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Review

Midcingulate cortex: Structure, connections, homologies, functions and diseases

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ABSTRACT

Midcingulate cortex (MCC) has risen in prominence as human imaging identifies unique structural and functional activity therein and this is the first review of its structure, connections, functions and disease vulnerabilities. The MCC has two divisions (anterior, aMCC and posterior, pMCC) that represent functional units and the cytoarchitecture, connections and neurocytology of each is shown with immunohistochemistry and receptor binding. The MCC is not a division of anterior cingulate cortex (ACC) and the "dorsal ACC" designation is a misnomer as it incorrectly implies that MCC is a division of ACC. Interpretation of findings among species and developing models of human diseases requires detailed comparative studies which is shown here for five species with flat maps and immunohistochemistry (human, monkey, rabbit, rat, mouse). The largest neurons in human cingulate cortex are in layer Vb of area 24 d in pMCC which project to the spinal cord. This area is part of the caudal cingulate premotor area which is involved in multisensory orientation of the head and body in space and neuron responses are tuned for the force and direction of movement. In contrast, the rostral cingulate premotor area in aMCC is involved in action-reinforcement associations and selection based on the amount of reward or aversive properties of a potential movement. The aMCC is activated by nociceptive information from the midline, mediodorsal and intralaminar thalamic nuclei which evoke fear and mediates nocifensive behaviors. This subregion also has high dopaminergic afferents and high dopamine-1 receptor binding and is engaged in reward processes. Opposing pain/avoidance and reward/approach functions are selected by assessment of potential outcomes and error detection according to feedback-mediated, decision making. Parietal afferents differentially terminate in MCC and provide for multisensory control in an eye- and head-centric manner. Finally, MCC vulnerability in human disease confirms the unique organization of MCC and supports the predictive validity of the MCC dichotomy. Vulnerability of aMCC is shown in chronic pain, obsessive-compulsive disorder with checking symptoms and attention-deficit/hyperactivity disorder and methylphenidate and pain medications selectively impact aMCC. In contrast, pMCC vulnerabilities are for progressive supranuclear palsy, unipolar depression and posttraumatic stress disorder. Thus, there is an emerging picture of the organization, functions and diseases of MCC. Future work will take this type of modular analysis to individual areas of which there are at least 10 in MCC.

Abbreviations: ACC, anterior cingulate cortex; aCG, apex of the cingulate gyrus; ADHD, attention-deficit/hyperactivity disorder; aMCC, anterior MCC; bcgs, branch of the cingulate sulcus; CC, corpus callosum; cCMA, caudal cingulate premotor area; dACC, dorsal anterior cingulate cortex; daMCC, dorsal anterior MCC; fcgs, fundus of the cingulate sulcus; fMRI, functional magnetic resonance imaging; FTD, frontotemporal dementia with tau pathology; IPS, intraparietal sulcus; MCC, midcingulate cortex; MITN, midline; OCD, obsessive-compulsive disorder; pACC, perigenual ACC; PCC, posterior cingulate cortex; pMCC, posterior MCC; PSP, progressive supranuclear palsy; PTSD, posttraumatic stress disorder; rCPMA, rostral cingulate premotor area; RSC, retrosplenial cortex; sACC, subgenual ACC; SMI32, antibody to nonphosphorylated intermediate neurofilament proteins; vaMCC, ventral anterior MCC.

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Contents

1. Introduction

The history of the human midcingulate cortex (MCC) extends back to the beginning of the 20th century but went unnoticed because Brodmann (1909) failed to recognize its presence. Smith (1907) first showed MCC and demonstrated its anterior and posterior divisions (aMCC, pMCC; see Vogt et al., 2003, for his figure). While the Vogts (1919) provided a map of cingulate cortex based on myeloarchitecture that was somewhat complex, it also showed subregions that could be related to aMCC and pMCC (Fig. 1A). While we identified caudal components of area 24 referred to as area 24′ and recognized then current imaging studies that differentiated these areas (Vogt et al., 1995), we continued for a few years to treat area 24′ as part of anterior cingulate cortex (ACC; Devinsky et al., 1995; Vogt et al., 2003). However, the evidence that area 24′ is fundamentally different from area 24 became so great that the MCC was introduced as a unique cingulate region in its own right to explain key cytoarchitectural differences with ACC and posterior cingulate cortex (PCC; Vogt, 2005) and their extensive functional differences (Vogt, 2009b; Fig. 1B).

The growing interest in MCC as a separate functional unit suggests a realization that MCC has unique contributions to brain function and is not a division of ACC. Indeed, the number of citations in Science Citation Index for “midcingulate” and “mid-cingulate” has been growing significantly over the past 20 years as shown in Fig. 2. The spike in citations starting in 2010 immediately followed publication of *Cingulate Neurobiology and Disease* in 2009 (Oxford University Press) which focuses primarily on primate cingulate organization, functions and diseases including those of MCC. The past five years has generated a diverse and thought provoking body of literature that leads to new insights into the functions and diseases of MCC. This is the first review of MCC and considers its key anatomical, connectional, and functional characteristics. Developing experimental animal models of human diseases requires a clear understanding of the comparative organization of MCC and it is now possible to link the distribution and characteristics of MCC in five species including humans. Finally, a critical part of validating MCC as a unique entity is demonstrating that human diseases have a differential impact on its structure and function as shown in the last section.

2. MCC≠ACC & dACC≠ACC

In spite of the past 20 years of detailed cytoarchitectural and immunohistochemical studies, many functional imaging studies report involvement of Brodmann areas for which there is no MCC equivalent. The use of Brodmann area 24 is inaccurate when activity is located only in MCC as his area 24 extends substantially more rostral and ventral to include subgenual ACC (sACC). Indeed, no functional imaging study has ever activated his entire ACC, thus demonstrating that it is not a single entity. The goal of analyzing cingulate cortex by subregion is to identify unique structure/function entities; not to verify Brodmann’s first view of cingulate cortex for which no neurobiology had yet evolved. The consequence of using the Brodmann map has been to engage other terminologies such as the dorsal ACC (dACC). Since dACC is not based on any structural substrate other than being above the corpus callosum and having a vague relationship to the Brodmann map, its application is variable and uncertain. A search of Science Citation Index with dACC in the title was made and randomly selected medial surface renderings were chosen from 8 studies. In some instances, dACC lined the cingulate or paracingulate sulci (Woodcock et al., 2015; Marsh et al., 2007; Whitman et al., 2013; Yücel et al., 2007). In one instance it reflected mainly the cingulate gyrus but also part of the cingulate sulcus that was either in pMCC (Hochman et al., 2014) or aMCC (Blair et al., 2006). Finally, some cases were located almost entirely on the cingulate gyrus in aMCC (McRae et al., 2008; Benedict et al., 2002). These studies describe activity or regions of interest in MCC and there are four patterns in these 8 studies alone and different areas in MCC were activated. Thus, these investigators are not discussing the same subregions and dACC is not ACC but rather MCC. A coherent subregion and area localization strategy based on stable anatomical characteristics, rather than location above the corpus callosum, serves more effective communication and determination of how subregion models function.

It is impossible to overlook the fact that ACC and MCC are unique regions even when MCC in not part of the analysis. Fig. 1D. demonstrates the default-mode network that does not involve MCC to any meaningful extent but is flanked on both sides by ACC and PCC activity (Vaishnavi et al., 2010). The ACC has a well established role in emotion and autonomic regulation, while MCC has a prominent role in decision making and skeletomotor control (Bush et al., 2000; Vogt, 2009a). These and many other observations discussed below lead to the conclusion that ACC≠MCC and dACC≠ACC.

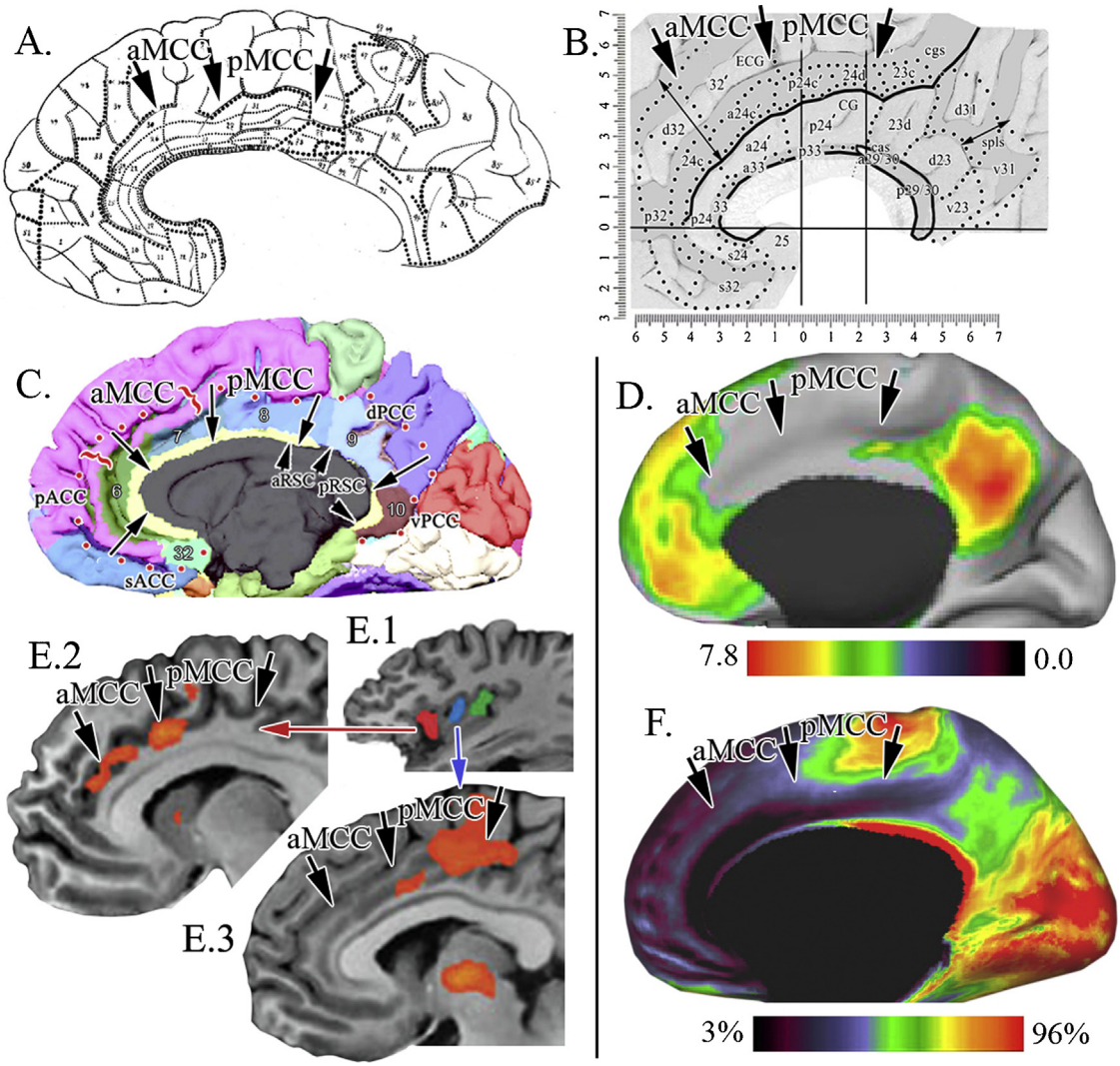

Fig. 1. Perspectives on MCC. (A) Vogts' map (1919) with aMCC and pMCC marked with arrows; (B) cingulate flat map (Vogt, 2009b); (C) FreeSurfer surface-based map (Destrieux et al., 2010); (D) default-mode network (Vaishnavi et al., 2010); (E) insula connectivity, E.1, ROIs, E.2 & 3 MCC correlations with anterior insula (2, right hemisphere) & midinsula (3, left hemisphere; Taylor et al., 2009); (F) *In vivo* myelin map (Glasser and Van Essen, 2011).

3. Regions/subregions are models of cortical function; not labels

The extent to which the four-region model of cingulate cortex including ACC, MCC, PCC, and retrosplenial cortex (RSC) has value is determined by its ability to predict relationships that are not apparent with other models. Defining cingulate regions and subregions is not simply a matter of taxonomy or even cytoarchitecture. Such designations are not just labels for descriptive structural and functional studies. Their use here represents cortical models that have predictive value; an example of which is interpreting MCC subregion findings in Tourette syndrome in the last section. To define a cytoarchitectural border is to declare that two parts of cingulate cortex constitute unique structure/function entities. For example, Bush et al. (2000) first demonstrated the functional border between ACC and MCC with the former activated during emotion-generating tasks and the latter during cognitive information processing tasks. This border has been repeatedly documented with differences in glucose metabolism, variations in the termination of amygdala and parietal afferents, electrical stimulation responses and cingulospinal projections (Vogt, 2009a).

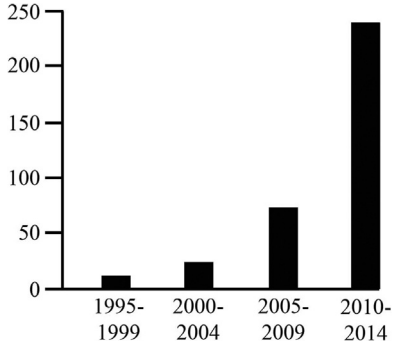

Fig. 2. Number of citations to "midcingulate" and "mid-cingulate over the past 20 years.

As important as confirmation of the subregion models are, non-confirmation raises new perspectives and this can be important to defining a model's unique properties. There are two examples of such divergences and the resulting reinterpretation of cingulate functions that emerge. First, the MCC was identified because of, among other reasons, its spinal skeletomotor projections (Vogt, 2009a); however, the dorsal perigenual ACC (pACC) has projections

to the motor nucleus of the 7th nerve (Morecraft et al., 1996). Indeed, it has been known for a long time that affectively modulated vocalizations are regulated by the cingulate vocalization area (Vogt and Barbas, 1988). Also, Moayedi et al. (2012) assessed patients with temporomandibular disorder compared to controls and reported accelerated, age-related cortical thinning in aMCC/pACC. Should dorsal pACC be incorporated into MCC? Not necessarily. These views are compatible with the role of ACC in emotion and this motor system regulating facial expression and vocalization. Thus, the face area of the rostral cingulate premotor area being in ACC is compatible with its role in emotional internal states. It should be noted, however, that there are not simple relationships between facial pain expression and cingulate activations. Kunz et al. (2011) showed that pACC activity was negatively correlated with facial expression in response to noxious heat, while painful events associated with facial expression of pain activate pMCC. While reflexive activation of pMCC during pain is expected (below), the negative correlation of pACC is not predicted. This view may also conflict with findings of Procyk et al. (2016) who showed that tongue movement and juice reward feedback are associated with activity in dorsal aMCC. Thus, the differential functions of pACC and daMCC remain unresolved, although reward coding of daMCC is consistent with other functional cognitive studies reviewed below. Second, while pMCC appears to be relatively uninvolved when generating emotion with faces, scripts or other stimuli (Vogt, 2005), aMCC is frequently activated during fear and not during non-emotional conditions. Does this mean that aMCC is part of ACC? While a wide range of emotion generating tasks activate ACC, not just fear, and ACC is involved in emotional awareness (Lane et al., 1997), aMCC employs evoked fear as a substrate for generating avoidance responses; i.e., this activity is coupled to the unique role of aMCC in motor control. It is postulated below that the fear response in aMCC is not a conscious emotional response but rather an implicit premotor signal. As such we have learned subtle distinctions about both fear and premotor aMCC functions.

4. The midcingulate dichotomy

The MCC is not uniform as it has aMCC and pMCC (Smith, 1907; Vogt and Vogt, 1919; Vogt, 2009b). It is to be expected that these divisions have differential connections and they have been identified in monkey and human. Indeed, amygdala and parietal afferents in the monkey differentiate them and this was one of the criteria for their dissociation (Vogt, 2009a). Before proceeding further, the terminology for various parts of MCC in primates is provided in Fig. 3 for reference throughout this review. The figure caption provides the definition of each part therein including the daMCC in the human with areas 32′ and a24c′ as well as the rCMA/rCPMA in the cingulate sulcus of daMCC and cCMA/CPMA in pMCC. The key difference with the monkey is a lack of an area 32′ in daMCC.

Beyond amygdala and parietal afferents, it is known that the monkey MCC and anterior insula are interconnected. An important study by Taylor et al. (2009) used resting state connectivity to analyze this interaction in human as shown in Fig. 1E. Fig. 1E1 shows their insular regions of interest, while E.2 shows interactions between the anterior insula and aMCC and E.3 those between the midinsula and pMCC. The conjunction of these findings with monkey monosynaptic connections is striking in that they are both located mainly in the cingulate sulcus where the cingulate premotor areas are located (Mesulam and Mufson, 1982; Mufson and Mesulam, 1982; Vogt and Pandya, 1987). Taylor et al. (2009) suggest that an emotional/salience monitoring system links the anterior insula with the pACC/aMCC and is responsible for integrating interoceptive information with emotional salience

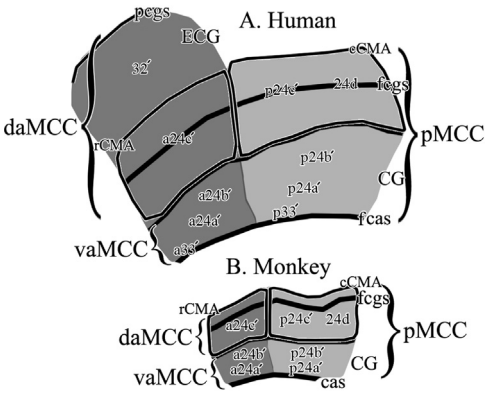

Fig. 3. Two images were extracted from Fig. 6 and the gross anatomical features of MCC identified including the cingulate gyrus (CG) and external cingulate gyrus (ECG). (A) The two human MCC divisions are aMCC (dark grey) and pMCC (light grey). The dorsal aMCC (daMCC) is bounded by the paracingulate sulcus (pcgs) and includes areas 32′ and a24c′ with their ventral border at the apex of the CG (parenthesis). The ventral aMCC (vaMCC) is comprised of CG areas a24a′ and a24b′ and callosal sulcal area a33′ (fcas, fundus of the callosal sulcus). The pMCC includes cingulate sulcal areas p24c′ and 24d, and dorsal and ventral parts of pMCC are not employed. Within each part of MCC are outlined the rostral cingulate motor area (rCMA; also rostral cingulate premotor area; rCPMA) and the caudal cingulate motor area (cCMA; also caudal cingulate premotor area; cCPMA). (B) Monkey MCC differs from the human as it does not appear to have an area 32′ and daMCC is comprised of only area a24c′. The rCMA/rCPMA and cCMA/cCPMA maintain a similar relative position in the cingulate sulcus.

forming a subjective image of our bodily state. They also concluded that a general salience and action system links the entire insula and MCC for environmental (sensory context) monitoring, behavioral response selection via skeletomotor control and body orientation.

Here we reconsider the dichotomy issue with immunohistochemical preparations of human MCC for neuron-specific nuclear binding protein (NeuN) and non-phosphorylated, intermediate neurofilament proteins (SMI32 antibody) in Fig. 4. The NeuN antibody reacts with neuronal nuclei only (i.e., glial cells are not reactive) and the neuropil staining is low compared to Nissl stains such as thionin. The SMI32 antibody, in contrast, reacts mainly with large, pyramidal neurons with extrinsic projections and these two antibodies provide a good overview of key features of cortical architecture. The macrophotographs of human MCC in A. show that layers II and VI in area a24b′ are thicker than in area p24b′ and layer III is poorly differentiated and thinner. The relatively poor differentiation of area 24b in pACC is shown for comparison and emphasizes the ACC/MCC distinction. While layer Va is of a similar thickness in both parts of MCC, neuron density is significantly higher in area p24b′. Fig. 4B shows these features in both parts of MCC with comparisons to SMI32 which has significantly greater expression in pMCC. Layer III in area p24′ is very high in layers III and Va compared to a24′ and area p24a′ has an additional peak in expression in the top of layer VI (layer VIa). Verification of neuron densities and SMI reactivity are shown at higher magnification in Fig. 4C. Finally, unique patterns of MCC myelination shown by Glasser and Van Essen (2011) on the medial surface for the Conte-69 average data are presented in Fig. 1F. While the myelin pattern is generally graded throughout the anterior-to-posterior extent of cingulate cortex, there are differences between aMCC and pMCC with the latter having higher myelin content than aMCC.

Another perspective of the MCC subregions is shown in Fig. 5 in horizontal, silver-stained sections kindly provided by Drs. Karl Zilles and Nicola Palomero-Gallagher (Jülich, Germany). The area differences can be more easily compared in horizontal sections, than in multiple coronal sections as in Fig. 4. The borders between pMCC (areas p24b′/p24a′) and aMCC (areas a24b′ and a24a′) shown

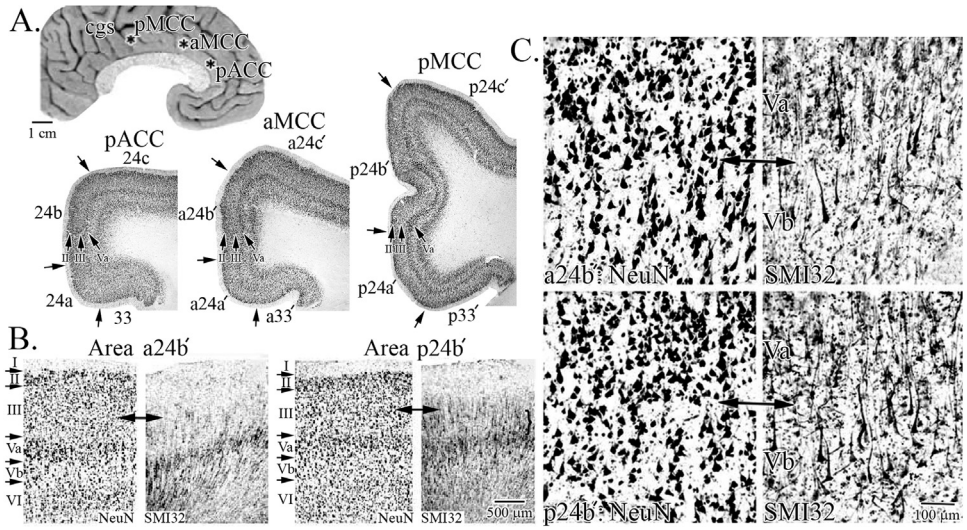

Fig. 4. The human midcingulate dichotomy. (A) Macrophotographs of 3 NeuN sections (levels shown on the medial surface with asterisks) to demonstrate the progressive laminar differentiation from pACC to pMCC; note layers II, III and V (arrows). (B) Area 24b′ differences compared to area 24b include a broad layer III with high densities of SMI32+ neurons and dendrites and substantially more SMI32 reactivity in layer Va. (C) Magnification of layer V shows greater overall density of neurons in layer Vb of area a24b′ (NeuN), while layer Va SMI32+ neurons are more dense in layer Vb of area p24b′.
Figure compiled from Vogt et al. (2003).

at the asterisks (B. and C.) are relatively sharp as seen by cortical thickness where aMCC is thinner than pMCC and overall density of neurons in layers V–VI of the former is higher. Magnification of these areas (D and E) shows that layer II is more dense in area a24b′, layer III is not differentiated and the higher density of neurons in layers V–VI of a24b′ is more apparent as also seen above with NeuN. Finally, the different densities of large neurons in layer Va are apparent in F. and G. Thus, differentiation of pMCC and aMCC is demonstrated in horizontal sections and the MCC dichotomy is confirmed.

5. Comparative organization of MCC

The use of experimental animals to evaluate cingulate functions and devise animal models of human diseases requires comparative analyses of the content of cingulate cortex in each species in relation to the human. The very substantial differences in daMCC between monkey and human species are of particular importance to cognitive research and area 32′ functions cannot be studied in monkeys where it likely does not exist. Further, the pain literature often reports that medial prefrontal cortex is active when in fact they are reporting findings in ACC or MCC. Since the human medial prefrontal cortex comprises many more areas than those of cingulate cortex including areas 6, 8, 9, 10, 11, while rodents only have ACC and MCC, the conclusions often do not converge. Here we emphasize the comparative organization of MCC and note at the outset that the MCC in rodents is poorly differentiated in comparison to that in primates. This has particular relevance to pain research as it is the aMCC that is most frequently activated in human acute pain studies and no such subregion is present in

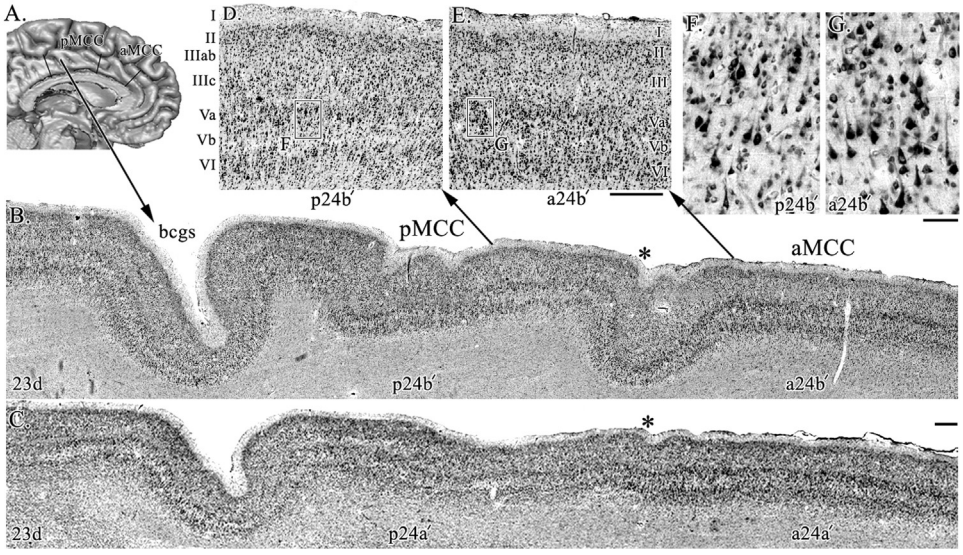

Fig. 5. The human MCC dichotomy in horizontal section. A. Medial surface with an arrow showing a branch of the cingulate sulcus (bcgs) to orient to the (B) and (C) macrophotographs. Asterisks identify the border between pMCC and aMCC. Arrows from (B) point to the levels where (D) and (E) were photographed for (D) and (E) and the boxes represent sites of further magnification of layer Va in (F) and (G). Scale bars; (B)–(E) 500 μm; (F) and (G) 100 μm.

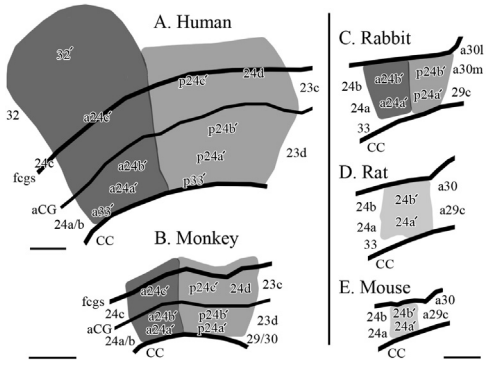

Fig. 6. Maps of MCC in five species. Three shades of grey refer to aMCC (darkest), pMCC (middle) and rodent MCC (lowest). The apex of the cingulate gyrus (aCG) and fundus of the cingulate sulcus (fcgs) are emphasized with thick lines. CC, corpus callosum. Scale bars for primates, 1 cm; for rabbit and rodents, 2 mm.

rodents (Vogt and Paxinos, 2014) but is in rabbits (Vogt, 2015). Finally, Brodmann (1909) was conflicted over the nature and terminology for cortex between anterior and retrosplenial cortices in the rabbit. While he localized "area 23" at this point, he said that it does not have a granular layer IV like area 23 in primates. Based on his localization of "area 23" in rabbit and the following observations, it appears he was analyzing pMCC.

The midcingulate maps in Fig. 6 were derived in larger studies of each species that should be consulted for the details of area borders and cytoarchitecture. These studies were for the human (Vogt et al., 1995; Vogt, 2009b), monkey (Vogt, 2005), rabbit (Vogt, 2015), and rat and mouse (Vogt and Paxinos, 2014). While the monkey looks like a smaller version of the human, it is not (1) it has a fundal division of each area on the ventral bank of the cingulate gyrus and the dorsal bank of the cingulate sulcus does not appear to have the anatomical characteristics of cingulate cortex (below). In contrast, the human has dorsal bank areas that equate to those on the ventral bank with differences in neuron packing in layers III and V. (2) The monkey does not appear to have an area 32′ and this is the reason for the greater expansion of aMCC in humans. (3) The monkey also does not have an area 33 that extends along the corpus callosum as does the human. Thus, these primates share similarities, but they are not scaled versions of each other.

Homologizing daMCC functions between monkey and human for cognitive research requires a clear understanding of the comparative anatomical features of sulcal architecture in these species. The detailed cytoarchitecture based on NeuN can be found in the articles cited above. Here the SMI32 preparations are used because they are easier to interpret at lower magnifications and most of the key issues in layer V are assessable with them. The human tissue was counter-stained with thionin and the monkey was not thus showing neurons in the superficial layers that are not stained in monkey. Three levels of sulcal MCC are shown in Fig. 7 for both species. Each of the monkey areas a24′, p24c′ and 24d begin just medial to the apex of the cingulate gyrus and have a fundal extension that terminates on the dorsal bank of the cingulate sulcus (fa24c′, fp24c′, f24d). The fundal divisions are not simply distortions around the sulcus but each layer has somewhat different architecture (Vogt, 2005). The boxes in Fig. 7 select strips of dorsal and ventral bank cortex for comparison. The dorsal bank cortex is substantially different from areas on the ventral bank as layers of the former cortex are much thicker and all are heavily SMI-immunoreactive. The human MCC is quite different in that its fundal cortex appears to be simply a distortion around the sulcal depths without essential laminar differences in neuron structure. Moreover, cortex on the dorsal bank appears similar to that on the ventral bank with variations noted with double arrows and associated boxes. This leads to a key comparative conclusion that the dorsal bank of the monkey cingulate sulcus is not comprised of cingulate cortex as also shown previously with receptor binding (Vogt and Palomero-Gallagher, 2012). This conclusion is critical for single unit neurophysiological studies of cognitive functions purported to be mediated by area a24c′ and cortex at more caudal levels of the sulcus.

Higher magnification of each ventral bank sulcal area (Fig. 7C1–C3 and D1–D3) shows that layers Va and Vb in monkey have an increasing intensity of staining and number of SMI+ neurons in the rostral-to-caudal plane. Also, layer IIIc has fewest such neurons in area a24c and most in area 24d. Finally, the gigantopyramidal field of Braak (1976) in human (area 24d) contains gigantopyramids noted with arrows in Fig. 7D3 and these neurons are not present in monkey. A thorough analysis of monkey and human comparative architecture in NeuN and SMI32 preparations is available elsewhere (Vogt, 2009b).

The rabbit does not have a cingulate sulcus or area 24c′ variants present in primates. It does, however, have a two part MCC and this is in substantial contrast to rodent brains that have but one division. Fig. 8 shows differences between the rabbit area a24a′ (aMCC) with the SMI32 antibody in comparison to that in the rostral and caudal parts of MCC in the rat. The robust area a24a′ SMI32 reaction is apparent in rabbit, while the rat has very little such reactivity and few differences between the rostral and caudal parts of MCC. Sections reacted for NeuN are shown for matched sections in rostral and caudal parts of MCC in rat. While there are a few minor differences between the sections, they do not rise to the level of declaring a dichotomous MCC. This is not to say that the rodents do not share features of MCC with the rabbit. Indeed, Nissl staining alone shows that large neurons in layer Va distinguish this region from ACC and RSC and this is a feature of both parts of the rabbit MCC.

6. Cingulate premotor area architecture, circuitry and imaging

One of the key features of MCC is its role in skeletomotor functions in contrast to ACC where emotion and autonomic regulation are predominant. In 1973, Talairach et al. (1973) reported that electrical stimulation of MCC evoked movements such as lip puckering, finger kneading, and bilateral limb movements; not movement in single muscle groups. These coordinated movements reflect behaviors that are valenced and context dependent. For example, lip puckering is not a routine movement but rather associated with kissing and this is not applied indiscriminately but rather to specific individuals in particular contexts. When such activities are indiscriminately applied, it suggests impairment in MCC function. In Tourette syndrome, for example, activity before tic onset is located mainly in the caudal CMA of pMCC (Bohlhalter et al., 2006).

Braak (1976) was the first to recognize a cingulate motor area with pigment/lipofuscin preparations (his gigantopyramidal field) which we now refer to as area 24d in the cingulate sulcus of the caudal part of pMCC (Matelli et al., 1991). This region was soon demonstrated to have spinal projections (Biber et al., 1978) and Dum and Strick (1991) showed a wide range of cingulospinal projections emitted from cortex in most of the cingulate sulcus including areas a24c′, p24c′, 24d and 23c and projections of area 24c to the motor nucleus of the 7th nerve (Morecraft et al., 1996). This wider view of cingulate motor projections leads to the conclusion that there is no single cytoarchitecture associated with premotor projection cortex. Additionally, since the rCMA has high dopamine system architecture (below) and reward and cognitive functions not necessarily directly involved in skeletomotor control, we refer to these as premotor areas (i.e., rCPMA).

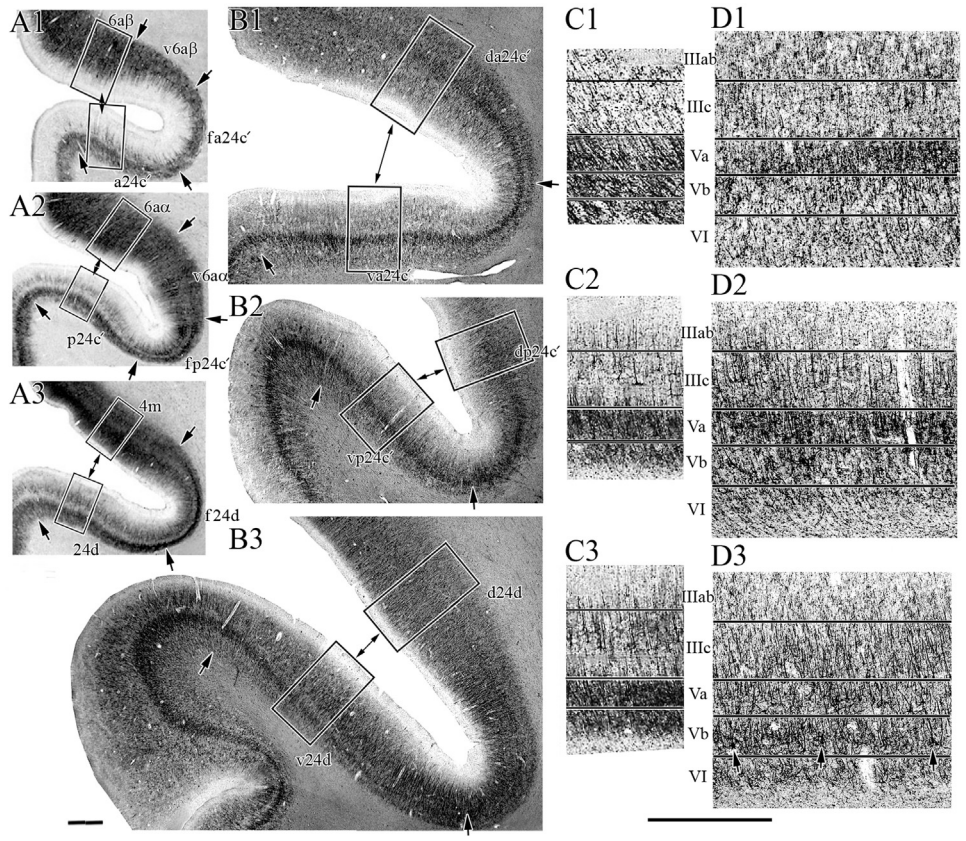

Fig. 7. Three levels of cingulate sulcal architecture in monkey (A, C) and human (B, D) shown with SMI32. Double arrows and boxes emphasize differences between dorsal and ventral banks in the monkey with its non-cingulate dorsal bank cortex versus the human in which the dorsal and ventral bank cortices are similar. C1-3 show monkey areas a24c′, p24c′ and 24d magnified further, while D1-3 are the same areas at the same magnification for the human. Comparison of C1 and C3 shows substantial differences in layer IIIc and Va SMI32+ neurons and dendritic processes which are much greater in C3 than C1. While a similar packing density occurs in human layer IIIc, layer V has a number of differences not apparent in the monkey. Area ventral p24c′ (vp24c′; D2) has the greatest number of labeled neurons in layer Va (vs D1 and D3) and layer Vb has relatively fewer neurons in D3 than D1. Layer Vb neurons in area 24d (D3) has the largest neurons in cingulate cortex that are the gigantopyramids of Braak (arrows). Scale bars, 1 mm and 0.5 mm.

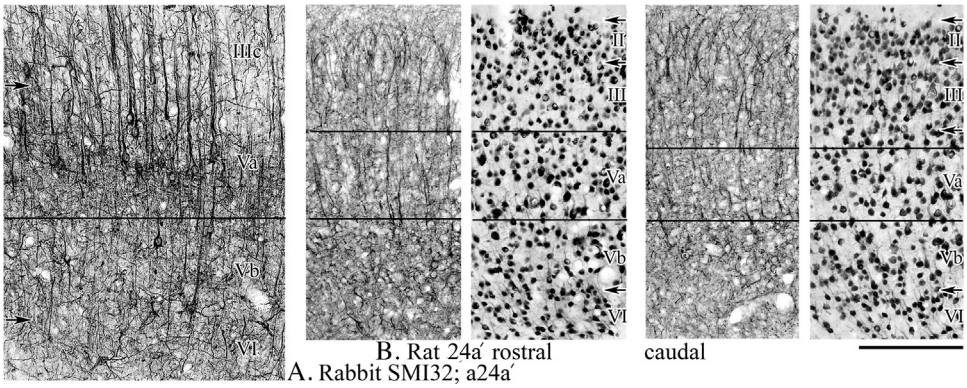

Fig. 8. Comparisons of MCC for rabbit (A. SMI32; a24a′) and rat (B. 24a′ pairs of SMI32 and NeuN sections). The cortex is aligned at the layer Va/Vb border as shown with black lines. Additional lines in rat reference the top of layer Va, while the arrows for rabbit refer to the top of layer Va and bottom of layer Vb, respectively. Rabbit area a24a' has a substantially greater number of SMI32-immunoreactive neurons than either the rostral or caudal parts of rat area 24a′. This argues against a dichotomous MCC in rat, although there are a few minor differences in NeuN staining. Scale bar, 200 μm.

The structure of each cingulate premotor area is unique both among them in the cingulate sulcus and in relationship to adjacent cingulate gyral areas. The cytoarchitecture of area a24c′ in the rCPMA and area 24d in the cCPMA is shown in Fig. 9 with NeuN preparations at low magnification and layers Va and Vb at higher magnification; area 24c in pACC is shown for comparison. Since the largest cingulate neurons are in layer Vb of area 24d (arrow; gigantopyramidal neurons of Braak), we consider this area in comparison to the other two. Layer II is quite broad and layer III is more neuron dense with slightly larger neurons. Layer VI is broad and neuron dense, whereas that in area a24c′ is quite thin and not nearly as neuron dense. Layer Va is more dense and contains larger neurons than in area a24c′, while that in area 24c is densely packed and neurons are substantially smaller. As noted, the arrow points to a column of very large pyramids that characterize area 24d. While the neuron sizes in layer Vb of area 24c is relatively

homogeneous, the large neurons in the other two areas are embedded in a matrix of smaller pyramids.

The receptor binding properties of areas a24c′ and 24d are also shown in Fig. 9 and demonstrate a number of critical features that modulate their functions. Area 24d has the lowest kainite binding in deep layers and lowest AMPA, NMDA and $GABA_A$ binding in superficial layers. Of particular note in terms of reward coding is the fact that area a24c′ has substantially higher dopamine-1 binding in the superficial layers, whereas area 24d has virtually none in superficial and none in deep layers. Also of note is the very weak $GABA_A$ regulation of area 24d in comparison to the other areas. This suggests that, although excitatory input may be relatively low in area 24d, kainite and AMPA activation goes relatively un-inhibited and may account for short-latency pre-movement activity in this area.

The functional properties of the rCPMA in areas 24c and a24c′ and cCPMA in areas p24c′, 24d and 23c are distinct (Morecraft and Tanji, 2009). The onset latency to evoked movements is long and variable in rCPMA, while the latency to onset in the cCPMA is short. Optimal activation of neurons in the rCPMA occurs during self-initiated and non-routine movements and is involved in temporal monitoring, while cCPMA responses occur to passive (signal-triggered) movements and code for direction, target acquisition and orienting movements in space (Akkal et al., 2002; Isomura et al., 2003).

The rCPMA plays a unique role in behavioral control (Shima et al., 1991; Shima and Tanji, 1998) as it is involved in action-reinforcement associations with only a modest selectivity tuning, while the cCPMA is engaged in visual and spatial location and neuron responses are tuned for the force and direction of movements. The rCPMA neurons engage during response selection in humans based on the amount of reward and in determining action-reward associations (Hadland et al., 2003; Procyk et al., 2016) and Shidara and Richmond (2002) showed in monkey that proximity to the reward enhanced neuron firing suggesting a role in reward expectancy. Thus, it is not surprising that dopaminergic afferents arise from the ventral tegmental area (Williams and Goldman-Rakic, 1998) and subserve key functional differences between the cingulate premotor areas. The rCPMA has a high content of dopamine (Miller et al., 2009) and dopamine-1 receptors (Fig. 9, area a24c′) and is involved in reward monitoring and reinforcing reward associations. In contrast, the cCPMA has low-moderate levels of dopamine and dopamine-1 receptors and is involved in orienting movements in sensory spaces with short-duration and reflexive activity without reward and reinforcement properties. Such functional and neurochemical differences substantiate the MCC dichotomy.

Beyond cingulospinal projections of the CPMAs and their dopaminergic afferents, there are other connections that are critical to the functions and dichotomy of MCC including afferents from the midline, mediodorsal and intralaminar thalamic nuclei (MITN) and parietal cortex (below). The MITN contain nociceptive neurons and they serve as the basis for the initial nociceptive trigger for pain processing in cingulate cortex (Vogt, 2005). An elegant study by Hatanaka et al. (2003) used two retrograde tracers in the monkey rCPMA and cCPMA to explore differences in thalamic afferents to both cortices. The percentage of all labeled neurons projecting from the MITN to the rCPMS was 12% from the mediodorsal nucleus, 13% from the centrolateral nucleus and 26% from the parafascicular nucleus. In contrast, these percentages were only a fraction of those projecting to the cCPMA with 7% from the mediodorsal, 2% from the centrolateral, and 12% from the parafascicular nuclei. Thus, the rCPMA area a24c′ receives a higher density of nociceptive inputs than do the cCMA areas p24c′ and 24d. Finally, Erpelding et al. (2012) showed in human subjects that greater warm detection sensitivity correlates with thinning in aMCC (Fig. 10A.1), while greater heat pain sensitivity correlates with thickening of pMCC in the cingulate sulcus (Fig. 10A.2). While it is unclear how differences in cortical thickness relate to functional output, it is possible that thickening in pMCC is a compensatory mechanism to enhance nociceptive processing.

7. aMCC & vaMCC: nociception, itch, fear, pain catastrophizing

Activity generated by acute nociceptive stimuli recorded with fMRI is located mainly in MCC as shown in Fig. 11A. While not overtly painful, itch evoked with cowhage spicules also activates aMCC (Fig. 10B; red–orange). In contrast, active scratching of such an itch activates pMCC enhancing the view that reflexive motor activity is mediated by this subregion and demonstrating a functional dissociation between aMCC and pMCC. Interestingly, both active and passive scratching of an itch inactivates pACC via a reciprocal inhibitory mechanism. This mechanism was first described during emotion-generating stimuli by Drevets and Raichle (1998) as discussed further below as it is bidirectional between MCC and pACC.

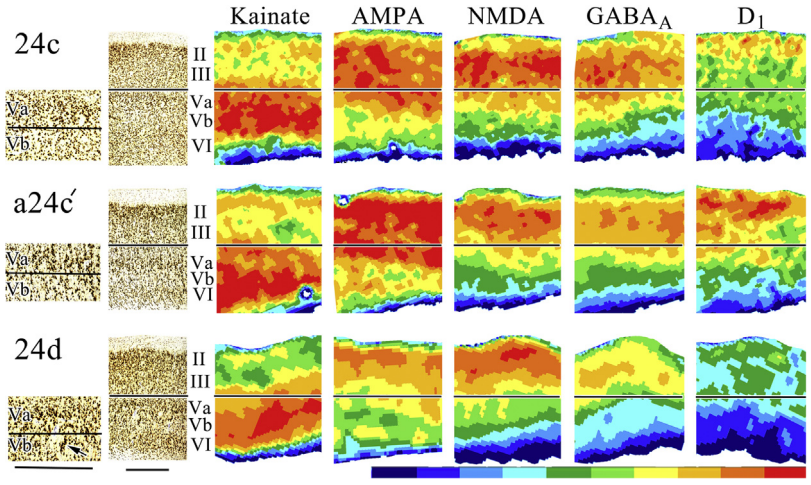

Fig. 9. Structure and receptor binding of cingulate premotor areas with area 24c for comparison. The gigantopyramidal neurons in layer Vb of area 24d are the largest in cingulate cortex (arrow). Large neurons in layer Vb are apparent in area a24c′ but less so in area 24c. Of particular note for receptor binding in area 24d is the low AMPA, $GABA_A$ and D_1 binding, and in area a24c′ particularly high D_1 binding. Scale bars, 500 μm; Receptor binding density high (red) to low (blue; modified from Palomero-Gallagher and Zilles (2009).

The conjunction between acute nociceptive and itch-evoked activation and fear-evoked activity in aMCC is apparent in Figs. 10B, 11A and B. Voluntary, action-related processing induced by a motor task during painful or non-painful stimulation also drives aMCC (Perini et al., 2013) emphasizing the linkage between pain processing and movement; other areas including the anterior insula do not show this association. Fear in this context refers to a premotor signal and may not be a matter of conscious awareness, since emotion systems form implicit rather than explicit memories (Phelps and LeDoux, 2005). Further, not all activations in acute pain studies are associated with affect as demonstrated by sensorimotor activations in the lateral pain system (Becerra et al., 1999; Frot et al., 2008); i.e., even cingulate pain activity may not be associated with affect per se and it is likely that aMCC fear activity is not explicit. Moreover, aMCC nociception is positively correlated with the expectation of pain relief (Petrovic et al., 2005) as is the case for itch relief (Papoiu et al., 2013). Finally, Singer et al. (2004; Fig. 10E, red) reported aMCC activation when subjects observed nociceptive stimulation of a loved one; pain empathy. Such a response engages an individual to respond, as they would in a similar situation for themselves, to assist another in achieving pain relief.

The loss of pain control evokes anxiety and is associated with suffering. This was shown by sites of atrophy in the vaMCC that are correlated with catastrophizing in patients with migraine headache (Hubbard et al., 2014; Fig. 11C) as discussed further under Diseases of MCC. Thus, the aMCC is in a unique position to cognitively interpret (pain empathy), anticipate and trigger avoidance responses to pending noxious stimulation and the pMCC is engaged in general orienting to sensory stimuli including noxious ones (below). The question arises as to the role of implicit fear in motor control.

Fear activations appear to be pivotal to selection between rewarded and punished responses made in aMCC. Since aMCC has rich dopaminergic innervation, is involved in reward functions and is activated during noxious stimulation, there is an overlap of both pain and reward systems in this subregion. Koyama et al. (2001) studied monkey aMCC and demonstrated that, of neurons activated during a response period, 58% were associated with nociceptive cutaneous electrical stimulation and 42% for obtaining a juice reward. Thus, the overlap of aversive and rewarding functions in aMCC requires a mechanism(s) for distinguishing and predicting pain or reward outcomes to select the appropriate response. One such mechanism is fear evoked by nociceptive afferents from the MITN that provides an implicit premotor signal to enhance nocifensive behaviors.

8. daMCC: components of the feedback-mediated decision making model

The pACC and aMCC are involved in different functions and reciprocal inhibition can enhance the unique functions of each subregion as noted later. Bush et al. (1998) and Whalen et al. (1998) performed two Stroop interference tasks that involved different sources of interference, one cognitive and one affective, in the same subjects during the same scanning session. Stroop testing

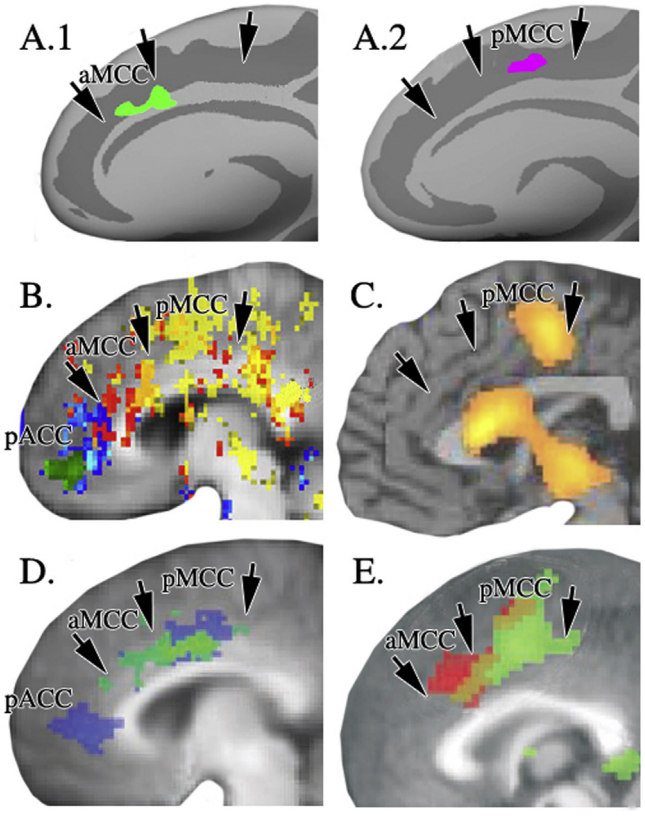

Fig. 10. Sensory activity unique to parts of MCC. (A.1) Warm detection sensitivity associated with thinning of aMCC, while (A.2) heat pain sensitivity is associated with thickening of sulcal pMCC (Erpelding et al., 2012). (B) Active scratching of an itch evoked with cowhage spicules is associated with activity in pMCC (yellow), while itch itself activates aMCC (red–orange). In contrast, reciprocal inhibition in pACC (deactivation with active scratching-blue and passive scratching-green) occurred in pACC (Papoiu et al., 2013). (C) Attention to the location of innocuous stimuli activates pMCC (Kulkarni et al., 2005). (D) Pain responses can be modulated by a subject's belief that they can regulate it in contrast to when they cannot (blue; Salomons et al., 2004; green is the overlap between pain controllability and sensory response). (E) Pain empathy. Area in green represents activation for pain versus no pain during the experience of one's own pain and area in red is the site for pain versus no pain when it is observed in another subject (Singer et al., 2004). (A2, B–D) rotated horizontally to match Fig. 1B flat map.

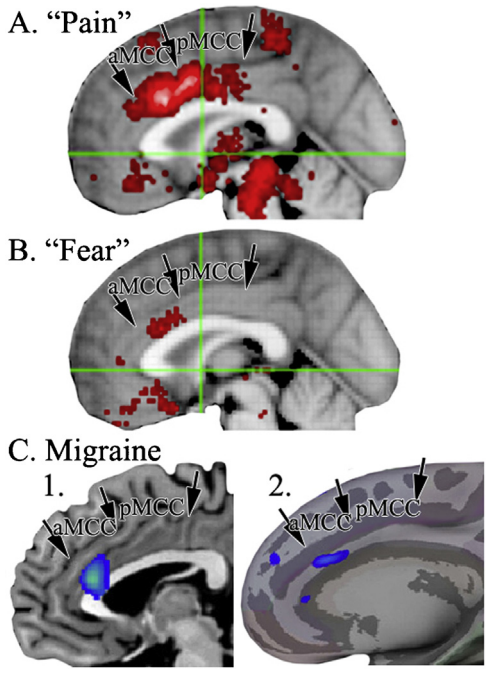

Fig. 11. (A) Cingulate activations during 'pain' (Neurosynth search; 420 fMRI studies as of 12/11/2015; see Yarkoni et al., 2011). (B) Activity evoked during "fear" (Neurosynth search; 132 studies). (C) Migraine patients with negatively correlated grey matter volume in vaMCC (C1) and atrophy correlated with pain catastrophizing (C2; Hubbard et al., 2014).

requires the subject to overcome reflexive responses to execute a button press. In the counting Stroop word stimuli are presented in sets of 1–4 identical words per trial and subjects select one of four buttons relating to the number of words on the screen. This produces a reliable interference effect when presented with number-words that are incongruent with the correct response. For example, a subject presented with the word "four," written two times, requires more time to respond correctly by pushing the second button compared to a similar presentation of a neutral word; i.e., non-number related such as "bird." For the emotional Stroop, emotionally valenced word stimuli are presented with alternating blocks of neutral and negatively valenced words. For example, during the neutral condition, a subject might see the word "cushion" written three times on the screen and would push the third button. During the negative condition, a subject might see the word "murder" written four times on the screen and would push the fourth button. Delays in reaction time in the negative compared to the neutral condition are interpreted as emotional interference.

Using these two tasks, a double-dissociation revealed that the counting Stroop activated daMCC but not pACC, whereas the emotional counting Stroop activated ACC but not MCC. A meta analysis by Bush et al. (2000) substantiated differences between these subregions with cognitive tasks activating the aMCC and emotionally-valenced tasks activating ACC. Importantly, the converse where cognitive tasks deactivate the pACC and emotionally-valenced tasks deactivate the aMCC was also reported (Drevets and Raichle, 1998; Mayberg et al., 1999; Raichle et al., 1994). The sensorimotor paradigm used by (Papoiu et al., 2013; Fig. 10B) also provides evidence of reciprocal inhibition; active scratching activated pMCC and inactivated pACC. Thus, *reciprocal inhibition* assures that the functions of these subregions are segregated for different aspects of information processing associated with emotion/autonomic and cognitive/skeletomotor control.

8.1. Cognitive functions of monkey area a24c′

The daMCC in monkeys refers to area a24c′ on the dorsal bank of the anterior cingulate gyrus and its fundal extension (Fig. 3B), while in human it is comprised of areas a24c′ and 32′ (Fig. 3A). The dorsal bank of the monkey anterior cingulate gyrus, beyond the fundal extension, is not cingulate cortex based on anatomical criteria (Fig. 7). Also, since monkeys do not appear to have an area 32′, human studies are the only means of assessing this area's functions. Monkey neurophysiological studies of area a24c′ suggest cognitive functions to be expected for human daMCC.

The reward-based, decision-making properties of neurons in the monkey rCPMA were shown by Shima and Tanji (1998); not only did different populations of neurons respond to target detection, motor responses and constant rewards, but many signaled unexpected, reduced rewards. Indeed, the proportions of each cell type were not equal as more than five times as many cells responded to movement selection based on reduced reward (37%) versus constant reward (7%). Also, muscimol block of a24c′ impaired motor selection based on reduced rewards. Neurons in monkey area a24c′ integrate information from working memory of task instructions with reward and error information to make decisions for simple and complex motor tasks (Akkal et al., 2002; Isomura et al., 2003; Procyk and Joseph 2001). Niki and Watanabe (1976) identified cells in the fundus of the cingulate sulcus and to a lesser extent its ventral bank that responded to cue location and response direction and whose activity during a delay period predicted whether the monkey would make a correct or incorrect choice. Shidara and Richmond (2002) reported that rCPMA cells responded differently based on reward expectations during a sequential motor task. Thus, area a24c′ synthesizes information from multiple sources and indicates that a particular decision has been made.

Neurons in monkey daMCC respond to stimulus anticipation, they are sensitive to targets, motor responses, rewards, and/or errors. Interestingly, error-sensitive cells also respond if the monkey is not rewarded for making the correct response (Niki and Watanabe, 1979). Gemba et al. (1986) reported that error potentials from electrodes covering the entire aMCC followed inappropriate, self-paced (non-rewarded) responses and such potentials did not follow correct (visually-cued and rewarded) responses. Nishijo et al. (1997) also found ACC neurons that were anticipatory, stimulus-related, response-related, and reward-related; adding that subsets responded to novel objects, while others could discriminate rewarding, aversive, and neutral objects. Thus, neurons in area a24c′ can engage in target detection, motor responses, constant rewards, and unexpected (reduced) rewards. They integrate information from working memory of task instructions with reward and error information to make decisions regarding routine and non-routine motor sequencing. They signal which sequence the monkey was performing and the expectation of reward based on context (anticipation).

8.2. Human cognitive studies of daMCC

As in monkeys, neurons in the human daMCC are intermingled with different response properties and each activation site is viewed from a similar perspective. Here we follow a course from novel stimulation through a series of steps that lead to motor output and feedback based on the detection of errors. These are the components of feedback-mediated decision making that serve as the basis for the model of daMCC function. The following consideration is based in part on the views of Bush (2009) and this excellent chapter should be read for further details of the emergence of cognitive theories of daMCC function and additional citations.

Raichle et al. (1994) reported novelty sensitivity in daMCC by showing that subjects performing a verb generation task (i.e., given an object, produce a related verb, such as when given 'hammer', say 'hit') initially had high daMCC blood flow, but with practice on the same list of nouns the blood flow decreased. However, daMCC blood flow again increased when a novel set of nouns was introduced. Similarly, two studies using the counting Stroop task showed significant daMCC activity initially, but it was not significant with successful practice as measured by decreases in reaction times (Bush et al., 1999, 1998).

The cognitive (vs purely motor control) functions of daMCC were first shown by Murtha et al. (1996) who reported that subjects anticipating performing tasks activated daMCC, before overt actions were made. Corbetta et al. (1991) reported daMCC activation during divided attention or shifting between tasks and Periánez et al. (2004) used magnetoencepalography during a Wisconsin card-sorting test to examine set shifting with a high degree of temporal resolution. Preparation for set-shifting, responses to shift, and relative to non-shift cues, occurred first in inferior frontal areas 45 and 47 at 100–300 ms from trial onset and then in the rCPMA of aMCC at 200–300 ms. Finally, Kirsch et al. (2003) used fMRI to show that subjects anticipating reward based on the presentation of a visual conditioned stimulus activated daMCC and that anticipated monetary rewards increased activity compared to positive verbal feedback. Thus, daMCC has a role in anticipation/expectancy and set shifting before a specific movement is chosen.

Hoffstaedter et al. (2013) employed an imaging paradigm in which movement selection was based on free choice, timed choice or no choice. The daMCC was the only region that had increasing activity with more intentional components during movement initiation. Furthermore, critical to movement control is the role of daMCC in error processing. Humans produce a medial-frontal error-related negativity (Coles et al., 1995, 2001; Gehring and Fencsik, 2001; Holroyd et al., 2005). Also, fMRI studies have shown daMCC activation in response to errors (Fiehler et al., 2004; Holroyd et al., 2004; Ullsperger and von Cramon, 2001). A single-trial fMRI study reported that the daMCC was active during both error and correct trials (Carter et al., 1998). Thus, daMCC is pivotal to response initiation in the context of free choice and this function is modulated by error processing signals.

An early cognitive theory of daMCC function was selection-for-action (Allport, 1980, 1987; Posner et al., 1988). It related attention and target identification with response selection by proposing that selective attention to target stimuli was biased by pre-existing conditions that make attention and target selection relevant to response selection. Selection-for-action meant selection, not only for overt responding, but for internal cognitive activity related to decision making, memory or information transformation. Norman and Shallice (1986) referred to this form of attention as "supervisory" and suggested that it was used whenever non-routine processing was required. The selection-for-action influence was evident during modality specific motor choice (Paus et al., 1993), motor control/monitoring and/or willed action (Badgaiyan, 2000; Liddle et al., 2001), Stroop tasks (Bush et al., 1998; Pardo et al., 1990) and tasks involving the over-riding or inhibition of pre-potent responses such as Go-NoGo tasks (Kawashima et al., 1996). Thus, the selection-for-action view fits with much of the data on daMCC involvement in selective/divided attention and conflict monitoring.

Working memory reflects a sustained neuronal representation of a stimulus or motor choice maintained over a delay period. A review of working memory research (Petit et al., 1998) indicated that daMCC is often activated by working memory tasks representing the neural substrate of being prepared to make a choice rather than motor preparations for executing a response once the choice was made. Schnell et al. (2007) evaluated visuomotor action monitoring and observed that incongruence between the subjects' actions versus their perceptions evoked activity in areas 32′ and 8. The monitoring observation, though, does not explain anticipatory activity when daMCC activation is obtained after task instructions are given but before a stimulus is presented (Kirsch et al., 2003; Murtha et al., 1996; Ploghaus et al., 2003). Mayr (2004) showed that the degree of conflict was not correlated with the reaction time on subsequent trials and explained how a repetition-priming effect could account for the behavioral data. Thus, daMCC is engaged in both action anticipation and monitoring of ongoing action outcomes.

Dopaminergic signals produced when a predicted reward is not received modulate daMCC activity and it uses these predictive error signals to modulate behavior. Holroyd et al. (2004) showed that daMCC responds in the predicted manner to internally and externally generated error signals with higher daMCC activity in response to unpredicted errors. Also, Brown and Braver (2005) compared the error-likelihood model against conflict-monitoring. Notably, the error likelihood computational model produced greater daMCC activity on trials calling for a motor change than for simple go trials, greater activity on change trials that had been previously cued as likely to produce high rates of errors (i.e., more likely to require change than go trials), and greater activity on correct go trials (which should not produce a conflict signal), and higher activity on correct, high likelihood of change/error trials than on correct, low-likelihood of error go trials. The prediction error theory accounts for error-related observations of daMCC and can explain anticipatory and correct trial performance.

8.3. Feedback-mediated decision making

The daMCC feedback-mediated decision making model (Bush, 2009) is an extension of the reward-based decision-making concept proposed by Shima and Tanji (1998),Bush et al. (2002) and Williams et al. (2004). It was broadened to accommodate more complex factors than simple rewards or reward omissions such as errors, stimulus-response associations, memory, motivation, emotional state, and pain that are encoded by daMCC and influence decisions. This concept argues that there is not a single function for daMCC, but rather that the daMCC is a local intracortical network comprised of functionally heterogeneous neurons that anticipate and detect motivationally salient targets, indicate novelty, influence motor responses, encode reward values and signal errors and its role in cognition is to act within cognitive/motor networks to increase the efficiency of decision-making and execution by integrating input from various sources including context, motivation, evaluation of reward and error, and representations from cognitive and emotional networks.

Bush et al. (2002) used fMRI to evaluate a task similar to that of Shima et al. (1991) that exploited the large difference in the proportions of reduced reward and constant reward cells and demonstrated daMCC activation in response to reward reduction. These data supported a role for daMCC in reward-based decision making. Subsequently, using the same task and intracranial recordings in human patients about to undergo daMCC ablation, Williams et al. (2004) showed that single daMCC neurons increased responses to reduced monetary rewards and the ablation impaired reward-based motor selection.

Thus, the mechanism of how a local daMCC network operates and contributes to cognition is consistent with observed behavior. Fig. 12 summarizes the broad steps engaged in this model. Novelty and target detection cells would similarly enhance attention to relevant stimuli. Set shifting is evoked before detailed motor planning to prepare for movements in a particular context. Signaling from anticipatory/timing cells have predictive value,

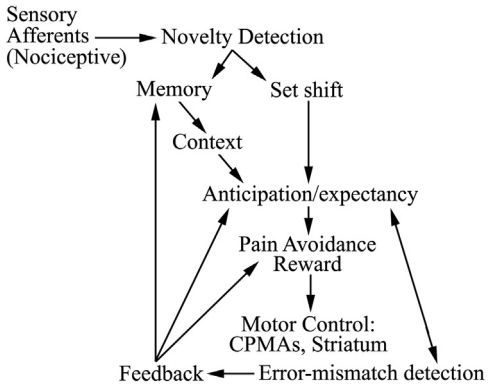

Fig. 12. Flow diagram of steps engaged during feedback-mediated, decision making in daMCC. It begins with sensory afferents, including nociceptive ones that signal a mismatch instantly, and a very early set shift signal. Depending on task demands, memory and sensory context are evaluated and determine anticipatory and motor preparation that controls motor output systems. Error-mismatch detection following a behavioral response modifies memory, expectations and the motor plan via a feedback mechanism.

and improve the processing of salient stimuli. Motor response cells in daMCC have been shown to contribute to complex motor behaviors, especially during non-routine tasks. Finally, reward and error neurons provide feedback that guides future actions based on memory and modifies anticipatory activity. It modifies pain avoidance and rewarded behaviors to accommodate current and predicted contexts and relevant movements.

9. pMCC: parietal input, rapid motor responses, body orientation, nociception

A primary role of pMCC in brain function is reflexive orientation of the body in space to sensory stimuli including noxious ones. It contrasts significantly from activity in aMCC where working memory requires longer times to modulate cognitive/motor functions. This view is supported by the fact that pMCC has almost no evoked emotion activity (Vogt, 2005), neuronal discharges in the cCPMA have short latency, pre-movement responses (above), and electrical stimulation of muscles evoke potentials that are likely in area 24d which is part of the cCPMA (Niddam et al., 2005). Moreover, the time delay to nociceptive evoked activity is too short for emotional or cognitive assessment. Frot et al. (2008) chronically implanted electrodes in human cingulate cortex and recorded laser-evoked noxious thermal responses. Responses in the pMCC (including cCPMA) had a delay to onset of ~150 ms. They concluded that the medial pain system is not devoted exclusively to pain affect, but is also involved in fast attentional orienting and motor withdrawal responses to nociceptive inputs.

Before exploring pMCC function further, the connections of this region need consideration to orient to the types of information that is available for processing therein. As frontal connections are widespread over all cingulate cortex (Morecraft and Tanji, 2009) and do not delimit parts of MCC, these projections will not be considered. Parietal afferents, however, distinguish between the two MCC subregions and mediate key pMCC functions.

9.1. Parietal afferents & functions

Parietal cortex plays a crucial role in modulating MCC during multisensory action monitoring. This includes responses to noxious stimuli as such stimuli are effective in alerting to a mismatch between expected and actual motor outcomes. Parietal afferents to MCC are shown in Fig. 13A and B with anterograde (Vogt and Pandya, 1987) and (C and D) retrograde (Morecraft et al., 2004) labeling. The projection map of the latter study was coregistered to the same flat map used in the former (Vogt, 2005). Inferior parietal cortex projects mainly to pMCC and only lightly to the posterior part of aMCC. A light projection to the gyral surface areas a24a′/b′ was also shown by Cavada and Goldman-Rakic (1989) but is not to the rCPMA or to any part of ACC. Injections of retrograde tracers into the cingulate sulcus show a substantial difference between afferents to areas p24c′ (Fig. 13C) and 24d (D). Input to the former arises from primary somatosensory and motor cortices, and areas 5, 7a and 7b of the medial intraparietal sulcus (IPS), and medial parietal areas 7m, Opt and MST. In contrast, area 24d receives input from only area 7b of the lateral IPS and areas Opt, MST and 7m.

Each parietal area provides specific information to pMCC to guide body orientation and reflexive movements. MacKay and Crammond (1987) analyzed neuron discharges in area 5 on either side of the IPS in behaving monkeys and observed anticipatory activity as discharge rates increased whenever a specific body part was approached as though contact would be made. They also responded to cutaneous and proprioceptive stimuli of the target body area and to expected reward, visual cues or sounds of familiar people. Area 7a had similar anticipatory output but without somatosensory receptive fields. Andersen (1995) and Andersen et al. (1990a, 1990b) evaluated posterior parietal area 7a and found eye-position dependent tuning for location of head-centered coordinate space. These neurons were light-sensitive, had memory properties (i.e., delay-period firing) and saccade-related activity, all of which were affected by eye position. They concluded that area 7a plays a role in making coordinated transformations for visually guided movement. Crowe et al. (2004) took this further by evaluating neurons during a maze solution task and found that 1/4 of neurons were spatially tuned to maze path direction and were not active in naïve animals. The neuron tuning was associated with the maze solution not saccades or visual receptive fields and this information is provided to pMCC.

The multisensory nature of lateral IPS neurons was shown by Stricanne et al. (1996) in monkeys; about 1/3 of neurons were

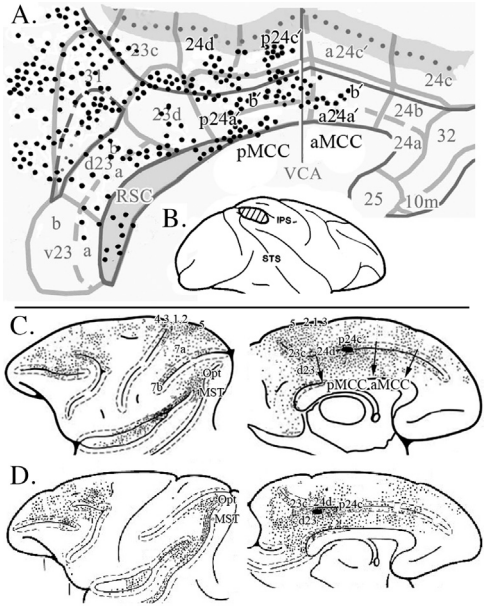

Fig. 13. Inferior parietal afferents (A) shown with labeled terminals following injection of [3H]-amino acids (B) hatched. Fundal cortex is grey lining the depth of the cingulate sulcus. Retrograde labeling of all neurons following tracer injections into area p24c′ (C) and area 24d (D).

driven by auditory or visual stimulation and half of cells showing auditory driving changed in an eye-centered manner and 1/3 of these responded in head-centered coordinates. Neurons showed significant auditory-evoked activity during the memory period and of these 44% discharged in an eye-centered manner. For a substantial number of neurons in all categories, the magnitude of the response was modulated by eye position. Thus, the lateral IPS cortex transforms auditory signals for oculomotor purposes and neurons are concerned with the abstract quality of where a stimulus is in space, independent of the exact nature of the stimulus, and this information is provided to pMCC.

9.2. Pain processing

Parietal nociceptive neurons provide context for visual and spatial orientation that reaches pMCC as noted above. Dong et al. (1994) evaluated neuronal discharges in the trigeminal region of area 7b in awake monkeys and many neurons were responsive only to visual stimulation. The somatosensory neurons were thermoreceptive with nociceptive or innocuous properties, while visually responsive neurons responded only to innocuous stimulation. Most importantly, threatening or novel visuosensory stimuli that approached the face aligned with the most sensitive portion of the cutaneous receptive field evoked the greatest discharges and these were often maintained by keeping the visual targets in place. These findings support the view that pending noxious stimuli provide orienting, anticipatory information to pMCC. Mohr et al. (2005) showed three parts of human cingulate cortex are differentially activated by either externally or self-administered noxious thermal stimuli and showed that pMCC is active during the application of externally generated noxious stimuli. Responses increased with increasing pain perception independent of certainty/uncertainty or self-/externally administered stimuli.

The features of noxious stimuli that drive each part of human MCC differ. Most activity generated by noxious and innocuous cutaneous stimulation in humans is in the rCPMA (Moulton et al., 2005). Büchel et al. (2002) generated nociceptive activity in the human rCPMA with stimulus intensity ramps and stimulus perception. In contrast, an increase in fMRI signal in the cCPMA occurs during noxious muscle but not noxious cutaneous stimulation (Henderson et al., 2006). This is the first demonstration of a nociceptive response in the cCPMA with fMRI, suggests a pivotal link to muscle stimulation and confirms the evoked potential work of Niddam et al. (2005). Since emotional activations are infrequent in this region (Fig. 11B) and nociceptive responses are too short (~150 ms; Frot et al., 2008) to engage conscious perception, it appears that deep tissue nociceptive driving of the cCPMA is linked to orienting the body toward noxious stimuli possibly via parietal afferents discussed above rather than evoking affect and motoric (targeted) decision making. These observations suggest that pMCC orients the body to sensory stimuli including nociceptive ones and sensory activations may not be specific for noxious stimuli.

The cCPMA, however, does not depend on parietal afferents for its primary nociceptive information. Noxious stimuli directly drive the MITN projections to MCC (above). These stimuli themselves are non-ambiguous and negatively coded. This short circuit provides for more rapid engagement of the rCPMA and bypasses a stage of evaluating sensory stimuli for significance thus providing an intermediate stage of motor processing for the body before more detailed and cognitively demanding outputs are generated in daMCC and the rCPMA.

While the cCPMA is engaged in rapid orientation of the body to noxious stimuli, this activity can be modulated by cognitive processes. Singer et al. (2004) (Fig. 10E, green) showed that pain-related activation associated with experiencing pain in oneself activates pMCC. This emphasizes the internal orientation function of this region in contrast to that of aMCC which engages decision-making processes associated with pain avoidance and relief. Salomons et al. (2004) (Fig. 10D) manipulated the subjects' belief that they had control over a nociceptive stimulus, while the stimulus itself was held constant. Pain that was perceived to be controllable resulted in activation in pMCC (blue, Fig. 10C), while the nociceptive stimuli evaluated for both controllable and uncontrollable conditions (green) overlapped rostrally with the controllable site and included aMCC. Finally, the active process of scratching an itch is a reflexive process that activates pMCC along with the supplementary motor area (Papoiu et al., 2013; Fig. 10B). Thus, subjects may have control over reflexive motor activity in pMCC, while nociceptive activity in aMCC requires conscious attending, assessment of relevant contextual cues and preparatory activity for cognitive processing, motor control and memory.

10. Diseases of midcingulate cortex and drug responses

The vulnerability of MCC in human disease both confirms the unique organization of MCC and provides a basis for developing animal models. This is not to say that MCC is the only region involved in a particular disease, only that it is prominent among multiple players and is often linked to specific symptoms and functional impairments shown with behavioral testing.

Not surprisingly, since aMCC is highly responsive to acute noxious stimuli, studies of **chronic pain** show a vulnerability of MCC and particularly aMCC to chronic activation. In a study of female patients with atypical facial pain, thermal hand stimulation evoked robust activation to noxious over innocuous stimuli in aMCC (Derbyshire et al., 1994). The importance of vaMCC in pain affect is suggested by Hubbard et al. (2014) who explored patients with migraine headaches not currently in pain that display high anxiety, maladaptive coping strategies and a high degree of pain catastrophizing. Catastrophizing is a cognitive strategy for coping with chronic pain (Osman et al., 2000) and reflects poor coping abilities (Turk and Rudy, 1992). Fig. 11C shows the outcomes of the Hubbard study that localized vaMCC atrophy negatively correlated with catastrophizing using voxel-based morphometry (C1) and assessment of tissue surface atrophy (C2). This site does not involve the daMCC suggesting a unique role of the vaMCC in pain fear, anxiety and coping. Finally, Kulkarni et al. (2007) evaluated glucose metabolism during the experience of osteoarthritic pain and observed elevated metabolism in aMCC, pACC and PCC. Thus, MCC can be a victim of its own acute pain processing functions during chronic stimulation.

Chiu et al. (2012) published an important study differentiating hypoperfusion of MCC in an analysis of **progressive supranuclear palsy** (PSP) and frontotemporal dementia with tau pathology (FTD) and their findings are shown in Fig. 14B. The black site of hypoperfusion is for PSP and is mainly in pMCC but also encroached on aMCC, while the grey site is for FTD and is mainly in aMCC (white dots emphasize overlap between the two sites). Note the additional site for FTD in sACC. Hypoperfusion in pMCC was correlated with the Stroop color-word and Weigl color-form sorting tests, while that in FTD engaged mainly aMCC and sACC. Thus, cognitive decline and behavioral changes during the course of PSP are associated with neuron loss and hypo-perfusion mainly in pMCC, while that in FTD is in aMCC and sACC (areas 25, s24 and s32). This study critically supports the differential vulnerability of MCC subregions to neurodegeneration and resulting cognitive decline.

Bertocci et al. (2012) (Fig. 14C) sought to identify biomarkers in female patients with either **unipolar depression** or bipolar disease to differentiate them with fMRI. Subjects performed an emotional face, n-back task with high (2—back) and low (0—back) memory

loads flanked by two positive, negative or neutral face distracters to examine executive control. High memory load with neutral face distracters elicited greater bilateral and left pMCC activity in unipolar than in healthy and bipolar females, respectively. During high memory load with neutral face distracters, elevated pMCC activity in unipolar depression suggests abnormal recruitment of attention-control circuitry for task performance. Differential patterns of functional abnormalities in neural circuitry supporting attentional control during emotion regulation, especially in the pMCC, is a potential measure to distinguish unipolar from bipolar

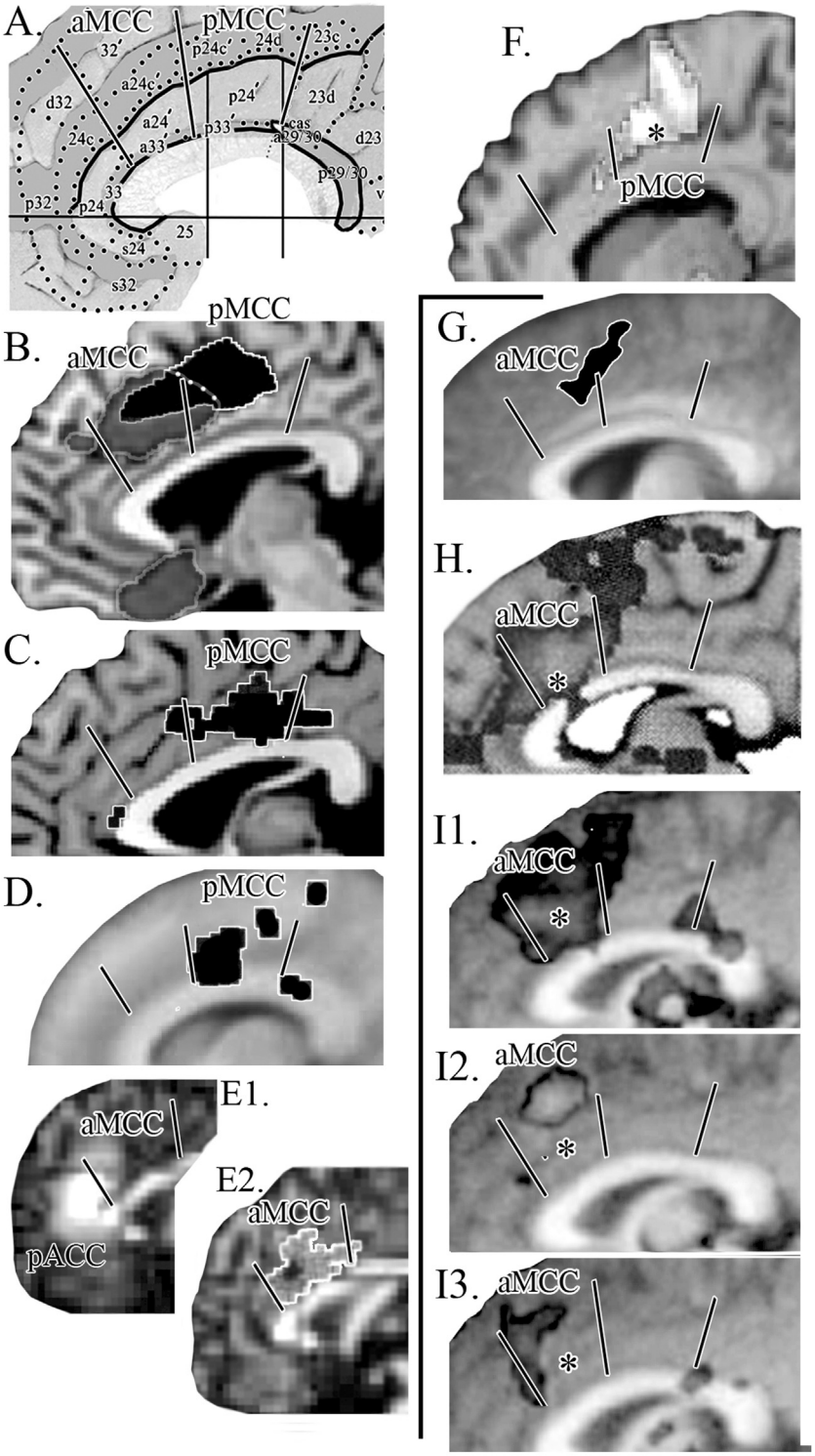

Fig. 14. Disease vulnerabilities of MCC. (A) Flat map showing MCC borders. (B) PSP, Chiu et al. (2012; overlap with FTD—grey-marked with white dots). (C) Unipolar depression, Bertocci et al. (2012). (D) PTSD, Shin et al. (2009); (E) spontaneous tic responses in patients with Tourette syndrome (TS; E1) and comparison to healthy control generation of tic behaviors (E2; Wang et al., 2011). (F) Pre-tic activity in TS, Bohlhalter et al. (2006) (B, C, D and F reoriented to match flat map). Right panel: aMCC drug responses. G. Methylphenidate in ADHD, Bush (2009). (H) Ibuprofen following molar extraction, Hodkinson et al. (2015). I1.-3. Placebo (H1), 0.05 (H2) and 0.1 (H3) mg kg^{-1} h^{-1} ketamine progressively blocks noxious thermal-evoked aMCC (asterisks; no response at highest dose; not shown; Sprenger et al., 2006).

females, it confirms the unique vulnerability of pMCC and provides a behavioral probe to study depression and other disorders that selectively impact pMCC.

Shin et al. (2009) published an important study that assessed glucose metabolism in veterans with **posttraumatic stress disorder** (PTSD) and their twin siblings without PTSD. Subtraction of glucose metabolism in the healthy twins from that in the combat-exposed veterans with PTSD revealed higher rates of resting glucose metabolism in pMCC (Fig. 14D). The previous two clinical studies suggest behavioral approaches to assessing this alteration in PTSD. The Stroop color-word and Weigl color-form sorting tests (Chiu et al., 2012) and the emotional face, n-back task with high and low memory load (Bertocci et al., 2012) could be used to examine executive control in conjunction with fMRI in PTSD.

Behavioral changes follow aMCC impairments in a number of other diseases including obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), and Tourette syndrome (TS) that can be traced to the essential role of this subregion in decision making and motor control. However, findings from two excellent studies of TS raise interesting questions as there is a mismatch between the findings. While the "ACC" activity appears to justify an overall congruence in the findings, a finer grain analysis of MCC subregions suggests the data are not consistent and the aMCC/pMCC dichotomy may help resolve such a problem. Thus, the paragraphs below on TS are meant to show how cingulate subregional models can perform as a predictive tool to generate new study designs and data analyses.

Disruption of aMCC function in **obsessive-compulsive disorder** is well established and a thorough review of this problem is provided by Saxena et al. (2009) that emphasizes the importance of checking symptomatology in relation to aMCC impairment. Indeed, cingulotomy ablation targeted at aMCC has been used for OCD (Ballantine et al., 1977) and a case of a young girl with focal seizure activity and OCD was reported by Levin and Duchowny (1991). She had medically resistant seizures and severe OCD symptoms including washing and checking compulsions combined with progressive intellectual and psychosocial deterioration. Intracranial electroencephalography showed a focal seizure in the right aMCC and a cingulotomy was performed (Fig. 15A). Post-cingulotomy she was seizure free and there was a significant improvement of her OCD symptoms.

Mataix-Cols et al. (2004) evaluated patients with a symptom-provocation protocol in four conditions with fMRI while viewing alternating blocks of emotional (washing-, checking-, hoarding-related, or aversive, symptom-unrelated) and neutral pictures, while imagining scenarios about the content of each picture. The different OCD symptom dimensions were mediated by relatively distinct structures that are implicated in cognitive processing and emotion. The activation in daMCC shown in Fig. 15B was associated

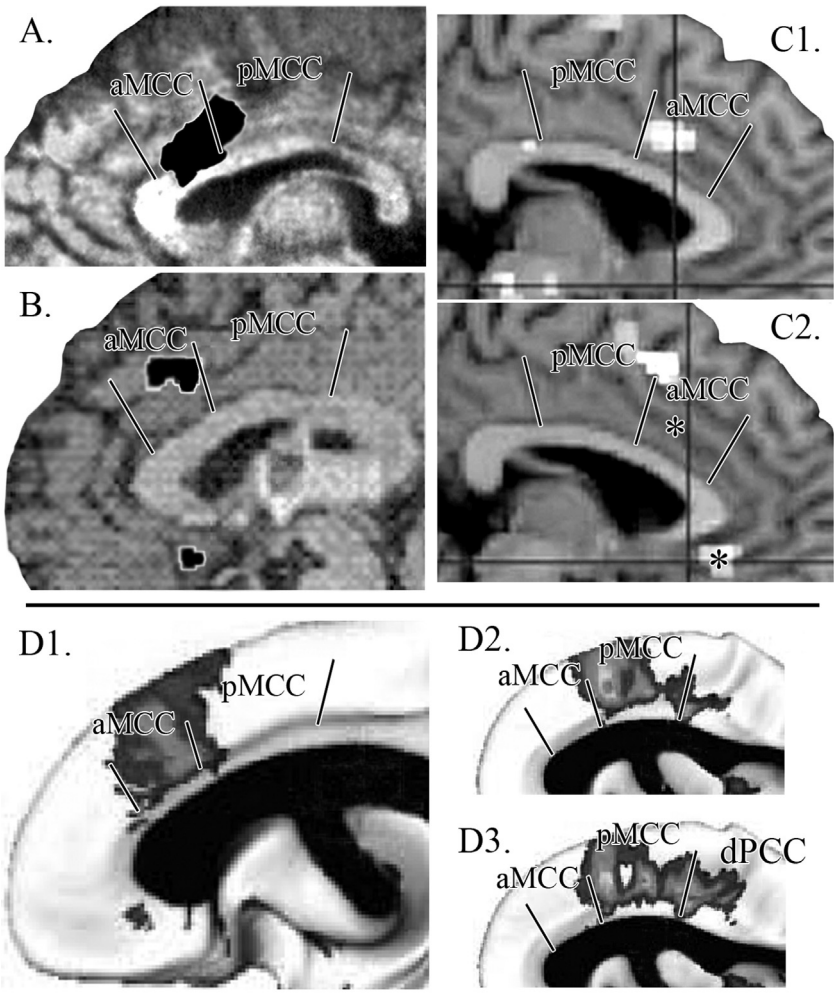

Fig. 15. aMCC vulnerabilities in OCD and ADHD. (A) Levin and Duchowny (1991); epilepsy case of OCD relieved with an aMCC-focused ablation. (B) Mataix-Cols et al. (2004); OCD with pronounced checking provocation. (C) Fitzgerald et al. (2005); (C1) control and (C2) OCD error-processing in the absence of OCD symptom expression (asterisks note two differences from controls). (D) Shaw et al. (2006); (D1) cortical shrinkage for all ADHD cases versus those with persistent (D2) and worst outcomes (D3) 5 years later.

with checking provocation and the cognitive roles of this subregion include error detection and feedback-mediated decision making. Fitzgerald et al. (2005) evaluated error processing in OCD during performance of a cognitive task designed to elicit errors but not OCD symptoms. As predicted, healthy subjects demonstrated aMCC activation during error commission (Fig. 15C1). In the OCD patients, however, the activation was more dorsal and involved mainly the pre-supplementary motor area. The failed response in aMCC is shown with an asterisk in Fig. 15C2. Additionally, there was a unique error-related activation of the pACC and activity in this region was positively correlated with symptom severity in the patients (asterisk in sACC). Thus, error-processing abnormalities are profound in both aMCC and pACC in the absence of symptom expression. Apparently OCD patients use emotional activations in pACC to resolve conflict rather than daMCC. Such a strategy has greatly reduced effectiveness as emotional associations provide only a limited range of options compared to cognitive associations available to daMCC.

The aMCC is also vulnerable in **attention-deficit/hyperactivity disorder** and a detailed account of this is provided by Bush (2009). The daMCC does not activate in ADHD during the counting Stroop (Bush et al., 1999) supporting an impairment in cognitive processing. Structural changes have also been shown in adults with ADHD as they express selective shrinkage in aMCC (Makris et al., 2007). A particularly intriguing study of children with ADHD was published by Shaw et al. (2006) who showed that, after adjustment for their intelligence quotient and mean overall cortical thickness, the aMCC had pronounced shrinkage (Fig. 15D1). These children were followed for 5 years after their first scans and cortical thickness in pMCC remained shrunken in individuals that had persistent symptoms (defined by DSM-IV criteria; D2) and worse outcomes (D3) measured by the Children's Global Assessment Scale. The latter group also showed atrophy in the dorsal PCC suggesting wide cingulate damage. Those children that remitted had better outcomes and showed no shrinkage and the differences were not due to stimulant drugs. Thus, children with ADHD can be differentiated according to persistence and outcomes based on the thickness of aMCC and pMCC.

10.1. The problem of Tourette syndrome

ADHD and OCD have a high comorbidity with TS; 60% for the former and 27% for the latter (Freeman et al., 2000). Thus, it is worth going one step further as syndrome overlap could be associated with aspects of MCC impairment. The data, however, are in conflict when viewed from the perspective of the MCC dichotomy. Wang et al. (2011) (Fig. 14E.) used independent components analysis of patients with TS during spontaneous tics and healthy controls while simulating tic behaviors. While both groups showed activation in pACC (shown for the TS group in Fig. 14E1), the activity in aMCC in the TS group was lower than controls (Fig. 14E2 inactivation site white-stroke highlighted) and lower activity was associated with more severe tics. This suggests that a failure to control tic behavior or premonitory urges that generate them is due to failure of aMCC function.

Bohlhalter et al. (2006) evaluated TS patients with fMRI 2 s before and at tic onset without regard to tic type (e.g., eye blinking, grimacing, abdominal tensing, arm stretching, coughing, grunting or barking). They found that pMCC and the supplementary motor area activated before tic onset (Fig. 14F) and, at tic onset, this activity was virtually non-existent. In contrast, significant activation at tic onset was generated in sensorimotor areas. It is striking that the cCPMA in the pMCC (asterisk in Fig. 14F) was a focal site of activity. This can be viewed as consistent with the function of pMCC in reflexive motor control versus feedback-mediated decision making of the daMCC and rCPMA. What is not consistent is the reduction in aMCC activity in Wang et al. (2011) and increased pre-tic activity in pMCC (Bohlhalter et al., 2006). There are a number of possible reasons for the mismatch in the two MCC subregions. (1) Both TS populations contained about equal proportions of patients with comorbid OCD and ADHD instead of TS only patients. (2) Each study had small group sizes of 10 and 13 subjects. (3) The tics themselves were variable and focused on those that would not cause motion artifact in the scanner. Selecting a uniform type of tic for analysis could be informative. (4) As TS evolves with age, a tighter age category may provide more consistent findings. While the available studies are excellent and there are problems finding an adequate number of patients with similar characteristics, the findings leave questions in terms of MCC impairment. This conundrum is an example of how subregion analysis provides models for further experimental testing that may lead to a coherent understanding of MCC-impaired function and biomarker(s) of TS.

10.2. Drug activity in aMCC

In view of the many differences in chemoarchitecture including receptor binding noted above, it is not surprising that drug selectivity is expressed in their actions in cingulate subregions including MCC. A few examples of this selectivity for aMCC are shown in the right panel in Fig. 14. That drug responses are being identified that are relatively selective for aMCC further enhances the predictive validity of the MCC dichotomy. Drugs that elevate activity can enhance lost aMCC functions, while drugs that block aMCC activity can reduce pain and other amplified functions that can be difficult to control. Here we consider three examples of such effects.

First, Bush (2009; Fig. 14G) showed in children with ADHD that 6 weeks of methylphenidate treatment increases multi-source interference-evoked activity in daMCC and the adjacent pre-supplementary motor area. Thus, ADHD hypoactivation of daMCC is reversed with methylphenidate and partially accounts for the drug's effectiveness. Second, Hodkinson et al. (2015; Fig. 14H) showed that the commonly used nonsteroidal anti-inflammatory drug ibuprofen does not alter cerebral blood flow under pain-free conditions, but blood flow following third molar extraction was significantly reduced in aMCC in conjunction with a significant reduction in pain ratings following ibuprofen administration. Third, Sprenger et al. (2006) evaluated healthy volunteers with fMRI while receiving noxious thermal stimuli in conjunction with placebo (Fig. 14I1.) or increasing doses of ketamine (I2, I3, and no response in aMCC, not shown). The ketamine isomer used is thought to have stronger analgesic potency and a preferable side effect profile including less intense psychomimetic adverse effects. During placebo administration, the pain network was activated including aMCC. Pain unpleasantness and intensity ratings declined as ketamine dosage was increased and decreased pain perception with ketamine was dose-dependent and associated with reduction of pain-induced activations. These latter two findings confirm the role of aMCC in acute pain as discussed above and suggest that more effective pain relief can be achieved by drugs that target aMCC.

11. Perspectives on midcingulate cortex and future challenges

Anatomical organization sets the table for functional studies as it is a stable perspective on functional units of cortex. The cytoarchitectural borders of aMCC and pMCC have proven to be of substantial value in assessing functional imaging findings as the past two decades has produced a plethora of observations to show that the eight-subregion model of cingulate cortex is robust and has predictive value. Clinical imaging studies including those of

drug activity, are finding this model more and more valuable as each subregion has restricted disease vulnerabilities. These findings not only verify the predictive validity of this model but suggest instances where specific behavioral tests will have value in exploring cognitive deficits mediated by impairments in individual subregions. Additionally, drug development may follow a more rational course as molecules are identified to target each subregion to mollify the functions of impaired subregions.

The problem of cingulate structure/function relationships and their impairment by disease is not solved, however. The next level of cingulate research will involve understanding the structure, functions and diseases of individual cingulate areas rather than subregions. Even with the current level of imaging resolution we are seeing activity in different parts of each subregion (i.e., sulcal versus gyral areas). The more demanding imaging problem of individual areas including correlation of cytoarchitectural features will require high resolution histological methods to produce accurate 3-demensional localizations. The current human flat map designates 30 cytoarchitectural areas; however, there are further divisions within such areas and more will become available over the coming years as we reach the ultimate goal of identifying 48 cingulate areas as proposed by the Vogt and Vogt (1919). Interestingly, the same essential structure/function approach will be used to evaluate individual areas as for regions and subregions. Thus, the challenge of human imaging is still quite large and has many more decades to play out until we understand the structure, functions and diseases of each cingulate area. This should result in more robust biomarkers for each disease, more cogent animal models and highly selective drug therapeutics.

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