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Regional Functional Molecular Profiles Within the Mammalian Cortex: A Commentary on Limbic Mesocortex

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Recently a shared profile of 46 selectively active/inactive genes was reported to characterize the adult mouse *limbic mesocortex* (MCx), which forms a transitional ring around the central isocortex (IsoCx) field, and is surrounded by a peripheral ring of allocortex (Puelles et al. 2024). The number of such selective mesocortical gene markers (differential with respect to both IsoCx and allocortex) keeps rising since then, and 83 limbic MCx markers are now known (Table 1). They characterize variably outer and/or inner mesocortical layer neurons (Figure 1), in all cases with boundaries coinciding precisely with the mapped topography of the mesocortical ring (Figure 2). Many of these genes code for proteins with clear-cut functional roles (see Table 1; right side column, codes explained in legend; over 40% of these markers are membrane channels or receptors, and many others relate to neurotransmitter and peptide metabolism, myelination, or synaptic/vesicular mechanisms). Other generic molecular properties shared selectively within limbic MCx are a relative scarcity of parvalbumin neurons and the lowest degree of cortical myelinization (possibly indicating a predominance of thinner—slower-conducting—axonal connections; Palomero-Gallagher and Zilles 2015; Puelles et al. 2024). The present combination of 83 markers (a list expected to increase) suggests that the observed differential profile when compared to both IsoCx and allocortex relates to a particular sort of cortical functional mode (i.e., operational algorithm) that may depend precisely on such a singular set of molecular properties. Contrast with neurophysiological experiments might throw light on this point.

The concept of "limbic" cortex was historically first applied to the limbus of cortex forming a medial border with the diencephalon (Broca 1878; Craigie 1925; Zeman and Innes 1963). This old idea included the hippocampal region in the limbic border zone, jointly with retrosplenial and cingulate areas; a now outdated concept of the diencephalon was used also; we now know that the cortex hardly limits directly with the diencephalon proper, as it bulges out of the alar hypothalamus (Puelles 2024). Modernly, this sort of limbus draws less interest, due to the singular three-layered structure and memory-related functions discovered specifically in the hippocampal cortex. After successive corrections, the cortical limbic system concept has come to represent a cortex domain involved specifically in emotional evaluation of experiences and behavioral plans. Recent study of this emotional system has laid emphasis on the amygdala (LeDoux 1996) and on the orbitofrontal, cingulate, and insular cortex areas (Rolls 1999, 2005, 2014; see also Panksepp 1998 and Damasio 1994, 1999, 2003). These three cortical fields form spatially dissociated parts of the ampler mesocortical ring conceived initially by Filimonoff (1947); subsequent literature is reviewed in Puelles et al. (2019, 2024). The anatomically mapped and genoarchitectonically unitary limbic MCx finally referred to by Puelles et al. (2024) happens to be an intracortical border or limbus zone, namely, the intermediate ring domain that separates isocortical and allocortical cortex all around. The possibility that this entire transitional cortical ring found to display unique functional molecular properties may somehow localize hypothetical cortical functions related to emotional evaluation merits experimental investigation. Such endeavor potentially may expand current knowledge on the emotion-related cingulate, insular, and orbitofrontal cortex areas to additional less studied parts of the mesocortical ring.

If we take shared expression of this growing mesocortical molecular profile as a modern genoarchitectonic definition of *what is limbic cortex* in the mouse (Figures 1 and 2; probably detectable also mutatis mutandis in other mammals, including primates), then it turns out that one cortical area previously long thought to be mesocortical and limbic—the retrosplenial

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TABLE 1 | Updated list of 83 mouse mesocortex (MCx) gene markers selected by their increased or differential positive expression (positive markers) or relatively decreased or differential negative expression (negative markers) against neighboring allocortex and isocortex expression patterns.

Positive MCx markers	Name	MCx layers labeled	Class
Adcyap1	Adenylate cyclase activating polypeptide 1	3, 4, 5	S
Bok	BCL2-related ovarian killer	3	AP
Brinp3	Bone morphogenic protein/retinoic acid inducible neural-specific 2	3 Partial	M
Cckbr	Cholecystokinin B receptor	2	R
Cdh13	Cadherin 13	2, 5, 6	Adh
Chrm1	Cholinergic receptor, muscarinic 1, CNS	2	R
Chrm3	Cholinergic receptor, muscarinic 3, cardiac	2	R
Chst2	Carbohydrate sulfotransferase	2, 5, 6	CE
Cnr1	Cannabinoid receptor 1 (brain)	2, 3, 5, 6	R
Col6a1	Collagen, Type VI, alpha 1	2, 3, 5, 6	EM
Col23a1	Collagen Type 23 alpha 1	2	EM
Coro6	Coronin 6	6	AB
Cpne7	Copine VII	2, 3, 5	M
Crym	Crystallin mu	2, 3, 5, 6	THB
Cux2	Cut-like homeobox 2	2, 3	TF
Dner	Delta/notch-like EGF-related receptor	2, 3, 5	R
Enc1	Ectodermal neural cortex 1	2, 3, 5	AB
Ets2	E26 avian leukemia oncogene 2, 3′ domain	2, 3, 5	TF
Etv1	Ets variant 1	5	TF
Fos	FBJ osteosarcoma oncogene	2, 3, 4, 6	
Fxyd6	FXYD domain-containing ion transport regulator 6	5	MT
Gpr88	G-protein coupled receptor 88	2, 3, 5	R
Gria4	Glutamine receptor, ionotropic, AMPA4 (alpha4)	2, 3	R
Grik5	Glutamine receptor, ionotropic, kainate 5 (gamma2)	2, 3, 6	R
Grm1	Glutamate receptor, metabotropic 1	2	R
Grm5	Glutamate receptor, metabotropic 5	2, 3, 5	R
Hap1	Huntingtin-associated protein 1	2, 5	VT
Hrh3	Histamine receptor H3	3, 5	R
Itpr1	Inositol 1,4,5-triphosphate receptor 1	2, 3, 6	R
Lrrtm1	Leucine rich repeat transmembrane neuronal 1	2, 5	TMP
Lypd1	Ly6/Plaur domain containing 1	2, 5	RBP
Matn2	Matrilin 2	2	EM
Meis2	Meis homeobox 2	2	TF
Met	Met proto-oncogene	2	RTK
Nnat	Neuronatin	2, 6	ICR
Nos1	Nitric oxide synthase 1 (neuronal)	2	S
Nov	Nephroblastoma overexpressed gene	2	EM
Otof	Otoferlin	2	VT
Prmt2	Protein arginine *N*-methyltransferase 2	2, 3, 5	ERB

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TABLE 1 | (Continued)

Positive MCx markers	Name	MCx layers labeled	Class
Ptgs2	Prostaglandin-endoperoxide synthase 2	2	PCS
Ptpru	Protein tyrosine phosphatase, receptor type, U	2, 5, 6	R
Pvrl3	Poliovirus receptor-related 3	2	R
6330403A02Rik	RIKEN cDNA 6330403A02 gene	2,3,5	
Rtn4r	Reticulon 4 receptor	2, 3	R
Scg2	Secretogranin II	2, 5	SPP
Sez6	Seizure-related gene 6	2, 3, 5, 6	SPP
Smoc2	SPARC related modular calcium binding 2	2	CBP
St6galnac5	ST6 (alpha-*N*-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-*N*-acetylgalactosaminide alpha-2,6-sialyltransferase 5	2, 4, 5	ST
Synpr	Synaptoporin	2	VP
Syt17	Synaptotagmin XVII	2, 3, 5	SP
Tmem145	Transmembrane protein 145	4	TMP
Tnnc1	Troponin C, cardiac/slow skeletal	4	CBP
Trhr	Thyrotropin releasing hormone receptor	2, 3, 5	R
Vat1l	Vesicle amine transport protein 1 homolog-like (*Torpedo californica*)	2, 3, 5	MT
Wfs1	Wolfram syndrome 1 homolog (human)	2	TMP
Wnt7b	Wingless-type MMTV integration site family, member 7B	2, 5	M
Ache	Acetylcholinesterase	2, 3, 4, 5, 6	H
Astn2	Astrotactin 2	2, 3, 4, 5, 6	AGM
Cadps2	Ca^{2+}-dependent activator protein for secretion 2	2	CBP
Cbln2	Cerebellin 2	2, 3, 5	Adh
Chrm2	Cholinergic receptor, muscarinic 2, cardiac	2, 3, 5	R
Glra3	Glycin receptor alpha 3 subunit	2 Caudal	R
Grik1	Glutamate receptor, ionotropic, kainate 1	2, 4, 5	R
Hcn1	hyperpolarization-activated, cyclic nucleotide-gated K^+ 1	2, 3, 4, 6	C
Kcnab3	Potassium voltage-gated channel, shaker-related subfamily. beta member 3	4, 5	C
Kcnk2	Potassium channel, subfamily K, member 2	2, 3, 4, 5	C
Lifr	Leukemia inhibitory factor receptor	2, 3	R
Mbp	Myelin basic protein	5, 6	My
Nefh	Neurofilament, heavy polypeptide	5	NFP
Ntng2	Netrin G2	2, 3, 5	AG
Pcp4	Purkinje cell protein 4	5	SP
Plcxd2	Phosphatidylinositol-specific phospholipase C, X domain containing 2	4, 5	PIH
Pvab	Parvalbumin	2, 3, 4, 5, 6	CBP
Rorb	RAR-related orphan receptor beta	4	R
Rxfp1	Relaxin/insulin-like family peptide receptor 1	5, 6	R (of Rln3)
Scn4b	Sodium channel, Type IV, beta	2, 3, 4, 5, 6	C

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TABLE 1 | (Continued)

Positive MCx markers	Name	MCx layers labeled	Class
Scn1a	Sodium channel, voltage-gated, Type I, alpha	2, 3, 5	C
Scnn1a	sodium channel non-voltage dependent 1 alpha	2, 3, 4, 5, 6	C
Sfrp2	Secreted frizzled-related protein 2	4	M
Slc17a6	Solute carrier family 17 (Na-depend. inorg. phosph. cotransp.), memb. 6	5	T
Tlc4	TLC domain 4	6	My
Trpc4	Transient receptor potential cation channel, subfamily C, member 4	5	C
Vamp1	Vesicle-associated membrane protein 1	2, 3, 4, 5, 6	SV

Note: Listed markers are classified according to Wikipedia information (Class) and comprise Actin-binding proteins (AB), adhesion proteins (Adh), axonal guidance proteins (AG), astroglial migration-related (AGM), apoptosis-related proteins (AP), membrane channels (C), calcium-binding proteins (CBP), carbohydrate-related enzymes (CE), extracellular matrix proteins (EM), estrogen receptor binding proteins (ERB), neurotransmitter hydrolysis enzymes (H), ion channel-related proteins (ICR); morphogens (M), membrane transport proteins (MT), myelination-related proteins (My), neurofilament proteins (NFP), prostacyclin synthesis (PCS), phosphatidylinositol hydrolysis (PIH), receptors (R), neurotransmitter receptor-binding proteins (RBP), receptor tyrosine kinases (RTK), neurotransmitter synthetic enzymes (S), synaptic proteins (SP), secreted peptide packaging (SPP), seizure-related peptide (SRP), syaliltransferase (ST), synaptic vesicle proteins (SV), transcription factors (TF), thyroid hormone binding proteins (THB), transmembrane proteins (TMP), vesicular trafficking proteins (VT). One item, a Riken gene, remained uncharacterized. Over 30% of listed markers are receptors or channel proteins (leaving aside other transmembrane or synapse- or vesicule-related proteins).

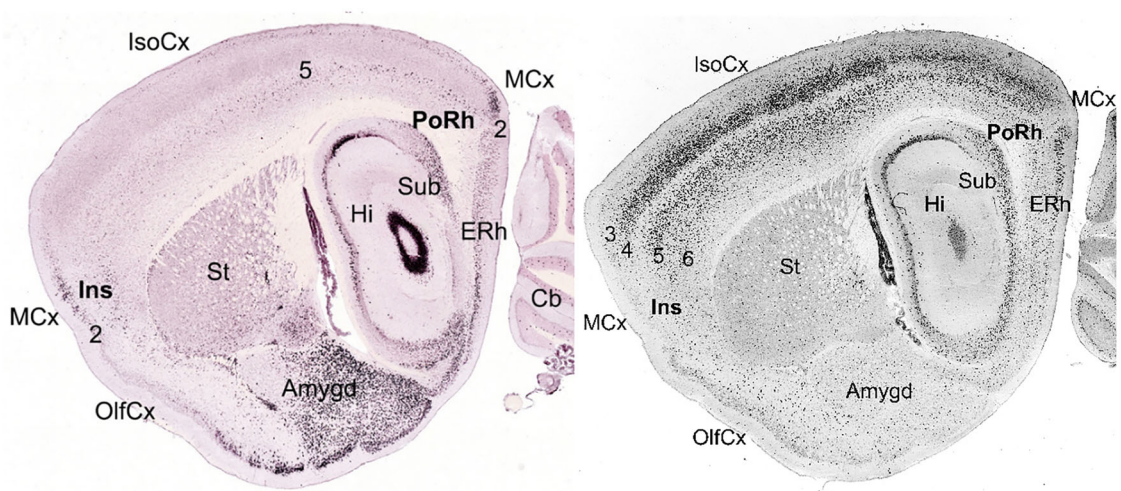


FIGURE 1 | Lateral sagittal sections of adult mouse brains in situ reacted at left for the gene *Lypd1*, one of the selective positive markers of the mesocortical ring (M18 material downloaded from the Allen Developing Mouse Brain Atlas), and at right for the gene *Kcnab3*, one of the selectively negative markers of the mesocortex (P56; same source). In the first image, we see labeling in mesocortical Layers 2 and 5 (both Ins and PoRh areas), in contrast to the negative Layer 2 and hardly marked Layer 5 in the isocortex (IsoCx). Note also the absence of this signal in the neighboring part of both the olfactory allocortex (OlfCx) and the parahippocampal entorhinal cortex (ERh). The hippocampus (Hi) mainly shows a signal at the CA1 field (rostrally to the subiculum, Sub) and at the dentate gyrus (central positive ring within the Hi). The pallial amygdala (Amygd) and the periamygdalar olfactory cortex (untagged) also express this marker. The second image presents the negative mesocortical marker *Kcnab3* that codes a potassium voltage-gated channel expressed mainly in IsoCx Layers 4 and 5 as well as in Hi, Sub, and ERh allocortex areas, but whose signal is absent in the Ins and PoRh and all other mesocortex sectors. This is one of the markers recently added to Table 1. There is scarce label in the OlfCx Layer 3 or in the pallial amygdala (Amygd). Material partly extracted from the Puelles et al. (2024) study (downloaded from the Allen Developing Mouse Brain Atlas).

cortex—is *not* so. It lacks all these novel molecular characteristics, and it rather resembles in molecular profile the neighboring presubicular parahippocampal cortex, thus entering into the sphere of allocortex (Yao et al. 2023; Puelles et al. 2024). The mesocortical ring, nevertheless, remains continuous at this region, as an area laterally adjacent to the retrosplenial cortex, previously ascribed to associative visual cortex or doubtfully classified as retrosplenial area 29d (or other alternative notions), was identified instead by the said molecular profile as the local MCx; it was renamed "parasplenial (PaSp) area" (Puelles et al.

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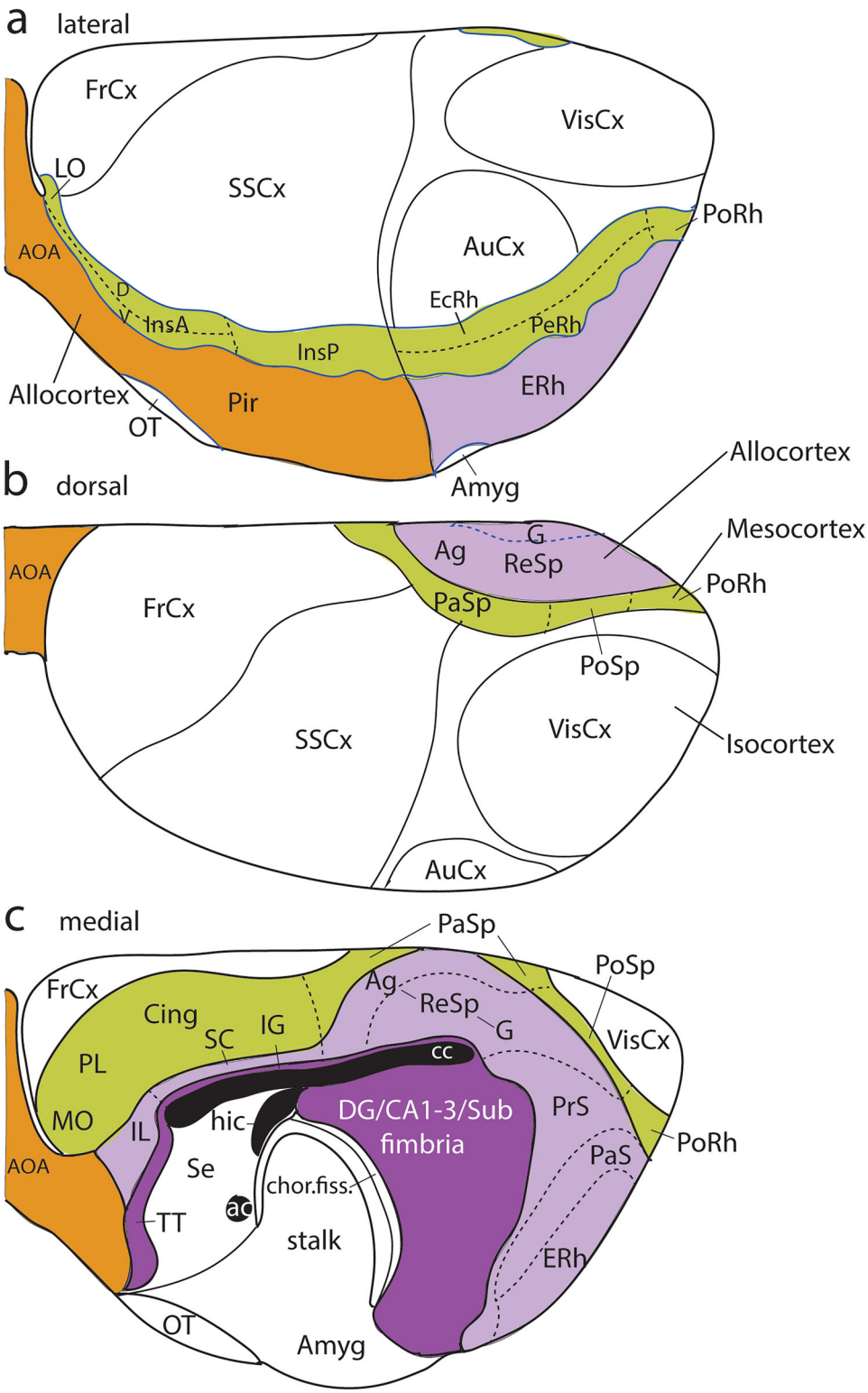


FIGURE 2 | Legend on next page.

(2024). The limbic mesocortical molecular profile also serves to define more precisely the previously somewhat vague concepts of the caudal postrhinal (PoRh) and rostral "posterior orbitofrontal" parts of the mesocortical ring. Citing Wise (2008) and Passingham and Wise (2012), Rolls (2014) holds that orbitofrontal cortex has expanded in primates into more rostral *granular* cortex. This may imply participation of prefrontal IsoCx areas in advanced limbic functions or, alternatively, may mean that significant structural evolution and planar expansion of the simpler original mesocortical orbitofrontal domain present in basal mammals occurred in primates. Comparative transcriptomic analysis probably can clarify this point.

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The retrosplenial cortex and the rostrally adjacent cingulate cortex were initially widely held to be mesocortical since Rose's (1926) first application of the "MCx" concept; this author actually defined only these two areas as unique transitional five-layered heterotypic cortex (implicitly devoid of Layer 4). Our new molecular criterion corroborates the cingulate cortex as a typical MCx (though it was discovered that MCx in general belongs to the six-layered category, due to the regular presence of a molecularly identified—*Rorb*-expressing— even if disgranular—that is, showing sparser positive cells—Layer 4 component), whereas the retrosplenial area falls molecularly into strictly non-limbic parahippocampal allocortex (Puelles et al. 2024). This last conclusion is consistent with recent neurophysiological notions about the retrosplenial area (e.g., Burles et al. 2017; Alexander et al. 2023). The details of bidirectional communications between associative IsoCx and parahippocampal/hippocampal circuits, thus, need to be reexamined; they apparently are modulated by the interposed limbic mesocortical ring that theoretically adds subjective value to objective sensory perception and intentional prospective behavior signals to be processed into long-term memory by the hippocampus. We know that hippocampal selection of patterns to be incorporated into long-term memory requires their preliminary emotional evaluation.

Filimonoff (1947) first conceived the notion that the cingulate limbic area (then thought to be five-layered) participates in a complete "intermediate" cortical ring surrounding the six-layered IsoCx and relating peripherally to either parahippocampal/hippocampal allocortex (medially) or olfactory allocortex (OlfCx) (laterally). He called this ring "intermediate cortex," rather than "MCx," though the latter name—introduced previously by Rose (1926)—continued being used in the field. The transitional ring conception was subsequently developed further by Sanides (1962, 1969), Mesulam and Mufson (1982), Swanson (1983), Swanson et al. (1987), Pandya and Yeterian (1985), Bayer and Altman (1991), Gloor (1997), and others, including L. Puelles as a coauthor in Pattabiraman et al. (2014). Such ideas, crystallized into the present concept of a central island of IsoCx surrounded by an inner mesocortical (limbic) ring and an outer allocortical ring (with hippocampal and olfactory cortical moieties), were found to be consistent with the structural model of the cortex (Barbas 1986, 1995, 2015; Barbas and Zikopoulos 2025; Zaldivar-Diaz and García-Cabezas 2026). The historic evolution of this notion of cortical overall structure, relevant for causal theories of phylogenetic and ontogenetic cortex emergence, was reviewed in Puelles et al. (2019, 2024), García-Cabezas et al. (2023), and Zaldivar-Diaz and García-Cabezas (2026).

In contrast with the cited recent molecular results, which essentially corroborate and partly correct some classic notions about the limbic mesocortical ring, the modern literature rarely studies gene expression patterns that define a particular function-correlated cortical area or region. The aim to study general developmental corticogenetic mechanisms (either patterning or histogenetic ones) or general adult structural and functional properties of the cortex has drawn the field to concentrate on general cortical gene markers often found to be layer specific. These are apparently shared by all meso- and isocortical regions, though not so by hippocampal or OlfCx areas (e.g., Yao et al. 2023). Unfortunately, this approach tends to suggest subliminally that the cortex is composed mainly by molecularly relatively homogeneous IsoCx, which does not acknowledge the differential functions of its reported cortical areas. One aspect that results obscured is the molecular and functional singularity of the MCx ring surrounding the whole IsoCx. Sometimes the MCx is not even recognized as a distinct category; see comments in (Puelles et al. 2019, 2024). A well-known neuromorphologist that stressed this simplistic concept was H. Kuhlenbeck, who stated "The neocortex in [primitive mammals] can be … regarded as a continuum …… the architectural characteristics … are not sufficiently defined for a sharp definition of different areas within the continuum of the neocortex …. all maps purporting a more complex parcellation …… represent, in my opinion, merely figments of the imagination" (Kuhlenbeck 1982, 173–174).

This skeptical scenario contrasts with the notion of structural and functional arealization developed by Brodmann (1909) and his many subsequent followers in what is regarded as the main line of cortical structural analysis. The subliminal notion that the IsoCx + MCx is molecularly or structurally homogeneous (as apparently concluded recently by Yao et al. 2023, possibly unwittingly) tends to throw doubt on the real existence and functional relevance of the MCx as distinct from the IsoCx, in contradiction with its recent sharp genoarchitectural delimitation from both IsoCx and allocortex (Puelles et al. 2024; present additional markers in Table 1). Within the continuum theory, the IsoCx plus MCx territory would seem to be a large field of similar cortical columns, whose molecular and functional properties would be basically the same, analogously to the uniform cybernetic neuronal units usually considered in artificial intelligence circuit designs. Such columns would essentially perform the same algorithmic operation on their respective inputs, perhaps only differing subtly at relative positional extremes, depending on differential thalamic or other inputs. This rather tendentious notion would obscure our accruing perspective on the possibility

FIGURE 2 | Surface maps of the mouse mesocortical main domains (green) according to the concentric ring theory in lateral, dorsal, and medial views (a–c). Rostral lies to the left (cut across the olfactory bulb). The outer *allocortex* ring (two shades of violet) displays hippocampal and parahippocampal moieties best seen medially (c; dark and pale violet color, respectively); this half-ring is completed by a largely lateral olfactory allocortex half (a–c; Pir/AOA; orange). Concentrically with the allocortex outer ring, there is the limbic *mesocortex* ring (a–c; green). Inside this ring we see the central field of *isocortex* (a–c; white). A number of specific mesocortical areas are identified by their abbreviated names. Note the white domain visible under the hippocampal allocortex in c, including OT, Se and Amyg, is not cortical but subpallial. Parahippocampal IL, SC and ReSp areas were first postulated by Puelles et al. 2024. Extracted from Puelles et al. (2024). ac, anterior commissure; Amyg, amygdala; AOA, anterior olfactory area; AuCx, auditory cx; CA1–3, cortex ammonis fields 1–3; cc, corpus callosum; chor.fiss., chorioidal fissure; Cing, cingulate cx; DG, dentate gyrus; EcRh, ectorhinal cx; ERh, entorhinal cx; FrCx, frontal cx; hic, hippocampal commissure; IG, indusium griseum; IL, infralimbic cx; InsA (D,V), anterior insular cx (dorsal/ventral parts); InsP, posterior insular cx; LO, lateral orbitary cx; MO, medial orbitary cx; OT, olfactory tuberculum; PaS, parasubiculum; PaSp, parasplenial cx; PeRh, perirhinal cx; Pir, piriform cx; PL, prelimbic cx; PoRh, postrhinal cx; PoSp, postsplenial cx; PrS, presubiculum; Resp (Ag,G), retrosplenial cx (agranular/granular parts; SC, supracallosal cx; Se, septum; SSCx, somatosensory cx; Sub, subiculum; TT, tenia tecta; VisCx, visual cx.

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of cortical areas displaying quite different functional properties (operational algorithms) such as the analysis of "what" occurs versus its "value" for the individual. It can be postulated that sensory, associative, and motor isocortical areas perform distinct logical integrative functions, as would the limbic or emotional MCx, if its role is the *subjective evaluation* of experience or action plans, as is usually assumed by psychologists and philosophers.

In any case, leaving aside the variability in the total number of cortical areas in different mammalian species (sufficiently reflected in the literature), more or less distinct cortical areas have been repeatedly described after examination with different cytoarchitectonic, myeloarchitectonic, pigment-architectonic, and hodologic methodologies, now for more than 100 years (as well as with recent network analysis; Fornito et al. 2016). Regional/area-specific differences seem to be more prominent during in utero development (Johnson et al. 2009; Kang et al. 2011; Li et al. 2018). It would be really surprising if there existed no regional- and areal-specific gene marker profiles.

In fact, there are occasional descriptions of sets of specific molecules mapped to particular cortical regions or areas, as occurs in the case of the somatosensory barrel field (Cooper and Steindler 1986; Couceyro et al. 1997; Vercelli et al. 1999; Kashani et al. 2006; Lazutkin et al. 2007; Huang et al. 2009; Terakawa et al. 2013; Hedrich et al. 2020). Curiously, no systematic effort has ensued to explore other primary sensory, motor, or associative areas for analogous partial molecular specificity, though various modern microarray and transcriptomics approaches have disclosed significant differential areal or regional results (e.g., Johnson et al. 2009; Kang et al. 2011; Voineagu et al. 2011; Li et al. 2018; Zhu et al. 2018; Markenscoff-Papadimitriou et al. 2020; Bhaduri et al. 2021; Gandal et al. 2022; Qian et al. 2025). These can all be *function-related* gene patterns, obviously of great theoretical interest, which are complementary to the more general *layer-related* gene patterns, which tend to uniformize the cortex.

The so far still only partly molecularly characterized mouse limbic MCx lists now 83 markers in a common molecular profile restricted positionally specifically to the MCx ring (Figure 2; Table 1), whereas the MCx shares generally with isocortical areas the amply represented layer-specific genes. This includes Layer 4 markers, such as *Rorb*, which indicates that MCx is actually six-layered (rather than five-layered as was assumed since the birth of the MCx concept; Rose 1926); this unexpected feature—actually involving a poorly developed (disgranular) Layer 4—makes the MCx potentially a variant form of IsoCx. This emphasizes a transitional aspect pointing in a different direction than used to be contemplated before (i.e., not with regard to gradually increasing number of layers but to gradually less developed Layer 4, which is totally absent generally only in the allocortex; this includes the retrosplenial areas). This gives to the allocortex–MCx boundary a sharper profile (Puelles et al. 2024).

Moreover, the MCx ring seems subdivided into various classically or modernly defined areal subdomains (e.g., insular [Ins], perirhinal [PeRh], ectorhinal, PoRh, postsplenial, PaSp, cingulate, prelimbic [PL], and posterior infraorbitary; Puelles et al. 2024). More detailed molecular analysis may yet correct up or down their number. Indeed, if such largely traditional mesocortical domains are real and imply differential limbic subfunctions, they may be also expected to display various molecular and structural singularities. These probably would be due to their respective topological developmental positions along the ring that may expose them preferentially to differential peripheral sources of diffusing morphogens (medial, lateral, caudal, and rostral) and accordingly to diverse developmental backgrounds (parabulbar, paraseptal, *para*-parahippocampal, pararhinal, and orbitofrontal). These ontogenetic differences may lead later to differential internal circuitry and specific external connective properties.

This sort of regional cortical molecular analysis related to differential function is aided by the now abundantly available mapped gene datasets in several mammalian species (including the human), which opens a novel scenario that probably will soon be explored to the benefit of cortical functional analysis. We have already noted in the mouse that the gene *Col23a1* (listed in Table 1) is mainly expressed in the postsplenial sector of the MCx ring, whereas the *Cyp26b1* and *Cyp26b2* genes are selectively expressed—with a small intervening negative boundary subregion—in the insular and perirhinal sectors of the same ring (Layer 5), with minor presence in Layer 6 in the infraorbitary cortex sector (shown in Puelles et al. 2019; their Figure 9). We also noted in Puelles et al. (2024) that some MCx markers are selectively absent from some of the three orbital sectors.

More such partial results are expected. They should lead to progress in our understanding of cortico-cortical and cortico-subcortical connectivity networks (Fornito et al. 2016). Other potential improvements of knowledge along this path might address the normal or pathologic neural correlates of higher mental functions, including the riddle of consciousness, as well as our phylogenetic or ontogenetic causal evo-devo understanding (e.g., comparative and developmental mappings of the differential mesocortical markers in both mammalian and nonmammalian vertebrates and appropriate spatial transcriptomic studies in primate brains).

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

To develop the present work, we used the Allen Mouse Brain Atlas-Gene Expression (https://brain-map.org/our-research/gene-expression).

Peer Review

For transparency, the peer review documents associated with this article are available at https://doi.org/10.1002/cne.70191.

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