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Anxiety and Fear from the Perspective of Cingulate Cortex

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Abstract

Anxiety and fear share similarities such as a feeling of unease and apprehension but the former is related to unpredictable threats with a distant time frame, while the latter is associated with short duration threats. This review considers these two entities from the perspective of cingulate cortex and shows that they activate different subregions; subgenual anterior cingulate cortex (sACC) for anxiety and anterior midcingulate cortex (aMCC) for fear. Functional studies in rodents, monkeys and humans show that each subregion has unique functions with sACC engaged in long-lasting arousal and vigilance that drive brainstem autonomic functions, while aMCC is involved in shorter duration cognitive functions that drive the cingulate premotor areas in the cingulate sulcus. While the two subregions are reciprocally connected, reciprocal inhibition has been shown in numerous human imaging studies that maintain functional segregation and suggest that inhibitory neurons intervene. A circuit model is presented to explain the role of cingulate cortex in anxiety and fear and may help interpret cortical reorganization in anxiety disorders.

Keywords: Cingulate cortex; Anxiety; Midcingulate cortex

Introduction

Anxiety and fear share some similarities such as a feeling of unease and apprehension. In the former there is not a clear and imminent danger, while in the latter there is. Davis et al. [1] emphasize their differences that raise interesting issues about the connections and functions of two different cingulate subregions. Fear is posited as an adaptive state to an imminent and real threat that begins and dissipates rapidly once the threat is removed. In contrast, anxiety is elicited by less predictable threats or by those that are more distant physically or psychologically with a future orientation. Importantly, it is associated with arousal and vigilance that is longer lasting. While this is an excellent conceptual framework for analyzing both psychological entities, their use of startle reflexes engages the amygdala and its projections to the bed nucleus of the stria terminalis and descending projections to other autonomic centers but does not engage cortical mechanisms.

The amygdala is one of the most frequently activated structures in studies of anxiety and fear, it is reciprocally connected with anterior cingulate cortex (ACC) and anterior midcingulate cortex (aMCC) and there is evidence of this interaction in human connection studies. One would predict from this connectivity alone that these cingulate subregions have overlapping anxiety and fear activity. However, this does not appear to be the case. Indeed, there are non-overlapping sites and connections that provide for conscious control and dissociation of both.

The goals of this review are threefold. First, identify those parts of cingulate cortex that are most active during anxiety and fear. Second, assess connections that subserve the above characteristics of each entity. Third, provide a working model by which these two systems can operate independently or in parallel via reciprocal inhibition.

Anxiety and Autonomic Function in Cingulate Cortex

While NeuroSynth has a number of shortcomings, it is a useful tool to summarize an ever growing body of literature. Figure 1 has three parts. The first is our flat map of the cytoarchitecture of cingulate cortex (explained in detail by [2]. The greatest density of anxiety activation sites is located in subgenual ACC area s24 and likely some of area 25. The connectivity map (C.) seeded in this subregion shows a rather striking projection throughout pregenual ACC areas 24 and 32 as well as orbitofrontal, dorsomedial and ventromedial prefrontal cortices. According to this imaging, these projections do not extend into the aMCC but this differs from findings in monkey (below, Figure 4E). Additionally, there is a robust interaction with vPCC and less with dPCC. We have argued that this connection provides for emotional coding of self-relevant objects and events [15].

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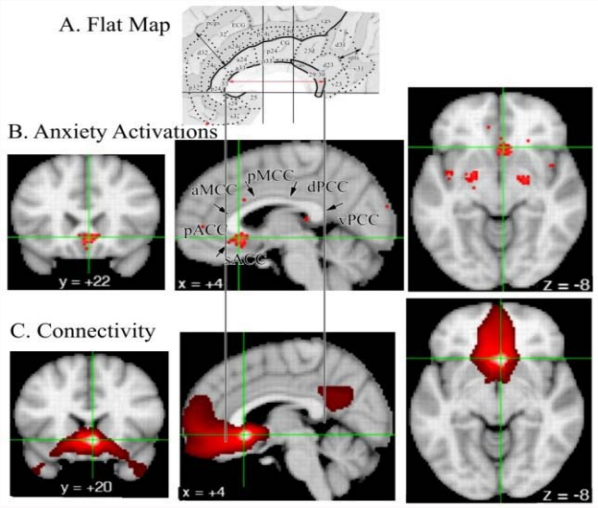

Figure 1: (A) Flat map to show sulcal cortex and dots are borders between areas. The uniform grey is cortex in the cingulate sulcus (cgs) and callosal sulcus (cas) and the two double-black arrows show the orientation of flattening. The red double arrow is the distance between the most rostral part of the genu and caudal part of the splenium of the corpus callosum. It is to these points that medial surfaces below (B & C) are normalized at the vertical black lines. Subregions are delimited with arrowheads in B.

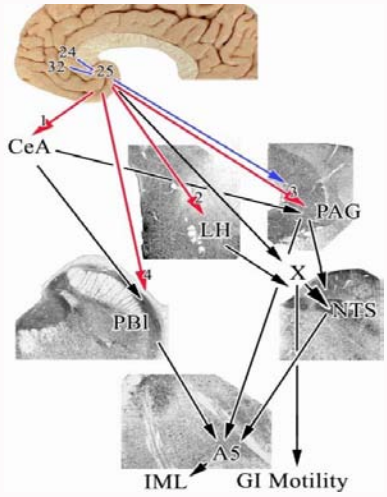

Figure 2: The efferent control of cardiovascular, GI motility, and other visceral functions are mediated primarily by reciprocally connected CeA and area 25. The four main area 25 subcortical projections are emphasized with large, red and numbered arrows. Areas 24 and 32 project to the PAG (blue arrow), while a projection in primates is shown to the dorsal motor nucleus of X (small black arrows). A few of the prominent projections of each of these four structures are shown to emphasize their direct role in visceromotor control (large, black arrows).

Critical to anxiety is its association with events that evoke arousal and vigilance that are longer lasting and less predicable than that for fear. This suggests that sACC has autonomic projections that are not shared by aMCC. Electrical stimulation studies generally support the conclusion that sACC is involved in depressor responses including heart rate reduction, while pressor responses are more frequent during stimulation of area p32 and occasionally from aMCC; however, this latter structure is not a consistent player and is not considered further as these changes may be due to white matter stimulation. Gastric motility has also been observed during electrical stimulation of area 25 [3,4] and ACC lesions block gastric ulcers caused by restraint stress in rats [5]. The descending projections of ACC to autonomic regulatory structures mediate these responses include the central nucleus of the amygdala (CeA), lateral hypothalamus (LH), periaqueductal grey (PAG), and lateral parabrachial nucleus (PBL), while much smaller projections to the nucleus of the tractus solitaries (NTS) and dorsal motor nucleus of the vagus (X) occur in monkey [6] than in rat [9] and rabbit [7]. Figure 2 summarizes the essential autonomic projections of sACC [8]. Area 25 is the main part of ACC to mediate depressor cardiovascular responses through the LH and PAG, while the role of area 32 in pressor responses is less well understood. The projections to the PAG, PBl and NTS are essential intermediates in these responses. Since autonomic activity may be modulated by area 25 projections to X and NTS are weak in the monkey [6], the projection is shown with small, black arrows. Finally, Figure 2 shows a few of the essential efferent projections of PAG, PBl and NTS that subserve a direct role in autonomic regulation to emphasize the position of ACC in these circuits.

Rodent research played an important role in uncovering the mechanisms of autonomic regulation and these culminated in a model of cingulate-mediated visceromotor control by EJ Neafsey et al. [4]. They conceived of the insula as a main site of viscerosensory function, while ACC would receive its sensory afferents from the insula that then drive subcortical visceral responses. While we now know that ACC receives its own visceral afferents, the electrical stimulation literature shows that's ACC/area 25 reduces heart rate and area 32 and possibly a24', increase heart rate. Burns and Wyss [9] showed the largest hypotensive responses were evoked from area 25 in anesthetized rats. Subsequently, Fisk and Wyss [10] injected lidocaine into either the lateral hypothalamus (LH) or PAG during electrical stimulation of area 25 and reported greatest reductions during block of PAG activity, although that in the LH was also significant. The projections of area 25 to the LH and PAG are well known (Figure 2) for monkey [6,11] cat [12], and rat [10].

Fernandes et al. [13] demonstrated that a pressor response evoked from area 32 was modulated by norepinephrine when injected into this region in unanesthetized rats. The differential role of areas 32 and 25 in blood pressure may be important because both project massively to the PAG and could help to select the appropriate autonomic and skeletomotor reflexes during emotional motor activity. Indeed, norepinephrine in the PAG selects between behavioral states and enhances fight-or-flight responses [14]. Thus, the circuitry, functional activation/inactivation, and electrical stimulation support the role of ACC in a wide range of autonomic functions including cardiovascular changes.

Fear, Movement and Cognition in Cingulate Cortex

Most studies that engage a fear component show activity in the ventral aMCC on the surface of the cingulate gyrus; i.e., peak activity sites are not present in the sulcus (Figure 3A; red asterisks). This subregion does not have direct autonomic projections like sACC but rather spinal and other sensorimotor connectivity likely via posterior parietal cortex. Fear in the context of aMCC appears to provide a premotor signal used by the cingulate premotor areas in the cingulate sulcus to assess threats and organize relevant behaviors. This perspective is a critical part of the summary circuitry below.

The amygdala has a well established role in fear and reciprocal connections between the amygdala and cingulate cortex should help

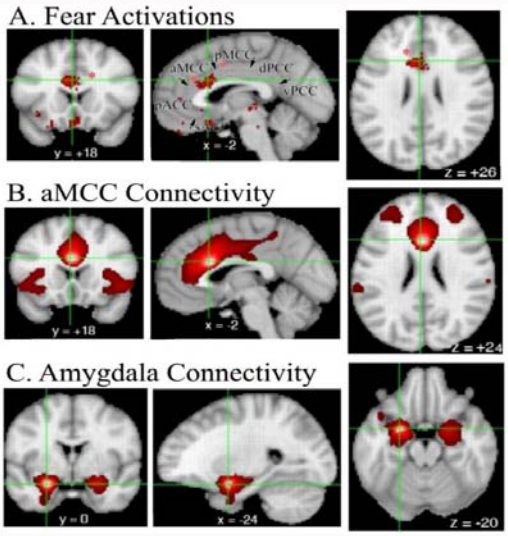

Figure 3: (A) Fear activity in aMCC; (B) Related connectivity. While the latter appears to comport with experimental monkey studies, that for the amygdala does not when compared to Figure 4A.

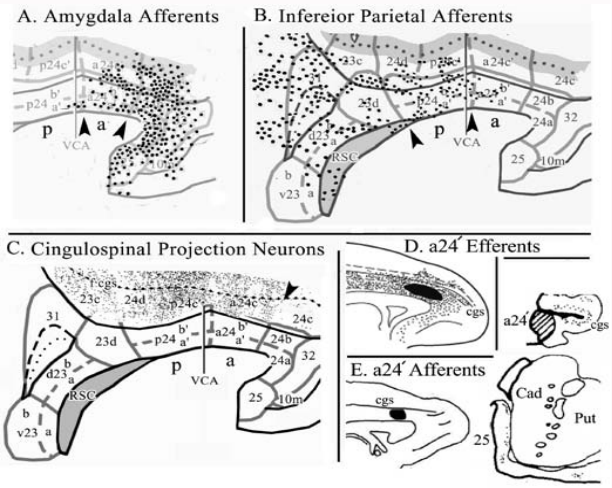

Figure 4: Projections to and within cingulate cortex (a=aMCC; p=pMCC). (A) Afferents from the amygdala; (B) Inferior parietal cortex [62]; (C) Cingulospinal projections delineate MCC [20]); (D) Area a24' projections to sACC (anterograde tracing; [63]); (E) Retrograde tracing showing area 25 inputs to area a24' [64]; note that cingulate sulcal projections are prominent to the gyral cortex. These latter two studies show reciprocal connections between aMCC and sACC.

identify emotion-specific processing areas. Amygdala connections are not evenly distributed throughout the monkey cingulate gyrus (Figure 4A). The latter figure has a co-registration of anterograde projections of the basolateral and accessory basal nuclei following tritiated amino acid injections to the cingulate cortex. The greatest amount of labeling is in pregenual areas 25, 24 and 32, there is a limited extension of labeled proteins into area a24' and almost none posterior to this area. It is important to note in these studies that human connectivity reports have not yet achieved a reliable level of resolution. Figure 3C., for example, fails to show amygdala projections to cingulate cortex that were demonstrated in the monkey.

Reciprocal connections between cingulate and parietal cortices are well known (see a thorough analysis in [15]). The distribution of inferior parietal projections is co-registered to the flat map in

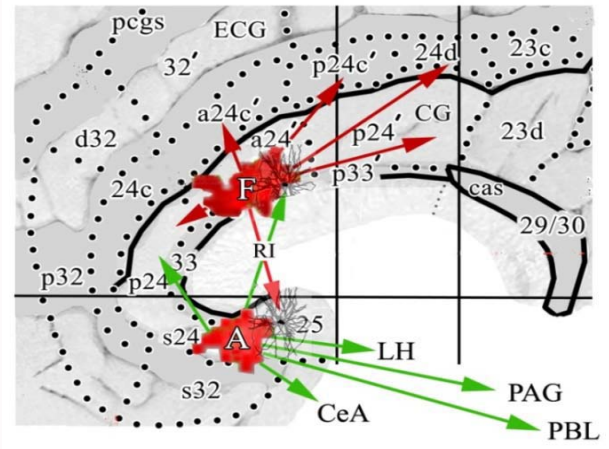

Figure 5: Summary diagram of anxiety (A) and fear (F) activations and their projections with green and red arrows, respectively. Substantial projections of "fear" cortex on the vaMCC are into the sulcal cortex where the cingulate premotor areas reside. In contrast, "anxiety" cortex has robust autonomic projections to the amygdala and brainstem. While it appears that aMCC and sACC are reciprocally connected (Figure 4D & 4E.), the reciprocal inhibition reported by numerous imaging studies suggest this bidirectional connection is inhibitory. Thus, the connections between these subregions are shown to terminate on inhibitory interneurons and are marked "RI" for Reciprocal Inhibition.

Figure 4B and they were pivotal to differentiating between pregenual ACC and MCC [62]. Although the major projection is to PCC and RSC, it extends with equal density into pMCC and minimally into aMCC. Parietal cortex plays a crucial role in modulating MCC during multisensory action monitoring including responses to noxious stimuli as such stimuli are effective in alerting to a mismatch between expected and actual motor outcomes.

The value of the cingulospinal projection system cannot be over emphasized as its presence supports the midcingulate concept and provides for motor outflow from limbic structures. The first demonstration of these large pyramidal neurons by Heiko Braak [17] suggested the presence of a motor field in the human cingulate sulcus and this discovery had a profound impact on how the functions of cingulate cortex were viewed; i.e., as a premotor region that may not always be engaged in emotion. The original topography and cytoarchitecture of the cingulate motor areas was described by Luppino et al. [18] and Matelli et al. [19]. The observations of Dum and Strick [20] are provided for co-registration to the flat map in Figure 4C because these investigators injected horseradish peroxidase into as many corticospinal projection axons as possible and the results provide an overview of the entire system. According to this co-registration, the most extensive cingulate labeling was in area p24c'. Robust labeling was also in area a24c' and almost none was in area 24c. Thus, the border between areas a24c' and 24c is the border between skeletomotor and autonomic regulation.

Electrical stimulation of MCC evokes complex and context-dependent gestures such as touching, kneading, rubbing or pressing the fingers or hands together or to the upper part of the chest or neck, and lip puckering or sucking, tongue movements, or moving the hand toward the face [21-23]. These movements are often adapted to the environment; i.e., they can be modified by sensory stimuli, and at times, resisted. Autonomic activity was also observed but this is likely due to stimulation of the white matter and projections of aMCC top ACC. These responses included mydriasis, and increased heart and

respiratory rate as well as mood changes mostly toward euphoria.

From a cognitive perspective, the concept of "attention-for-action" proposed by Allport [24] and Posner et al. [25] provided the first premotor orientation for MCC function. This designation is useful because it does not preclude its role in mismatch detection/conflict resolution [26,27], selecting among cognitive options that do not require movement [28], selecting action verbs to noun lists that may or may not generate movement [29], anticipation of cognitive processing [30], or working memory [31]. Selection-for-action means selection, not only for overt responding, but for internal cognitive activity related to decision making, memory or information transformation. Norman and Shallice [32] referred to this form of attention as "supervisory" and suggested it was used whenever non-routine processing was required. The selection-for-action influence was evident during modality specific motor choice [33], motor control/monitoring and/or willed action [36,37], Stroop tasks [36,37] and tasks involving the over-riding or inhibition of pre-potent responses such as Go-NoGo tasks [38]. Response selection does not refer to a single cognitive activity because MCC has many areas and individual layers in each area might contribute to more than one function. Midcingulotomy lesions can disrupt reward-guided response selection [39]. Finally, the role of MCC in punishment and avoidance is stressed by a substantial literature on acute nociceptive stimulation [40]. Thus, the selection-for-action view fits with much of the data on daMCC involvement in selective/divided attention and conflict monitoring.

Areas in the cingulate sulcus contain neurons with premotor discharge properties [41] that are coded according to the changing reward properties of particular behaviors [42]. Not only did different populations of neurons respond to target detection, motor responses and constant rewards, but many signaled unexpected, reduced rewards. Neurons in monkey area a24c′ integrate information from working memory of task instructions with reward and error information to make decisions for simple and complex motor tasks [43-45]. Niki and Watanabe [46] identified cells that responded to cue location and response direction and whose activity during a delay period predicted whether the monkey would make a correct or incorrect choice. Shidara and Richmond [47] reported that rostral cingulate premotor area cells responded differently based on reward expectations during a sequential motor task. Thus, area a24c′ synthesizes information from multiple sources and indicates that a particular decision has been made.

Finally, functional imaging studies show altered blood flow in this region during sequences of complex finger apposition movements [48]. Hoffstaedter et al. [49] employed an imaging paradigm in which movement selection was based on free choice, timed choice or no choice. The daMCC was the only region that had increasing activity with more intentional components during movement initiation. A single-trial fMRI study reported that the daMCC was active during both error and correct trials [26]. Thus, daMCC is pivotal to response initiation in the context of free choice and this function is modulated by error processing signals. These findings take us to the role of aMCC in pain, fear and anxiety.

Pain Affect, Fear and Anxiety in vaMCC

Voluntary, action-related processing induced by a motor task during painful or non-painful stimulation drives aMCC [50] emphasizing the linkage between pain processing and movement; other limbic areas including the anterior insula do not show this association. Fear in this context refers to a premotor signal and all activations in acute pain studies are not associated with affect as demonstrated by sensorimotor activations in the lateral pain system [51,52]. Moreover, aMCC nociception is positively correlated with the expectation of pain relief [53] as is also the case for itch relief [54]. Finally, Singer et al. [55] reported aMCC activation when subjects observed nociceptive stimulation of a loved one; pain empathy. Such a response engages an individual to respond, as they would in a similar situation for themselves, to assist another in achieving pain relief.

The loss of pain control evokes anxiety and is associated with suffering. This was shown by sites of atrophy in the vaMCC that are correlated with catastrophizing in patients with migraine headache [56]. This site does not involve the daMCC suggesting a unique role of the vaMCC in pain fear, anxiety and coping. Thus, the vaMCC is in a unique position to cognitively interpret (pain empathy), anticipate and trigger avoidance responses to pending noxious stimulation, while the pMCC is engaged in general orienting to sensory stimuli including noxious ones. The question arises as to the role of implicit fear in motor control.

Fear activations appear to be pivotal to selection between rewarded and punished responses made in aMCC. Since aMCC has rich dopaminergic innervation, is involved in reward functions and is activated during noxious stimulation, there is an overlap of both pain and reward systems in this subregion. Koyama et al. [57] studied monkey aMCC and demonstrated that, of neurons activated during a response period, 58% were associated with nociceptive cutaneous electrical stimulation and 42% for obtaining a juice reward. Thus, the overlap of aversive and rewarding functions in aMCC requires a mechanism(s) for distinguishing and predicting pain or reward outcomes to select the appropriate response. One such mechanism is fear evoked by nociceptive afferents from the midline, mediodorsal and intralaminar thalamic nuclei that provides an implicit premotor signal to enhance nocifensive behaviors.

In conclusion, MCC provides a cognitive interface with skeletomotor systems via projections to the spinal cord, striatum, and supplementary/pre-supplementary motor cortices. The MCC is critical to decisions selecting between pain or reward outcomes. The response selection process may require movement and/or corollary discharges associated with it, mismatch and/or outcome assessment, assessment of internal requirements and reward consequences, and defining optimal output and reprogramming other motor areas for routine behaviors. The daMCC may play a pivotal role in reorganizing activity in many motor structures to produce new behavioral outputs that adapt to changing rewards and punishments, while activity in the vaMCC during fear has a role in modulating the cingulate premotor areas in terms of threat avoidance.

Reciprocal Inhibition

As the pACC and aMCC are involved in different functions yet are reciprocally connected, it appears that a reciprocal inhibition mechanism maintains the unique functions of each subregion. This expectation is supported by observations that cognitive tasks deactivate pACC and emotionally-valenced tasks deactivate aMCC [58-60]]. The sensorimotor paradigm used by Papoiu et al. [54] also provides evidence of reciprocal inhibition, since active scratching activated pMCC and inactivated pACC.

Bush et al. [36] and Whelan et al. [61] performed two Stroop

interference tasks that involved different sources of interference, one cognitive and one affective, in the same subjects during the same scanning session. Stroop testing requires the subject to overcome reflexive responses to execute a button press. In the counting Stroop word stimuli are presented in sets of 1-4 identical words per trial and subjects select one of four buttons relating to the number of words on the screen [65,66]. This produces a reliable interference effect when presented with number-words that are incongruent with the correct response. For the emotional Stroop, emotionally valenced word stimuli are presented with alternating blocks of neutral and negatively valenced words. For example, during the negative condition, a subject might see the word "murder" written four times on the screen and would push the fourth button. Delays in reaction time in the negative compared to the neutral condition are interpreted as emotional interference. Using these two tasks, a double-dissociation revealed that the counting Stroop activated daMCC but not pACC whereas the emotional counting Stroop activated ACC but not MCC. Thus, reciprocal inhibition assures that the functions of these subregions are segregated for different aspects of information processing associated with emotion/autonomic and cognitive/skeletomotor control.

Conclusions

The primary conclusion of this review is that anxiety and fear are part of separate systems in cingulate cortex. Moreover, their projections differ substantially and, although they are connected, there is a reciprocal inhibitory system that maintains the integrity of differential functions: anxiety/autonomic and fear/cognitive. Figure 5 summarizes the differential circuitries of anxiety and fear subregions in sACC and aMCC, respectively. These connections fit well with established autonomic and cognitive functions of each subregion. The preferential termination of these inputs on inhibitory neurons has not yet been demonstrated but the functional imaging literature appears to require such an organization.

It is also possible that the inhibitory system is hyper-activated in pathological states such as anxiety disorders and this predicts that fear as a premotor feature of cognitive control may be lost. The converse may also be true in stress disorders where uncontrolled fear may hyper-inhibit anxiety via an intracingulate connection.

Finally, there is still concern about human connection findings as noted for the amygdala in human (Figure 3C) when compared to that in monkey (Figure 4A). Additionally, human area s24 projections do not terminate in area a24′ (Figure 1C), while they do in monkey (Figure 4E). Thus, the full distribution of human connections has not been demonstrated likely due to the fact that they cannot follow axons to their termination sites. Such findings should be viewed with caution at this time.

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