Chapter 7

Network convergence zones in the anterior midcingulate cortex

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Abstract

Situated medially and centrally in the brain, the anterior midcingulate cortex (aMCC) is a nexus of control. This specialized neocortical brain region participates in large-scale brain networks underlying attention, motor, and limbic processes. The functional diversity and proximity of cognitive and affective subdivisions within this region are its distinguishing features, rendering it an effective site for integration across domains. Here we review comparative neuroanatomic, meta-analytic, and connectomic analyses contributing to the emerging picture of the aMCC as comprising functionally diverse, flexible network nodes involved in multiple regulatory behaviors. We further present data providing evidence for an organizing gradient along the anterior and midcingulate cortex and explore the implications of these findings for understanding the functional role of the anterior midcingulate within this spectrum. We conclude by highlighting open questions and proposing future directions for investigations into the functional role of this important network convergence zone.

INTRODUCTION

The rostral cingulate cortex is a diverse cortical structure. It has classically been conceptualized as being comprised of several subdivisions, each with distinct structural features and patterns of connectivity that enable a range of self-regulatory functions. Broadly, a subdivision rostral to the genu of the corpus callosum is known as the anterior cingulate cortex (ACC) and is thought to play a crucial role in initiation, motivation, and goal-directed behaviors (Devinsky et al., 1995), while the caudal subdivision, referred to as the midcingulate cortex (MCC), is implicated in action monitoring and motoric processes (Amodio and Frith, 2006). An early meta-analysis of human neuroimaging studies of rostral cingulate function described regionally specific patterns of activation suggesting an anterior and posterior midcingulate cortex (aMCC, pMCC, respectively) vs subcallosal ACC, and

limbic vs paralimbic subdivisions (Paus et al., 1998). Subsequent research corroborated the notion that the rostral cingulate is comprised of subdivisions with distinct anatomic and functional properties and linked the commonly observed anterior-to-posterior gradient with affective and cognitive functions, respectively (Koski and Paus, 2000). Taken in context, these lines of research suggest that the rostral cingulate contributes to behavior by modifying responses, particularly in reaction to challenges requiring effortful cognitive control (Gasquoine, 2013), and that it may serve an integrative function of translating intentions into actions (Paus, 2001).

This chapter aims to situate a specific portion of the rostral cingulate—the aMCC—along this complex processing stream. We begin by describing its topography based on studies of cortical microstructure and connectivity. We then turn to the complex and, at times, contentious functional literature, offering a parsimonious

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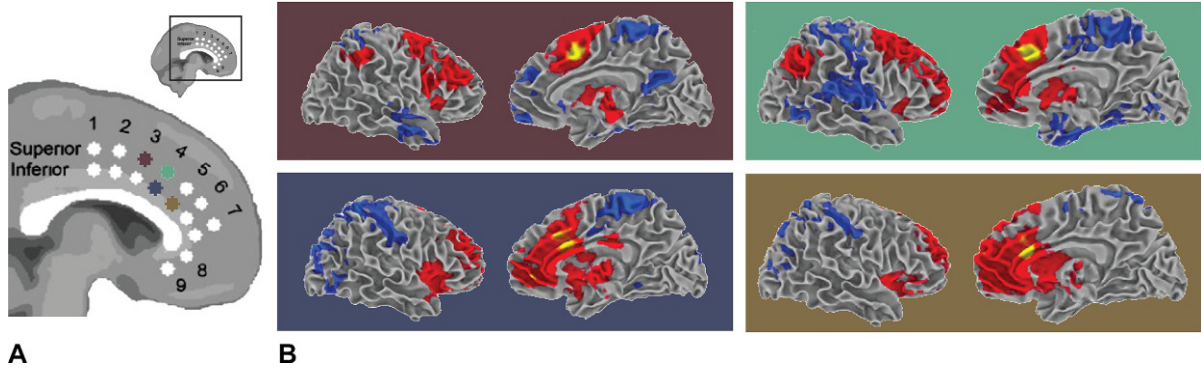
Fig. 7.1. Functional connectivity of four seed regions located within the anterior midcingulate cortex. (A) Location of seed regions, where functional connectivity is presented in (B). *Red* = positive functional connectivity; *blue* = negative functional connectivity. Adapted from Margulies DS, Kelly AMC, Uddin LQ, et al. (2007). Mapping the functional connectivity of anterior cingulate cortex. Neuroimage 37: 579–588.

summary of functional gradients that situate aMCC at the motoric and control end of the spectrum. Finally, we turn to the recent literature on large-scale functional networks, describing the participation of aMCC in several functional systems subserving attention and control processes, with special attention to the widely studied salience network (Seeley et al., 2007; Uddin, 2015). By establishing the salience network between caudal motoric systems and rostral affect regulation circuitry (Ochsner and Gross, 2005) and the default mode network (Greicius et al., 2003), these lines of research support interpretation of the aMCC as a crucial nexus of control along a macroscale gradient of cortical function.

DELINEATING THE aMCC

To situate the aMCC within large-scale cortical networks and functional hierarchies, we begin by clarifying its location along the cingulate cortex. This definition is necessary at the outset, as the aMCC is often described in the cognitive neuroimaging literature using the anterior cingulo-centric nomenclature of "dorsal anterior cingulate cortex" to describe what is in fact one of the most frequently activated cortical regions (Yarkoni et al., 2011). However, based on the proximity of its cyto architectonic and receptor architectonic features to more caudal midcingulate areas (Palomero-Gallagher and Vogt, 2009), this area is more accurately described as an anterior subdivision of the midcingulate cortex. aMCC, as we will refer to this region going forward, is located caudal to the genu of the corpus callosum, including area a33′, area a24′ in the cingulate gyrus, and area 32′ within the external cingulate gyrus. In the recently released Human Connectome Project atlas (Glasser et al., 2016), these areas correspond to the anterior portion of area 33′, area a24′, and area p32.

In the first systematic seed region of interest (ROI)–based study of intrinsic functional connectivity,

Margulies et al. (2007) delineated anterior/posterior and dorsal/ventral functional subdivisions within the ACC, recapitulating early meta-analyses of PET studies (Picard and Strick, 1996) and further underscoring the heterogeneous connectivity patterns of subdivisions within this region. Seed regions i4, i5, s3, and s4 (with *i* representing *inferior* and *s* representing *superior*) in this study were most consistent with the topographic location of aMCC (Fig. 7.1). Subsequently, Kelly et al. (2009) examined a subset of these ROIs in a developmental context and found that functional connectivity of networks associated with social and emotional functions (e.g., seeds in subgenual ACC and ventromedial prefrontal cortex) showed the greatest developmental effects, while connectivity of networks associated with motor control and conflict monitoring, including aMCC, did not change appreciably from late childhood through early adulthood.

Clustering of structural connectivity patterns also confirmed the distinct features of aMCC (Beckmann et al., 2009). Using diffusion-weighted imaging-based tractography, Beckmann et al. (2009) divided the cingulate into nine clusters, three of which were located within the midcingulate cortex (clusters 4–6). The rostral-most cluster 4, which was topographically consistent with the location of aMCC, revealed high probability of connectivity with the motoric dorsal striatum, as well as premotor cortex, but shared high connectivity with the dorsal prefrontal cortex—a feature distinguishing it from more caudal regions of the midcingulate cortex.

The location of aMCC between the anterior cingulate regions and the motoric midcingulate regions was also confirmed by functional connectivity analyses in the macaque monkey (Hutchison et al., 2012). Of the four subdivisions described by Hutchison et al. (2012), the aMCC of the macaque monkey is homologous with the cluster that is functionally described as "attention orienting" and shares patterns of dorsal prefrontal and

premotoric connectivity that are both unique to this area and consistent with prior observations in the human.

Unlike the consistency observed across these primate species, the rodent cortex has only one uniform midcingulate cortex that acts as a transition between adjacent ACC and retrosplenial areas. While the rodent has a clearly defined MCC—comprised of areas 24a′ and 24b′—it remains uniform, lacking the distinct anterior–posterior subdivisions described in monkeys (Vogt and Laureys, 2005) and humans (Vogt et al., 2004). An additional notable distinction between rodents and primates is the connectivity of the corticospinal system, which in primates originates in the MCC, while in rats it originates in the ACC (Gabbott et al., 2005; Vogt and Paxinos, 2014). This shift in primate rostral cingulate organization suggests that the role of aMCC in primates may indeed reflect the emergence of a unique functional system involved in the regulation and mediation of cognitive content and motoric planning.

Nevertheless, while smooth transitions across the cingulate gyrus are a staple of rodent cortical architectonics, they have also been described within the human cingulate cortex, where cytoarchitectural features are generally observed to transition gradually (von Economo and Koskinas, 1925). The answer to the question of whether and to what degree sharp distinctions between subdivisions of the ACC/MCC exist may come from novel approaches to brain parcellation. Tian and colleagues (2018) recently introduced the concept of a "diversity curve" to describe a gradient of functional connectivity observed in the human insular cortex using resting-state fMRI. They find that the "connectional diversity" of the insula is best explained as a continuum of gradual change along a dorsal-posterior to ventral-anterior axis (Tian and Zalesky, 2018). While similar analyses have yet to be conducted along the cingulate, it has been well observed that the aMCC and insular cortex are intimately connected (Taylor et al., 2009). As such, it is reasonable to suspect that similar gradients of connectivity might also exist along the cortex of the rostral cingulate cortex (ACC and MCC).

Von Economo neurons and the aMCC

The aMCC contains a special type of neuron that has only been observed in the brains of humans, great apes, and a select few other species including whales and elephants (Butti et al., 2009). More recently, these neurons have also been discovered in the brains of macaque monkeys (Evrard et al., 2012). These special pyramidal cells are known as spindle cells or von Economo neurons (VENs). VEN concentrations are greatest in humans, declining with increasing taxonomic distance from humans (Nimchinsky et al., 1999). VENs are large cells with distinct morphology (Seeley et al., 2012) and are only found in the cingulate and insular cortex. VENs appear to be unique from both phylogenetic and ontogenetic standpoints, emerging postnatally around 4 months of age in humans. Retrograde tracers injected into the cingulum fiber bundles indicate that VENs have extrinsic projections, though their ultimate targets are at present unknown (Allman et al., 2001).

The unique properties of VENs have led to some interesting speculation regarding the function of these cells. The fact that they are large projection neurons, which are proposed to underlie conscious access (Dehaene and Changeux, 2011), has led some to speculate that VENs are potential neural correlates of consciousness (Critchley and Seth, 2012). It has been posited that VENs function to relay outputs of the ACC to the association cortex to aid rapid intuitive assessments of complex situations, for example, during social cognitive processes (Allman et al., 2005). This leads to the hypothesis that VENs are affected in disorders of social cognition such as autism spectrum disorder (ASD). However, to date there is no empirical support for this notion. Postmortem investigations report that the number of VENs in the ACC appears to not differ significantly between individuals with ASD and typically developing individuals (Kennedy et al., 2007; Uppal et al., 2014).

FUNCTIONS OF THE aMCC

In one of the earliest positron emission tomography (PET) studies of language, Petersen et al. (1989) observed aMCC activation during semantic association tasks. They suggested that this activation might reflect nonspecific arousal from either task difficulty or selection for action (Petersen et al., 1989). Since this work, human neuroimaging studies have reported aMCC activation across a range of paradigms. One striking observation from meta-analytic findings summarizing thousands of fMRI task activation studies is that the aMCC activates during the performance of nearly every externally demanding task (Behrens et al., 2013). This ubiquitous activation has led to the suggestion that the aMCC is an important functional hub in the brain. Indeed, network centrality analyses of fMRI data collected during the performance of emotion, gambling, motor, relational, and working memory tasks demonstrate that the most consistent hubs are found in the dorsal portions of ACC and aMCC (Bolt et al., 2017).

Another means for assessing cortical function is through electrical stimulation of patients undergoing monitoring for refractory focal epilepsy. In a study involving 329 patients, the highest number of active sites
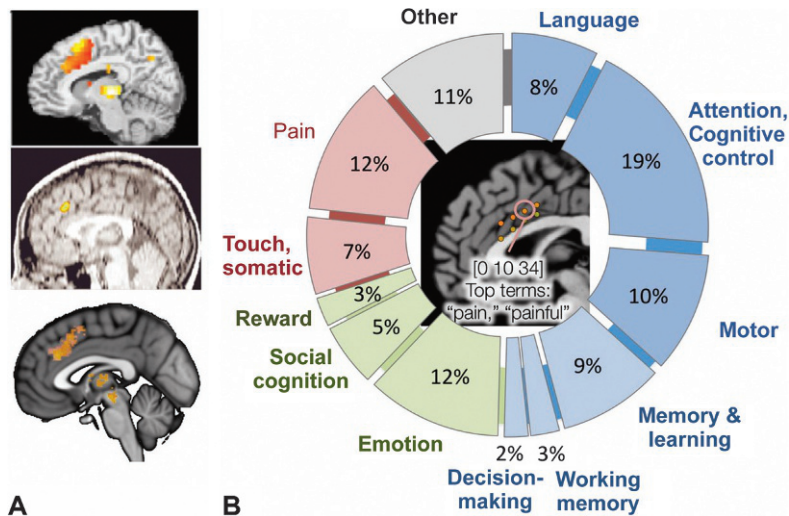
Fig. 7.2. Functions of the anterior midcingulate cortex. Using an automated meta-analytic tool (Neurosynth) to calculate posterior probabilities of activation, Wager et al. (2016) demonstrate that the anterior midcingulate cortex is involved in pain in 12% of the activation studies (*red*), whereas 50% of the studies reporting activation in this region were investigating cognition (*blue*) and 20% focused on socioemotional processes (*green*). Figure adapted from Wager TD, Atlas LY, Botvinick MM, et al. (2016). Pain in the ACC? Proc Natl Acad Sci U S A 113: E2474–5.

was found in ventral and dorsal aMCC. Goal-oriented behaviors and simple motor responses were most often elicited by the stimulation of aMCC, with goal-oriented behaviors defined as getting-up impulses, reaching and grasping actions, body-directed actions, and exploratory eyes-head movements (Caruana et al., 2018). The authors speculate that aMCC encodes ancient behaviors that are implemented through descending projections. These findings are consistent with a proposed role for aMCC in cognitive motor control and intentional movement generation put forth by authors of a recent combined resting-state fMRI and meta-analytic connectivity modeling study (Hoffstaedter et al., 2014). This key role in motor control is thought to be linked with other important aspects of aMCC function, including responsiveness to error and reward (Rushworth et al., 2011).

Among the multiple stimuli and task conditions that activate the ACC/MCC, pain is one of the most well studied. In 2015, Lieberman and Eisenberger published a paper using automated meta-analysis and quantitative reverse inference analysis to suggest that aMCC is selective for pain (Lieberman and Eisenberger, 2015). The logic of this study was that in order to uncover the best general psychologic account of cingulate function, one can use large-scale neuroimaging databases (in this case Neurosynth, Yarkoni et al., 2011) to identify which psychologic process, from among hundreds, is likely to have been invoked when brain activity in a particular region was observed. The pain selectivity claim was heavily critiqued in subsequent reports, including some authored by the creators of Neurosynth (Wager et al., 2016) who argue that the tool is useful for exploring structure–function mappings but cannot provide definitive

inferences about the functions of specific brain regions. Wager and colleagues calculated posterior probabilities of activation to demonstrate that the pain selective regions identified by Lieberman and Eisenberger were only involved in pain in 12% of the studies, whereas 50% of the studies reporting aMCC activation were investigating cognition and 20% focused on socioemotional processes (Fig. 7.2). This latter finding is in line with other meta-analytic work attesting to the functional diversity of ACC/MCC (Anderson et al., 2013). However, the debate regarding segregation vs integration of function in aMCC is far from settled, as recent work using multivariate pattern analysis does point to domain-specific representations for pain in this brain region (Kragel et al., 2018). Interestingly, however, electrical stimulation of aMCC does not result in perception of pain (Caruana et al., 2018). The authors of the electrical stimulation work suggest that aMCC is triggered by experiences characterized by a strong motivation to initiate actions (including nociceptive ones, but not limited to them).

Indeed, some have suggested that the overlap of activation in aMCC observed in studies of pain, negative affect, and cognitive control can be attributed to the fact that this region acts as a domain-general hub where information about reinforcers links to motor centers for expression of affect and execution of goal-directed behavior (Shackman et al., 2011). This view challenges earlier notions of a clean segregation between ACC involvement for affective processes and aMCC involvement for cognitive processes (Devinsky et al., 1995; Bush et al., 2000). The adaptive control hypothesis is the idea that aMCC uses information about punishment
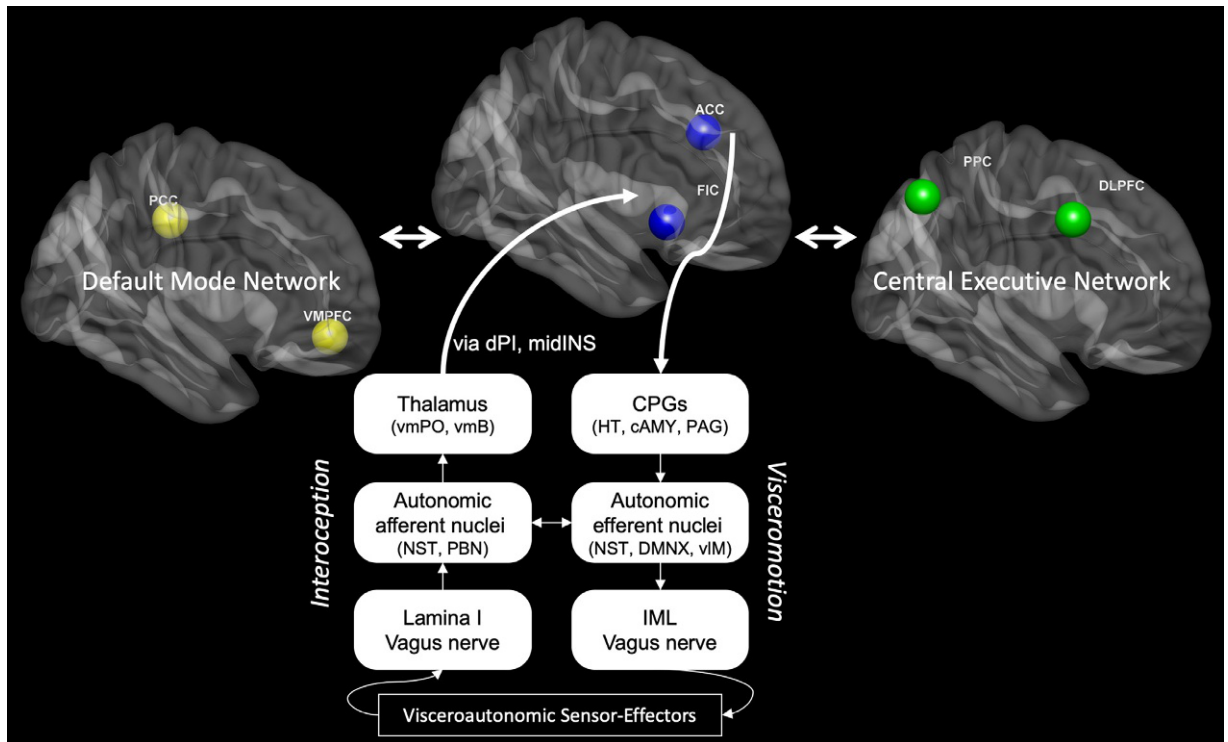
Fig. 7.3. Salience network anatomy. Ascending inputs conveying information about the body are integrated in the frontoinsular cortex (FIC), which, together with the midcingulate cortex, comprises the major cortical nodes of the salience network. Interoceptive signals travel via the vagus nerve through autonomic afferent nuclei (NST = nucleus of the solitary tract; PBN = parabrachial nucleus) and the thalamus (vmPO = ventromedial nucleus of the thalamus, posterior; vmB = ventromedial nucleus of the thalamus, basal) up to the FIC via the dorsal posterior insula (dPI) and mid-insula (midINS). The salience network communicates with visceromotor central pattern generators (CPGs: HT = hypothalamus; cAMY = central nucleus of the amygdala; PAG = periaqueductal gray) that transmit to autonomic efferent nuclei (NST; DMNX = dorsal motor nucleus of the vagus nerve) and the vagus nerve (IML = intermediolateral cell column). Salient signals integrated in FIC causally influence the default mode network (DMN, *yellow*; key nodes in PCC = posterior cingulate cortex; VMPFC = ventromedial prefrontal cortex) and the central executive network (CEN, *green*; key nodes in PPC = posterior parietal cortex; DLPFC = dorsolateral prefrontal cortex). Communication between the salience network and brain regions for interoception and visceromotion allows integration of salient signals to guide behavior (Uddin, 2015).

to control aversively motivated actions, engaging the same processes as those described by theories of cognitive control to solve conceptually similar problems when the most adaptive course of action is uncertain (Shackman et al., 2011).

While the functional specificity of the aMCC and its surrounding regions remains a topic of ongoing investigation and debate, broadening the perspective from the single region to the macroscale network provides a complementary perspective to understand its role in global brain organization.

aMCC AND THE SALIENCE NETWORK

A significant portion of the literature in neuroscience and psychology deals with the topic of salience detection and processing, where salience is defined as objects, ideas, or events that are very important or noticeable and thus attract attention. Salience is well defined and relatively straightforward to operationalize in vision research and computational models of attention. However, the term is also used in other contexts to mean personal relevance, where stimuli or events that are meaningful or emotionally provocative are described as salient. Thus, the concept of salience provides a broad construct that is relevant to the domains of pain, error detection, and attention, among others.

In 2007, a seminal paper was published describing a "salience network," including aMCC, frontoinsular (FIC)/anterior insular (AI) cortex, dorsomedial thalamus, hypothalamus, periaqueductal gray, sublenticular extended amygdala, substantia nigra/ventral tegmental area, and temporal pole (Seeley et al., 2007). The anatomy of this network (Fig. 7.3) suggests that it serves the function of enabling communication of cortical areas with subcortical regions to integrate interoceptive and visceromotor signals that can be used to guide behavior (Seeley et al., 2012).
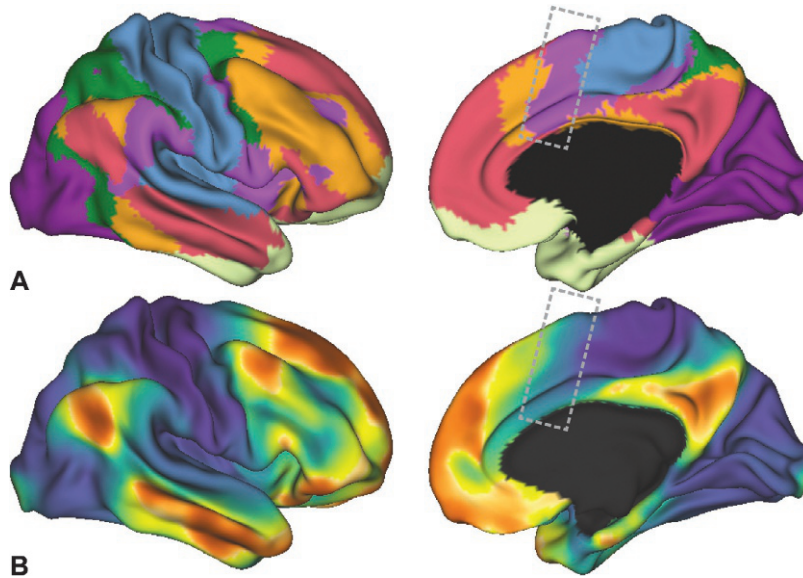
Fig. 7.4. The anterior midcingulate cortex and salience network in relation to global connectivity organization. Rectangle denotes approximate location of the anterior midcingulate cortex with respect to (A) the 7-network from Yeo et al. (2011) and (B) the principal functional connectivity gradient from Margulies et al. (2016).

Of particular interest to scholars of the cingulate cortex, the salience network is one large-scale brain network through which this region enacts widespread effects. Resting-state functional connectivity studies demonstrate strong connections between the anterior insula and the aMCC and pMCC (Margulies et al., 2007; Taylor et al., 2009), suggesting that the most likely cingulate subdivision to participate in the salience network is one that is centered midway along the cingulate gyrus within the MCC. In the more general context of human resting-state fMRI studies, the aMCC participates in several large-scale functional brain networks, including the ventral attention network of the 7-network description from Yeo et al. (2011) (Fig. 7.4A), which corresponds to the independently described salience (Seeley et al., 2007) and cingulo-opercular task control networks (Dosenbach et al., 2007).

Network-level descriptions help to situate a region within a broader interconnected functional system (Passingham et al., 2002; Mars et al., 2018). Complementary to this approach, networks can be described in relation to one another. A recent approach mapped gradients in connectivity patterns, observing that throughout the cortex, networks are arranged in a consistent spatial order. Within this spectrum, the salience network is situated between unimodal regions and the frontoparietal control network. The location of aMCC along this principal gradient suggests its role—and the more general role of the salience network within the global cortical hierarchy—is one of mediating between motoric output and the higher-level cognitive representations of the ACC and medial prefrontal cortex (Margulies et al., 2016) (Fig. 7.4B).

The salience network exhibits modality-independent responses to novel stimuli. For example, the classic oddball paradigm in which a series of identical stimuli are interspersed with a different stimulus at unpredictable intervals elicits robust activation in the salience network when contrasting infrequent vs frequent trials (Levy and Wagner, 2011; Kim, 2014). A meta-analysis also revealed areas of the salience network including aMCC and AI cortex to be important for interference processing during paradigms including the Stroop, flanker, and Simon tasks (Chen et al., 2018). The fact that one can observe consistent activation across these various paradigms is consistent with the view that the salience network functions in rapid, transient transmission of relevant information to other cortical and subcortical areas.

Early network analyses suggested that the salience network, and right anterior insula in particular, may play a causal role in switching between other large-scale networks including executive control and default mode networks (Sridharan et al., 2008). This and subsequent work has formed the basis for a model of brain network dynamics that has been particularly influential in the field of psychiatry (Uddin, 2015). The function of the aMCC in the context of the salience network likely involves rapid access to the motor system to facilitate appropriate behavioral responses to salient inputs from the environment (Menon and Uddin, 2010). Of note, salience network dynamics appear to be related to individual differences in self-control (Steimke et al., 2017) and the aMCC has been observed as the locus of distinct functional connectivity associated with attention deficit hyperactivity disorder (ADHD) (Castellanos et al., 2008).

Returning to the previously described notion of aMCC as a functional hub, one can imagine that when critical functional hubs are impaired due to disease, widespread effects can be observed across the brain. In an fMRI meta-analysis of studies examining cognitive control (performance or conflict monitoring, response inhibition or selection, set shifting, verbal fluency, and working memory) in individuals with schizophrenia, depression, anxiety, or substance abuse disorders, trans-diagnostic abnormal activation was observed in some of these hub regions including the midcingulate and insular cortex (McTeague et al., 2017). These findings corroborate earlier meta-analytic work demonstrating atypical gray matter volume of ACC and insular cortex across diagnoses (Goodkind et al., 2015). The authors take these findings to suggest that brain networks necessary for flexible cognition such as those anchored in aMCC are vulnerable to a wide spectrum of psychopathology.

CONCLUSIONS

The findings reviewed here, while partially consistent with traditional views of a subdivisional organization within the cingulate cortex, leave room for a view that incorporates recent evidence for functional gradients that capture the overarching layout. While the classic conceptualization of an anterior-to-posterior gradient delineating affective and cognitive functions of the ACC still holds up under many circumstances, other lines of empirical work point to alternate, more gradual delineations. The growing emphasis on understanding neural context in order to more accurately describe large-scale network function informs the current debate regarding functions of the aMCC (McIntosh, 2004; Ciric et al., 2017). Here we have aimed to highlight how the unique patterns of structural and functional connectivity observed in aMCC render this region an effective network convergence zone, with the salience network poised to integrate cognition and affect to produce desired motor outcomes.

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