Journal of Chemical Neuroanatomy 74 (2016) 28–46

Contents lists available at ScienceDirect

Journal of Chemical Neuroanatomy

journal homepage: www.elsevier.com/locate/jchemneu

Review

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

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ARTICLE INFO

Article history:
Received 13 October 2015
Received in revised form 28 January 2016
Accepted 28 January 2016
Available online 15 March 2016

Keywords:
Neurocytology
Cognition
Pain
Neurofilament proteins
Comparative neuroanatomy
Insula
Parietal
Primate
Obsessive-compulsive disorder

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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http://dx.doi.org/10.1016/j.jchemneu.2016.01.010
0891-0618/

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.