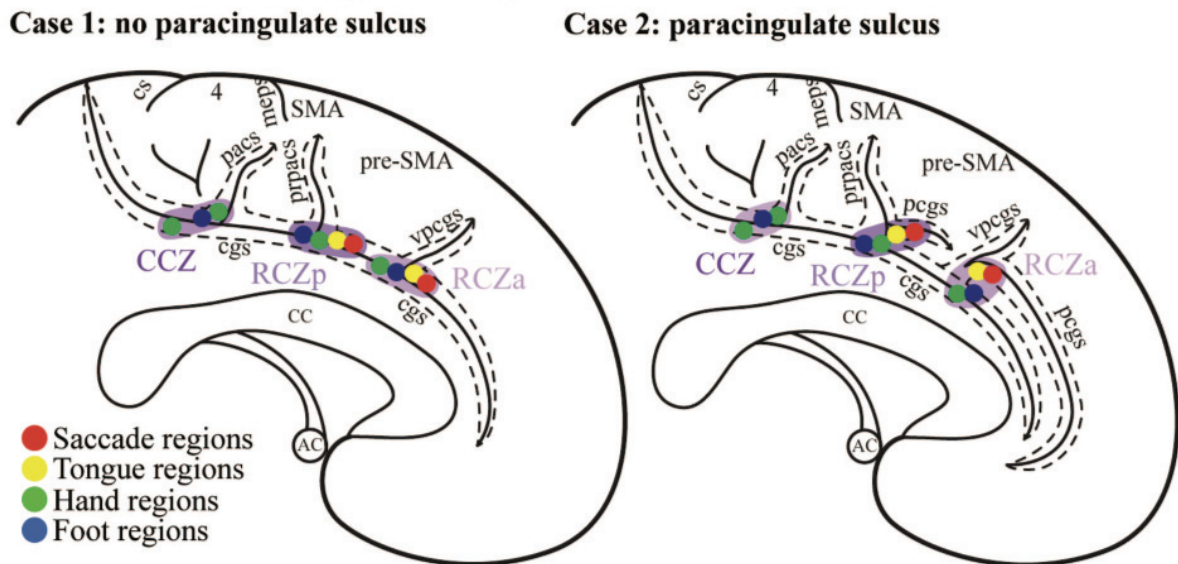
The morphological feature of focus in the human dorsal pLFC is the junction between the superior precentral sulcus (SPS) and the caudal end of the superior frontal sulcus (SFS). The SPS constitutes two distinct sulci – a dorsal SPS-d that joins the end of the SFS and a ventral SPS-v that might, or might not join the SPS-d at the junction with the SFS (Amiez et al., 2006). As subjects selected between competing hand actions based on previously learnt conditional visuo-hand associations (i.e. if visual stimulus A, then hand action 1), the peak activity was precisely located on the SPS-d based on single-subject analyses (Amiez et al., 2006; Amiez & Petrides, 2018). Correspondingly, the basic performance of hand actions evoked activity in the “precentral knob” area within the central sulcus (the well-established anatomical landmark for the primary hand representation; Boling et al. (1999)). On the other hand,

as subjects conditionally selected between saccadic movements, the peak activation was precisely found in the anterior sfs area in individual brains (Amiez & Petrides, 2018). Correspondingly, across subjects, the volitional execution of saccadic movements always evoked activity in the SPS-v, a region directly caudal to the area associated with conditional saccadic movements. This set of findings provided strong support for a caudal-rostral gradient in the posterior LFC for increasingly higher-levels of behavioural control: whereas the caudal premotor/motor areas are involved in the volitional performance of motor actions associated with different effectors, the directly anterior pLFC regions are involved in conditional operations on motor actions involving the same effectors as the caudal premotor/motor areas. There is also a dorsal-ventral organization in the pLFC and the caudal motor areas for the different motor effectors. Importantly, these anatomo-functional relationships can be observed at the level of individual subjects and can be precisely localized via sulcal-based landmarks (i.e. the SPS-d and precentral knob for conditional and simple hand actions, and SPS-v and anterior SFS for conditional and simple saccadic movements).

#### 4.3 Cingulate motor areas

Three distinct cingulate motor areas (CMAs) have been identified along the anterior-posterior axis of human cingulate cortex (Amiez & Petrides, 2014; Loh, Hadj-Bouziane, Petrides, Procyk, & Amiez, 2017a; Picard & Strick, 1996; 2001). Whereas the two anterior CMAs (RCZa and RCZp) both contain one hand, one foot and one face motor representation each, the posterior CMA (CCZp) contains two hand and a foot representation. As reviewed in section 1.4.1, the three CMAs appear to be organized along a caudal-rostral functional gradient with increasingly rostral/caudal CMAs being

implicated in higher-order cognitive/lower-order motor control functions (Loh, Hadj-Bouziane, Petrides, Procyk, & Amiez, 2017a). Notably, the rostral-most RCZa appear to play a key role in the evaluation of action feedback for behavioural adaptations (Procyk et al., 2016).



**Figure 8. Anatomofunctional organization of the human cingulate motor areas in hemispheres without (left) and with (right) a paracingulate sulcus.** Figure reproduced from (Amiez & Petrides, 2014). Abbreviations: cs, cingulate sulcus; pcgs, paracingulate sulcus; pacs, paracentral sulcus; prpacs, pre-paracentral sulcus; vpcgs, vertical paracingulate sulcus; cs, central sulcus; meps, medial paracentral sulcus.

A key morphological feature of the human cingulate cortex is that while all humans possess a cingulate sulcus (cgs) in both hemispheres, some might present a second cingulate sulcus dorsal and parallel to the cgs – the para-cingulate sulcus (pcgs) in one or both hemispheres (Petrides, 2012). The pcgs is present in around 70% of subjects in at least one hemisphere (Fornito et al., 2008; Paus et al., 1996; B. A. Vogt et al., 1995). There is a strong relationship between the presence/absence of pcgs and the cytoarchitectonic organization in the mid-cingulate cortex: when a pcgs is absent, areas 24c' and 32' will occupy the ventral and dorsal banks of the cgs; when a pcgs is present, area 32' will occupy the para-cingulate gyrus and the pcgs, and area 24c' will cover both banks of the cgs (B. A. Vogt et al., 1995). Given that the CMAs

occupy or overlap with these cytoarchitectonic areas, it was conceivable that the presence or absence of a pcgs could affect the locations of the CMAs. Indeed, Amiez and colleagues (Amiez & Petrides, 2014; Loh, Hadj-Bouziane, Petrides, Procyk, & Amiez, 2017a) have consistently shown that when a pcgs was present, the face motor representations in RCZa and RCZp would be reliably found in the pcgs; but when a pcgs was absent, they would be always located in the cgs. Secondly, the relative locations of the three CMAs can also be reliably determined based on sulcal landmarks in the cingulate cortex. Along the anterior-posterior extent of the human cingulate cortex, three vertical sulci are typically found that intersect the pcgs/cgs perpendicularly. Going rostrally, these correspond to the paracentral sulcus (pacs), pre-paracentral sulcus (prpacs) and vertical paracingulate sulcus (vpcgs). Critically, the locations of the RCZa, RCZp and CCZ are consistently found to be located at the intersections between the pcgs/cgs with the vpcgs, prpacs and pacs respectively (Amiez & Petrides, 2014).

## **Chapter 2: Cognitive control of orofacial and vocal responses in the human frontal cortex**

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## Abstract

Two main regions in the frontal cortex of the human brain are critical for speech production: Broca's region in the ventrolateral frontal cortex of the language dominant hemisphere and a set of dorsomedial frontal areas including the mid-cingulate cortex (MCC) and pre-supplementary motor area (preSMA). Intriguingly, the homologs of these regions exist also in non-speaking primates and are linked with cognitive vocal control, suggesting a generic role that evolved across primates to enable speech production. Here we developed a functional magnetic resonance imaging (fMRI) protocol to explore the specific contribution of the different components of this network. The posterior component of Broca's region (area 44), which is directly linked to the precentral motor region representing the orofacial musculature, is involved in the cognitive selection of orofacial, vocal non-speech, and speech (but not manual) responses, whereas the anterior component of Broca's region (area 45) is only involved in vocal/speech response selections. The orofacial representation of MCC is involved in motor acts independently of the effector and analysis of vocal/verbal feedback for learning and the pre-SMA is specifically involved in driving verbal action selections based on auditory verbal feedback.

## Introduction

The identification of brain networks for the cognitive control of vocal production and how they may have evolved in primates to enable speech in the human brain lies at the core of research on the neural mechanisms underlying language. Two regions of the frontal cortex are critically involved in the human brain: one is the classic Broca's region in the ventrolateral frontal cortex in the language dominant hemisphere and the other less well-known region is the dorsomedial frontal cortex (DMF). Damage to the ventrolateral frontal cortex (Broca's region) yields severe impairments in speech. Broca's region is traditionally considered to comprise cytoarchitectonic areas 44 and 45 (Petrides, 2014). Area 44 is a dysgranular cortical area located on the pars opercularis immediately anterior to the ventral precentral motor region that is involved in the control of the orofacial musculature. Electrical stimulation of the pars opercularis, where area 44 lies, in patients undergoing surgical operations results in speech arrest, i.e. the cessation of speech (e.g. Penfield & Roberts, 1959). The granular area 45 that lies on the pars triangularis (immediately anterior to area 44) also plays a more complex role in language. Functional neuroimaging studies have suggested a role in controlled verbal memory retrieval (e.g. Petrides, Alivisatos, & Evans, 1995) which is often expressed in verbal fluency (e.g. Amunts et al., 2004; Wagner, Sebastian, Lieb, Tüscher, & Tadić, 2014).

The importance of the dorsomedial frontal region (DMF) for language was highlighted by Penfield and colleagues who demonstrated that electrical stimulation there results in vocalization in a silent patient, and speech interference or arrest in a speaking patient (Penfield & Roberts, 1959). The DMF comprises the supplementary motor area (SMA), the pre-supplementary motor area (preSMA), and the adjacent mid-cingulate cortex (MCC) which recent research has shown includes 2 cingulate

motor regions (Palomero-Gallagher, Mohlberg, Zilles, & Vogt, 2008). The cingulate motor areas were first demonstrated in the macaque monkey (Dum & Strick, 2002) and, more recently, in the human brain (Amiez & Petrides, 2014; Loh, Hadj-Bouziane, Petrides, Procyk, & Amiez, 2018). These mid-cingulate motor areas contain orofacial motor representations that are likely to be involved in the control of vocalization/speech. Several studies have shown that DMF lesions yield long-term reduction in verbal output. A recent study has confirmed this classic finding (Chapados & Petrides, 2013) and has shown that lesions of the dorsolateral, orbital, and ventromedial prefrontal cortex do not lead to reduced verbal fluency. Thus, only lesions involving Broca's region in the ventrolateral frontal cortex and the DMF region lead to reduction in speech output. Second, lesions limited to SMA are not sufficient to lead to verbal fluency reduction. The DMF lesions must include SMA, pre-SMA and the MCC region to induce deficits, suggesting the existence of a local DMF network contributing to vocal and speech production.

Importantly, it has been shown in a comparative cytoarchitectonic investigation (Petrides & Pandya, 1994; 2002; Petrides, Cadoret, & Mackey, 2005) that macaque monkeys possess the cytoarchitectonic homologue of the human area 44 that is considered a key area for speech production in the human brain, as shown by the reliable speech arrests occurring upon stimulation of the pars opercularis where this area lies (Penfield & Roberts, 1959). Macaque monkeys also possess the various areas that comprise the DMF region (Procyk et al., 2016). It may therefore appear somewhat surprising that these ventrolateral and dorsomedial frontal areas that play important roles in human language production exist also in non-speaking primates and raise fundamental questions about their role in cognitive vocal control and the evolution of language (reviewed in Loh, Petrides, Hopkins, Procyk, & Amiez, 2017).



Our hypothesis is that the ventrolateral frontal region (known as Broca's region in the language dominant hemisphere) and the areas of the dorsomedial frontal (DMF) region may constitute a brain network that is conserved across primate evolution and has a critical role in the cognitive control of voluntary vocalization that is generic in the primate order. This network may have evolved originally in pre-linguistic primate brains as a specialized network for the high-level selection of motor orofacial and vocal responses.

The aim of the present functional neuroimaging study was to disentangle the specific roles of the different components of this Broca-DMF network in vocal and speech production. To examine the high-level cognitive selection of orofacial and vocal responses, we adopted a paradigm that has been used successfully in the dorsolateral frontal region to examine the high-level cognitive selection of motor responses (e.g. hand response), namely the conditional associative response paradigm. Here the subject is required to learn to select different motor acts cued by arbitrary external sensory stimuli. In the dorsolateral frontal region, it has been shown that lesions of the transition zone between the precentral motor zone and the dorsolateral prefrontal cortex do not impair motor action per se but result in severe impairments in learning to select between different competing motor responses based on conditional (if, then) relations established during learning (Petrides, 1982; 1985; 2005). Furthermore, activity in this anterior premotor region increases during the learning and performance of such conditional motor acts (Amiez & Petrides, 2018). Based on the above research, one may therefore ask whether ventrolateral area 44 that lies at the interface between the ventral precentral gyrus (where orofacial/vocal motor acts are represented) and the ventrolateral prefrontal cortex (area 45) might be the critical area for the high-level flexible selection of orofacial and vocal acts based

on conditional rules (e.g., in response to stimulus A, select vocal/orofacial act X, but in response to stimulus B, select vocal/orofacial act Y, and in response to stimulus C, select vocal/orofacial act Z).

The acquisition of such conditional actions depends on the analysis of behavioral feedback and the DMF areas may be critical for such processing (Procyk et al., 2016). It must be noted that, in the primate social world, orofacial and vocal responses are most often driven by auditory primate conspecific vocalization feedback. However, although the available scientific literature has extensively shown the involvement of the MCC in the analysis of behavioral feedback in learning situations (Amiez, Hadj-Bouziane, & Petrides, 2012a; Amiez et al., 2013; Amiez, Sallet, Procyk, & Petrides, 2012b), these studies never used auditory vocal feedback.

To test the hypothesis that the generic role of the Broca – DMF network may be the cognitive control of orofacial and vocal responses (including speech responses in the human brain) based on the analysis of vocal feedback, we developed an fMRI protocol that involved learning to select the correct orofacial, vocal nonspeech and speech responses to visual cues (i.e. the learning of conditional associations) driven by auditory vocal feedback, a task that can successfully be performed by primates. To understand what the uniqueness of this network in the human brain might be, we also added a human-specific task involving the learning of visuo-verbal conditional associations driven by auditory verbal feedback. In addition, to define clearly the specific role of the Broca-DMF network, we also included a version of the conditional task that involved manual responses, which according to our hypothesis, should not involve the Broca region, but rather the dorsal premotor cortex (PMd) (Amiez & Petrides, 2018; Amiez, Hadj-Bouziane, & Petrides, 2012a; see Petrides, 2005 for a review).

The results revealed the critical role of the Broca-DMF network and the respective role of its elements: Area 44 on the pars opercularis, i.e. the transitional posterior part of Broca's region is specifically involved in the cognitive selection of conditional orofacial, vocal, and verbal responses (but *not* manual responses) on the basis of vocal and verbal feedback both during learning novel associations (learning period) and also during the performance of learnt ones. The mid-cingulate cortex (MCC) is involved in the cognitive selection of visuo-motor conditional responses and analysis of both vocal and verbal feedback, *independently of the effector of the response*, and specifically during the learning period. By contrast, the preSMA is specifically recruited for verbal conditional selection and verbal feedback processing during the learning period. These results clearly demonstrate the common involvement of Broca-MCC network in exerting cognitive control of orofacial versus vocal responses on the basis of vocal feedback, strongly suggesting that the function of this network may be generic across primates. By contrast, the preSMA is selectively involved in cognitive control of verbal response selection based on verbal feedback, suggesting that the recruitment of this area, in addition to the Broca-MCC network, may allow cognitive control exerted on complex speech in humans.

## **Method**

### ***Subjects***

For this study, 22 healthy, right-handed native French speakers were recruited to participate in a training session and 3 fMRI sessions. Data from two subjects (S2, S13) were omitted from our analyses as they showed poor performance across the three experimental sessions. Two other subjects (S6, S9) did not participate in any of the sessions due to claustrophobia. Consequently, the final dataset consisted of 18 subjects (10 males, mean age=26.22 (SD=3.12)). The study was carried out in accordance with the recommendations of the Code de la Santé Publique and was approved by the “Agence Nationale de Sécurité des médicaments et des produits de santé (ansm)” and the “Comité de Protection des Personnes (CPP) Sud-Est III” (N° EudraCT: 2014-A01125-42). It also received a Clinical Trial Number (NCT03124173, see <https://clinicaltrials.gov>). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

### ***Tasks***

Two main tasks were used in the current study: 1) A visuo-motor conditional learning task (Fig. 1A), and 2) a visuo-motor control task (Fig. 1B). The sequence of events was similar for the two tasks: At the start of each task block, an instruction screen lasting for 2 seconds informed the participant of the type of task to be performed. Here, one of two possible instruction statements would be presented: “Find the correct associations” or “Select the X response”, which indicated the start of a learning task or the control task block, respectively. Following the instructions, a black screen with

a central fixation cross was presented during a variable inter-trial interval of 0.5-8 seconds (mean=3.5 seconds). In each subsequent trial, one of three possible visual stimuli (abstract grayscale images) was presented on the center of the screen for 2 seconds. Stimulus presentation was ordered as randomly permuted blocks of the three possible images (i.e. abc, bca, acb, etc.). In response to each presented stimulus, the subject had to perform one of three possible motor responses (learning task) or an instructed motor response (control task). After a variable delay (0.5-6 seconds, mean=2 seconds), an auditory feedback (1 second) was provided to inform the subject whether the response correctly matched the presented image (learning task) or the instructed response (control task). The next trial commenced after a variable inter-trial delay (0.5-8 seconds, mean=3.5 seconds). For half of the task blocks, verbal feedback was provided (positive: "Correct"; negative: "Error"). For the remaining blocks, vocal feedback was provided (positive: "Aha"; negative: "Boo"). The subject was instructed about the type of feedback by the text color on the instruction screen at the start of each task (Verbal: Yellow, Vocal: Red). The four different auditory feedbacks were recorded from the same male voice and processed using Audacity software.

In each visuo-motor conditional learning task block (Fig. 1A), subjects had to acquire three visuo-motor conditional associations (if visual stimulus A, then motor response X) via trial-and-error. On every trial, one of the three possible stimuli were presented and the subject had to select one of the three possible responses to perform (Response Selection). Auditory vocal/verbal feedback was then provided to inform the subject whether the selected response matched the presented stimulus or not. This trial-and-error learning period continued until the subject identified the correct response for each stimulus. When a correct response had been performed once for each of the three visual stimuli, the task proceeds to the "post-learning" period where

the subject had to perform each of the learnt conditional associations twice (6 trials). Note that in each visuo-motor conditional learning task block, a novel set of 3 stimuli was presented.

In each visuo-motor control task block (Fig. 1C), subjects were informed of the specific response to perform on the instruction screen. Subsequently, they had to perform the same instructed response to all of the three different visual stimuli over five trials. In contrast with the learning task, subjects did not have to select the appropriate motor response to perform based on the presented stimuli nor to adjust their selections based on the provided feedback. Importantly, different sets of abstract visual images were used in all learning and control task blocks. Note that in each control task block, a novel set of 3 stimuli was presented.

In the present study, there were three versions of the visuo-motor conditional learning and control tasks that corresponded to three different response effectors: manual, orofacial, vocal and verbal (Fig. 1B). In the visuo-manual condition, subjects acquired associations between three button presses on an MRI compatible button box and visual stimuli in the conditional learning task and performed instructed button presses in the control task.

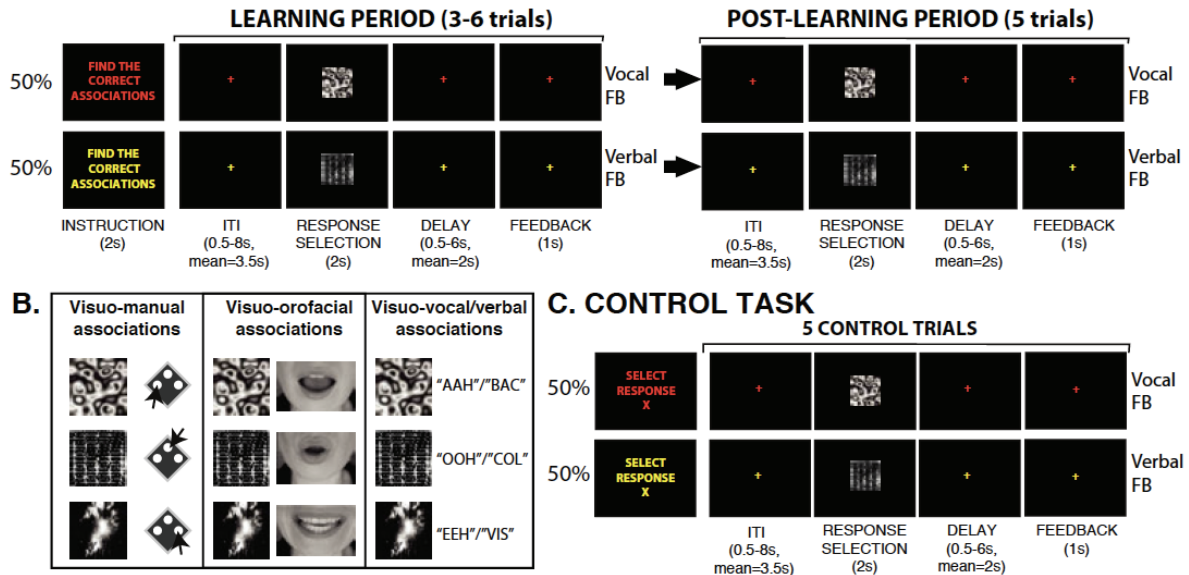
In the visuo-orofacial condition, subjects performed the conditional learning task and control tasks using three different orofacial movements (Fig 1B, middle panel). In the visuo-vocal/verbal condition (Fig 1B, right-most panel), either three different meaningless vocal responses (e.g. “Ahh”, “Ihh”, “Ohh”) or verbal responses that were French words (e.g. “Bac”, “Vis”, “Col”) were used during the learning and control tasks and the feedback provided was either vocal or verbal. These vocal and verbal responses were selected to match, as closely as possible, the orofacial movements performed in the visuo-orofacial condition: The first orofacial action (top image in the

orofacial panel; Fig 1B) is almost identical to the mouth movements engaged in producing the vocal action 'AAH' and similar to the verbal action "BAC". In the same manner, the second and third orofacial actions corresponded to vocal actions "IIH" and "OHH", and verbal actions "VIS" and "COL", respectively. Subjects were informed of which set of responses to use via the text color of the instructions (red – "vocal", yellow - "verbal"). For the manual and orofacial conditions, subjects used the same set of responses for verbal and vocal feedback.

Each subject participated in three fMRI sessions. In the first session (visuo-manual fMRI session), they performed the visuo-manual conditional learning task and the visuo-manual control task. In the second session (visuo-orofacial fMRI session), they performed the visuo-orofacial conditional learning task and the visuo-orofacial control task. In the third session (visuo-vocal/verbal fMRI session), they performed the visuo-vocal/verbal conditional learning task and the visuo-vocal/verbal control task. To ensure optimal performance during the actual fMRI sessions, all subjects were familiarized with all three versions of the learning and control tasks in a separate training session held outside the scanner. During the training session, subjects practiced the visuo-manual, visuo-orofacial, and visuo-vocal/verbal conditional learning tasks until they consistently met the following criteria in each version: 1) not more than one sub-optimal search (i.e. trying the same incorrect response to a particular stimulus or trying a response that had already been correctly associated to another stimulus) during the learning phase, and 2) not more than one error in the post-learning phase.

**FIG 1**

**A. CONDITIONAL ASSOCIATIVE LEARNING TASK**



**Figure 1. Experimental tasks.** **A.** Conditional associative learning task. In the learning phase, subjects have to discover, by trial-and-error, the correct pairings between three possible motor responses and three visual stimuli. In each trial, one visual stimulus was randomly presented for 2 seconds, in response to which the subjects selected and performed one of the three motor responses (Response Selection). If the instruction font and fixation cross were red (in 50% of learning sets), vocal feedback was provided to indicate whether the response was correct (“AHA”) or wrong (“BOO”). If the instruction font and fixation cross were yellow (in 50% of learning sets), verbal feedback was provided to indicate whether the response was correct (“CORRECT”) or wrong (“ERROR”). After a subject has performed a correct response to each one of the three stimuli (i.e. the end of the learning period), the subjects had to perform each of learnt associations twice (i.e. post-learning period). **B.** Visuo-motor associations that subjects have to learn in the 3 versions of the visuo-motor conditional associative learning task. In the visuo-manual condition, subjects learn associations between 3 button presses and 3 visual stimuli. In the visuo-orofacial condition, subjects learn associations between 3 orofacial movements and 3 visual stimuli. In the visuo-vocal/verbal condition, subjects learn associations between 3 vocal (“ahh”, “ihh”, “ooh”) or 3 verbal (“bac”, “vis”, “col”) responses and 3 visual stimuli. **C.** Visuo-motor control task with vocal feedback (50% of trials, indicated by red colored fonts of the instructions and fixation crosses) or verbal feedback (50% of trials, indicated by yellow colored fonts of the instructions and fixation crosses). In the control task, the subjects perform the instructed (X) motor response to every presented stimulus during response selection for 5 consecutive trials. All motor responses used in the conditional associative learning task (the 3 manual, 3 orofacial, and 3 vocal/verbal) are instructed to be performed in control trials over the 3 fMRI sessions.



## ***MRI acquisition***

Scanning was performed on a 3T Siemens Magnetom Prisma MRI Scanner (Siemens Healthcare, Erlangen, Germany). To minimize movements during the motor tasks, subjects' heads were tightly cushioned throughout the acquisition. The main experimental protocol consisted of three MRI sessions (~2hrs), each involving a different version of the visuo-motor conditional learning and control tasks (visuo-manual, visuo-orofacial, and visuo-vocal/verbal). For each fMRI session, subjects performed four to six experimental runs in the scanner. Experimental runs were programmed and presented using Presentation (Neurobehavioral systems). Visual stimuli were presented via an LCD projector with a mirror system. Auditory feedback was delivered via MRI-compatible earphones (Siemens Healthcare, Erlangen, Germany).

The start of each run was synchronized to the 5th TTL pulse from the MRI scanner following scan initiation. Each run began with a fixation task followed by two motor mapping task blocks involving either: hand and eye movements (visuo-manual session), verbal and vocal responses (visuo-vocal/verbal session) or mouth and tongue movements (visuo-orofacial session). The details of the fixation and motor mapping tasks are described in (Loh et al., 2018). After the three fixation/motor mapping task blocks (total duration = 28.5 sec), subjects were presented with the six learning task blocks (3 x 2 feedback types) and six control task blocks (3 motor responses x 2 feedback types) that were randomly interleaved in each run. The total length of each run was limited to a maximum of 14.6 mins, yielding 400 T2\*-weighted gradient echo planar EPI volumes (40 descending oblique slices, voxel resolution = 2.7mm x 2.7mm x 2.7mm, TR = 2.2s, TE = 30.0s, flip angle = 90°). The initial five

volumes of each acquisition were discarded to avoid confounds of unsteady magnetization. High-resolution T1 structural images (MPRAGE, 0.9mm<sup>3</sup> isotropic voxels, 192 slices, TR=3.5 sec, TE=2.67 sec), together with Diffusion Tensor Imaging (DTI) and resting state functional scans (not analyzed in the current study) were each acquired in one of the three MRI sessions at the end of all experiment task runs.

### ***Behavioral data processing and analyses***

In the visuo-manual fMRI session, subjects responded directly to the task within the scanner via an MRI-compatible button box (Current Designs, Philadelphia, USA) connected to the Presentation computer. Raw trial data, including trial events, reaction times and accuracies were directly extracted from the Presentation logfiles.

In the visuo-vocal/verbal fMRI session, an MRI-compatible microphone was installed on the head-coil, near the subjects' mouths, to record their vocal/verbal responses during the task. Outside the scanner, an experimenter monitored the subjects' vocal/verbal responses in real-time and responded to the task via keyboard presses on the Presentation computer. A Biopac MP150 system (Biopac Systems Inc, Goleta, CA) was used to simultaneously acquire, and synchronize: 1) the digital and analog audio signals from the microphone, 2) task event signals from Presentation, and 3) TTL signals from the MRI scanner. After the experiment, the subjects' actual vocal/verbal response onsets were computed from the analog audio signal (time-synchronized to task events and MRI pulses) using a customized onset detection algorithm (written by R. Neveu and available upon request) implemented on Matlab ([www.mathworks.com](http://www.mathworks.com)). The detected vocal/verbal responses in the audio recordings were subsequently used to verify the responses made by the experimenter during the

task (logged by the Presentation software). The trial event timings were acquired directly from the Presentation logfiles.

In the visuo-orofacial fMRI session, a video-camera was used to record the subjects' mouth responses as they performed the task in the scanner. As in the visuo-vocal/verbal experiment, an experimenter responded to the task outside of the scanner according to the subjects' mouth responses. The Biopac system was also used to acquire the video data, in parallel with task event and MRI TTL signals. A customised Matlab program (written by K. Loh and available upon request) was used to synchronize the video recordings with the timings of the task events, and subsequently, allow the experimenter to manually playback each video segment frame-by-frame to determine the onset of each orofacial response. The orofacial responses detected from the video were cross-checked with the responses made by the experimenter during the task. The trial event onsets were acquired directly from the Presentation logfiles.

We used three main performance measures from the learning and control tasks: 1) the proportion of correctly performed blocks, 2) the number of trials constituting the learning period (learning period length), and 3) the response time (RT) for each trial. With the proportion of correct blocks, we examined the effects of block type (learning/control), response type (manual/orofacial/vocal-verbal) and feedback type (vocal/verbal), and their possible interactions. A generalized linear mixed effect regression with binomial distribution was performed via the *glmer* function (Bates, Mächler, Bolker, & Walker, 2015) in R statistical software. With trial RTs, we examined the effects of trial type (learning/post-learning/control), response type (manual/vocal/orofacial), and feedback type (vocal/verbal), and their possible interactions. Only behavioral data from the correctly performed learning and control

task blocks were analyzed. A linear mixed effect regression with a normal distribution was performed via the *glmer* function (Bates et al., 2015).

### ***MRI data processing and analyses***

The preprocessing and analyses of MRI data were performed with Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, University of College London, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) and Matlab 15b ([www.mathworks.com](http://www.mathworks.com)).

First, structural and functional images were reoriented by setting their origins to the anterior commissure. The first 5 volumes of each run were excluded to remove T1 equilibrium effects. Next, within each session, we realigned all successive images to the first image of the session. Using the Artefact Detection Toolbox (ART; [http://www.nitrc.org/projects/artifact\\_detect/](http://www.nitrc.org/projects/artifact_detect/)), motion outliers were computed from the realigned images and realignment parameters. The realignment parameters and detected motion outliers were saved as covariates to model out potential nonlinear head motion artefacts in subsequent statistical analyses. Slice-timing correction was applied with the time centre of the volume as reference. The subject-mean functional images were co-registered with the corresponding structural images using mutual information optimization. Functional and structural images were then spatially normalized into standard MNI space. Finally, functional images were smoothed using a 6-mm full-width half-maximum Gaussian kernel (Friston, Frith, Frackowiak, & Turner, 1995a; Friston, Frith, Turner, & Frackowiak, 1995b; Friston et al., 1995c).

For each subject, fMRI data from the 3 fMRI sessions (manual/orofacial/vocal/verbal) were modeled separately. At the first level, each trial

was modeled with impulse regressors at the two main events-of-interest: 1) Response Selection (RS) – the 2s epoch after the stimulus onset, during which the subject had to perform a response after stimulus presentation, and 2) Auditory Feedback (FB) – the 1s epoch after the onset of auditory feedback. RS and FB epochs were categorized into either learning ( $RS_L$ ,  $FB_L$ ), post-learning ( $RS_{PL}$ ,  $FB_{PL}$ ) or control ( $RS_C$ ,  $FB_C$ ) trial events. These regressors were then convolved with the canonical hemodynamic response function and entered into a general linear model of each subject's fMRI data. The six scan-to-scan motion parameters produced during realignment and the ART-detected motion outliers were included as additional regressors in the general linear model to account for residual effects of subject movement.

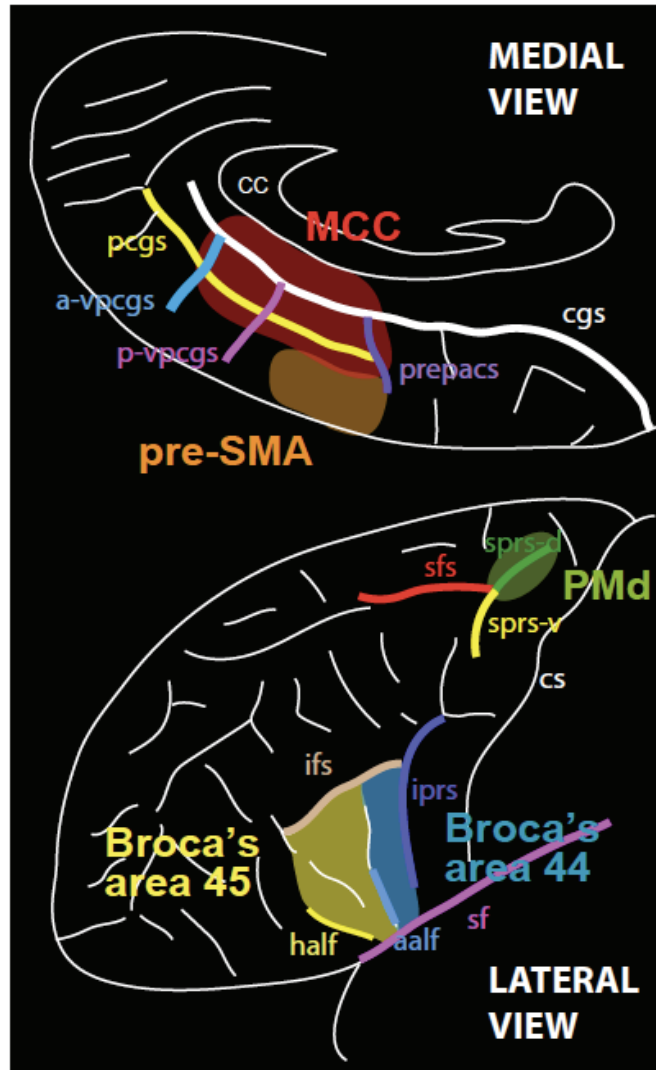
First, to assess the brain regions involved in the visuo-motor conditional response selection, we contrasted the blood oxygenation-level dependent (BOLD) signal during  $RS_L$  and  $RS_{PL}$  events, where subjects actively selected their responses on the basis of the presented stimulus, with  $RS_C$  events, where subjects performed instructed responses. The two main contrasts (i.e.  $RS_L - RS_C$  and  $RS_{PL} - RS_C$ ) were examined for each response version at the group level and at the subject-by-subject level. At the group level, verbal and vocal response selection trials are pooled in order to increase statistical power. To examine possible differences between vocal and verbal responses, we distinguished between the two conditions in our subject-level analyses.

A second set of analyses was performed to determine the brain regions involved in the processing of auditory feedback during the learning of visuo-manual, visuo-orofacial, and visuo-vocal-verbal conditional associations. Firstly, we examined the contrasts between  $FB_L$  and  $FB_{PL}$  events and between  $RS_L$  and  $RS_{PL}$  in each response version to determine if distinctive networks are involved in the processing of

auditory feedback for adapting different response modalities. To determine if verbal and vocal feedback processing recruited different brain regions, we performed the above analyses separately each response type (manual, vocal-verbal, orofacial) with verbal or vocal feedback.

In consideration of individual variations in PMd, Broca's area and medial frontal cortical sulcal morphology, the above analyses were also assessed at a subject-by-subject level. In PMd, we identified activation peaks in relation to the dorsal branch of the superior precentral sulcus, the ventral branch of the superior precentral sulcus, and the superior frontal sulcus (Amiez & Petrides, 2018; Amiez, Kostopoulos, Champod, & Petrides, 2006) (Fig 2). In Broca's area, we identified activation peaks in relation to the BA's limiting sulci, i.e. the inferior precentral sulcus (iprs), the ascending ramus of the lateral fissure (aalf), the horizontal ramus of the lateral fissure (half), and the inferior frontal sulcus (ifs). In the medial frontal cortex, we identified activation peaks in relation to the cingulate sulcus (cgs), paracingulate sulcus (pcgs), and the vertical sulci joining the cgs and/or pcgs (i.e. paracentral sulcus (pacs), pre-paracentral sulcus (prpacs), posterior vertical paracingulate sulcus (p-vpcgs). It should be noted that the pcgs is present in 70% of subjects at least in one hemisphere and several studies have shown that the functional organization in the cingulate cortex depends on the sulcal pattern morphology. As such, we also performed sub-group analyses of fMRI data in which we separated hemispheres with versus without a pcgs (see Amiez et al. 2013 for the full description of the method).

**FIG 2**



**Figure 2. Sulci characteristic of the MCC and the pre-SMA (medial view), as well as area 44 in Broca's region and the dorsal premotor cortex (PMd) (lateral view).** In the PMd the characteristic sulci are the dorsal branch of the superior precentral sulcus (sps-d), the ventral branch of the superior precentral sulcus (sps-v), and the superior frontal sulcus (sfs). Area 44 in Broca's region is bounded by the inferior precentral sulcus (ips), the anterior ramus of the lateral fissure (aalf), and the inferior frontal sulcus (ifs). In the medial frontal cortex, the characteristic sulci are the cingulate sulcus (cgs), the paracingulate sulcus (pcgs), and the vertical sulci joining the cgs and/or pcgs, i.e. the paracentral sulcus (pacs), the pre-paracentral sulcus (prepacs), the posterior vertical paracingulate sulcus (p-vpcgs), and the anterior vertical paracingulate sulcus (a-vpcgs).

For the group, sub-group, and individual subject analyses, the resulting  $t$  statistic images were thresholded using the minimum given by a Bonferroni correction and random field theory to account for multiple comparisons. Statistical significance for the group analyses was assessed based on peak thresholds in exploratory and directed search, and the spatial extent of consecutive voxels. For a single voxel in a directed search, involving all peaks within an estimated grey matter of  $600 \text{ cm}^3$  covered by the slices, the threshold for significance ( $p < 0.05$ ) was set at  $t = 5.18$ . For a single voxel in an exploratory search, involving all peaks within an estimated grey matter of  $600 \text{ cm}^3$  covered by the slices, the threshold for reporting a peak as significant ( $p < 0.05$ ) was  $t = 6.77$  (Worsley et al., 1996). A predicted cluster of voxels with a volume extent  $>118.72 \text{ mm}^3$ , with a  $t$ -value  $> 3$  was significant ( $p < 0.05$ ) corrected for multiple comparisons using the method of Friston et al. (1995c). Statistical significance for individual subject analyses was assessed based on the spatial extent of consecutive voxels. A cluster volume extent  $> 444 \text{ mm}^3$ , associated with a  $t$  value  $> 2$ , was significant ( $p < 0.05$ ), corrected for multiple comparisons (Friston et al., 1995c).



## Results

### *Behavioral analyses*

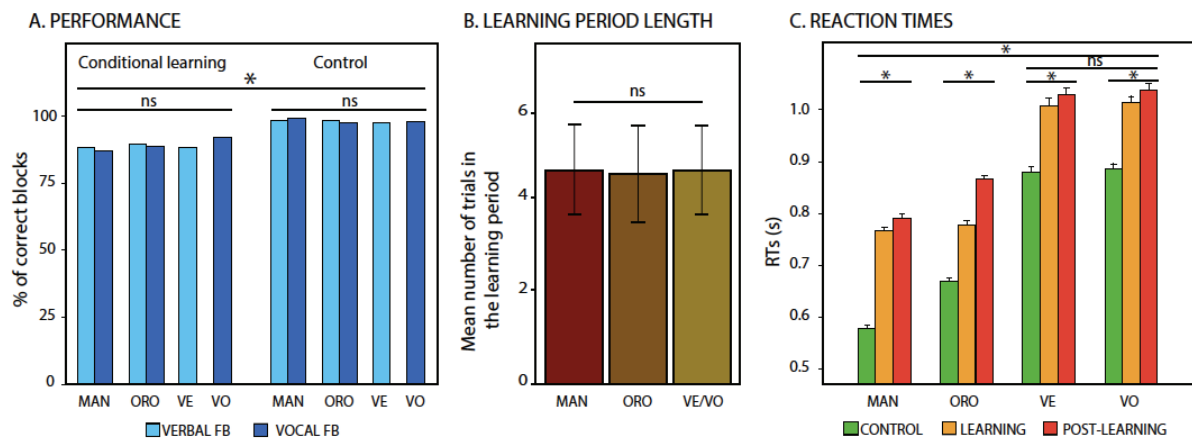
First, we assessed the percent of completed blocks in the 3 versions of both the visuo-motor conditional learning and the control task. Learning blocks were considered completed if subjects achieved not more than 1 sub-optimal search during learning, and not more than 1 post-learning error, whereas control blocks were considered completed if there was not more than 1 error trial. Results showed similar percent of completed blocks (Fig 3A) across the 3 versions of the conditional learning task ( $\chi^2=3.22$ ,  $df=3$ ,  $p=0.36$ ), strongly suggesting that subjects are equally able to learn conditional associations between visual stimuli and the various response effectors. Importantly, the feedback type (vocal versus verbal) did not influence the ability to learn optimally these associations ( $\chi^2=0.05$ ,  $df=1$ ,  $p=0.83$ , Fig 3A). As expected, we observed higher proportions of completed blocks in control than visuo-motor conditional learning blocks due to the cognitive load required in the conditional learning task (Fig 3A,  $\chi^2=82.2$ ,  $df=1$ ,  $p<2\times 10^{-16}$ ).

Importantly, the learning period of the three versions of the visuo-motor conditional task required similar number of learning trials, suggesting that the level of difficulty between the conditions was equal (Fig 3B,  $\chi^2=3.05$ ,  $df=2$ ,  $p=0.218$ ).

Reaction times (RTs) which were assessed in correctly performed conditional learning and control task blocks were analyzed. The RTs were not significantly different between the two feedback types ( $\chi^2=2.02$ ,  $df=1$ ,  $p=0.16$ ) (Fig 3C). There was a significant main effect of response type ( $\chi^2=2.8\times 10^3$ ,  $df=3$ ,  $p<2.2\times 10^{-16}$ ): subjects were fastest with manual responses, followed by orofacial, and vocal-verbal responses. Note that RTs in visuo-vocal and visuo-verbal conditional learning

associations task were not significantly different ( $p=1.00$ ). As expected, RTs were faster in control than learning trials, and in learning than post-learning trials ( $\chi^2=1.5 \times 10^3$ ,  $df=2$ ,  $p<2.2 \times 10^{-16}$ ). Lastly, there was a significant interaction ( $\chi^2=63.4$ ,  $df=6$ ,  $p<8.9 \times 10^{-12}$ ) between the response modality and trial type on the RTs, indicating that the effect of trial type (learning, post-learning, control trials) on RTs differed across the response types (manual, orofacial, vocal, verbal). Post-hoc comparisons revealed that, while the main effect of trial type (i.e. control RTs are faster than learning RTs, and learning RTs are faster than post-learning RTs) was present in each response modality (all  $p<0.05$ ), the magnitude of differences between the trial types differed with response types. To understand the response-trial type interaction, we focused on the differences between post-learning and learning RTs with control RTs as these provide insights into the effects of additional cognitive selection demands during post-learning and learning above basic motor execution processes. The difference between post-learning and control trials appear to be the smallest for vocal and verbal responses ( $t=12.7$ ,  $12.3$ , respectively,  $p<0.0001$ ), followed by orofacial ( $t=21.9$ ,  $p<0.0001$ ) and manual responses ( $t=24.3$ ,  $p<0.0001$ ). This indicated that conditional response selection mechanisms had the largest RTs effect on manual, followed by orofacial and vocal-verbal responses. The difference between learning and control trials appeared to be the smallest for orofacial responses ( $t=12.3$ ,  $p<0.0001$ ), vocal and verbal responses ( $t=10.6$ ,  $10.7$ , respectively,  $p<0.0001$ ); and manual ( $t=21.5$ ,  $p<0.0001$ ) responses. This suggested that feedback-driven response selection mechanisms had the largest effect for manual, followed by vocal and verbal responses and orofacial responses.

**FIG 3**



**Figure 3. Behavioral data.** **A.** Proportion of blocks successfully completed in the conditional associative learning and control tasks displayed by response types (MAN-manual, ORO-orofacial, VE-verbal and VO-vocal) and feedback types (verbal – light blue bars, vocal – dark blue bars). **B.** Mean number of trials in the learning period in the manual (red), orofacial (orange) and vocal-verbal (yellow) response task versions. **C.** Mean reaction times in control (green bars), learning (orange bars) and post-learning (red bars) trials displayed by response types (MAN-manual, ORO-orofacial, VE-verbal and VO-vocal).

## ***fMRI results***

***The conditional selection of manual, vocal/verbal, and orofacial responses during learning and post-learning phases is organized along a gradient in the posterior lateral frontal cortex:***

To identify the brain regions associated with conditional response selection, the BOLD signal observed during the conditional response selection epochs was compared with the appropriate control: conditional learning block trials minus control block trials and conditional post-learning block trials minus control block trials. These two contrasts were assessed in each of the three task versions: manual, vocal-verbal, and orofacial at the group and single-subject levels.

In line with previous findings (Amiez, Hadj-Bouziane, & Petrides, 2012a), group level analyses demonstrated increased BOLD activity relative to the control in the dorsal premotor region (PMd) during the conditional selection of manual responses in both the learning and post-learning periods (Table 1, Fig. 4A). Single-subject analyses further revealed that individual PMd activation peaks, during both learning (left PMd observed in 17/18 subjects) and post-learning phases (left PMd observed in 18/18 subjects), were consistently located in the dorsal branch of the superior precentral sulcus. Importantly, no significant activation was observed in the ventral part of area 44 (Broca region) during both learning and post-learning manual selections (Fig. 4A).

By contrast, orofacial response selection during both the learning and post-learning periods relative to control were associated with increased BOLD activity in both the ventral area 44 and the PMd (Table 1, Fig 4B). Subject-level analyses in the left hemisphere revealed that the ventral area 44 (observed in 14/18 subjects in both

learning and post-learning periods) and PMd activations (observed in 14/18 subjects during learning period and in 17/18 subjects in post-learning period) were consistently found in the pars opercularis where area 44 lies and in the dorsal branch of the superior precentral sulcus respectively (Fig 4B, Table 1).

	<u>Learning minus Control</u>				<u>Post-Learning minus Control</u>			
	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>
<b>Manual</b>								
L. PMd	-26	-4	54	8.79	-56	8	-2	5.64
L. BA44 (Dorsal)	-54	8	18	8.36	-	-	-	-
L. BA44 (Ventral)	-	-	-	-	-	-	-	-
<b>Orofacial</b>								
L. PMd	-26	-2	50	4.19	-30	-8	52	6.48
L. BA44 (Dorsal)	-54	14	20	6.58	-	-	-	-
L. BA44 (Ventral)	-52	12	10	11.0	-54	10	-4	5.85
<b>Vocal/Verbal</b>								
L. PMd	-	-	-	-	-	-	-	-
L. BA44 (Dorsal)	-50	14	24	6.26	-	-	-	-
L. BA44 (Ventral)	-52	18	6	4.49	-56	8	-2	5.64
L. BA 45	-48	32	-2	4.69	-	-	-	-

**Table 1**– Group level analysis. Foci of increased activity in the posterior lateral frontal cortex observed during manual, orofacial, and vocal/verbal conditional selection in the learning and post-learning periods compared to their respective control conditions, i.e. during manual, orofacial, and vocal/verbal control selection. The *x*, *y*, *z*, coordinates are in MNI stereotaxic space. T-statistics are significant at  $p_{corrected} < 0.05$ .

Finally, the vocal response selection condition during both learning and post-learning was associated with increased BOLD activity in the left ventral area 44 and not the PMd, (Table 1, Fig. 4C). At the single-subject level, we assessed the activations for verbal and vocal responses separately. We observed that individual subject ventral area 44 activation peaks (dark blue circles) during both learning (verbal peaks: 14/18 subjects, vocal peaks: 9/18 subjects) and post-learning phases (verbal peaks: 10/18 subjects, vocal peaks: 12/18 subjects), were consistently located in the pars opercularis region bounded anteriorly by the ascending ramus of the Sylvian

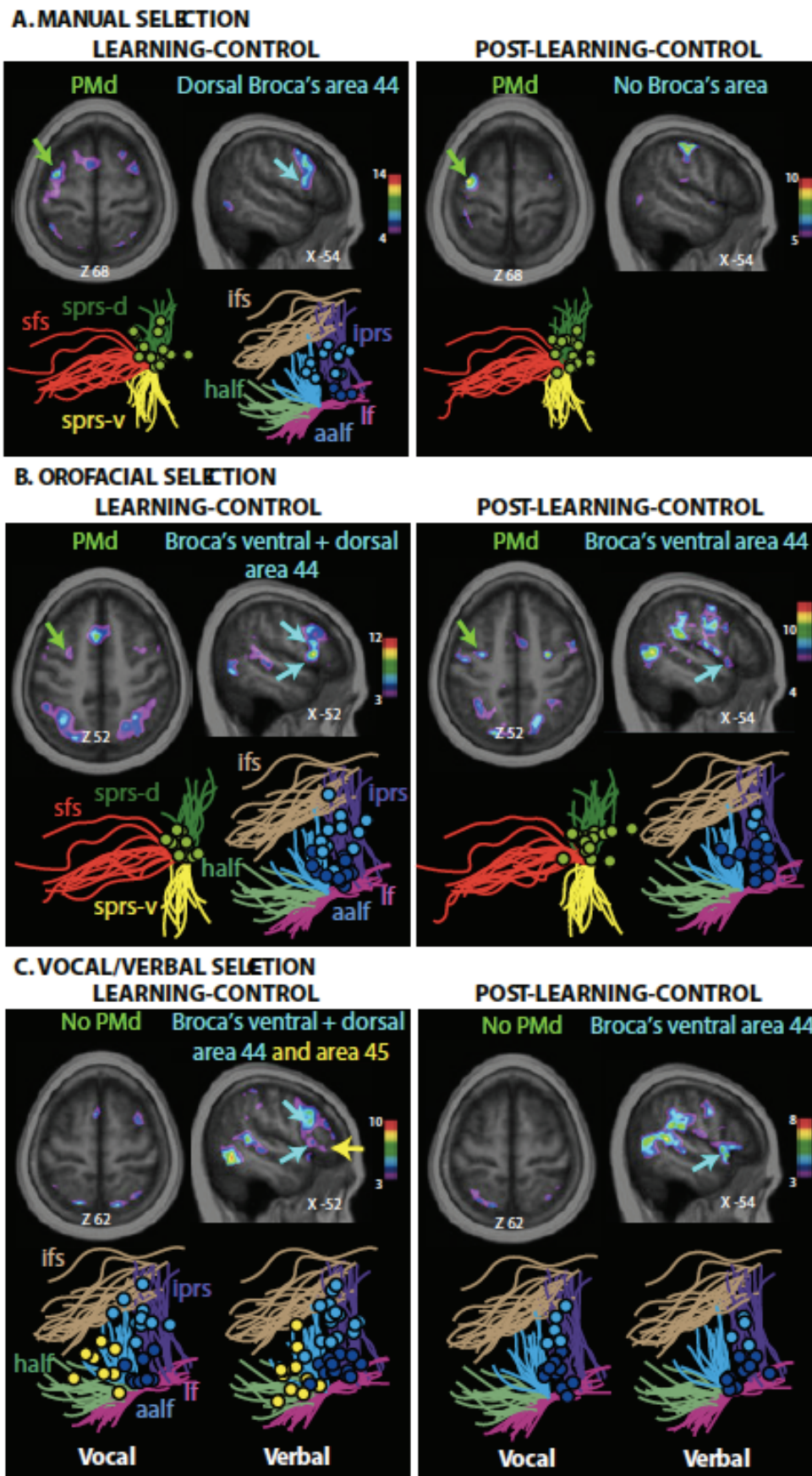
fissure, posteriorly by the inferior precentral sulcus, dorsally by the inferior frontal sulcus, and ventrally by the Sylvian fissure (Fig 4C). This indicated that both verbal and vocal response selections implicated the same ventral area 44.

In all conditions, an increased activity was located in the dorsal part of area 44 specifically during the learning period (Fig 4). This region is therefore specifically involved in learning process but is not effector specific.

Altogether, these results demonstrate the existence of a functional gradient in which the anterior dorsal premotor region (PMd) is involved in the conditional selection of manual but not vocal responses, whereas the ventral area 44 is involved in the conditional selection of vocal but not manual responses. The conditional selection of orofacial responses recruited both regions.

By contrast to the involvement of the dysgranular area 44 on the pars opercularis (i.e. the posterior part of Broca's region) in all conditional response selections examined (except for the manual selections), the granular area 45 on the pars triangularis (i.e. the anterior part of Broca's region) was only involved in the vocal/verbal conditional response selections during the learning period (see Fig 4C).

**FIG 4**



**Figure 4. Conditional response selection in the posterior lateral prefrontal cortex.** Group (above) and individual activations (below) shown as dots around relevant sulci during **(A)** manual response selection in the learning and post-learning periods, **(B)** during orofacial response selection in the learning and post-learning periods, **(C)** during vocal and verbal response selection in the learning and post-learning periods. Green circles depict individual PMd activations for manual and orofacial response selection during learning and post-learning respectively. Light and dark blue circles depict individual dorsal and ventral area 44 activations and yellow circles depict area 45 activity during response selection. Abbreviations: cs, central sulcus, sprs-d, dorsal superior precentral sulcus, sprs-v, ventral superior precentral sulcus, sfs, superior frontal sulcus, ifs, inferior frontal sulcus, iprs, inferior precentral sulcus, as, ascending sulcus, hs, horizontal sulcus, lf, lateral fissure.

***The medial frontal cortex is specifically involved only during the learning of conditional visuo-motor associations:***

The comparison between the BOLD signal observed at the response selection epochs in learning versus control trials and post-learning versus control trials demonstrated that activity in the medial frontal cortex increased only during the learning period as no activity was observed during the post-learning period (Fig 5). Thus, by contrast to the posterior lateral frontal cortex, the dorsomedial frontal cortex is not significantly involved in the selection of known conditional responses from various effectors.

Two foci of increased activity in the aMCC were observed in the 3 versions of the task (Fig 5A, 5B, 5C, 5D, Table 2). As demonstrated by a conjunction analysis (Fig 5D), these 2 foci of increased activity were at the same location in the 3 versions of the task. Because of the strong inter-subject and inter-hemispheric sulcal variability observed in this region (Paus et al., 1996; B. A. Vogt, Nimchinsky, Vogt, & Hof, 1995), we performed a group analysis that included only hemispheres displaying a cingulate sulcus (cgs) and no paracingulate sulcus (pcgs) and a group analysis including only hemispheres displaying both a cgs and a pcgs. The results revealed that the foci of



increased activity were located in the pcgs when present and in the cgs when the pcgs is absent. These results suggest that the aMCC is involved in the conditional selection of all effector types during learning when the learning is based on auditory vocal/verbal feedback.

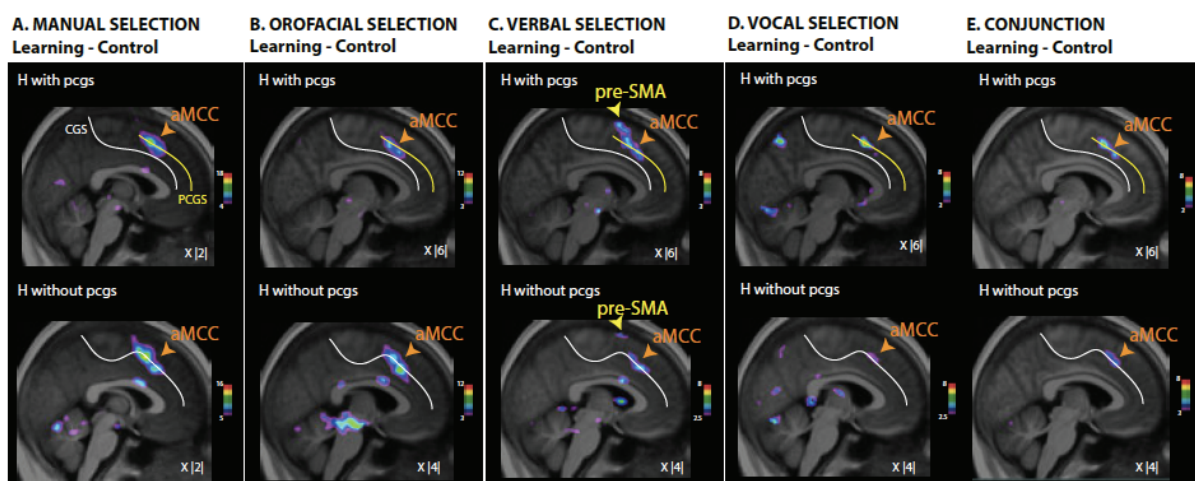
	<u>Hemispheres with a pcgs</u>				<u>Hemispheres without a pcgs</u>			
	x	y	z	t	x	y	z	t
<b>Manual</b>								
MCC	4	14	52	12.93	2	14	50	13.95
MCC	10	18	44	8.23	4	22	38	10.35
Pre-SMA	-	-	-	-	-	-	-	-
<b>Orofacial</b>								
MCC	2	14	50	6.92	6	14	50	5.81
MCC	2	24	38	8.36	6	24	42	5.56
Pre-SMA	-	-	-	-	-	-	-	-
<b>Verbal</b>								
MCC	2	14	54	5.94	2	18	50	4.17
MCC	2	26	46	6.22	4	26	40	4.65
Pre-SMA	4	8	68	4.52	4	8	72	4.16
<b>Vocal</b>								
MCC	4	16	50	6.60	2	16	50	3.62
MCC	6	26	38	3.72	4	24	44	3.32
Pre-SMA	-	-	-	-	-	-	-	-

**Table 2**—Increased activity in the medial frontal cortex observed during manual, orofacial, vocal, and verbal conditional selection in learning period compared to that observed during manual, orofacial, vocal, and verbal control selection in hemispheres with and without a pcgs. X, Y, and Z coordinates correspond to the coordinates of the increased activities in the MNI stereotaxic space. T-statistics are significant at  $p_{corrected} < 0.05$ .

By contrast, the pre-SMA displayed increased activity specifically during the selection of verbal responses during learning visuo-verbal associations, not during learning associations between visual stimuli and the other response effectors (manual, orofacial, and vocal) (Fig 5C, Table 2). Pre-SMA displayed clearly increased activity in all types of hemispheres (with or without a pcgs). This point is confirmed in Fig 5D which shows that the pre-SMA does not display increased activity in the conjunction analysis.

Note that a set of other frontal regions display increased activity specifically during the learning period at the response selection event independently of the response effector. A conjunction analysis (data not shown) revealed common activity increases in the dorsolateral prefrontal cortical areas 46 (Left hemisphere: X -44, Y 40, Z 12, conjunction t value = 4.81) and 9/46 (Left hemisphere: X -48, Y 30, Z 26, conjunction t value = 4.50; Right hemisphere: X 42, Y 34, Z 34, conjunction t value = 4.18), the orbitofrontal cortex (Right hemisphere: X 26, Y 36, Z -14, conjunction t value = 4.37), the frontal operculum (Left hemisphere: X -30, Y 24, Z 0, conjunction t value = 6.17; Right hemisphere: X 32, Y 22, Z 2, conjunction t value = 3.80), and the inferior frontal junction (Left hemisphere: X -48, Y 6, Z 34, conjunction t value = 6.56; Right hemisphere: X 48, Y 8, Z 28, conjunction t value = 6.26).

## FIG 5



**Figure 5. Conditional learning response selection in the medial frontal cortex.** Top panel: group analysis results of increased activity during response selection in the learning period in comparison with control trials in hemispheres displaying a cingulate (cgs) and a paracingulate sulcus (pcgs). Bottom panel: group analysis results of increased activity during response selection in the learning period in comparison with the control trials in hemispheres displaying no paracingulate sulcus. **A.** during manual response selection, **B.** during orofacial response selection, **C.** during verbal response selection, and **D.** during vocal/verbal response selection. **E.** Top panel: conjunction

analysis between the 3 contrasts presented in the group analysis in A, B, C, and D in hemispheres displaying both a cgs and a pcgs in A, B, and C. Bottom panel: conjunction analysis between the 3 contrasts presented in hemispheres displaying no pcgs in A, B, C, and D in hemispheres displaying no pcgs. The color scales represent the range of the t-statistic values. The X values correspond to the medio-lateral level of the section in the MNI space.

***Auditory vocal/verbal feedback (FB) analysis during learning conditional visuo-motor associations recruits the Broca-medial frontal cortex network***

To identify the brain regions associated with the analysis of vocal versus verbal feedback during the learning of conditional relations, we compared, respectively, 1) the BOLD signal at the occurrence of vocal feedback during learning visuo-motor conditional associations from various motor effectors and control trials in which motor responses from corresponding effectors were performed (i.e. vocal feedback epoch during visuo-manual conditional associative learning trials minus vocal feedback epoch during visuo-manual control trials, vocal feedback epoch during visuo-orofacial conditional associative learning trials minus vocal feedback epoch during visuo-orofacial control trials, vocal feedback epoch during visuo-vocal conditional associative learning trials minus vocal feedback epoch during visuo-vocal control trials), and 2) the BOLD signal at the occurrence of verbal feedback during learning visuo-motor conditional associations from various motor effectors and control trials in which motor responses from corresponding effectors were performed (i.e. verbal feedback epoch during visuo-manual conditional associative learning trials minus verbal feedback epoch during visuo-manual control trials, verbal feedback epoch during visuo-orofacial conditional associative learning trials minus verbal feedback epoch during visuo-orofacial control trials, vocal feedback epoch during visuo-verbal

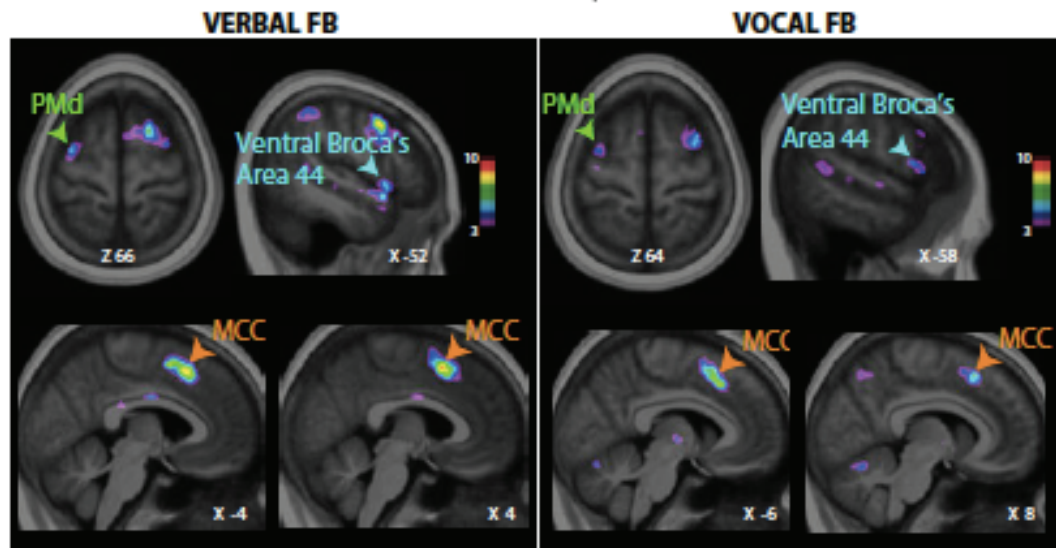
conditional associative learning trials minus verbal feedback epoch during visuo-verbal control trials).

	<u>Verbal FB during learning</u> <u>minus control</u>				<u>Vocal FB during learning</u> <u>minus control</u>			
	x	y	z	t	x	y	z	t
<b>Manual</b>								
<i>Left hemisphere</i>								
PMd	-32	-4	66	5.18	-32	-4	64	4.31
MCC	0	14	50	9.93	0	14	50	9.31
MCC	-8	22	46	7.33	-8	22	42	8.35
BA 44 (Ventral)	-50	12	-4	5.20	-58	10	10	3.58
<i>Right hemisphere</i>								
MCC	-	-	-	-	10	20	48	5.84
<b>Orofacial</b>								
<i>Left hemisphere</i>								
MCC	-6	20	44	5.30	-8	18	48	5.13
Pre-SMA	-4	4	66	5.12	-	-	-	-
BA 44 (Ventral)	48	16	8	4.53	-56	14	4	3.34
<i>Right hemisphere</i>								
MCC	4	18	48	4.77	6	22	48	4.80
<b>Verbal</b>								
<i>Left hemisphere</i>								
MCC	-6	18	44	5.18	-4	16	50	5.40
Pre-SMA	-6	10	64	4.87	-	-	-	-
BA 44 (Ventral)	-50	12	0	3.35	-52	12	2	4.04
<i>Right hemisphere</i>								
MCC	8	20	48	4.50	8	20	46	4.15
<b>Vocal</b>								
<i>Left hemisphere</i>								
MCC	-6	18	44	5.18	-4	16	50	5.40
Pre-SMA	-6	10	64	4.87	-	-	-	-
BA 44 (Ventral)	-50	12	0	3.35	-52	12	2	4.04
<i>Right hemisphere</i>								
MCC	8	20	48	4.50	8	20	46	4.15

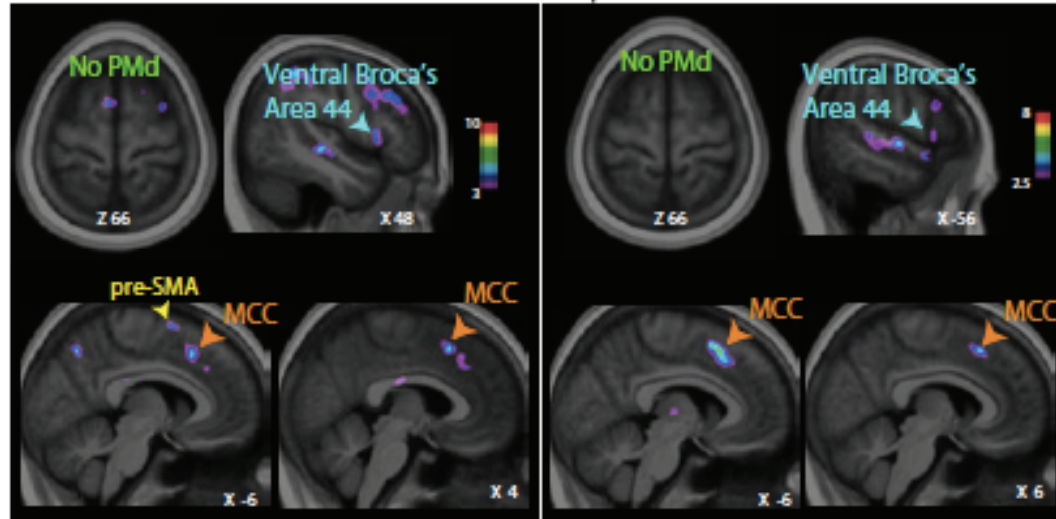
**Table 3**– Group level analysis. Increased activity in the posterior lateral frontal cortex observed during manual, orofacial, and vocal/verbal conditional selection in learning and post-learning periods compared to that observed during manual, orofacial, and vocal/verbal control selection. X, Y, and Z coordinates correspond to the coordinates of the increased activities in the MNI stereotaxic space. T-statistics are significant at  $p_{corrected} < 0.05$ .

# FIG 6

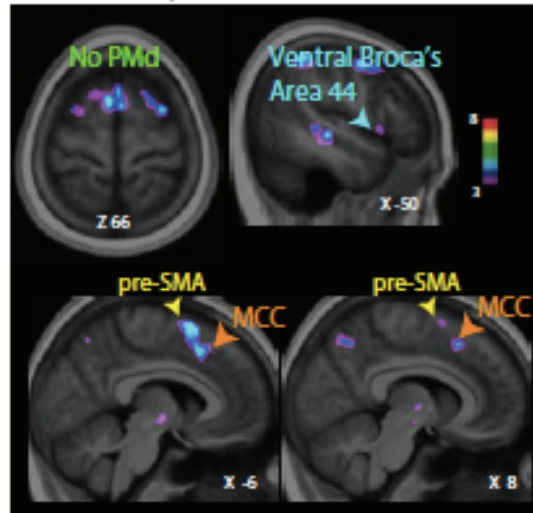
A. FB ANALYSIS DURING LEARNING - Effector of response = Manual



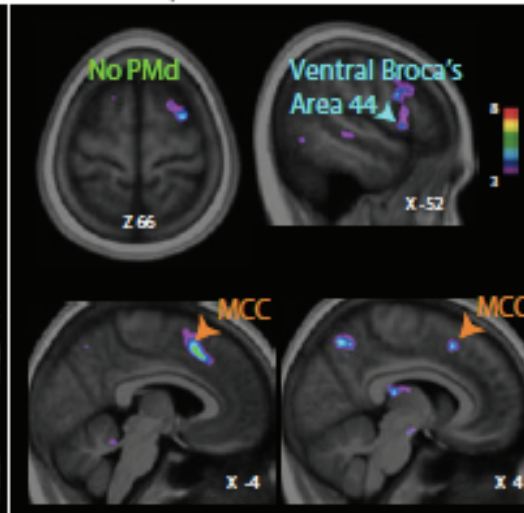
B. FB ANALYSIS DURING LEARNING - Effector of response = Orofacial



C. FB ANALYSIS DURING LEARNING - Effector of response = Verbal



D. FB ANALYSIS DURING LEARNING - Effector of response = Vocal



**Figure 6. Verbal versus vocal feedback analysis during the visuo-motor conditional learning period in the posterior lateral prefrontal and medial frontal cortex.** **A.** Group analysis results displaying increased activity during the analysis of verbal (left panel) and vocal (right panel) feedback during learning visuo-manual conditional associations compared to that during the analysis of verbal (left panel) and vocal (right panel) feedback during visuo-manual control trials. **B.** Group analysis results displaying increased activity during the analysis of verbal (left panel) and vocal (right panel) feedback during learning visuo-orofacial conditional associations compared to that during the analysis of verbal (left panel) and vocal (right panel) feedback during visuo-orofacial control trials. **C.** Group analysis results displaying increased activity during the analysis of verbal feedback during learning visuo-verbal conditional associations compared to that during the analysis of verbal feedback during visuo-verbal control trials. **D.** Group analysis results displaying increased activity during the analysis of vocal feedback during learning visuo-vocal conditional associations compared to that during the analysis of vocal feedback during visuo-vocal control trials. The color scales represent the ranges of the t-statistic values. The X and Z values correspond to the medio-lateral and dorso-ventral levels of the section in the MNI space, respectively.

The results show that the analysis of feedback during learning visuo-manual associations recruits both ventral area 44 and the MCC (Fig 6A, Table 3). As previously shown, it also recruits the left PMd (Amiez, Hadj-Bouziane, & Petrides, 2012a). This network was equally involved in the analysis of vocal and verbal feedback. By contrast, the analysis of feedback during learning visuo-orofacial, visuo-vocal, and visuo-verbal associations does not recruit PMd but it also recruits both ventral area 44 and the MCC (Fig 6B-C-D, Table 3). This network was also equally involved in the analysis of vocal and verbal feedback.

To identify the precise location of the MCC region involved in auditory verbal/vocal processing, we compared the BOLD signal during the analysis of vocal versus verbal feedback during learning conditional visuo-motor associations to those during visuo-motor control trials in hemispheres with and without a pcgs (see Methods). The results revealed that both vocal and verbal FB processing are performed in the pcgs when present and in the cgs when the pcgs is absent (Fig 7, Table 4). The same

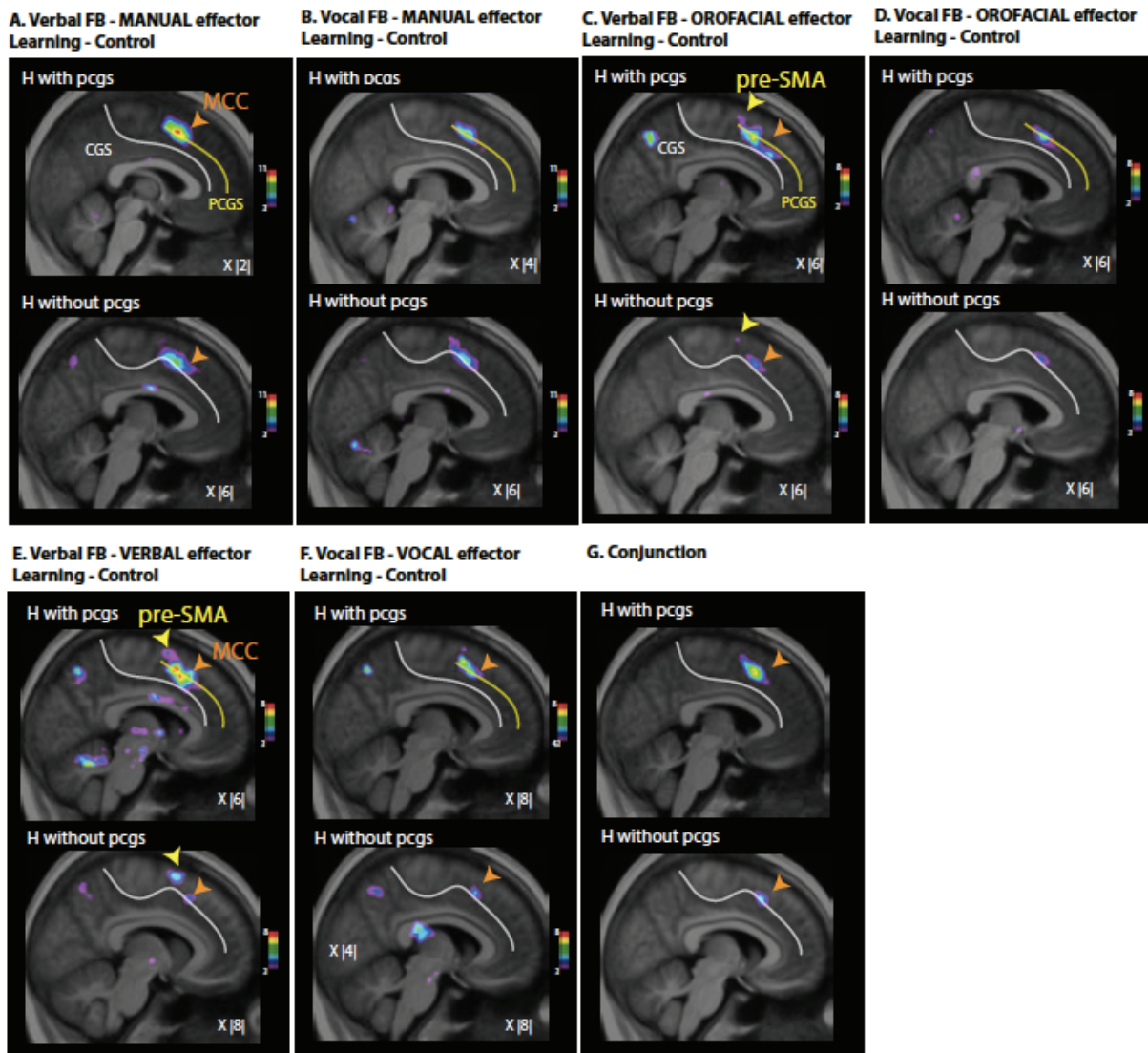
region is involved across the 3 effectors of responses (manual-Fig 7A-B, orofacial-Fig 7C-D, verbal-Fig 7E, vocal-Fig 7F) as shown by the conjunction analysis (Fig 7G).

	<u>Hemispheres with a pcgs</u>				<u>Hemispheres without a pcgs</u>			
	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>
<b>Verbal FB / Manual effector</b>								
MCC	10	20	48	7.22	6	18	48	8.46
Pre-SMA	-	-	-	-	-	-	-	-
<b>Vocal FB / Manual effector</b>								
MCC	2	16	50	7.20	8	22	46	7.48
Pre-SMA	-	-	-	-	-	-	-	-
<b>Verbal FB / Orofacial effector</b>								
MCC	6	18	46	7.93	2	18	48	4.22
	6	30	34	5.91				
Pre-SMA	6	8	62	3.96	4	4	66	3.27
<b>Vocal FB / Orofacial effector</b>								
MCC	6	20	46	4.79	2	16	50	4.18
Pre-SMA	-	-	-	-	-	-	-	-
<b>Verbal FB / Verbal effector</b>								
MCC	6	16	46	7.33	8	20	46	4.10
Pre-SMA	4	6	64	4.05	4	10	64	4.48
<b>Vocal FB / Vocal effector</b>								
MCC	6	10	56	7.00				
MCC	6	16	48	6.02	6	18	46	4.24
Pre-SMA	-	-	-	-	-	-	-	-

**Table 4**—Increased activity in the medial frontal cortex observed during vocal and verbal feedback analysis in visuo-manual, visuo-orofacial, visuo-vocal, and visuo-verbal conditional learning period compared to that observed during vocal and verbal feedback obtained in manual, orofacial, vocal, and verbal control trials in hemispheres with and without a pcgs. X, Y, and Z coordinates correspond to the coordinates of the increased activities in the MNI stereotaxic space. T-statistics are significant at  $p_{corrected} < 0.05$ .

Importantly, pre-SMA was only involved in the analysis of verbal feedback when the response effectors were verbal or orofacial. Pre-SMA is not involved in the analysis of verbal feedback when the effector of response is manual. This strongly suggests that the pre-SMA has a particular role in exerting cognitive control on verbal and orofacial responses and to monitor performance based on verbal feedback specifically (Fig 7C, 7C, 7E).

# FIG 7



**Figure 7. Group analysis of vocal/verbal feedback during visuo-motor conditional learning in the MCC** in the group analysis (top panels), in hemispheres (H) exhibiting both a cingulate sulcus (cgs) and a paracingulate sulcus (pcgs) (middle panels) and in hemispheres without a paracingulate sulcus (bottom panels). **A.** Comparison between the BOLD signal at the occurrence of feedback during learning visuo-manual conditional associations versus during visuo-manual control trials. **B.** Comparison between the BOLD signal at the occurrence of feedback during learning visuo-orofacial conditional associations versus during visuo-orofacial control trials. **C.** Comparison between the BOLD signal at the occurrence of feedback during learning visuo-vocal/verbal conditional associations versus during visuo-vocal/verbal control trials. **D.** Conjunction between the contrasts presented in A, B, and C in hemispheres displaying or not a pcgs. The color scales represent the ranges of the t-statistic values. The X values correspond to the medio-lateral levels of the section in the MNI space, respectively.



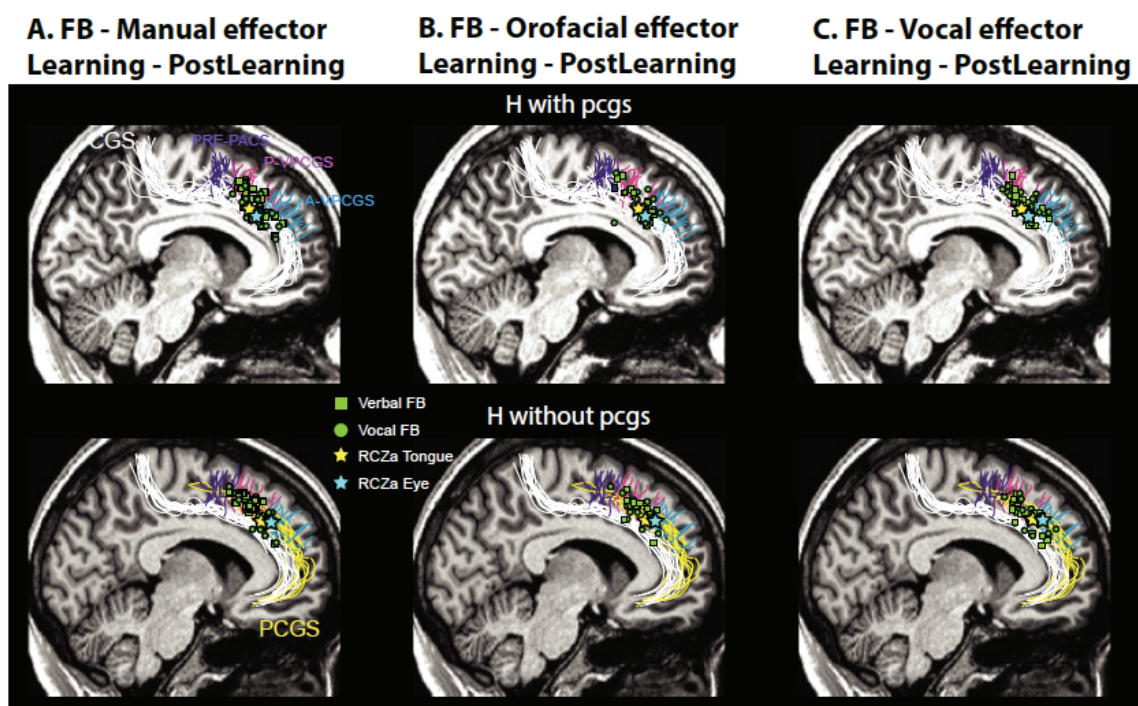
Note that a set of other frontal regions display increased activity specifically during the learning period at the feedback processing event independently of the response effector. A conjunction analysis (data not shown) revealed common activity increases in the dorsolateral prefrontal cortical areas 46 (Right hemisphere: X 40, Y 44, Z 20, conjunction t value = 4.12) and 9/46 (Left hemisphere: X -42, Y 36, Z 32, conjunction t value = 3.09; Right hemisphere: X 42, Y 36, Z 32, conjunction t value = 4.27), the orbitofrontal cortex (Right hemisphere: X 24, Y 46, Z -14, conjunction t value = 3.77), the frontal operculum (Left hemisphere: X -30, Y 24, Z 2, conjunction t value = 4.31; Right hemisphere: X 30, Y 22, Z 2, conjunction t value = 4.78), and the inferior frontal junction (Left hemisphere: X -42, Y 12, Z 32, conjunction t value = 4.09; Right hemisphere: X 44, Y 10, Z 36, conjunction t value = 5.54).

***The MCC region that is involved in the analysis of auditory vocal/verbal feedback is the face motor representation of the cingulate motor area***

To identify more precisely the brain regions associated with the analysis of vocal/verbal feedback during learning, we compared the BOLD activity at the occurrence of feedback during learning versus during post-learning trials. This specific contrast was used to relate findings to previous studies assessing the neural basis of feedback analysis in tasks including a learning and a post-learning period (Amiez et al., 2013). This contrast was assessed in the six response-feedback combinations: Manual-Vocal, Manual-Verbal, Vocal-Vocal, Verbal-Verbal, Orofacial-Vocal and Orofacial-Verbal (Fig 8). The results from this contrast were also assessed in individual subjects to relate them to local sulcal morphology. This analysis showed that the increased activities were consistently found in the same MCC region across the three

response modalities (manual – red squares/circles, vocal-verbal – dark blue squares/circles, orofacial – green squares/circles) and two feedback types (vocal – circles, verbal squares). Specifically, individual increased activities were found close to the intersection between the posterior vertical paracingulate sulcus (p-vpcgs) with the cgs when there is no pcgs and with the pcgs when present. This position likely corresponded to the location of the face motor representation of the anterior rostral cingulate zone (RCZa) (Amiez & Petrides, 2014) (Fig 8). To confirm if these auditory feedback processing-related activation peaks corresponded to the RCZa ‘face’ motor representation, we compared their locations with the average activation peaks corresponding to the tongue and eye RCZa motor representations obtained in a previous study from the same set of subjects (Loh et al., 2018). As displayed in Fig 8, the feedback-related peaks obtained in the current study were located near the average RCZa face (eye and tongue) representation.

**FIG 8**



**Figure 8. Auditory vocal/verbal feedback processing during learning visuo-motor conditional associations in relation to the anterior cingulate motor area.** **A.** Comparison between the BOLD signal at the occurrence of verbal (squares) and vocal (circles) feedback during learning visuo-manual conditional associations versus during visuo-manual control trials in individual subjects (each square/circle represent the location of increased activity of one subject) and in hemispheres displaying both a cingulate sulcus (cgs) and a paracingulate sulcus (pcgs, top diagrams) and in hemispheres without a pcgs (bottom diagrams). **B.** Identical as A but increased activities are based on the comparison between the BOLD signal at the occurrence of feedback during learning visuo-orofacial conditional associations versus during visuo-orofacial control trials. **C.** Identical as A and B but increased activities are based on the comparison between the BOLD signal at the occurrence of feedback during learning visuo-vocal/verbal conditional associations versus during visuo-verbal/vocal control trials. Yellow and blue stars represent average locations of the tongue and eye motor representations in the RCZa that were derived from a motor mapping task in Loh et al. 2018. Abbreviations: cs, cingulate sulcus; pcgs, paracingulate sulcus; pre-pacs, pre-paracentral sulcus; a/p-vpcgs, anterior/posterior vertical paracingulate sulcus.

## Discussion

The present study provides critical insights into the specific role of the various components of the human Broca – Dorsomedial Frontal network that is involved in the cognitive control of vocalization. First, the results demonstrated the critical role of area 44 on the pars opercularis (the region that leads to pure speech arrest upon electrical stimulation) in the cognitive conditional selection of orofacial, vocal, and verbal responses, but not manual responses which are selected by the anterior dorsal premotor zone) during both the learning of novel associations (learning period) and also during the selection based on known conditional relations (post-learning period). Second, the mid-cingulate motor cortex (MCC) was also shown to be involved in the cognitive selection of visuo-motor conditional responses independently of the effector of the response but specifically during the learning period which requires the use of vocal/ verbal feedback. Finally, the preSMA was specifically recruited for the conditional selection of verbal responses with verbal feedback during the learning period.

The ventral part of area 44 was shown to be specifically involved in the cognitive conditional selection between competing orofacial, vocal and verbal actions, i.e. during both the acquisition (learning period) and also the execution (post-learning period) of conditional responses (Fig 4B, 4C). Importantly, it is not recruited for manual response selection during the learning and execution of visuo-manual associations, which, instead, recruited the PMd (Fig 4A). Single-subject analyses confirmed that individual ventral area 44 peaks were consistently situated in the pars opercularis region, i.e. the region bordered by the inferior frontal sulcus, the Sylvian fissure, the ascending ramus of the Sylvian fissure and the inferior precentral sulcus. This is the region where cytoarchitectonic area 44 lies and the region stimulation of which results in pure

speech arrest. Thus, the results demonstrate the validity of the hypothesis suggesting the involvement of primate area 44 in the cognitive selection of orofacial and vocal/speech responses (Loh et al., 2017; Petrides, 2006). This hypothesis was based on the anatomical connectivity profile of area 44, namely the fact that it is located immediately in front of the precentral gyrus orofacial region and is directly connected to it (Petrides, 2006). Frey and colleagues (2014) have shown that area 44 has rich links with the prefrontal cortex (area 45 and mid-dorsolateral area 9/46V), receives somatosensory inputs from the parietal operculum, insula and the inferior parietal cortex, and has strong connections with both lateral and medial premotor regions (ventral premotor area, cingulate areas 23 and 24, supplementary motor areas). This pattern of connectivity suggests that area 44 is well-placed to mediate top-down or cognitive (prefrontal cortex) and somatosensory (parietal cortex) influences on vocal and orofacial actions (premotor areas). Secondly, indicative of area 44's involvement in orofacial and vocal motor control, direct electrical stimulation of area 44 in the human brain has been associated with lip, jaw, tongue and laryngeal movements and speech interference (Breshears, Molinaro, & Chang, 2015; Penfield & Rasmussen, 1949). Finally, a wealth of functional neuroimaging studies has also implicated area 44 in speech control and production (Poldrack et al., 1999; Price, 2012). Area 44 in non-human primates is also associated with vocal and orofacial control: Electrical stimulation in the macaque homologue of area 44 have evoked orofacial but not laryngeal movements (Petrides et al., 2005). Neural activity in this area has also been associated with the conditioned production of calls (Coudé et al., 2011; Hage & Nieder, 2013), suggesting its role in volitional vocal control.

Furthermore, the ventral area 44 is also involved in the analysis of vocal and verbal feedback during the learning period of conditional associations across all

response modalities. This observation is congruent with monkey and human studies that found that the ventrolateral prefrontal cortex (vIPFC) is not only involved in the production of vocal responses but also the processing of auditory information during vocal adjustments. In monkeys, Hage and Nieder (2015) found that the same vIPFC neurons that are involved in conditioned vocal productions also responded to auditory information. They suggested that this mechanism could underlie the ability of monkeys to adjust vocalizations in response to environmental noise or calls by conspecifics. In human subjects, Chang et al. (2013) have shown, via intracortical recordings, that as subjects adjusted their vocal productions in response to acoustic perturbations, the ventral prefrontal cortex reflected compensatory activity changes that were correlated with both the activity associated with auditory processing and the magnitude of the vocal pitch adjustment. This suggested that the same ventral prefrontal region was involved in processing auditory information and adjusting vocal production. In support of this observation, functional neuroimaging investigations have also shown that human area 44 is activated during both the processing of articulatory/phonological information and production of verbalizations (Poldrack et al., 1999; Price, 2012).

By contrast, the dorsal part of the BA44 was involved specifically during the learning period of visuo-motor conditional associations across all response modalities, and not during the execution of learnt associations. These results suggest a functional dissociation between the dorsal and ventral parts of the pars opercularis. In support of this dissociation, recent parcellations of the pars opercularis on the basis of cytoarchitecture (Amunts et al., 1999), receptor architecture (Amunts et al., 2010), and anatomical connectivity (Neubert, Mars, Thomas, Sallet, & Rushworth, 2014) have demonstrated that the pars opercularis (area 44) can be further sub-divided into dorsal and ventral parts. Recent neuroimaging studies have also shown functional

dissociations between the dorsal and ventral area 44. However, the precise roles attributed to the two sub-regions are currently still debated. For instance, Molnar-Szakacs and colleagues (2005) found that the dorsal area 44 was activated during both action observation and imitation, while the ventral area 44 was activated only during action imitation. In agreement, Binkofski et al. (2000) also showed that the ventral, but not dorsal area 44, was implicated during movement imagery. Lastly, during language production, the ventral area 44 was found to be involved in syntactic processing (Indefrey, Hagoort, Herzog, Seitz, & Brown, 2001) and comprehension (Friederici, 2006), while the dorsal area 44 was involved in phonological processing (Heim & Friederici, 2003). As such, our findings are clearly in agreement with the emerging view that the pars opercularis can be sub-divided into dorsal and ventral parts.

The present study demonstrated a major difference between the dysgranular transitional area 44 on the pars opercularis and the granular prefrontal area 45 on the pars triangularis, although both are usually considered to comprise Broca's region in the language dominant hemisphere (see Petrides, 2014). Unlike area 44 which was involved in orofacial, vocal and verbal response selections both during the learning and the post-learning period, activation in area 45 was related only to the conditional selection of vocal/verbal responses and only during the learning period. Thus, area 44 is the fundamental area regulating orofacial output regardless of whether this is just orofacial movements, nonspeech vocal or speech responses and regardless of whether these selections occur during learning or post-learning periods. It may therefore not be surprising that electrical stimulation in a speaking patient leads to pure cessation of speech. By contrast, area 45 contributes only to vocal / speech selections and only during the learning period because it reflects controlled memory

retrieval during the time that the relations are not well learned. There is functional neuroimaging evidence of the involvement of area 45 in the controlled effortful mnemonic retrieval of verbal information, such as the free recall of words that appear within particular contexts (Petrides et al., 1995) and a more recent study has shown that patients with lesions to the ventrolateral prefrontal region, but not those with lesions involving the dorsolateral prefrontal region, show impairments in the active controlled retrieval of the contexts within which words were presented (Chapados & Petrides, 2015). These findings are consistent with the hypothesis that the prefrontal granular component of Broca's region, i.e. area 45, is the critical element for the cognitive retrieval of verbal information, which is then turned into speech utterances by the adjacent dysgranular area 44, leading to the final motor output via the precentral orofacial region (Petrides, 2016). According to this hypothesis, cognitive selection of verbal/semantic information to be communicated is based on mnemonic retrieval with granular prefrontal cortex and the selection of the motor instantiation of the utterance depends on the dysgranular frontal area 44 that controls the orofacial motor apparatus. The results of the present investigation also demonstrate various aspects of the specific role of the mid-cingulate motor cortex (MCC) during the learning of conditional responses based on auditory vocal and verbal feedback. Note that the MCC was not involved in response selection during the post-learning period, indicating its specific role in adaptive learning, in agreement with previous studies (Amiez et al., 2013; Amiez, Hadj-Bouziane, & Petrides, 2012a; Amiez, Sallet, Procyk, & Petrides, 2012b). Furthermore, the MCC's role during learning visuo-motor conditional associations is not effector-specific as the same MCC region is activated during visuo-manual, orofacial and verbal/vocal conditional associative learning. Importantly, subject-by-subject analyses further indicated that this region corresponded to the 'face' motor



representation within the anterior mid-cingulate motor region (RCZa). In other words, vocal and verbal feedback processing was carried out in the 'face' motor region in the RCZa. Together, our findings indicate that the 'face' motor representation of RCZa, within the MCC, contributes to the processing of auditory vocal and verbal feedback for behavioral adaptation. Consistent with our results, accumulating evidence from both monkey and human functional investigations converges on the role of the primate MCC in driving behavioral adaptations via the evaluation of action outcomes (Amiez, Hadj-Bouziane, & Petrides, 2012a; Amiez, Sallet, Procyk, & Petrides, 2012b; Procyk et al., 2016; Quilodran, Rothé, & Procyk, 2008; Rushworth, Walton, Kennerley, & Bannerman, 2003; Shima & Tanji, 1998). Importantly, based on a review of the locations of outcome-related and motor-related activity in the monkey and human MCC, Procyk and colleagues (2016) reported an overlap between the locations for the evaluation of juice-rewarded behavioral outcomes and the face motor representation in the monkey rostralmost CMA (rCMA). As such, the authors proposed that behavioral feedback evaluation in the MCC is embodied in the rCMA motor representation corresponding to the modality of the feedback. Consistent with this interpretation, we showed that adaptive auditory feedback is being processed by the face motor representation in the anterior cingulate motor area. Thus, the current literature strongly supports our proposed role of the MCC (specifically, the RCZa 'face' motor representation) in the analysis of verbal and vocal feedback for behavioral adaptation and this role is likely conserved across human and non-human primates.

Finally the present results indicate that the preSMA is selectively recruited in during the learning of conditional verbal (but not vocal, orofacial, or manual) response selections based on verbal (but not vocal) feedback. These findings suggest that the preSMA has a special role in the learning of verbal responses and the processing of

verbal feedback for such learning. The current literature has suggested that the preSMA is involved in the learning of associations between visual stimuli and sequences of motor actions (Hikosaka et al., 1996; Sakai et al., 1999). A possible explanation of the preSMA's unique involvement in the learning visuo-verbal associations might be that, in the current study, only verbal responses involve a sequence of motor acts (i.e. sounds), whereas manual (single button presses), orofacial (single mouth movements) and vocal responses (single sounds) responses involve individual movements. In support of the preSMA's role in verbal processing, Lima and colleagues (2016) have shown that the preSMA is often engaged in the auditory processing of speech. Importantly, these investigators also suggested that the preSMA is involved in the volitional activation/retrieval of the specific speech motor representations associated with the perceived speech sounds. This could explain our observation that the preSMA was active during both the processing and selection of verbal responses during learning. The role of the preSMA in the learning of context-motor sequence associations appears to be conserved in the macaque (Nakamura, Sakai, & Hikosaka, 1998). Although nonhuman primates do not produce speech, it has been shown that the preSMA in monkeys is associated with volitional vocal production (Loh et al., 2017): Stimulation in the pre-SMA/anterior SMA region produces orofacial movements, but not vocalizations (Mitz & Wise, 1987). Lesions of the preSMA region led to increased latencies of spontaneous and conditioned call productions (Kirzinger & Jürgens, 1982). Based on these findings, it appears that the role of preSMA in the volitional control of orofacial/vocal patterns may have been adapted in the human brain for the control of speech patterns via context-motor sequence associations.

Together, our results have shown that ventral area 44, preSMA and MCC regions have important contributions to the cognitive control of orofacial and vocal

responses: Whereas the ventral area 44 is involved in the cognitive selection of vocal and orofacial actions, area 45 is involved in the selective retrieval of verbal/semantic information. The MCC is involved in the evaluation of vocal/verbal feedback that lead to behavioural adaptation in learning conditional associations between vocal/orofacial actions and arbitrary external visual stimuli. The pre-SMA is specifically involved in driving verbal action selections based on auditory verbal feedback processing. These specific roles of the components of the Broca – DMF network are central to vocal communicative behaviours that involve the selection of appropriate vocal/orofacial responses based on vocal feedback from the communicating partner. In a previous review (Loh et al., 2017), we have argued that the above functions of area 44, preSMA and MCC are generic across humans and nonhuman primates based on anatomical and functional homologies of these regions in cognitive vocal control. Importantly, providing strong evidence that these regions constitute a network, anatomical work in both human and monkeys has demonstrated strong links between the ventrolateral areas 44 and 45, preSMA and anterior MCC regions (reviewed in Loh et al., 2017).

How might this ventrolateral frontal Broca – dorsomedial frontal (Broca-DMF) network have changed to enable the transition from the adaptive control of innate and affective calls in nonhuman primates to that of complex verbal and non-verbal vocalizations in humans? One potential change could be the emergence of a cortical laryngeal representation in the human primary motor face area that afforded increased access to fine-motor control over oro-laryngeal movements (Simonyan, 2014). As such, ventral area 44, with strong connections to the primary motor face area via the ventral premotor area, would be able to exercise conditional sensory-vocal associations over a wider range of oro-laryngeal constructions. The preSMA, which is also strongly linked to the primary motor face representation, would also be able to

build context-motor sequence associations with complex speech motor patterns and activating them based on their auditory representations. The MCC, which is directly connected to the ventral premotor area, would also be able to drive oro-laryngeal adaptations, based on feedback evaluation, at the fine motor level. This could explain the expanded capacity of the human brain to generate flexibly and modify vocal patterns. In contrast, the primary motor face area in nonhuman primates only has access to fine motor control over orofacial musculature and not the larynx (Kuypers, 1958). Thus, nonhuman primates are capable of adaptively modifying orofacial but not vocal movements. Indeed, the great apes are capable of novel species-atypical sounds such as “raspberries” and whistling that largely involve articulatory modulations (Hopkins, Taglialatela, & Leavens, 2007; Wich et al., 2009). For vocalizations, they are largely restricted to the context-dependent production and modifications of innate vocal patterns that are generated via the cingulate vocalization pathway (Jürgens, 2002).

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### **Chapter 3: Rostro-caudal Organization of Connectivity between Cingulate Motor areas and Lateral Frontal Regions**

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# Rostro-Caudal Organization of Connectivity between Cingulate Motor Areas and Lateral Frontal Regions

**Kep Kee Loh<sup>1</sup>, Fadila Hadj-Bouziane<sup>2</sup>, Michael Petrides<sup>3</sup>, Emmanuel Procyk<sup>1</sup> and Céline Amiez<sup>1\*</sup>**

<sup>1</sup> Univ Lyon, Université Claude Bernard Lyon 1, Institut National de la Santé Et de la Recherche Médicale, Stem Cell and Brain Research Institute U1208, Bron, France, <sup>2</sup> Institut National de la Santé Et de la Recherche Médicale, U1028, Centre National de la Recherche Scientifique UMR5292, Lyon Neuroscience Research Center, ImpAct Team - University UCBL Lyon 1, Lyon, France, <sup>3</sup> Department of Neurology and Neurosurgery, Montreal Neurological Institute, Montreal, QC, Canada

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### \*Correspondence:

Céline Amiez  
celine.amiez@inserm.fr

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According to contemporary views, the lateral frontal cortex is organized along a rostro-caudal functional axis with increasingly complex cognitive/behavioral control implemented rostrally, and increasingly detailed motor control implemented caudally. Whether the medial frontal cortex follows the same organization remains to be elucidated. To address this issue, the functional connectivity of the 3 cingulate motor areas (CMAs) in the human brain with the lateral frontal cortex was investigated. First, the CMAs and their representations of hand, tongue, and eye movements were mapped via task-related functional magnetic resonance imaging (fMRI). Second, using resting-state fMRI, their functional connectivity with lateral prefrontal and lateral motor cortical regions of interest (ROIs) were examined. Importantly, the above analyses were conducted at the single-subject level to account for variability in individual cingulate morphology. The results demonstrated a rostro-caudal functional organization of the CMAs in the human brain that parallels that in the lateral frontal cortex: the rostral CMA has stronger functional connectivity with prefrontal regions and weaker connectivity with motor regions; conversely, the more caudal CMAs have weaker prefrontal and stronger motor connectivity. Connectivity patterns of the hand, tongue and eye representations within the CMAs are consistent with that of their parent CMAs. The parallel rostral-to-caudal functional organization observed in the medial and lateral frontal cortex could likely contribute to different hierarchies of cognitive-motor control.

**Keywords:** frontal cortex, functional gradient, resting-state fMRI, task-related fMRI, humans, cingulate motor areas

## INTRODUCTION

Prevailing theories about the functional organization of the frontal lobe suggest that the lateral frontal cortex is organized along a rostral-to-caudal axis of behavioral/cognitive control where higher level cognitive processing is implemented rostrally and motor control processing, caudally (Petrides, 2005a,b; Koechlin and Summerfield, 2007; Badre and D'Esposito, 2009). Whether the medial frontal cortex, which is strongly connected

with the lateral frontal cortex (Dum and Strick, 1991; Bates and Goldman-Rakic, 1993; Lu et al., 1994), is organized along a similar axis remains to be demonstrated. A recent study has provided support for this hypothesis by showing that, along a rostral-caudal axis, progressively rostral medial frontal regions are involved in monitoring the reliability of more complex behavioral rules maintained in progressively rostral lateral frontal regions, and to seek out new alternatives as current rules become unreliable (Domenech and Koehlin, 2015). Within the medial frontal cortex, the rostral cingulate motor region appears to play a key role in frontal medio-lateral interactions during complex adaptive decision-making (Procyk et al., 2016). In this context, the goal of the present article is to provide new insights into the organization of the human cingulate motor cortex, by examining its functional connectivity with the lateral frontal cortex.

Anatomical investigations of the monkey cingulate cortex have demonstrated at least 3 cingulate motor areas (CMAs): CMAR, CMA<sub>D</sub>, and CMA<sub>V</sub> based on their relative positions in the rostral, dorsal and ventral parts of the cingulate sulcus, respectively (He et al., 1995). The two posterior areas have sometimes been regarded as a single CMA<sub>C</sub> caudal region. Anterior and posterior CMAs have also been labeled as M3 and M4 by Morecraft et al. (1996). CMAs constitute the main sites of cingulate connections with the precentral motor and premotor cortex, and the spinal cord (Dum and Strick, 1991; Morecraft and Van Hoesen, 1992). The CMAs also display reciprocal connections with the prefrontal cortex (Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen, 1993; Picard and Strick, 1996). Notably, the most rostral region, CMAR, in contrast with the more caudal CMA<sub>D</sub> and CMA<sub>V</sub>, has denser connections with the pre-SMA, orbital, medial and lateral prefrontal cortex, weaker connections with the dorsal premotor and primary motor cortex, and fewer but a more complex pattern of cortico-spinal projections (Dum and Strick, 1991; Luppino et al., 1993; He et al., 1995; Hatanaka et al., 2003; Morecraft et al., 2004, 2012; Petrides and Pandya, 2006). These findings suggest that, along a rostro-caudal axis, CMAs show graded relationships with prefrontal (decreasing connectivity) and motor regions (increasing connectivity). These connectivity trends corroborate that the anterior CMA is more implicated in higher-order cognitive functions in association with the prefrontal cortex and the posterior CMAs in motor functions associated with the motor, premotor cortex and spinal cord.

In the human brain, the cingulate cortex contains three premotor areas—also known as the cingulate motor zones: the rostral anterior cingulate zone (RCZ<sub>a</sub>) and the rostral posterior cingulate zone (RCZ<sub>p</sub>) in the midcingulate cortex (MCC), and the caudal cingulate zone (CCZ) in the posterior cingulate cortex (Picard and Strick, 1996, 2001; Beckmann et al., 2009; Amiez and Petrides, 2014). Neuroimaging experiments suggest that these zones are somatotopically organized, with RCZ<sub>a</sub> and RCZ<sub>p</sub> containing both limb and face motor representations, and the CCZ containing only limb motor representations (Amiez and Petrides, 2014). Several studies and meta-analyses have emphasized the anatomo-functional correspondence between RCZ<sub>a</sub> in humans and CMAR in monkeys (Shackman et al., 2011; Amiez and Petrides, 2014; Procyk et al., 2016) and suggested

possible correspondences between the human RCZ<sub>p</sub> and CCZ with the monkey posterior cingulate motor regions (Amiez and Petrides, 2014). At this point, an important question remains unresolved: Is the rostral-to-caudal organization of decreasing prefrontal and increasing motor cortex connectivity observed in the monkey CMAs also present in the human cingulate zones? This question is critical not only in establishing the anatomo-functional homologies between monkey CMAs and human cingulate zones but also in shedding light on the functional interactions between the human medial and lateral frontal cortical areas.

Here, we aim to describe the connectivity profiles of the 3 cingulate zones in the human brain (that we group under the generic term CMAs) and crucially, to test if they reflect a rostro-caudal cognitive-to-motor functional organization as in the lateral frontal cortex. To this end, we combined task-related fMRI, to map the CMAs and their motor representations, with resting-state fMRI, to examine their functional connectivity with various lateral frontal cortical regions situated along a rostro-caudal axis. Importantly, these analyses were conducted on a subject-by-subject basis, since this is the only way to dissociate the various motor representations in the RCZ<sub>a</sub> and RCZ<sub>p</sub>. Indeed, Amiez and Petrides (2014) have demonstrated that the relative locations of motor map subdivisions in RCZ<sub>a</sub> and RCZ<sub>p</sub> vary according to individual sulcal morphology: when a paracingulate sulcus (PCGS) is present (in about 70% of subjects in at least one hemisphere), the face motor representations of the RCZ<sub>a</sub> and RCZ<sub>p</sub> are located in the PCGS, whereas the limb motor representations are located in the cingulate sulcus. Conversely, when a PCGS is absent, all motor representations of each CMA are located in the cingulate sulcus.

The present study demonstrates the existence of a rostro-caudal functional organization of the CMAs in the human brain based on their differential coupling with lateral frontal brain regions along a rostro-caudal axis. The most anterior CMA has stronger functional connectivity with the rostral prefrontal areas, whereas posterior CMAs, exhibiting an opposite pattern of connectivity, have stronger connectivity with the (more caudal) motor regions. We discuss the implications of these findings in the context of the involvement of frontal medio-lateral brain networks in behavioral control.

## METHOD

### Subjects

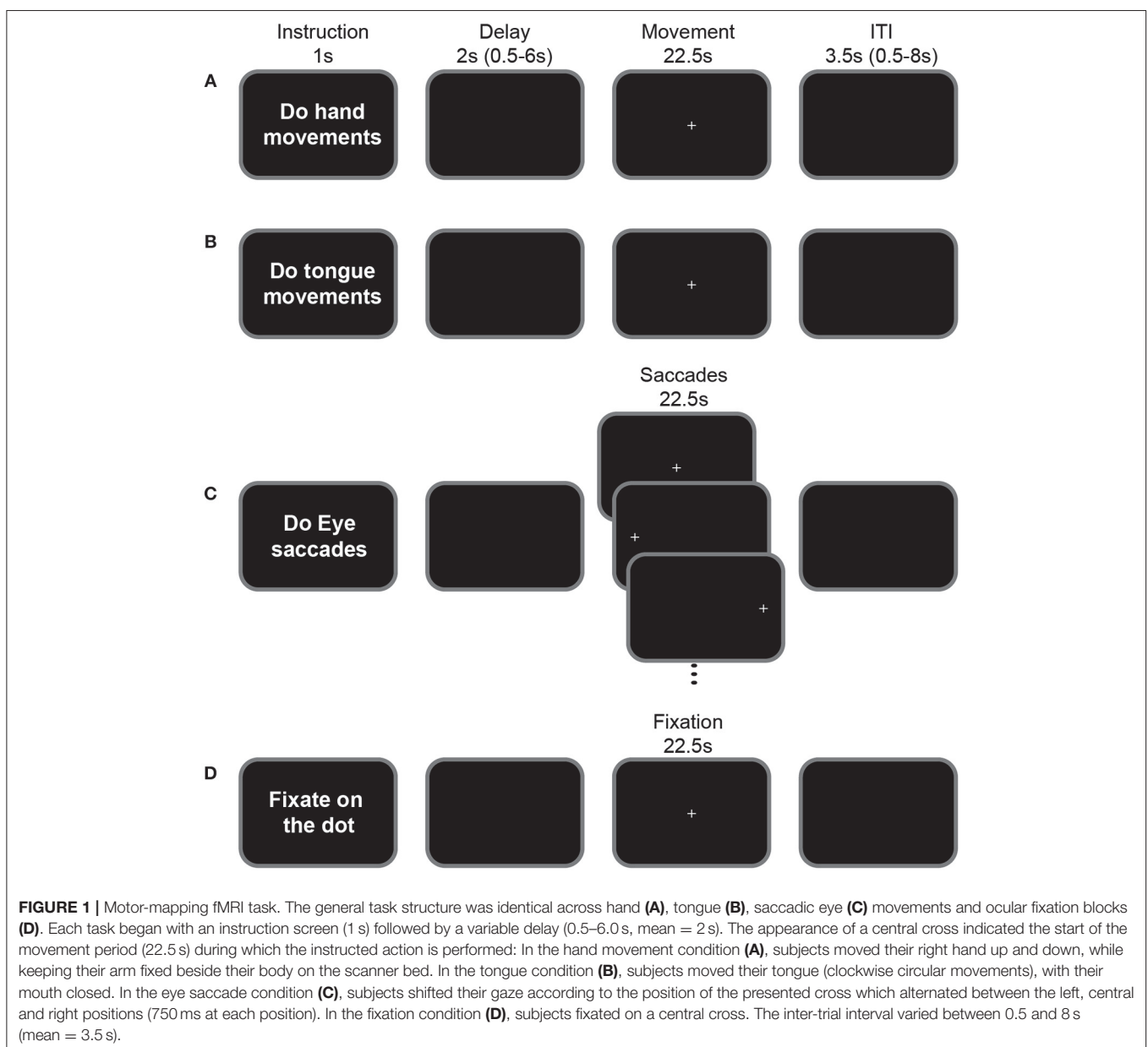
For this study, 23 healthy, right-handed native French speakers were recruited, but two subjects had to be excluded because of claustrophobia. Thus, 21 subjects (12 males; mean age of all subjects 26.0, SD = 3.94) were included in the final analysis. The study was carried out in accordance with the recommendations of the Code de la Santé Publique and was approved by the “Agence Nationale de Sécurité des médicaments et des produits de santé (ansm)” and the “Comité de Protection des Personnes (CPP) Sud-Est III” (N° EudraCT: 2014-A01125-42). It also received a Clinical Trial Number (NCT03124173, see <https://>

clinicaltrials.gov). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

## Tasks

To map the different motor areas in the cingulate cortex, we adopted the protocol described in Amiez and Petrides (2014). Subjects performed right hand, tongue, and saccadic eye movements during fMRI scanning (see **Figure 1**). A short sentence was presented on the screen for 1 s indicating to the subject the type of movement that they would have to perform in the trial (instruction period). After a jittered delay varying from 0.5 to 6.0 s (average = 2 s), a fixation point was presented for 22.5 s. The occurrence of this fixation point was the signal to perform the movement indicated in the preceding

instruction period while maintaining eye fixation during the performance of the required movement. The disappearance of the fixation point 22.5 s later instructed the subject to stop performing the movement and an inter-trial interval (ITI) followed. The short instruction sentence “Do hand movements” informed the subject to move the right hand up and down while keeping the arm and wrist on the scanner bed and the fingers straight (**Figure 1A**) and the instruction “Do tongue movements” informed the subject to rotate the tongue clockwise while keeping the mouth closed (**Figure 1B**). The protocol was slightly different for the assessment of the eye fields since the subjects were asked to perform saccadic eye movements. In this case, the sentence “Do eye saccades” indicated to the subjects that, after the 0.5–6 s jittered delay (average = 2 s),



they would have to perform a saccade to follow a dot presented in 1 of 3 possible locations on the screen (left, middle, or right), for 22.5 s. Each dot appeared for 750 ms at each location (Figure 1C). This protocol has been described in detail in Amiez et al. (2006) and Amiez and Petrides (2009, 2014). Finally, in the control condition, the instruction sentence was “Fixate the central cross” and the subject had to maintain an ocular fixation on the dot presented in the center of the screen during 22.5 s (Figure 1D). After the movements/ocular fixation, an inter-trial interval 0.5–8.0 s (average = 3.5 s) was presented. The presentation of the stimuli was controlled via Presentation software (Neurobehavioral systems). The subjects viewed the stimuli in the scanner via an LCD projector with a mirror system.

## MRI Acquisition

Scanning was performed on a 3T Siemens Magnetom Prisma MRI Scanner (Siemens Healthcare, Erlangen, Germany). To minimize movements during the motor tasks, the head of the subject was tightly cushioned throughout the acquisition of fMRI data. The functional MRI data ( $T_2^*$ -weighted gradient echo planar EPI images, 40 oblique slices, voxel resolution =  $2.7 \times 2.7 \times 2.7$  mm, TR = 2.2 s, TE = 30.0 s, flip angle =  $90^\circ$ ) from the fixation and motor mapping tasks were acquired over two MRI sessions. In the first session, each run consisted of one fixation and one tongue mapping block. In the second session, subjects performed one fixation and two mapping blocks (hand and saccades) in each run. Note that in both sessions, subjects had additionally performed a second cognitive task, as part of a separate protocol, after the fixation and motor mapping blocks. However, in the present article, we analyze only the data from the fixation and motor-mapping blocks. In both sessions, subjects performed 4–6 acquisition runs. In the first session, we acquired in each subject, 160–240 TRs of data corresponding to the fixation ( $22.5 \text{ s}/2.2 \text{ s} * 4\text{--}6 \text{ runs} = 80\text{--}120 \text{ TRs}$ ) and tongue movement trials ( $22.5 \text{ s}/2.2 \text{ s} * 4\text{--}6 \text{ runs} = 80\text{--}120 \text{ TRs}$ ). In the second session, we acquired in each subject, 240–360 TRs of data from the fixation, saccadic eye and hand movement trials. High resolution  $T_1$ -weighted anatomical scans (MPRAGE,  $0.9 \text{ mm}^3$  isotropic voxels, 192 slices, TR = 3.5 s, TE = 2.67 s) were also acquired during one of the experimental sessions.

The resting-state functional MRI scan was performed in one experimental session after all the task runs. Three-hundred EPI images were acquired over 11 min with identical scanning parameters as the task-based functional scans. During this acquisition, subjects were instructed to keep still and maintain fixation on a white dot presented on the center of the screen while blinking normally. Photoplethysmography (PPG) data were acquired via an infrared pulse oximeter (Siemens Healthcare, Erlangen, Germany) attached to the subject's left index finger. A Biopac MP150 system (Biopac Systems Inc, Goleta, CA) was used to acquire simultaneously and synchronize the PPG signal from the oximeter with the TTL pulses from the MRI scanner. Eye-tracking was achieved by using monocular corneal reflection and pupil tracking via an SR Research Eyelink 1,000 long-range MRI Eyetracker (SR Research, Ontario, Canada) sampling at 1,000 Hz. For synchronizing fMRI and eyetracking

data, TTL pulses from the scanner were delivered into the computer controlling the eye movements via a parallel port connection.

## MRI Data Analysis

### Task-Related fMRI

Functional data from the mapping/fixation task runs were preprocessed via Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, UCL, UK; <http://www.fil.ion.ucl.ac.uk/spm>) and Matlab 16a (<http://www.mathworks.com>). The first 5 volumes of each run were removed to allow for  $T_1$  equilibrium effects. We applied a slice-timing correction using the time center of the volume as reference. Then, head motion correction was applied using rigid-body realignment. These realignment parameters were used as covariates during the statistical analysis to model out potential nonlinear head motion artifacts. Functional and morphological images were spatially normalized into standard MNI space using SPM's default templates. Functional data were finally smoothed using a 6-mm full-width half maximum Gaussian kernel (Friston et al., 1995a,b,c). A 128-s temporal “high-pass filter” regressor set was included in the design matrix to exclude low-frequency confounds.

Each task trial was modeled with impulse regressors at the time of the presentation of the fixation point that initiated the performance of the hand, tongue, and saccadic eye movements, as well as ocular fixation. These regressors were then convolved with the canonical hemodynamic response function and entered into a general linear model (GLM) of each subject's fMRI data. The 6 scan-to-scan motion parameters produced during realignment were included as additional regressors in the GLM to account for residual effects of subject movement. Statistical significance in the resulting single-subject contrast images was assessed with a  $p_{uncorrected} < 0.001$  voxel-wise threshold.

### Resting State fMRI

The preprocessing of resting-state scans was also performed with SPM 12. The first 5 volumes of each run were removed to allow for  $T_1$  equilibrium effects. We then applied a slice-timing correction using the time center of the volume as reference. The head motion correction was applied using rigid-body realignment and, then, using the AFNI software (Cox, 1996), a temporal filtering was applied to extract the spontaneous slowly fluctuating brain activity (0.01–0.1 Hz). Finally, a linear regression was used to remove nuisance variables (the six parameter estimates for head motion, the cerebrospinal fluid and white matter signals from the SPM segmentation, the number of heart pulses per TR, and the mean pupil size per TR). Note that a customized Matlab program was used to detect and count the number of peaks in the PPG signal in each TR window. Automatic peak detection was performed using the “findpeaks” function from the Signal Processing Toolbox (<https://www.mathworks.com>). Raw pupil diameter data were extracted from the Eyelink datafile and subsequently averaged in each TR window via Matlab. Finally, a spatial smoothing with a 6-mm FWHM Gaussian kernel was applied to the output of the regression.

The main goal of the resting-state fMRI analyses was to investigate, on a subject-by-subject basis, the differential functional connectivity associated with the various CMAs as well as their individual motor representations (i.e., tongue, eye, and hand). Specifically, our analyses were focused on the left intra-hemispheric connectivity of the CMAs (and their motor representations) with the lateral prefrontal and motor cortical areas, as well as with connectivity between the CMAs. For this analysis, a total of 15 locations in the left hemisphere of each subject were identified: in the CMAs (8 seeds), prefrontal cortex (5 ROIs), and motor cortex (3 ROIs) (see below and **Figure 3**).

### Seed Selection in CMAs

For each subject, 8 CMA seed locations in the left cingulate cortex were identified based on activation peaks from the fMRI motor-mapping task. These included the hand, eye, and tongue motor representations in RCZa and RCZp, and the two hand motor representations in CCZ (see **Figures 2, 3**).

### ROIs Selection in Motor Cortical Areas

For each subject, 3 ROIs within the left motor cortex were identified based on activation peaks from the fMRI motor-mapping task. These included the hand motor region (the precentral knob) within the central sulcus –M-H– (Boling et al., 1999; Amiez et al., 2006), the tongue motor region within the ventral part of the posterior part of the precentral gyrus –M-T– (Weiss et al., 2013), the frontal eye field –FEF– within the ventral branch of the superior precentral sulcus (Amiez et al., 2006). Monkey studies have shown that the CMAs are anatomically linked with the motor cortex (e.g., Dum and Strick, 1991; Procyk et al., 2016). The motor ROIs were selected to verify the connectivity profiles of the individual motor representations in the various CMAs with the motor system. Considering that the CMAs contain tongue, eye, and hand motor representations (Amiez and Petrides, 2014), we assessed the connectivity of these regions with the primary tongue area, the FEF, and the primary hand area. Note that the CMAs also contain foot motor representations but these had not been mapped in our mapping task. As such, in the present study, we did not assess CMAs' connectivity with the primary foot motor cortex (Amiez and Petrides, 2014). **Figure 3** displays the location of these ROIs.

### ROIs Selection in the Prefrontal Cortex

For each subject, 5 ROI locations within the left prefrontal cortex were identified based on local anatomy. These included area 10 –a10– (located at the intersection between the vertical segment of the intermediate frontal sulcus, the lateral and the medial frontomarginal sulcus, see Petrides, 2014), dorsolateral prefrontal areas 46 –a46– [within the dorsal paraintermediate frontal sulcus (pimfs-d)] and 9/46 –a9/46– [within the anterior segment of the posterior middle frontal sulcus (pmfs-a), see Amiez and Petrides, 2007], area 44 –Broca– [Broca's area, in the center of the pars opercularis, i.e., between the anterior ramus of the lateral fissure (aalf) and the inferior precentral sulcus (iprs), see (Petrides, 2014)], and the frontal operculum –Fo– (intersection between the frontal operculum and the circular sulcus, see Amiez et al., 2016). These ROIs were selected because of their known

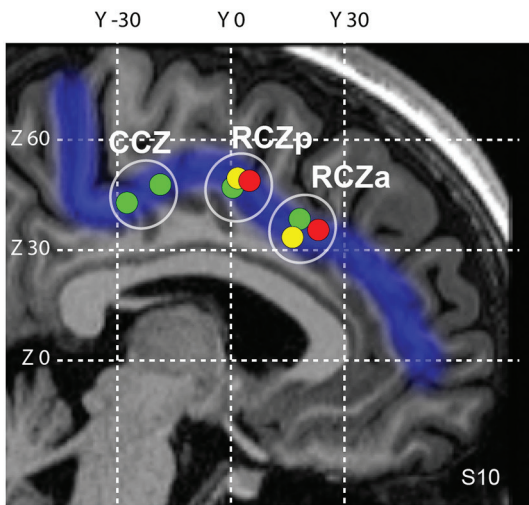
frequent co-activation with the MCC in a large range of cognitive tasks (Amiez and Petrides, 2007; Amiez et al., 2012a,b, 2013). ROI locations on the lateral surface of the prefrontal cortex are shown in **Figure 3**. Note that the center of each of the ROIs located in the sulci was positioned about 5 mm below the surface given the chosen size of the radius sphere (i.e., 4 mm, see below).

Based on the above 15 locations, seed/ROI spheres with a 4 mm radius were generated for each subject using the AFNI software and the mean signal from these regions was extracted. Note that this radius size was selected in order to allow the separate assessment of functional connectivity of seeds located in the CGS from those located in the PCGS when present. Indeed, the PCGS and CGS are most often separated of about 8–12 mm, so a larger radius would have prevented us to assess this putative dissociation. For each subject, correlation coefficients between the different CMA seeds with the various ROIs in the prefrontal cortex, motor cortex and other CMA seeds were computed and normalized using the Fisher's *r*-to-*z* transform formula. Significant threshold at the individual subject level was  $Z = \pm 0.2$  ( $p < 0.001$ ) and  $Z = \pm 0.15$  ( $p < 0.01$ ). These normalized correlational coefficients, which corresponded to the functional connectivity strength between each CMA seed and each ROI/other CMA seed in individual subjects, were subsequently processed with R statistical software (<https://www.r-project.org/>) for all the following analyses.

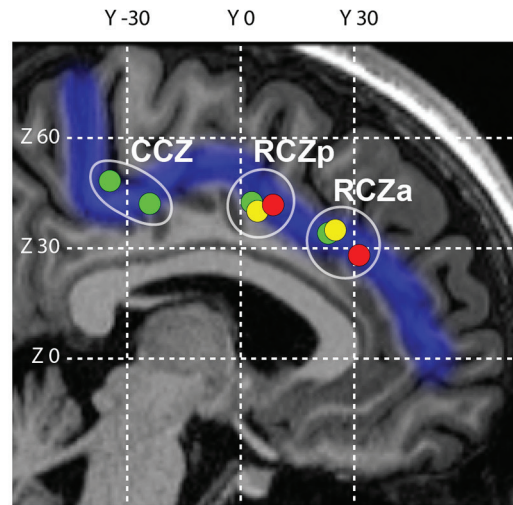
### Automatic Clustering Based on Seed-ROI Correlations

To compare the connectivity between the different CMAs and lateral frontal cortex, we first averaged the normalized correlation coefficients for each seed-ROI pairing across subjects. Next, Euclidean distance vectors were separately computed for the 8 CMA seeds (based on their mean connectivity values with the ROIs) and the 8 prefrontal/motor ROIs (based on their mean connectivity values with the CMA seeds). Finally, unsupervised hierarchical clustering was performed for the CMA seeds and ROIs separately. This clustering was generated using the `hclust` function in R which uses the complete linkage method for hierarchical clustering. This particular clustering method defines the cluster distance between two clusters to be the maximum distance between their individual components. At every stage of the clustering process, the two nearest clusters are merged into a new cluster. The process is repeated until the whole data set is agglomerated into one single cluster. This clustering method assumes a representation of data in an Euclidean space in which it is possible to summarize a collection of points by their centroid (i.e., the average of the points) (for more details, see <http://www.r-tutor.com/gpu-computing/clustering/hierarchical-cluster-analysis>). The outcome was used to construct dendrograms and heatmaps. To better display clusters across ROIs, values in the heatmaps were normalized (*z*-scored) by column. Hence values (and sign) in the heatmap do not represent actual connectivity measures.

**A Hemispheres without PCGS**

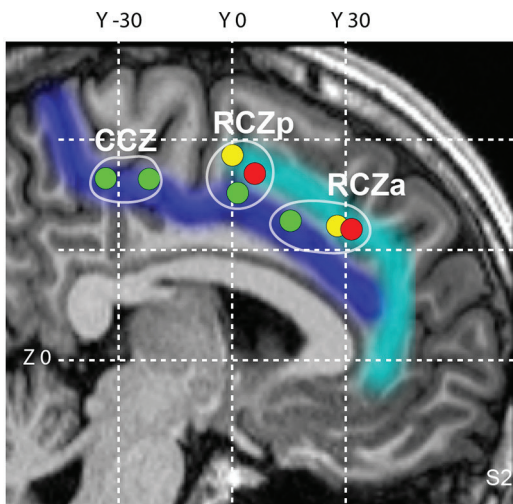


Average coordinates in LH

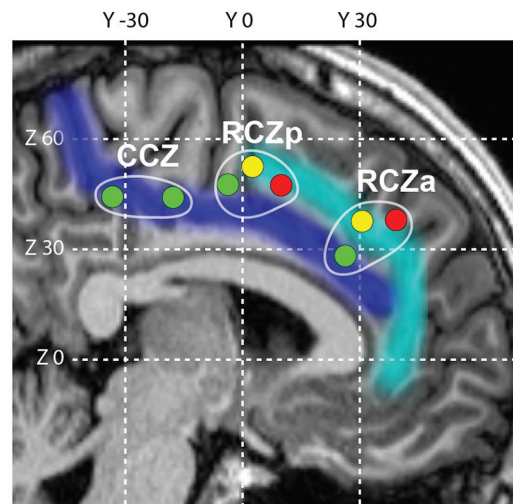


Average coordinates in RH

**B Hemispheres with PCGS**



Average coordinates in LH



Average coordinates in RH

- Hand motor representation
- Tongue motor representation
- Eye motor representation

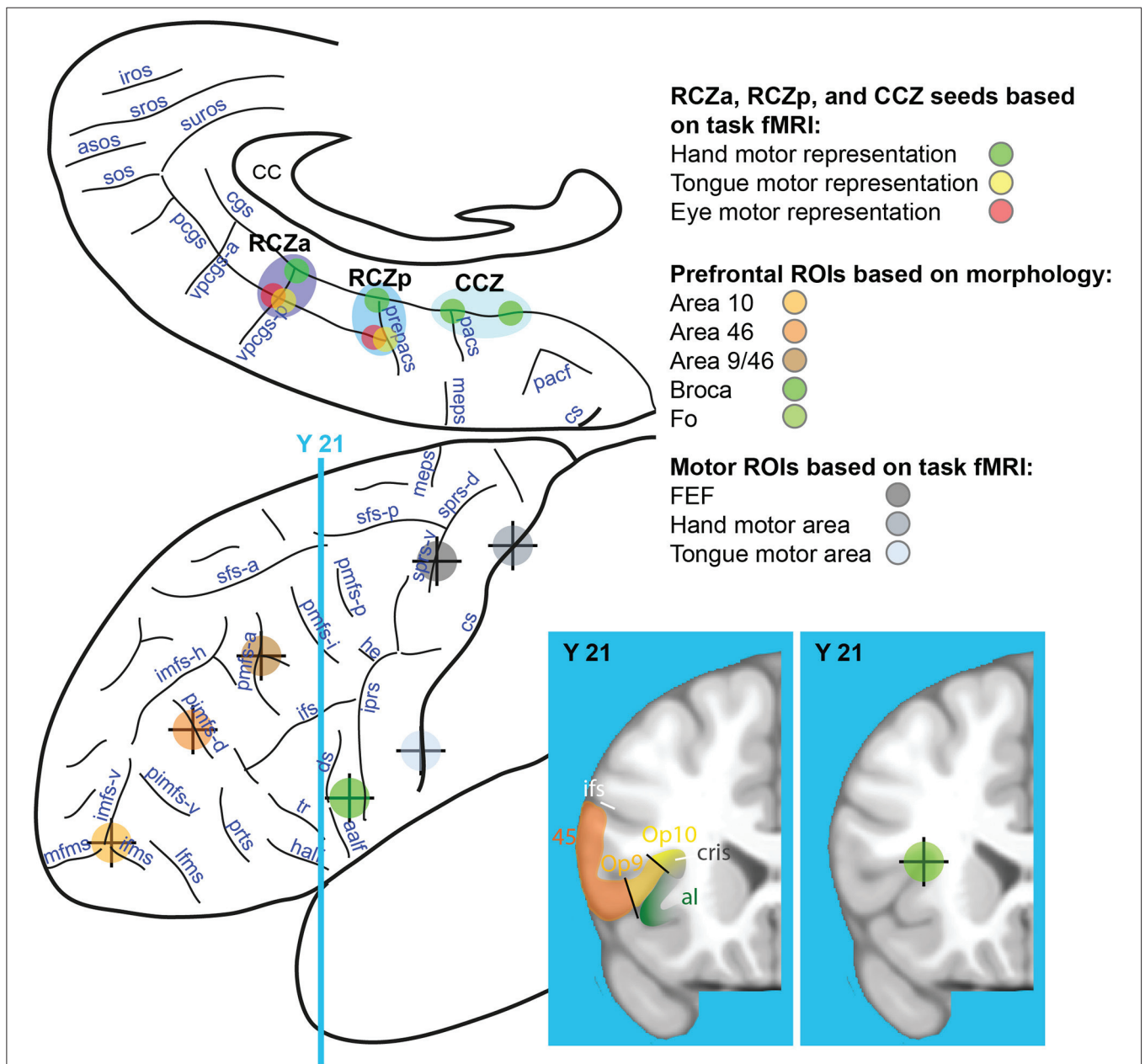
**FIGURE 2 |** Somatotopic organization of the human cingulate motor areas. The average locations of individual subject's peak activations associated with the performance of hand (green), eye saccadic (red) and tongue (yellow) movements plotted on a typical hemisphere with cingulate sulcus (**A**, Subject 10) and paracingulate sulcus (**B**, Subject 2). In both the hemispheres without (**A**) and with (**B**) paracingulate sulcus, three anterior-to-posterior clusters of activations can be observed with the two anterior-most clusters (RCZa and RCZp) containing all hand, eye and tongue representations, and the posteriormost cluster (CCZ) which contains two hand representations. The CGS and PCGS are marked in dark blue and cyan respectively. The antero-posterior (y) and dorso-ventral (z) coordinates in the MNI standard stereotaxic space are indicated as white grid lines. cgs, cingulate sulcus; pcgs, paracingulate sulcus; RCZa, anterior rostral cingulate zone; RCZp, posterior rostral cingulate zone; CCZ, caudal cingulate zone.

**Rostro-Caudal Frontal Axis Analyses**

To compare the connectivity profile of each CMA with the various lateral frontal ROIs, we constructed boxplots

corresponding to the correlation strength of each CMA location (RCZa, RCZp, CCZa, and CCZp) with each of the 8 ROIs (**Figure 4B**). Note that we divided the CCZ into an anterior and

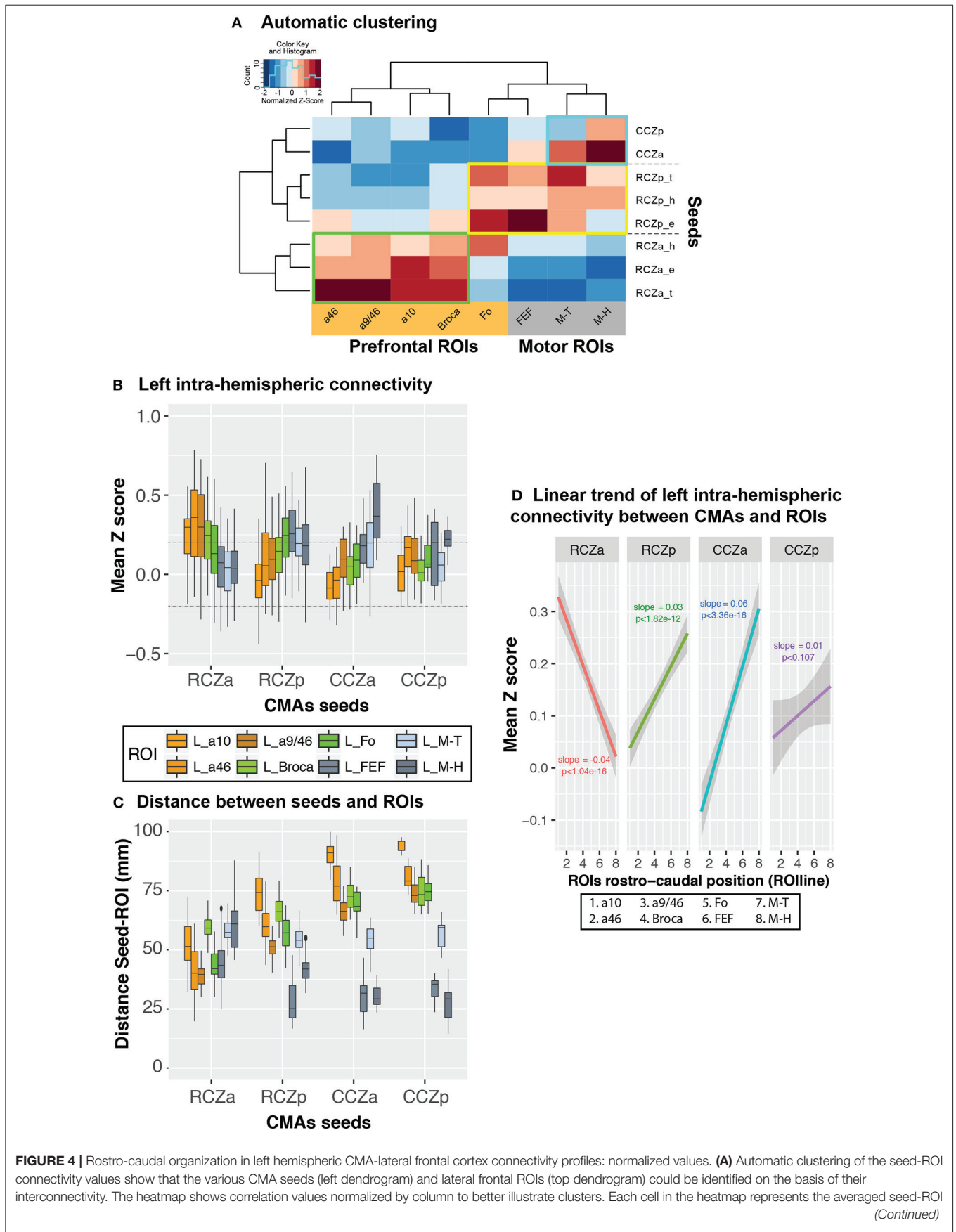




**FIGURE 3 |** Rostro-caudal CMAs seed locations on the medial frontal cortex and ROI locations on the lateral frontal cortex. Eight seeds were identified on the basis of task-fMRI results in the medial frontal cortex: hand (in green), tongue (in yellow), and eye (in red) motor representations of the RCZa (dark blue), RCZp (medium blue), and CCZ (light blue). Seven ROIs were identified in the lateral frontal cortex along a rostral-to-caudal axis based on individual subject anatomy (4 prefrontal ROIs: Area 10, Area 46, Area 9/46 and Broca’s Area) and from the motor mapping task (3 ROIs: FEF, hand and face precentral motor regions). The center of the crosses indicates the point of the sulci in the depth of which the various ROIs/seeds are located. CC, corpus callosum; cs, central sulcus; meps, medial precentral sulcus; pacf, paracentral fossa; cgs, cingulate sulcus; pcgs, paracingulate sulcus; pacs, paracentral sulcus; prepacs, pre-paracentral sulcus; vpcgs-p and vpcgs-a, posterior and anterior vertical paracingulate sulcus; suros, supra-rostral sulcus; sros and iros, superior and inferior rostral sulcus; sos, sus-orbitalis sulcus; asos, accessory sus-orbitalis sulcus; iprs, inferior precentral sulcus; he, horizontal extension; ifs, inferior frontal sulcus; sfs-a and sfs-p, anterior and posterior part of the superior frontal sulcus; imfs-h, and imfs-v, horizontal and ventral extension of the intermediate frontal sulcus; mfms, ifms, and lfms, medial, intermediate, and lateral fronto-marginalis sulcus; pimfs-v and pimfs-d, ventral and dorsal para-intermediate frontal sulcus; pmfs-a, pmfs-i, pmfs-p, anterior, intermediate, and posterior posteromedial frontal sulcus; ds, diagonalis sulcus; ts, triangularis sulcus; aalf, anterior ramus of the lateral fissure; half, horizontal anterior ramus of the lateral fissure.

posterior part in view of the fact that there were two distinct CCZ hand representations. This allowed us to compare the connectivity profiles of the two CCZ hand representations. The

correlation strength of each CMA location with a particular ROI was obtained by averaging the correlation values from its constituent motor representations with the same ROI. The



**FIGURE 4** | connectivity value (transformed correlation coefficients) across subjects and with a color scale mapped on values z-scored by column (red and blue corresponding respectively to negative and positive normalized values, not to actual connectivity correlation values). Three distinct clusters of strong correlations could be observed: (1) Green box: strong connectivity between RCZa seeds and prefrontal ROIs; (2) Blue box: strong connectivity between CCZ seeds and motor ROIs; Yellow box: RCZp seeds, which showed an intermediate pattern of connectivity between CCZ and RCZa. **(B)** Boxplots displaying the mean ( $\pm$ SD) z-transformed correlation between each CMA location (RCZa, RCZp, CCZa, CCZp) on the x-axis, and the various ROIs (color-coded) in all subjects. **(C)** Boxplots displaying the mean ( $\pm$ SD) Euclidian distance between each seed (RCZa, RCZp, CCZa, CCZp) on the x-axis, and the various ROIs (color-coded) in all subjects. **(D)** Significant linear organization in the connectivity of each CMA location with the rostral-caudal lateral frontal ROIs. The rostro-caudal organization variable (ROIline) was obtained by recoding the ROIs in terms of their relative rostro-caudal rank: 1, area 10; 2, area 46; 3, area 9/46; 4, Broca's area; 5, Fo; 6, FEF; 7, M-Face; 8, M-Hand. The dashed lines indicate the level of statistical threshold at  $p < 0.001$  ( $Z = \pm 0.2$ ).

CCZa and CCZp locations contained the anterior and posterior CCZ hand representations respectively. Based on these boxplots, it can be discerned that more frontal CMAs had stronger connectivity with prefrontal regions and weaker connectivity with premotor and motor areas, whereas the opposite was true for more posterior CMAs –reflecting a rostro-caudal coupling of the CMAs with the lateral frontal cortex. The statistical significance of these effects with connectivity  $z$  values was tested via a general linear model with CMA location (RCZa, RCZp, CCZa, and CCZp), ROI zone (prefrontal and motor cortex) and their interaction as factors. Note that in the second factor, the prefrontal and motor zones were, respectively, obtained by pooling the correlation values of the 5 prefrontal ROIs (a10, a46, a9/46, Broca, Fo) and 3 motor/premotor ROIs (FEF, M-H, and M-T).

We then characterized the rostro-caudal functional axis based on the correlation profiles of the CMAs with the lateral frontal cortex by estimating linear trends in the correlation strength for each CMA location (RCZa, RCZp, CCZa, and CCZp) with the 8 rostro-caudal lateral frontal ROIs. The 8 ROIs were first ranked along a rostro-caudal axis based on their averaged  $Y$  coordinate values across subjects and recoded into a numeric axis variable (ROIline): a10 (most anterior)-1, a46 - 2, a9/46 - 3, Broca - 4, Fo - 5, FEF - 6, M-T - 7, M-H (most posterior) - 8. We then performed linear regressions of the connectivity  $z$  values on CMA location and the linear axis variable (ROIline).

Additionally, we were interested in whether the connectivity profiles of the distinct motor representations (hand, eye, tongue) in the CMAs adhered to the same rostral-caudal functional organization. We focused on the two rostral CMAs (RCZa and RCZp) that both had a complete set of hand, tongue and eye motor representations. Given that the locations of the face motor representations (eye and tongue) in the RCZs varied depending on cingulate sulcal morphology (i.e., whether a PCGS was present), we also questioned if the connectivity profiles of the CMA motor representations were affected by the presence of a PCGS. To test the possible effects of the type of motor representation and cingulate morphology on the rostro-caudal connectivity organization in each RCZ, we linearly regressed the connectivity  $z$  values on motor representation type (hand, eye, and tongue), cingulate morphology (with or without PCGS) and the linear axis variable (ROIline). Here, the significance of the motor representation-ROIline and cingulate morphology-ROIline interaction terms would indicate, respectively, if motor representation and cingulate morphology significantly impacted the rostro-caudal connectivity organization in the RCZs.

Importantly, all linear model fits were evaluated using graphic diagnostic tools to ensure that all linear model assumptions were met.

## RESULTS

### Morphological Description of the Cingulate Cortex

Based on individual cingulate morphology, subjects could be divided into 3 main groups (Table 1): Group 1 included 10 subjects who had a PCGS in one hemisphere but not the other. These subjects were further divided into two sub-groups depending on whether a PCGS appeared on the left (Group 1A; 7 subjects) or right hemisphere (Group 1B; 3 subjects). Group 2 consisted of 4 subjects with PCGS on both hemispheres. Lastly, Group 3 consisted of 7 subjects with no PCGS either on the left or the right hemispheres. Note that the CGS and/or the PCGS could be segmented as opposed to a single continuous sulcus. In this case, the number of segments were also reported in Table 1.

### Task-Related fMRI Data

#### Activity within the Cingulate Cortex

The goal of the task-related fMRI study was to map the hand, tongue, and eye motor representations within the various CMAs as seeds for the subsequent resting-state connectivity analyses.

To map the hand representations in the various CMAs, we compared the BOLD signal during right hand movements with the BOLD signal during ocular fixation. Subject-level analysis was performed to assess the impact of the presence of a paracingulate sulcus on the location of this activity. Four hand-motor related activity peaks were observed: (1) at the intersection of the CGS and the vertical paracingulate sulcus (vpvcs) (anterior peak), (2) at the intersection of the CGS and the pre-paracentral sulcus (prepacs) (middle peak), (3) at the intersection of the CGS and the paracentral sulcus (PACS) and (4) posterior to this intersection. Thus, the locations of the two anterior peaks related to the hand fell within the RCZa and RCZp, respectively. The locations of the two posterior peaks related to the hand fell within the CCZ. Indeed, as previously shown (Amiez and Petrides, 2014), the CCZ displays 2 peaks related to hand movement. In the following resting-state data analysis, note that we dissociate the peak located at the intersection of the CGS and the PACS (CCZa) from the peak located posterior to this intersection (CCZp), in an effort to disentangle their relative functional connectivity pattern.

It was also evident that the presence of a PCGS did not have an impact on the location of these hand-related activity peaks

**TABLE 1** | Morphological sulcal variability in the cingulate cortex.

		Left hemisphere		Right hemisphere	
		CGS	PCGS	CGS	PCGS
Group 1A	S2	Not segmented	Not segmented	2 segments	–
	S5	Not segmented	Not segmented	Not segmented	–
	S7	Not segmented	3 segments	2 segments	–
	S8	Not segmented	Not segmented	Not segmented	–
	S11	Not segmented	Not segmented	2 segments	–
	S14	Not segmented	Not segmented	Not segmented	–
	S19	Not segmented	Not segmented	2 segments	–
Group 1B	S13	2 segments	–	Not segmented	Not segmented
	S16	Not segmented	–	2 segments	2 segments
	S20	Not segmented	–	Not segmented	Not segmented
Group 2	S3	Not segmented	Not segmented	Not segmented	Not segmented
	S6	Not segmented	2 segments	2 segments	Not segmented
	S9	2 segments	Not segmented	Not segmented	3 segments
	S17	Not segmented	2 segments	Not segmented	Not segmented
Group 3	S1	2 segments	–	3 segments	–
	S4	Not segmented	–	Not segmented	–
	S10	Not segmented	–	2 segments	–
	S12	Not segmented	–	2 segments	–
	S15	Not segmented	–	2 segments	–
	S18	Not segmented	–	Not segmented	–
	S21	2 segments	–	Not segmented	–

in RCZa and RCZp (note that a PCGS is never observed at the level of CCZ). Note that the activity remained in the CGS even when a PCGS was present (with the exception of 2/21 subjects who showed hand motor-related activity in the PCGS in RCZa). These results were in line with our previous findings (Amiez and Petrides, 2014). Finally, we also found that the performance of right handed movements evoked activity in the CMA hand motor representations, bilaterally. Average MNI coordinates of hand movement representations in the cingulate cortex in left and right hemispheres with or without a PCGS are shown in **Table 2** and **Figure 2**.

To map the tongue movement representations in the various CMAs, we contrasted the BOLD signal during tongue movements with the BOLD signal during ocular fixation. Tongue-motor related activity was observed: (1) at the intersection of the CGS and the vpcgs when no PCGS was present, and at the intersection of the PCGS and the vpcgs when a PCGS was present (anterior peak), (2) at the intersection of the CGS and prepacs when no PCGS was present and at the intersection of the PCGS and prepacs when a PCGS was present (middle peak). These observations suggested that the anterior and the middle peaks were located in the RCZa and RCZp, respectively. Note that both peak locations were clearly influenced by the presence of a PCGS: when a PCGS was present, tongue-motor related activity was found in the PCGS (with the exception of 2/21 subjects who had tongue motor activity

in the CGS in RCZa). The absence of a third posterior peak corroborated our earlier observation that the CCZ does not contain tongue movements representation. These results are congruent with our previous observations (Amiez and Petrides, 2014). Finally, as with hand movements, tongue movements evoked bilateral activation in the CMA tongue regions. The average MNI coordinates of tongue movement representations in the cingulate cortex in left and right hemispheres with and without a PCGS are in **Table 2** and **Figure 2**.

To map the saccadic eye movement representations in the various CMAs, we compared the BOLD signal during saccadic eye movements with that during ocular fixation. Saccadic eye movement-related activity was observed: (1) at the intersection of the CGS and the vPCGS when no PCGS was present and at the intersection of the PCGS and the vPCGS when it was present (anterior peak), (2) at the intersection of the CGS and prepacs when no PCGS was present and at the intersection of the PCGS and prepacs when it was present (middle peak). These observations suggest that the anterior and the middle peaks belong, respectively, to RCZa and RCZp. The location of the two peaks were impacted by the presence of PCGS: both saccadic movement-related activity peaks were located in the PCGS when it was present (with the exception of 1/21 subjects which showed saccadic eye movement activity in the CGS in RCZp). As with tongue movements, a third posterior saccadic movement related peak was absent confirming that there is no saccadic eye

**TABLE 2** | Average coordinates of hand, tongue and eye motor representations in RCZa, RCZp, and CCZ in hemispheres in which the PCGS is present vs. absent.

	NO PCGS			Peak location	PCGS			Peak location
	Average MNI coordinates $\pm$ sem				Average MNI coordinates $\pm$ sem			
	X	Y	Z		X	Y	Z	
<b>LEFT HEMISPHERE</b>								
<b>RCZa</b>								
Hand	-4.4 $\pm$ 0.7	18.1 $\pm$ 3.4	39 $\pm$ 3	CGS	-6.1 $\pm$ 1	15.4 $\pm$ 2.8	37.9 $\pm$ 1.7	CGS
Tongue	-4.3 $\pm$ 0.8	16.2 $\pm$ 2.9	34 $\pm$ 2.4	CGS	-7.7 $\pm$ 0.8	27.7 $\pm$ 2.6	36.5 $\pm$ 2.1	PCGS
Eye	-7.2 $\pm$ 1.6	23 $\pm$ 4.2	36 $\pm$ 3.5	CGS	-7.6 $\pm$ 0.9	31.6 $\pm$ 4.2	35.7 $\pm$ 3.1	PCGS
<b>RCZp</b>								
Hand	-6.1 $\pm$ 0.7	0.4 $\pm$ 1.5	47.6 $\pm$ 1.8	CGS	-5.6 $\pm$ 1.3	1.4 $\pm$ 1.8	46.3 $\pm$ 3.5	CGS
Tongue	-5.5 $\pm$ 0.7	1.7 $\pm$ 1.1	50.2 $\pm$ 2.1	CGS	-5.8 $\pm$ 0.3	0.1 $\pm$ 1.8	54.8 $\pm$ 1.9	PCGS
Eye	-6.8 $\pm$ 1	4.8 $\pm$ 0.9	49.5 $\pm$ 1.6	CGS	-7.3 $\pm$ 1.1	6 $\pm$ 3.7	50.1 $\pm$ 2.5	PCGS
<b>CCZ</b>								
Hand ant	-8.2 $\pm$ 1.2	-18.7 $\pm$ 1.8	48.5 $\pm$ 1.1	CGS	-5.9 $\pm$ 1	-22 $\pm$ 1.7	48.6 $\pm$ 1.3	CGS
Hand post	-11 $\pm$ 0.7	-27.5 $\pm$ 2.6	43.5 $\pm$ 2.8	CGS	-7.3 $\pm$ 0.8	-33.5 $\pm$ 3.5	48.8 $\pm$ 2	CGS
<b>RIGHT HEMISPHERE</b>								
<b>RCZa</b>								
Hand	8.5 $\pm$ 1	23 $\pm$ 3.1	35 $\pm$ 2.4	CGS	9 $\pm$ 1.8	26 $\pm$ 4.7	28.9 $\pm$ 4	CGS
Tongue	9.6 $\pm$ 0.9	24.9 $\pm$ 2	36 $\pm$ 2	CGS	8 $\pm$ 1.2	30.3 $\pm$ 2.4	38.3 $\pm$ 2	PCGS
Eye	9.8 $\pm$ 1.1	31.2 $\pm$ 5.6	28.8 $\pm$ 4.4	CGS	6.6 $\pm$ 0.6	39 $\pm$ 2.8	38.8 $\pm$ 1.9	PCGS
<b>RCZp</b>								
Hand	8.1 $\pm$ 0.8	2.7 $\pm$ 1.8	43.7 $\pm$ 1.5	CGS	8 $\pm$ 0	-4 $\pm$ 2	49 $\pm$ 1	CGS
Tongue	8.8 $\pm$ 0.9	4.2 $\pm$ 2.4	41.1 $\pm$ 2.3	CGS	7.7 $\pm$ 1.5	2.3 $\pm$ 4.9	53.3 $\pm$ 1.8	PCGS
Eye	7.4 $\pm$ 0.8	8.4 $\pm$ 2.8	42.9 $\pm$ 2.7	CGS	11 $\pm$ 1.5	9.6 $\pm$ 2.4	48.2 $\pm$ 3.8	PCGS
<b>CCZ</b>								
Hand ant	11 $\pm$ 1.1	-24.4 $\pm$ 1.7	43.2 $\pm$ 1.4	CGS	9.5 $\pm$ 1.8	-18 $\pm$ 1.8	44.8 $\pm$ 1.1	CGS
Hand post	9.9 $\pm$ 1.6	-35 $\pm$ 1.3	49.6 $\pm$ 1.1	CGS	11.5 $\pm$ 6.5	-33.5 $\pm$ 5.5	45 $\pm$ 5	CGS

movement representation in the CCZ. The above results were in line with our previous observations (Amiez and Petrides, 2014). Finally, we also observed that saccadic eye movements induced bilateral activation in the CMAs. The average MNI coordinates of saccadic eye movement representations in the cingulate cortex in left and right hemispheres with and without a PCGS are shown in **Table 2** and **Figure 2**.

Across all subjects, the 8 motor-related peaks could be observed in the cingulate cortex (3 peaks in RCZa, 3 in RCZp, and 2 in CCZ) in both hemispheres. Note that not all subjects showed all of the 8 peaks. On average, subjects display 6.1 peaks  $\pm$  1.2 stdev in the left hemisphere and 5.1 peaks  $\pm$  1.7 stdev in the right hemisphere, consistently with the results of Amiez and Petrides (2014).

### Activity within the Precentral Gyrus Motor Cortex

We used the same contrasts described above to identify the primary hand motor region (hand vs. fixation), primary tongue motor region (tongue vs. fixation), and FEF (saccades vs. fixation). Subject by subject analysis confirmed, for each subject, the location of the hand motor region in the precentral knob in the central sulcus, the location of the tongue motor region in the posterior part of the ventral precentral gyrus, and the

location of the FEF in the ventral branch of the superior precentral sulcus. The average x, y, z coordinates  $\pm$  s.e.m. of precentral motor ROIs in each of the 21 subjects are presented in **Table 3**.

### Resting State fMRI Data

To demonstrate the pattern of intra-hemispheric connectivity of RCZa, RCZp, CCZa, and CCZp seeds with the lateral prefrontal and motor ROIs, we first performed a hierarchical clustering of the seeds and ROIs based on their inter-correlations across all subjects (see Method). Resulting dendrograms from the seed and ROI clustering are displayed in **Figure 4A** along with a heatmap reflecting the correlation strength between each pair of seed-ROI clusters. This analysis demonstrated the existence of three CMA clusters based on their functional connectivity with the prefrontal and the motor cortex: RCZa, RCZp, and CCZ.

The Boxplots in **Figure 4B** further depict the average Z values of correlations between seeds and ROIs across subjects and, therefore, how the activity of each CMA is differentially correlated with the activity of the prefrontal/motor ROIs. We tested these differences in connectivity z values with a generalized linear model with CMA location (RCZa, RCZp, CCZa, and CCZp) and ROI zones (prefrontal zones: a10, a46, a9/46, Broca,

**TABLE 3** | Average coordinates of hand, tongue and eye motor representations in motor areas.

	MNI coordinates $\pm$ sem			Location
	X	Y	Z	
<b>LEFT HEMISPHERE</b>				
Hand motor area	$-33.9 \pm 1.02$	$-26.3 \pm 0.58$	$58.2 \pm 0.99$	Precentral knob in the central sulcus
Tongue motor area	$-55.9 \pm 1.04$	$-4.6 \pm 1.02$	$32.2 \pm 1.14$	Ventral precentral gyrus
FEF	$-31.7 \pm 1.95$	$-5.8 \pm 0.91$	$53.4 \pm 1.22$	Ventral branch of the superior precentral sulcus
<b>RIGHT HEMISPHERE</b>				
Hand motor area	–	–	–	–
Tongue motor area	$58.4 \pm 0.92$	$-2.2 \pm 0.90$	$30.8 \pm 1.42$	Ventral precentral gyrus
FEF	$31 \pm 1.93$	$-2.8 \pm 0.98$	$55.5 \pm 1.28$	Ventral branch of the superior precentral sulcus

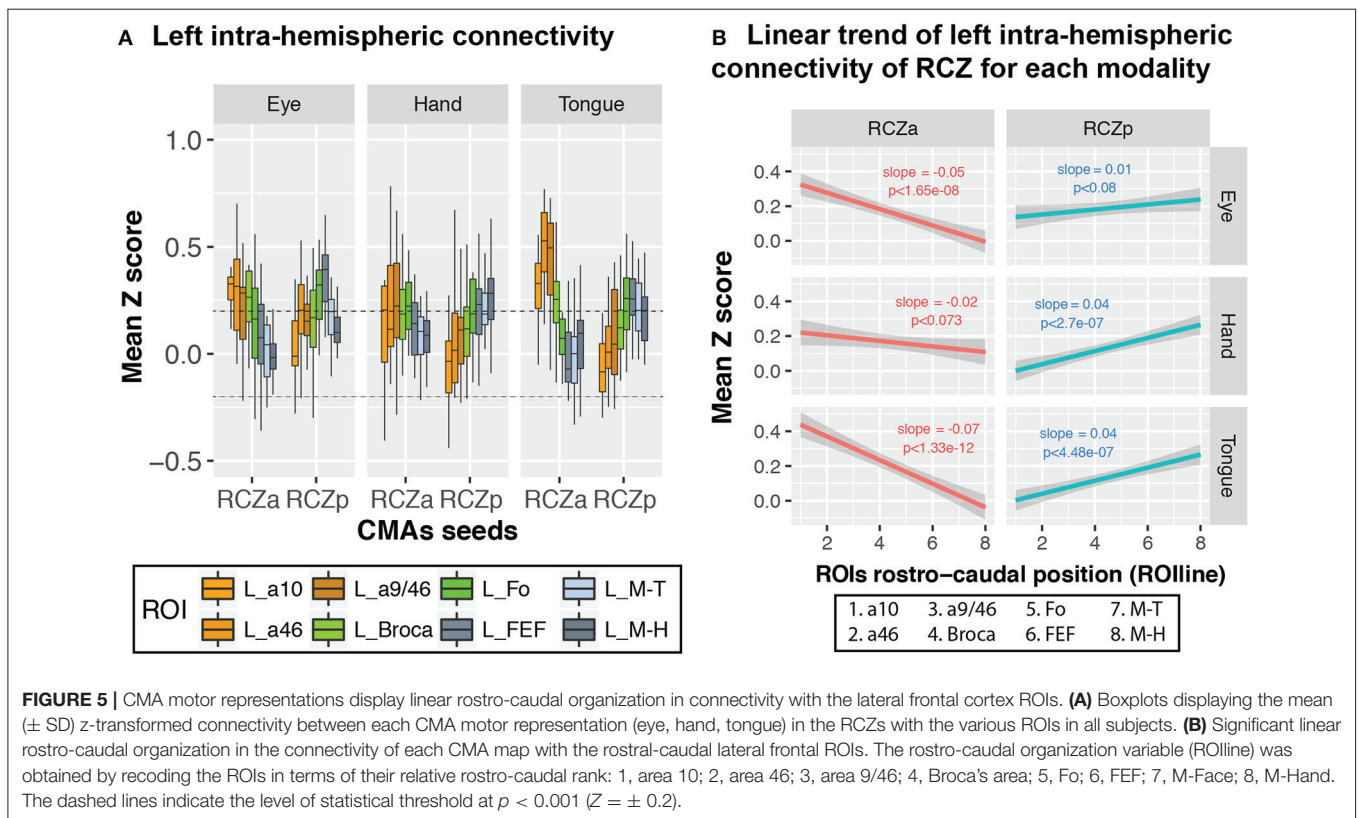
and Fo, and motor zones: FEF, Face –M-T– and Hand –M-H–) as fixed effect. The results indicated that the connectivity profiles with the prefrontal and motor zones differ significantly between CMA (ANOVA, ROIs  $\times$  CMAs,  $df = 7$ ,  $F = 21.296$ ,  $p < 2 \times 10^{-16}$ ): (1) the activity of RCZa is more correlated with that of the prefrontal zone but less correlated with that of the motor areas than the RCZp, CCZa, and CCZp, and (2) the activity of RCZp, CCZa, and CCZp are more correlated with that of the motor areas, but less correlated with that of prefrontal areas in comparison with RCZa. This analysis thus further suggests a topological organization of the correlation profiles of the CMAs with lateral frontal areas. We also assessed whether this correlation profiles can be a function of physical distance between seeds and ROIs. We calculated the Euclidian distances between the different seeds and the ROIs tested (Figure 4C). Results strongly suggest that the z-scores (displayed in Figure 4A) do not strictly varies as a function of distance as the shorter distances are not systemically associated with the higher z-scores and vice versa.

Nevertheless, the above analyses do not provide any estimation of the linearity of trends of correlation with lateral frontal areas along the rostro-caudal axis. To test and quantify these linear trends from anterior prefrontal to motor areas, we recoded the various lateral frontal ROIs into a numeric axis variable (ROIline) that corresponded to their relative posterior-to-anterior positions (see Method). Based on this coding, the lowest value (1) corresponds to a10 (the most anterior ROI) and the largest value (8) corresponds to M-H (the most posterior ROI). We then performed multiple linear regressions on the correlation values with CMA location and ROIline as predictors. The analysis revealed a significant CMA  $\times$  ROIline interaction (Figure 4D,  $df = 3$ ,  $F = 66.3$ ,  $p < 2 \times 10^{-16}$ , ANOVA with CMAs and ROIline as factors), which indicates that the linear trends in connectivity within the rostral-to-caudal axis of lateral frontal cortex differed between the CMAs: a negative linear trend was observed for RCZa (more strongly correlated with rostral prefrontal areas), positive slopes were observed for the other CMAs (more strongly correlated with posterior motor areas). Thus, the connectivity profiles of CMAs with the lateral frontal cortex regions follow a rostro-caudal organization: the anterior CMA has stronger functional coupling with the prefrontal cortex

and weaker with the motor cortex; the posterior CMAs have stronger coupling with the motor cortex and weaker with the prefrontal cortex.

We further investigated whether the same rostro-caudal cognitive-to-motor pattern of connectivity existed for each motor representation in the CMAs. Because only RCZa and RCZp contain both hand and face (tongue and saccadic eye) movement representations, this analysis was performed only with these two CMAs, independently. Seeds for resting-state data analyses were derived from the CMA motor activation peaks described above, and they are named “motor representations” in the description below. Overall, the rostro-caudal anatomo-functional organization described above is observed for all motor representations in both the RCZa and RCZp (Figure 5A) (Hand motor representation:  $df = 7$ ,  $F = 3.6$ ,  $p < 0.001$ ; Tongue motor representation:  $df = 7$ ,  $F = 17.436$ ,  $p < 2.2 \times 10^{-16}$ ; Eye motor representation:  $df = 7$ ,  $F = 6.1$ ,  $p < 1.6 \times 10^{-6}$ , ANOVA with CMAs type (i.e., RCZa and RCZp) and ROIs as factors). The slopes of seed-ROI connectivity strength against ROIline slightly varied between seed motor representations in RCZa (after stepwise model selection: ROIline  $\times$  Seed interactions,  $df = 2$ ,  $F = 10.2$ ,  $p < 1 \times 10^{-4}$ , ANOVA). This is obviously related to the specific connections between each motor representations with the corresponding primary motor fields (see Figure 5A). Concerning RCZp, these slopes varied marginally (after stepwise model selection: ROIline  $\times$  Seed interactions,  $df = 2$ ,  $F = 3.02$ ,  $p < 0.05$ , ANOVA) but they were all negative for RCZa (stronger connectivity with more rostral lateral regions) and all positive for RCZp (stronger connectivity with more caudal regions) (Figure 5B).

We then assessed whether cingulate morphology (i.e., the presence or absence of a PCGS, see Table 1) affected the connectivity profiles of RCZa and RCZp. Note that a PCGS is never observed at the level of CCZ. The results show that the rostro-caudal anatomo-functional organization is similar for all motor representations in both the RCZa and RCZp independently of the presence of a PCGS (Figure 6A) (In hemispheres with PCGS: interaction between CMAs identity and ROIs:  $df = 7$ ,  $F = 13.77$ ,  $p < 2 \times 10^{-16}$  but no interaction between CMAs identity, ROIs, and motor representations:  $df = 14$ ,  $F = 1.63$ ,  $p < 0.07$ ; In hemispheres with no PCGS: interaction



between CMAs identity and ROIs:  $df = 7$ ,  $F = 7.96$ ,  $p < 4.75 \times 10^{-9}$  but no interaction between CMAs identity, ROIs, and motor representations:  $df = 14$ ,  $F = 0.62$ ,  $p < 0.84$ , ANOVA). **Figure 6B** shows that when morphology (presence/absence of a PCGS) is taken into account, connectivity with lateral frontal areas always follows negative and positive slopes for RCZa and RCZp seeds, respectively (**Figures 6C,D**). In RCZa, these slopes were not influenced by the presence of a PCGS (interaction dropped by model selection) although the main effect of morphology was significant ( $df = 1$ ,  $F = 15.6$ ,  $p < 1 \times 10^{-4}$ , ANOVA) showing that overall correlation values ( $Z$ ) between RCZa and lateral frontal regions were lower in the presence of a PCGS. In RCZp, the morphology did interact with the rostro-caudal organization (interaction after stepwise selection, RCZp,  $df = 2$ ,  $F = 11.87$ ,  $p < 1 \times 10^{-3}$ , ANOVA) as slopes of ROIlane for Hand and Tongue representations were steeper than the gradient for Hand representation in presence of a PCGS. Yet, the rostro-caudal slopes of ROIlane was positive in all cases in RCZp.

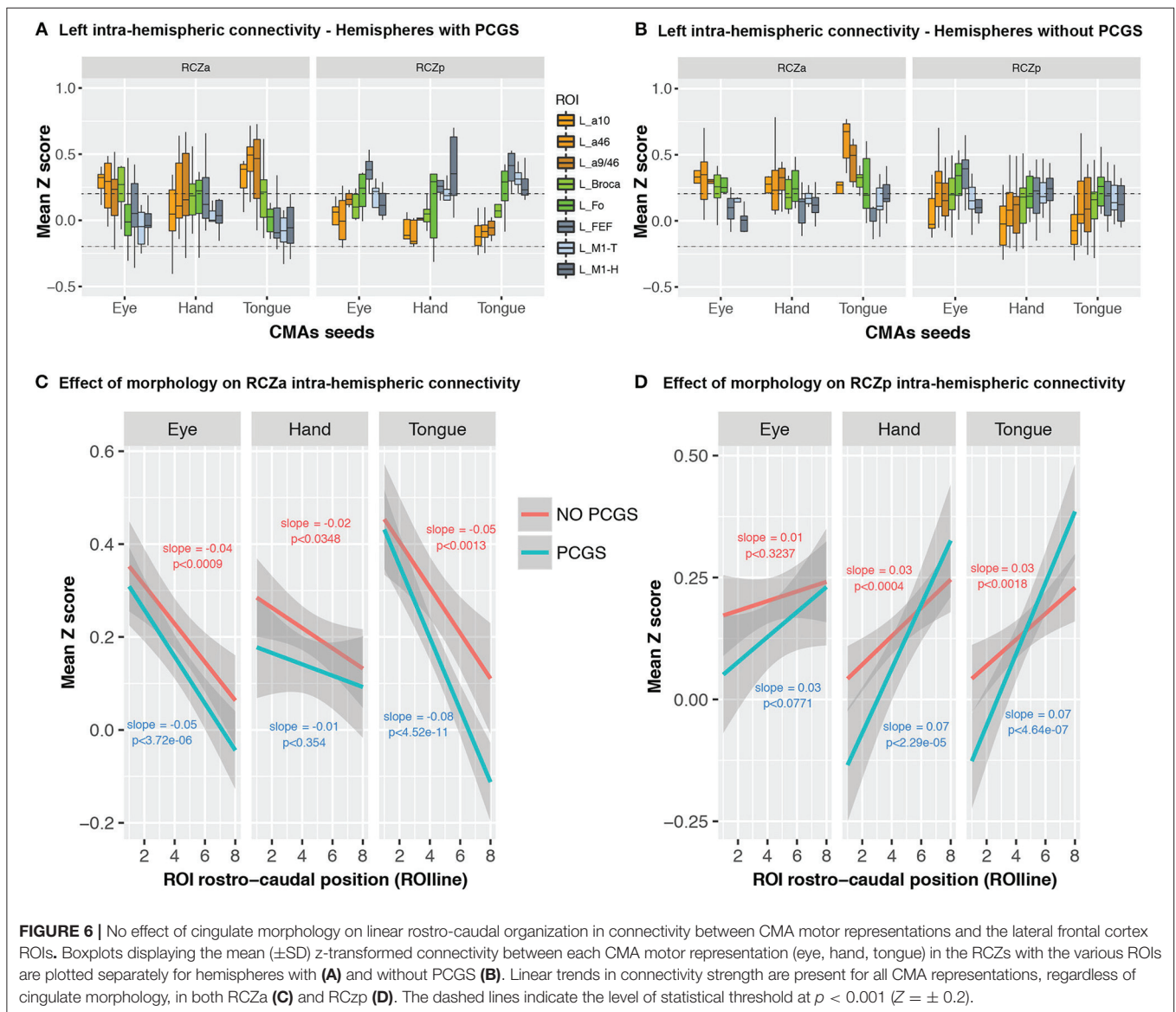
Taken together, these findings suggest that the type of motor representation and cingulate morphology had no qualitative impact on the rostral-caudal functional connectivity organization between the CMAs and the lateral frontal cortex.

## DISCUSSION

The main aim of the present study was to examine the resting-state functional connectivity of the 3 human cingulate motor areas and their motor representations with the lateral prefrontal

and motor cortical regions taking into account inter-individual anatomical variations. The present study confirmed the existence of 3 CMAs and their somatotopic organization, as reported in our former study (Amiez and Petrides, 2014) and demonstrated, for the first time, the functional connectivity profiles of the various motor subdivisions within the different CMAs. A key finding that emerged from the present study is that the anterior CMA displays an opposing linear trend of connectivity with the lateral frontal cortex in comparison with the more caudal CMAs. The anterior CMA shows a negative trend of decreasing connectivity strength with rostral-to-caudal lateral frontal regions, whereas positive trends of increasing connectivity strengths with rostral-to-caudal lateral frontal regions are observed for the caudal CMAs.

As in our previous fMRI work which sought to identify the locations of the human CMAs (Amiez and Petrides, 2014), we identified the presence of 3 CMAs that can be predicted from local morphology: the rostral anterior cingulate motor zone (RCZa) is located at the intersection of the CGS or PCGS with the posterior vertical paracingulate sulcus (vPCGS-p), the rostral posterior cingulate motor zone (RCZp) is located at the intersection of the CGS or PCGS with the preparacentral sulcus (prepacs), and the CCZ is located at the intersection of the CGS and the paracentral sulcus (pacs) and extends posterior to this intersection. Importantly, the present data confirmed that the hand motor representation in RCZa and RCZp is located in the CGS independently of the presence of a PCGS. By contrast, the face motor representation in both these cingulate motor areas is located in the CGS when the PCGS is absent, but in



the PCGS when present. The location of the monkey homologs of the human CMAs remains debated. However, Picard and Strick (1996, 2001, 2003) and then Amiez and Petrides (2014) suggested that the CMAR, CMAV, and CMA<sub>D</sub> in the monkey may be homologous to the human RCZa, RCZp, and CCZ motor zones, respectively. These suggested homologies are based on several pieces of evidence: (1) Intracortical microstimulations in the macaque cingulate cortex has shown that CMAR contains a face, a hand, and a leg representation, and that CMA<sub>D</sub> contains 2 arm representations and a leg representation. Correspondingly, the same sets of motor maps have been observed in the human RCZa (one face, hand and leg representation) and CCZ (two hand and one leg representation) (Amiez and Petrides, 2014). In the CMAV, microstimulation studies have shown a hand and a leg but not a face motor representation. However, a connectivity study (Wang et al., 2004) and a (14C)-2-deoxyglucose functional imaging study (Moschovakis et al., 2004)

in the monkey reported the existence of a cingulate eye field located adjacent to the forelimb movement region within the CMAV, strongly suggesting that CMAV might contain a face motor representation. This point has recently been confirmed in a macaque neuroimaging study (Cléry et al., 2018). CMAV could therefore be considered the monkey homolog of the human RCZp, since both display a hand, a leg, and a face motor representation.

The connectivity profiles of the 3 human CMAs (RCZa, RCZp, and CCZ) with lateral frontal regions reflect a linear rostro-caudal organization. The anterior CMA's activity is strongly correlated with that of the prefrontal cortex, and weakly correlated with that of the motor cortex, exhibiting a negative rostro-caudal linear trend of correlation strength. In contrast, the activity of posterior CMAs (RCZp and CCZ) is strongly correlated with that of the motor cortex, and weakly correlated with that of the prefrontal cortex. These results are



consistent with experimental anatomical data from non-human primate studies (Dum and Strick, 1991; Bates and Goldman-Rakic, 1993; He et al., 1995; Petrides and Pandya, 1999, 2002; Wang et al., 2001, 2004) and support the functional homology between human and monkey CMAs. Although all CMAs contain projections to the motor cortex and spinal cord, the connections are progressively denser as one proceeds from the rostral to the caudal CMAs: CMAR, CMAd, and finally CMAv (Dum and Strick, 1991; Bates and Goldman-Rakic, 1993; He et al., 1995; Wang et al., 2001, 2004). This organization suggests an increased role of caudal CMAs in motor control. In addition, micro-stimulations in caudal, as compared to rostral, CMAs evoked movements more consistently and with reduced onset latencies (Morecraft and Tanji, 2009). In contrast, interconnections with the prefrontal cortex are more commonly present in rostral CMA (Bates and Goldman-Rakic, 1993; Lu et al., 1994), suggesting an increased role in higher-order cognitive processing compared with posterior CMAs. Furthermore, monkey CMAR also receives denser dopaminergic projections from the ventral tegmental area (Williams and Goldman-Rakic, 1998), supporting its involvement in feedback-driven behaviors (Quilodran et al., 2008). It should also be noted that the rostral, but not the caudal, CMAs have connections with vocalization-related brain regions (Vogt and Barbas, 1988; An et al., 1998) and also the ventrolateral prefrontal cortical area 45 (Petrides and Pandya, 2002), consistent with their potential role in voluntary vocal and orofacial control (Loh et al., 2016). Given the anatomical-functional correspondence between the human and macaque CMAs (Picard and Strick, 2001; Amiez and Petrides, 2014), one could expect the functional organization of the CMAs to be similar between the two species. The present results provide strong support for this hypothesis.

The connectivity profiles of the 3 CMAs with Fo demonstrate major differences: Fo displays positive correlations with all motor representations of RCZp, but only with the hand motor representation of RCZa. By contrast, CCZ is not functionally connected with Fo (**Figure 4B**). Although the literature shows that the anterior MCC -where the RCZa probably lies (Procyk et al., 2016)- is systematically co-activated with Fo in fMRI studies assessing performance monitoring abilities (e.g., Amiez et al., 2012a,b, 2013, 2016), the functional relationships between the two structures and the role of Fo are not understood. The present results strongly suggest a complex relationship between the anterior MCC and Fo and future studies are required to disentangle the role of Fo in performance monitoring.

Importantly, the demonstration that the CMAs follow a rostral-to-caudal organization in their links with lateral frontal cortex also contributes to the growing body of evidence that the human frontal cortex is organized along a rostro-caudal axis (Petrides, 2005a,b; Koechlin and Summerfield, 2007; Badre and D'Esposito, 2009) with parallel links to the medial cingulate motor region. Several hypotheses suggest that progressively rostral lateral frontal regions are linked with increasingly complex and abstract processes and rules for behavioral control. For instance, Petrides has provided evidence that the mid-dorsolateral prefrontal region is critical for the monitoring of

information in working memory (the eopptic process) while more posterior lateral frontal regions are involved in the allocation of attention to environmental stimuli and movement selection (Petrides, 2005a,b, 2013). A few studies have shown that more rostral/caudal CMAs could be involved in monitoring the reliability of higher/lower-order behavioral actions and rules, and initiating searches for alternative options as existing ones become obsolete (Kouneiher et al., 2009; Domenech and Koechlin, 2015). Congruent with these propositions, Stoll et al. (2016) found increased neuronal activity in the rostral mid-cingulate cortex for decisions to shift away from a default task. Regarding caudal regions, Debaere et al. (2003) found that performing coordinated hand movements with external visual guidance (when a simple behavioral rule, i.e., performing action according to visual cue, is valid) vs. without (when behavioral rule is invalid and there is a need to self-initiate novel actions) activated, respectively, the caudal lateral prefrontal vs. the caudal MCC.

The present study revealed, for the first time, the functional connectivity profiles of the various CMA motor representations with the lateral prefrontal and motor areas. We found that the connectivity profiles of CMA motor representations are similar within the same CMA. For instance, the connectivity profile of the RCZa face representation is more similar to that of the RCZa hand representation than the RCZp face representation. This strongly indicates that the motor representations found in a particular CMA likely function as part of the same CMA. Also, RCZa and RCZp face motor representations that were situated in the paracingulate sulcus or the cingulate sulcus (when the paracingulate sulcus was absent) exhibited similar connectivity trends. This finding indicates that even though the presence of a paracingulate sulcus influences the physical location of the face motor representations in RCZa and RCZp, their functional position remains the same. Likewise, the trends in the connectivity patterns of the hand motor representations are also conserved regardless of the presence of a paracingulate sulcus.

To the best of our knowledge, only two previous studies had sought to characterize the connectivity profile of human CMAs, one via diffusion-tract imaging (DTI; Beckmann et al., 2009) and the other via resting-state fMRI (Habas, 2010). In the study by Beckmann et al. (2009), three seed clusters corresponding to the three CMAs of the human brain were obtained via blind connectivity-based parcellations performed on voxels within the cingulate cortex. The most rostral cluster 4 (corresponding to RCZa) showed the highest connection probability with the dorsal prefrontal cortex, while their most caudal cluster 6 (CCZ) had the highest connection probability with the parietal and motor cortex (Beckmann et al., 2009). Habas (2010) examined the resting-state functional connectivity of the rostral cingulate sulcal region extending 10 mm anterior to the vertical line from the anterior commissure and a caudal cingulate sulcal region extending 10 mm posterior to the anterior commissure and showed that the rostral region had higher connectivity with prefrontal and language-associated cortical areas while the caudal region had increased connectivity with sensory-motor regions. Notably, both studies had shown that, as in the macaque, the human CMAs generally exhibit a rostro-caudal functional organization

with progressively rostral/caudal CMAs being associated with more cognitive/motor brain regions. However, there are two important limitations associated with the above studies: in both investigations, the CMA seeds had not been defined on the basis of task-based fMRI, and not on individual subject brain morphology. The present study provides new insights into the functional organization of the human CMAs and, crucially, their motor representations and their relationship with lateral frontal areas.

Note that a limitation of the present study is that the selection of the ROIs in the prefrontal cortex has been based of their known frequent co-activation with the MCC in a large range of cognitive tasks (Amiez and Petrides, 2007; Amiez et al., 2012b, 2013). The extent of functional connectivity of the CCZ with the prefrontal cortex may therefore have been underestimated. However, at the present time of knowledge, studies aiming to assess the putative role of the CCZ are critically lacking. Only one recent study has shown the existence of a cingulate sulcus visual area (CSv) at the level of CCZ. This region is anatomically and functionally connected with the ventral premotor area 6 and sensory areas involved in processing moving visual (V6) and vestibular (VIP) stimuli, suggesting a role in the online control of locomotion (Smith et al., 2017). The authors report also a lack of connections with their ventrolateral prefrontal cortical ROIs (areas 44, 45, and 47). Our results are consistent with these findings, suggesting that this region -occupied by CCZ and CSv- is functionally connected with the motor system but not with the prefrontal cortex. Future studies should focus on (1) how the CSv relates to the two

hand representations in the CCZ, and (2) how these areas are anatomically and functionally connected to the whole prefrontal cortex.

To conclude, the present study demonstrated that the 3 CMAs are organized along a rostro-caudal organization in parallel with the prefrontal and motor areas and could likely contribute to different hierarchies of cognitive-motor controls.

## AUTHOR CONTRIBUTIONS

KL set up the experiment, acquired data, analyzed the task-related fMRI data, and wrote the paper. FH-B analyzed the resting state data, and wrote the paper. MP wrote the paper. EP performed the statistics and wrote the paper. CA set up the experiment, analyzed the resting state data, and wrote the paper.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Chapter 4: Cognitive control of vocalizations in the primate ventrolateral-dorsomedial frontal (VLF-DMF) brain network.**

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### Review article

# Cognitive control of vocalizations in the primate ventrolateral-dorsomedial frontal (VLF-DMF) brain network

Kep Kee Loh<sup>a,\*</sup>, Michael Petrides<sup>b</sup>, William D. Hopkins<sup>c,d</sup>, Emmanuel Procyk<sup>a,1</sup>, Céline Amiez<sup>a,1</sup>

<sup>a</sup> Univ Lyon, Université Lyon 1, Inserm, Stem Cell and Brain Research Institute U1208, 69500, Bron, France

<sup>b</sup> Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada

<sup>c</sup> Neuroscience Institute, Georgia State University, Atlanta, Georgia, USA

<sup>d</sup> Division of Developmental and Cognitive Neuroscience, Yerkes National Primate Research Center, Atlanta, Georgia, USA

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### ABSTRACT

This review centers on the neural mechanisms underlying the primate cognitive control of vocalizations, i.e. the capacity to regulate vocal productions in a goal-directed manner. In both human and non-human primates (NHPs), two main frontal brain regions are associated with top-down vocal control: a ventrolateral frontal region (VLF), comprising the ventrolateral prefrontal cortex and ventral premotor region; and a dorsomedial frontal region (DMF), comprising the mid-cingulate cortex, pre-supplementary and supplementary motor areas. These regions are cytoarchitecturally comparable across humans and NHPs and could serve generic functions in primate vocal control. Here, we first summarize the key anatomical properties of VLF and DMF regions as well as their involvements in the motor and cognitive control of vocalizations in both humans and NHPs. Finally, in light of the reviewed evidence, we discuss the existence of a primate VLF-DMF network and its generic functions in the cognitive control of vocalizations. We further suggest how this network and its functions may have changed across primate evolution to enable modern human speech.

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\* Corresponding author.

E-mail address: [kep-kee.loh@inserm.fr](mailto:kep-kee.loh@inserm.fr) (K.K. Loh).

<sup>1</sup> These authors contributed equally.

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1. Introduction

Primates produce a range of vocalizations for social communication (Ackermann et al., 2014; Seyfarth and Cheney, 2014). Dominating the non-human primate (NHP)’s vocal repertoire are innate vocalizations that are typically affectively driven and serve to signal critical emotional and motivational states (Hammerschmidt and Fischer, 2008). Classical examples include ‘alarm’ and ‘food’ calls that are produced in response to predator and food detection, respectively (Hauser and Marler, 1993a; Seyfarth et al., 1980). Innate affective vocalizations are also present in humans (Owren et al., 2011), such as pain-triggered ‘screams’ and ‘shrieks’, as well as laughing and crying sounds that are associated with positive and negative emotional states, respectively. In both human and NHPs, innate vocalizations are associated with the “cingulate vocalization pathway” (Jürgens and Pratt, 1979), which includes the anterior/mid-cingulate cortex (ACC/MCC) and the periaqueductal grey region (PAG) that is connected to the various vocalization-related motor neuron pools via brainstem premotor nuclei, such as the ventral parabrachial area, reticular formation and nucleus retroambiguus (Jürgens, 2002) (Fig. 1).

A second type of primate vocalizations are acquired vocalizations that can be arbitrarily associated with both affective and non-affective referents (Janik and Slater, 1997). These exist almost exclusively in humans as the repository of meaningful speech sounds and songs that are gradually established across the lifespan via learning and experience (Hammerschmidt and Fischer, 2008). The ability to generate and use species-atypical sounds have been documented in captive great apes, such as chimpanzees (Hopkins et al., 2007) and orangutans (Lameira et al., 2015, 2016; Wich et al., 2009). However, some of these sounds, such as the “raspberry” in chimpanzees (Hopkins et al., 2007) and human-like “whistles” in orangutans (Wich et al., 2009), do not constitute acquired vocalizations since they primarily involve only articulatory and expiratory but not vocal fold actions. The “extended grunts” produced by chimpanzees to attract their caregivers’ attention (Hopkins et al., 2007) recruit the larynx but it remains controversial whether these are novel vocalizations or just prolonged versions of existing grunt calls (Owren et al., 2011). At this juncture, evidence of acquired vocalizations in NHPs is limited to two captive orangutans which could each produce a species-atypical voiced call, namely, “faux-speech” (Lameira et al., 2015) and “wookies” (Lameira et al., 2016). Production of acquired vocalizations is typically associated with the “neocortical vocalization pathway” (Ploog, 2002) which extends from the ventrolateral prefrontal cortex (vLPFC), ventral premotor (PMv) and the adjacent primary motor cortex, via the corticobulbar tracts, to the orofacial and laryngeal motor nuclei (Fig. 1). This is the main pathway involved in human speech production. In NHPs, it has been associated with the volitional control of articulators and conditioned production of innate calls (Coudé et al., 2011; Hage and Nieder, 2013).

1.1. Cognitive control of vocalization in primates

Although humans are capable of generating a wide range of innate and acquired vocalizations and flexibly associate them with

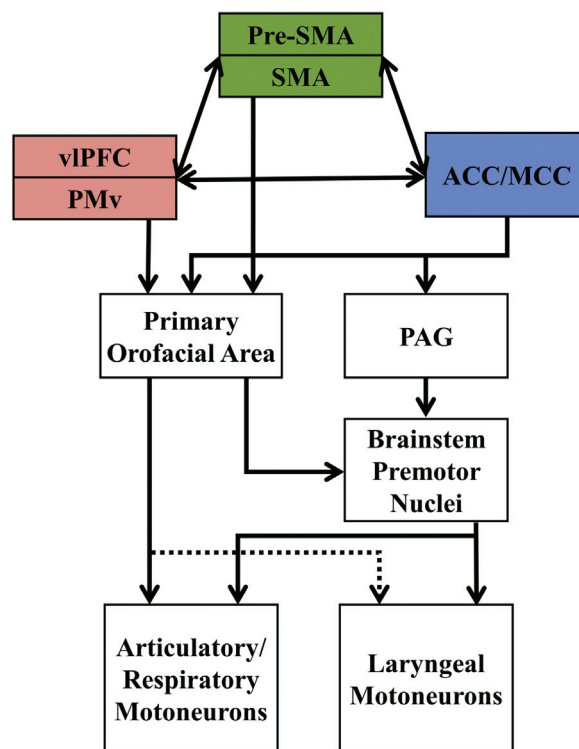


Fig. 1. Schematic diagram summarizing the major connections between VLF-DMF regions and the various vocal motoneurons in the cognitive control of vocalizations. Black solid arrows represent connections that are present in both human and non-human primates. Black dotted arrows represent connections that exist only in humans. Abbreviations: vLPFC, ventrolateral prefrontal cortex; PMv, ventral premotor area; ACC, anterior cingulate cortex; MCC, mid-cingulate cortex; Pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; PAG, periaqueductal gray.

new meanings and contexts, vocal behavior in NHPs is constrained to a small set of innate and largely unmodifiable vocal patterns that are produced under highly predictable contexts such as affective, motivational, or social situations (Hammerschmidt and Fischer, 2008; Seyfarth and Cheney, 2010). These observations, coupled with findings that specific vocal patterns could be directly elicited via subcortical stimulations (e.g. Jürgens and Ploog, 1970), have perpetuated arguments that NHP vocalizations are reflexive and involuntary (e.g. Arbib, 2005; Terrace, 1983). However, recent research has produced evidence that NHP vocalizations are not purely reflexive responses and could be subjected to cognitive control (e.g. Hage et al., 2013; for reviews of evidence for volitional vocal control in NHPs, see Hammerschmidt and Fischer, 2008; Owren et al., 2011; Seyfarth and Cheney, 2010).

Ethological observations have shown that context-specific NHP vocalizations (i.e. food or alarm calls) are not necessarily produced when the associated context (i.e. food or threat detection) is present (e.g. Gros-Louis, 2004; Hauser and Marler, 1993a, 1993b; Seyfarth and Cheney, 1990). For instance, Hauser and Marler (1993a, 1993b) reported that, as free-ranging rhesus monkeys encountered food sources, the likelihood of food call production was dependent on

the monkey's relative social rank: adult females (versus males), adult females with smaller (versus larger) matriline or peripheral (versus resident) adult males were more likely to produce food calls upon food detection. Wild capuchin monkeys also tend to produce food calls when other group members are present, and more so when these members are of a higher relative social rank (Gros-Louis, 2004). Even under highly stressful threat situations, several NHP species appear to produce (or withhold) alarm call productions depending on the presence, absence and composition of their social audience (Crockford et al., 2012; Schel et al., 2013; Seyfarth and Cheney, 1990). These examples suggest that NHP vocalizations are not purely reflexive but instead can be produced or withheld depending on the social context. However, one could contend that varying social conditions may still be indirectly driving NHP call productions via affective state changes (Owren et al., 2011). In this light, the above instances of social context-dependent food and alarm call productions provide limited evidence of cognitively driven vocal production in NHPs.

Evidence for cognitive vocal direction in NHPs comes from work involving the operant conditioning of vocalizations in NHPs (e.g. Coudé et al., 2011; Hage et al., 2013; Koda et al., 2007; see Pierce, 1985, for a review of early attempts to condition NHP vocalizations). As reviewed in Pierce (1985), several NHP species, including rhesus macaques (Aitken, 1981; Sutton et al., 1973) and chimpanzees (Randolph and Brooks, 1967) can be conditioned to increase the rate, amplitude or duration of their vocalizations, depending on the presence of a particular stimulus in order to obtain rewards. More recently, Hage et al. (2013) demonstrated that rhesus monkeys could be conditioned to produce or withhold calls as instructed by arbitrary visual cues. Furthermore, monkeys could perform the task using two different call types ("coos" or "grunts") that are innately linked with hedonistic or aversive states, respectively. This finding suggested that monkeys could detach these calls from their original emotional contexts and produce them in response to arbitrary cues to obtain rewards. Notably, in the same study, one of the two monkeys could conditionally switch between the two call types based on two visual cues. Taken together, the above work provides convincing evidence that NHPs have cognitive control over call production. However, it is important to note that the above studies typically recruited a subset of monkeys that were younger and vocalized more than their counterparts. In addition, all subjects underwent intensive training to instrumentalize their vocalizations. As such, it remains unclear if volitional vocal production is naturally accessible to all individuals and across the whole lifespan in NHPs. Indeed, there are instances in which vocal operant conditioning had been unsuccessful (Pierce, 1985) and evidence that volitional vocal production diminished as subjects aged (Hage et al., 2016).

In contrast with call production, evidence for volitional call modifications in NHPs remains scarce (Hammerschmidt and Fischer, 2008; Owren et al., 2011). NHPs appear to be able to increase or decrease the rate, amplitude and duration of their calls based on discriminative stimuli (Pierce, 1985). However, changes in these call parameters could reflect motivational or arousal state changes in response to the conditioned stimulus rather than volitional control (discussed in Hage et al., 2013). There are also findings suggesting that NHPs modify their vocalizations in a goal-dependent manner. Hage et al. (2013) had noted that conditioned calls produced by monkeys during the go/no-go visual detection task to obtain rewards had significantly longer durations and lower frequencies than spontaneously emitted calls. Hihara et al. (2003) reported that acoustically different "coos" were produced by Japanese macaques to obtain a food item directly than to obtain a tool when the food item was out of reach. These findings could indicate that NHPs were modifying their calls in a goal-dependent way since calls produced for different purposes showed acoustic

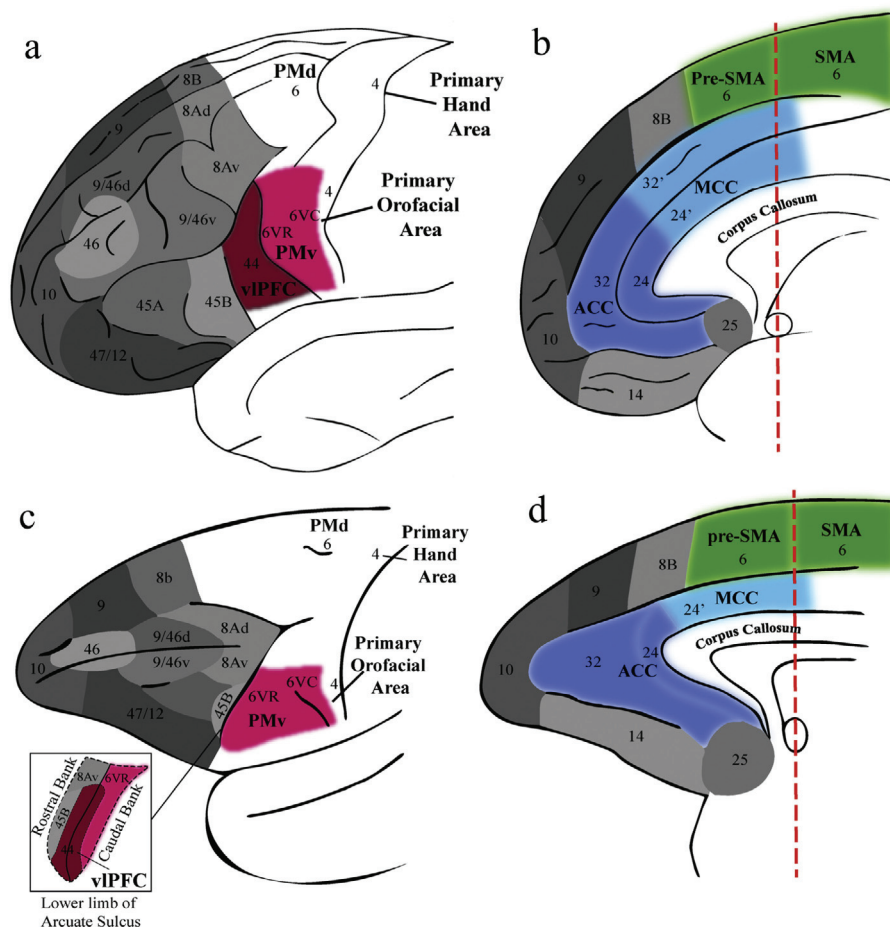
variations. At the same time, in these tasks, it was possible that the observed acoustic changes were hedonistic responses to the expected outcomes following vocalizations (i.e. obtaining reward versus no reward or obtaining a reward directly versus indirectly via a tool). As such, currently, the evidence for volitional call modifications in NHPs is still weak. The apparent inability of NHPs to modify their calls volitionally may be associated with a lack of direct cortical laryngeal control (Simonyan and Horwitz, 2011). Indeed, NHPs appear to have volitional control over articulatory and expiratory movements as evidenced by the generation and instrumental control of species-atypical "raspberries" and "whistles" in great apes that involve articulatory and respiratory modulations (Hopkins et al., 2007; Wich et al., 2009).

Overall, there are strong indications that NHP vocalizations are not purely reflexive involuntary responses since they are not necessarily produced even when call-associated motivational or emotional conditions are present. Furthermore, through conditioning, NHPs are able to initiate, withhold or even switch between calls in response to arbitrary cues. Although NHPs seem to modify certain parameters of their calls, such as rate, amplitude, duration and frequency, during conditioned productions, it remains unclear whether these modifications are subject to cognitive control or are a product of motivational or arousal changes. In conclusion, current evidence suggests that the cognitive control of vocalizations in NHPs is restricted to the flexible production but not modification of innately determined calls. The lack of volitional call modifications could be linked with a lack of direct cortical laryngeal control since there is evidence that NHPs can volitionally modulate articulatory and respiratory movements to generate and use novel sounds.

## 1.2. A common primate VLF-DMF network for cognitive vocal control

This review is centered on the neural mechanisms underlying the cognitive control of vocalizations in primates, i.e. the capacity of primates to regulate their vocal productions according to situational goals and demands. Seated at the top of the two vocal control pathways, two main frontal brain regions have been commonly implicated in the top-down control of vocalizations in both human and NHPs (Fig. 2): a ventrolateral frontal region (VLF; including the vlPFC and PMv) and a dorsomedial frontal region (DMF; including the MCC, SMA, and pre-SMA). The various VLF and DMF areas have been shown to be cytoarchitecturally comparable in macaque and human brains (Petrides et al., 2012), including the two ventrolateral frontal areas that are usually considered to comprise Broca's region: areas 44 and 45 (Petrides et al., 2005; Petrides and Pandya, 1994). Thus, this network of VLF-DMF regions, which is homologous across monkeys and humans, could serve generic functions in the cognitive control of vocalizations across primate species. At this point in time, the precise contributions of these frontal regions in the cognitive control of human and NHP vocalizations remain poorly characterized. As such, this review endeavors to highlight the generic contributions of these VLF-DMF regions to flexible vocal control across primates and, subsequently, discuss the probable differential roles they may play in the cognitive control of NHP and human vocalizations.

With the above goal in mind, we begin the review with an account of how vocal motor control is achieved by VLF and DMF regions. In particular, we summarize the key anatomical properties of these regions and their differential involvements in the motor control of NHP and human vocalizations. Next, we discuss the possible roles of the VLF and DMF regions in the cognitive control of NHP and human vocalizations. Finally, in light of the reviewed evidence, we propose the existence of a primate VLF-DMF network and its generic functions in the cognitive control of vocalizations.



**Fig. 2.** The human and macaque VLF-DMF network. Cytoarchitectonic labels are based on Petrides et al. (2012). Delineations of ACC/MCC regions and pre-SMA/SMA regions are based on Palomero-Gallagher et al. (2009) and Picard and Strick (1996), respectively. (a) Human VLF regions. (b) Human DMF regions. (c) Macaque VLF regions. Bottom left panel shows an expanded view of the lower limb of the arcuate sulcus. (d) Macaque DMF regions. Bold dashed line represents the vertical line drawn from the anterior commissure. Abbreviations: vLPFC, ventrolateral prefrontal cortex; PMv, ventral premotor area; PMd, dorsal premotor area; ACC, anterior cingulate cortex; MCC, mid-cingulate cortex; Pre-SMA, pre-supplementary motor area; SMA, supplementary motor area. (Please refer to the web version of this article for the same figure in full color.)

We further suggest how this network and its functions may have changed across primate evolution.

## 2. VLF and DMF regions and the motor control of vocalizations

As summarized in Jürgens (2002), all primate vocalizations, whether innate or acquired, recruit the action of three basic muscular systems: the respiratory, laryngeal, and articulatory systems. The respiratory system, comprising the diaphragm, abdominal and intercostal muscles, generates the initial airflow required for vocalization from the lungs into the vocal tract. As this expiratory airflow passes through the larynx, the laryngeal musculature controls how the vocal folds move and vibrate to the passing air. This, in turn, produces the earliest sounds in the vocal tract. Finally, these sounds are further modified, along the rest of the vocal pathway, by the various articulators (e.g. the tongue, jaw, lips, velum, etc.) which constitute the articulatory system. The three muscular systems are directly innervated by motoneuron pools situated in the pons: trigeminal motor nucleus (jaws and velar); medulla: nucleus ambiguus (laryngeal and velar), nucleus facialis (lips and jaw) and nucleus hypoglossus (tongue); and the ventral horn of the spinal cord: cervical (laryngeal and jaw) and thoracic regions (abdominal and intercostal). At the top of the neural hierarchy for vocal motor control lie DMF and VLF areas that regulate the three muscular systems for innate and acquired vocalizations, respectively (Fig. 1).

### 2.1. DMF regions

In the “cingulate vocalization pathway”, the coordination of the various vocalization-related motoneuronal pools is achieved via a network of brainstem premotor areas such as the ventral parabrachial area, reticular formation and nucleus retroambiguus that serve as vocal pattern generators (Jürgens, 2002). The next critical structure is the periaqueductal gray (PAG) which directly projects to the various premotor nuclei and produces vocalizations upon electrical stimulation (Jürgens and Pratt, 1979; Ploog, 2002). PAG-elicited vocalizations typically include species-typical and affective calls, such as agonistic shrieking and yelping in monkeys (Jürgens and Ploog, 1970) and laughing in humans (Sem-Jacobsen and Torkildsen, 1960). Receiving direct inputs from both sensory and motivational limbic regions and directly connecting to the vocalization motor nuclei, the PAG is considered an obligatory relay station that releases affective vocalizations upon afferent emotional or motivational signals (Jürgens, 1994). Above the PAG, a set of dorsomedial frontal (DMF) brain areas, comprising the MCC and the adjacent SMA and pre-SMA, is associated with the voluntary control of vocalizations in both humans (Chapados and Petrides, 2013; Fried et al., 1991) and NHPs (Aitken, 1981; Sutton et al., 1974). Notably, amongst the DMF regions, the MCC, but not the SMA and pre-SMA, projects directly to the PAG (An et al., 1998; Jürgens, 1984) and is directly associated with the production of affective vocalizations via the cingulate vocalization pathway (Jürgens and



Pratt, 1979). The SMA and pre-SMA have been associated with the voluntary initiation of innate vocalizations in NHPs and speech in humans (Jürgens, 2002).

To ensure consistency in our discussion of these areas, we here define the nomenclature that will be used throughout the present article. Based on a recent architectonic and functional parcellation of the cingulate cortex (Palomero-Gallagher et al., 2009), we use the label 'ACC' (anterior cingulate cortex) to refer to the cingulate region anterior to the genu of the corpus callosum and 'MCC' (mid-cingulate cortex) to refer to a more posterior region dorsal to the anterior part of the corpus callosum (Fig. 2b, d). We define pre-SMA and SMA regions based on the delineation proposed by Picard and Strick (1996) in which the vertical line from the anterior commissure (VCA) separates the SMA from the more rostrally located pre-SMA (Fig. 2b, d).

#### 2.1.1. Mid-cingulate cortex

On the dorsomedial wall of the frontal lobe, the MCC lies ventral to the pre-SMA and SMA and dorsal to the anterior part of the corpus callosum just behind the ACC region, which extends anteriorly and ventrally below the genu (Fig. 2b, d). The MCC comprises cytoarchitectonic area 24, the dorsalmost subdivision of which (24c') and area 32' are partly buried in the cingulate sulcus; and the immediately ventral perigenual areas 24a' and 24b' on the cingulate gyrus (Palomero-Gallagher et al., 2009). Importantly, areas 24c' and 32' have been found to contain the most rostral of the three cingulate motor areas (CMAr; Fig. 3) in monkeys (Dum and Strick, 2002) and there is evidence in the human brain that this may also be the case (Amiez and Petrides, 2014; Picard and Strick, 1996). Relative to the more caudal cingulate motor areas, the CMAr has dense connections with the lateral prefrontal cortex and the pre-SMA, but weak connections with the primary motor cortex, spinal cord and SMA (Dum and Strick, 1991; Lu et al., 1994; Luppino et al., 1993). Consistent with this pattern of anatomical connectivity, electrical stimulation of the CMAr evokes movements less clearly in comparison with the caudal CMAs (Dum and Strick, 1991; He et al., 1995). However, CMAr neurons exhibit a stronger association with movement initiation and respond earlier before movement onsets (Shima et al., 1991). As such, the CMAr appears to contribute more to the higher-order initiation and preparation of motor responses, while the more caudal areas appear to be more directly involved in motor execution. In contrast to the MCC, the ACC, which comprises pregenual and subgenual areas 24c and 32, as well as area 25 on the subcallosal gyrus, has rich connections to limbic structures such as the amygdala (Barbas and De Olmos, 1990; Pandya and Vogt, 1987) and the ventral striatum (Kunishio and Haber, 1994). Palomero-Gallagher et al. (2008) further demonstrated increased serotonergic and GABAergic receptor densities in the ACC in comparison with the MCC. These findings suggest an increased involvement of the ACC in emotional and arousal related functions (Paus, 2001). Of direct relevance to the current review is the cingulate vocalization area that is located in the anterior MCC (Jürgens and Ploog, 1970; Paus et al., 1993). This region, at the rostral end of CMAr, has direct projections to the facial motor nuclei (Morecraft et al., 1996) and the PAG region (An et al., 1998) which provide direct access to affective facial movements and affective vocal patterns, respectively. Together with direct connections to the amygdala, spinothalamic system and ventral striatum, the anterior MCC appears to play an important role in primate emotional expression via facial and vocal movements (Shackman et al., 2011).

In NHPs, innate affective calls can be directly evoked by ACC/MCC stimulation (Jürgens and Ploog, 1970; Robinson, 1967). Lesions in this region of the cingulate gyrus reduce spontaneous calling in socially isolated settings (MacLean and Newman, 1988) and severely impair the ability to produce calls in response to discriminant stimuli (Aitken, 1981; Sutton et al., 1974), demonstrating

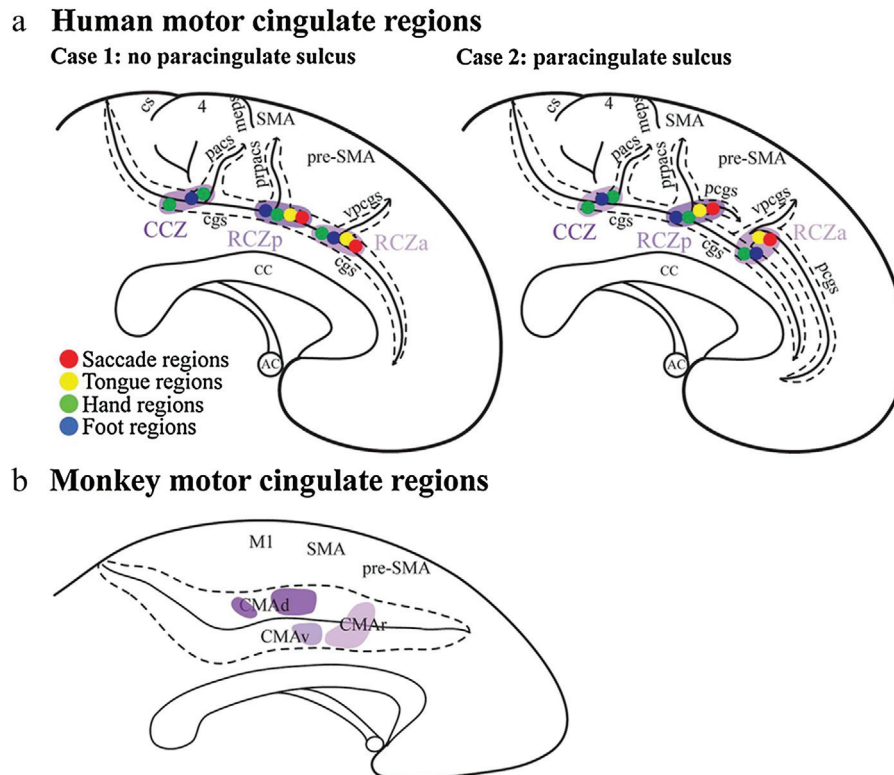
its critical role in the voluntary production of spontaneous and conditioned calls. In humans, electrical stimulation of the MCC evokes orofacial and tongue movements but less consistently produces affective vocalizations in comparison with similar stimulation in NHPs (Talairach et al., 1973). However, more recent investigations demonstrated that ACC/MCC stimulation triggered laughter, along with positive emotions, in some patients (Caruana et al., 2015; Sperli et al., 2006). Patients with ACC/MCC lesions experience akinetic mutism, which is associated with a lack of motivation to speak (Ackermann and Ziegler, 1995; Brown, 1988). These patients typically display a reduction in spontaneous speech and increased hesitation when responding to direct questions, suggesting that the human MCC may be involved in the motivational initiation of speech. However, the MCC is not critical for volitional speech production in humans: in a comprehensive review of cingulectomy cases, Brotis et al. (2009) reported that patients with bilateral ACC/MCC resections could generally recover their verbal abilities and social functioning with time.

#### 2.1.2. SMA and pre-SMA

The SMA and pre-SMA represent architectonically different brain regions that are associated with distinct connectivity patterns. In the human brain, the SMA has been related to cytoarchitectonic area 6α and the pre-SMA to cytoarchitectonic area 6β as defined by Vogt and Vogt (1919). In the macaque monkey, the SMA has also been referred to as area F3 and the pre-SMA as area F6 (Luppino et al., 1993). In the macaque, the pre-SMA receives rich inputs from the dorsolateral prefrontal cortex, the vlPFC and the PMv. In contrast, projections from the primary motor and dorsal premotor regions are sparse (Luppino et al., 1993). The SMA, on the other hand, is strongly linked with the primary motor cortex and dorsal premotor areas and has weak connections with the lateral prefrontal regions (Luppino et al., 1993). Diffusion tensor imaging (DTI) in healthy human subjects and post-mortem dissections, Vergani et al. (2014) showed that, as in NHPs, the human SMA, but not the pre-SMA, may be directly connected to the primary motor cortex. This pattern of connectivity reflects the dissociation of primate pre-SMA and SMA regions in terms of cognitive and motor-related functions, respectively (Luppino et al., 1993; Vergani et al., 2014). Further support for SMA's direct involvement in motor control comes from electrical stimulation studies which revealed the existence of somatotopic motor maps in the SMA in both NHPs and monkeys (Fried et al., 1991; Mitz and Wise, 1987). In these somatotopic maps, the leg representation is situated in the most caudal part of the SMA, followed by the hand, and finally the orofacial representation around the pre-SMA/anterior SMA border. Concerning the pre-SMA, movements could also be evoked by electrical stimulations, but these were less consistent and required higher currents (Nachev et al., 2008).

In NHPs, stimulations in the pre-SMA/anterior SMA region produces orofacial movements but not vocalizations (Mitz and Wise, 1987). Kirzinger and Jürgens (1982) reported that lesions invading the anterior, but not the posterior part of the SMA, led to increased latencies of spontaneous and conditioned calls. Notably, the areas that Kirzinger and Jürgens (1982) referred to as the "anterior" and "posterior" SMAs corresponded to the Vogt and Vogt (1919) areas 6β and 6α, respectively, and therefore, are considered pre-SMA and SMA in this article. In addition, monkeys with lesions in the pre-SMA/anterior SMA area still successfully perform vocal operant conditioning tasks (Sutton et al., 1985). As such, in the NHPs, the pre-SMA/anterior SMA region, but not the SMA, seems to contribute to voluntary call initiation.

Contrary to NHPs, stimulations in the human pre-SMA/anterior SMA have been associated both with orofacial and tongue movements as well as vocalizations (Fried et al., 1991; Penfield and Welch, 1951). These vocalization-triggering sites were clustered



**Fig. 3.** Somatotopic body maps in the human and macaque cingulate motor areas adapted from Amiez and Petrides (2014). (a) Human cingulate motor areas are labelled as RCZa (referred to as CMAr in the current paper), RCZp and CCZ. Cingulate motor areas for subjects with (case 1) and without a paracingulate sulcus (case 2) are shown. (b) Macaque cingulate motor areas are labelled as CMAr, CMAv and CMAAd based on Dum and Strick (2002). Abbreviations: cgs, cingulate sulcus; pcgs, paracingulate sulcus; pacs, paracentral sulcus; prpacs, pre-paracentral sulcus; vpcgs, vertical paracingulate sulcus; cs, central sulcus; meps, medial paracentral sulcus.

near the pre-SMA/SMA border, where direct connections to the VLF are found (Vergani et al., 2014). Notably, the triggered vocalizations included speech-like sounds such as vowels instead of affective vocalizations. Stimulation of these regions during verbalizations also resulted in speech disruption and arrest (Fried et al., 1991; Penfield and Welch, 1951). Patients with pre-SMA/SMA lesions show a great reduction in spontaneous but not externally-cued (e.g. reading a passage aloud or responding to questions) speech production (reviewed in Brown, 1988). These findings indicate that the human pre-SMA and SMA regions contribute to the volitional initiation of speech, but like the MCC, are not critical for speech production. Functional imaging studies of human speech production have also converged on the involvement of the pre-SMA and SMA in the volitional initiation and production of verbalizations (Price, 2012, 2010). Alario et al. (2006) suggested a dissociation between the pre-SMA and SMA for the higher-level cognitive planning and lower-lever motor control aspects of volitional vocal behaviors. Examining the impacts of frontal lesions on verbal fluency performance, Chapados and Petrides (2013) found that verbal fluency was only compromised when lesions included the SMA, pre-SMA and the ventrally adjacent MCC region. In other words, voluntary speech production in humans critically depend on the integrity of all three DMF regions.

## 2.2. VLF regions

The primate neocortical vocalization pathway consists of the orofacial part of the primary motor cortex together with the adjacent ventral premotor (PMv) and ventrolateral prefrontal (vlPFC) region (Ploog, 2002). Unlike the cingulate pathway, this system is not critical for innate and affective vocalizations. In humans, anencephalic infants with complete absence of forebrain tissue are still

able to cry like normal babies (Barnet et al., 1966; Nielsen and Sedgwick, 1949). Similarly, bilateral lesions invading the ventral-most part of the premotor region do not significantly impair vocal production in NHPs (Aitken, 1981; Sutton et al., 1974). Instead, this pathway is associated with the voluntary control of articulators (i.e. jaws, lips and tongue) and vocal folds in primates (Jürgens, 2002), which may be crucial for the production of learned vocalizations (Simonyan, 2014).

### 2.2.1. Primary orofacial motor area

The orofacial part of the primary motor cortex (area 4) is located in the ventrolateral part of the precentral gyrus close to the Sylvian fissure (Fig. 2a, c). In monkeys and chimpanzees, there are direct projections from this area to the various orofacial motor nuclei, such as the trigeminal, facial and hypoglossal nuclei, that enable direct neocortical control over the jaw, lips and tongue musculature, respectively (Kuypers, 1958a). Notably, these direct corticobulbar fibers are almost non-existent in the cat and denser in the chimpanzee than in the monkey. These findings indicate that the neocortical control of orofacial musculature is more elaborate in primates than in other mammals, and appears to increase across primate evolution (Sherwood et al., 2005, 2004). In contrast, direct projections to the nucleus ambiguus, which controls laryngeal muscles, is sparse in the chimpanzee, and almost absent in the monkey (Kuypers, 1958a). Electrical stimulation of the NHP orofacial motor area has consistently yielded lips, jaw, tongue, and vocal fold movements, but no vocalizations (Jürgens, 2002). Stimulations during vocalizations, however, produced changes in the acoustic structure of the vocalizations (Jürgens and Zwirner, 2000), suggesting that the NHP orofacial motor area is not involved in vocal production but can contribute to the articulatory modulation of calls. Monkeys with lesions in the orofacial region of the motor

cortex showed a severe weakening of lower facial and tongue muscles, impairments in biting, chewing and licking movements, but were still able to produce calls (Jürgens et al., 1982). Furthermore, monkeys with orofacial motor area lesions were able to voluntarily increase vocalization rates (Aitken, 1981), but not tongue and orofacial responses during operant conditioning tasks (Murray et al., 1991). As such, the cortical orofacial region in NHPs appears to be critical for the volitional control of tongue and orofacial musculature but not vocalizations.

As in NHPs, the human motor cortex has direct projections to the various articulatory nuclei implicated in vocalizations (Kuypers, 1958b). However, additional direct corticobulbar projections to the nucleus ambiguus are found in the human motor cortex, which enable direct neocortical control over laryngeal musculature (Simonyan and Horwitz, 2011). By virtue of these additional connections, electrical stimulations of the human orofacial motor area could evoke speech-like vocalizations along with orofacial and tongue movements (Breshears et al., 2015; Penfield and Rasmussen, 1949). Interestingly, the laryngeal representation in the human primary motor cortex is more caudally located in the precentral gyrus relative to NHPs (Simonyan and Horwitz, 2011). This suggests a shift of neocortical laryngeal control from premotor regions (area 6) into the primary motor cortex (area 4) across primate evolution, which provided increased fine motor control over both articulatory and laryngeal muscles that is necessary for human verbalization (Simonyan, 2014). Lesions of the orofacial motor region in humans leads to the loss of voluntary control over orofacial muscles and speech production, while monkeys with comparable lesions can still vocalize voluntarily (Jürgens et al., 1982).

### 2.2.2. Ventrolateral prefrontal and ventral premotor cortical areas

The orofacial motor region which lies in the lower part of the precentral gyrus comprises the primary motor cortex (area 4) and two premotor areas: ventrocaudal area 6 (6VC) and ventrorostral area 6 (6VR) (see Petrides, 2014). Anterior to these motor/premotor areas lies a transitional prefrontal cytoarchitectonic area 44 and a fully prefrontal area 45 that are often referred to as Broca's area (Amunts et al., 1999; Petrides, 2014; Petrides and Pandya, 1994). In the current review, we use the label 'PMv' to refer to both areas 6VC and 6VR; and 'vIPFC' to refer to transitional area 44 (Fig. 2a, c). In the human brain, the PMv occupies most of the ventral surface of the precentral gyrus and, immediately caudal to this premotor region and extending into the anterior bank of the central sulcus, is the orofacial and laryngeal representation of the primary motor cortex (area 4). The transitional vIPFC is situated in the pars opercularis, immediately rostral to the precentral gyrus followed further rostrally by ventrolateral prefrontal area 45 that occupies the pars triangularis (Amunts et al., 1999; Petrides, 2014; Petrides and Pandya, 1994). Comparative cytoarchitectonic analysis has demonstrated a similar anatomical organization in the macaque ventrolateral frontal cortex: the rostral premotor region (area 6VR) lies in the rostral precentral gyrus extending into the upper part of the caudal bank of the inferior arcuate sulcus and is succeeded in the fundus of this sulcus by the homologue of human area 44 and, further rostrally, by area 45 (Petrides et al., 2005; Petrides and Pandya, 2002; 1994). The PMv has widespread connections with motor regions such as the CMAr, pre-SMA/rostral SMA, and the primary motor cortex (Dancause et al., 2006; Dum and Strick, 2005; Gerbella et al., 2010; Luppino et al., 1999). In addition to the direct projections to the motor nuclei controlling tongue, jaw and lip movements, the human PMv connects directly to the nucleus ambiguus, the laryngeal motor nuclei (Kuypers, 1958b). In contrast, the monkey PMv is indirectly linked to the nucleus ambiguus via the reticular formation in the brainstem (Jürgens, 2002). Consis-

tent with this observation, stimulation of the PMv evoked orofacial movements in both humans and monkeys but vocalizations only in humans (Penfield and Rasmussen, 1949; Petrides et al., 2005). Relative to the PMv, area 44 (the transitional vIPFC) has richer links with the prefrontal regions, such as the adjacent area 45 and the mid-dorsolateral area 9/46v. This transitional vIPFC also receives somatosensory inputs from the parietal operculum, insula and inferior parietal lobule and is also connected to premotor regions such as the PMv, the cingulate (area 23 and 24) and supplementary motor areas (Frey et al., 2014). Located between higher-order cognitive multimodal and premotor regions, Petrides (2005) suggested that the transitional vIPFC, namely area 44, is well-positioned to exert high-level control over orofacial and vocal actions and to mediate prefrontal cortical influences on such motor acts.

Both the PMv and transitional vIPFC are associated with voluntary vocal control in NHPs. As mentioned, these regions project directly to the orofacial motor nuclei (Kuypers, 1958a) and have been associated with orofacial movements but not call productions upon electrical stimulations (Petrides et al., 2005). Despite the absence of direct projections to the laryngeal motor nuclei, a larynx representation exists in the PMv that evokes vocal fold movements upon stimulation (Hast et al., 1974). Neural activity in the macaque vIPFC and PMv increased with the conditioned initiation of 'coo' calls (Coudé et al., 2011) and both 'coo' and 'grunt' calls (Hage and Nieder, 2013). In these studies, vIPFC and PMv activity was higher for conditioned versus spontaneous vocalizations. The recruitment of ventrolateral frontal cortex in voluntary vocal production was also demonstrated in chimpanzees (Tagliatalata et al., 2011, 2008). In Tagliatalata et al. (2011), the intentional production of vocal signals to obtain rewards from human experimenters led to increased activation in both the vIPFC and PMv regions. Congruently, it was also revealed that chimpanzees who could produce attention-getting sounds had increased grey matter in the vIPFC region (Bianchi et al., 2016). Hage and Nieder (2013) found that vIPFC neurons discharged before vocal onset while PMv neurons discharged mostly with onset, demonstrating a dissociation between the PMv and vIPFC contributions to voluntary vocal control. These investigators argued that the vIPFC might be involved in the higher-order preparation of volitional vocalizations, whereas the PMv is more involved in motor control. However, as mentioned earlier, monkeys with PMv lesions could still produce calls in operant contexts (Aitken, 1981; Sutton et al., 1974). This suggested that PMv in NHPs is involved, but not critical for conditioned vocal productions.

The volitional control of vocalizations in humans is also associated with the PMv and the vIPFC. As in the caudally adjacent orofacial motor area, these regions elicit lip, jaw and tongue movements and vocalizations upon electrical stimulation (Breshears et al., 2015; Penfield and Rasmussen, 1949). However, language interference was evoked more frequently and extensively from stimulation in vIPFC compared to stimulation of the orofacial motor region. Penfield and Rasmussen (1949) reported that after precentral gyrus stimulation, i.e. motor/premotor PMv-evoked speech arrests, patients reported having the word or number in mind but being unable to vocalize them due to a loss of control over articulatory muscles. With vIPFC-evoked speech arrest, patients rather felt they had muscular control but were disrupted in their thoughts and lost track of the content to be vocalized. Breshears et al. (2015) further showed that the peak probabilities of evoking lips, jaw, tongue and throat movements were situated in the PMv, whereas the peak probability of evoking speech arrest was located in the vIPFC. Long et al. (2016) demonstrated that focal cortical cooling in awake patients of the PMv impaired the articulatory quality but not the temporal structure of verbalizations (i.e., the duration and temporal spacing of speech elements), whereas the opposite pattern was observed with vIPFC deactivations. Taken together,

these findings suggest that, within the human ventrolateral frontal region, the PMv is more involved in the motor control of articulatory and laryngeal musculature, while the vlPFC is associated with the higher-level cognitive planning of verbalizations.

### 2.3. Differential roles of VLF and DMF in NHP and human vocal motor control

Even though both the VLF and DMF regions contribute to top-down vocal motor control in primates, there are differences in their involvement in NHP and human vocalizations. In the NHPs, the MCC serves as a crucial bridge between the PAG (which triggers innate vocal patterns via the brainstem premotor nuclei) and the cognitive brain regions, explaining its critical involvement in both the voluntary initiation and conditioned production of affective calls. The pre-SMA, with links to both the MCC and lateral frontal regions, contributes to volitional call initiations in NHPs. The SMA, on the other hand, appears to play a limited role in NHP vocal control. Finally, the VLF region in NHPs has direct control over articulatory muscles and is involved in the conditioned production of affective calls. However, it is not critical for volitional vocal production since monkeys with PMv lesions could still perform vocal operant conditioning tasks.

Similar to NHPs, the human MCC is associated with affective vocalizations and contributes to the motivational initiation of vocal responses. However, ACC/MCC lesions in humans do not abolish voluntary speech production. This indicates that the MCC-PAG pathway, which appears to be critical for innate affective vocalizations in NHPs, is not crucial for volitional human verbalizations. Instead, fluent speech production is impaired only when lesions include the MCC, along with the pre-SMA and SMA regions. VLF lesions also severely impair voluntary speech production in humans. Furthermore, stimulations of human pre-SMA, SMA and VLF regions interfere with speech production. Lastly, both SMA and PMv regions are strongly connected with the precentral motor region, which provides direct articulatory and laryngeal control in humans. Together, these findings suggest that volitional speech control in humans, in contrast to the control of NHP vocalizations, critically depends on a set of VLF-DMF regions that include the pre-SMA, SMA and VLF regions, in addition to the MCC.

## 3. VLF and DMF regions and the cognitive control of vocalizations

### 3.1. Pre-supplementary and supplementary motor areas

Functionally, primate pre-SMA and SMA regions are associated with voluntary action initiation, the motor sequencing of actions and the learning of context-action rules (Nachev et al., 2008; Passingham et al., 2009; Rushworth et al., 2003). Here, we define actions as a series or combination of movements performed to attain a specific goal. Suggestive of a role in action initiation, neurons in the macaque SMA show increased effector-specific activity prior to movement onset (Brinkman and Porter, 1979; Tanji and Kurata, 1982). Monkeys who learned to perform self-initiated movements to obtain rewards no longer do so after SMA lesions (Thaler et al., 1995). However, these monkeys can still perform the movement when cued by a tone. As such, the SMA seems to be specifically involved in self-initiated and not externally triggered actions. In humans, Cunnington et al. (2002) demonstrated that the SMA shows increased BOLD activity prior to both internally and externally triggered actions, but the pre-SMA shows higher activity preceding internally relative to externally triggered actions. This finding suggests that the pre-SMA plays a central role in driving self-initiated actions. Consistent with this interpretation, the pre-

SMA is more active when subjects can freely decide their actions (Nachev et al., 2008) and when they focus on their volitional intentions (Lau et al., 2004). Apart from voluntary action initiation, the pre-SMA and SMA regions are also important for the sequencing of movements into goal-directed actions. Neural recordings in macaques indicate that pre-SMA/SMA neurons respond prior to specific movement sequences (Shima and Tanji, 2000; Tanji and Shima, 1994). Interestingly, some of the pre-SMA/SMA neurons even reflect the relative rank of the movement within a sequence (Clower and Alexander, 1998). Muscimol inactivations of the pre-SMA/SMA region impair the performance of learned movement sequences but again, these sequences can be triggered via an external cue (Shima and Tanji, 1998a).

With regard to the learning of context-action associations, studies have consistently shown the involvement of the pre-SMA and not the SMA in both monkeys and humans (Hikosaka et al., 1996; Nakamura et al., 1998; Sakai et al., 1999). The study by Hikosaka et al. (1996), in which subjects learned and performed sequences of button presses guided by visual information (color or position), demonstrated that the pre-SMA is more active during the learning of visuo-motor sequence associations while the SMA is more active during the performance of learned associations. In another fMRI study, Sakai et al. (1999) confirmed that the pre-SMA in the human brain specifically contributed to the learning of visuo-motor sequence associations rather than the learning of motor sequences *per se*, which is typically attributed to the SMA (Tanji and Shima, 1994).

The results of the above studies can shed light on the likely involvement of the pre-SMA and SMA regions in the voluntary control of innate vocalizations in NHPs and of verbalizations in humans. As mentioned earlier, the pre-SMA in NHPs is directly linked with the MCC (Luppino et al., 1993) which can trigger innate vocal patterns via the PAG. Thus, the pre-SMA might be involved in the initiation of vocal patterns via the MCC as well as binding them with contextual inputs by virtue of its connections with the lateral frontal regions (Luppino et al., 1993). As such, this pre-SMA-MCC-PAG pathway could underlie the ability of NHPs to initiate innate vocalizations conditioned to sensory cues. Human speech involves acquired complex vocal motor sequences that can be arbitrarily associated with different contexts. As such, in humans, the SMA, which has access to oro-laryngeal control via the orofacial motor area (Vergani et al., 2014), might be involved in the sequencing of vocal/orofacial movements into the various speech elements (e.g., phonemes, words, etc.; Alario et al., 2006). The pre-SMA, which is connected with the SMA and the VLF (Vergani et al., 2014), could then be involved in the learning of novel vocal actions, binding them to contexts, and initiating them via these context-action associations.

### 3.2. Mid-cingulate cortex

Recent functional investigations highlight the role of the MCC in the evaluation of action outcomes for behavioral adaptations in both humans and NHPs (Amiez et al., 2012b; Procyk et al., 2016; Quilodran et al., 2008; Rushworth et al., 2003; Shima and Tanji, 1998b). In a study by Quilodran et al. (2008), monkeys had to first search for a rewarded response among other non-rewarded responses via trial-and-error, and subsequently perform the correct response repeatedly to obtain rewards. In this task, incorrect responses and the first correct responses both indicated a need for behavioral change on the next trial: an incorrect response would prompt the monkey to try another response while the first correct response informed a switch from an exploratory to an exploitation strategy. Critically, MCC neurons showed increased activity following the performance of both incorrect responses and the first correct response as compared to subsequent cor-

rect responses. This finding indicates that the MCC is involved in the processing and discrimination of outcomes relevant for behavioral adaptation. Adopting the same experimental paradigm, Amiez et al. (2012b, 2013) obtained the same set of findings in an fMRI study with human subjects: increased BOLD signal in the MCC was observed as subjects processed feedback during exploration vs repetition periods. Reviewing evidence from both monkey and human experiments, Procyk et al. (2016) further suggested that feedback evaluation in the MCC occurred in an embodied manner: feedback-related activity of a specific modality (e.g. juice) was produced by the region of the CMAR carrying the corresponding motor representation (e.g. rostral face region; see Fig. 3).

In the context of vocal production, the MCC could be involved in motivating the initiation and adjustment of vocal responses based on the outcomes of previous vocalizations. According to this account, monkeys with ACC/MCC lesions are impaired on vocal operant conditioning tasks because they are no longer able to motivate the call initiation or adjustments that were previously rewarded. In humans, the MCC is also involved in motivating speech production since patients with MCC lesions exhibit a reduced motivation to produce speech spontaneously. As discussed earlier, the MCC is critical for the volitional production of calls in NHPs since it constitutes a crucial link between the cognitive brain regions and the PAG. Human verbalizations, in contrast, do not critically depend on the MCC-PAG pathway but instead on another set of regions including the pre-SMA, SMA, VLF and precentral motor cortex.

### 3.3. Ventrolateral prefrontal and ventral premotor cortical areas

In a series of experiments involving selective lesions in the monkey, Petrides (2005) demonstrated the existence of a rostral-caudal functional gradient within the lateral prefrontal cortex (Fig. 2). In front of the precentral gyrus (area 4 and caudal area 6) that is directly involved in the motor control and execution of sensorimotor associations, the caudal frontal region (rostral area 6 and area 8) is critical for the conditional rule-based selection between competing alternative responses. Importantly, particular parts of the caudal frontal region appear to be involved in different types of these conditional if-then selections between competing responses based on the motor output region they have access to (Petrides, 2005). For instance, area 8, which is linked to oculomotor and visuospatial processing regions, was shown to be critical for selecting between alternative visual stimuli in the spatial environment based on learned if-then rules, while the dorsal part of rostral area 6, which is linked to the hand motor region and the parietal areas that represent the hand position in space, was critical for selecting between different motor actions based on pre-learned if-then conditional rules. By the same reasoning, the ventral caudal prefrontal region (i.e. the transitional vlPFC), adjacent to the part of the precentral gyrus that is strongly associated with orofacial/vocal motor control (i.e. PMv), could play an important role in the conditional selection of orofacial/vocal responses (Petrides, 2006). Consistent with this proposal, vlPFC neurons showed increased activity as monkeys produced conditioned calls based on visual discriminative cues (Coudé et al., 2011; Hage and Nieder, 2013). Hage and Nieder (2015) further showed that the same vlPFC neurons that are involved in conditioned vocal productions based on visual cues also responded to auditory information in macaques. These findings suggest that the vlPFC is involved in the operant control of vocalizations not only based on visual but possibly also on auditory information. This mechanism could underlie the ability of monkeys to adjust vocalizations in response to ambient noise or calls by conspecifics. Similarly, Chang et al. (2013), via intracortical recordings, demonstrated that, as human subjects adjusted their vocal productions in response to acoustic perturbations, the PMv reflected compensatory activity changes that were correlated with

both the activity associated with auditory processing as well as the magnitude of vocal pitch adjustment. Functional neuroimaging investigations also revealed that human area 44 is activated for both the processing of articulatory/phonological information and production of verbalizations (Poldrack et al., 1999; Price, 2012, 2000). Taken together, the primate VLF region appears to be involved in the higher-order control of orofacial/vocal responses based on incoming sensory information. This functional contribution is congruent with the VLF region's strong anatomical connections with temporoparietal regions that provide access to multisensory inputs and the motor regions that provide control over orofacial/vocal movements (Petrides, 2006).

Within area 6VR (often referred to as F5 in macaque monkeys) of the PMv (Fig. 2c), there are 'mirror neurons' which respond both to the performance of a specific motor action and the observation of the same action (Rizzolatti et al., 1996). Interestingly, Ferrari et al. (2003) found mirror neurons in the anterior part of area 6VR that responded specifically to the performance and observation of orofacial actions, such as feeding and communicative movements (i.e. lip-smacking). These orofacial mirror neurons could contribute to the imitative learning of orofacial actions by forming an internal representation of observed orofacial actions via direct connections with the primary orofacial motor area (Ferrari et al., 2006). With reduced direct laryngeal access in the primary orofacial motor area, the PMv in NHPs might be less disposed to generate orofacial-laryngeal motor representations of heard vocalizations. This could explain why vocal imitative abilities are limited in NHPs (Ackermann et al., 2014; Lameira et al., 2016, 2015). In contrast, with direct access to both orofacial and laryngeal motor output, the human PMv can 'mirror' heard vocalizations via the orofacial-laryngeal motor circuitry. Congruent with this account, Belyk et al. (2016) recently showed that the imitative production of vocalizations in humans involved the VLF, along with preSMA/SMA and MCC regions. This capacity for vocal learning and imitation is crucial for the emergence of human speech (Fitch, 2000).

## 4. The existence of a primate VLF-DMF network and its general functions in the cognitive control of vocalizations

We have argued that a comparable set of primate VLF-DMF regions may contribute to voluntary vocal control in both NHPs and humans. In this section, we propose the existence of a primate VLF-DMF network and its generic contributions to the cognitive control of vocalizations in both human and NHPs. Anatomically, the primate VLF-DMF regions are interconnected (Fig. 1): The anterior MCC (the part associated with vocalizations) has strong connections to the pre-SMA (Luppino et al., 1993; Vergani et al., 2014) as well as the PMv (Lu et al., 1994). The pre-SMA is also strongly connected with the PMv (Luppino et al., 1993). Interestingly, within this primate VLF-DMF network, there is a core network of regions, i.e. the pre-SMA, MCC and PMv, which show strong interconnections and are involved in vocal control in both the human and NHP brain (Fig. 1).

Functionally, the VLF-DMF regions appear to perform generic functions in NHPs and humans. Primate VLF regions, including the vlPFC and PMv, could be involved in linking vocal/orofacial responses to different contexts via conditional if-then rules. With access to both multimodal contextual information and vocal-orofacial motor outputs, the vlPFC is well-placed to establish context-orofacial/vocal response conditional operations that are then executed via the PMv (Petrides, 2006). In both humans and monkeys, the pre-SMA is associated with volitional action initiation and the learning of context-action associations (Nachev et al., 2008). The observation that pre-SMA lesions increased the latencies of voluntary call and speech initiations in both monkeys and

humans strongly suggests that the primate pre-SMA generally contributes to the volitional initiation of vocalizations. Finally, the MCC region in both monkeys and humans is associated with the evaluation of action outcomes to adapt future behaviors. In the context of vocalizations, it is important for motivating the initiation of new vocalizations or adjustments to current vocal behaviors based on the outcomes of previous actions. Indeed, MCC lesions result in reduced volitional vocalizations in both NHPs and humans. With strong links to emotional processing regions and the PAG, the MCC also contributes to affective vocalizations in both humans and monkeys.

Based on the above discussion, we propose the following relative roles of the primate VLF-DMF regions that are generic to cognitive control of vocalizations in both humans and NHPs: *Whereas VLF areas contribute to the conditional selection of orofacial/vocal responses based on sensorimotor associations, the MCC is involved in the evaluation of orofacial/vocal action outcomes to drive future orofacial/vocal responses. The pre-SMA is generally involved in the initiation and adjustments of orofacial/vocal responses.* Notably, the above regions (i.e. VLF, MCC, and pre-SMA) are also the regions with the strongest interconnections within the VLF-DMF network. As such, these regions might constitute the core network for the primate cognitive control of vocalizations. One possible way to test our proposed functions of the VLF and DMF regions in parallel would be via a conditional associative learning protocol (see Amiez et al., 2012a) that involves both the learning and the production of conditional associations between arbitrary sensory cues and orofacial/vocal responses.

## 5. How has the VLF-DMF network changed during primate evolution?

In NHPs, the MCC serves as the crucial link between the PAG and the other DMF and VLF cognitive brain regions, and is thus critical for the production of affective vocalizations in NHPs. The MCC is also likely involved in the limited adjustments of affective calls (i.e. amplitude, rate and frequency) based on the feedback evaluation of previous vocalizations. This could account for the observations that monkeys could still perform conditioned vocal responses following PMv lesions. The VLF, receiving inputs from both sensory and motor regions, contributes to the conditioned selection of innate vocal patterns based on sensory inputs. This could explain the ability of NHPs to initiate their innate calls based on visual cues (Hage et al., 2013). The pre-SMA, which is linked with both the MCC and VLF, could be involved in the initiation of affective call production and adjustments based on feedback evaluation and sensory-vocal selections.

In humans, the VLF, pre-SMA and MCC are not only involved in the cognitive control of affective vocalizations but also acquired vocalizations. This expanded role could be attributed to two key differences in the human VLF-DMF network relative to NHPs. Firstly, as suggested by Simonyan (2014), the emergence of a laryngeal representation in the human orofacial motor area afforded increased fine-motor control over oro-laryngeal movements. As such, areas in the human VLF which are directly connected to the orofacial motor area, would be able to construct and exercise conditional sensory-vocal motor associations not only at the level of well-formed orofacial/vocal responses but also at the level of fine oro-laryngeal movements. Similarly, the human MCC region would also be able to drive adjustments in oro-laryngeal actions at a fine motor level. This could account for the increased capacity of humans to generate and modify flexibly their vocal patterns based on contextual rules or vocal behavioral feedback. Secondly, apart from the core primate VLF, pre-SMA and MCC regions, the cognitive control of human vocalizations additionally recruits the SMA. As discussed earlier,

the SMA is associated with the sequencing of motor actions and could be vital in the sequencing of vocal/orofacial movements into novel vocal patterns via the human orofacial motor area, which has direct access to laryngeal and orofacial control. These novel vocal patterns could then be conditionally linked with contextual representations in the VLF, adjusted based on vocal behavioral feedback analyses in the MCC, and initiated via the pre-SMA.

### 5.1. How might the above mentioned changes in the human VLF-DMF network and its functions contribute to the emergence of complex speech behaviors?

The increased fine-motor control over oro-laryngeal musculature and the recruitment of the SMA for oro-laryngeal movement sequencing have enabled the generation of speech elements (e.g. phonemes, words, phrases, etc.) that involve complex combinations of oro-laryngeal movements as well as the acoustic variations of these elements (e.g. pitch, amplitude, timbre, etc.). These speech units, along with their acoustic variations, could then be selectively produced in different contexts based on first-order conditional sensorimotor rules (i.e. if stimulus A, then speech pattern X) in the VLF (Petrides, 2006). Beyond the VLF, rostral lateral frontal regions (i.e. areas 45, 9, 46 and 10) might be implicated in higher-order monitoring of selections of speech actions (Petrides, 2005) and there have been suggestions that perhaps also on progressively abstract rule representations (Badre and D'Esposito, 2009; Donoso et al., 2014; Koehlin, 2003). Thus, in the lateral frontal cortex, the most caudal premotor region (area 6) represent basic sensorimotor associations, middle regions (areas 44, 45, 8) are involved in selecting these sensorimotor associations based on higher-order contextual rules consistent with the demonstration of the role of these regions in conditional associative learning (Petrides, 2005). Finally, more anterior regions (dorsolateral prefrontal areas 9/46, 46, 9, ventrolateral prefrontal area 47/12, and frontal pole area 10) may select these context-sensorimotor rules based on episodic representations, such as past experiences and internal goals. Along with this rostral-caudal functional gradient, we have shown earlier that, within the VLF region, the vIPFC and PMv are associated with higher and lower aspects of vocal sensorimotor control, respectively. Furthermore, regions rostral to the VLF have consistently been found to be involved in higher aspects of speech production (Bourguignon, 2014; Price, 2012). Heim et al. (2009) demonstrated a dissociation between areas 45 and 44 for semantic and phonological processing during verbal generations. Area 45 has been shown to be a critical region in the selective retrieval of information from memory and this fundamental role of area 45 may explain its greater involvement in semantic as opposed to phonological processing (Petrides, 2016, 2006). As such, the human VLF, together with the rostral lateral frontal regions, enable the selective production of speech patterns based on a cascade of increasingly complex rules. As in the lateral frontal regions, a rostro-caudal organization has also been proposed for the medial frontal cortex (Domenech and Koehlin, 2015; Donoso et al., 2014): while more caudal medial-frontal regions (including the MCC and pre-SMA) evaluate actual action outcomes for adjusting current behaviors, the more rostral ventromedial prefrontal cortex assesses the reliability of behaviors in predicting action outcomes. Within this framework, one might suggest that the DMF region contributes to adjusting speech productions based on current outcomes, whereas more rostral medial frontal regions would be involved in determining the expected outcomes of speech productions for guiding future speech behaviors.

To conclude, this review provided an overview of the potential integrated functions of two systems involved in the cognitive control of vocalizations in the primate brain. Future work will need to address how these systems work as a whole to elaborate and adjust

flexibly complex speech productions, and also how these systems evolved across primate species to gain these properties.

### Disclosure/conflict of interest

None declared.

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## **Chapter 5: Resting-state connectivity profile matching of the human and macaque cingulate motor areas.**

### **Introduction**

Three distinct cingulate motor areas (CMAs) can be found in both the monkey and human cingulate cortex (Amiez & Petrides, 2014; Dum & Strick, 1991; Loh, Hadj-Bouziane, Petrides, Procyk, & Amiez, 2017a). In the monkey, the rostral-most CMA (CMAr) occupy both banks of the cingulate sulcus, while the two caudal CMAs (CMA<sub>d</sub> and CMA<sub>v</sub>) are respectively located on the dorsal and ventral banks posterior to the CMAr (Dum & Strick, 2002). In the human, the three CMAs are located along a rostral-caudal axis along the para-cingulate/cingulate sulcus with RCZa situated most anteriorly followed by the RCZp and CCZ (Amiez & Petrides, 2014).

The CMAs appear to be homologous across macaques and humans. In both species, they are directly involved in motor control: In the monkey, retrograde tracing studies have revealed efferent projections from the CMAs to the ventral horn of the spinal cord, the premotor, and primary motor cortices (Dum & Strick, 1991; 1993; He et al., 1995; Luppino et al., 1991; Morecraft & Van Hoesen, 1992; Shima et al., 1991). Intra-cortical stimulation experiments have revealed a full set of face, hand, and leg motor representations in both the CMAr and CMA<sub>v</sub>, and 2 arm, and one leg representations in the CMA<sub>d</sub> (Dum & Strick, 1993; Luppino et al., 1991). In humans, recent functional neuroimaging experiments have revealed activations in the CMA as subjects performed voluntary hand, foot, mouth, and saccadic movements (Amiez & Petrides, 2014). Critically, as in the monkey, a set of hand, face, and leg motor representations

is found in each of the two rostral CMAs (RCZa and RCZp), while the caudal-most CCZ contains two hand and a foot representation. Apart from motor control, the macaque and human CMAs also have comparable functions in cognitive control. In particular, in both species, the anterior-most CMA (i.e. macaque CMAr and human RCZa) appear to have a crucial role in the monitoring of action outcomes/feedback to adapt future behaviors (Amiez, Hadj-Bouziane, & Petrides, 2012a; Amiez, Sallet, Procyk, & Petrides, 2012b; Quilodran et al., 2008). A more recent review had suggested that this feedback processing could be “embodied” in the somatotopic maps within the CMAr/RCZa (Procyk et al., 2016), such that behavioural feedback that is associated with certain response modality (e.g. juice reward) is evaluated in the corresponding motor representation (e.g. face motor representation). Taken together, the above summarized correspondences in somatotopic organization and function are suggestive of homologies between the monkey (CMAr, CMAv and CMAv) and human CMAs (RCZa, RCZp and CCZ).

While the locations of the human CMAs and their respective somatotopic organization have been intricately mapped via fMRI protocols involving voluntary movements (Amiez & Petrides, 2014; Loh, Hadj-Bouziane, Petrides, Procyk, & Amiez, 2017a), the relative positions of the macaque CMAs and their somatotopic maps, have not been precisely investigated. Characterizing the functional organization of the CMAs and their motor representations in the macaque brain is a crucial first step for further invasive investigations into the CMAs’ exact functioning via electrophysiological, pharmacological and lesion approaches and also, for the comparative study of the macaque and human CMAs. As such, the main goal of the present work is to determine the exact locations of the macaque CMAs and their respective motor

representations. To achieve this goal, we adopt a novel and non-invasive method – connectivity fingerprint matching (Mars et al., 2016), that enabled the matching of a specific region across different brains on the basis of its connectivity profile. This method is based on the principle that every brain region can be defined by a unique set of important connections with other brain regions (connectivity fingerprint) that is crucial for achieving its functions (Passingham, Stephan, & Kötter, 2002). With this method, we aim to match the three human CMAs and their respective motor representations in the macaque brain based on their connectivity fingerprints. In our earlier work (Loh, Hadj-Bouziane, Petrides, Procyk, & Amiez, 2017a), we have identified the locations of the CMAs and their motor maps in human subjects via an fMRI protocol and investigated their resting-state functional connectivity with a set of lateral frontal brain regions. Using this data, we first constructed the connectivity fingerprints corresponding to the connectivity of each human CMA motor representation with a set of lateral frontal brain regions. Next, we performed a voxel-wise search in the macaque brain for regions that show the same connectivity fingerprint as each of the human CMAs and their motor maps. The steps of this approach are further detailed in the Method section.

Previous investigations have shown that the two caudal macaque CMAs, CMA<sub>d</sub> and CMA<sub>v</sub>, are respectively located in the dorsal and ventral banks of the cingulate sulcus between the genu of the arcuate sulcus and 10 mm posterior to this genu (reviewed in Dum and Strick, 2002). In a recent meta-analysis, Procyk and colleagues (2016) reviewed 26 studies that localized the CMA<sub>r</sub> via feedback-related neuronal activity, intracortical stimulations and tract-tracing. Procyk et al. reported that the face motor representation of the CMA<sub>r</sub> is situated in the cingulate sulcus between 5-10 mm

anterior to the genu of the arcuate. Based on these findings, we expected to locate the CMAR in the cingulate sulcus between 5-10 mm anterior to the arcuate genu, and the CMA<sub>d</sub> and CMA<sub>v</sub> to occupy the dorsal and ventral banks of the cingulate sulcus 0 to 10mm posterior to the arcuate genu. We also expected the same somatopic organization in the 3 macaque CMAs as reported in previous studies: while the CMAR and CMA<sub>v</sub> contained a set of face, hand and foot representations, CMA<sub>d</sub> contained a set of 2 hand and one foot representation.

## Method

### MRI data acquisition

Human data.

Anatomical, rs-fMRI and motor-mapping task fMRI data were acquired from 21 healthy subjects as part of an earlier experimental protocol (Loh, Hadj-Bouziane, Petrides, Procyk, & Amiez, 2017a). Anatomical images were acquired via an MPRAGE sequence with  $0.9\text{mm}^3$  isotropic voxels, 192 slices, TR=3.5s and TE=2.67s. Functional images (rs-fMRI and motor-mapping fMRI data) were acquired via a T2\*-weighted gradient echo planar EP sequence with 40 oblique slices, voxel resolution =  $2.7 \times 2.7 \times 2.7\text{mm}$ , TR = 2.2s, TE = 30.0s and flip angle=  $90^\circ$ .

Briefly, the motor-mapping task involved the performance of fixation trials, where the subject fixated on a central cross, and movement trials that involved hand, tongue and saccadic movements (further details about the experimental protocol can be found in Loh, Hadj-Bouziane, Petrides, Procyk, & Amiez, 2017a). Both fixation and movement trials lasted 22.5s. Each subject contributed a total of 160-240 TRs of data for the fixation trials, and 80-120 TRs each for hand, tongue and saccadic movement trials. For the rs-fMRI scans, 300 EPI images were acquired for each subject over a duration 11mins. Subjects were instructed to keep still and maintain fixation on a central dot. Photoplethysmography (PPG) and eye-tracking data were also acquired during the resting-state scans for the modelling of eye-movement and cardiac noise in the rs-fMRI signal.

Macaque data.

2 high resolution T1 anatomical scans (MPRAGE, 0.5mm<sup>3</sup> isotropic voxels, 144 slices, TR=3000ms, TE=366ms) and 5 rs-fMRI (EPI, 1.7mm<sup>3</sup>, 420 slices, TR=1700ms, TE=330ms) were acquired for each of the 2 rhesus macaque monkeys (Monkey L and Monkey N). Both monkeys were scanned under light anaesthesia using isoflurane. Scanning was performed on a 3T Siemens Magnetom Prisma MRI scanner (Siemens Healthcare, Erlangen, Germany).

### **MRI data pre-processing**

Human data.

Anatomical and functional data were pre-processed using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>) running on Matlab 16a (<http://www.mathworks.com>). For the motor-mapping task, the main pre-processing steps included: 1) Discarding of first 5 volumes to account for T1 equilibrium effects, 2) slice-timing correction, 3) realignment, 4) co-registration with T1 images, and 5) smoothing via a 6-mm full-width half maximum Gaussian kernel. Each fixation or movement task trial was modelled with impulse regressors at the onset of the cue that indicated the start of the fixation or movement. The impulse regressors were then convolved with the canonical hemodynamic response function and entered into a general linear model (GLM) to model each subject's data with 6 motion regressors as additional covariates.

The rs-fMRI scans were pre-processed with the identical steps as the motor-mapping data. Additionally, a temporal filter (0.01–0.1 Hz) was applied using AFNI (Cox, 1996) to extract the spontaneous low-frequency fluctuations in the rs-fMRI signal. Subsequently, the variances in the brain activity associated with head motion, cerebrospinal fluid, white matter, heart rate and pupil activity were removed from the filtered signal via linear regression. Finally, the data was smoothed with a 6-mm FWHM Gaussian kernel.

Macaque data.

Pre-processing of the macaque anatomical and rs-fMRI data was performed using AFNI and SPM12 softwares. Before pre-processing, all anatomical and functional scans were reoriented by setting the image origin to the anterior commissure using SPM Display. For the anatomical data, the two T1 images of each monkey were first averaged to increase the signal-to-noise ratio. The averaged T1 image was then co-registered and resliced to the D99 macaque template brain (<http://afni.nimh.nih.gov/pub/dist/atlas/macaque>) using SPM12. A brain mask was first created using the D99 template via AFNI's 3dAutomask function, and manually adjusted to cover the whole brain in individual monkeys. This adjusted brain mask was then used to extract the brain voxels from the averaged T1 images. Segmentation of the skull-stripped images into gray (GM), white matter (WM) and cerebrospinal fluid (CSF) tissue types was subsequently performed via FSL's FAST function.

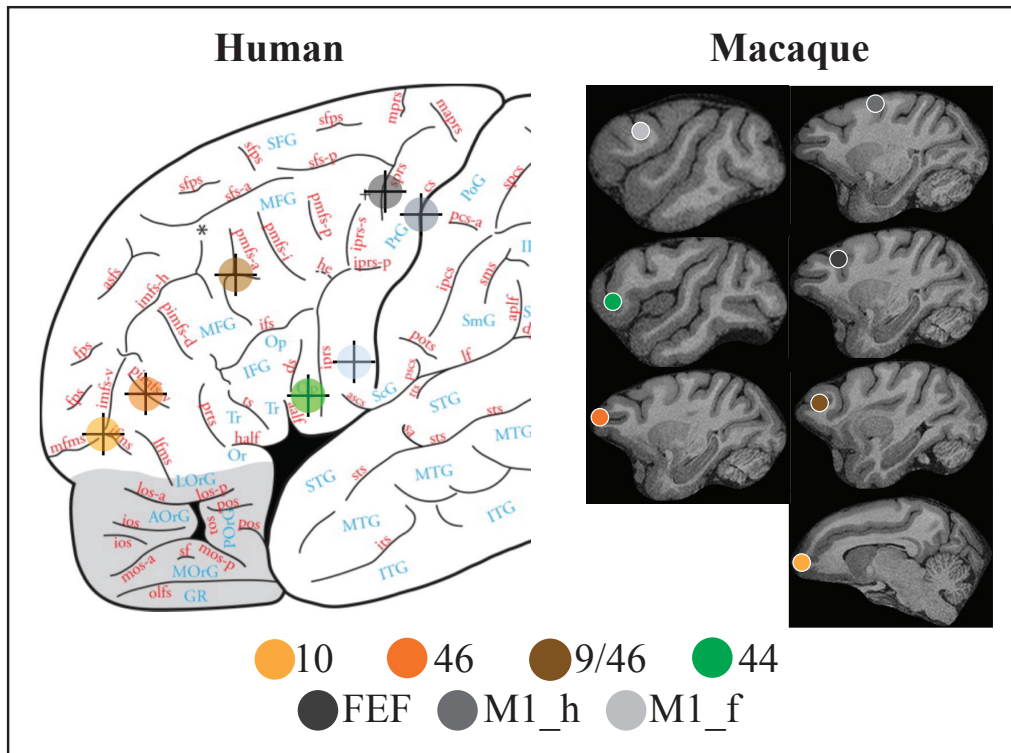
For the rs-fMRI data, the first 5 volumes of each run were discarded to avoid T1 signal inhomogeneities. The following steps were then applied for each run via SPM12: 1)



Slice-timing correction with reference to the middle slice, 2) realignment of all volumes to the first slice of the first volume, 3) co-registration with the pre-processed anatomical images. Subsequently, a temporal filter (0.01–0.1 Hz) was applied using AFNI to extract low frequencies fluctuations in the BOLD signal. Lastly, the signal noise associated with head movement, WM and CSF were removed via linear regression in AFNI for each run separately. Note that no smoothing was performed on the data.

### **Connectivity fingerprint matching analyses**

Connectivity fingerprint matching (Mars et al., 2016) provides a non-invasive approach to match a particular region across different brains based on its unique connectivity pattern. This method is based on the idea that any brain region (seed area) can be uniquely defined by a set of important connections it has with other regions (target areas) which is essential for accomplishing its function (Passingham et al., 2002). In the present study, we adopted this method to identify the locations of the CMAs in the macaque brain based on the functionally-localised CMA seeds in the human brain.

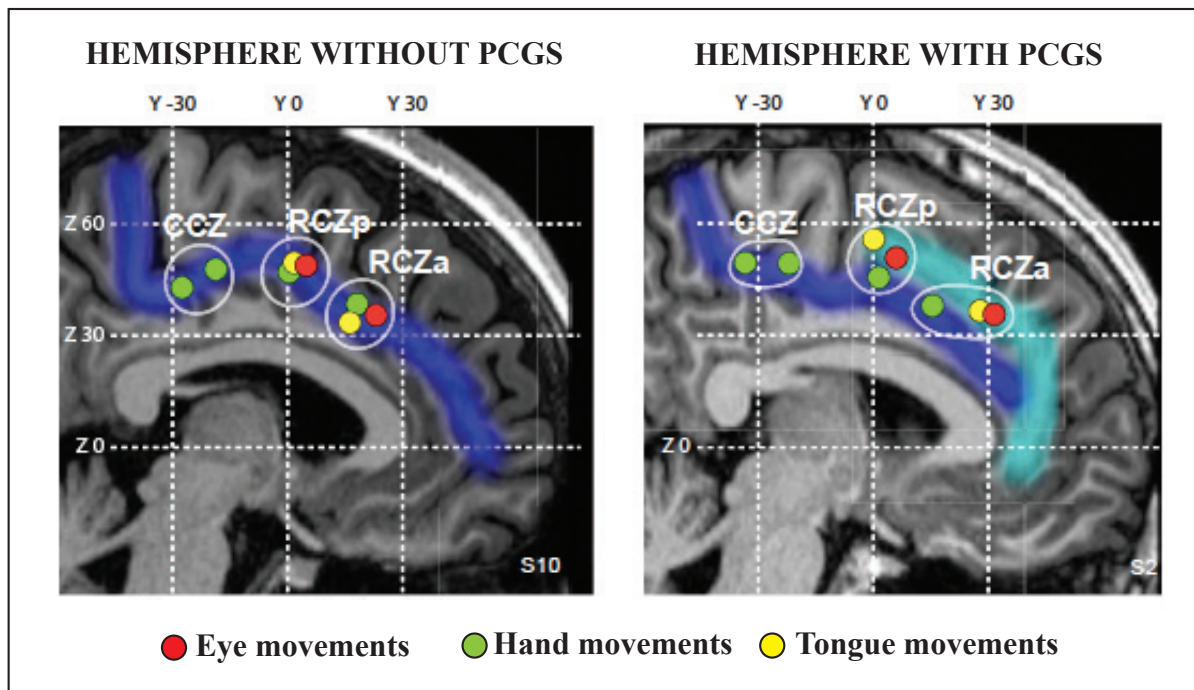


**Figure 1. Target areas in the human and macaque brain.**

Selection of target areas.

The first step in this analysis involves determining a set of homologous target areas in both the macaque and human brain that are able to, based on their connections with the CMAs, 1) distinguish the CMAs from other regions in the brain; and 2) distinguish each CMA from the other CMAs. In the present work, we decided on 7 target areas in the left hemisphere that include the prefrontal areas 10, 46, 9/46, 44, the frontal eye fields (FEF) and the primary hand (M1h) and face (M1f) motor areas (Fig. 1). These areas are homologous across humans and macaques (Petrides et al., 2012). Although it was not clear if the connectivity of the CMAs with these areas can optimally distinguish the CMAs from other brain regions, we have previously shown that they can sufficiently differentiate the anterior-most CMA (RCZa) from the posterior ones (RCZp and CCZ): RCZa was more strongly connected with the prefrontal areas and

less with the FEF, whereas RCZp and CCZ were more strongly linked with motor areas and weakly linked with the prefrontal areas (Loh, Hadj-Bouziane, Petrides, Procyk, & Amiez, 2017a). As such, with these target areas, we expected to distinguish the anterior-most CMA from the posterior ones in the macaque.

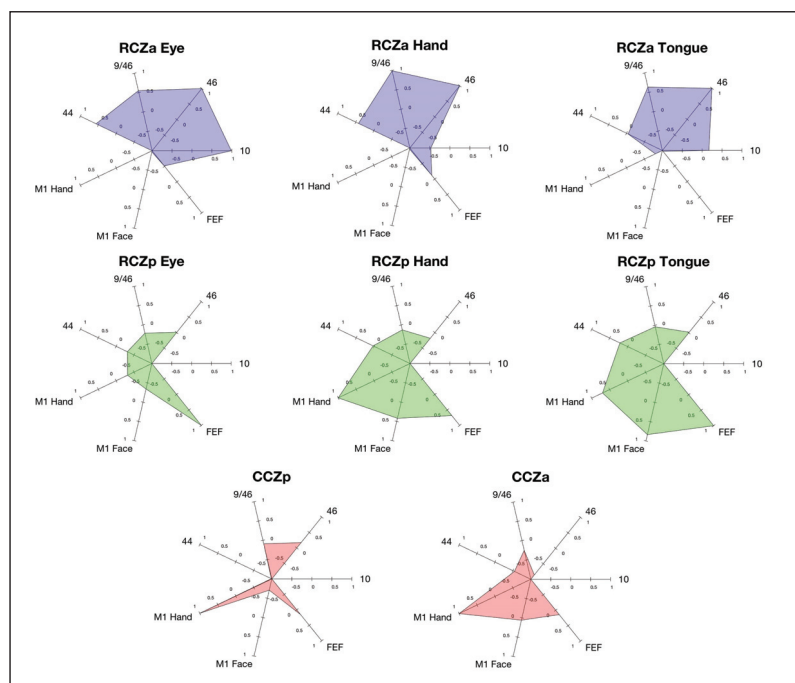


**Figure 2. Human CMA seeds in hemispheres with and without para-cingulate sulcus.** Abbreviations: RCZa, anterior rostral cingulate zone, RCZp, posterior rostral cingulate zone, CCZ, caudal cingulate zone, pcgs, paracingulate sulcus.

Constructing human CMA connectivity fingerprints.

The seed (Fig. 2) and target area locations (Fig. 1) for computing the human connectivity fingerprints were derived from Loh et al. (2017a): The seven left-hemispheric target areas were identified in individual subjects based on anatomy (area 44, area 46, area 9/46 and area 10) or activations on the movement task (FEF, M1h and M1f). The 8 seed regions, which included a full set of hand, eye and tongue representations in the RCZa (RCZa\_hand, RCZa\_eye, RCZa\_tongue) and RCZp

(RCZp\_hand, RCZp\_eye, RCZp\_tongue), and two hand representations in the CCZ (CCZa, CCZp), were also localised in the left hemisphere via the motor-mapping task. With the seed and target area locations, regions-of-interest (ROIs) with a 4mm radius were generated on each subject functional brain space using the AFNI software. The mean signal from these ROIs was then extracted and used to compute correlations between each CMA seed area with the 7 target areas in individual subjects. This resulted in 8 connectivity fingerprints corresponding to the functional connectivity profiles of each CMA seed with the 7 target areas (Fig. 3). The connectivity fingerprints were then averaged across subjects. Within each averaged connectivity fingerprint, the connectivity strengths (seed-target correlations) are scaled to the maximum and minimum values in the fingerprint.



**Figure 3. Averaged normalised human CMA connectivity fingerprints.** Connectivity strengths are scaled between 0 and 1 within each fingerprint. Abbreviations: RCZa, anterior rostral cingulate zone, RCZp, posterior rostral cingulate zone, CCZa, anterior caudal cingulate zone, CCZp, posterior caudal cingulate zone.

Voxel-wise matching of human CMA fingerprints in the macaque brain.

The 7 target areas were first identified on the individual macaque brains based on anatomy. Fig 1. shows the locations of the target areas in Monkey L. In each monkey, spherical masks with a radius of 2mm, corresponding to the 7 target areas, were drawn on the mean T1 image. These target masks were then linearly registered into rs-fMRI space via the FLIRT tool in FSL. In each monkey, we computed the correlation between the mean signal in each of the 7 target area masks with every other voxel in the brain using FSL's `fsl_sbca` (O'Reilly, Beckmann, Tomassini, Ramnani, & Johansen-Berg, 2010). This yielded 7 whole-brain correlation maps that depicted the connectivity of each target area with each other voxel in the brain. In each monkey, the 7 target correlation maps were then concatenated in the "time" dimension into a single 4D matrix. In this 4D matrix, each voxel thus contained 7 connectivity values in the "time" dimension that indicated the connectivity between that voxel and each of the 7 target areas. Finally, permutation testing, via FSL `randomise` (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) was performed to determine which voxels in each monkey's concatenated correlation maps show a statistically significant GLM fit in their pattern of connectivity with the connectivity profile associated with each of the 8 human CMA seeds. For the permutation test, the sampling distribution was derived by shuffling the order of the 7 correlation maps and re-computing the test statistic. We assessed the significance of the results at an uncorrected  $p < 0.01$  threshold.

## Results

Voxel-wise connectivity profile matching was performed in individual macaque brains in order to identify the 8 CMA seed regions corresponding to the eye, hand and tongue motor representations in the RCZa and RCZp, and the two hand representations in the CCZ. Given the exploratory nature of this work, we had assessed the results at a less stringent threshold of  $p < 0.01$ , uncorrected for multiple comparisons. As our main interest is in locating the CMAs, we focused specifically on the significant voxels that were situated within the cingulate sulcus in the left hemisphere. Fig 4 shows the locations of the brain voxels that shows a matching connectivity profile to each of the human CMA fingerprints.

### Monkey L

In Monkey L, we observed three clusters of significant voxels corresponding to the RCZa, RCZp and CCZ seeds. At the most anterior end, between -4mm to +16mm relative to the level of the arcuate genu (+6mm relative to the AC), we observed a cluster of voxels showing significant matches in connectivity profiles with the RCZa seeds. The observed location of the cluster at +8 to 12mm from the arcuate genu was also congruent with a recent meta-analysis of stimulation and single-unit recording studies that reported the macaque CMAr to be around +10mm from the arcuate genu (Procyk et al., 2016). Within this cluster, the peak voxels associated with the RCZa eye (Coordinates in mm relative to the AC (AC coordinates): -1, 17, 12;  $t=3.32$ ) and tongue representations (AC coordinates: 0, 14, 14;  $t=4.96$ ) appeared to be situated rostral to the RCZa hand peak voxel (AC coordinates: -3, 13, 11;  $t=4.69$ ). This finding

was in accordance with studies that revealed that in the macaque CMAr, the face/eye motor representation is found anterior to the front limb representation (Luppino et al., 1991; Morecraft et al., 1996; Y. Wang, Matsuzaka, Shima, & Tanji, 2004). As such, this cluster likely corresponded to the macaque CMAr. Apart from the main cluster, there were other significant voxels located more posteriorly that showed a matching connectivity profile to the RCZa seeds.

A second cluster of voxels that was situated around -8 mm from the arcuate genu showed similar connectivity profiles with the human RCZp seeds. This was congruent with Dum and Strick (2002)'s suggestion that the caudal CMAs are found between 0 and -10mm from the arcuate genu. Since the matching was performed with RCZp seeds, we had expected to find the homologous CMAv in the ventral bank based on previous studies. However, our observed cluster was situated in the dorsal bank instead. Nevertheless, the somatotopic organization in this cluster was congruent with that of the CMAv: the peak voxel corresponding to the RCZp eye representation (AC coordinates: -1, 1, 17;  $t=4.95$ ) was situated anterior to that corresponding to the hand representation (AC coordinates: -2, -1, 18;  $t=3.08$ ). This finding corroborated the findings of Wang and colleagues (2004), which revealed that in the caudal CMA, the eye representation was rostral to the hand representation. Overall, matching with RCZp seeds yielded a cluster of voxels that were situated in the expected caudal-rostral position along the cingulate sulcus. Furthermore, this cluster showed a congruent somatotopic organization as the CMAv. However, our cluster was found in the ventral, rather than the dorsal bank in the cingulate sulcus. As with the RCZa matching, there were also significant voxels corresponding to the RCZp seeds situated outside of the main cluster.

Lastly, the peak voxels associated with the CCZa (Coordinates in mm relative to the AC: -2, -1, 19;  $t=2.77$ ) and CCZp (AC coordinates: -1, 6, 14;  $t=5.00$ ) representations did not constitute a distinct cluster but were situated within the RCZp cluster and between the RCZa cluster respectively. Instead, there was a set of significant CCZa (AC coordinates: -3, -10, 14;  $t=2.69$ ) and CCZp (AC coordinates: -1, -16, 15;  $t=3.4$ ) voxels that was clustered around -16mm from the arcuate genu. Having two hand representations, this cluster potentially corresponded to the macaque CMAd (Petrides and Amiez, 2014). However, its location was too caudal than that expected of the CMAd.

## **Monkey N**

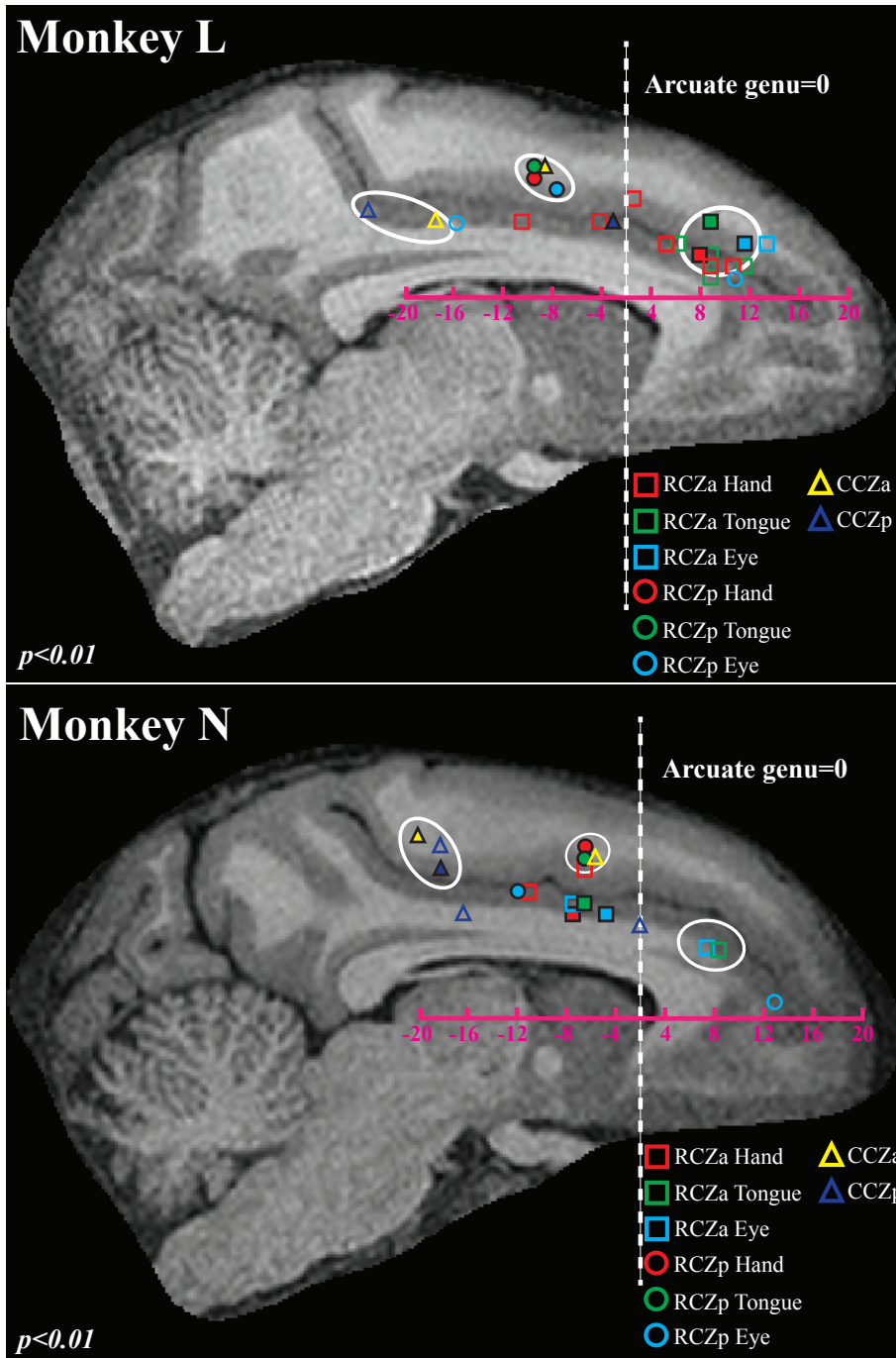
In Monkey N, we also observed 3 clusters of voxels that had matching connectivity profiles as the 3 human CMA seeds. Firstly, at about +8 mm anterior to the arcuate genu (+8mm relative to the AC), there were two significant voxels that matched the RCZa tongue (AC coordinates: -3, 15, 10;  $t=3.57$ ) and RCZa eye (AC coordinates: -4, 14, 10;  $t=4.01$ ) representations. Since the location of this cluster coincided with the position of the CMAr based on Procyk et al. (2016) and that a face motor representation was present, this cluster could potentially be the CMAr in Monkey A. However, there were no voxels corresponding to the hand representation in this cluster. The human RCZa seeds also matched a second cluster of voxels between -4 to -8 mm caudal to the arcuate genu. Notably, this cluster contained the peak voxels that show the best match in connectivity with the RCZa hand (AC coordinates: -1, 2, 13;  $t=5.6$ ), eye (AC coordinates: -4, 5, 13;  $t=4.34$ ) and tongue (AC coordinates: -1, 3, 14;



t=6.14) representations respectively. Even though this cluster of voxels contained a full set of hand, eye and tongue motor representations, it is not likely to be the CMAR due to its posterior location.

The RCZp seeds matched a cluster of voxels located between -4 to -12mm posterior to the arcuate genu. This cluster contained the peak voxels that showed a similar connectivity profile as the RCZp hand (AC coordinates: -3, 3, 19; t=4.38) and tongue representations (AC coordinates: -3, 3, 18; t=3.78). This group voxels likely corresponded to the macaque CMAv, which is found to be situated caudal to the CMAR and contained both hand and face motor representations. However, as with Monkey L, the cluster was situated in the dorsal rather than the ventral part of the cingulate sulcus. In addition, the voxels that matched the RCZp eye seeds did not fall within this main cluster.

Lastly, the CCZa and CCZp seeds matched a cluster of voxels situated between 16mm to -20mm posterior to the arcuate genu (CCZa peak voxel: AC coordinates = -2, -12, 20, t=3.65; CCZp peak voxel: AC coordinates = -3, -10, 17, t=7.87). With two hand representations, this cluster could constitute the putative homolog of the macaque CMAd. However, it was situated too caudal than the location expected of the CMAd based on previous studies.



**Figure 4. Connectivity profile matching of left-hemispheric human CMA seeds in the two macaques.** Filled shapes indicate the peak voxels matching the respective CMA seeds. Unfilled shapes indicate voxels that are significant at the  $p > 0.01$  level. Only significant voxels that are situated within the cingulate sulcus are shown. Abbreviations: RCZa, anterior rostral cingulate zone, RCZp, posterior rostral cingulate zone, CCZ, caudal cingulate zone.

## Summary

Overall, connectivity profile matching of the 8 human RCZa, RCZp and CCZ seeds in the macaque brain generally revealed the presence of 3 significant clusters of voxels that could potentially correspond to the CMAR, CMAv and CMAAd respectively. In both monkeys, consistent with the findings of Procyk and colleagues (2016), the CMAR cluster was located around +8 to +12mm anterior to the arcuate genu. Furthermore, a face motor representation was observed at the anterior extent of the CMAR cluster in both monkeys. In Monkey L, the somatopic organization within the CMAR, with a set of eye, hand and tongue representations, was consistent with previous investigations (e.g. Luppino et al., 1991; Wang et al., 2004; Morecraft et al., 1996). In Monkey N, only the eye and tongue, but not hand motor representation were found in the CMAR cluster. In both monkeys, a second cluster of voxels that was located around -8mm from the arcuate genu showed matching connectivity profiles as the human RCZp seeds. In both monkeys, a face motor representation could be found in this cluster, suggesting that this could be the macaque CMAv region. While a full set of eye, tongue and hand representations was observed in Monkey L, only tongue and hand maps were found in Monkey N. However, in both monkeys, this cluster was situated in the dorsal rather than the ventral bank of the cingulate sulcus. Lastly, in both monkeys, a posterior-most cluster corresponding to the human CCZ was observed around -18mm caudal to the arcuate genu. This cluster contained two motor representations and could correspond to the macaque CMAAd. However, this position was too caudal than the expected location of CMAAd based on previous studies.

## Discussion

The present work aims to determine the location of the CMAs and their motor representations in the macaque brain via connectivity fingerprint matching with functionally-defined human CMA seeds. We first generated connectivity fingerprints corresponding to the connectivity of each CMA motor representation with a series of lateral prefrontal regions in the human brain. Subsequently, we searched voxel-wise in two individual macaque brains for regions showing matching connectivity profiles with the human CMA seeds.

The key contribution of this work is in showing that the macaque CMAr can be reliably identified from the human RCZa based on their connectivity profiles with the 7 frontal target areas. In both monkeys, connectivity profile matching with the human RCZa seeds successfully identified a cluster of significant voxels in an anterior part of the cingulate sulcus that likely corresponded to the macaque CMAr: This cluster was found at the hypothesized location of the CMAr (i.e. around +10mm anterior to the arcuate genu) based on previous work (e.g. Procyk et al., 2016) and contains the expected set of face and hand motor representations. However, as mentioned in the results section, the matching was still not optimized as there were voxels outside of the main cluster that significantly matched the connectivity profile of the RCZa seeds. Furthermore, in the case of monkey N, the voxels that best matched the RCZa seeds were actually situated nearer to the RCZp cluster (Fig 4). To reduce the likelihood of false positive findings, it is imperative to increase the sample size and also to conduct group-level analyses. Another possibility is to constrain our search area to just the anterior part of the cingulate sulcus rather than performing a whole-brain match.

Nevertheless, the technique has proved to be a promising approach of identifying the CMAr non-invasively. Moving forward, the same set of target regions can be potentially used to non-invasively identify the CMAr in other primate species.

In comparison with RCZa, the matching results with RCZp and CCZ seeds were less optimal. In both monkeys, the RCZp seeds showed matching connectivity profiles with a region situated at around -8 mm posterior to the arcuate genu, and contained the same somatopic organization as the macaque CMAv. However, contrary to the expected location of the CMAv, this matched region was located in the dorsal rather than the ventral bank of the sulcus. Despite sharing the same somatopic organization, the cluster that had a similar connectivity profile as the CCZ seeds was situated too caudal (-16 mm to the arcuate genu) from the expected location of the CMAv (-8 mm caudal to the arcuate genu). Why was the connectivity fingerprint matching better for the CMAr, and not the caudal CMAs? One possibility is that the target areas we selected for constructing the connectivity fingerprints were more suited for summarizing the connectivity of the CMAr rather than the caudal CMAs. Indeed, previous anatomical studies have shown that, relative to the caudal CMAs, the CMAr has more extensive connections with the prefrontal cortex (Dum & Strick, 1991; Hatanaka et al., 2003; He et al., 1995; Luppino, Matelli, Camarda, & Rizzolatti, 1993b; Morecraft et al., 2004; Petrides & Pandya, 2006). As such, since our selected target areas included mainly prefrontal areas, they were more appropriate in characterising the main connectivity of the CMAr, as compared to the more caudal CMAs, which are less connected with the prefrontal areas. In order to improve the matching of the caudal CMAs, one possible solution is to include a wider range of target areas that are known to be more well-connected with the CMAv and CMAr.

Finally, we discuss the practical challenges associated with the application of the connectivity fingerprint matching analyses on macaque resting-state data. Firstly, there is currently a lack of a well-established and optimized pipeline in the field for pre-processing macaque MRI data. While the main pre-processing steps remain generally the same, certain steps have to be customized for individual macaque images. For instance, in the current study, while skull-stripping can be efficiently performed in monkey L via an inflated mask created from the D99 template, skull-stripping in monkey N had to be accomplished via a manually edited mask after applying FSL's Brain Extraction Tool. The steps involved in the segmentation of the T1 images also differed between the two monkeys. For monkey L, optimized segmentation was achieved using just the mean T1 images, whereas for monkey N, optimal segmentation was achieved via a two-channel segmentation using both T1 and T2 images. This suggested that during the processing of macaque MRI data, the user has to make informed and flexible customizations on a case-by-case basis. Secondly, we also encountered difficulty in normalizing the two macaque brains onto a single template for group analyses. We had utilised the D99 macaque brain as the normalization template for monkey L and monkey N. While monkey L's brain could be successfully linearly transformed and non-linearly warped onto the D99 template, there were many problems with the normalizing monkey N's brain onto the template. This could be related to the fact that the D99 template was constructed from a single macaque brain. Moving forward, we intend to try a recently published population-based monkey brain template (NIMH Macaque Template; Seidlitz et al., 2018) that involved 31 monkeys for the normalization of our data.

## Conclusion

The connectivity fingerprint matching approach has allowed us to non-invasively identify the location of the CMAr in the macaque brain based on functionally-defined human RCZa seeds. This was largely attributed to the fact that the 7 frontal target areas (area 10, area 46, area 9/46, area 44, m1\_h, m1\_f and the FEF) were able to sufficiently capture the main connectivity of the RCZa/CMAr. To further improve the statistical power of the results, future work will involve increasing the sample size and also to decrease the search area in which the matching is performed. Given the successful matching of the macaque CMAr, it could be interesting to perform the matching, using the same set of target areas, to identify the location of the CMAr in other primate species such as the chimpanzee and baboons. This would enable us to perform comparative analyses of the CMAr regions across primate species. In comparison, the matching of the caudal CMAs was less ideal as more target regions from other parts of the brain are needed to adequately summarize the connectivity profile of these regions.

## Chapter 6 : General Discussion

The present dissertation is focused on revealing how the human frontal cortex is organized to support the learning and performance of conditional associations between arbitrary environmental stimuli and specific motor actions. This mechanism is fundamental for adapting our behaviours to environmental changes and is present also in non-human primates (NHPs). Distinguishing us from other NHPs, we are more able to flexibly adapt actions in the vocal modality, and also, to acquire and use more complex and abstracted rules to adapt our behaviours. These increased capacities to acquire and perform vocal conditional associations and to implement adaptive behavioural control via more abstract and complex rules might have contributed to the emergence of human vocal communicative abilities that require the higher-order flexible adaptation of vocal responses.

The above proposition was investigated via 3 main research questions: I first examined, in Chapter 2, how the human frontal cortex, in particular, the posterior lateral frontal cortex (pLFC) and the mid-cingulate cortex (MCC), are anatomically and functionally organized to acquire and execute multimodal visuo-motor conditional associations involving manual, orofacial and vocal actions. Next, I investigated, in Chapter 3, how the MCC is functionally coupled with the lateral frontal cortex to enable more abstracted levels of adaptive behavioural control. And finally, in Chapter 4, I reviewed existing literature about the neural correlates of vocal control in human and non-human primates to determine how might the pLFC-MCC network have changed between NHPs and humans to enable increased flexibility in adapting vocal behaviours?



## **Anatomo-functional organization in the human pLFC and MCC for the learning and performance of manual, orofacial and vocal conditional associations.**

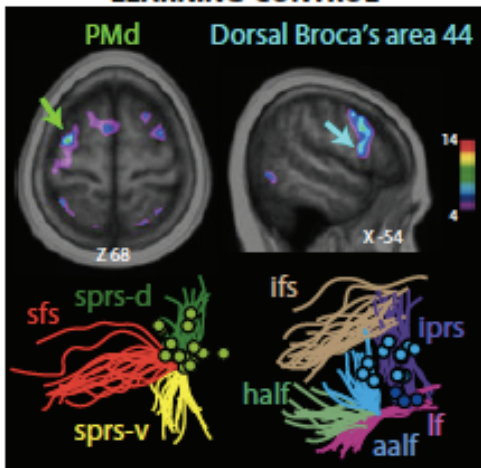
To investigate how the posterior lateral frontal cortex (pLFC) and the mid-cingulate cortex (MCC) are involved in the learning and performance of manual, orofacial and vocal conditional associations, three fMRI experiments were conducted where subjects performed three versions of a conditional associative learning task involving manual, vocal and orofacial responses. The conditional associative learning task involved a learning phase, where subjects had to discover via trial-and-error, correct pairings between three visual stimuli and motor responses, and a post-learning phase, where subjects performed the learnt conditional responses.

The first key finding from this investigation was in revealing a dorso-ventral functional organization in the pLFC for the conditional selection of hand, orofacial and vocal/verbal responses (Fig 1): The selection between competing hand actions during both learning and post-learning recruited the posterior part of the rostral PMd (pPMdr) in the dorsal pLFC showing a dissociation from manual selections, vocal and verbal selections recruited area 44 in the ventral pLFC. These results were generally consistent with previous work: The pPMdr has been consistently implicated in the conditional selection of hand responses in both macaque (Petrides, 1982) and human studies (Amiez et al., 2006; Amiez & Petrides, 2018; Amiez, Hadj-Bouziane, & Petrides, 2012a). Area 44 is suggested to be involved in vocal and orofacial control in both humans and macaques (Loh, Petrides, Hopkins, Procyk, & Amiez, 2017b) and has a connectivity profile indicative of a role in the higher-order sensorimotor control over

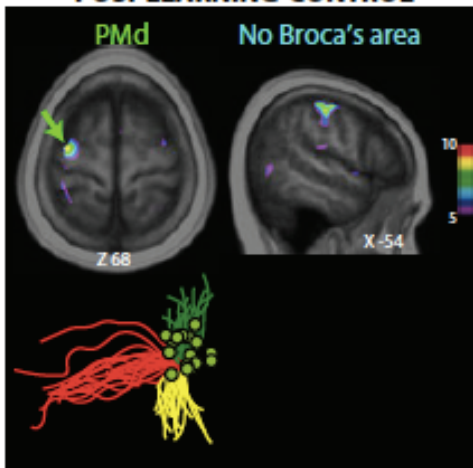
orofacial and vocal responses (Petrides, 2006). Intriguingly, the conditional selection of orofacial responses recruited also the pPMDr along with area 44. As discussed in Chapter 2, existing findings in both monkeys and humans have revealed the presence of facial motor control in the dorsal premotor area (Godschalk et al., 1995; Grabski et al., 2012; Morecraft et al., 2001; e.g. Preuss et al., 1996). However, these studies generally agree that orofacial motor control is diffusely spread along the dorsal-ventral axis of the lateral premotor cortex and more consistently associated with the ventral than the dorsal part of the lateral premotor cortex. Since orofacial motor control is diffusely organized in the dorsal and ventral parts of the precentral gyrus, it is thus conceivable that the adaptive selection of orofacial responses would simultaneously involve the pPMdr and area 44.

**A. MANUAL SELECTION**

**LEARNING-CONTROL**

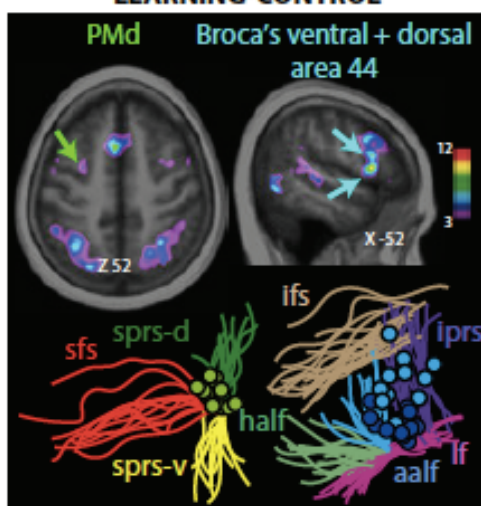


**POST-LEARNING-CONTROL**

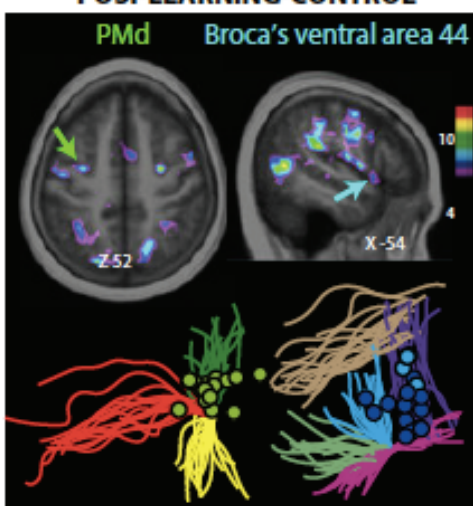


**B. OROFACIAL SELECTION**

**LEARNING-CONTROL**

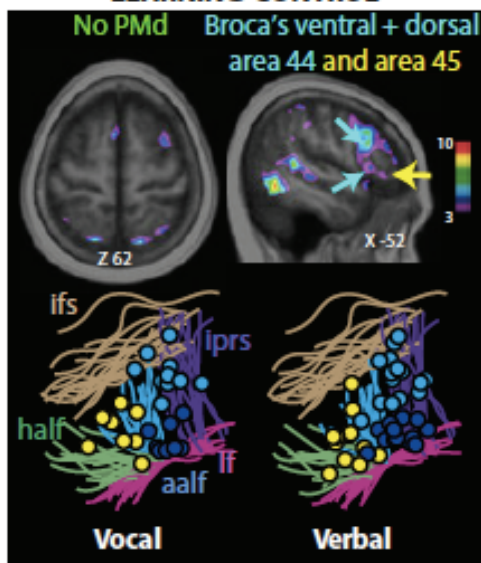


**POST-LEARNING-CONTROL**

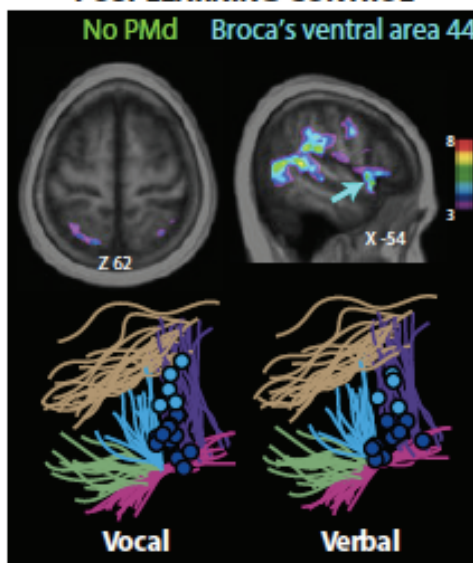


**C. VOCAL/VERBAL SELECTION**

**LEARNING-CONTROL**

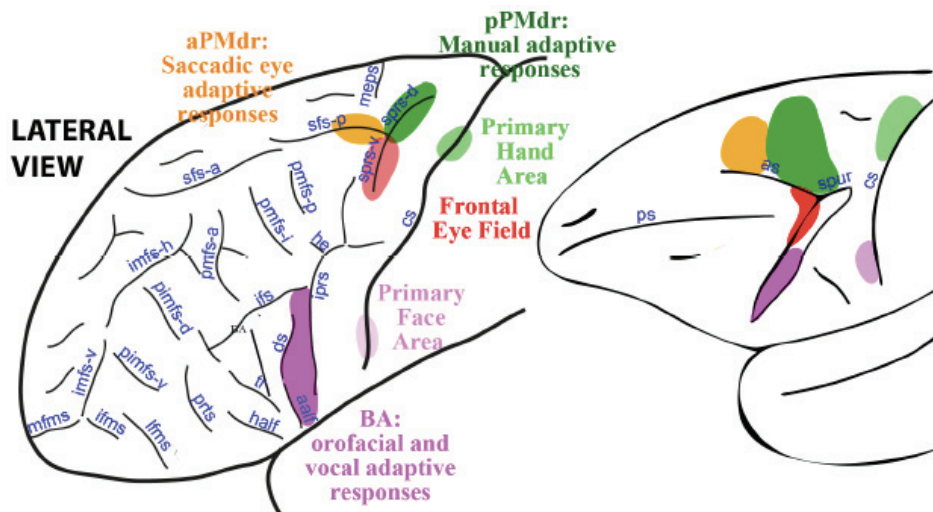


**POST-LEARNING-CONTROL**



**Figure 1. Conditional response selection in the posterior lateral prefrontal cortex.** Group (above) and individual activations (below) shown as dots around relevant sulci during **(A)** manual response selection in the learning and post-learning periods, **(B)** during orofacial response selection in the learning and post-learning periods, **(C)** during vocal and verbal response selection in the learning and post-learning periods. Green circles depict individual PMd activations for manual and orofacial response selection during learning and post-learning respectively. Light and dark blue circles depict individual dorsal and ventral area 44 activations and yellow circles depict area 45 activity during response selection. Abbreviations: cs, central sulcus, sprs-d, dorsal superior precentral sulcus, sprs-v, ventral superior precentral sulcus, sfs, superior frontal sulcus, ifs, inferior frontal sulcus, iprs, inferior precentral sulcus, as, ascending sulcus, hs, horizontal sulcus, lf, lateral fissure.

These findings, coupled with recent findings by Amiez and colleague (2006; Amiez & Petrides, 2018), provided support for the existence of a rostro-caudal gradient in the posterior lateral frontal cortex (Fig. 2), where the more rostral and dysgranular part is involved in conditional visuomotor operations on the motor actions executed by the immediately caudal and agranular premotor/motor cortex. Indeed, Amiez and Petrides (2018) have recently shown that the functional activations associated with conditional hand and saccadic action selections are situated immediately anterior to the regions involved in basic hand and saccadic control respectively. Along the same vein, the present results showed that the selection of vocal and orofacial actions recruited area 44, which is directly anterior to the orofacial and vocal motor representation in the ventral premotor/motor cortex. These results demonstrate that my thesis hypothesis (see also Loh, Petrides, Hopkins, Procyk, & Amiez, 2017b) is validated.

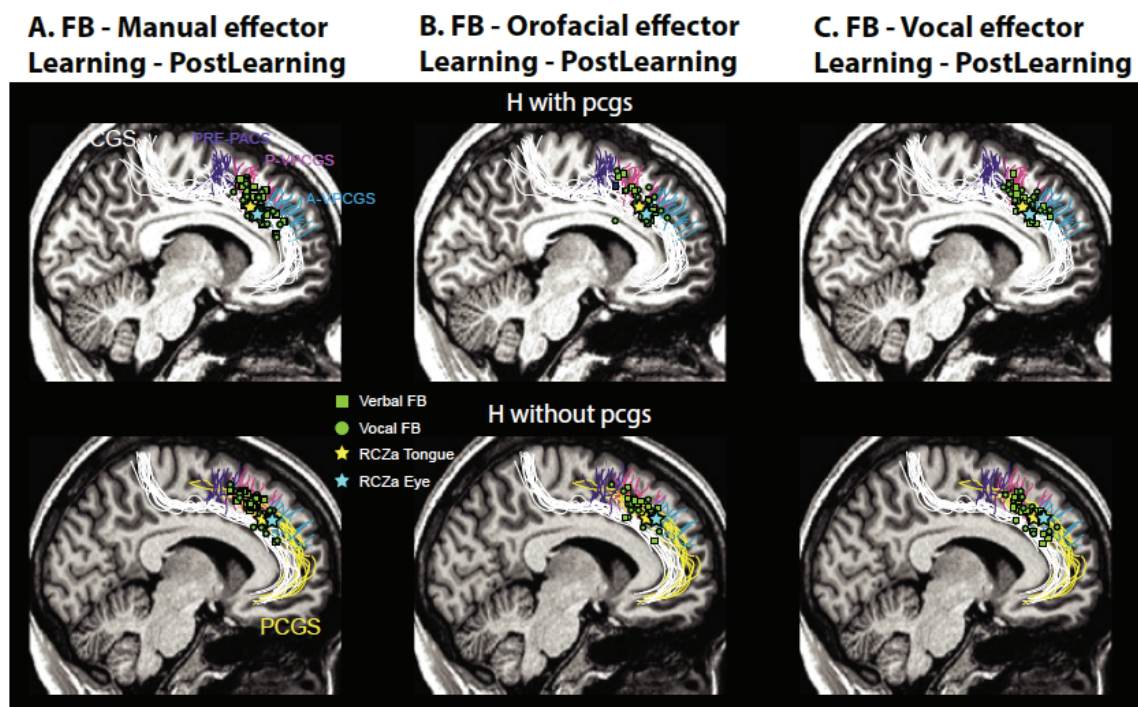


**Figure 2. Rostro-caudal organization in the posterior lateral frontal cortex.**

Another critical contribution of this work is in revealing that the various pLFC regions involved in the conditional selection of manual, vocal and orofacial actions can be precisely localised based on individual sulci anatomy. While manual selections reliably activate the dorsal branch of the superior precentral sulcus, orofacial and vocal selection-related activations are reliably located in the pars opercularis area bounded by the inferior frontal sulcus, lateral sulcus, ascending sulcus and inferior precentral sulcus. Together, these findings indicate that the rostro-caudal organization in the human pLFC for the conditional selection and basic execution of motor actions can be identified on the basis of individual sulcal anatomy.

A second key finding of this study was that the same anterior MCC region was found to be involved in the evaluation of auditory feedback during the trial-and-error learning of visuo-manual, vocal and orofacial conditional associations (Fig. 3). This suggested that the feedback-related activity observed in the anterior MCC was not specific to the modality of the adaptive behavioural response but to the modality of the feedback. Individual subject analyses further revealed that the feedback-related activity was

found in the ‘face’ motor representation in the RCZa (Fig. 3). This finding was consistent with Procyk et al. (2016)’s hypothesis that the monitoring of action outcomes in the anterior MCC was embodied in the various somatotopic representations in the RCZa that is associated with the modality of the feedback. Critically, as with the pLFC, the feedback-related activations in the anterior MCC could be reliably localised on the basis of individual anatomy: when a para-cingulate sulcus (pcgs) is present, the peak activity is always localised at the intersection between the pcgs and the vertical paracingulate gyrus (vpcgs), otherwise, the activity is located at the intersection between the cgs and vpcgs.



**Figure 3. Auditory vocal/verbal feedback processing during learning visuo-motor conditional associations in relation to the anterior cingulate motor area.** **A.** Comparison between the BOLD signal at the occurrence of verbal (squares) and vocal (circles) feedback during learning visuo-manual conditional associations versus during visuo-manual control trials in individual subjects (each square/circle represent the location of increased activity of one subject) and in hemispheres displaying both a cingulate sulcus (cgs) and a paracingulate sulcus (pcgs, top diagrams) and in hemispheres without a pcgs (bottom diagrams). **B.** Identical as A but increased activities are based on the comparison between the BOLD signal at the occurrence of feedback during learning visuo-orofacial conditional associations versus during visuo-orofacial control trials. **C.** Identical as A and B but increased activities are based on the comparison between the BOLD signal at the occurrence of feedback during

learning visuo-vocal/verbal conditional associations versus during visuo-verbal/vocal control trials. Yellow and blue stars represent average locations of the tongue and eye motor representations in the RCZa that were derived from a motor mapping task in Loh et al. 2018. Abbreviations: cs, cingulate sulcus; pcgs, paracingulate sulcus; pre-pacs, pre-paracentral sulcus; a/p-vpcgs, anterior/posterior vertical paracingulate sulcus.

Together, this study has revealed the anatomo-functional organization in the human pLFC and MCC in the learning and execution of conditional visuo-hand, vocal and orofacial associations. Importantly, this organization can be precisely localised in individual brains based on sulcal morphology. The knowledge of sulcal-functional relationships has important practical applications in neurosurgery as surgeons would be able to quickly localise critical brain regions based on a visual inspection of the sulci patterning (Tomaiuolo & Giordano, 2016). Secondly, the organization in the human pLFC and MCC for conditional visuo-hand, vocal and orofacial associations appear to be highly conserved across macaques and humans. With regards to the pLFC, previous work has revealed that the dorsal part of the macaque pLFC (peri-superior arcuate region) was critical in the learning and performance of visuo-hand conditional associations (Petrides, 1982), while area 44 in the macaque had also been implicated in cognitive vocal and orofacial control (Loh, Petrides, Hopkins, Procyk, & Amiez, 2017b). With regards to the MCC, the macaque CMAr shares the same somatopic organization as the human RCZa (Amiez & Petrides, 2014), and has also been proposed to be involved the evaluation of adaptive feedback in an embodied manner (Procyk et al., 2016). Having established a common ground in the human and macaque pLFC-MCC for the learning and performance of visuo-motor conditional associations, future work can seek to explore how this brain network might differ across primates, in terms of structural (i.e. relative cortical sizes, anatomical

connectivity) and functional properties, to enable the more complex adaptive abilities present in humans.

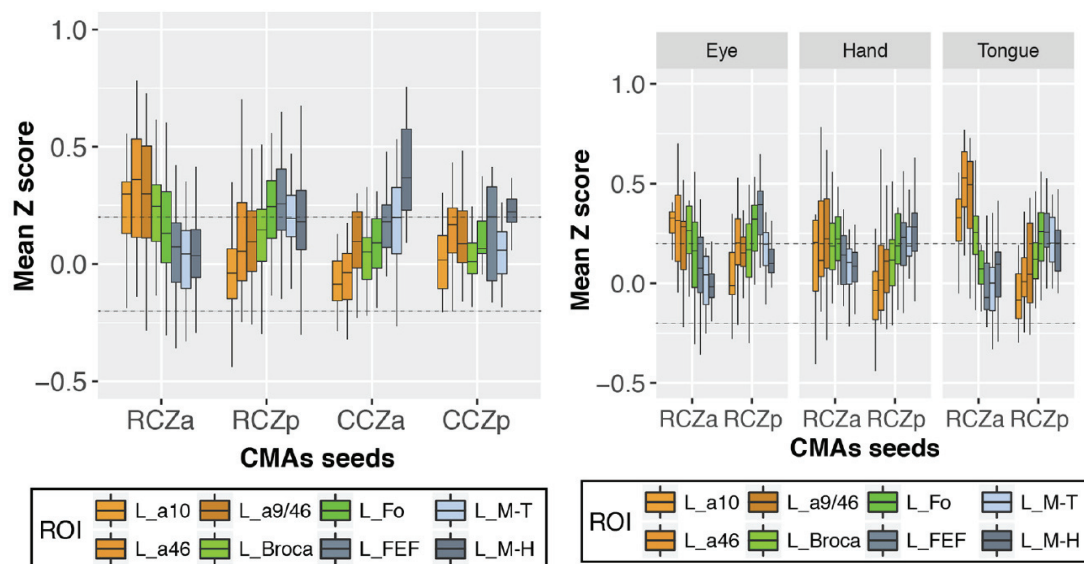
### **Rostro-caudal functional coupling between the human lateral frontal cortex and CMAs**

In Chapter 3, we investigated the functional connectivity between each motor representation in the 3 human cingulate motor areas with rostral-caudal regions on the lateral frontal cortex. The main aim of this work was to investigate if the cingulate motor areas exhibited the same rostro-caudal functional organization as the lateral frontal cortex, where increasingly rostral/caudal areas are more involved in higher-order cognitive/basic motor control over behaviours. A fMRI motor-mapping task (identical to that in Amiez & Petrides, 2014) was first employed to localize the various motor representations in the cingulate motor areas in individual subjects. The various lateral frontal cortical seeds were also identified in each subject based on individual anatomy. Finally, correlations in resting-state BOLD activity were computed between each CMA seed with each lateral frontal cortical seed in individual subjects.

The primary result was that the 3 human CMA seeds are functionally coupled with the lateral frontal cortex along a rostral-caudal axis: while the rostral-most RCZa is more strongly connected with more rostral lateral frontal regions, the posterior CMAs (RCZp, CCZ) are more strongly connected with more caudal lateral frontal regions (Fig. 3, left panel). Notably, the individual motor representations associated with each CMA showed a consistent pattern of connectivity with the parent CMA (Fig. 3, right panel). Our findings was consistent with previous human studies that revealed that the



anterior and posterior CMAs are more strongly connected with frontal and motor brain regions respectively (M. Beckmann et al., 2009; Habas, 2010). Importantly, the same rostro-caudal organization was observed with the macaque CMAs. In the macaque, more rostral/caudal CMAs have stronger anatomical connectivity with the prefrontal and motor cortex respectively (J. F. Bates & Goldman-Rakic, 1993; Dum & Strick, 1993; He et al., 1995; Y. Wang et al., 2001; 2004). Showing a functional dissociation between rostral and caudal CMAs in higher-order cognitive and motor control functions, electrical stimulations evoke motor movements more reliably in more caudal CMAs (Morecraft & Tanji, 2009), while the anterior-most CMAr is often implicated in performance monitoring functions (Procyk et al., 2016). As such, this suggested a strong homology between the functional organization of the human and macaque CMAs.

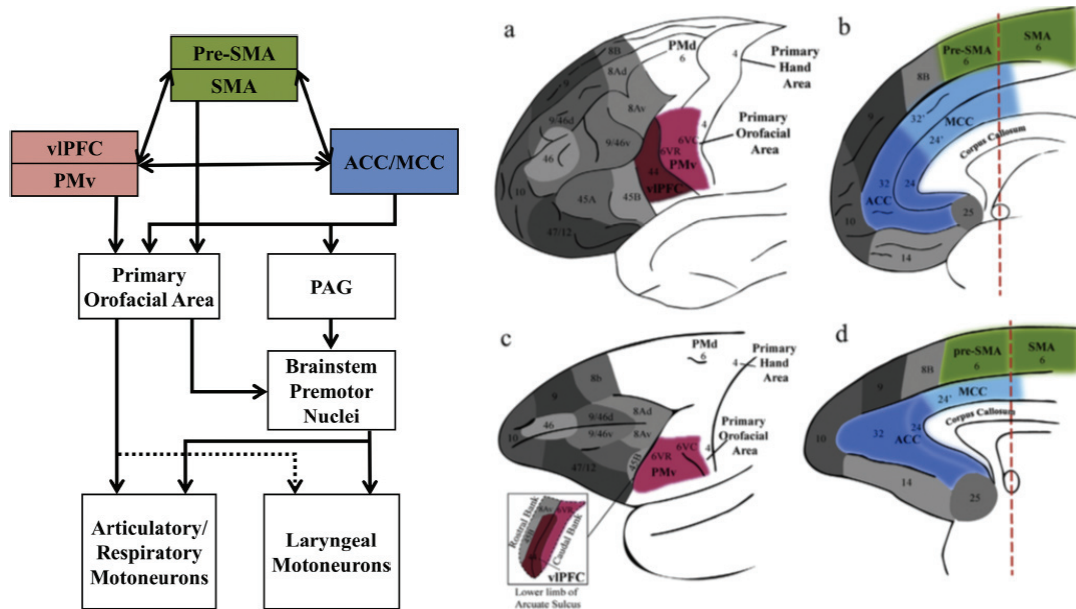


**Figure 3.** Left panel: Left-hemispheric connectivity between CMA regions with lateral frontal regions. Right panel: Left-hemispheric connectivity between RCZa, RCZp with lateral frontal regions for each motor representation.

How does the present results contribute to the current understanding about the organization of lateral-medial frontal interactions during behavioural control? Current

models about the functional organization of the frontal cortex generally agree that lateral and medial frontal regions functionally interact along a caudal-to-rostral axis to exert increasingly levels of behavioural control (Domenech & Koechlin, 2015; Kouneiher et al., 2009). Kouneiher and colleagues (2009) demonstrated that posterior-to-anterior medial frontal regions contribute to the processing of increasingly abstract motivational information to drive increasingly abstract levels of cognitive control along the lateral frontal cortex. Domenech and Koechlin (2015) proposed that the lateral and medial prefrontal regions constitute two parallel tracks that are involved between exploiting or adjusting previously learnt behavioural sets versus exploring or creating new ones. Notably, in both models, the MCC is considered a single entity that participated in a specific level of behavioural control. In Kouneiher et al.'s model, the MCC is proposed to directly influence the mid-DLPFC region during the processing of a higher-order cue, as opposed to the immediately caudal pre-SMA having an influence on the pLFC for processing a lower-order cue. In Domenech and Koechlin's model, the MCC is also engaged at a specific level of cognitive control - the monitoring of current task sets for switching towards exploration and creating new task sets, as opposed to the more anterior VMPFC which is involved in assessing the reliability of the current task set. Our current findings have revealed that within the MCC itself, anterior and posterior regions exhibit differential connectivity with the rostral and caudal lateral frontal areas. This suggested that the anterior and posterior MCC could be participating in different levels of behavioural control with the various lateral frontal cortical regions. Future work should seek to clarify the differential functional interaction of the 3 CMAs with the lateral cortex during behavioural control.

How might the area 44-MCC network have changed from NHPs to humans to enable increased flexibility in adapting vocal behaviours?



**Figure 4. Left panel: Summary of connections between vocal control brain regions in human and non-human primates.** The dotted arrow refers to a connection that exist uniquely in humans. Right panel: Ventrolateral and dorsomedial prefrontal regions that are involved in cognitive vocal control in humans (a,b) and macaques (c,d).

Reviewing existing literature about the neural correlates of vocal control in human and non-human primate (NHP) species in Chapter 4, we have shown that a common frontal brain network including area 44 and the anterior MCC are involved in the top-down control of vocalizations across primates via distinct neural pathways (Fig. 4, left panel): While area 44, and its associated ventral premotor area and primary orofacial area, is implicated in the volitional control over the various articulatory and laryngeal musculature for the production of species-atypical and acquired vocalizations, the MCC is often associated with the control of species-typical and emotional vocal patterns. Given that both regions are anatomically homologous and have similar roles in vocal motor control in human and NHPs, we further argue that they could also

perform similar cognitive operations on vocal actions across primates (Fig. 4, right panel). In particular, we postulated that area 44 is involved in conditional operations on vocal/orofacial actions, while the MCC is involved in the evaluation of action outcomes and feedback for adapting vocal/orofacial behaviours. This hypothesis was based on the current theories about functions of the primate pLFC (Petrides, 2005) and MCC (Procyk et al., 2016) in cognitive control. Through our findings in Chapter 2, this hypothesis was confirmed in humans: while area 44 is implicated in the conditional selection of vocal and orofacial actions, the ‘face’ representation in the RCZa (anterior MCC) is involved in evaluating auditory feedback for adapting vocal/orofacial behaviours.

An important next step in this work is to establish the same functions in the macaque area 44 and MCC. To do so, we had endeavoured to prepare and train macaque monkeys to perform the same conditional learning paradigm in the fMRI scanner. However, this was challenging to achieve within the course of my doctoral training. As such, we opted to establish functional homologies between the human and macaque area 44-MCC network via an indirect methodology – the connectivity profile matching method (Mars et al., 2016). The main goal is to match the task-related activations in the area 44 and MCC from our human experiment onto the macaque brain via connectivity profile matching. This would allow us to identify the macaque brain areas that are associated with the same connectivity profile (which implies that they can perform the similar functions) as the task-relevant human area 44 and MCC regions. In chapter 5, we have provided preliminary results showing that this method was promising in identifying the rostral CMA in the macaque via the human RCZa.

If this area 44-MCC network and its role in cognitive vocal control is largely conserved across primates, how might we account for the greatly expanded capacity in humans to flexibly generate and use novel vocal patterns? A critical difference between human and NHPs is that only the human primary orofacial area has direct corticobulbar projections to both the orofacial and laryngeal motor nuclei (Kuypers, 1958a) (Fig. 4 left panel). These projections could have afforded the increased fine-motor control over both orofacial and laryngeal movements that is required for the generation of novel vocal patterns (Simonyan, 2014). As such, in humans, area 44, via the ventral premotor area, would be able to exercise conditional sensory-vocal associations over a wider range of oro-laryngeal constructions. The MCC, which is directly connected to the ventral premotor area, would also be able to drive oro-laryngeal adaptations at the fine motor level. This could explain the expanded capacity in human to flexibly generate and modify our vocal patterns. In contrast, the primary orofacial area in NHPs only has access to fine motor control over orofacial musculature and not the larynx (Kuypers, 1958b). As such, NHPs are capable of adaptively modifying orofacial but not vocal movements. Indeed, macaques are able to perform orofacial imitations (Ferrari et al., 2006), and great apes are capable of novel species-atypical sounds such as “raspberries” and whistling that largely involve articulatory modulations (Hopkins et al., 2007; Wich et al., 2009). For vocalizations, NHPs remain largely restricted to the context-dependent production and modifications of innate vocal patterns that are generated via the cingulate vocalization pathway (Jürgens, 2002). Another critical factor that could have contributed to increased vocal flexibility in humans is that frontopolar area 10 appears to be more expanded in humans as compared to NHPs (Neubert et al., 2014; Ongür et al., 2003). As reviewed earlier, this area appears to be involved in the highest level of behavioural control in the primate

prefrontal cortex and, in particular, has been implicated in the ability to arbitrate between alternative courses of actions and allocating the cognitive resources as necessary (Mansouri et al., 2017b). As such, an expanded area 10 could have contributed to increased high-level executive control over the human area 44-MCC network to enable increased flexible vocal control. A last possible factor is that the SMA is recruited for speech production in humans (Alario et al., 2006; Chapados & Petrides, 2013), but not in monkey vocalizations (Kirzinger & Jürgens, 1982; Mitz & Wise, 1987). As discussed in Chapter 4, the SMA is associated with the sequencing of motor actions and could be vital in the sequencing of vocal/orofacial movements into novel vocal patterns via the human primary orofacial area, which has direct access to laryngeal and orofacial control. The reduced role of the SMA in vocal control in NHPs could be related to the fact that there is reduced access to laryngeal motor control via the primary orofacial area. Indeed, stimulations in the human, but not macaque SMA, result in vocal productions (Mitz & Wise, 1987; Penfield & Welch, 1951). A comparative investigation of the connectivity associated with the human and NHP area 44-MCC network with the SMA, area 10 and primary motor cortex is essential to empirically confirm the above potential explanations about how might the vocal control network changed from NHP to humans to enable modern human speech.

## **Conclusions and Future Perspectives**

The current thesis has provided important insights about how the human frontal cortex, in particular, the posterior lateral frontal cortex and the mid-cingulate cortex, is organized to enable the learning and performance of conditional associations involving manual, vocal and orofacial responses based on auditory feedback. Firstly, consistent

with existing theories, we demonstrated 1) a dorsal-ventral organization in the dysgranular caudal prefrontal area for the conditional selection of hand and vocal/orofacial actions, and 2) a rostral-caudal organization in the posterior lateral frontal cortex where more rostral regions are involved in higher-order conditional operations over motor actions, while caudal regions are involved in basic motor execution. Additionally, providing support for the theory of embodied adaptive feedback processing in the anterior CMA, we showed that adaptive auditory feedback processing is localised in the 'face' representation of the RCZa. Lastly, we also revealed a rostral-caudal organization in the three human CMAs, where more anterior/posterior CMAs are more strongly connected with the rostral/caudal lateral prefrontal areas. This suggested that the CMAs and the lateral frontal cortex could functionally interact along a caudal-rostral axis to enable increasing levels of behavioural control. Importantly, all the functional activations associated with the above findings can be precisely located in individual brains based on local sulcal morphology.

An important follow-up to this work is to investigate whether the above sulcal-based anatomo-functional organization in the pLFC and MCC is preserved across other primate species. We have shown in chapter 5 that the connectivity profile matching technique could be used to locate the same functional brain region across different species. As such, with the same technique, we could potentially identify the corresponding brain regions in other primate species based on the human functional activations and further determine if the same organization principles exist in the other primate species. We could also verify if the same sulcal-functional relationships exist in the other primate species.

Secondly, this thesis also revealed how the human pLFC-MCC network is involved in the adaptive control of vocal responses. Specifically, we showed that area 44 is involved in the conditional selection of orofacial and vocal actions, while the anterior MCC is involved in monitoring the behavioural outcomes to adapt orofacial and vocal behaviours. Based on a review in Chapter 5, we proposed that the above role of the area 44-MCC network in cognitive vocal control could be common across primates. An important follow-up to this work is to confirm if our proposed role of the area 44-MCC network is common in other primate species. Given the challenges involved in training NHPs on the same experimental paradigm, a promising approach would be to match the human area 44-MCC regions, that has been localised via our experimental task, to the NHP brains based on the connectivity profile matching approach (Mars et al., 2016). After locating the functionally homologous area 44-MCC regions in the NHP brains, we can further investigate the differences or similarities between the human and NHP area 44-MCC regions.



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