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Motor and emotional behaviours elicited by electrical stimulation of the human cingulate cortex

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The cingulate cortex is a mosaic of different anatomical fields, whose functional characterization is still a matter of debate. In humans, one method that may provide useful insights on the role of the different cingulate regions, and to tackle the issue of the functional differences between its anterior, middle and posterior subsectors, is intracortical electrical stimulation. While previous reports showed that a variety of integrated behaviours could be elicited by stimulating the midcingulate cortex, little is known about the effects of the electrical stimulation of anterior and posterior cingulate regions. Moreover, the internal arrangement of different behaviours within the midcingulate cortex is still unknown. In the present study, we extended previous stimulation studies by retrospectively analysing all the clinical manifestations induced by intracerebral high frequency electrical stimulation (50 Hz, pulse width: 1 ms, 5 s, current intensity: average intensity of 2.7 ± 0.7 mA, biphasic) of the entire cingulate cortex in a cohort of 329 drug-resistant epileptic patients (1789 stimulation sites) undergoing stereo-electroencephalography for a presurgical evaluation. The large number of patients, on one hand, and the accurate multimodal image-based localization of stereo-electroencephalography electrodes, on the other hand, allowed us to assign specific functional properties to modern anatomical subdivisions of the cingulate cortex. Behavioural or subjective responses were elicited from the 32.3% of all cingulate sites, mainly located in the pregenual and midcingulate regions. We found clear functional differences between the pregenual part of the cingulate cortex, hosting the majority of emotional, interoceptive and autonomic responses, and the anterior midcingulate sector, controlling the majority of all complex motor behaviours. Particularly interesting was the 'actotopic' organization of the anterior midcingulate sector, arranged along the ventro-dorsal axis: (i) whole-body behaviours directed to the extra-personal space, such as getting-up impulses, were elicited ventrally, close to the corpus callosum; (ii) hand actions in the peripersonal space were evoked by the stimulation of the intermediate position; and (iii) body-directed actions were induced by the stimulation of the dorsal branch of the cingulate sulcus. The caudal part of the midcingulate cortex and the posterior cingulate cortex were, in contrast, poorly excitable, and mainly devoted to sensory modalities. In particular, the caudal part of the midcingulate cortex hosted the majority of vestibular responses, while posterior cingulate cortex was the principal recipient of visual effects. We will discuss our data in the light of current controversies on the role of the cingulate cortex in cognition and emotion.

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Abbreviations: (p/s)ACC = (pregenual/subgenual) anterior cingulate cortex; (a/p)MCC = (anterior/posterior) midcingulate cortex; (d/v)PCC = (dorsal/ventral) posterior cingulate cortex; SEEG = stereo-electroencephalography

Introduction

It is widely acknowledged that the cingulate cortex is a mosaic of many different anatomical fields, whose functional characterization is still a matter of debate. The cingulate architecture was originally subdivided by Brodmann in a rostral, agranular, region and caudal, granular/dysgranular, one. Subsequent architectonical studies suggested that this parcellation is too coarse, suggesting that the cingulate region can be subdivided in at least three main sectors: the anterior, the mid and the posterior cingulate cortices, named ACC, MCC and PCC, respectively.

Although ACC and MCC are both agranular cortices, anatomical data suggest that these two regions are separated units (Vogt, 2016), each of them including further anatomical subdivisions. There is general agreement that both ACC and MCC are subdivided in two anatomically distinct subsectors. The ACC is composed of a ventral (subgenual) and a dorsal (pregenual) sectors, referred to as sACC and pACC (Palomero-Gallagher *et al.*, 2008, 2015). MCC is partitioned into an anterior and a posterior field (aMCC and pMCC), based on cytoarchitectonics, myelinization and immunohistochemistry (Vogt *et al.*, 2003; Palomero-Gallagher *et al.*, 2009; Glasser and Van Essen, 2011) (Fig. 1). Finally, a similar subdivision has been suggested for the PCC, often subdivided into dorsal (dPCC) and ventral (vPCC) sectors (Vogt *et al.*, 2006).

In contrast to the exhaustive picture of the anatomical organization, the functional role of each cingulate region is less straightforward. The role of the ACC in affect is rather established, with the pACC playing a major role in positive affect and the sACC being involved in negative ones (Vogt, 2005). In contrast, the functional role of the MCC is still controversial. Procyk *et al.* (2016) reported a large number of MCC functions, ranging from feedback processing, to pain, salience, action-reward association, premotor functions, and conflict monitoring (Ingvar, 1999; Bush *et al.*, 2000; Davis *et al.*, 2000, 2005; Kerns *et al.*, 2004; Vogt, 2005; Botvinick, 2007; Seeley *et al.*, 2007; Rushworth, 2008; Shackman *et al.*, 2011; Hoffstaedter *et al.*, 2013; Ide *et al.*, 2013; Menon, 2015). Given their heterogeneity, the specific contribution of MCC to these functions represents a long-lasting and yet unsettled issue. Furthermore, a clear picture of the functional differences of MCC sectors, aMCC and pMCC, is not yet available. As far as the posterior most part of the cingulate (PCC) is concerned, this region is considered to be involved in visuospatial and memory functions, with little or no involvement in affect and motor functions.

One method that may provide useful conceptual and clinical insights on the role of the different parts of the cingulate cortex is intracortical electrical stimulation in humans. This technique is often adopted in candidates for surgical treatment of epilepsy. In fact, stimulations performed by means of intracerebral electrodes may provide information helpful not only to the definition of the epileptogenic zone, but also to the investigation of normal cortical functions when stimulated leads are seated in healthy cortex. Such studies are, however, rather rare and, as far as the cingulate cortex is concerned, the available literature reports only few data (Escobedo *et al.*, 1973; Meyer *et al.*, 1973; Talairach *et al.*, 1973; Kremer *et al.*, 2001; Chassagnon *et al.*, 2008; Parvizi *et al.*, 2013). Among these, the most interesting and detailed study is the classical one by Talairach *et al.* (1973), which describes a large number of highly integrated types of motor behaviours elicited from the cingulate gyrus. Although this paper remains fundamental as far as the description of the cingulate motor behaviours is concerned, the detailed localization of these behaviours remains largely undescribed. In addition, this investigation was limited to the midcingulate cortex, and performed during acute experiments by means of high voltages (range 2–15 V) and large electrodes (2.4 mm in diameter). More recently, an investigation on the effects of the stimulation of the cingulate cortex was carried out by Caruana *et al.* (2015), but this study was focused only on laughter production, which was mainly elicited from the pACC.

The aim of the present study was to investigate the functional properties of the entire cingulate cortex by analysing the effect of high frequency electrical stimulation applied to 1789 cingulate sites, in 329 patients. The large number of patients, on one hand, and the accurate multimodal image-based localization of stereo-electroencephalography (SEEG) electrodes, on the other hand, allowed us to provide a complete map of the specific contributions of each cingulate region to behavioural, affective and sensory functions and, most important, to describe the inner distribution of different behavioural and affective responses within the cingulate regions.

Materials and methods

Patients

In this study, we reviewed the effect of high frequency electrical stimulations on the entire cingulate cortex performed on patients who underwent SEEG for refractory focal epilepsy between May 1996 and December 2016, at the 'Claudio Munari' Epilepsy Surgery Centre of Niguarda Hospital, Milan (Italy). We retrospectively reviewed anatomo-electro-clinical data of 645 patients to assess patient eligibility.

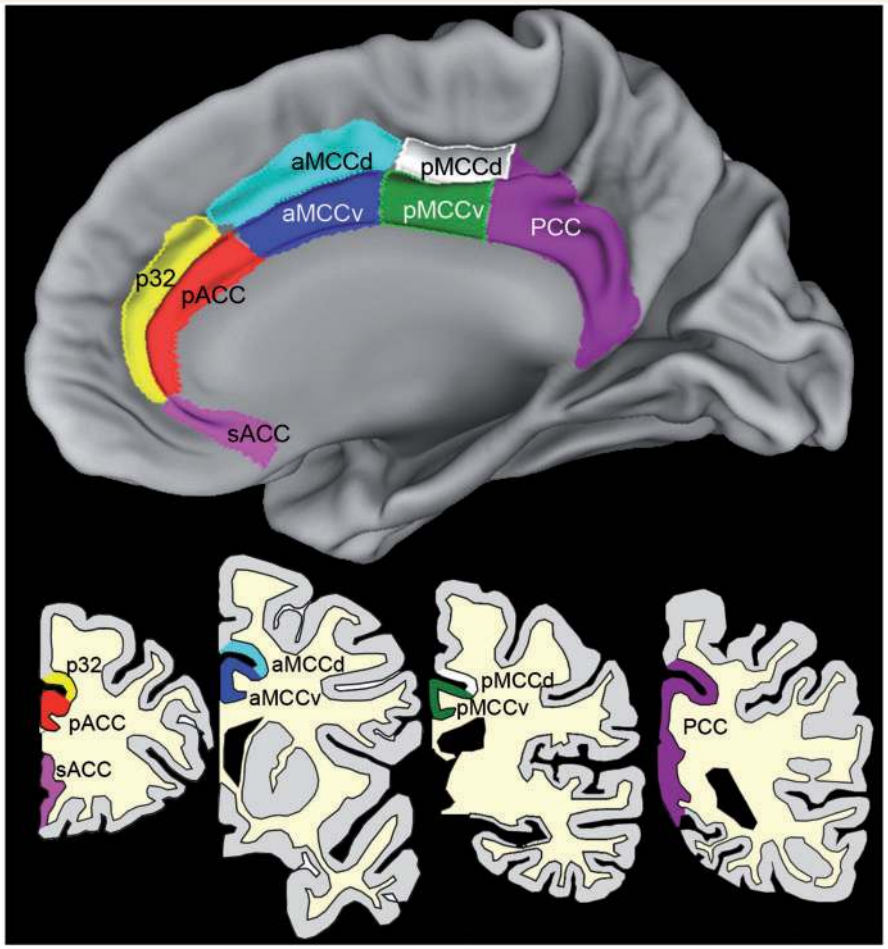

Figure 1 Anatomical boarders of the cingulate cortex. The *top* panel shows eight cingulate sectors in a mesial view of the fs_LR brain template, using Caret software. The *bottom* panel shows the same subdivision in four representative coronal sections. Anatomical boarders of the cingulate cortex were adapted from the following anatomical studies: the subgenual sector of ACC (sACC) includes area 25, s24 and s32 from Palomero-Gallagher *et al.* (2015). The pregenual ACC (pACC) and pregenual area 32 (p32) are from Palomero-Gallagher *et al.* (2008). The rostro-caudal subdivision of MCC in anterior and posterior sectors (aMCC and pMCC) was derived from Vogt *et al.* (2003), Vogt (2005) and Palomero-Gallagher *et al.* (2009). In addition, following Palomero Gallagher *et al.* (2009), both aMCC and pMCC were further subdivided in dorsal (aMCCd and pMCCd) and ventral (aMCCv and pMCCv) sectors, corresponding to their areas 24c'd and 24c'v. Finally, PCC was retrieved from Vogt *et al.* (2003) and Leech and Sharp (2014).

Inclusion criteria were the following: (i) availability of clear-cut anatomical-clinical data; and (ii) location of at least one lead in the cingulate cortex. An epileptogenic zone including the cingulate cortex was considered as an exclusion criterion. Data were gathered from 1789 stimulation sites (left, $n = 759$; right, $n = 1030$), collected over 329 patients (348 hemispheres: left = 149; right = 199) (Fig. 2A and Supplementary Fig. 1A). The number of stimulation sites for each patient ranged from 1 to 10 but the majority of patients contributed with one/two stimulation sites (Supplementary Fig. 2). Each of the subregions of the cingulate cortex was sampled in at least 10 different patients (Fig. 2B). All stimulations eliciting electrical post-discharge in cerebral structures potentially responsible for the observed clinical responses were discarded.

The topographic strategy of implantations was based on hypotheses about the epileptogenic zone, arising from clinical history and examination, non-invasive long-term video-EEG monitoring, and neuroimaging (Munari *et al.*, 1994; Cossu *et al.*, 2005). The stereotaxic planning of electrode trajectories has been based on patient-specific multimodal images for all subjects (Cardinale *et al.*, 2013). The SEEG-dedicated electrodes are 0.8 mm in diameter, including 5–18 leads 2 mm in length, 1.5 mm apart (Dixi or Alcis). Electrodes were implanted only for clinical purposes. All details on the (i) planning of electrodes trajectories; (ii) electrodes implantation; and (iii) electrodes localization are provided in the Supplementary material. The procedures for merging multi-patients' data on a brain template (Fs-LR-average) are fully in line with Avanzini *et al.* (2016).

After the recordings of spontaneous seizures, high frequency stimulations (50 Hz, pulse width: 1 ms, duration: 5 s; biphasic) were performed through the electrodes in many cerebral structures, aimed at both inducing seizures and brain mapping, in line with previous work from our group (Caruana *et al.*, 2015, 2016, 2017*a*). Stimulations were usually (>70%) performed with at 3 mA, current intensity ranging from 0.4 mA to 5 mA,

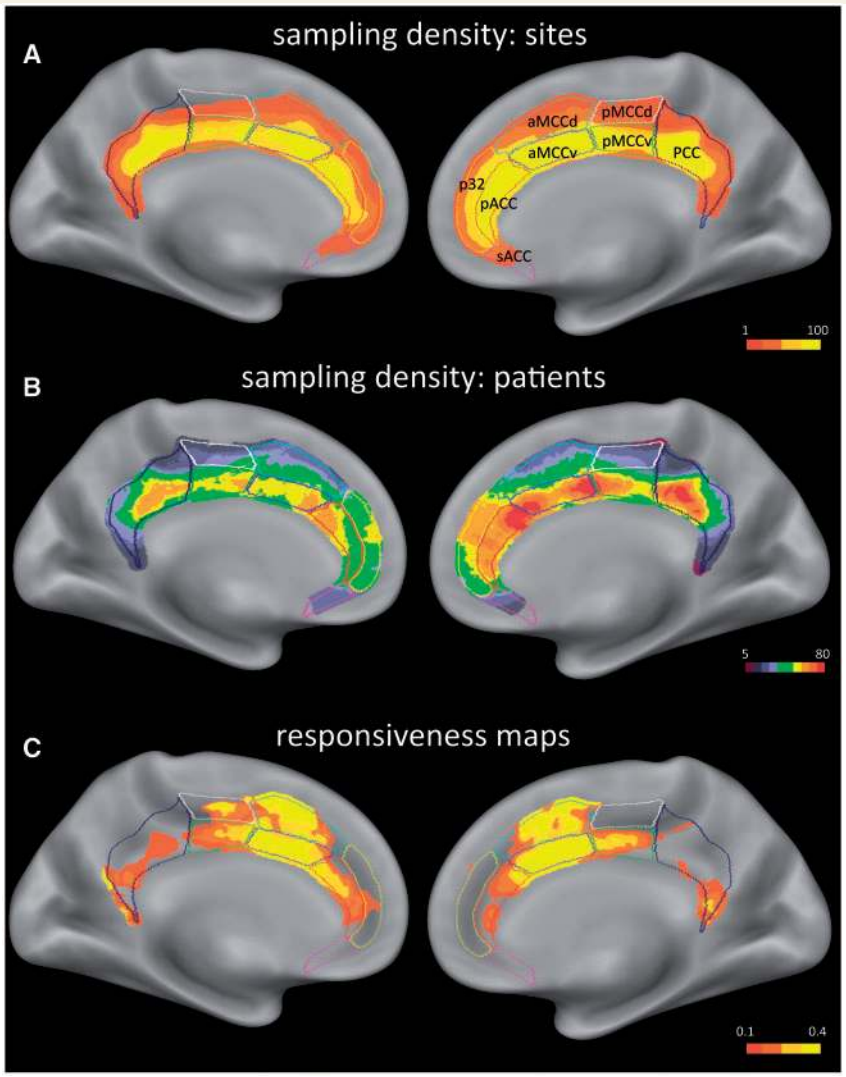

Figure 2 Sampling density and responsiveness maps. (**A**) The site sampling density is shown on the inflated surface of fs_LR brain template. The colour scale indicates the number of leads within a disk of 1 cm of radius and centred on each node of the mesh. (**B**) The patient sampling density is reported; the colour scale reflects the number of patients with at least a lead in the disk. Note that only regions with at least five different stimulated patients are plotted. (**C**) Proportion of responsive sites out of the overall number of stimulated sites, is plotted on the fs_LR brain template. The colour scale indicates the percentage of responsive sites within a disk 1 cm in radius and centred on each node of the mesh, in line with Caruana *et al.* (2017*b*) and Avanzini *et al.* (2018).

with an average intensity of 2.7 ± 0.7 mA (see Supplementary material for further details on the stimulation procedure). Bipolar stimulations of two adjacent contacts, spaced 1.5 mm one from another, were carried out by means of biphasic rectangular stimuli of alternating polarity. All the stimulation-induced effects were video-recorded and prospectively stored in clinical report documents. We reviewed 263 videos of responsive stimulations, collected in 114 different patients; for the remaining patients, we obtained clinical data from the SEEG clinical report documents.

All patients, or their guardians, gave their informed consent to the surgical procedure and to the reviewing of data for scientific purposes. The present study received the approval of the Ethical Committee of Niguarda Hospital (ID 939 - 12.12.2013).

Data availability

Some data that support the findings of this study are available from the corresponding author, upon reasonable request. The data are not publicly available because they contain information that could compromise the privacy of our patients.

Results

Behavioural or subjective responses were elicited in the 32.3% of all cingulate stimulations (left = 135, right = 166; Supplementary Table 1). Stimulable sites were equally distributed across the two hemispheres (χ^2

$P = 0.44$). These sites were mainly located in the ventral and dorsal aMCC, pACC and ventral pMCC. The dorsal pMCC and PCC had few eloquent sites, while sACC and p32 were virtually unresponsive (Fig. 2C and Supplementary Fig. 1B). Unresponsive stimulations represented 67.7% of all cingulate stimulations (left = 260, right = 372), and they were distributed in all cingulate regions (Supplementary Table 1).

The threshold of all stimulations was 2.73 ± 0.72 mA and 2.77 ± 0.63 mA in the left and right hemispheres, respectively. The threshold of stimulations eliciting responses (2.76 ± 0.61 mA and 2.72 ± 0.66 mA, respectively) and that of unresponsive stimulations (2.72 ± 0.77 mA and 2.77 ± 0.62 mA, respectively) were not statistically different, as confirmed by a two-way ANOVA using responsiveness and hemisphere as main factors ($P > 0.05$).

Behavioural and subjective responses were subdivided into six main categories: (i) goal-oriented behaviours; (ii) affective; (iii) somatosensory; (iv) vestibular; (v) visual; and (vi) speech impairment; in addition, other miscellaneous effects were grouped in a unique additional category. The statistical evaluation of the distribution of different subjective and objective responses in each subregion is shown in Table 1. Below, we illustrate the regional distribution of these effects, and then concentrate on the motor and the affective responses, as these were the most represented.

Goal-oriented behaviours

Goal-oriented behaviours and simple motor responses were observed following 94 stimulations (left = 38, right = 56). These responses represented the most frequent effect following cingulate stimulation, constituting 31.2% of all elicited responses (Supplementary Table 1). They were unequally distributed, as their presence was significant only in bilateral aMCC regions (Table 1), with a few also in the adjacent ventral pMCC sector and pACC (Figs 3 and 4). None of the other regions were involved in motor responses. Goal-oriented responses were similarly distributed across the two hemispheres (χ^2 $P = 0.45$).

Goal-oriented behaviours include getting-up impulses, reaching and grasping actions, body-directed actions, and exploratory eyes-head movements. All these behaviours were constituted by the combination of simple movements into an integrated pattern, and they were often executed in a smooth natural way. In addition, simple arm, hand or leg movements or negative effects to the same body districts (atonia) were also found.

Getting-up impulses

Getting-up impulses were elicited 11 times (left = 3, right = 8), representing 11.7% of all goal-oriented behaviours (Supplementary Table 1). They consisted of sudden attempts to get up from the bed and go away. Movements were characterized by postural adjustments, during which the patient carried the legs closer to the body and grasped the bars of the bed to push up (Supplementary Video 1). At the subjective level, some patients justified the induced behaviour as an attempt to find a more comfortable position, while some other patients clearly described their behaviour as an attempt to get up and go away (e.g. 'I felt I was willing to go away'). Almost all such responses were elicited by the stimulation of the most ventral sector of the ventral aMCC (Fig. 5).

Reaching and grasping actions

Reaching and grasping actions were elicited 35 times (left = 17, right = 18), representing 37.2% of all goal-oriented behaviours. They were characterized by movements performed with the contralateral hand/arm. These responses were often executed in a smooth natural way, but jerky and awkward graspings were also present. While in some cases the evoked behaviour was limited to the grasping phase (i.e. involving only the hand), other stimulations elicited more complex actions, combining reaching and grasping movements. In these last cases, the patient directed his action toward some region of the peripersonal space, or even attempting to reach the extrapersonal space, anticipating the distal movements by proximal and axial ones (Supplementary Video 2). It occurred that the patient reached and grasped some objects close to him, albeit in many cases the grasping actions were not specifically directed to the surrounding objects. At the subjective level, some patients were not able to justify the induced behaviour, often recognizing it was a consequence of the stimulation. As far as the localization is concerned, reaching and grasping actions were sharply clustered in the ventral aMCC (Fig. 5).

Body-directed actions

Body-directed actions were elicited 15 times (left = 8, right = 7), representing 16% of all goal-oriented behaviours (Supplementary Table 1). They consisted of a variety of hand/arm actions directed to different body parts, and in particular to the face. Example of these types of responses were: rubbing the eyes, bringing the hand to the mouth, mimicking the retrieve of something from the mouth, or putting fingers in the nose (Supplementary Video 3). These actions were often evocative of natural impulses aimed at protecting the face region. When asked to explain the reason behind their behaviour, some patients offered a *post hoc* explanation, but the most common result was astonishment. As shown in Fig. 5, body-directed actions were elicited by the stimulation of the dorsal aMCC.

Exploratory gaze movements

Exploratory gaze movements were elicited 18 times (left = 7, right = 11), representing 19.1% of all goal-oriented behaviours (Supplementary Table 1). They were characterized by eye and neck movements directed to the space contralateral to the stimulated hemisphere. In some cases, the movement was followed by alternating movements of the eyes/head in different directions, as if the

Table 1 Distribution of effects across cingulate subsectors

	Goal-directed behaviours	Affective responses	Somatosensory sensations	Vestibular responses	Speech impairment	Visual	Miscellaneous responses
Left							
aMCCv	38 (24,15)*	6 (19,86)	8 (10,12)	4 (4,28)	7 (6,62)	0 (3,5)	7 (16,75)
aMCCd	16 (5,97)*	1 (4,91)	0 (2,5)	0 (1,06)	2 (1,63)	0 (0,86)	0 (4,14)
pMCCv	6 (10,95)	4 (9,01)	14 (4,59)	2 (1,94)	7 (3)	0 (1,59)	8 (7,59)
pMCCd	0 (0,24)	1 (0,2)	2 (0,1)	0 (0,04)	0 (0,06)	0 (0,03)	0 (0,17)
pACC	2 (12,94)	35 (10,65)*	0 (5,42)	1 (2,29)	0 (3,55)	0 (1,87)	9 (8,97)
p32	0 (1,24)	1 (1,02)	0 (0,52)	0 (0,22)	0 (0,34)	0 (0,18)	0 (0,86)
sACC	(0)	(0)	(0)	(0)	(0)	(0)	(0)
PCC	0 (6,47)	3 (5,32)	2 (2,71)	4 (1,14)	1 (1,77)	9 (0,93)*	19 (4,48)*
Right							
aMCCv	59 (34,67)*	7 (20,64)	16 (11,68)	6 (10,9)	3 (3,11)	0 (3,89)	6 (12,07)
aMCCd	14 (8,57)*	0 (5,1)	3 (2,89)	3 (2,69)	0 (0,77)	0 (0,96)	4 (2,98)
pMCCv	7 (15,72)	10 (9,36)	8 (5,3)	16 (4,94)*	3 (1,41)	0 (1,76)	0 (5,47)
pMCCd	0 (0,35)	0 (0,21)	0 (0,12)	1 (0,11)	0 (0,03)	0 (0,04)	0 (0,12)
pACC	8 (18,58)	33 (11,06)*	1 (6,26)	0 (5,84)	2 (1,67)	0 (2,08)	8 (6,47)
p32	1 (1,78)	1 (1,06)	0 (0,6)	0 (0,56)	0 (0,16)	0 (0,2)	3 (0,62)
sACC	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PCC	0 (9,29)	2 (5,53)	2 (3,13)	2 (2,92)	0 (0,83)	10 (1,04)*	10 (3,23)*

The table indicates the absolute number of stimulation sites evoking specific effects in each cingulate subsector. Columns represent the effect types, classified in motor, affective, somatosensory, vestibular, verbal, visual and miscellaneous behaviours. Rows represent cingulate subsectors. Statistical analysis was conducted with a chi-square test, comparing each cell with the value that would be expected if the variables were truly independent of each other. The sACC was not included as no eloquent site was found. In addition, to identify the effect-subsector combinations mostly contributing to the effect, we computed the individual chi-values for each cell. Asterisks indicate cells whose individual chi-value exceeds an absolute χ^2 of 5, thus indicating an effect specificity for a subsector.

patient was looking for something (Supplementary Video 4). Sometimes the stimulation was also associated with blurred vision, or to the feeling that the eyes were oscillating. Exploratory eyes/head movements were mainly found in the most rostral part of the aMCC, in particular at the rostral border between the ventral aMCC and dorsal aMCC, albeit a few sites were also found in the adjacent pACC and in the ventral pMCC (Fig. 5).

Simple movements and/or negative effects

Simple movements and/or negative effects were also elicited 15 times (left = 3, right = 12), representing 16% of all goal-oriented behaviours (Supplementary Table 1). Simple movements consisted of twitches or tremors of the contralateral upper or lower body parts (hand, arm, leg or foot). Negative effects consisted of atonia of the upper and lower limbs. Both simple movements and negative effects were found in the ventral aMCC, largely overlapping the reaching and grasping triggering region (Supplementary Fig. 3, left).

Affective responses

Affective responses constituted 22.6% of all responses elicited from the entire cingulate cortex and were observed following 68 stimulations (left = 33, right = 35). The presence of these responses was significant only in the right and left pACC region (Table 1). Affective responses also extended to the adjacent ventral aMCC and, in a few cases, to the ventral pMCC, while in other regions the number of affective responses was negligible (Fig. 4). All these responses were similarly distributed across the two hemispheres (χ^2 $P = 0.58$).

Affective responses were not always characterized by specific overt behaviours, but their identification was possible thanks to patient's verbal reports of subjective sensations. These reports allowed us to classify these responses into three main categories: mirthful and mirthless laughter, interoceptive sensations and autonomic responses.

Mirthful and mirthless laughter

Mirthful and mirthless laughter was elicited 25 times (left = 12, right = 13), representing 36.8% of all affective responses (Supplementary Table 1). Following the stimulation of these sites, the patient produced laughter or smiling. In most cases, a sense of mirth was associated with the perceived tendency to laugh. The patients were often astonished and usually did not offer explanations about their behaviour. Laughter was elicited from the most dorsal sector of the pACC, bordering with the ventral aMCC, and typically from the gyrus (Fig. 6, top). A subset of these results has been reported in Caruana *et al.* (2015, 2017*a*).

Interoceptive sensations

Interoceptive sensations were elicited 19 times (left = 12, right = 7), representing 27.9% of all affective responses (Supplementary Table 1). These responses were mainly reported as a feeling of emptiness in the stomach or burning sensation located at the abdominal level. Concerning its localization, the majority of these responses were evoked by

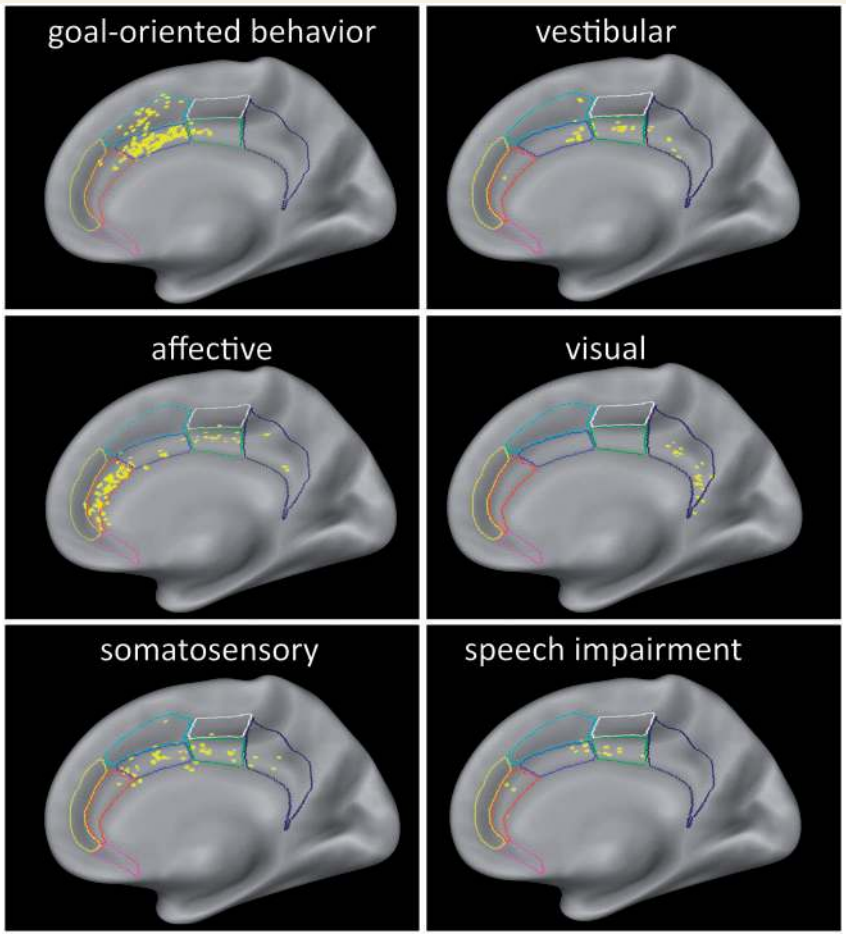

Figure 3 Anatomical distribution of behavioural and subjective responses. Anatomical distribution of the sites whose stimulation elicits behavioural and subjective responses belonging to the main six categories or response. Both left and right sites are plotted on the right hemisphere of the inflated surface of the fs_LR brain template.

the stimulation of the most ventral sector of pACC (Fig. 6, middle), albeit some interoceptive responses were elicitable following ventral pMCC stimulation.

Autonomic responses

Autonomic responses were elicited 24 times (left = 9, right = 15), representing 35.3% of affective responses (Supplementary Table 1). This category encompasses a range of vegetative symptoms, including hot flushes in the face, cold sweats, shivers and tachycardia. These responses had a clear emotional aspect and, interestingly, many patients explicitly interpreted these symptoms in terms of fear and anxiety. Vegetative responses were distributed along the entire pACC. In addition, some similar responses were collected from ventral pMCC (Fig. 6, bottom).

Somatosensory responses

Somatosensory responses were elicited 41 times (left = 18, right = 23) and constituted 13.6% of all cingulate responses (Supplementary Table 1). They were almost exclusively elicited by the stimulation of the ventral aMCC and ventral pMCC, albeit their presence in these regions was not statistically significant (Table 1). In addition, a few leads eliciting somatosensory responses were found in the PCC, dorsal aMCC, dorsal pMCC and pACC (Figs 3 and 4). They were similarly distributed across the two hemispheres (χ^2 $P = 0.91$). In the majority of cases (71%), these effects consisted of paraesthetic symptoms (29 effects), but sensations of electric shock or heat were also reported (29%; 12 effects; Supplementary Table 1). Effects were contralateral to the stimulated hemisphere or, in some case, bilateral. All somatosensory sensations were localized at different body parts (face, hand, arm, whole body) without a clear somatotopical organization.

Vestibular responses

Vestibular responses were elicited 25 times (left = 6, right = 19), representing 8.3% of all cingulate responses (Supplementary Table 1). They were almost exclusively elicited by the stimulation of the right ventral pMCC (Table 1) and, to a lesser extent, of the adjacent caudal part of the ventral aMCC and the dorsal part of the PCC

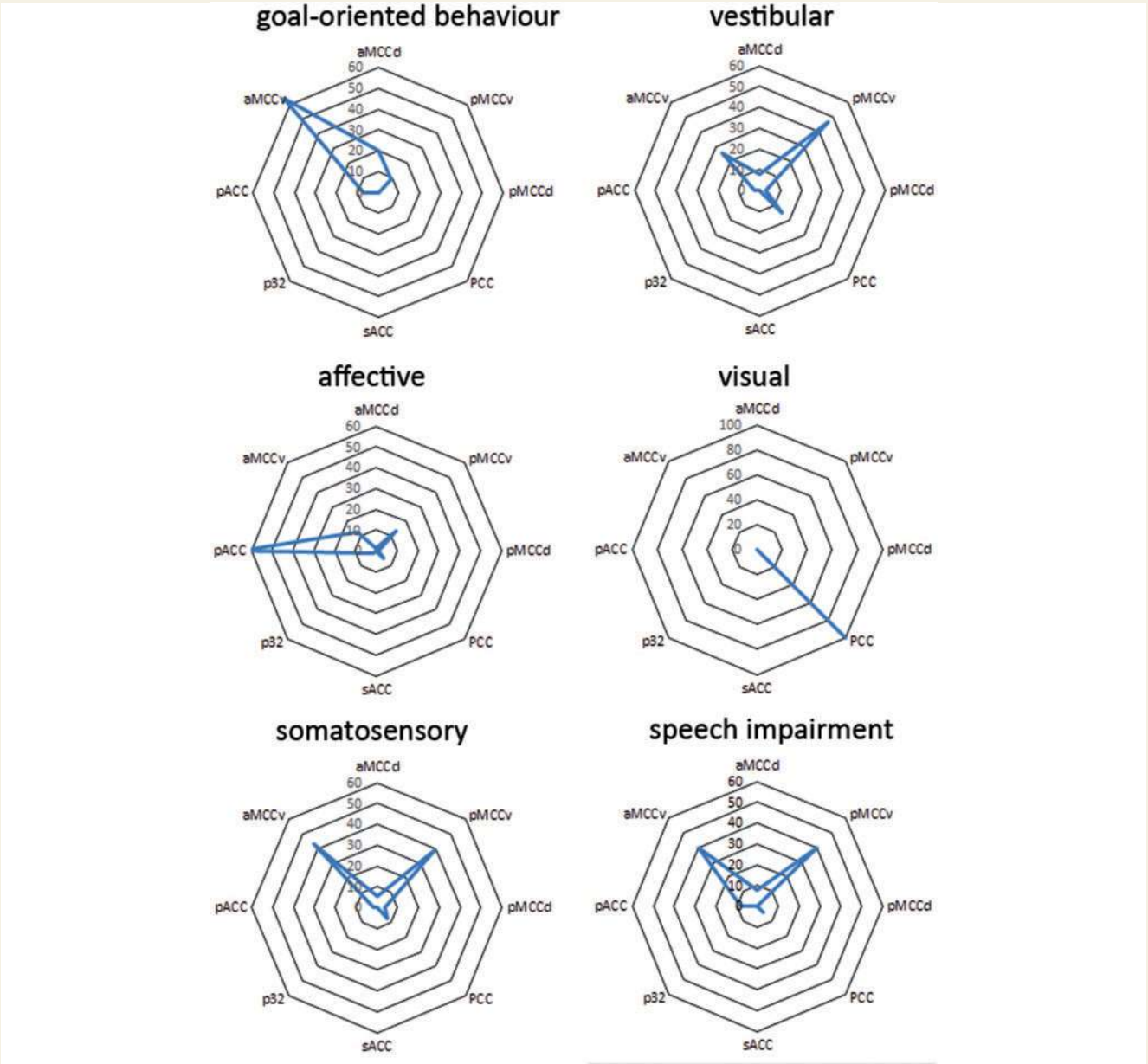

Figure 4 Percentage distribution of behavioural and subjective responses. Radar plots illustrate the distribution of each category in the eight cingulate regions. Values are expressed in percentage (0–60% in all cases, with the exception of visual responses, where 100% of responses are in the PCC). Suffixes: d = dorsal; v = ventral.

(Figs 3 and 4). The presence of vestibular responses in the dorsal aMCC, dorsal pMCC and pACC was negligible. Vestibular responses consisted of vertigo, dizziness and the feeling of falling into a void.

Visual responses

Visual responses were elicited 11 times (left = 6, right = 5), representing 3.7% of all cingulate responses. They were similarly distributed across the two hemispheres (χ^2 $P = 0.53$) and exclusively reported following the stimulation of PCC (Figs 3, 4 and Table 1), albeit they appeared to be clustered in two different PCC sectors. The dorsal one is likely located in the dPCC, and partially overlaps vestibular responses. The ventral one, possibly corresponding to the vPCC, was uniquely associated with visual responses. In both clusters, visual responses included blurred vision, feeling that the eyes were trembling, and a variety of low-level visual hallucinations such as white lights or coloured lines in specific parts of the visual field. No déjà-vu or other complex forms of visual hallucination were reported.

Speech impairments

Speech impairments were elicited 15 times (left = 8, right = 7) and constituted 5% of all cingulate responses

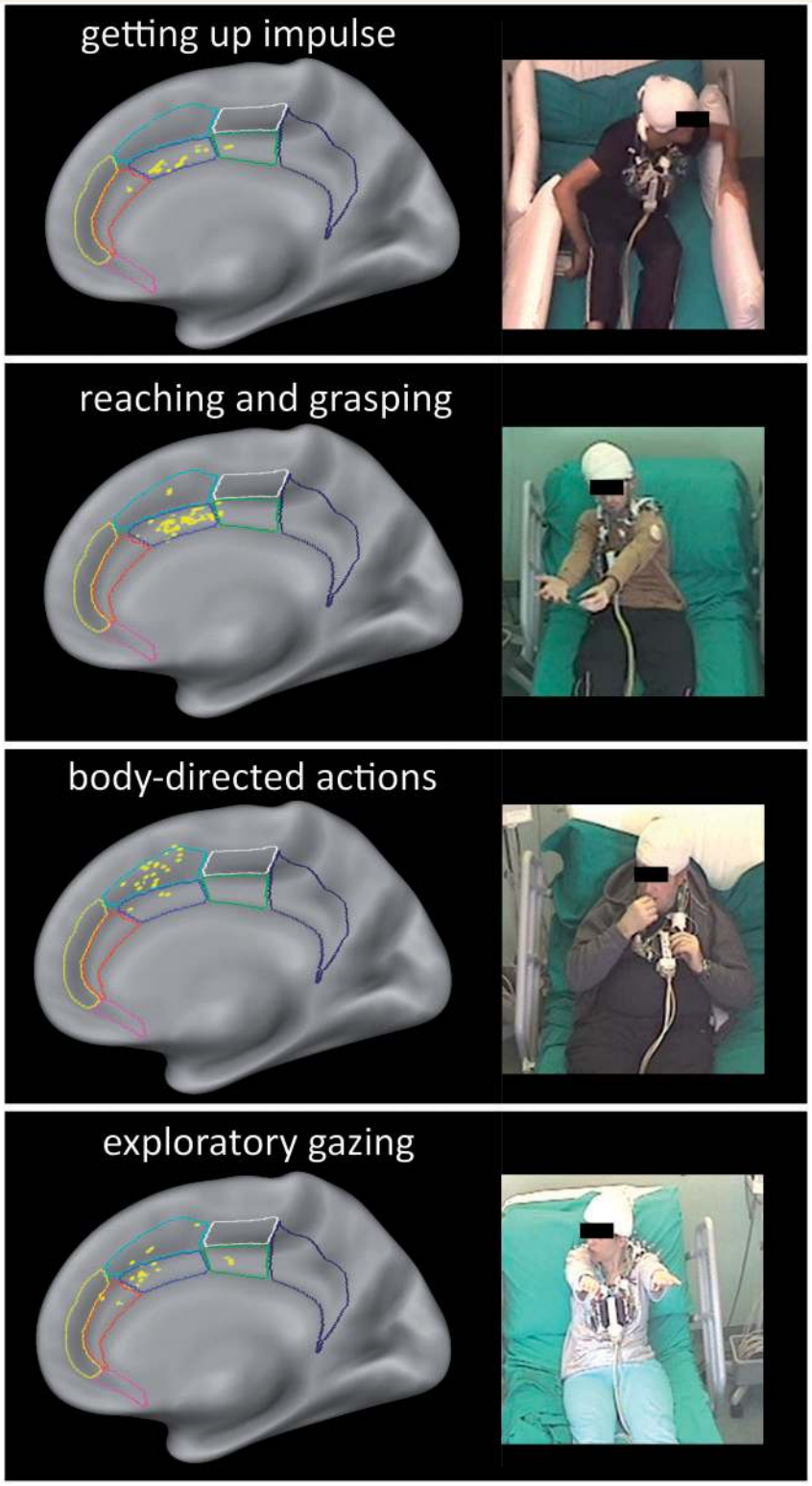

Figure 5 Goal-oriented behavioural responses. Anatomical distribution of the four main subcategories of goal-oriented behavioural responses. For each of them, the *left* panel depicts the anatomical location of sites whose stimulation elicits goal-oriented behaviours. *Right*: For each subcategory a representative frame recovered from Supplementary Videos 1–4 is shown.

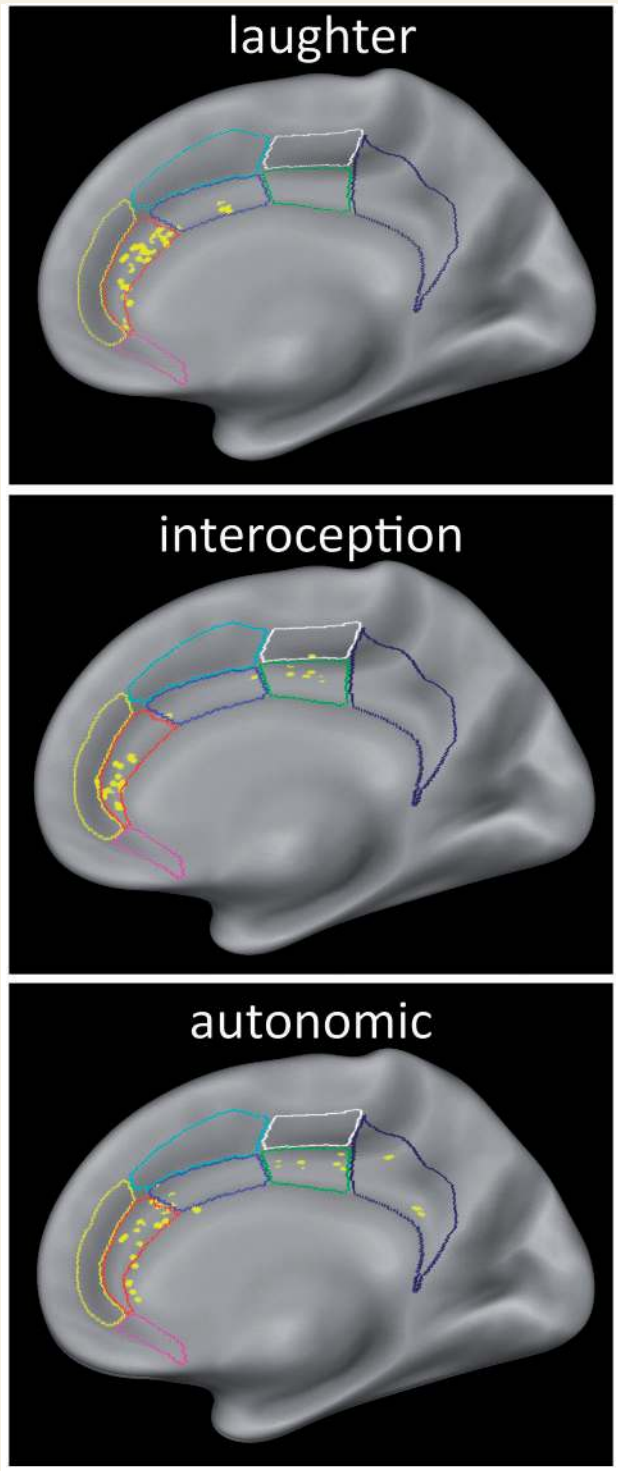

Figure 6 Affective responses. Anatomical distribution of all sites whose stimulation elicits affective responses, subdivided in the three subcategories described in the text: mirthful and mirthless laughter, interoceptive sensations and autonomic responses.

(Supplementary Table 1). Of note, speech impairments were clustered, albeit in a non-significant way, in the ventral sectors of the MCC, i.e. the ventral pMCC and ventral aMCC, while effects in the dorsal aMCC, pACC and PCC were negligible (Figs 3, 4 and Table 1). They were similarly distributed in the two hemispheres (χ^2 $P = 0.52$). This category includes speech arrest, dysarthria and tachyphemia.

Miscellaneous responses

Unspecific responses constituted 15.6% of all cingulate responses, and were elicited 47 times (left = 26, right = 21). Although distributed in several regions, they were significantly clustered following the stimulation of PCC and frequent, albeit in a non-significant way, following the stimulation of the pACC (Supplementary Fig. 3, right and Table 1). They were mostly characterized by a weak sense of confusion, haze, absence, or by the feeling that something strange was happening. In some cases, it was difficult for the patient to describe the elicited feeling. Although these sites cannot be considered as unresponsive, it is difficult to assign these stimulations a clear functional connotation. These miscellaneous responses were similarly distributed across the two hemispheres (χ^2 $P = 0.18$).

Discussion

We report the results of a systematic study on the effect of the electrical stimulation of 1789 sites distributed along the entire cingulate cortex, subdivided in eight different regions. The large sample of cingulate stimulations and its precise localization allowed us to obtain a detailed mapping of the functional properties of the cingulate region.

The highest number of active sites was found in the ventral and dorsal aMCC, whose stimulation triggered a variety of goal-oriented behaviours involving the upper limbs or the entire body. A high number of active sites was observed also in the rostrally-located pACC, which appears to be involved in the production of facial emotional displays, affective, autonomic and interoceptive functions. While these two rostral regions—corresponding to the Brodmann agranular area 24—were characterized by motor responses, the stimulation of more posterior regions was less responsive and predominantly associated to sensory responses. The pMCC hosted mostly vestibular and somatosensory responses, albeit some interoceptive and autonomic responses were also found in this region. Speech impairments were occasionally observed in the ventral sector of the pMCC. More caudally, the stimulation of the PCC was largely unresponsive and fundamentally associated to low-level visual sensations and phosphenes. Finally, the sACC and p32 had little or no responsivity to stimulations.

The ‘actotopic’ organization of aMCC

The role of the midcingulate region in producing complex behaviours was originally demonstrated by the seminal work of Talairach *et al.* (1973). The higher percentage of responses reported by Talairach and coworkers is likely

explained by the higher stimulation intensities and the larger diameter of electrodes. Nonetheless, the behaviours described in their study are fully in line with those described here. In addition, in our study the larger number of patients and the new multimodal image-based localization of SEEG electrodes allowed us to highlight the 'actotopic' arrangement of these behaviours along a ventro-dorsal axis. Although spatial limitations of bipolar stimulations with SEEG electrodes impede the attribution of these different behaviours to the different band-like cytoarchitectonical subdivisions of aMCC, it is tempting to propose that they correspond to the classical subdivision of area 24, in 24a, 24b and 24c, respectively. Actions developing in the extrapersonal space, mostly resembling the initial phase of the attempt to rise from the bed, were elicited from the most ventral part of the ventral aMCC, corresponding to the evolutionary ancient periallocortex (24a). Moving dorsally in the ventral aMCC (24b), actions became directed toward the peripersonal space, and mostly performed with the contralateral upper limb. Finally, the stimulation of the dorsal aMCC (24c) elicited movements directed toward different parts of the upper body and especially to the face, such as mimicking the retrieval of something from the mouth, or putting fingers in the nose. From a small number of sites in the most rostral part of the aMCC, stimulation elicited glancing movements. These behaviours appeared to be exploratory in nature. The anatomical location of these responses appears to match the so-called cingulate eye-field described by previous imaging data during saccadic eye movements (Amiez and Petrides, 2014) or oculomotor conditional tasks (Paus *et al.*, 1993).

Based on evolutionary considerations, we speculate that the aMCC, regardless of its subdivisions, encodes ancient behaviours whose implementations occur through a series of different descending projections such as corticospinal (Luppino *et al.*, 1994), reticulospinal (Kuypers, 1981) and tectospinal pathways (Leichnetz *et al.*, 1981). Note that, unlike classically thought, the reticulospinal pathway is involved not only in postural control but also in forelimb actions, including coordinated finger movements (Honeycutt *et al.*, 2013). Similarly, the tectospinal pathway, besides controlling eyes and neck movements, is also involved in forelimb control (Werner *et al.*, 1997). In addition, the aMCC projects to the forelimb and hindlimb motor striatal territories (Takada *et al.*, 2001) and to the lateral column of the periaqueductal grey (PAG), known to control the production of defence responses to incoming threatening stimuli (An *et al.*, 1998) (Fig. 7).

The motor functions of the anterior midcingulate cortex are also highlighted by its cortical connectivity, as demonstrated by monkey studies. The strongest aMCC connections are with the mesial and dorsal premotor areas (Luppino *et al.*, 2003), while sparse connections with ventral premotor cortex are also documented (Gerbella *et al.*, 2011). The aMCC is also connected to large sectors of the lateral prefrontal cortex, including both ventral and dorsal parts of area 46 and with opercular frontal areas (Gerbella *et al.*, 2013, 2016; Borra *et al.*, 2017). Parietal connections of the aMCC are with the inferior parietal lobe and posterior insula (Pandya *et al.*, 1981; Mufson and Mesulam, 1982; Vogt and Pandya, 1987; Rozzi *et al.*, 2006) (Fig. 7). Since all these regions control the execution of skilled motor acts (Gerbella *et al.*, 2017*a*), we speculate that the aMCC might provide the motivational drive to perform actions, playing an excitatory and/or inhibitory role on these motor circuits. Finally, at the temporal lobe level there is evidence of aMCC connections with the entorhinal cortex and the middle part of the superior temporal sulcus (Vogt and Pandya, 1987), possibly providing memory and high-order visual information. There are few connections with the amygdala and other emotional centres, whereas almost no connections are documented with the primary motor cortex (Pandya *et al.*, 1981).

The action-oriented contribution of the aMCC to sensory and cognitive functions

Imaging literature on the aMCC suggested two main lines of interpretation. On one hand, the aMCC has been interpreted as a crucial region for pain processing (Talbot *et al.*, 1991; Ingvar, 1999; Ploghaus *et al.*, 1999; Mohr *et al.*, 2005; Vogt, 2005; Shackman *et al.*, 2011). On the other hand, it has been suggested that the aMCC (occasionally dubbed 'dACC') is part of a distributed attentional network contributing to a range of cognitive tasks, including divided attention, cognitive control, response selection and prediction error (Bush *et al.*, 2000; Kerns *et al.*, 2004; Botvinick, 2007; di Pellegrino *et al.*, 2007; Seeley *et al.*, 2007; Rushworth, 2008; Hoffstaedter *et al.*, 2013; Ide *et al.*, 2013). We argue that evaluating the effects of aMCC stimulation could provide a solid framework on which one may ground the interpretation of imaging findings.

The frequent observation that the cingulate cortex is activated by peripheral nociceptive stimulation led to postulate that this region has a fundamental role in pain perception and pain-avoidance learning (Sikes and Vogt, 1992; Vogt *et al.*, 1996; Hutchison *et al.*, 1999; Jeon *et al.*, 2010; Vogt, 2016). This view is conceptualized maintaining that the aMCC is part of a distributed network called the 'Pain Matrix' (Ingvar, 1999; Ploghaus *et al.*, 1999; Derbyshire, 2000; Singer and Frith, 2005). The nociceptive interpretation of the aMCC is, however, unsupported by the paucity of nociceptive-like effects following aMCC stimulation in our patients, and by similar reports from previous studies (Talairach *et al.*, 1973; Bancaud *et al.*, 1976; Hutchison *et al.*, 1999; Kremer *et al.*, 2001; Chassagnon *et al.*, 2008). Notably, Hutchison *et al.* (1999) reported that electrical stimulation, even with high currents, failed to elicit painful or unpleasant sensations at the same sites where they recorded pain-sensitive neurons. Interestingly, early interpretations of cingulate reactivity to pain were cautious,

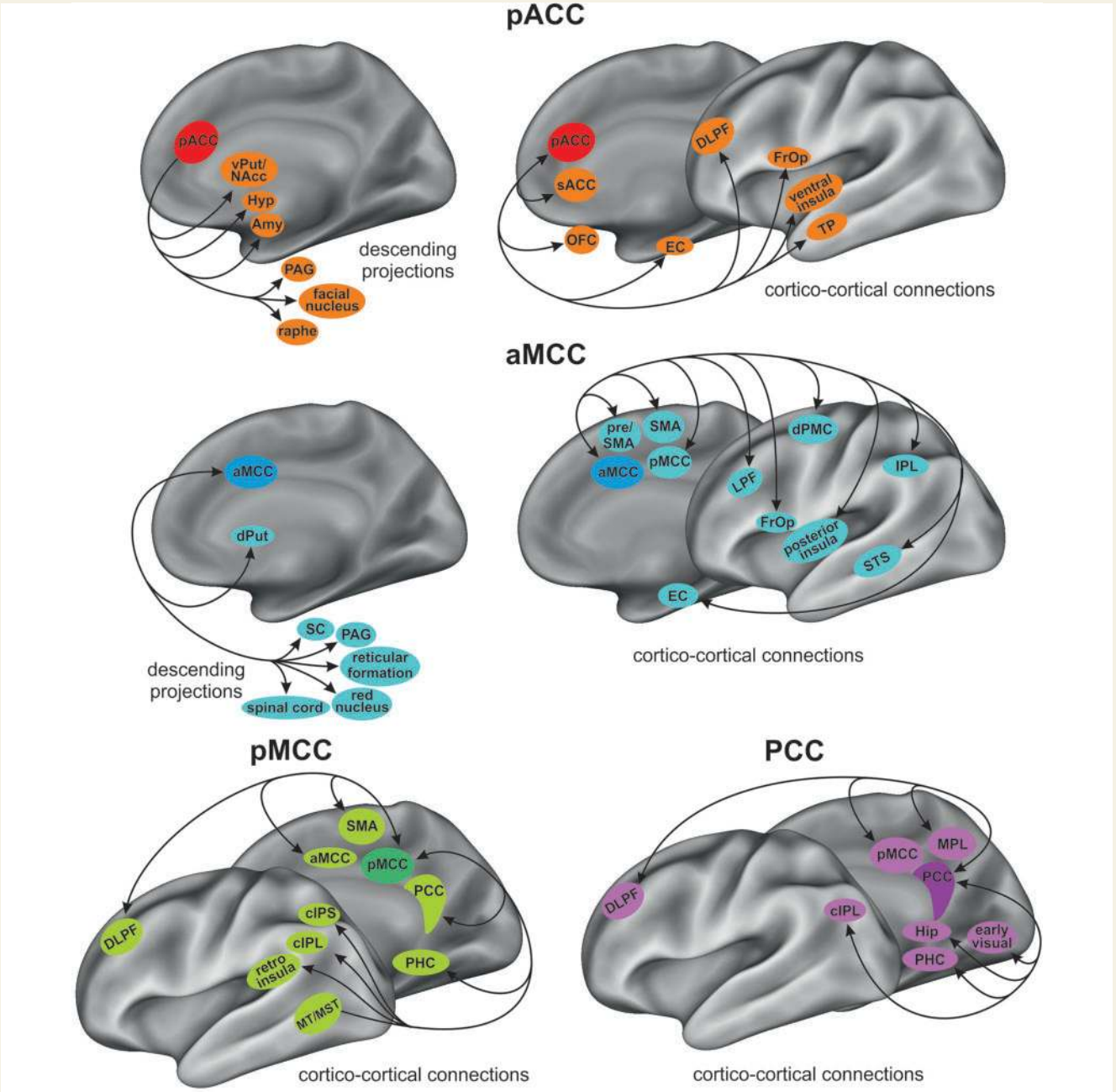

Figure 7 Anatomical connections of pACC, aMCC, pMCC and PCC. Descending projections and cortico-cortical connections are based on tract-tracing experiments following neural tracer injections in pACC, aMCC, pMCC and PCC homologue regions of the monkey (Kuypers, 1981; Pandya *et al.*, 1981; Vogt and Pandya, 1987; Luppino *et al.*, 1993, 1994, 2003; An *et al.*, 1998; Morris *et al.*, 1999; Takada *et al.*, 2001; Rozzi *et al.*, 2006; Morecraft *et al.*, 2007; Gerbella *et al.*, 2013). Amy = amygdala; cIPL = caudal inferior parietal lobule; cIPS = caudal inferior parietal sulcus; DLPF = dorsolateral prefrontal cortex; dPMC = dorsal premotor cortex; dPut = dorsal putamen; EC = entorhinal cortex; FrOp = frontal operculum; Hip = hippocampus; Hyp = hypothalamus; IPL = inferior parietal lobule; LPF = lateral prefrontal cortex; MPL = mesial parietal lobule; OFC = orbitofrontal cortex; PAG = periaqueductal gray; PHC = perirhinal cortex; SC = superior colliculus; TP = temporal pole; vPut = ventral putamen.

leaving open the possibility that such reactivity could also reflect more general arousing and alerting effects (Carmon *et al.*, 1976; Chapman *et al.*, 1981; Stowell, 1984; but see Iannetti and Mouraux, 2010). Recent data support this alternative interpretation. Indeed, the specificity for pain of the aMCC has been questioned by imaging data showing that many different types of salient stimuli, regardless of whether visual, auditory or tactile, elicit brain activations with a similar regional configuration, overlapping with that determined by painful stimuli (Mouraux *et al.*,

2011). Moreover, musical experience modulates the aMCC (Koelsch, 2010, 2014), whose activation correlates with music-induced chills intensity ratings (Blood and Zatorre, 2001), suggesting that action tendencies and motor alertness mediated by this region also contribute to some aspects of musical experience. Taken together, it seems reasonable to assume that the aMCC is triggered by many different experiences characterized by a strong motivation to initiate actions, including nociceptive ones, but not limited to them.

The same interpretation holds for the finding that the dorsal aMCC is active during tasks requiring cognitive efforts, such as divided attention, cognitive control and response selection (Botvinick, 2007; Rushworth, 2008; Ide *et al.*, 2013; Menon, 2015). In all these tasks, action tendencies, tension, and readiness to act are triggered by endogenous attention rather than by exogenous stimuli. Consistent with this view, the dorsal aMCC has been involved in evaluating the motivation to exert both cognitive and physical efforts (Scholl *et al.*, 2015; Chong *et al.*, 2017; Hauser *et al.*, 2017).

The role of the pACC in emotional experience and expression

The result of electrical stimulation of the pregenual sector of ACC assigns to this region an unequivocal role in determining motor behaviours linked to affective functions, the most common response consisting in the production of emotional facial displays, interoceptive sensations or autonomic responses. Emotional responses are coarsely arranged according to a rostro-caudal axis. The caudal part of the pACC, close to the aMCC, is involved in the production of emotional expressions, and in particular in laughter and smiling displays, while the stimulation of the most rostral part of the pACC, close to the the sACC, frequently triggered interoceptive responses such as emptiness in the stomach or burning sensation located at the abdominal level. Autonomic responses and vegetative symptoms, in contrast, were equally distributed along the entire pACC. Emotional responses are located in the ventral aspect of the anterior cingulate region (pACC), while absent in the adjacent dorsal bank (p32). This result is in line with imaging literature suggesting that the socio-emotional specialization is limited to the most ventral aspect of ACC, while p32 is involved in domain-general cognitive processing (Apps *et al.*, 2016).

The view that the pACC plays a major role in emotional expression and experience is in line with previous results from our group (Caruana *et al.*, 2015), reporting that the electrical stimulation of this region triggers both mirthless and mirthful laughter. The present result is also in accord with stimulation and single neurons studies showing that the rostral sector of ACC contributes to the production of emotional facial displays and vocalizations in monkeys, and with the evidence that emotional facial displays and vocalizations are impaired following the lesion of this area (Smith, 1945; Jürgens and Pratt, 1979; Jürgens and von Cramon, 1982; Hadland *et al.*, 2003; Livneh *et al.*, 2012; see also von Cramon and Jürgens, 1983; Jürgens, 2009).

It is particularly interesting to note that impairments following ACC lesion include not only the production of overt emotional displays, but also deficits in social interactions and emotional experience (Hadland *et al.*, 2003; Hornak *et al.*, 2003; Rudebeck *et al.*, 2006). In line with this finding, a considerable functional MRI literature supports the role of pACC in empathy and socio-emotional functions (Behrens *et al.*, 2009; for reviews see Apps *et al.*, 2016; Lockwood, 2016; Wittmann *et al.*, 2018). As far as intracranial recording and stimulation is concerned, we reported a case where electrical stimulation induced smiling and laughter was also activated by the observation of others' laughter (Caruana *et al.*, 2017*a*), further supporting the role of the pACC in social behaviour, laughter contagion and the sharing of positive emotional state.

Connectivity studies on the monkey ACC show descending connections with the face/mouth field of the motor putamen, the vocalization centres of the caudolateral part of the PAG, and the facial nerve nuclei (Müller-Preuss and Jürgens, 1976; Porrino and Goldman-Rakic, 1982; Devinsky *et al.*, 1995; An *et al.*, 1998; Morecraft *et al.*, 2001) (Fig. 7). These latter projections reach bilaterally both the dorsal and intermediate nuclei of the bulb, thus controlling upper face muscles that, in humans, characterize 'true' emotional laughter. This region is also connected to subcortical emotional centres, such as the nucleus accumbens, where mirth has been induced by deep brain stimulation (Gibson *et al.*, 2016), and amygdala (Morecraft *et al.*, 2007), whose stimulation elicits fear and anxiety (Meletti *et al.*, 2006; Lanteaume *et al.*, 2007). Interestingly, some patients explicitly interpreted the vegetative symptoms induced by the stimulation in terms of fearful experiences and increased anxiety. Given that the pACC and amygdala are mostly associated with opposite positive (pACC) and negative (amygdala) emotional states, it is tempting to speculate that the interplay between these regions plays a role in regulating negative emotions (Etkin *et al.*, 2015).

The cortical connections of monkey ACC are with ventral insula, basal and polar temporal cortex, orbitofrontal, frontal operculum and dorsolateral prefrontal cortex (Vogt and Pandya, 1987; Morecraft and Van Hoesen, 1998; Morecraft *et al.*, 2012; Jezzini *et al.*, 2015; Gerbella *et al.*, 2016) (Fig. 7). It is interesting to note that laughter and smiling in humans, and similar affiliative gestures in the monkey, have also been elicited from many of these regions (Schmitt *et al.*, 2006; Caruana *et al.*, 2011, 2016; Fernández-Baca Vaca *et al.*, 2011; Jezzini *et al.*, 2012; Yamao *et al.*, 2015; for a review see Caruana, 2017*b*) suggesting that the pACC is a crucial node of a network controlling positive emotional expressions (Gerbella *et al.*, 2017*b*). In line with this, it has been shown that social laughter modulates endogenous μ-opioid receptors activity

in a network including the pACC and many of the regions listed above (Caruana, 2017*a*; Manninen *et al.*, 2017). In all the studies mentioned above, almost no connections are reported between the pACC and premotor, supplementary motor and primary motor cortices, nor with the parietal lobe. Taken together, this connectivity pattern and the functional data described above make a strong case for a role of the ACC in orchestrating social emotional behaviours.

Functional considerations on the role of posterior cingulate regions

The stimulation of the posterior regions (pMCC and PCC) was characterized by lower stimulability, absence of motor responses, and predominance of subjective reports of vestibular, interoceptive, somatosensory and visual sensations. Although the interpretation of these data is not as straightforward as that concerning anterior cingulate regions, yet some aspects deserve to be discussed.

The evidence that pMCC stimulation induces vestibular and somatosensory responses is particularly interesting if considering its putative role in integrating vestibular, visual, and somatosensory information for online control of locomotion (Wall and Smith, 2008). This interpretation is compatible with anatomical data, showing pMCC connected with motor (supplementary motor area, aMCC), vestibular (retroinsula) and visual motion-sensitive centres in the temporal (MT, MST) and parietal (caudal inferior parietal sulcus) lobe [see Morecraft *et al.* (2004) for monkey, and Smith *et al.* (2017) for human studies] (Fig. 7). However, the attribution of vestibular functions to the pMCC is based on indirect evidence, such as its selectivity to (visual) optic-flow stimuli compatible with self-motion, during imaging studies (Wall and Smith, 2008; Cardin and Smith, 2010; Fischer *et al.*, 2012; Field *et al.*, 2015). We suggest that the present data, showing that the stimulation of the pMCC induces vertigo, dizziness and feeling of falling into a void, add new evidence in favour of this interpretation.

As far as the PCC is concerned, this region appears as the more enigmatic cingulate region, also because of its frequent unresponsiveness to stimulation. Yet it is interesting that PCC hosted the totality of sites whose stimulation elicited phosphenes, and that it is the principal recipient of stimulations eliciting confusion, haze and absence. While it is difficult to interpret these results in the light of the functions frequently attributed to the PCC—episodic and autobiographical memory, visuospatial orientation, self-monitoring, attention, internally-directed cognition (Vogt *et al.*, 2006; Leech and Sharp, 2014)—our results are coherent with its connectivity, mainly involving low- and high-level visual regions, such as the middle occipital gyrus and the anterior middle temporal gyrus, and visuospatial memory-related regions such as the parahippocampal cortex (Morris *et al.*, 1999; Cha *et al.*, 2017).

Conclusion

To the best of our knowledge, the present work represents the only currently available stimulation study of the entire cingulate cortex. The large number of patients and the multimodal image-based localization of SEEG electrodes allowed us to assign specific functional properties to modern anatomical subdivisions of the cingulate cortex. Our results support the notion of a segregation of different functional fields distributed along a rostro-caudal axis, with an anterior sector (pACC) devoted to emotional and interoceptive functions, an anterior midcingulate field (aMCC) controlling goal-oriented behaviours according to a dorso-ventral 'actotopic' organization, and a posterior region devoted to vestibular and somatosensory processing (pMCC), and visual responses (PCC).

These findings provide a clear neurophysiological perspective of how motor functions constitute the unifying hallmark of the whole cingulate cortex. From a clinical perspective, these findings advance our understanding of the symptomatology of seizures localized or involving the cingulate cortex, thus improving the epileptological strategy of implantation of SEEG electrodes and allowing more tailored surgery for drug-resistant patients. In addition, this study clarifies the role of the cingulate cortex in a variety of emotional, motor and sensory processes, highlighting the internal arrangement of different behaviours within the emotional and motor sectors, and redefining the cingulate contribution to highly debated topics, including the one concerning pain processing.

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Competing interests

Dr Cardinale is key opinion leader to Renishaw mayfield, the manufacturer of the Neuromate robotic assistant. All the other authors have no conflicts of interest to disclose.

Supplementary material

Supplementary material is available at *Brain* online.

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