The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain

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Little is known about the function of the retrosplenial cortex and until recently, there was no evidence that it had any involvement in emotional processes. Surprisingly, recent functional neuroimaging studies show that the retrosplenial cortex is consistently activated by emotionally salient words. A review of the functional neuroimaging literature reveals a previously overlooked pattern of observations: the retrosplenial cortex is the cortical region most consistently activated by emotionally salient stimuli. Evidence that this region is also involved in episodic memory suggests that it might have a role in the interaction between emotion and episodic memory. Recognition that the retrosplenial cortex has a prominent role in the processing of emotionally salient stimuli invites further studies to define its specific functions and its interactions with other emotion-related brain regions.

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WHILE SOME NEUROSCIENTISTS might know the approximate location of the retrosplenial cortex in the brain, few would have any inkling of what function it performs. In fact, the retrosplenial cortex is a relatively unstudied region in the most caudal portion of the posterior cingulate cortex. Recent studies have suggested that the retrosplenial and posterior cingulate cortices might be involved in memory and visuospatial processing[1–3]. However, until recently, there was almost no evidence to show that it had any involvement in emotion processing. The lack of such a role seemed perfectly consistent with the neuroanatomical observation that the retrosplenial cortex had no direct connection with the amygdala[4], a structure that clearly has a major role in emotional perceptions and responses[5].

Recent functional MRI (fMRI) studies of human subjects, however, have forced a re-evaluation of the role of the retrosplenial cortex[6–8]. It appears that this region could have an important and previously unrecognized role in human emotion responses. These fMRI studies were designed to reveal activation in limbic and cortical regions that occurred while subjects judged the pleasantness of emotionally salient spoken words. Surprisingly, it was found that the retrosplenial cortex was the region most consistently and most robustly activated by such stimuli. In a study of threat-related spoken words (for example, terror, dangerous, emergency) compared with matched emotionally neutral spoken words (for example, margin, pertinent, translation), eight out of ten normal volunteers showed highly significant activation of retrosplenial cortex. None of the 62 other cortical regions examined was activated in more than one in ten volunteers[6]. Subsequent studies demonstrated similar retrosplenial-cortex activation occurring in response to both intensely unpleasant and intensely pleasant words, and in both normal volunteers and in patients with panic disorder[7,8]. These findings prompted a review of the functional neuroimaging literature in order to determine whether these retrosplenial cortex observations were anomalous. The results of this review, coupled with the consistent experimental results, argue that the retrosplenial cortex has a prominent but previously unrecognized role in the response of human subjects to emotionally salient information. However, the specific emotion-related function that is mediated by this region is not yet clear.

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Where is the retrosplenial cortex?

The cingulate cortex arches around the genu, body and splenium of the corpus callosum. The posterior cingulate cortex (Fig. 1) is the part that is posterior to the transition from Brodmann's area 24 to area 23 (Talairach y coordinate ~ −12), and includes the isocortex of areas 23 and 31. The posterior cingulate cortex also includes the retrosplenial cortex, which comprises area 29, which lies within the callosal sulcus, and area 30, which extends from the callosal sulcus onto the convexity of the cingulate gyrus[9,10]. The demarcation between area 30 of the retrosplenial cortex and the adjacent area 23 of the posterior cingulate isocortex on the convexity of the cingulate gyrus has not been delineated clearly in the human brain. The studies by Braak[9] provide the most-detailed description of the extent and subregions of the human retrosplenial cortex. He has shown that the retrosplenial cortex lies within the callosal sulcus from its most caudal extent and extends anteriorly within this sulcus to the border between areas 23 and 24. In addition, it includes much of the convexity of the posterior cingulate gyrus posterior to the splenium and inferior to the medial parietal (precuneate) cortex.

What is the evidence for a specific function of the retrosplenial cortex?

Although a variety of affective, cognitive, nociceptive and motor functions have been associated with specific subregions of the anterior cingulate cortex, the functions

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associated with the posterior cingulate cortex have been less well studied[2,11,12]. The pattern of cortical afferent connections to different regions of the cingulate cortex varies primarily with respect to the rostrocaudal axis. Retrosplenial cortex, the most caudal region of the cingulate cortex, is largely devoid of primary motor and sensory inputs, and receives major inputs from the orbital and dorsolateral prefrontal cortex, the anterior cingulate cortex, parahippocampal cortex, superior temporal sulcus, precuneus, claustrum, and the anterior and lateral thalamic nuclei[13–15]. Recent studies suggest that the posterior and retrosplenial subregions of the posterior cingulate cortex might be involved in memory[1–3,16,17], while the rostral and middle subregions of the posterior cingulate could subserve proprioceptive and visuospatial functions[2,14]. Evidence for these functional properties led Vogt *et al.*[2] to characterize the functions of the posterior cingulate cortex as 'evaluative' in contrast to the 'executive' functions of the anterior cingulate cortex. The evidence that the retrosplenial cortex could be involved in memory, visual–spatial processes and proprioception will be briefly reviewed.

The retrosplenial cortex and memory

Converging evidence from neuroanatomical studies, clinical lesion studies and functional neuroimaging studies suggests that the retrosplenial cortex has a memory-related function, although its specific function has not been defined. The retrosplenial cortex provides the largest projection to areas TH and TF of the parahippocampal cortex in the monkey and is second only to parahippocampal and perirhinal cortices as a source of input to entorhinal cortex[16]. The posterior cingulate and retrosplenial cortices are also linked by reciprocal pathways to prefrontal and anterior cingulate cortices and the anterior and lateral thalamic nuclei, and might serve to connect the dorsolateral prefrontal cortex with the hippocampal formation[13–15]. These connections are consistent with lesion and imaging evidence that the retrosplenial cortex is involved in memory. Several cases of amnesia associated with lesions of the retrosplenial cortex have been reported. Specifically, loss of verbal episodic memory has been associated with left retrosplenial damage[1,18,19] and loss of memory for spatial relationships has been associated with right retrosplenial damage[20]. This 'retrosplenial amnesia' could reflect the interruption of connections between the prefrontal and mesial temporal memory regions as they traverse the retrosplenial region, or it might indicate that the retrosplenial region itself has intrinsic memory-related functions.

Recent PET studies suggest that the retrosplenial cortex indeed has intrinsic, episodic-memory-related functions. Grasby *et al.*[3] compared a working (immediate) memory task to an episodic (long-term) verbal memory task and found that activation of the retrosplenial cortex was associated with the episodic memory task. Similar retrosplenial activation has been demonstrated during retrieval of autobiographical episodic memories[21,22]. Retrosplenial-cortex activation has also been observed in association with the retrieval of verbal, spatial and visual episodic memories[23–25]. In a PET study of episodic-memory acquisition, Shallice *et al.*[17] concluded that the retrosplenial and prefrontal cortices were the primary regions activated during acquisition of verbal episodic memory. However, other studies of episodic memory have failed to observe retrosplenial activation and a few have observed a relative decrease in the activation of this region during episodic-memory retrieval[12,26,27]. Overall, the evidence from anatomical, clinical and neuroimaging studies suggests the retrosplenial cortex has functions that are related to episodic memory, although its specific role in acquisition, retrieval and other memory processes awaits further elucidation.

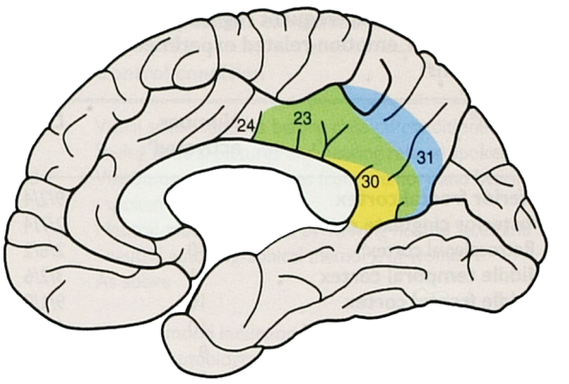

Fig. 1. *Locations of posterior cingulate and retrosplenial cortices. The yellow, green and blue areas indicate approximate locations of Brodmann's areas 30, 23 and 31 on the medial surface of the cerebral cortex. These three shaded regions represent the posterior cingulate cortex. The retrosplenial cortex is classically defined as area 30 and area 29 (within the callosal sulcus adjacent to area 30 and not visible in this orientation).*

Visuospatial and proprioceptive functions

The posterior cingulate cortex in the monkey is connected to cortical areas that are responsive to visual stimuli, eye movements, spatial orientation and body movements[2]. Olson *et al.*[28] showed that some monkey posterior-cingulate neurons have responses that are correlated with eye-gaze angle, and the size and direction of eye movements. These neurons were located predominantly anterior to the splenium, although some retrosplenial neurons demonstrated similar responses. In contrast, functional-neuroimaging studies have generally not found evidence of activation in the posterior cingulate cortex that is associated with eye movements or visuospatial processing in human subjects[12], and a relative decrease in activation in this region is often observed during active visual tasks[29]. Physiological studies in the monkey, as well as stimulation and imaging studies in humans, have observed a relationship between proprioceptive function and posterior-cingulate activity, but not retrosplenial-cortex activity[30–32]. However, Vitte *et al.*[33] reported retrosplenial-cortex activation in response to vestibular stimulation in humans. These studies suggest that the anterior and middle subregions of the posterior cingulate cortex could have functions that are related to visuospatial processing and proprioception, but there is little evidence that the retrosplenial cortex has such functions in humans.

A review of functional-neuroimaging studies of emotional processes

In reviewing functional-neuroimaging studies of emotion, it is useful to discuss what is meant by the term 'emotion'. Although emotion is sometimes defined narrowly as the conscious experience of one of several specific feeling states, such as happiness or fear, the neuroimaging studies of emotion reviewed in this article have generally relied on a broader conceptualization of the term. An important idea within this

TABLE 1. The most-frequent regional activations reported in 51 emotion-related experiments from 25 publications[a]

Region[b]	Number activated[c]	L/R/B[d]
Inferior frontal cortex	15	9/2/4
Posterior cingulate cortex	13	2/7/4
Retrosplenial cortex[e]	10	2/6/2
Middle temporal cortex	11	3/2/6
Middle frontal cortex	10	9/1/0
Anterior cingulate cortex	10	6/2/2
Mesial temporal region	9	5/2/2
Amygdala	5	2/1/2
Caudate	9	2/3/4
Putamen	9	2/5/2
Orbital frontal cortex	8	4/2/1
Medial frontal cortex	8	4/0/4
Cortical area 17	8	4/1/3
Cortical area 19	8	1/4/3

[a]All 25 studies measured regional brain perfusion, using either PET (22 studies) or fMRI (three studies). Forty nine of the experimental comparisons involved either the evaluation of emotionally salient stimuli without mood induction (25 experiments) or combined the evaluation of emotionally salient stimuli with mood induction (24 experiments). Two experiments investigated induced moods in the absence of emotionally salient stimuli.
[b]Regions in which activation peaks were located.
[c]The number of experiments reporting significant activation in each region.
[d]Number of left, right or bilateral activations.
[e]Retrosplenial cortex refers to areas 29 and 30, and the adjacent posterior cingulate cortex posterior to the splenium of the corpus callosum.

broader conceptualization of emotion is that emotional phenomena include both evaluative and response-related processes, and that these two types of processes could have distinct neural substrates[5,34,35]. Emotional evaluation processes include the automatic perception of the emotional salience of a stimulus and the subsequent appraisal of its specific motivational significance. For example, a study of perception of emotional expressions in facial stimuli is assessing an emotional evaluation process. Emotional response processes include response dispositions (that is, preparing to respond) and overt responses to the emotional or motivational significance of a stimulus or event. For example, an experiment that induces a specific mood state in a subject (typically by means of emotionally salient images or memories) is studying an emotional response process. Most experimental paradigms used in recent functional-neuroimaging studies of emotion have involved either evaluative processes alone, or a combination of evaluative and response processes.

Studies included in this article

This article reviews only peer-reviewed English-language studies that used functional neuroimaging methods to investigate mental processes explicitly conceptualized as 'emotional' and that employed repeated-measures designs, thus allowing a comparison of emotional and non-emotional conditions in the same subjects. Studies were excluded from this literature review if they involved patient populations or drug-induced emotional states, or if the analysis did not include most cortical regions. A search of MEDLINE Plus, PsycINFO, Current Contents and BrainMap databases yielded 25 publications that reported the results of 51 experimental comparisons between 1994 and 1997, which met these criteria.

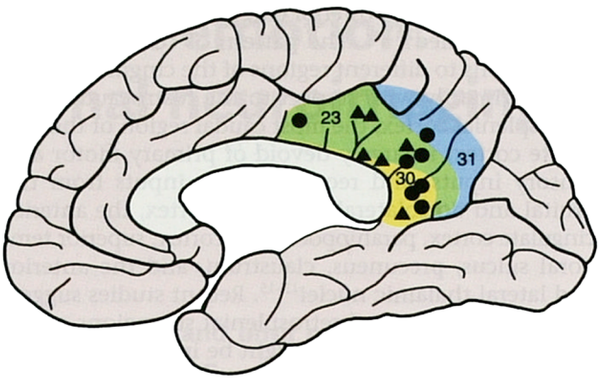

Fig. 2. *Locations of posterior cingulate cortex and retrosplenial cortex activations from functional imaging studies of emotion. Activations from all experiments reviewed in this article are indicated by ▲ or ●. Activations from the controlled experiments summarized in Tables 2 and 3 are indicated by ●. Locations of activations are superimposed on a drawing of the medial surface of the cerebral cortex. Yellow, green and blue areas indicate approximate locations of Brodmann's areas 30, 23 and 31.*

The specific emotional stimuli or responses associated with each experiment could be grouped into one of five categories: fear–threat, disgust, sadness, happiness, or of mixed content. In general, three types of design were used in these experiments: (1) comparison of emotional and non-emotional conditions matched for perceptual and task-related characteristics (for example, gender identification of fearful faces compared with matched neutral faces); (2) comparison of two different but matched emotional conditions with contrasting emotional content (for example, gender identification of happy faces compared to matched sad faces); and (3) comparison of an emotional condition to an unmatched 'baseline' condition (for example, recall of a sad autobiographical memory compared to resting with eyes closed). Statistical contrast of the experimental condition to the comparison condition was used to create an image of the brain activation associated with the experimental condition.

These studies employed a variety of statistical methods to describe the activation of brain regions. Wherever possible, only the regions that exhibited emotion-related increases in activity associated with a P value of ≤ 0.001 were considered to be activated, as this statistical threshold is most commonly used in functional neuroimaging studies. The application of this threshold was possible in 15 of the 22 PET studies. For the remaining PET studies and the 3 fMRI studies, all regions considered to be activated by the authors were counted as activated, which in most cases involved statistically more-conservative definitions of activation.

Do functional-imaging studies of emotion find activation in the retrosplenial cortex?

Table 1 shows the brain regions that are most commonly activated in these experiments. The posterior cingulate cortex was frequently activated by emotional conditions and was second only to the inferior frontal cortex in frequency of activation. Within the posterior cingulate cortex, activation was typically observed posterior to the splenium, in the retrosplenial cortex and in the adjacent caudal region of the posterior cingulate cortex (Fig. 2). As the boundary between the retrosplenial cortex and the adjacent cingulate cortex posterior to

TABLE 2. Eleven studies reporting 20 experiments that compared emotionally salient conditions to matched neutral conditions

Study	Emotionally salient condition	Control condition	Ref.
1	Visual snake stimulus after classical conditioning to shock	Visual snake stimulus before classical conditioning to shock	36
2a	Seeing disgusting pictures and hearing related spoken words	Seeing neutral pictures and hearing related spoken words	37
2b	Visualizing disgusting pictures from memory and hearing related spoken words	Visualizing neutral pictures from memory and hearing related spoken words	
3a	Sad-mood induction by viewing sad faces and recalling sad autobiographical memory, in women	Neutral-mood induction by viewing neutral faces and recalling neutral autobiographical memory, in women	38
3b	Happy-mood induction by viewing happy faces and recalling happy autobiographical memory, in women	As above	
3c	Sad-mood induction by viewing sad faces and recalling sad autobiographical memory, in men	Neutral-mood induction by viewing neutral faces and recalling neutral autobiographical memory, in men	
3d	Happy-mood induction by viewing happy faces and recalling happy autobiographical memory, in men	As above	
4	Viewing a video of a previously experienced bank robbery	Viewing a video of people engaged in leisure activity	39
5	Sad-mood induction by recalling sad autobiographical memory	Neutral-mood induction by recalling neutral autobiographical memory	40
6a	Seeing combat pictures and hearing related spoken words	Seeing neutral pictures and hearing related spoken words	41
6b	Visualizing combat pictures from memory and hearing related spoken words	Visualizing neutral pictures from memory and hearing related spoken words	
7a	Sad-mood induction by recall of sad autobiographical memory	Neutral-mood induction by recall of neutral autobiographical memory	42
7b	Happy-mood induction by recall of happy autobiographical memory	As above	
7c	Disgust-mood induction by recall of disgusting autobiographical memory	As above	
8a	Viewing fearful pictures	Viewing neutral pictures	43
8b	Viewing happy pictures	As above	
9a	Making gender discrimination of fearful faces	Making gender discrimination of neutral faces	44
9b	Making gender discrimination of disgusted faces	As above	
10	Evaluating threat-related spoken words	Evaluating neutral spoken words	6
11	Viewing words with mixed emotional meanings	Viewing neutral words	45

the splenium is not well defined, this whole area will be referred to as retrosplenial cortex for the purposes of this article. This analysis of 51 functional-neuroimaging experiments suggests that the retrosplenial cortex could have an important role that is related to emotional processing.

Is retrosplenial-cortex activation associated specifically with emotionally salient stimuli?

Many of the studies summarized in Table 1 did not involve comparisons with well-matched emotionally neutral conditions. Thus, it is possible that other, non-emotional, characteristics of the experimental conditions were responsible for the observed activation of the retrosplenial cortex. Among the 51 experiments, 20 experiments from 11 published studies[6,36–45] compared specifically a task that involved an emotional condition to the same task involving a matched, non-emotional condition. Because they differ only in emotional salience, comparing these experimental conditions involves fewer potentially confounding effects. The stimuli and tasks used in these 20 experiments are described in Table 2. Examination of these experiments would be expected to identify brain regions activated specifically by the emotional salience of the experimental conditions.

The region that most frequently shows increased activity in these 20 experiments was the posterior cingulate cortex (Table 3). This activation was observed in the retrosplenial region in all but one case. Figure 2 illustrates the clustering of activation peaks in the retrosplenial cortex, which is especially pronounced among the well-controlled studies described in Table 2. The region of activation includes Brodmann's area 29 within the cingulate sulcus, the proisocortex of area 30, and the parasplenial and adjacent isocortex of areas 23 and 31 posterior to the splenium. This analysis strongly supports the hypothesis that the retrosplenial cortex has a prominent role in the processing of emotionally salient stimuli.

Is the retrosplenial cortex frequently activated in non-emotional conditions?

A possible alternative explanation for these results is that the retrosplenial cortex could become activated in response to a variety of experimental conditions in addition to emotion-related conditions. However, recent reviews have shown that retrosplenial cortex is not activated by a variety of experimental conditions and is more typically reported to show 'negative activation' (less activation during the experimental condition than the control condition). When reviewing PET studies of cognition, Cabeza and Nyberg[12] summarized 101 experiments that involved attention, visual and spatial perception, language, and various types of memory. They found only eight reports of activation in the posterior cingulate or retrosplenial cortices. Of these, six were observed in studies involving memory. Shulman *et al.*[29] performed a meta-analysis of nine PET studies that compared active visual tasks with passive viewing of the same visual stimuli. They observed that the retrosplenial cortex was one of the regions that most robustly and consistently showed 'negative activation' during the active visual tasks. Thus, there is no evidence to suggest that activation of the retrosplenial cortex occurs as consistently in experimental tasks that involve non-emotional stimuli as it does in tasks involving emotionally salient stimuli.

TABLE 3. Regional activations associated specifically with the emotional salience of stimuli, from the 20 experiments described in Table 2

Region[a]	Number activated[b]	L/R/B[c]	F/D/S/H/M[d]	Studies[e]
Posterior cingulate cortex	7	2/4/1	5/1/1/0/0	1,3c,4,6a,6b,9b,10
Retrosplenial cortex[f]	6	1/4/1	4/1/1/0/0	3c,4,6a,6b,9b,10
Caudate	6	1/3/2	0/0/3/3/0	3a,3b,3c,3d,8a,8b
Middle frontal cortex	5	4/1/0	1/3/1/0/0	2a,2b,3a,6a,9b
Cortical area 19	5	1/2/2	3/2/0/0/0	2a,4,6a,8a,9b
Putamen	5	2/2/1	1/1/0/3/0	3b,3d,7b,9a,9b
Anterior cingulate cortex	4	3/0/1	1/1/1/1/0	1,3a,3b,9b
Medial frontal cortex	4	2/0/2	1/0/1/1/1	1,3a,3d,11
Thalamus	4	2/1/1	1/1/1/1/0	1,3a,8b,9b

[a]Regions in which activation peaks were located.
[b]The number of experiments reporting significant activation in each region.
[c]Number of left, right or bilateral activations.
[d]Number of activations with fear, disgust, sadness, happiness or mixed stimuli.
[e]Study numbers from experiments described in Table 2.
[f]Retrosplenial cortex refers to areas 29 and 30, and the adjacent posterior cingulate cortex posterior to the splenium of the corpus callosum.
Regions with 1–3 reports of activation: insula (3), inferior frontal (3), superior temporal (2), middle temporal (2), mesial temporal (2) (both including activation in amygdala), post central (2), area 17 (2), area 18 (2), superior frontal (1), orbital frontal (1), temporal pole (1), inferior temporal (1), inferior parietal (1), angular (1), supramarginal (1) and precuneus (1).

The 'negative activation' of the retrosplenial cortex, which is frequently observed during cognitive tasks[21,29], could reflect the involvement of this region in both emotional and memory processes. When comparing a word-generation task to a 'resting baseline' condition, Andreasen *et al.*[21] observed that the greatest relative decrease in activation occurred in the retrosplenial and adjacent precuneate cortices. The authors suggested that this change in retrosplenial activity might be associated with the spontaneous mentation that occurs when human subjects are not engaged in a focused cognitive task. This mentation would typically include the retrieval of emotionally salient mental contents from autobiographical memory and possibly the re-encoding into memory of these episodes of reflection and thought. This ongoing mentation would be suspended when the subject became engaged in the active 'experimental task', thus, the retrosplenial cortex would show decreased activity during the active task compared with the rest condition. This account of 'negative activation' in the retrosplenial cortex is consistent with a role for this region in both episodic memory and the evaluation of emotionally salient stimuli.

Neuroimaging studies of the retrosplenial cortex in clinical populations

Do studies of patients with neuropsychiatric disorders support the idea that this region has functions related to emotion and memory? In addition to the cases of 'retrosplenial amnesia' described above, there is increasing evidence for an association between Alzheimer's disease and hypofunction of the retrosplenial cortex. Several PET studies have demonstrated prominent reduction of metabolic rate in the posterior cingulate and retrosplenial cortices in Alzheimer's disease[46,47]. The most striking results show the posterior cingulate to be the region with the greatest reduction in metabolic activity in patients with very early Alzheimer's disease, when memory impairment is the only symptom[48], and in completely asymptomatic subjects at risk of developing Alzheimer's disease (homozygous for the apolipoprotein E ε4 allele and having a positive family history for Alzheimer's disease)[49]. In contrast to this decreased activity of the posterior cingulate and retrosplenial cortices in Alzheimer's disease, increased activity of this region has been observed in neuropsychiatric disorders that are characterized by prominent abnormalities in emotional functioning. Activity of the posterior cingulate cortex is elevated in schizophrenia[50,51] and major depression[52], and correlates with severity of anxiety symptoms in mood and anxiety disorders, including major depression[53], obsessive–compulsive disorder[54,55] and social phobia[56].

What specific emotion-related functions might be mediated by the retrosplenial cortex?

This question has not yet been addressed experimentally; however, some hypotheses have arisen from the examination of functional-neuroimaging studies of emotion. For example, it appears that the function served by the retrosplenial cortex is not restricted to a single sensory modality. Among the studies summarized in Table 2, the retrosplenial cortex was activated both by studies that used auditory stimuli alone[6] and by studies that used visual stimuli alone[38,39,44]. In addition, there is suggestive evidence for a lateralization of retrosplenial-cortex function. All but one of the experiments that demonstrated activation of the retrosplenial cortex observed greater right- than left-sided activation. In these studies, subjects either viewed or recalled pictorial stimuli. The one study in which greater left-sided retrosplenial activation was observed involved only verbal stimuli[6]. This pattern of results suggests an association between the right retrosplenial cortex and emotionally salient pictorial stimuli, and between the left retrosplenial cortex and emotionally salient verbal stimuli.

Is there a specific association between retrosplenial cortex and unpleasant stimuli? Among the 20 controlled experiments, retrosplenial activation was seen in six of 15 experiments that involved unpleasant stimuli (fearful, disgusting or sad), and in none of five experiments involving pleasant (happy) or mixed stimuli. This demonstrates an association between retrosplenial-cortex activation and unpleasant stimuli. However, there have been insufficient studies of pleasant stimuli to conclude that this association is specific to unpleasant stimuli. Two studies not meeting the inclusion criteria for this literature review have reported retrosplenial activation by pleasant stimuli. Left retrosplenial activation was observed in response to pleasant, emotionally salient words in a study that was not explicitly conceptualized as emotional[57]. A preliminary study of nine subjects has recently shown consistent left retrosplenial-cortex activation in response to both intensely pleasant and intensely unpleasant spoken words[7]. While the studies reviewed in this article show an association between retrosplenial cortex activation and unpleasant stimuli, preliminary data[7] and the report by Demonet *et al.*[57] suggest that pleasant stimuli also activate this region.

Does retrosplenial activation reflect emotional evaluation processes?

In general, emotionally salient stimuli are automatically perceived and evaluated as such, whether or not an overt emotional response occurs[34,58]. The studies reviewed in this article suggest that the evaluation of

emotionally salient stimuli is sufficient to activate the retrosplenial cortex, and that the provocation of an overt emotional response is not a necessary condition for such activation. Activation of the retrosplenial cortex was observed in two out of nine experiments that combined mood induction with the evaluation of emotionally salient stimuli, and in four out of 11 experiments involving the evaluation of emotionally salient stimuli without mood induction. This suggests that the emotion-related function of the retrosplenial cortex might be more closely associated with emotional perception and evaluation processes than with the generation of emotional responses.

Does the retrosplenial cortex have a role in the interaction between emotion and episodic memory?

As the retrosplenial cortex appears to have functions that are related to episodic memory, one hypothesis about its role in emotion is that it mediates an interaction between emotion and episodic memory. The retrosplenial cortex is well positioned anatomically to have a role in the interaction between emotion and memory. Two possible 'circuits' that mediate such an interaction are suggested by the connectivity of this region. Its strong afferent inputs from the anterior cingulate, the orbital frontal cortex and the anterior dorsal bank of the superior temporal sulcus (all of which receive significant input from the amygdaloid complex) are a potential source of information about the emotional and motivational significance of ongoing stimuli and events, which could be integrated in the retrosplenial cortex[4,14,15]. The strong efferent connections from the retrosplenial cortex to the parahippocampal and entorhinal cortices provide a means by which the retrosplenial cortex can influence episodic-memory processes subsequently in a way that reflects emotional and motivational priorities[16]. Alternatively, the significant input from the amygdaloid complex to the entorhinal cortex could provide a primary emotional and motivational influence on episodic-memory processes[4,59]. The entorhinal cortex provides strong afferent input to the retrosplenial cortex, which in turn provides input to the anterior cingulate cortex, the dorsolateral prefrontal cortex, superior temporal sulcus and precuneus[13,15]. Thus, the retrosplenial cortex might have a role in implementing emotional memory processes that received their emotional prioritization at an earlier processing stage. Either scenario confers a role in the interaction between emotion and memory upon the retrosplenial cortex.

This interaction could involve emotional influences on memory encoding, memory retrieval or other memory processes. Emotionally salient stimuli can influence the encoding of episodic memory in many ways[60]. The most-consistent observation has been that emotionally salient stimuli are better recalled than matched neutral stimuli[6,59–62]. This enhancement of episodic memory for emotionally salient stimuli was preserved in patients with memory impairment resulting from Korsakoff's syndrome or damage to the hippocampal formation[63], but not in a patient with bilateral amygdala lesions[64]. The retrosplenial cortex could have a role in the enhancement of episodic-memory encoding of emotionally salient stimuli. The significant correlation observed between the activation of the retrosplenial cortex by emotionally salient words and the enhancement of recall for the same words is consistent with this proposal[6]. This hypothesis could be tested by comparing episodic memory for emotionally salient and neutral stimuli in patients with lesions of the retrosplenial cortex.

In humans, the evaluation of an emotionally salient stimulus engages a variety of cognitive processes, many of which rely on episodic-memory retrieval[34,58]. These memory-based evaluation processes have an important influence over whether or not an overt emotional response is expressed[65]. Activation of the retrosplenial cortex by emotionally salient stimuli could reflect the retrieval of episodic memories in support of such automatic evaluation processes. Functional-imaging studies, in which episodic retrieval processes and emotional salience are systematically varied, could provide approaches to testing this hypothesis.

Concluding remarks

This review of functional neuroimaging studies of emotional processes demonstrates that the retrosplenial cortex is the cortical region that is most consistently activated by the emotional salience of experimental stimuli. These observations suggest that the retrosplenial cortex has a prominent role in the processing of emotionally salient information. The evidence that this region also has episodic-memory functions raises the possibility that it has a role in the interaction between emotion and episodic memory. This unexpected discovery challenges the neuroscientists that are studying human emotion to direct their attention to the retrosplenial cortex, in order that future studies might elucidate the as yet undefined emotion-related function served by this region.

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CART peptides: novel addiction- and feeding-related neuropeptides

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CART peptides are novel, putative brain–gut neurotransmitters and co-transmitters that probably have a role in drug abuse, the control of feeding behavior, sensory processing, stress and development. They are abundant, processed and apparently released. Exogenously applied peptides cause inhibition of feeding and have neurotrophic properties. Although the precise sequences, relative abundance and efficacy of all CART peptides are currently being determined, small molecules that are active at putative CART receptors could have substantial therapeutic promise.

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A NEW putative peptide neurotransmitter(s)[1,2] has been discovered that appears to have an important role in a variety of physiological processes, including feeding, sensory processing, development, reinforcement and reward, and stress. Research on these peptides, the products of CART (cocaine and amphetamine regulated transcript)[3] has produced many exciting findings and more are expected. (While the term 'CART' implicitly refers to the mRNA, the explicit phrases 'CART mRNA', 'CART protein' or 'CART peptide' are used in this article to avoid ambiguity.)

CART peptides represent peptides of the modern era, which means that the mRNA was discovered before the peptide itself using PCR followed by differential display[3]. CART was identified as an mRNA whose levels were significantly elevated in the rat striatum following psychostimulant-drug administration. Following this discovery, the deduced amino-acid sequence was examined and it was found that some CART-protein fragments had previously been found in brain, although at that time their significance was not known[4]. This contrasts with the usual pattern of discovery where peptides are first identified as unknown compounds that have biological activity in a tissue extract, and then are purified, sequenced and cloned. This 'reverse genetic' approach of finding the mRNA first and then determining whether or not a significant product is made and used in the brain is a modern one. It has been successful in identifying other peptides[5] and is certainly a forerunner of the future, given the expected completion of genome projects over the next few years.

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Recent history

As mentioned above, CART mRNA was identified in the rat striatum as an mRNA whose levels were increased after administration of cocaine or amphetamine[3]. While the mRNA was found in other brain areas and tissues, its levels were not changed by psychostimulant-drug administration in those regions. These studies suggested that the products of CART mRNA might be involved in psychostimulant-drug action and, given the presence of CART mRNA in other brain regions, they further suggested that CART products could also have a role in neuronal processes in these regions.

Douglass *et al.*[3] reported that CART was a new, previously uncharacterized mRNA that was not significantly related to any known mRNA. Alternate poly-A-site use in the 3′ noncoding region results in the appearance of an RNA doublet, which is either 700 or 900 bases in length. Alternate splicing also produces further diversity within the coding region of the transcripts in the rat and results in two mRNA species, one with the absence of an inframe 39-base insert within the protein-coding region[3]. As a result, the predicted translation products

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