

## Opinion

Where is Cingulate Cortex?  
A Cross-Species View

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**To compare findings across species, neuroscience relies on cross-species homologies, particularly in terms of brain areas. For cingulate cortex, a structure implicated in behavioural adaptation and control, a homologous definition across mammals is available – but currently not employed by most rodent researchers. The standard partitioning of rodent cingulate cortex is inconsistent with that in any other model species, including humans. Reviewing the existing literature, we show that the homologous definition better aligns results of rodent studies with those of other species, and reveals a clearer structural and functional organisation within rodent cingulate cortex itself. Based on these insights, we call for widespread adoption of the homologous nomenclature, and reinterpretation of previous studies originally based on the nonhomologous partitioning of rodent cingulate cortex.**

### Cingulate Cortex – a Cross-Species History

Evolutionary success depends on the ability to operate flexibly in a changing environment. This encompasses skills such as planning tasks, selecting among sensory inputs, inhibiting learned actions, and over-riding automatic behaviours. Such operations are mediated to a large extent by prefrontal circuits [1]. Prefrontal cortex consists of several substructures, among them the cingulate cortex. Cingulate cortex plays a particularly central role in various functions related to behavioural flexibility, ranging from autonomic regulation to action selection and performance monitoring – both in health [2–5] and disease [6,7].

While evidence broadly suggests that cingulate cortex can be divided into a number of structurally and functionally distinct regions [5,8,9], the definition of these regions has undergone several changes throughout the past century. In the past decades, the field has begun to converge on a partitioning system that divides cingulate cortex into several regions along the rostrocaudal axis. The two most anterior of these regions are referred to as anterior cingulate cortex (ACC) and midcingulate cortex (MCC), or alternatively have often been described as ventral ACC (vACC) and dorsal ACC (dACC) (for clarity, we will adhere to the ACC/MCC designation throughout the article (see Box 1 for details on the history of partitioning systems for cingulate cortex). This nomenclature has successfully been implemented across species, including nonhuman primates and rabbits, but has rarely been used in mice and rats (Figure 1, Key Figure).

Even though studies in mice and rats have played a key role in elucidating neuronal mechanisms by which cingulate cortex drives behavioural regulation [8], the anatomical partitioning system they most commonly use, as discussed in more detail later, cannot be directly translated to findings in virtually any other species, in terms of both structure and function [10–13]. Specifically, the nomenclature typically applied in rodents divides cingulate cortex into cingulate area 1 (Cg1)

### Highlights

Cingulate cortex is a hub of cognitive and emotional control, and it is highly preserved across mammals. As such, much of our knowledge on cingulate cortex relies on a synthesis of findings across species.

One crucial obstacle to such cross-species comparisons is a striking discrepancy in anatomical definitions. In most mammals, the border between subregions of the cingulate cortex is drawn along the rostrocaudal axis, but in mice and rats it has been routinely drawn perpendicularly to this axis.

This rarely discussed discrepancy has given rise to apparent inconsistencies in cingulate cortex structure and function, within and across species.

A homologous nomenclature of cingulate cortex across species was proposed in 2005, but has so far been rarely used in relevant studies.

We argue that applying the homologous definition aligns the structure and function of rodent cingulate cortex with that of other species. It also better reflects the inherent structure of rodent cingulate cortex itself.

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**Box 1. History of Human Cingulate Cortex**

Human cingulate cortex has undergone several remappings over the past century. Brodmann [121] originally divided it into precingulate and postcingulate cortex, with precingulate cortex corresponding to what researchers have since referred to as the ACC and postcingulate cortex corresponding to what today is known as posterior cingulate cortex (PCC). However, in the early 1990s, following the advent of functional neuroimaging methods, studies failed to demonstrate a uniform activation of the ACC in a variety of contexts [122–126]. For instance, emotional processing; for example, in tasks involving emotive facial expressions or emotionally charged voices, results in activation of a portion of perigenual ACC; whereas cognitive processing, for example, in stimulus-response selection tasks under cognitive load, results in activation of the posterior part of ACC, adjacent to the PCC [3,27].

To account for this observed dichotomy in activation patterns, ACC was subsequently subdivided into vACC (indicating the anterior segment, surrounding the genu of the corpus callosum; also referred to as rostral ACC) and dorsal ACC (indicating the posterior part, dorsal to the corpus callosum and adjacent to PCC; [127]). Around the same time, Vogt [5,119] argued that based on anatomical features such as cytoarchitectural borders, receptor distribution, and connectivity profile, as well as on functional divisions, vACC differ from each other to an extent that suggests they should be regarded as distinct structures altogether, rather than as subdivisions of the same 'anterior cingulate' structure. To this end, Vogt [128] introduced a nomenclature by which vACC is referred to as ACC and dACC is considered part of midcingulate cortex (MCC (see Figure 1 in main text)). Since the publication of Vogt's book on the cingulate cortex in 2009 [5], which was based on a wide-ranging synthesis of the literature available at the time, argued in favour of a clear distinction between ACC and MCC, the scientific community has increasingly adopted this nomenclature. This transition has proved useful, laying the ground for integrating data on differences in function, connectivity, and potential malfunctions into a comprehensive model of ACC and MCC functioning [15]. Furthermore, cross-species comparisons were bolstered as ACC and MCC could be identified consistently in the primate, rabbit, and rodent brains [15].

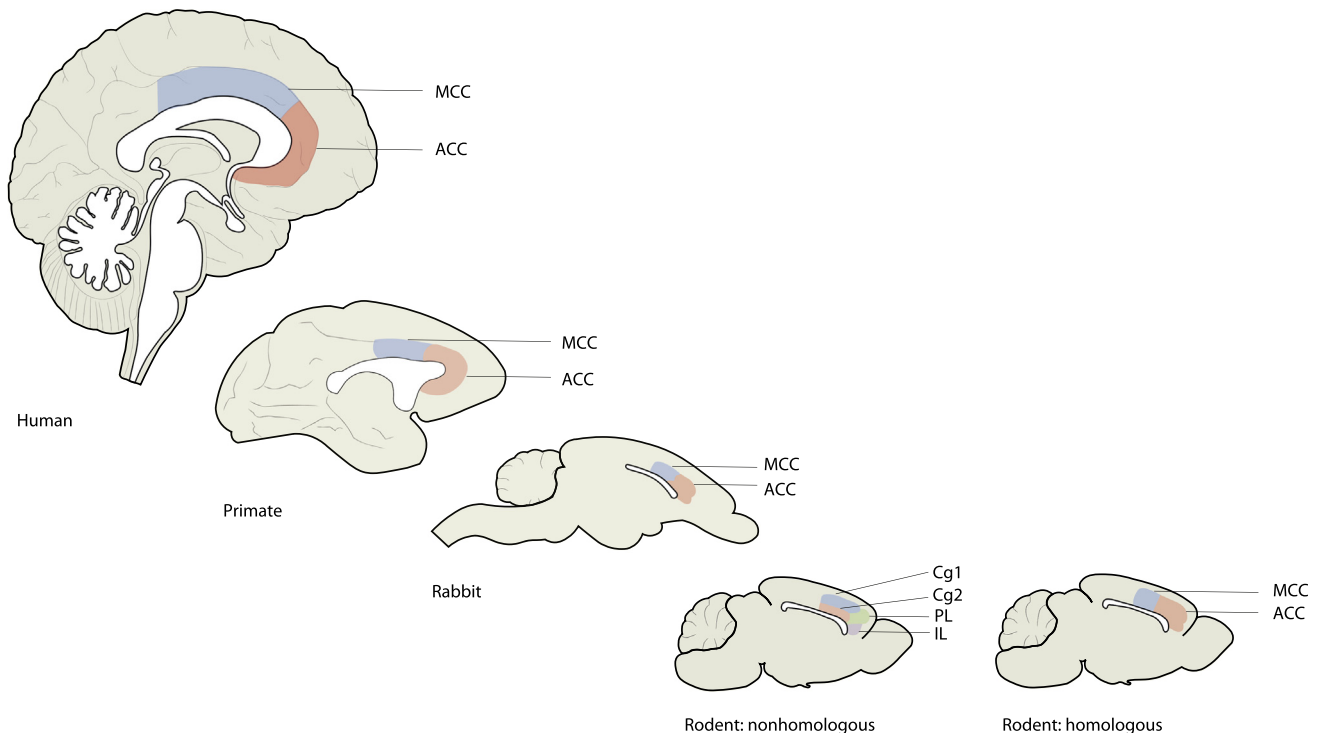
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**Key Figure****Midsagittal View of ACC and MCC across Species**

**Trends in Neurosciences**

**Figure 1.** Light red, ACC. Light blue, MCC. Presented are the human, monkey, rabbit, and rodent brains. For the rodent, both the non-homologous Cg1/Cg2 and the homologous ACC/MCC nomenclature are shown. Abbreviations: ACC, anterior cingulate cortex; Cg1, cingulate area 1; Cg2, cingulate area 2; IL, infralimbic cortex; MCC, midcingulate cortex; PL, prelimbic cortex.

and cingulate area 2 (Cg2), drawing the border between Cg1 and Cg2 exactly perpendicularly to that between ACC and MCC as applied in other mammals [5,11,14,15]. As a result, both Cg1 and Cg2 cover parts of what would be considered ACC and MCC in other mammalian species.

This breakdown in cross-species comparability was first addressed by Vogt *et al.* [16]; and a map of rodent ACC and MCC homologous to that in other mammals was subsequently generated and validated [11], with rodent ACC covering Brodmann areas 24, 25, and 32, and rodent MCC covering A24' (from here on, areas will be denoted by A, e.g., area 24 = A24). This homologous map has been adopted in recent versions of rodent atlases [17,18], but has so far been applied only sparsely even in recent studies of rodent cingulate cortex [14,19–21]).

Recently, Laubach *et al.* [10] have traced the current usage of different definitions for rodent prefrontal cortex, including cingulate cortex. By tracking the appearance of terms such as prefrontal cortex and cingulate cortex in >10 000 studies in several species including humans, primates, and rodents, the authors were able to explicitly demonstrate the lack of consensus on anatomical definitions. While this constitutes a crucial step towards a more unified approach, their review (partly in view of its breadth) did not address how well different nomenclatures reflect the actual anatomical/functional boundaries within cingulate cortex.

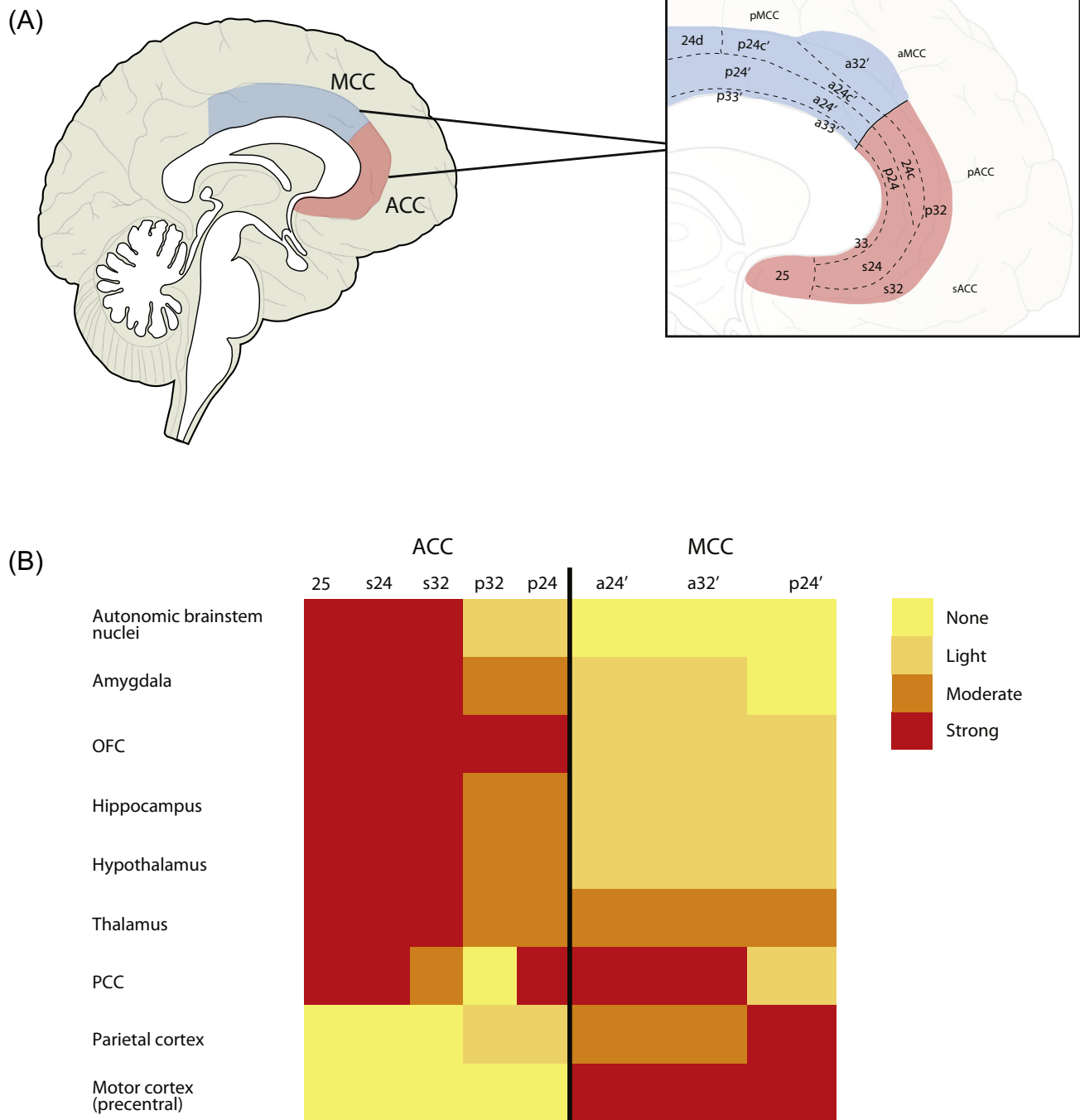
Here, we set out to add this perspective. To this end, we directly compare the structural and functional distinctiveness of cingulate cortex regions based either on the homologous ACC/MCC or the nonhomologous Cg1/Cg2 nomenclature of rodent cingulate cortex. Our comparisons suggest that applying the ACC/MCC definition not only reconciles findings on cingulate cortex across species, but also clarifies the functional and structural organization within rodent cingulate cortex itself.

In the following sections, we first briefly introduce the structure and function of human ACC/MCC as a benchmark, then discuss competing nomenclatures of rodent cingulate cortex and their functional implications. We conclude with recommendations for how future studies on cingulate cortex may provide new grounds for cross-species comparison and synergy.

### Human ACC and MCC – Anatomy and Connectivity

Human ACC encompasses the frontal third of cingulate cortex, surrounding the rostral part of the corpus callosum (A24a–c, A25, A32, and A33), while MCC occupies the middle third of the cingulate cortex (A24a'–c', A32', and A33'). Both ACC and MCC can be subdivided into two subregions – pregenual (pACC) and subgenual ACC (sACC), and anterior MCC (aMCC) and posterior MCC (pMCC; Figure 2A, zoom-in inset). While human cingulate cortex additionally contains other regions – specifically, posterior cingulate cortex and retrosplenial cortex (RSC) – this article focuses solely on ACC/MCC and their homologous definition across species. In this section, we mainly summarize diffusion-weighted magnetic resonance imaging studies that investigated the connectivity patterns of human ACC and MCC. Due to the limited spatial resolution of these techniques, it is difficult to make specific statements about the exact laminar origin and termination of projections. We thus use the term connectivity to refer to the existence of tracts between ACC/MCC and other brain regions.

Like all prefrontal areas, ACC and MCC are both highly connected with frontal cortex: they show strong connections with orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC), and dorsolateral prefrontal cortex (dlPFC) [22–24]. Apart from this, the connectivity patterns of ACC and MCC relate to distinct functional purposes. ACC strongly connects to areas involved in processing emotional salience, motivation, and autonomic function, such as the amygdala and vmPFC. Connections to autonomic brainstem nuclei are mostly centred in sACC, while extensive



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**Figure 2. Cingulate Cortex Connectivity in Humans.** (A) Anatomy of the human ACC (light red) and MCC (light blue). The ACC and MCC are depicted in the medial wall of one hemisphere, adjacent to the corpus callosum. Zoom-in inset: Human ACC and MCC can be subdivided into several subregions. (B) Connectivity profile of ACC and MCC, based mainly on the diffusion-tensor imaging analysis of [22], and further validated via additional literature (see Human ACC and MCC – Anatomy and Connectivity in main text [5,15,25,26,29]). In [22], the authors measured the likelihood that a seed area connects with another area by generating a probabilistic connectivity profile of cingulate cortex with the rest of the brain. While DTI cannot reveal the exact origin and termination points of projections with full certainty, the results reveal a connectivity pattern of ACC and MCC that is comparable to that observed in monkey studies using axonal fibre-tracing techniques. Connectivity is colour-coded here in four categories, from strong (red) to nonexistent (light yellow). To highlight some of the key differences in the connectivity patterns: Amygdala, (Figure legend continued at the bottom of the next page.)

connections to amygdala, hypothalamus, nucleus accumbens (NAc), and periaqueductal grey (PAG) are seen throughout sACC and pACC. By contrast, MCC mainly connects to areas involved in action control and decision making, such as dlPFC, sensorimotor and parietal cortex, as well as motor cortices and pontine and PAG nuclei. MCC also contains the cingulospinal motor area. While aMCC receives moderate amygdalar input, this input is absent in pMCC. Unlike ACC, MCC is not part of the default-mode network, but is considered to be part of the salience network [25,26]. Figure 2B summarizes the connectivity profiles of ACC and MCC.

### Human ACC and MCC – Function

The functional importance of human ACC and MCC was first highlighted by studies of patients with ACC and/or MCC lesions, who were reported to suffer from diverse symptoms, including apathy, as well as dysregulation of autonomic functions, emotion, attention, and error monitoring [27,28]. In the past few decades, neuroimaging work has expanded on these initial findings, demonstrating that ACC serves as a processing hub for the regulation of autonomic responses, as well as assessing emotional and motivational aspects of internal and external information [29]. For instance, emotional contexts such as seeing emotional faces or listening to emotionally charged voices, reliably activate ACC [30]. Consistent with ACC's strong interconnection with autonomic brainstem nuclei, one of the most robust findings across species is that electrical stimulation of ACC depresses autonomic activity [31], leading to reduced blood pressure/heart rate, and respiratory inhibition.

MCC, by contrast, has been highlighted to play a role in different facets of cognitive control, such as response selection, attentional processing, monitoring conflict, and detecting errors [3,27]. MCC's role in decision-making seems to be especially pronounced in reward-based decision-making [32,33]. Given the strong activation of this area in a multitude of task domains, an overarching theory is difficult to establish and has been the topic of intense debate [34,35]. Overall, MCC activity seems to relate to multiple aspects of updating beliefs and internal models of the environment to guide decision-making [36]. Studies using sophisticated task designs have also shown that ACC and MCC are often active during the same task but code for complementary task-related parameters [37]. Figure 3 summarizes to which behavioural aspects ACC and MCC have been found to contribute.

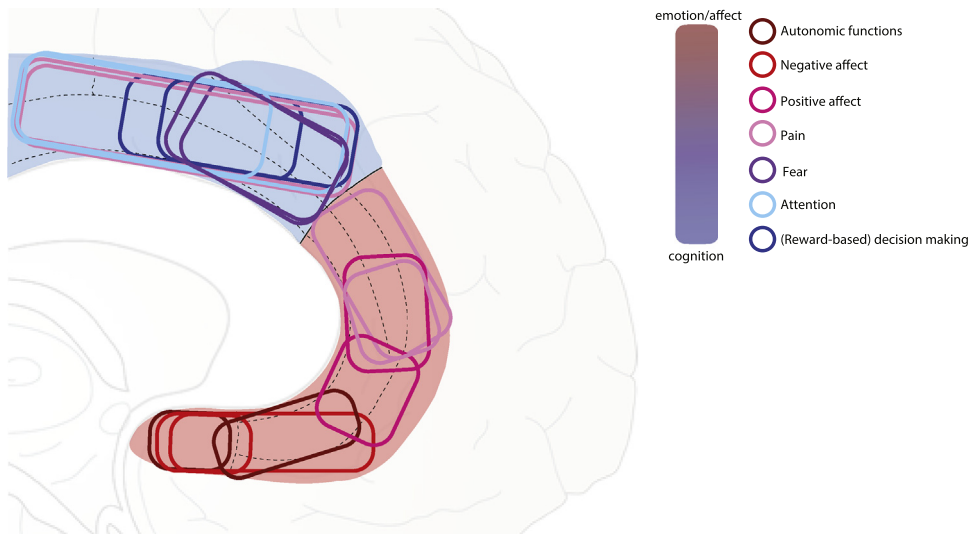
### Rodent ACC and MCC – Anatomy and Connectivity

#### Cg1/Cg2 Nomenclature

The most popular partitioning system for rodent cingulate cortex defines two subareas: Cg1 and Cg2, located dorsally to each other (Figure 4A). Cg1 encompasses A24b and A24b' and Cg2 consists of A24a and A24a'. A25 and A32, which are considered as part of ACC in other mammals, are not part of either Cg1 or Cg2, but treated as separate areas [infralimbic cortex (IL) and prelimbic cortex (PL), respectively; Figure 4A]. As Figures 1 and 4 show, although this definition can be applied consistently in rats and mice, it is not homologous to the ACC/MCC definition used in other mammals [5,11,14,15,21]. This discrepancy arises because the border between ACC and MCC is drawn perpendicularly to that between Cg1 and Cg2 (Figure 4A). In other words, while A24 and A24' form the border between ACC and MCC in other mammals, in rats and mice, they are each covered by both Cg1 and Cg2, whereas A25 and A32 (part of ACC) are excluded by both Cg1 and Cg2.

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hypothalamus, and OFC are strongly connected with ACC, whereas the parietal cortex and motor cortices are strongly connected with MCC. Please note that for simplicity, the schematic refers to connections of ACC and MCC to entire brain areas, and does not examine connections between ACC and MCC to specific subdivisions of the connected brain areas. Differential connections, for instance to subdivisions of the thalamus, are discussed in the main text. Abbreviations: ACC, anterior cingulate cortex; aACC, anterior ACC; aMCC, anterior MCC; DTI, diffusion tensor imaging; MCC, midcingulate cortex; OFC, orbitofrontal cortex; pACC, posterior ACC; PCC, posterior cingulate cortex; pMCC, posterior MCC.



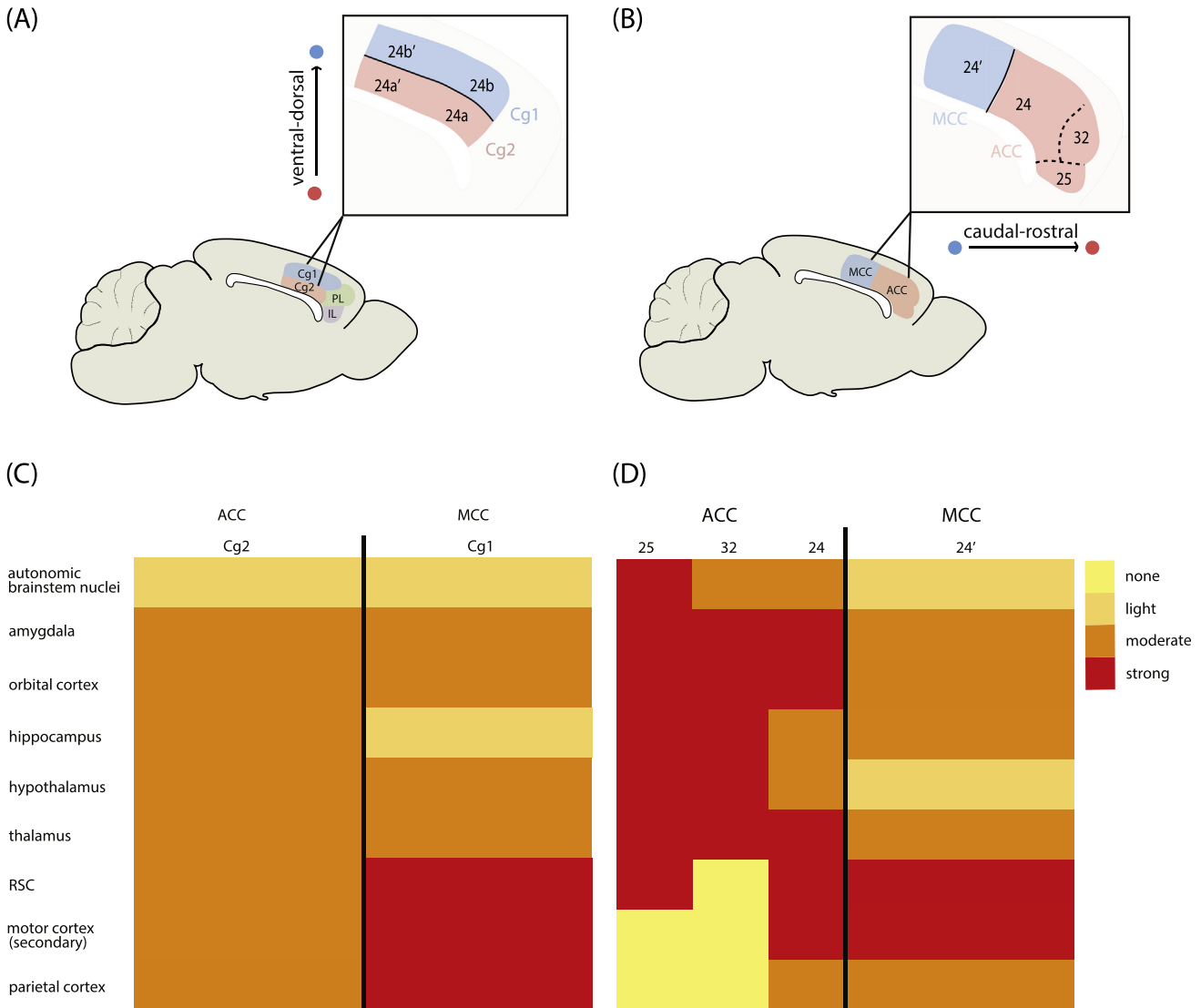
## Trends in Neurosciences

**Figure 3. Behavioural and Cognitive Functions Associated with Different Subregions of Cingulate Cortex in Humans.** Behavioural functions are colour-coded roughly on a ‘hot–cold axis’ from highly affective (red) to highly cognitive functions (blue; see inset legend). ACC is shaded in light red and MCC in light blue. Rectangles denote individual studies. To generate Figure 3, we used a systematic literature search in PubMed to find studies (from year 2000 onwards) that investigated the functional role of ACC and MCC. The following keywords were used, combined with ACC and MCC as search terms: autonomic function/control, negative emotion, positive emotion, pain, fear, attention, and decision-making. Note: given that MCC is a relatively new concept, even in human literature, we extended our search to include the term dorsal ACC, which is anatomically similar to MCC. Studies were only included if it were possible to determine which subregions of ACC/MCC were investigated, either because authors explicitly stated the examined subregions and/or because they gave anatomical coordinates that could be used to infer subregions. The studies included in Figure 3 are [35,44,93–104]. As can be seen, affective functions generally group towards ACC, whereas more cognition-centred functions cluster in MCC. Abbreviations: ACC, anterior cingulate cortex; MCC, midcingulate cortex.

As long as anatomical definitions are set out clearly, the partitioning of cingulate cortex into Cg1/Cg2 does not pose a problem in itself. In fact, most of the insights into how rodent cingulate cortex mediates emotional and cognitive control have so far been gained using the Cg1/Cg2 nomenclature [38–42]. However, this approach does create a fundamental obstacle for cross-species comparisons, because most studies of rodent cingulate cortex do not investigate ACC and MCC independently, whereas studies in other species do [3,5,6,34,43,44].

In theory, this would mean that rodent studies regarding subregions of cingulate cortex should simply not be compared directly to the corresponding studies conducted in other species. However, in practice, rodent studies of cingulate cortex are obviously not treated – nor should they be treated – as an entirely separate research field. To compare and synthesise findings across species, studies have sometimes treated rodent Cg1 and/or Cg2 as directly comparable to human ACC [38–40,45–55]; mostly without assigning a direct counterpart to human MCC [39,40,45,46,56–63]; on other occasions, Cg1 and Cg2 have been equated to MCC [64]; and in still other cases, rodent Cg1 has been treated as the counterpart of human dACC [38,42,65–67] and Cg2 as the counterpart of human vACC [68–70]. All of these approaches overlook the fact that the border between Cg1 and Cg2 is defined perpendicularly to both the border between ACC/MCC and between dACC/vACC, so that results gained using the Cg1/Cg2 nomenclature will necessarily represent a mix of data that would have been studied separately under the ACC/MCC (or dACC/vACC) nomenclature.





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**Figure 4. Comparison of ACC/MCC and Cg1/Cg2 Nomenclature for Parcellating Rodent Cingulate Cortex.** (A) In the Cg1/Cg2 nomenclature, Cg1 is often treated, explicitly or implicitly, as corresponding to human MCC (light blue) and Cg2 as corresponding to human ACC (light red; for details see main text). PL (which is almost entirely equivalent to A32, light green) and IL (equivalent to A25, light purple) are not considered parts of rodent cingulate cortex in this nomenclature. The border between Cg1 and Cg2 is drawn across the ventral–dorsal axis. The zoom-in inset depicts subregions of Cg1 and Cg2. (B) The ACC/MCC definition draws the border between ACC and MCC across the caudal–rostral axis, as in other mammalian species. This definition also includes A25 and A32 as part of the ACC. The zoom-in inset depicts subregions of the ACC and MCC. (C) and (D) show the afferent connectivity of ACC and MCC in mice and rats when applying the Cg1/Cg2 and ACC/MCC nomenclature, respectively. The connectivity diagram (color-coded as in Figure 3) was generated based on [14,71] and validated via [5,11,21,72–78,105]. Note that the connectivity profile for the ACC/MCC nomenclature more closely resembles the connectivity found in humans than the connectivity for the Cg1/Cg2 nomenclature. As in Figure 3, only connections to entire brain areas, but not their subdivisions, are represented here. Abbreviations: ACC, anterior cingulate cortex; Cg1, cingulate area 1; Cg2, cingulate area 2; IL, infralimbic cortex; MCC, midcingulate cortex; PL, prelimbic cortex; RSC, retrosplenial cortex.

### ACC/MCC Nomenclature

In the ACC/MCC nomenclature (Figure 4B), rodent ACC consists of A24a-b, A25, A32, and A33 (although it should be noted that A33 is present in rats but not mice). Compared to human ACC, this excludes A24c and A24d because rodents do not have a cingulate sulcus. For the same reason, A32' and A24c' are absent as well and rodent MCC thus encompasses only A24a' and A24b'

(A33 does not extend into MCC). While in humans, MCC can be subdivided into anterior and posterior MCC, rodent MCC is comparatively uniform and based on the current literature, does not seem to require further subdivisions. The border between A24 (ACC) and A24' (MCC) is outlined by clear differences in cytoarchitecture [11] as well as connectivity (see below).

To explore how the use of the two different nomenclatures impacts measurements of cingulate cortex connectivity, we reinterpreted available studies concerning cingulate cortex connectivity. A particularly informative study in this regard is [14], given that the authors reported the afferent connectivity profile for A24a/A24b (ACC) and A24a'/A24b' (MCC) separately. This allows us to estimate how the connectivity profile would look for Cg1 (A24b/A24b') and Cg2 (A24a/A24a'), as well as for ACC (A24a/A24b) and MCC (A24a'/A24b'), thereby enabling a direct comparison between the ACC/MCC definition and the Cg1/Cg2 definition. For the afferent connectivity profile of A25 and A32, which form part of ACC in the ACC/MCC nomenclature, we relied on [71], since [14] focuses on A24 and A24' only.

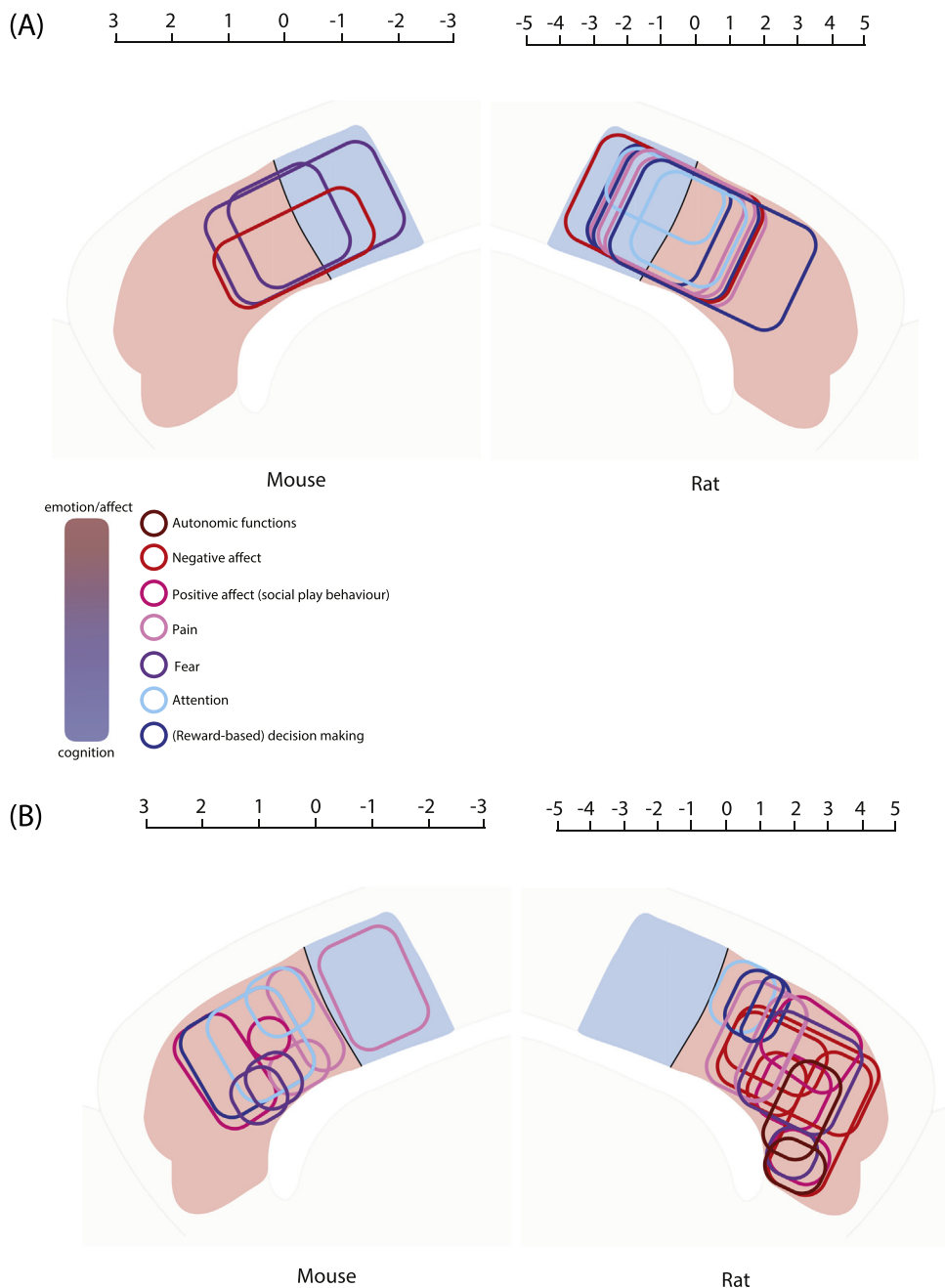
Based on these and additional studies that investigated either the afferent or efferent connectivity profile of cingulate cortex [11,21,72–74] we observed that rodent Cg1/Cg2 seem to show a mixed connectivity pattern, with both Cg1 and Cg2 being moderately connected to a wide range of areas, including subcortical and cortical structures involved in a wide range of functions such as pain processing and performing cognitively demanding tasks (Figure 4C). By contrast, when using the ACC/MCC nomenclature, rodent ACC and MCC show a connectivity pattern that is noticeably better demarcated (Figure 4D), and better matched to that observed in humans (Figure 3). Centred in A32 but extending throughout ACC, there is strong connectivity with structures involved in processing emotional information, such as the OFC, hypothalamus, amygdala, and autonomic brainstem nuclei [72,74,75]. Rodent ACC further connects with cortical areas involved in sensory processing, RSC, and monoaminergic brainstem nuclei [14,74,76]. Rodent MCC, by contrast, has limited connections to amygdala and hypothalamus [14,77], while being strongly connected to parietal association cortex, RSC, motor cortices, and pontine nuclei [14,21,78]. As in humans [22], the border between MCC (A24') and ACC (A24) is outlined by a difference in overall connection density (A24 having denser connections), as well as a divergence of thalamic targets [11,14]).

One reason for this difference in connection specificity between the two nomenclatures is that the Cg1/Cg2 nomenclature does not include A25 and A32, which maintain strong and specific reciprocal connections to amygdala, OFC, insula, and autonomic brainstem nuclei [71,72,75,79] (Figure 4C). Most importantly, given that in this nomenclature both Cg1 and Cg2 span parts of A24 (considered ACC) and A24' (considered MCC), differentially strong connections to A24 and A24', respectively, will appear as uniformly intermediate across Cg1/Cg2. In other words, connectivity differences that in the ACC/MCC nomenclature define the border between separate areas, connect roughly equally to Cg1 and Cg2, suggesting that the ACC/MCC nomenclature is better suited to highlight intrinsic connectivity differences among cingulate cortex regions.

### Rodent ACC and MCC – Function

To map the functional organization of rodent ACC and MCC in a way that parallels the one typically discussed in humans, we conducted a literature search, mapping the functional categories shown in Figure 3 (relating to humans) onto rodent cingulate cortex based on the anatomical coordinates (bregma coordinates) provided by each study (Figure 5). Figure 5A includes research that used the Cg1/Cg2 nomenclature. In the resulting map, the transition from emotional to cognitive aspects of behaviour is noticeably less clear cut than in the human brain (Figure 3).





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**Figure 5. Behavioural and Cognitive Functions Associated with Different Subregions of Cingulate Cortex in Rodent.** Following the same visualization principle as in Figure 3, this figure shows the distribution of behavioural and cognitive functions across rodent ACC (light red) and MCC (light blue). Rectangles denote individual studies; colours represent the behavioural/cognitive function investigated. The left hemisphere shows mouse studies while the right hemisphere is based on rat studies, taking into account the specific anatomical anterior-posterior bregma coordinates per study (see scale on top of each hemisphere). The same search strategy as for Figure 3 was used to search for rat and mouse studies that investigated the functional role of Cg1/Cg2 (A) or ACC/MCC (B). Given that positive emotions, such as happiness, are rather difficult to study directly in rodents, we added a search term for studies that investigated social play

*(Figure legend continued at the bottom of the next page.)*

Specifically, functions that in humans are uniquely attributed to either ACC or MCC seem to be shared by rodent Cg1 and Cg2. In addition, autonomic functions that in humans are shaped by sACC (A25/A32) appear to be absent in the Cg1/Cg2 nomenclature.

While this could in part reflect genuine differences between species, it is most likely a matter of methodology: Cg1 and Cg2 both span parts of A24 and A24', which as discussed earlier have different connectivity profiles (Figure 4) and are therefore likely to also show functional differences. As a result, when using the Cg1/Cg2 parcellation, most experimental treatments and recordings are done in either both areas jointly, or only the centre of Cg1/Cg2, which happens to fall into A24 (i.e. ACC in the ACC/MCC nomenclature). In either case, A24' (i.e. MCC in the ACC/MCC nomenclature) is not investigated separately in the Cg1/Cg2 parcellation. It follows that any functional differences that might exist between A24 and A24' will not be visible to studies that do not investigate these areas separately. In addition, since A25 and A32 are considered neither as part of Cg1 nor of Cg2, functions that are specifically mediated by these brain regions in humans, including the control of autonomic function, have generally not been investigated as part of cingulate function when using the Cg1/Cg2 definition.

This raises the question whether using the ACC/MCC nomenclature would improve the segregation of functional roles across rodent cingulate cortex. To address this question, we consulted the few existing studies that explicitly use the ACC/MCC nomenclature, and systematically searched and reinterpreted studies that investigate rodent ACC and/or MCC individually irrespective of nomenclature, based on the anatomical coordinates they provide and/or the Brodmann areas they refer to (Figure 5). The studies identified in this way converge on two main conclusions, set out in more detail in the following paragraphs. First, A24 and A24' appear to fulfil separable and largely complementary functions, which are addressed independently by the ACC/MCC definition but merged together by the Cg1/Cg2 definition. Second, rodent A25 and A32 seem to mediate similar functions to human A25 and A32, which the ACC/MCC definition treats as part of cingulate cortex just like in other mammals, but the Cg1/Cg2 definition does not.

Concerning the functional role of A25 and A32, numerous studies based on the Cg1/Cg2 definition have investigated rodent A25 and A32 individually, generally referring to them as IL and PL. These studies indicate that rodent A25 and A32 fulfil largely similar functions to human A25 and A32. For example, as in humans [5], rodent A25 and A32 are involved in the regulation of autonomic functions [80] as well as in depressive-like behaviours [81]. Note that rodent A25 and A32 also seem to be involved in fear-related behaviours [82]; a function that in humans is mainly attributed to MCC [5]. However, this apparent discrepancy seems to at least partially stem from the fact that unlike human studies, rodent studies mostly use fear conditioning paradigms, which in humans also activate all subregions across ACC and MCC [3]. Overall, given these similarities, we advocate that A25 and A32 in rodents should be classified in the same way as in humans – that is, as part of ACC.

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behaviours, which is often considered to reflect positive affect in rats. For positive emotions, we did not include studies on reward processing, since such studies generally featured both reward processing and reward-based decision making, introducing a confound. Studies were only included if specific bregma coordinates were reported. For (A) (functions associated with Cg1/Cg2), studies included: [39,40,45,46,56–63]; for (B) (functions associated with rodent ACC/MCC), studies included: [19,41,42,49,54,82,83,87,106–120]. Abbreviations: ACC, anterior cingulate cortex; Cg1, cingulate area 1; Cg2, cingulate area 2; MCC, midcingulate cortex.

Similarly, studies that have investigated rodent A24 (ACC) independently of A24' (MCC) have confirmed the role of A24 in reward [83], negative affect [84], and pain [84–86] – a close match with human ACC (Figure 5B). In addition, A24 also seems to regulate functions mainly associated with MCC in humans, for example, attention and decision-making [41,54,83,87]. This could suggest that the functional segregation of ACC and MCC in rodents is in fact more blurred than in humans. However, another possible explanation is that due to the nature of behavioural testing in rodents, effortful tasks like attention and decision-making tests will nearly always feature an element of reward and/or punishment – and both reward and punishment are clearly mediated by ACC in both rodents and humans [8]. Thus, even though some cognitive functions may be less anatomically segregated in rodents than humans, the functional partitioning of rodent cingulate cortex is quite evidently more structured and more comparable to the human cingulate cortex when applying the ACC/MCC than the Cg1/Cg2 definition.

Finally, there are almost no studies explicitly investigating rodent A24' (MCC) independently of A24 (ACC; Figure 5B). We identified studies focusing on MCC through a systematic search for the terms 'A24', 'MCC', or 'caudal part of ACC', manually checking the anatomical coordinates the respective studies applied. This search yielded a handful of articles [11,14,19–21,78,88]. Only four of these investigated the link between MCC and behaviour, either in the context of pain processing [19,88] or the regulation of aggression [20,89]. These four studies further support a close homology between humans and rodents when the ACC/MCC nomenclature is applied. As in humans, MCC's role in behaviour seems to be separate from, and often complementary to, that of ACC. For instance, as seen in humans, MCC's role in rodent pain processing was demonstrated by a study showing increased activity within MCC after noxious stimulation of the forepaw [88]. Expanding on this, another study [19] demonstrated that rodent ACC and MCC play differential roles in pain perception, with MCC involved in the gating of sensory hypersensitivity, while ACC mediates acute pain and affect-related behaviours [84,86]. This is consistent with human literature demonstrating complementary roles of ACC (affect-like behaviours) and MCC (appraisal/approach-avoidance) in pain processing [90]. Finally, in the remaining two studies on rodent MCC, we were able to confirm another clear functional dissociation between mouse ACC and MCC by demonstrating complementary contributions to aggressive behaviour [20,89]. ACC volume was increased in aggressive BALB/cJ mice (relative to BALB/cByJ controls), whereas MCC volume was decreased [20]. Interestingly, when volumes were recalculated using the Cg1/Cg2 definition, behaviour-related volumetric differences vanished. Furthermore, the concentration of parvalbumin interneurons in MCC but not ACC predicted differences in aggressive behaviour [89].

Although few in number, the above-mentioned studies demonstrate the advantages of studying ACC and MCC as independent structures also in rodents. With more research utilizing the ACC/MCC definition, the function of rodent MCC is bound to be outlined more clearly in the future. So far, the available functional studies discussed above, and the strong efferent connectivity to RSC and visual association cortices as well as visual thalamus [21] point towards a role of rodent MCC in modulating attentional and visuospatial orientation – a good match with human MCC. Thus, both functional and anatomical evidence favours a split between rodent ACC and MCC according to the homologous definition. As we have shown above, this can also benefit existing work originally based on the Cg1/Cg2 nomenclature. By examining the anatomical coordinates provided by individual studies, data can be reinterpreted according to the ACC/MCC nomenclature – often clarifying the original observations. Apart from refining insights into the functional organisation of rodent cingulate cortex itself, this also better aligns results with those from other species.

### Concluding Remarks

Here, we have presented functional and anatomical evidence indicating that a homologous definition of ACC and MCC across rodents and other mammals is not only available and advantageous to cross-species research, but also warranted by the structural and functional segregation within the rodent cingulate cortex itself.

Why, one might wonder, has the homologous definition of rodent ACC/MCC not been more widely adopted, particularly given that it was proposed over a decade ago [11,91]? One possible reason is that researchers are prioritising consistency across studies. New studies may rely on established definitions, either because they accept the definition based on the available literature or to keep new insights comparable to previous studies. In addition, many laboratories may be using brain atlases that still feature the Cg1/Cg2 definition [83,86].

Given these obstacles, what can be done to promote wider acceptance of the homologous ACC/MCC nomenclature? As in many other contexts, a crucial first step would be to increase awareness of the issue, as has been done recently with regards to broader questions around interspecies homologies of the prefrontal cortex [10]. At a more practical level, an important step to make in the context of the cingulate cortex, regardless of which nomenclature is applied in a particular study, is to take note of reporting the exact anatomical definition being used. Researchers should preferably state not only which areas have been investigated, but also name the corresponding Brodmann areas and stereotactical coordinates. Similarly, review articles need to verify whether rodent studies they cite have in fact studied ACC and MCC, or Cg1 and Cg2.

Of course, not all features of rodent cingulate cortex are directly homologous to those in humans. Functionally, for instance, rodent MCC may serve certain functions that are different from those of human MCC (see [Outstanding Questions](#)). Such differences obviously set limits to translating findings between rodents and humans. However, we would argue that this is all the more reason to strive for anatomical definitions that are as homologous as possible. How else can we begin to investigate in which way homologous areas have differentially evolved since their common ancestor, and what similarities and discrepancies have arisen as a result [92]?

Ultimately, we advocate for a complete transition to the ACC/MCC nomenclature of rodent cingulate cortex. Studies investigating the functional role of rodent MCC are particularly needed, because the Cg1/Cg2 nomenclature has so far prevented MCC from being studied as an independent structure. In addition, the shift towards the ACC/MCC nomenclature should also involve some reinterpretation of existing results. For example, researchers that previously investigated ACC and MCC as one structure may want to reanalyse their data to disentangle the specific contributions of ACC and MCC. The brief reanalyses presented here give reason to believe that such analyses may often yield more compelling results. Although these steps are time consuming, they promise to enhance the clarity and cross-species synergy of future findings.

Interspecies translation lies at the heart of neuroscience. Using a homologous nomenclature of cingulate cortex opens up avenues for new cross-species comparisons, but also for discovering hidden insights in data that have so far used the Cg1/Cg2 definition. Together, these long-term advantages are set to far outweigh the short-term drawbacks of transitioning between nomenclatures. We strongly recommend that researchers interested in rodent cingulate cortex make the switch – the sooner the better.

### Outstanding Questions

Homologous areas in human and rodent cingulate cortex are embedded in partially different cortical networks, including an expanded granular prefrontal cortex in humans. How does this affect their function in the two species?

Sulcal areas of cingulate cortex are present in primates but not rodents. Do they simply reflect a size constraint that results in folding of larger but essentially homologous areas, or do they contribute unique functions to primate prefrontal cortex?

The use of the Cg1/Cg2 definition has so far largely prevented rodent MCC from being studied separately from ACC. Based on the few studies investigating rodent MCC, it seems to be less involved in cognitive functions like attention and decision-making than primate MCC. Where and how are these functions shaped in rodents? And what functions can be attributed uniquely to rodent MCC?

In contrast to human/primate MCC, rodent MCC so far appears to be a uniform structure. With the function of the rodent MCC bound to be outlined more clearly in future, will subcircuits similar to those in human/primate MCC be revealed?

Rodent MCC has strong reciprocal connections with visual cortex. Since rodents are thought to be less vision-driven than many other mammals are, what purpose do these connections serve?

Behavioural tasks to more precisely dissect cognitive function are needed in rodents. Can one devise rodent tests that approach the meticulous segregation of cognitive functions as achieved by primate tasks? If so, will such paradigms confirm a similar mapping of cognitive functions across cingulate cortex, and/or highlight differences in functional organization?

The definition of homologous areas across species has so far mainly relied on either structural or functional markers in isolation. Can one merge anatomical and functional indicators, for example, microcircuit structure, long-range connectivity, and functional

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activation, to pinpoint homologous areas more consistently?

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### References

- Rainer, G. (2007) Behavioral flexibility and the frontal lobe. *Neuron* 53, 321–323
- Allman, J.M. *et al.* (2006) The anterior cingulate cortex. *Ann. N. Y. Acad. Sci.* 935, 107–117
- Etkin, A. *et al.* (2011) Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn. Sci.* 15, 85–93
- Rushworth, M.F.S. *et al.* (2007) Contrasting roles for cingulate and orbitofrontal cortex in decisions and social behaviour. *Trends Cogn. Sci.* 11, 168–176
- Vogt, B.A. (2009) *Cingulate Neurobiology and Disease*, Oxford University Press
- Bush, G. *et al.* (1999) Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the counting Stroop. *Biol. Psychiatry* 45, 1542–1552
- Marsh, A.A. *et al.* (2013) Empathic responsiveness in amygdala and anterior cingulate cortex in youths with psychopathic traits. *J. Child Psychol. Psychiatry* 54, 900–910
- Vogt, B.A. (2014) Submodalities of emotion in the context of cingulate subregions. *Cortex* 59, 197–202
- Vogt, B.A. *et al.* (2003) Structural and functional dichotomy of human midcingulate cortex. *Eur. J. Neurosci.* 18, 3134–3144
- Laubach, M. *et al.* (2018) What, if anything, is rodent prefrontal cortex? *eNeuro* 5, ENEURO.0315-18.2018
- Vogt, B.A. and Paxinos, G. (2014) Cytoarchitecture of mouse and rat cingulate cortex with human homologues. *Brain Struct. Funct.* 219, 185–192
- Lee, I.-S. *et al.* (2015) A new animal model of placebo analgesia: involvement of the dopaminergic system in reward learning. *Sci. Rep.* 5, 17140
- Rovira, V. and Gejjo-Barrientos, E. (2016) Intra- and interhemispheric propagation of electrophysiological synchronous activity and its modulation by serotonin in the cingulate cortex of juvenile mice. *PLoS One* 11, e0150092
- Fillinger, C. *et al.* (2016) Afferents to anterior cingulate areas 24a and 24b and midcingulate areas 24a' and 24b' in the mouse. *Brain Struct. Funct.* 222, 1509–1532
- Vogt, B.A. (2016) Midcingulate cortex: structure, connections, homologies, functions and diseases. *J. Chem. Neuroanat.* 74, 28–46
- Vogt, B.A. *et al.* (2005) Architecture and neurocytology of monkey cingulate gyrus. *J. Comp. Neurol.* 485, 218–239
- Franklin, K.B.J. and Paxinos, G. (2013) *Paxinos' and Franklin's The Mouse Brain in Stereotaxic Coordinates*, Academic Press
- Paxinos, G. and Watson, C. (2014) *Paxinos' and Watson's The Rat Brain in Stereotaxic Coordinates*, Academic Press
- Tan, L.L. *et al.* (2017) A pathway from midcingulate cortex to posterior insula gates nociceptive hypersensitivity. *Nat. Neurosci.* 20, 1591–1601
- van Heukelum, S. *et al.* (2018) Aggression in BALB/cJ mice is differentially predicted by the volumes of anterior and midcingulate cortex. *Brain Struct. Funct.* 224, 1009–1019
- Fillinger, C. *et al.* (2017) Efferents of anterior cingulate areas 24a and 24b and midcingulate areas 24a' and 24b' in the mouse. *Brain Struct. Funct.* 223, 1747–1778
- Beckmann, M. *et al.* (2009) Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *J. Neurosci.* 29, 1175–1190
- Koski, L. and Paus, T. (2000) Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. *Exp. Brain Res.* 133, 55–65
- Neubert, F.-X. *et al.* (2015) Connectivity reveals relationship of brain areas for reward-guided learning and decision making in human and monkey frontal cortex. *Proc. Natl. Acad. Sci.* 112, E2695–E2704
- Palomero-Gallagher, N. *et al.* (2008) Cytology and receptor architecture of human anterior cingulate cortex. *J. Comp. Neurol.* 508, 906–926
- Seeley, W.W. *et al.* (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. *J. Neurosci.* 27, 2349–2356
- Bush, G. *et al.* (2000) Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn. Sci.* 4, 215–222
- Lovstad, M. *et al.* (2012) Anterior cingulate cortex and cognitive control: Neuropsychological and electrophysiological findings in two patients with lesions to dorsomedial prefrontal cortex. *Brain Cogn.* 80, 237–249
- Stevens, F.L. *et al.* (2011) Anterior cingulate cortex: unique role in cognition and emotion. *J. Neuropsychiatry* 23, 121–125
- Killgore, W.D.S. and Yurgelun-Todd, D.A. (2004) Activation of the amygdala and anterior cingulate during nonconscious processing of sad versus happy faces. *NeuroImage* 21, 1215–1223
- Cechetto, D.F. (2013) Cortical control of the autonomic nervous system. *Exp. Physiol.* 99, 326–331
- Rushworth, M.F. and Behrens, T.E. (2008) Choice, uncertainty and value in prefrontal and cingulate cortex. *Nat. Neurosci.* 11, 389–397
- Heilbronner, S.R. and Hayden, B.Y. (2016) Dorsal anterior cingulate cortex: a bottom-up view. *Annu. Rev. Neurosci.* 39, 149–170
- Kolling, N. *et al.* (2016) Multiple signals in anterior cingulate cortex. *Curr. Opin. Neurobiol.* 37, 36–43



35. Shenhav, A. *et al.* (2016) Dorsal anterior cingulate cortex and the value of control. *Nat. Neurosci.* 19, 1286–1291
36. Kolling, N. *et al.* (2016) Value, search, persistence and model updating in anterior cingulate cortex. *Nat. Neurosci.* 19, 1280–1285
37. Kolling, N. *et al.* (2018) Propection, perseverance, and insight in sequential behavior. *Neuron* 99, 1069–1082.e1067
38. Delatour, B. and Gisquet-Verrier, P. (2001) Involvement of the dorsal anterior cingulate cortex in temporal behavioral sequencing: subregional analysis of the medial prefrontal cortex in rat. *Behav. Brain Res.* 126, 105–114
39. Han, C.J. *et al.* (2003) Trace but not delay fear conditioning requires attention and the anterior cingulate cortex. *Proc. Natl. Acad. Sci.* 100, 13087–13092
40. Holec, V. *et al.* (2014) Not all effort is equal: the role of the anterior cingulate cortex in different forms of effort-reward decisions. *Front. Behav. Neurosci.* 8, 12
41. Hvoslef-Eide, M. *et al.* (2018) Effects of anterior cingulate cortex lesions on a continuous performance task for mice. *Brain Neurosci. Adv.* 2, 239821281877296
42. Koike, H. *et al.* (2015) Chemogenetic inactivation of dorsal anterior cingulate cortex neurons disrupts attentional behavior in mouse. *Neuropsychopharmacology* 41, 1014–1023
43. Apps, M.A.J. *et al.* (2013) The role of the midcingulate cortex in monitoring others' decisions. *Front. Neurosci.* 7, 251
44. Ramirez-Mahaluf, J.P. *et al.* (2017) Subgenual anterior cingulate cortex controls sadness-induced modulations of cognitive and emotional network hubs. *Sci. Rep.* 8, 8566
45. Schweimer, J. and Hauber, W. (2005) Involvement of the rat anterior cingulate cortex in control of instrumental responses guided by reward expectancy. *Learn. Mem.* 12, 334–342
46. Weible, A.P. *et al.* (2017) Rhythmic brain stimulation reduces anxiety-related behavior in a mouse model based on meditation training. *Proc. Natl. Acad. Sci. U. S. A.* 114, 2532–2537
47. Koga, K. *et al.* (2019) Stimulating muscarinic M1 receptors in the anterior cingulate cortex reduces mechanical hypersensitivity via GABAergic transmission in nerve injury rats. *Brain Res.* 1704, 187–195
48. Stolyarova, A. *et al.* (2019) Contributions of anterior cingulate cortex and basolateral amygdala to decision confidence and learning under uncertainty. *Nat. Commun.* 10, 4704
49. Achterberg, E.J.M. *et al.* (2015) Methylphenidate and atomoxetine inhibit social play behavior through prefrontal and subcortical limbic mechanisms in rats. *J. Neurosci.* 35, 161–169
50. Mashhoori, A. *et al.* (2018) Rat anterior cingulate cortex recalls features of remote reward locations after disfavoured reinforcements. *eLife* 7, e29793
51. Um, S.W. *et al.* (2019) Pain-relieving effects of mTOR inhibitor in the anterior cingulate cortex of neuropathic rats. *Mol. Neurobiol.* 56, 2482–2494
52. Wang, J. *et al.* (2017) Astrocytic l-lactate signaling facilitates amygdala-anterior cingulate cortex synchrony and decision making in rats. *Cell Rep.* 21, 2407–2418
53. Torres-Garcia, M.E. *et al.* (2017) Differential effects of inactivation of discrete regions of medial prefrontal cortex on memory consolidation of moderate and intense inhibitory avoidance training. *Front. Pharmacol.* 8, 842
54. Wu, D. *et al.* (2017) Persistent neuronal activity in anterior cingulate cortex correlates with sustained attention in rats regardless of sensory modality. *Sci. Rep.* 7, 43101
55. Zhou, H. *et al.* (2018) Ketamine reduces aversion in rodent pain models by suppressing hyperactivity of the anterior cingulate cortex. *Nat. Commun.* 9, 3751
56. Totah, N.K.B. *et al.* (2009) Anterior cingulate neurons represent errors and preparatory attention within the same behavioral sequence. *J. Neurosci.* 29, 6418–6426
57. LaGraize, S.C. *et al.* (2004) Differential effect of anterior cingulate cortex lesion on mechanical hypersensitivity and escape/avoidance behavior in an animal model of neuropathic pain. *Exp. Neurol.* 188, 139–148
58. Yi, M. *et al.* (2011) Anterior cingulate cortex is crucial for contralateral but not ipsilateral electro-acupuncture in the formalin-induced inflammatory pain model of rats. *Mol. Pain* 7, 1744–8069-1747-1761
59. Jhang, J. *et al.* (2018) Anterior cingulate cortex and its input to the basolateral amygdala control innate fear response. *Nat. Commun.* 9, 2744
60. Donahue, R.R. *et al.* (2001) Electrolytic lesion of the anterior cingulate cortex decreases inflammatory, but not neuropathic nociceptive behavior in rats. *Brain Res.* 897, 131–138
61. Ng, C.W. *et al.* (2007) Double dissociation of attentional resources: prefrontal versus cingulate cortices. *J. Neurosci.* 27, 12123–12131
62. St-Laurent, M. *et al.* (2009) Does the cingulate cortex contribute to spatial conditional associative learning in the rat? *Hippocampus* 19, 612–622
63. Wei, K. *et al.* (2018) Changes of the brain activities after chronic restraint stress in rats: a study based on 18F-FDG PET. *Neurosci. Lett.* 665, 104–109
64. Hu, T.T. *et al.* (2019) Activation of the intrinsic pain inhibitory circuit from the midcingulate Cg2 to zona incerta alleviates neuropathic pain. *J. Neurosci.* 39, 9130–9144
65. Delevich, K. *et al.* (2015) The mediodorsal thalamus drives feedforward inhibition in the anterior cingulate cortex via parvalbumin interneurons. *J. Neurosci.* 35, 5743–5753
66. Ragozzino, M.E. and Rozman, S. (2007) The effect of rat anterior cingulate inactivation on cognitive flexibility. *Behav. Neurosci.* 121, 698–706
67. Gisquet-Verrier, P. and Delatour, B. (2000) Functional dissociation between dorsal and ventral regions of the medial prefrontal cortex in rats. *Psychobiology* 28, 248–260
68. Kuriwaki, J. *et al.* (2004) Comparison of brain activity between dopamine D2 receptor-knockout and wild mice in response to dopamine agonist and antagonist assessed by fMRI. *Neurosignals* 13, 227–240
69. Maily, P. *et al.* (2013) The rat prefrontostriatal system analyzed in 3D: evidence for multiple interacting functional units. *J. Neurosci.* 33, 5718–5727
70. Cerqueira, J.J. *et al.* (2008) The stressed prefrontal cortex. Left? Right! *Brain Behav. Immun.* 22, 630–638
71. Hoover, W.B. and Vertes, R.P. (2007) Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat. *Brain Struct. Funct.* 212, 149–179
72. Gabbott, P.L.A. *et al.* (2005) Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers. *J. Comp. Neurol.* 492, 145–177
73. Shibata, H.Y.M. (2009) Thalamocingulate connections in the monkey. In *Cingulate Neurobiology and Disease* (Vogt, B.A., ed.), pp. 95–112, Oxford University Press
74. Vertes, R.P. (2003) Differential projections of the infralimbic and prelimbic cortex in the rat. *Synapse* 51, 32–58
75. Azuma, M. and Chiba, T. (1996) Afferent projections of the infralimbic cortex (area 25) in rats: a WGA-HRP study. *Kaibogaku Zasshi* 71, 523–540
76. Gutman, D.A. *et al.* (2012) A DTI tractography analysis of infralimbic and prelimbic connectivity in the mouse using high-throughput MRI. *NeuroImage* 63, 800–811
77. Jones, B.F. *et al.* (2005) Intrinsic connections of the cingulate cortex in the rat suggest the existence of multiple functionally segregated networks. *Neuroscience* 133, 193–207
78. Vogt, L.J. *et al.* (2001) Colocalization of mu-opioid receptors and activated G-proteins in rat cingulate cortex. *J. Pharmacol. Exp. Ther.* 299, 840–848
79. Heidbreder, C.A. and Groenewegen, H.J. (2003) The medial prefrontal cortex in the rat: evidence for a dorso-ventral distinction based upon functional and anatomical characteristics. *Neurosci. Biobehav. Rev.* 27, 555–579
80. Fassini, A. *et al.* (2015)  $\kappa$ -Opioid receptors in the infralimbic cortex modulate the cardiovascular responses to acute stress. *Exp. Physiol.* 100, 377–387
81. Carlson, D. *et al.* (2017) Dynamically timed stimulation of corticolimbic circuitry activates a stress-compensatory pathway. *Biol. Psychiatry* 82, 904–913
82. Kim, E.J. *et al.* (2013) The prelimbic cortex is critical for context-dependent fear expression. *Front. Behav. Neurosci.* 7, 73
83. Elston, T.W. and Bilkey, D.K. (2017) Anterior cingulate cortex modulation of the ventral tegmental area in an effort task. *Cell Rep.* 19, 2220–2230



84. Johansen, J.P. and Fields, H.L. (2004) Glutamatergic activation of anterior cingulate cortex produces an aversive teaching signal. *Nat. Neurosci.* 7, 398–403
85. Navratilova, E. *et al.* (2015) Endogenous opioid activity in the anterior cingulate cortex is required for relief of pain. *J. Neurosci.* 35, 7264–7271
86. Qu, C. *et al.* (2011) Lesion of the rostral anterior cingulate cortex eliminates the aversiveness of spontaneous neuropathic pain following partial or complete axotomy. *Pain* 152, 1641–1648
87. Solinsky, C. and Kirby, B.P. (2013) Medial prefrontal cortex lesions in mice do not impair effort-based decision making. *Neuropharmacology* 65, 223–231
88. Yang, P.-F. *et al.* (2011) Functional tracing of medial nociceptive pathways using activity-dependent manganese-enhanced MRI. *Pain* 152, 194–203
89. van Heukelum, S. *et al.* (2019) Gradient of parvalbumin- and somatostatin-expressing interneurons across cingulate cortex is differentially linked to aggression and sociability in BALB/cJ mice. *Front. Psychiatry* 10, 809
90. Vogt, B.A. (2005) Pain and emotion interactions in subregions of the cingulate gyrus. *Nat. Rev. Neurosci.* 6, 533–544
91. Vogt, B.A. *et al.* (2004) Cingulate cortex and disease models. In *The Rat Nervous System*, pp. 705–727, Elsevier
92. Mars, R.B. *et al.* (2016) Comparing brains by matching connectivity profiles. *Neurosci. Biobehav. Rev.* 60, 90–97
93. Allen, B. *et al.* (2014) Resting high-frequency heart rate variability is related to resting brain perfusion. *Psychophysiology* 52, 277–287
94. Brassens, S. *et al.* (2011) Anterior cingulate activation is related to a positivity bias and emotional stability in successful aging. *Biol. Psychiatry* 70, 131–137
95. Drevets, W.C. *et al.* (2008) The subgenual anterior cingulate cortex in mood disorders. *CNS Spectrums* 13, 663–681
96. Ichesso, E. *et al.* (2011) Altered functional connectivity between the insula and the cingulate cortex in patients with temporomandibular disorder: a pilot study. *Headache* 52, 441–454
97. Klein-Flügge, M.C. *et al.* (2016) Neural signatures of value comparison in human cingulate cortex during decisions requiring an effort-reward trade-off. *J. Neurosci.* 36, 10002–10015
98. Kulkarni, B. *et al.* (2005) Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. *Eur. J. Neurosci.* 21, 3133–3142
99. Lane, R.D. *et al.* (2013) Subgenual anterior cingulate cortex activity covariation with cardiac vagal control is altered in depression. *J. Affect. Disord.* 150, 565–570
100. Levar, N. *et al.* (2017) GABA concentrations in the anterior cingulate cortex are associated with fear network function and fear recovery in humans. *Front. Hum. Neurosci.* 11, 202
101. Matsunaga, M. *et al.* (2016) Structural and functional associations of the rostral anterior cingulate cortex with subjective happiness. *NeuroImage* 134, 132–141
102. Milad, M.R. *et al.* (2007) A role for the human dorsal anterior cingulate cortex in fear expression. *Biol. Psychiatry* 62, 1191–1194
103. Misra, G. and Coombes, S.A. (2014) Neuroimaging evidence of motor control and pain processing in the human midcingulate cortex. *Cereb. Cortex* 25, 1906–1919
104. Weissman, D.H. (2004) Dorsal anterior cingulate cortex resolves conflict from distracting stimuli by boosting attention toward relevant events. *Cereb. Cortex* 15, 229–237
105. Bray, N. (2016) Calculating error. *Nat. Rev. Neurosci.* 17, 670–670
106. Bissiere, S. *et al.* (2006) The rostral anterior cingulate cortex modulates depression but not anxiety-related behaviour in the rat. *Behav. Brain Res.* 175, 195–199
107. Finlay, J.M. *et al.* (2015) Effects of prefrontal cortex and hippocampal NMDA NR1-subunit deletion on complex cognitive and social behaviors. *Brain Res.* 1600, 70–83
108. Johansen, J.P. *et al.* (2001) The affective component of pain in rodents: direct evidence for a contribution of the anterior cingulate cortex. *Proc. Natl. Acad. Sci.* 98, 8077–8082
109. Kim, H.-S. *et al.* (2015) Selective control of fear expression by optogenetic manipulation of infralimbic cortex after extinction. *Neuropsychopharmacology* 41, 1261–1273
110. Lim, L.W. *et al.* (2015) Electrical stimulation alleviates depressive-like behaviors of rats: investigation of brain targets and potential mechanisms. *Transl. Psychiatry* 5, e535–e535
111. Miyamoto, K. *et al.* (2017) Role of microglia in mechanical allodynia in the anterior cingulate cortex. *J. Pharmacol. Sci.* 134, 158–165
112. Morawska, M.M. and Fendt, M. (2012) The effects of muscimol and AMN082 injections into the medial prefrontal cortex on the expression and extinction of conditioned fear in mice. *J. Exp. Biol.* 215, 1394–1398
113. Müller-Ribeiro, F.C.d.F. *et al.* (2012) Contribution of infralimbic cortex in the cardiovascular response to acute stress. *Am. J. Phys. Regul. Integr. Comp. Phys.* 303, R639–R650
114. Okamoto, K. *et al.* (2018) GABAergic malfunction in the anterior cingulate cortex underlying maternal immune activation-induced social deficits. *J. Neuroimmunol.* 321, 92–96
115. Ren, L.Y. *et al.* (2008) Distinct roles of the anterior cingulate cortex in spinal and supraspinal bee venom-induced pain behaviors. *Neuroscience* 153, 268–278
116. Selmeijer, J. *et al.* (2018) Hyperactivity of anterior cingulate cortex areas 24a/24b drives chronic pain-induced anxiodepressive-like consequences. *J. Neurosci.* 38, 3102–3115
117. Tavares, R.F. *et al.* (2009) Opposite role of infralimbic and prelimbic cortex in the tachycardiac response evoked by acute restraint stress in rats. *J. Neurosci. Res.* 87, 2601–2607
118. van Kerckhof, L.W.M. *et al.* (2013) Social play behavior in adolescent rats is mediated by functional activity in medial prefrontal cortex and striatum. *Neuropsychopharmacology* 38, 1899–1909
119. Wang, S. *et al.* (2016) The roles of the anterior cingulate cortex and its dopamine receptors in self-paced cost-benefit decision making in rats. *Learn. Behav.* 45, 89–99
120. Hewlett, K.A. *et al.* (2014) 'Not-so-minor' stroke: lasting psychosocial consequences of anterior cingulate cortical ischemia in the rat. *Exp. Neurol.* 261, 543–550
121. Brodmann, K. (1909) Beiträge zur histologischen Lokalisation der Grosshirnrinde. III. Mitteilung: die Rindenfelder der niederen Affen. *J. Psychol. Neurol.* 4, 177–226
122. Goodwin, G.M. (1997) Neuropsychological and neuroimaging evidence for the involvement of the frontal lobes in depression. *J. Psychopharmacol.* 11, 115–122
123. Grossman, M. *et al.* (1992) Attention and sentence processing deficits in Parkinson's disease: the role of anterior cingulate cortex. *Cereb. Cortex* 2, 513–525
124. Nordahl, T.E. *et al.* (1998) Regional cerebral metabolic asymmetries replicated in an independent group of patients with panic disorder. *Biol. Psychiatry* 44, 998–1006
125. Paus, T. *et al.* (1993) Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. *J. Neurophysiol.* 70, 453–469
126. Vogt, B.A. *et al.* (1992) Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cereb. Cortex* 2, 435–443
127. Devinsky, O. *et al.* (1995) Contributions of anterior cingulate cortex to behaviour. *Brain* 118, 279–306
128. Vogt, B.A. (1993) Structural organization of cingulate cortex: areas, neurons, and somatodendritic transmitter receptors. In *Neurobiology of Cingulate Cortex and Limbic Thalamus*, pp. 19–70, Birkhäuser Boston