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The Tenacious Brain: How the Anterior Mid-Cingulate Contributes to Achieving Goals

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Abstract

Tenacity--persistence in the face of challenge--has received increasing attention, particularly because it contributes to better academic achievement, career opportunities and health outcomes. We review evidence from non-human primate neuroanatomy and structural and functional neuroimaging in humans suggesting that the anterior mid cingulate cortex (aMCC) is an important network hub in the brain that performs the cost/benefit computations necessary for tenacity. Specifically, we propose that its position as a structural and functional hub allows the aMCC to integrate signals from diverse brain systems to predict energy requirements that are needed for attention allocation, encoding of new information, and physical movement, all in the service of goal attainment. We review and integrate research findings from studies of attention, reward, memory, affect, multimodal sensory integration, and motor control to support this hypothesis. We close by discussing the implications of our framework for educational achievement, exercise and eating disorders, successful aging, and neuropsychiatric disorders such as depression and dementia.

Keywords

tenacity; anterior mid-cingulate cortex; energy regulation

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When faced with a difficult challenge, such as mastering complex equations or training for a marathon, many individuals will find the effort too costly, and withdraw. Others, however, will marshal their resources, and persist in their efforts against the same challenges, even in the absence of immediate reward. This individual difference has received a great deal of attention in recent years, as growing research indicates that individuals who persevere in the face of challenging situations show better life outcomes in the domains of health, academic achievement, and career success (Duckworth and Quinn, 2009; Duckworth and Gross, 2014).

This tendency to carry on despite difficulty has been called by multiple names. Recent studies of life achievement describe it as ‘grit’ (Duckworth and Quinn, 2009; Duckworth and Gross, 2014), defined as ‘passion and perseverance toward especially long-term goals’ (Duckworth and Quinn, 2009; Duckworth and Gross, 2014). Others have used the term ‘persistence’, (defined as ‘the ability to generate and maintain arousal internally’)(Cloninger et al., 1993; Holroyd and Umemoto, 2016), ‘perseverance’ (defined as ‘the maintenance of effort over time’)(Patzelt et al., 2019), or defined it against its opposite, ‘apathy’ (Le Heron et al., 2019). Here we use the term tenacity to describe both a persistent pattern of behavior, and a fundamental bias in effort computations (as described by (Shenhav and Botvinick, 2013; Shenhav et al., 2013; Shenhav et al., 2017)), by which the costs of effort are devalued, and the value of long-term rewards is emphasized.

Multiple prominent theories of effort and motivation posit an important role for the anterior portion of the cingulate cortex in mediating individual differences in personality which promote tenacious behavior (Holroyd, 2016; Holroyd and Umemoto, 2016; Le Heron et al., 2017; Le Heron et al., 2019; Patzelt et al., 2019).

In this paper, we will review evidence supporting this view, focusing on how anterior mid-cingulate cortex (aMCC) plays a central role in establishing tenacity. Due to its position at the intersection of multiple intrinsic networks, the aMCC can integrate signals related to interoception, allostasis, executive function, motor planning, and sensory integration. We will argue that this uniquely connected position allows aMCC to weigh predicted energy requirements against predicted rewards and allocate physiological and attentional resources to achieve desired goals.

To support this view, we will first present evidence from neuroanatomy, tractography, and intrinsic functional connectivity imaging indicating that the aMCC is a major hub, sitting at the intersection of multiple intrinsic brain networks, and among the most broadly connected regions of the brain. Next, we will review functional evidence of a variety of task domains to show that the aMCC is a domain-general ‘hot-spot’ in the brain, implicated in a wide variety of tasks. We will then consider how variability in aMCC function may account for the difference between tenacity and withdrawal in the face of challenge. Finally, we will review studies of aMCC structure and function in cases of tenacity as well as apathy or withdrawal, and consider the implications of our hypothesis for educational achievement, successful aging, exercise and obesity, and neuropsychiatric disorders such as depression and dementia

Anterior Mid-Cingulate Cortex as a Structural and Functional hub: Neuroanatomy and Connectivity

Since 1907 when the anterior division of the mid-cingulate cortex was first described (Smith, 1907; see (Vogt, 2016)), our understanding of the aMCC organization has significantly advanced. In humans, the agranular aMCC is located dorsal to the genu of the corpus callosum, extending rostrally to the border of the superior frontal gyrus, encompassing areas 32' and a24c' and areas in the rostral and caudal cingulate premotor areas (rCMA/ rCPMA) (Picard and Strick, 2001; Palomero-Gallagher et al., 2008; Vogt, 2016) (see Figures 1A, B, C; see also Figure 1 and 3 in (Vogt, 2016)). The cytoarchitecture and neurocytology of aMCC point to fundamental differences between the aMCC and anterior cingulate cortex (ACC) (see Figures 3, 4 in (Vogt, 2016)). However, many neuroimaging studies often employ other terminologies such as dorsal ACC to refer to aMCC. In this article, all figure labels refer to aMCC. This may not be the term used in the papers we discuss but using this term we aim to accurately refer to the neuroanatomical region reported in the original text.

Invasive tract tracing studies in macaques (the monkey aMCC comprises areas a24a', a24b' and a24c' but lacks area 32'; see Figure 3 in Vogt, 2016) (Bates and Goldman-Rakic, 1993; Picard and Strick, 2001; Morecraft et al., 2012; Procyk et al., 2016) and diffusion weighted tractography in humans (see Figure 5 in (Beckmann et al., 2009)) have both demonstrated a distinct aMCC structural connectivity pattern from the rest of the cingulate cortex. The aMCC has strong connections with frontoparietal and temporal regions (i.e., dorsal prefrontal cortex, medial and lateral orbitofrontal cortex, anterior and posterior insula, caudal parietal cortex, rostral superior temporal gyrus), motor regions (i.e., premotor, supplementary motor cortices) as well as subcortical structures (i.e., thalamus, dorsal striatum, amygdala, hypothalamus, and periaqueductal gray) (Mesulam and Mufson, 1982; Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen, 1998; Picard and Strick, 2001; Morecraft et al., 2012; Procyk et al., 2016). This pattern of aMCC structural connectivity led Morecraft and Van Hoesen (Morecraft and Van Hoesen, 1998) to propose that the aMCC may serve as a cortical entry point for limbic influence on the voluntary motor system. The aMCC includes also dopaminergic, noradrenergic and serotonergic terminals (Williams and Goldman-Rakic, 1998; Bar et al., 2016). These dense monoamine innervations suggest a crucial role in motivational functions for aMCC (Vogt, 2016).

Recent advances in human brain connectomics have further identified aMCC as a major structural hub central to maximizing communication between multiple areas (Hagmann et al., 2008; van den Heuvel and Sporns, 2011; Nijhuis et al., 2013; van den Heuvel and Sporns, 2013b, a) (see Figure 1D). Compared to other brain regions, hub regions, such as the aMCC, are substantially more structurally connected with the rest of the brain (Hagmann et al., 2008; van den Heuvel et al., 2012) and are metabolically more active (Collin et al., 2014). Network analysis studies of intrinsic brain connectivity have also identified the aMCC as a functional hub on the basis of its spontaneous activity (Margulies et al., 2007). It has been demonstrated that aMCC is as a key region in a multimodal network that integrates information originating from primary sensory regions (e.g., visual, auditory, and

somatosensory) (Sepulcre et al., 2012) (see Figure 1E). Furthermore, neuroimaging studies reveal that the aMCC belongs to at least five, partially overlapping, intrinsic brain networks. Some of these have been associated with visceromotor functions conventionally referred to as the “salience” (Seeley et al., 2007; Touroutoglou et al., 2012) and “allostatic-interoceptive” networks (Kleckner et al., 2017) (see Figures 1F, G) and others with executive function, attention, and motor control conventionally referred to as “frontoparietal control” (Vincent et al., 2008), “ventral attention” (Fox et al., 2006), and “cingulo-operculum control” networks (Dosenbach et al., 2007; Nelson et al., 2010) (see Figures 1H, I, J). Collectively, the findings above point to the possibility that the aMCC serves as a structural and functional hub of communication, that synchronizes information from otherwise segregated systems (see Figure 1F). We propose that the aMCC’s connections allow it to integrate information from multiple brain networks to drive goal-directed behaviors. In other words, its position allows it to participate in the willed control of our behavior (Paus, 2001; Parvizi et al., 2013).

Anterior Mid-Cingulate Cortex as a “Hot Spot” in the Brain: Task-related fMRI

Due to its hub centrality, the aMCC is well situated to receive a wide range of signals from other brain regions. Consistent with its diverse inputs, the aMCC region has been implicated in a large and diverse set of distinct tasks (see Table 1 for examples of evidence supporting the ubiquity of aMCC activations across tasks), including those involving motor function and executive function, memory, emotion, pain, and somatosensation (Beckmann et al., 2009; Shackman et al., 2011; Bahlmann et al., 2015; Wager et al., 2016). Meta-analytic evidence further indicates that the aMCC is among the most consistently reported areas of activation in functional MRI (fMRI) studies over the past 20 years (Yarkoni et al., 2011); for a meta-analysis of 1,114 studies see (Nelson et al., 2010); for a meta-analysis of 5,633 studies see (Clark-Polner et al., 2016)) (see Figures 2A and B). Compared to other activation foci, the aMCC also exhibits the highest degree of functional diversity (Anderson et al., 2013; Bertolero et al., 2015) and flexibility (Yeo et al., 2015; Betzel et al., 2017) (see Figures 2C, D). Furthermore, due to its participation in a diverse range of tasks, the aMCC is included in a set of co-activating regions collectively known as the “multiple demand network” (Duncan, 2010)(see Figure 2E).

The common engagement of the aMCC by diverse tasks suggests that the region may play an integrative role across multiple brain systems. A number of convergent functions have been suggested, including integration of information about pain and negative affect in guiding behavior (Shackman et al., 2011), integration of signals related to motivation with cognitive control (Bahlmann et al., 2015), the computation of optimal levels of cognitive control or effort (Botvinick and Braver, 2015; Shenhav et al., 2016; Shenhav et al., 2017), the processing of prediction error in effortful tasks (Vassena et al., 2017a), and the selection of and persistence in pursuit of high-level goals (Holroyd and Yeung, 2012; Holroyd and Umemoto, 2016) (See Box 1).

We hypothesize that the aMCC performs all of these functions in the service of a broader common goal: efficient energy regulation. On this view, aMCC activation is ubiquitous because energy regulation computations are ubiquitous, accompanying the consideration of every action or personally relevant event (see (Barrett and Simmons, 2015; Barrett, 2017b, a)) (see also Box 1). Our hypothesis is that the aMCC's position as a hub at the nexus of motor, visceromotor and attention systems allows it to integrate information related to interoception, executive function, sensory processing and motor control to anticipate expected physiological demands and then to effectively deploy the body's energy resources to achieve goals. This domain general function would require multiple component computations, which have been observed as aMCC engagement in a wide variety of tasks.

An important component of efficient energy computations, observed in multiple task-evoked fMRI studies of aMCC (Jocham et al., 2009; Sheth et al., 2012; Kolling et al., 2016) is the *prediction of behavioral outcomes*, so that the value of potential actions can be assessed. Consistent with the predictive function of aMCC (see also Box 1), there is substantial evidence of aMCC activation in situations where pain or reward is anticipated, or novel unexpected events occur (Raichle et al., 1994; Kouneiher et al., 2009; Mobbs et al., 2010). The aMCC activations during the experience of reward or punishment (Kouneiher et al., 2009; Lindquist et al., 2012; Bahlmann et al., 2015) can thus be understood as testing expected hedonic values against experience. Activations during social behavior (Kirk et al., 2011; Apps et al., 2013) may represent comparisons between the anticipated and actual behavior of others. Similarly, the aMCC is active during task selection (Kolling et al., 2014) as predicted outcomes are compared; during task performance (Modirrousta and Fellows, 2008; Sheth et al., 2012) as outcomes are tested against predictions; and during effortful tasks (Boehler et al., 2011; Engstrom et al., 2013; Fedorenko et al., 2013) as predictions of available resources are updated and additional cognitive and physiological resources are deployed to meet the task demands.

In addition to potential rewards, *assessment of the energetic costs of task performance* is crucial to efficient energy regulation. The aMCC appears to encode not only the value of a reward but also the cost of the effort required to obtain it (Harris and Lim, 2016). This effort may take the form of increased cognitive control, which is frequently experienced as aversive (Dreisbach and Fischer, 2012; Schouppe et al., 2012; Kurzban et al., 2013; Inzlicht et al., 2015; Saunders et al., 2015). Indeed, activity of the aMCC region during difficult tasks is positively correlated with a subjective sense of frustration (Spunt et al., 2012), as well as desire to avoid the task (McGuire and Botvinick, 2010).

Additionally, some evidence suggests that the aMCC also represents physiological costs of action by *monitoring the internal state of the body*. Multiple studies have implicated the aMCC in tasks involving interoception and pain, hunger, thirst, and breathlessness, leading Lieberman and Eisenberger (2015) to describe the aMCC as a 'neural alarm', that serves to direct attention toward potential conflicts with enduring survival goals.

When expectations of the cost and benefit of goal pursuit are violated, it is crucial for efficient energy regulation that resource allocation be quickly recalibrated. Multiple theories suggest a role for aMCC in preparing control systems for future demands by *adjusting to*

prediction errors (Alexander and Brown, 2011; Barrett and Simmons, 2015; Alexander and Brown, 2017). For example, its activity in learning tasks is modulated by previous trials in a way that speeds responses to trials of equivalent difficulty, and slows them when difficulty levels change (Modirrousta and Fellows, 2008; Sheth et al., 2012). In another example, the aMCC responses to pain are modulated by the belief that the pain can be controlled (Salomons et al., 2004), suggesting that this region may play a role in anticipating and predicting pending noxious stimulation, so as to prepare avoidance responses (Vogt, 2016).

Following recalibration of energetic computations, it may be necessary to deploy additional energy resources to support task demands, or to limit resources in order to suppress costly behavior. Consistent with this view, some studies (Beissner et al., 2013) indicate that the aMCC may also serve to *modulate the internal state of the body to prepare for action*, through alterations in blood pressure, heart rate, and hormonal responses. A potential mechanism through which this could be achieved is by the regulation of arousal to prepare for action. The aMCC is well equipped to modulate states of arousal through its connections to mid-brain nuclei (Bar et al., 2016), and substantial research indicates that the aMCC indeed exerts regulatory control over various autonomic processes (Beissner et al., 2013). For example, cognitive and social stressors known to evoke autonomic stress responses robustly engage the aMCC (Wager et al., 2009; Gianaros and Wager, 2015) and increased blood flow in the aMCC is correlated with increases in blood pressure and heart rate variability, evoked by both mental (working memory) and physical (isometric exercise) exertion (Critchley et al., 2000; Critchley et al., 2003). Acute stressors of the sort that evoke stress hormone release also activate the aMCC (Gianaros and Wager, 2015), and the degree of stress-evoked activation predicts the magnitude of the hormonal stress response (Hermans et al., 2011).

Thus, due to its position as a network hub, the aMCC can synchronize information from diverse systems in order to guide behavior towards efficient energy balance. However, the effectiveness of aMCC computations are likely to vary between individuals, particularly in situations when the cost of effort is high, and rewards are uncertain or deferred. Under these circumstances, some will demonstrate tenacity and persist while others may simply quit. In the following section, we will consider how variability in aMCC function could underlie individual differences of this sort in tenacity.

Holroyd & Yeung (2012) attempted to reconcile evidence for the aMCC role in motivation and decision-making, with their Hierarchical Learning Model, which holds that the primary role of aMCC is the selection and maintenance of ‘options’, or high-level abstract behavioral plans generated from nested reinforcement learning (Holroyd and Yeung, 2012). Thus, the aMCC will be particularly active when the value of competing options must be compared, or when habitual responses must be suppressed in service of a larger goal. It will also be engaged when behavioral plans must be re-evaluated in the face of changing demands or reward conditions. On this view, then, the aMCC serves to direct behavior towards goals computed to be most valuable by regulating systems involved in cognitive control and task execution (Holroyd and Yeung, 2012).

Others have emphasized the notion that the aMCC computes not only the value of competing options, but also the hedonic costs of exerting effort and cognitive control to pursue selected goals. Thus, on this view, aMCC activation during action selection primarily represents the computation of the resources required to complete the task (Botvinick, 2007; Botvinick and Braver, 2015). In their Expected Value of Control model, Shenhav and colleagues (Shenhav et al., 2013; Shenhav et al., 2017) argue that the role of the aMCC is to track the cost of both mental and physical effort exerted during task performance, predict the cost of effort required for all available options, and then integrate that information with expectations of reward to determine if the exertion of cognitive control is worthwhile (Shenhav et al., 2013; Shenhav et al., 2017). This theory can thus account for aMCC activation in response to effort, changes in reward, action selection and cognitive control as expressions of the same core function.

Value computations of this sort, however, depend critically on the accuracy of estimates of future behavioral outcomes. Thus, some theories hold that the core, domain-general function of aMCC is preparing control systems for future demands by predicting the results of possible actions, and comparing these predictions to experience (Alexander and Brown, 2011, 2017). According to these models, mismatches between predicted and experienced outcomes generate a ‘prediction error’ signal, which can be used to update future predictions. On this view, aMCC activity in response to increased effort represents the processing of error in the prediction of expected task demands (Vassena et al., 2017b). Consistent with predictive models of aMCC function, there is substantial evidence of aMCC activation in situations where there is no choice to be made, or behavior to perform, such as when pain or reward is simply anticipated, or novel events occur (Vassena et al., 2014; Vassena et al., 2017b).

Other predictive models have argued that the aMCC’s serves not only to predict external events, but also internal states of the body, allowing for the maintenance of allostasis (i.e. efficient energy regulation through prediction of future energy needs) (Barrett and Simmons, 2015) [see also (Barrett, 2017b, a)]. To effectively calculate the expected value of a behavior, it is crucial to anticipate the costs in terms of physiological resources, and to deploy additional resources through arousal regulation when necessary. To maintain goal-directed behavior, these interoceptive predictions must be compared to experience, so that prediction error can be used to adjust energy resources to meet task needs. Chanes and Barret (2016) have also speculated that aMCC with its extensive connections is well suited to provide an integrated workspace for unified conscious experience due to its ability to represent information across different modalities based on allostatic relevance.

The Role of Anterior Mid-Cingulate Cortex in Tenacity

Together, the various aMCC computations described in the previous section serve to regulate the amount of effort directed toward any potential behavior. The function of such effort regulation has been debated, with most theories falling into two broad categories (see(Shenhav et al., 2017)). Some accounts hold that effort serves to manage intrinsic costs to finite resources such as metabolic resources (Gailliot and Baumeister, 2007; Gailliot et al., 2007; Holroyd, 2016), short-term memory(Elmore et al., 2011), or processing capacity

(Wickens, 1984; Feng et al., 2014). Other accounts emphasize the management of opportunity costs (Kurzban et al., 2013); see also (Shenhav et al., 2017), arguing that effort regulation ensures that cognitive control will be exerted only towards the highest value option currently available.

Our view is that the overarching function of effort computations (and indeed, a fundamental goal of the nervous system – see (Kleckner et al., 2017)) is the maintenance of allostasis. While we posit that the allocation of effort towards any particular behavior is a result of computations which serve to minimize opportunity costs, we also hold that information about available resources and distance from energy balance are important factors entering into these computations, as the estimated value of prospective rewards and costs of prospective effort are in part determined by the current and predicted energy state of the individual.

This account suggests that individual differences in effort computations could make the difference between persistence and withdrawal during demanding tasks. An individual might continue to exert effort on a demanding task because she estimates the value of an expected reward as greater than others do, because he perceives the cost of action as lower than others do, or because she perceives the body's available resources to be relatively greater. Indeed, while high levels of effort are generally experienced as aversive, some individuals rate effort as more aversive than others (McGuire and Botvinick, 2010; Dreisbach and Fischer, 2012; Schouppe et al., 2012; Spunt et al., 2012; Kurzban et al., 2013; Inzlicht et al., 2015; Saunders et al., 2015).

We propose that tenacity can be understood as a kind of bias in aMCC computations: a tendency to maintain the representation of expected rewards, devalue the cost of effort and to judge one's available physiological resources as meeting or exceeding task demands even in the face of negative affect. There are three sources of evidence that the aMCC is involved in tenacity: lesion studies, neuroimaging studies, and stimulation studies. We review each in turn.

Lesion Studies:

In animal research, lesion studies in rodents and primates have long implicated a region homologous to MCC to be critical for integration of reward and effort costs to motivate behavior (Walton et al., 2007; Kampe et al., 2009; Holroyd and McClure, 2015; Salamone et al., 2016) (see also (Le Heron et al., 2019) for animal studies showing the role of MCC in motivation). Indeed, in rats, inactivation of ACC (a region homologous to aMCC in humans) causes animals to reduce willingness to expend mental effort (Hosking et al., 2014) and decrease the energy/time expenditure required to obtain a proportional reward (Wang et al., 2017a). In monkeys, lesion studies also (Chudasama et al., 2013) demonstrate a critical role for ACC/MCC in sustaining effective choice behavior in the face of changing biological needs. Consistent with these findings, we recently demonstrated that the monkey aMCC is part of an intrinsic connectivity network that subserves arousal regulation (Touroutoglou et al., 2016).

Clinical research in humans has also indicated that damage to the aMCC or its connections can produce profound motivational changes. Reports of damage to the cingulate influencing motivation go back to Papez (1937, see (Szczepanski and Knight, 2014)], who observed that tumors pressing on the cingulate cortex led to “indifference to the environment, change in personality or character, [and a] stuporous or comatose state”. More recent studies have connected damage to the aMCC region with motivational impairment, apathy and inability to plan for long term goals (Devinsky et al., 1995; van Reekum et al., 2005; Szczepanski and Knight, 2014; Ducharme et al., 2017).

Naccache et al. (2005) examined the motivational disruptions associated with cingulate damage in a revealing case study of an individual with a lesion encompassing aMCC extending to dorsomedial prefrontal cortex (Naccache et al., 2005). The patient was presented with a number of tasks requiring executive function designed such that the difficulty of the tasks could be systematically varied. While the patient was able to perform these tasks in a relatively unimpaired manner, he reported no subjective sense of effort, or change in perceived effort as the difficulty increased. Furthermore, he showed no physiological evidence of increased effort, unlike controls, whose skin conductance increased along with difficulty.

Neuroimaging Studies:

Multiple neuroimaging studies have indicated that variability in aMCC function may account for the difference between tenacity and withdrawal in the face of challenge.

A major potential source of individual variability in tenacity is the strength of communication between the aMCC and other regions involved in signaling reward, autonomic processing or exercising cognitive control. It has been shown that the strength of intrinsic functional connectivity between aMCC and striatal regions predicted survey measures of both ‘grit’ and ‘growth mindset’ (the belief that cognitive abilities are malleable, and can be improved through hard work) (Myers et al., 2016). Furthermore, stronger structural and functional connectivity between aMCC and supplementary motor area predicts lower levels of apathy (apathy defined as lack of motivation to initiate behavior or respond to environmental stimuli) (Bonnelle et al., 2016) (see Figures 2A and 2B).

More direct evidence comes from a recent study examining the neural substrates of grit, demonstrating that individual’s grit is related to the spontaneous activity of aMCC (Wang et al., 2017b)(see Figure 2C). The magnitude of activity within the aMCC during effort judgments has also been shown to predict persistence (see Figure 2D). Indeed, aMCC activity during trials where participants chose a more difficult task over an easier one was positively associated with trait-level persistence (Kurniawan et al., 2010). In another study, Bonnelle et al. (2016) further reported that greater activity in the aMCC during cost-benefit weighing was associated with willingness to exert more effort (Bonnelle et al., 2016) (see Figure 2E). Relatedly, Scholl and colleagues (2015) reported that aMCC activity was greater during the choice of high effort vs. low effort options (Scholl et al., 2015) (see Figure 2F). Consistent with these findings, Spielberg and colleagues place the aMCC in a network involved in maintaining goal pursuit (Spielberg et al., 2012) (see their Figure 3c).

Other task-related studies have indicated that the aMCC serves to integrate information about cost and benefit to sustain motivated behavior. Chong et al. (2017) reported that aMCC activity was associated with a preference to make an effort in return for reward, regardless of whether the task required mental or physical effort exertion (Chong et al., 2017) (see Figure 2G).

Additionally, at least one study has related aMCC anatomy to a tenacious mindset. Van Schuerbeek and colleagues (Van Schuerbeek et al., 2011) reported that greater gray matter volume in a cluster including the aMCC and pMCC predicted higher levels of persistence as assessed by personality inventory (see Figure 4 in (Van Schuerbeek et al., 2011)).

Taken together, these findings indicate that the aMCC plays an important role in judgments of the subjective value of effort that can influence the choice between responding with tenacity or withdrawal.

Stimulation Studies:

Perhaps the strongest evidence for a role of aMCC in tenacity can be found in studies of experimental stimulation of the aMCC. Multiple studies have reported goal-oriented behaviors in response to aMCC stimulation (Escobedo and Cravioto, 1973; Talairach et al., 1973; Bancaud et al., 1976; Kremer et al., 2001; Chassagnon et al., 2008; Caruana et al., 2018). In a recent well-designed study, Caruana and colleagues analyzed the effect of electrical stimulation applied to 1789 cingulate sites, in 329 patients and provided causal data related to role of aMCC in motivation. Consistent with the role of aMCC in tenacity, the authors found that the stimulation of aMCC elicits a variety of goal-oriented behaviors [(see Figure 3 in Caruana et al. (2018)]. The results lead the authors to suggest that “aMCC might provide the motivational drive to perform actions, playing an excitatory and/or inhibitory role on these motor circuits”. Interestingly, they authors further demonstrated that aMCC controls these goal-oriented behaviors according to a dorsoventral ‘actotopic’ organization: stimulation of dorsal aMCC evoked movements directed towards the body (e.g., rubbing the eyes); stimulation of middle aMCC elicited actions in the peripersonal space (e.g. exploratory gaze movements); and stimulation of ventral aMCC led to whole body movements towards extrapersonal space (e.g. the impulse to get up as some patients described it: ‘I felt I was willing to go away’). Taken together, it is possible that the aMCC function in motivation may be embodied, as suggested by Apps (2018) organized within a space- or body-framed topography.

In another study that used a structured task assessing effort perception, Zenon and colleagues (2015) reported that transcranial magnetic stimulation of supplementary motor area (an area strongly connected to aMCC) significantly reduced the perceived aversiveness of a physically demanding task. This resulted in a greater willingness to exert effort, even for a reduced reward (Zenon et al., 2015). However, given the close proximity of supplementary motor area and aMCC, it is difficult to assess the degree of aMCC contribution to this effect.

A more compelling example is provided by Parvizi and colleagues (Parvizi et al., 2013), who employed direct electrical stimulation of the aMCC, producing what they described as an increase in the ‘will to persevere (Parvizi et al., 2013) (see Figure 2H). Patients generally

described the experience of aMCC stimulation as evoking the feeling of preparing for a difficult challenge. As one patient put it: “I started getting this feeling like ... I was driving into a storm. [...] like, you’re headed towards a storm [...] and you’ve got to get across the hill and all of a sudden you’re sitting there going how am I going to get over that, through that?”

Implications of the aMCC Role in Tenacity for Achievement, Aging, Health, and Illness

Tenacity will influence performance particularly wherever there is challenge. In this section, we will consider evidence that aMCC structure and function predicts life and health outcomes across multiple domains. We will limit our focus on the extreme ends of aMCC variability. We will first consider the role of aMCC dysfunction in apathy (or absence of motivation), specifically in cases of depression and neurodegenerative disease. We will then review findings indicating that greater aMCC integrity predicts tenacity that is associated with positive life outcomes in aging, health, and academics.

Depression:

Apathy, defined by DSM-5 as a pronounced lack of motivation, goal-directed behavior and emotional responsiveness, is among the most commonly reported symptoms of depression (Pizzagalli, 2014). Numerous studies demonstrate that patients with depression are less willing to expend effort for rewards than controls (Treadway et al., 2012). Given the role of aMCC in effort processing, as Holroyd (2012) and others have argued, it seems likely that the aMCC is compromised in depressed individuals. Indeed, a substantial body of evidence also implicates aMCC dysfunction in depression (Chen et al., 2007; Steele et al., 2007; Crossley et al., 2014) (see also (Holroyd and Umemoto, 2016; Vogt, 2016)). It should be noted, however, that depression is a heterogeneous clinical syndrome and as such, distinct dimensions of symptomology are associated with alteration of brain function in distinct regions (Drysdale et al., 2017). Indeed, in addition to apathy, depression is defined by a pronounced anhedonia and negative attentional bias which have been alleviated by deep brain stimulation of other brain regions, notably the subgenual ACC (Holtzheimer and Mayberg, 2012).

Dysfunction of the aMCC seems particularly relevant to motivational problems, rather than hedonic components of depression. It has been shown that the degree of reduction in aMCC volume predicts severity of apathetic symptoms in depression (Lavretsky et al., 2007). Furthermore, depressed individuals exhibit reduced activation of aMCC during a complex planning task (Elliott et al., 1997) (see Figure 3A). Disruption of aMCC function could mediate apathy through disruption of reward processing (Holroyd and Umemoto, 2016), as aMCC response to reward learning is reduced in depression (Kumar et al., 2008). Apathy may also be related to impaired ability of aMCC to effectively adjust to prediction errors. In one study employing a gambling task (Steele et al., 2007), healthy individuals responded to negative feedback with aMCC activation and improved reaction times, while depressed individuals showed neither aMCC engagement nor behavioral improvement following errors (Steele et al., 2007). Collectively, these studies are consistent with the proposal that

depression disrupts the aMCC's ability to act as the central hub (Pizzagalli, 2014), thus compromising motivation (Holroyd and Umemoto, 2016).

Neurodegenerative Disease:

Apathy has also been observed in a wide range of neurological disorders, including Alzheimer's disease (Mega et al., 1996), behavioral variant of frontotemporal dementia (bv-FTD) (Ducharme et al., 2017) and Parkinson's disease (Aarsland et al., 2009). In a recent review, Le Heron and colleagues argue that despite the diversity among these disorders in causes and behavioral symptoms, all of these disorders share a common neural feature: the disruption of an interconnected group of brain regions involved in reward processing and cognitive control, with the aMCC at its core (see Figure 4 in (Le Heron et al., 2017).

Indeed, in Alzheimer's disease, the magnitude of abnormal aMCC function (Migneco et al., 2001; Schroeter et al., 2011; Le Heron et al., 2017) is linked to apathetic symptoms (see Figure 3B). In bvFTD, apathy has been associated with atrophy, hypometabolism and/or hypoperfusion in aMCC and its connected regions, including dorsolateral prefrontal cortex, orbitofrontal cortex, and the medial and ventromedial superior frontal gyri (Franceschi et al., 2005; Schroeter et al., 2011; Ducharme et al., 2017; Le Heron et al., 2017). Similarly, altered metabolism in aMCC region is associated with the degree of apathy in Parkinson's disease (Huang et al., 2013; Le Heron et al., 2017).

Superaging:

Emerging research suggests that exceptional cases of healthy aging may be associated with increased tenacity. While in the majority of elderly people, episodic memory function declines with age (Grady and Craik, 2000; Cansino, 2009) accompanied by a number of age-related neurobiological changes, including structural atrophy (Brickman et al., 2007; Bakkour et al., 2013), loss of intrinsic network coherence (Andrews-Hanna et al., 2007; Wang et al., 2010), and altered brain activity during memory (Grady et al., 2006; Maillet and Rajah, 2014), there are exceptions. Multiple recent studies have identified a remarkable subgroup of elderly people, known as 'superagers', whose performance on some cognitive measures is equivalent to middle aged (Gefen et al., 2014) and even young (Sun et al., 2016) adults, despite their advanced age.

Many of the most pronounced neurobiological differences between superagers and typical older adults involve the structure and function of the aMCC. Anatomically, we showed that the cortical thickness of aMCC in superagers is actually equivalent to young controls (Sun et al., 2016), exceeding the thickness of the middle-aged (Harrison et al., 2012). Recently, we further demonstrated that superagers not only have greater cortical thickness in aMCC but also exhibit greater intrinsic functional connectivity between aMCC and major nodes of the salience network when compared to typical older adults (Zhang et al., 2019). Importantly, the thickness and network connectivity of the aMCC can predict successful memory performance in older adults (see Figure 3C). Thus, superagers show a more 'youthful' pattern of memory function, aMCC structure and network connectivity than most elderly people.

Given that cognitive effort is especially costly for older adults (Westbrook et al., 2013), does this preserved aMCC function and cognitive ability in superagers indicate a more ‘tenacious’ attitude towards challenging tasks? As aMCC activity is associated with exertion of effort in response to multiple cognitive demands (Fedorenko et al., 2013), persistence in the face of difficulty should be associated with greater aMCC activity during memory performance. Indeed, during difficult trials on a memory task, elderly people show greater aMCC activity than during easier trials (see Figure 3D) (Dhanjal and Wise, 2014).

Exercise and Obesity and Eating Disorders:

Another area where an understanding of the neural basis of tenacity could have profound implications for public health is the study of exercise and obesity. Maintenance of an exercise regimen requires tenacity, and indeed individual differences in grit predict adherence to physical exercise (Reed et al., 2013). Studies of brain metabolism during exercise further indicate that aMCC metabolism relates to exercise intensity, and also that this coupling is significantly stronger in individuals with greater exercise capacity (who most likely exercise regularly) (Kemppainen et al., 2005)(see Figure 3E). Thus, aMCC may be better able to accurately assess the metabolic costs of exertion in tenacious individuals. Additionally, some evidence suggests that regular exercise may actually increase aMCC volume (Colcombe et al., 2006) (see Figure 3F), suggesting the exciting possibility that it may be possible to physically ‘train up’ aMCC function, and in turn, tenacity.

Tenacity may also influence weight loss outcomes through the ability to defer rewards, as well as the willingness to engage in effortful exercise. As such variability in aMCC function may be an important predictor of success in dieting. Choosing healthy foods over more calorically dense options is associated with greater aMCC activity (Harding et al., 2017), and a greater aMCC response to calorically dense foods is associated with reduced obesity risk (Carnell et al., 2017) (see Figure 3G). Thus, increased aMCC activation in response to food seems to be related to the deployment of cognitive control. Notably, formerly obese individuals who have successfully maintained weight loss show substantially enhanced aMCC (superior frontal/cingulate by authors) activation in response to food cues (McCaffery et al., 2009), indicating that aMCC responses to food stimuli is associated with a greater ability to self-regulate appetite.

If aMCC activation in response to food-associated cues indicates the deployment of cognitive control resources, then treatments that augment aMCC activity could potentially result in more effective self-regulation of cravings. In fact, at least one attempt to experimentally bolster aMCC processing has shown some success in influencing appetite. Leong et al. (2018) showed in women with obesity that transcranial pink noise stimulation targeted at the aMCC region results in a reduction in self-reported appetite on a ‘desire to eat’ scale (Leong et al., 2018) (see Figure 3H).

We note, however, that increased fixation to goals achieved by aMCC may be linked to abnormal self-monitoring problems that are commonly seen in the pathophysiology of eating disorders (EDs). Indeed, a recent review of fMRI studies demonstrated that anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) are associated with altered activation and connectivity in aMCC (Gaudio et al., 2016; Steward et al., 2018). It has been

shown that patients with BN and AN tend to exhibit greater functional connectivity of MCC (dACC by the authors) and precuneus (Lee et al., 2014), and this connectivity predicts higher levels of body shape concerns seen in these patients. Consistent with these findings, Geisler et al. used a probabilistic reversal learning task and showed increased activation of aMCC during negative feedback in a group of patients with AN. Importantly, this activation correlated with higher levels of perfectionism (Geisler et al., 2017). As the authors suggest, hyperfunctioning of aMCC may be related to increased fixation to goals (e.g. skinny body) often associated with AN. Interestingly, the abnormal functioning of the aMCC (and its connected regions) seems to improve in recovered patients with ED (for a review see (Steward et al., 2018)).

Taken together, these findings suggest the possibility of neuromodulation of the aMCC as a treatment for obesity and eating disorders, although further research is necessary to assess whether the effects of neuromodulation would lead to lasting behavioral change.

Academic Achievement and Professional Success:

In addition to conveying resilience to negative health outcomes, substantial and growing evidence indicates that grit and persistence predict achievement in multiple areas, such as educational achievement and professional success (Duckworth and Gross, 2014). Both grit and persistence have been associated with aMCC function; spontaneous aMCC activity predicts grit (Wang et al., 2017b), and greater aMCC volume predicts persistence (Van Schuerbeek et al., 2011). This suggests that aMCC may contribute to the increased achievement associated with tenacity.

Indeed, growing evidence connects tenacity, aMCC activity and better performance. Mulert et al. (2005) has demonstrated that when individuals follow task instructions, there is a close relationship between conscious effort and aMCC activity (Mulert et al., 2005)(see Figure 3I). Across three different tasks, Naito et al. (2000) also found a significant positive correlation between blood flow in aMCC and speeded reactions (Naito et al., 2000) (see Figure 3J). More direct evidence comes from a recent study that demonstrated a link between aMCC function and academic performance, noting that spontaneous activity in this region is correlated with both grit scores (see Figure 2C) and academic performance (Wang et al., 2017b). Critically, mediation analysis showed that the grit-academics relationship is mediated by the aMCC activity, indicating that superior aMCC function explains greater academic achievement in tenacious individuals.

Conclusion and Future Directions:

Tenacity is a powerful predictor of health and achievement and research on its neural basis could offer greater understanding of the qualities that promote exceptional achievement. The preceding evidence suggests a central role for the aMCC in subserving tenacity. Positioned at the intersection of systems involved in autonomic processing, interoception, executive function, motor planning, and sensory integration, the aMCC receives the information necessary to perform domain-general computational functions to mobilize physiological and cognitive resources to meet task needs. Such processes may include the (a) prediction of behavioral outcomes, (b) assessment of the energetic costs of task performance, (c)

monitoring the internal state of the body, (d) adjusting to prediction errors, and (e) modulation of the internal state of the body to prepare for action. We propose that tenacity can be understood as a kind of bias in these aMCC computations: a tendency to maintain the representation of expected rewards and to judge one's available physiological resources as meeting or exceeding task demands. Consistent with this view, we presented emerging evidence indicating that greater aMCC structure and function are linked to tenacious behavior in many domains of life and health. In contrast, the disruption of aMCC has been associated with apathy and other motivational problems implicated in many neuropsychiatric disorders (Le Heron et al., 2017). Thus, understanding how the aMCC can contribute to achieving goals can also potentially provide therapeutic insight into health difficulties ranging from obesity and eating disorders to depression and dementia.

One intriguing possibility is that the structure and function of aMCC could be altered with sufficient behavioral training. Indeed, as a flexible hub, the MCC may be better equipped than other brain regions to reshape its connectivity in response to learning. It has been proposed that protein receptors important for plasticity (such as CaMKII, NR2B, NMDA) are highly expressed in limbic circuits including aMCC (Wei et al., 1999; Palomero-Gallagher et al., 2008; Garcia-Cabezas et al., 2017; Burt et al., 2018; Palomero-Gallagher and Zilles, 2019). Interestingly, Garcia-Cabezas et al. (2017) recently showed that in adult monkeys, markers of synaptic plasticity are high in MCC (and other limbic regions) while markers of stability (as expressed by cellular factors that inhibit synaptic plasticity) are low. These findings suggest that training related improvement in behaviors requiring tenacity may be mediated through the aMCC. We have seen evidence that aMCC can be 'trained up' in the domain of exercise (Colcombe et al., 2006). Future studies (see Outstanding Questions Box) might focus on the development of interventions in aMCC activity and connectivity in other domains. Such interventions may have a broad therapeutic value (Downar et al., 2016; Le Heron et al., 2017).

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Box 1:**Theories of anterior Mid-Cingulate Cortex Function**

Early theories of aMCC function focused on the aMCC's role in selecting actions, as in cases where two behaviors are in conflict (Botvinick et al., 2001; van Veen et al., 2001; Botvinick et al., 2004), or when errors must be monitored (Brown and Braver, 2005; Holroyd and Coles, 2008); see (Vassena et al., 2017a) for review). This led to the view that the aMCC's role is the deployment of cognitive control to aid in action selection (see (Vassena et al., 2017a)). However, these theories cannot account for evidence of increased aMCC engagement in situations when participants have only one response option, but motivational conditions are altered through changes in reward or task demands (Vassena et al., 2014).

Outstanding Questions Box

- If preserved aMCC anatomy is associated with successful aging, does early aMCC development predict later life success?
- Does the ability of aMCC to efficiently regulate energy resources in response to laboratory challenges also translate to resilience to stressful life events such as grief, professional failure, or divorce?
- Can you make a person be tenacious? Can tenacity be trained behaviorally in school or later in life? If for example regular exercise influences aMCC volume, could exercise also influence tenacity?
- Can we alter the level of tenacity via noninvasive stimulation of the aMCC in a way that leads to lasting behavioral changes? Which neuromodulation techniques can specifically stimulate the aMCC?
- Given that the aMCC is a linchpin area receiving inputs from multiple brain networks, does tenacity imply a more functionally connected brain?

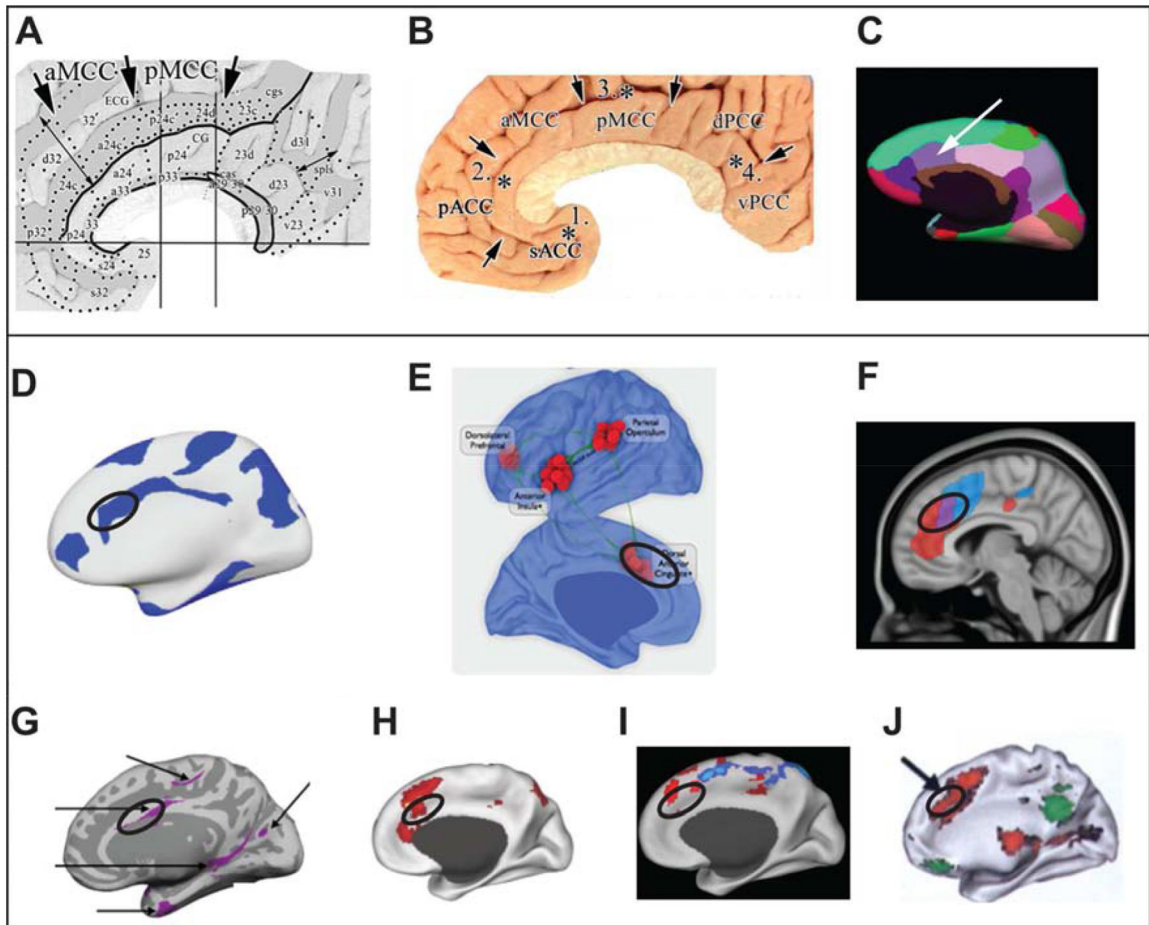


Figure 1.

Neuroanatomy and connectivity of the aMCC. Four Cingulate Regions & Subregions proposed by Vogt (A)(Vogt, 2016) and (B)(Vogt, 2005); Freesurfer cortical parcellation of the aMCC (white arrow) (C) (Desikan et al., 2006); aMCC (black circle) as a member of the brain’s ‘rich club’ hubs (D)(van den Heuvel and Sporns, 2013a); aMCC (black circle, labeled as ‘dACC’ by the authors) as a key region of the multimodal integration network (E) (Sepulcre et al., 2012); aMCC (black circle) sits at the nexus (purple) of two salience subsystems; the dorsal salience subsystem (blue) associated with executive function and the ventral salience subsystem (red) associated with viscerosomatic processing (F) (Touroutoglou et al., 2012); aMCC (black circle) as a key region of the large-scale allostatic/interoceptive system (G)(Kleckner et al., 2017), frontoparietal control system (H)(Vincent et al., 2008), ventral attention system (I)(Fox et al., 2006), and cinguloopercular network (J) (Dosenbach et al., 2007).

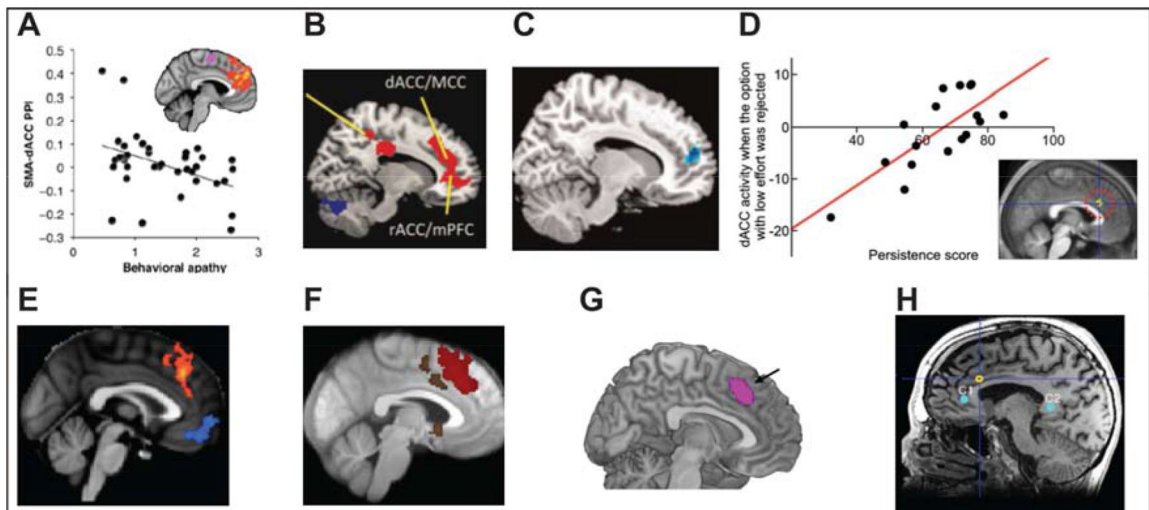


Figure 2.

The role of aMCC in tenacious behaviors. Stronger functional connectivity between aMCC (labeled as ‘dACC’ by the authors) and supplementary motor is linked to lower levels of apathy (**A**) (Bonnelle et al., 2016); stronger functional connectivity between aMCC and ventral striatum is associated with grit (**B**) (Myers et al., 2016); spontaneous aMCC activity predicts grit (**C**) (Wang et al., 2017b); greater aMCC (labeled as ‘dACC’ by the authors) activity is associated with higher levels of persistence (**D**) (Kurniawan et al., 2010); aMCC signal is associated with willingness to exert more effort (**E**) (Bonnelle et al., 2016); aMCC activity increases during effort magnitude estimation (**F**) (Scholl et al., 2015); aMCC signal tracks the subjective value of effort exerted (**G**) (Chong et al., 2017); aMCC stimulation (yellow circle) increases the will to persevere (**H**) (Parvizi et al., 2013).

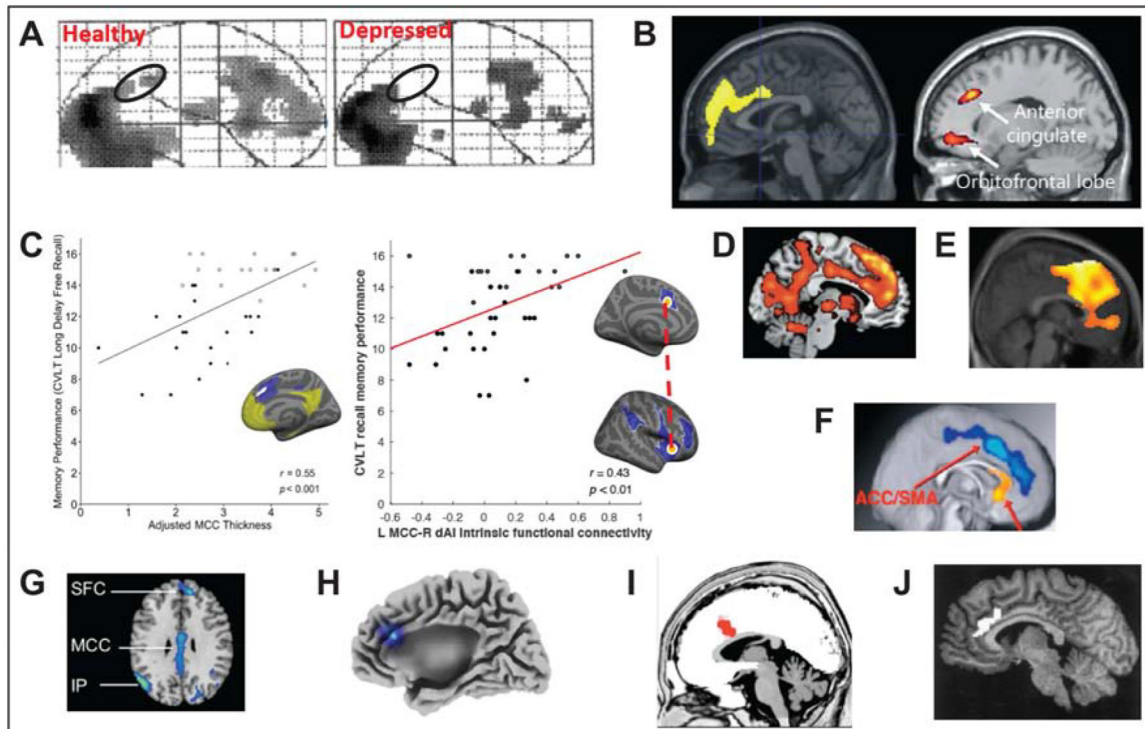


Figure 3.

Implications of the aMCC role in tenacity. Compared to healthy controls, patients with depression show reduced regional cerebral blood flow in the aMCC (black circle) during an effortful task (A)(Elliott et al., 1997); apathy scores correlate with altered glucose metabolism in aMCC in early dementia including Alzheimer's disease, frontotemporal dementia (left, (Schroeter et al., 2011) and Parkinson's disease (right, labeled as 'ACC' by the authors (Huang et al., 2013) (B); aMCC cortical thickness (left, aMCC indicated with white)(Sun et al., 2016) and intrinsic connectivity to anterior insula (right (Zhang et al., 2019)) both predict successful memory performance in superagers and typical older adults (C); aMCC signal increases during effortful memory retrieval in older adults (D)(Dhanjal and Wise, 2014); high exercise intensity is linked to metabolic changes in aMCC (E) (Kemppainen et al., 2005); gray matter volume in frontal regions including the aMCC was increased (blue) for aerobic exercisers relative to nonaerobic controls (F)(Colcombe et al., 2006); obese adolescents show aMCC weaker activation in response to foods compared to lean adolescents (G) (Carnell et al., 2017); transcranial pink noise stimulation of aMCC decreases self-reported desire to eat in women with obesity (H)(Leong et al., 2018); aMCC activity during task increases in individuals who follow the task instructions closely (I) (Mulert et al., 2005); aMCC regional blood flow is associated with faster reaction times in a somatosensory reaction time task (J)(Naito et al., 2000).

Table 1.

Examples of neuroscience evidence that aMCC participates in a wide range of tasks.

Observation	Task domain	Citations	Example Figure
aMCC is robustly engaged by pain and negative affect.	<i>Pain, Negative affect</i>	(Derbyshire et al., 2004; Vogt, 2005; Shackman et al., 2011; Yarkoni et al., 2011; Lindquist et al., 2012; Lieberman and Eisenberger, 2015)	See Fig.2 in Derbyshire et al., 2004
aMCC functions as a 'neural alarm', directing attention toward potential conflicts with enduring survival goals. For example, aMCC is implicated in the experience of hunger, thirst, and breathlessness.	<i>Pain, Negative affect</i>	(Lieberman and Eisenberger, 2015)	See Fig. 6 in Lieberman & Eisenberger, 2015
aMCC activation is associated with a variety of emotions, such as fear, disgust, anger and sadness.	<i>Pain, Negative affect</i>	(Lindquist et al., 2012; Touroutoglou et al., 2015; Raz et al., 2016)	See Fig. 4 in Lindquist et al., 2012
aMCC is anticipating and predicting pending noxious stimulation, so as to prepare avoidance responses. For example, aMCC activity increases as a function of the proximity of a tarantula to the participants' foot.	<i>Pain, Negative affect</i>	(Mobbs et al., 2010; Vogt, 2016)	See Fig. 2 in Mobbs et al., 2010
aMCC activity in difficult tasks is linked to negative affect during task. For example, aMCC response to error processing tracks within-subject changes in felt frustration.	<i>Pain, Negative affect</i>	(McGuire and Botvinick, 2010; Spunt et al., 2012)	See Fig. 2 in Spunt et al., 2012
The aMCC is engaged by positive experiences, particularly in reward-based decision-making tasks. The aMCC tracks both the magnitude and the probability of predicted rewards.	<i>Reward decision making</i>	(Kouneiher et al., 2009; Lindquist et al., 2012; Bahlmann et al., 2015)	See Fig. 3A in Kouneiher et al., 2009
aMCC integrates reward with motor responses. For example, a reduction in an anticipating reward significantly increases the firing rate of aMCC neurons in a way that is directly linked with the movement ultimately made.	<i>Reward decision making</i>	(Williams et al., 2004)	See Fig. 1 in Williams et al., 2004
The aMCC is sensitive to both increases and decreases in reward. Its signal during reward-decision making approximates an underlying U-shaped function, indicative of signal related to arousal or salience processing.	<i>Reward decision making</i>	(Bush et al., 2002; Rushworth and Behrens, 2008; Bartra et al., 2013)	See Fig. 10 in Bartra et al., 2013
aMCC is engaged by the degree of difficulty in demanding tasks. For example, greater aMCC activity is associated with increased working memory load, more challenging mental arithmetic, memory retrieval over longer delays and more precise visual discrimination.	<i>Effort Cognitive and Motor Control</i>	(Duncan and Owen, 2000; Davis et al., 2005; Cole and Schneider, 2007; Duncan, 2010; Boehler et al., 2011; Duncan, 2013; Engstrom et al., 2013; Fedorenko et al., 2013; Power and Petersen, 2013; Dhanjal and Wise, 2014; Hoffstaedter et al., 2014)	See Fig. 2 in Fedorenko et al. 2013
aMCC plays a role in predicting effort requirements. For example, its activity in learning tasks is modulated by previous trials in a way that speeds responses to trials of equivalent difficulty, and slows them when difficulty levels change.	<i>Effort, Cognitive and Motor Control</i>	(Modirrousta and Fellows, 2008; Sheth et al., 2012)	See Fig. 1 in Sheth et al. 2012
aMCC activates when requirements change, errors are detected, available options are in conflict, novel tasks are encountered or alternative course of actions are being considered.	<i>Effort, Cognitive and Motor Control</i>	(Raichle et al., 1994; Bush et al., 1998; Barch et al., 2001; Ullsperger and von Cramon, 2001; Botvinick et al., 2004; Jessup et al., 2010; Nee et al., 2011; Kolling et al., 2014).	See Fig. 9 in Nee et al., 2011
aMCC signal increases in response to prediction errors.	<i>Effort, Cognitive and Motor Control</i>	(Jocham et al., 2009; Sheth et al., 2012; Kolling et al., 2016)	See Fig. 5 in Jocham et al., 2009

Observation	Task domain	Citations	Example Figure
aMCC is engaged in social processing. For example, aMCC activations are observed during the Ultimatum Game, a social interaction task that particularly requires predicting and monitoring the effects of decisions on the behavior of others.	<i>Social Cognition tasks</i>	(Kirk et al., 2011; Apps et al., 2013)	See Fig. 2 in Kirk et al., 2011
The aMCC is a core node of the central autonomic network that calibrates bodily reactions to match anticipated outcomes. The magnitude of aMCC responses is linked to various stress-induced physiological changes, including blood pressure and heart rate variability, pupil dilation, and neuroendocrine stress responses.	<i>Autonomic reactivity tasks</i>	(Beissner et al., 2013) (Critchley et al., 2000; Critchley et al., 2003; Critchley, 2009; Wager et al., 2009; Hermans et al., 2011; Gianaros and Wager, 2015)	See Fig. 1 in Beissner et al. 2013
aMCC integrates pain, arousal, motivation and cognitive control.	<i>Integrative function</i>	(Shackman et al., 2011; Bahlmann et al., 2015).	See Fig. 2 in Shackman et al., 2011