CHAPTER 26

Altered Processing of Valence and Significance-Coded Information in the Psychopathic Cingulate Gyrus

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Chapter contents

The official diagnostic classification system for mental disorders in the United States, *DSM-IV*, recognizes anti-social personality as a distinct entity. In contrast, psychopathy is not recognized as a distinct disorder. Both disorders involve behavioral impulsivity and actions that violate social norms and what distinguishes psychopathy from anti-social personality disorder is that the former includes a deficit in emotional responses to others and the latter does not. This deficit, like other behavioral disturbances involving emotion in psychiatric disorders (e.g., blunted affect in schizophrenia), is difficult for clinicians to rate reliably, which may account for its lack of inclusion in *DSM-IV*. However, recent empirical findings have advanced our understanding of the brain and behavioral basis of psychopathy and the associated emotional deficits and these abnormalities include alterations in the functioning of subregions of the cingulate gyrus as well as other areas. As such, these new findings advance our understanding of how the brain mediates emotional responses and how disruption of these functions may result in clinical conditions such as psychopathy. A deeper understanding of the brain basis of disorders of emotion regulation may ultimately contribute to the inclusion of their behavioral manifestations in the definition of these disorders.

The modern concept of psychopathy was strongly influenced by the work of Herve Cleckley, who, over the course of 40 years of clinical observations, identified 16 characteristics of psychopaths. These characteristics were operationalized into *the Hare Psychopathy Checklist* (PCL) and *the Hare Psychopathy Checklist Revised* (*PCL-R*; Hare, 1991). The latter addresses the 16 key characteristics of psychopathy that segregate into two factors: an interpersonal/affective factor and a social deviance factor. These characteristics have been further refined recently into a four-factor model of psychopathy that divides the first factor into separate interpersonal and affective factors and the second into lifestyle and anti-social factors:

1 *Interpersonal*. Glibness/superficial charm, grandiose sense of self-worth, pathological lying, and conning/manipulative.

2 *Affective*. Lack of remorse or guilt, shallow affect, callous/lack of empathy, and failure to accept responsibility.

3 *Lifestyle*. Need for stimulation; parasitic lifestyle, lack of realistic long–term goals, impulsivity, and irresponsibility.

4 *Anti-social*. Poor behavioral controls, early behavioral problems, juvenile delinquency, revocation of conditional release, and criminal versatility.

The *DSM-IV* diagnosis of anti-social personality disorder is based primarily on the lifestyle and anti-social factors. Although lack of remorse or guilt is listed among the possible criteria that must be met for the diagnosis, it is the only interpersonal or affective characteristic listed and is not required for the diagnosis. The affective and interpersonal components of psychopathy are considered critical from a clinical perspective; whereas 80–90% of the prison population meets the criteria for anti-social personality disorder and only 15–25% are psychopathic. The greater specificity of the diagnosis of psychopathy is important because, compared with other inmates; psychopathic offenders commit a disproportionate amount of repetitive, often violent, criminal acts (Kiehl *et al.*, 2001). To the extent that psychopathy constitutes a more extreme form of anti-social personality disorder, it may provide insights into the neurobiological basis of both disorders. Before considering the specific deficits in behavior and cingulate functions, a detailed analysis of emotional processes is needed to guide interpreting the nature of emotional deficits in psychopathy.

Implicit and Explicit Aspects of Emotion

The distinction between implicit (non-conscious) and explicit (conscious) processes is relevant to understanding the mental state of psychopathic individuals. The distinction was first applied to memory where explicit memory, for facts and events, requires participation of medial temporal lobe structures and the diencephalon, whereas implicit memory requires structures such as the striatum (skills and habits), neocortex (priming), amygdala and cerebellum (classical conditioning), and reflex pathways (non-associative learning) (Gazzaniga *et al.*, 2002). Antonio Damasio's (1994) distinction between primary emotion and feeling, and their dissociable neural substrates, paved the way for the application of the implicit–explicit distinction to emotion. Primary emotion is the phylogenetically older behavioral and physiological expression of an emotional response. Primary emotion occurs automatically and without the necessity of conscious processing. Feeling, on the other hand, involves the conscious experience of that emotional state. According to Damasio (1994), primary emotion and feeling are separable, both conceptually and neuroanatomically. While primary emotion is necessary for successful adaptation to environmental challenges and the physiological adjustments needed to meet those challenges, a conscious feeling state enables previous emotional experiences to be consciously recalled or current experiences to be accessed and used for decision making and navigation of the social world.

Brain imaging studies demonstrate that amygdala activation can occur in response to emotional stimuli

in the absence of conscious awareness of the stimulus. This is consistent with the notion that the amygdala performs its functions implicitly and plays a key role in establishing whether exteroceptive stimuli have an emotional meaning. LeDoux (1996) has written about the distinction between the thalamoamygdala pathway for processing exteroceptive stimuli rapidly and crudely in the absence of conscious awareness, and the neocortical-amygdala pathway that provides more precise and differentiated identification of the stimulus requiring an additional 12 msec of processing time. The time saved by having behavior directed by implicit processes could potentially mean the difference between life and death in life-threatening situations. This is not inconsistent with the view that the capacity for explicit processes such as reflection, deliberation, delay of impulses, planning, and the like are arguably more important to adaptive success in modern human cultures, in which success or failure, rather than life or death, is the more salient issue (Goleman, 1995).

Within the field of consciousness research, a distinction is made between phenomenal and reflective awareness. Phenomenal awareness refers to the actual content of consciousness (feelings and background feelings) whereas reflective awareness involves the performance of cognitive operations upon the contents of conscious experience (Farthing, 1992). Reflective awareness, or metacognition, requires the creation of a representation of experience and this representation will affect how future emotional information is interpreted and experienced. Lane *et al.* (1997) examined the pattern of neural activation associated with attending to one's own emotional experience. To confirm that subjects were attending as instructed, subjects indicated on a keypad how each emotion-evoking picture made them feel. In essence, the study examined an aspect of conscious experience involving commentary on that experience. By having subjects attend to and valence their experience in this study, we were examining reflective awareness. During valencing of subjective emotional responses, increased neural activity was elicited in area 32 of pregenual anterior cingulate cortex (pACC) and medial prefrontal cortex, right temporal pole, and insula. The medial surface activation from this study is shown in Figure 26.1 (turquoise). Under the same stimulus conditions when subjects attended to spatial aspects of the picture sets, activation was observed in parieto-occipital cortex bilaterally; a region known to participate in the evaluation of spatial relationships. Thus, explicit awareness of one's own emotional state engages cingulate cortex and this has implications for understanding some of the symptoms of psychopathic behavior.

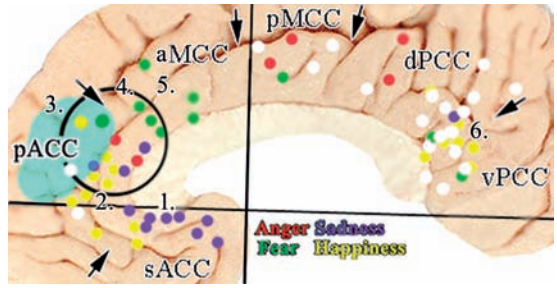

Fig. 26.1 Reanalysis of the plots of simple emotion activations in relation to cingulate subregions (Vogt et al., 2003). Aggregates of activity (peak voxels plotted by color coded dots and numbered): #1. sadness, subgenual anterior cingulate cortex (sACC); #2. happiness, pregenual anterior cingulate cortex (pACC); #5. fear; #6. Non-emotion-specific activity, posterior cingulate cortex (PCC) where white dots are activations generated by non-emotional stimuli as controls for the emotional conditions. In addition, #3. shows the full distribution of activity while attending to one's own emotional experience (Lane et al., 1997), #4. is the smallest diameter circle that can be struck around the greatest number of types of emotional responses.

Cingulate Activations During Explicit Emotion

In addition to activation of pACC area 32 in reflective awareness through conscious coding of sensory stimuli (Lane *et al.*, 1997; turquoise in Fig. 26.1), an *a priori* hypothesis is suggested that the place in ACC that has direct access to the most activity during multiple simple emotions is the site of emotional awareness. This is proposed because it would be surprising that emotional awareness is achieved in parts of the cortex, cingulate or otherwise, that are not specifically activated during emotion. Moreover, the more emotions that so activate such a site, the more likely it would be that it serves the general purpose of emotional awareness rather than the specific features of valencing and storage of episodic memory associated with a particular emotion. A visual survey suggests that such a site likely exists in pACC and not in posterior cingulate cortex (PCC) as commented in other chapters and Vogt *et al.* (2003), as the white dots represent non-emotional, control conditions and tend to negate the notion of a specific role of a region in emotion for PCC (#6. in Fig. 26.1). Progressively larger circles were drawn around the center of the site in pACC until samples of activated cortex involved all four emotions. The final circle (#4. in Fig. 26.1) is large enough to include activations of all the four emotions as well as most of that generated in the study by Lane *et al.* (1997). The circle includes areas 24 and 32 as well as part of area a24′ in anterior midcingulate cortex (aMCC). Thus, the site of reflective awareness is located mainly in pACC but also extends into aMCC.

Although this site may not play a key role in particular emotions, what are its specific functions? First, it participates as a 'scale' to weigh the average content of emotion to determine the overall mood state. In the case of sadness, for example, the greatest number of sites are in subgenual ACC (sACC) and there is reasonably good evidence this subregion is involved in the storage of episodic memories relating thereto. The activity associated with reflective awareness may not have specific information related to sadness *per se* but rather play a role in determining mood from many forms of emotional activity; this site would essentially work as an emotional scale in regulating ongoing mood. If negative stimuli and experiences dominate for a period of time, the level of sadness and negative mood might weigh more heavily than a positive mood requiring happiness. Second, it likely contributes to expression of general mood states. As all emotions generate activity in this region, it may be relevant to immediate changes in facial expression associated with changes in mood. This region has projections to the facial motor nucleus to regulate the muscles of facial expression and vocalization associated with emotional expression as discussed in Chapters 5, 13, 15, 16, 17, 19, 23, and 24. This particular localization is important to understanding some of the deficits in information processing in the psychopathic cingulate cortex mediating emotional awareness and expression including emotional language impairments.

In sum, of critical importance to the symptoms of psychopathy, is the glibness, grandiose sense of self-worth, lack of remorse or guilt, shallow affect, and callous/lack of empathy for others. Each of these features may reflect the psychopath's inability to attend to their own emotions and those of others. Thus, Figure 26.1 provides a framework within which to analyze subregional impairments in cingulate processing in the psychopathic brain. The subregional functions can be summarized:

1 sACC, storage of negatively valenced events and primary regulation of autonomic functions;

2 pACC area 32, activation by positively valenced events and emotional awareness;

3 pACC area 24, emotional awareness and scaling of mood state and expression;

4 aMCC, involved in fear and avoidance behaviors,

5 posterior MCC (pMCC), coordinates skeletomotor and autonomic reflex outputs; and

6 Ventral PCC (vPCC), interacts with ACC to allow context-dependent and emotional-relevant sensory information to flow into the cingulate cortex as discussed in the six-stage model of emotional processing outlined in Chapter 13.

With these summary views, we can address alterations in the flow of valence- and context-dependent information throughout cingulate cortex in the psychopathic brain.

Goals of This Chapter

The ultimate test of any model in biology requires that its physical disruption occur along some consistent neurochemical dimension. This can be a phenotypically unique cytoarchitectural entity, a particular transmitter system, and/or a cortical network with contributions to a particular function. We approach the psychopathic brain in the context of the eight-subregion neurobiological model with specific functions for each sector and the flow of information into, within, and out of the cingulate gyrus to regulate motor systems. The goal of this cingulocentric consideration is not to imply that cingulate cortex is the only critical player but rather to emphasize the specific symptoms to which cingulate impairment contributes. The specific goals follow:

1 Provide an overview of the pivotal symptoms observed in psychopathic individuals.

2 Evaluate correlations between a cingulate subregional functions with imaging including monoamine oxidase A, genetic predisposition in psychopathy and how these might affect cingulate functions demonstrated with changes in blood flow in three key subregions; pACC, aMCC, and vPCC.

3 Discuss specific cingulate functions that are impaired in psychopathy:

   (a) autonomic control,

   (b) significance, valence, and context-dependent sensory processing,

   (c) decision making, planning, empathy, and language, and

   (d) cingulate outflow systems that regulate behavior.

4 Develop a new theoretical model of information processing impairment in psychopathy that has three levels of disruption:

   (a) blocked inflow of self-relevant information,

   (b) failure of intracingulate information flow including the interpretation of behavioral contexts and the emotional content of other's emotional state, and

   (c) altered outflow patterns that regulate autonomic and skeletomotor responses.

Cingulate Dysfunction in Psychopathy

The consideration of cingulate pathology in psychopathy does not imply that this is the only region that explains

critical symptoms and brain impairments in this disorder. Certainly, the amygdala, orbitofrontal, and insular cortices are also involved. Reduced emotion-modulated startle responses, reduced aversive conditioning, and reduced emotion-enhanced memory all implicate the amygdala (Blair, 2005; Kiehl, 2006); however, symptoms irrelevant to cingulate function, such as the emotion-modulated, startle reflex, are not considered here. Figure 26.2 is partially based on Figure 26.1 where the latter was reduced in opacity such that a few findings of key studies of psychopathy could be coregistered to cingulate cortex in the framework of normal emotion. Most studies of psychopathy report reductions in cingulate regional cerebral blood flow (rCBF) in contrast to controls or other populations that are free of psychopathy. Thus, impairments in cingulate functions here always refer to a loss of some critical information processing activity.

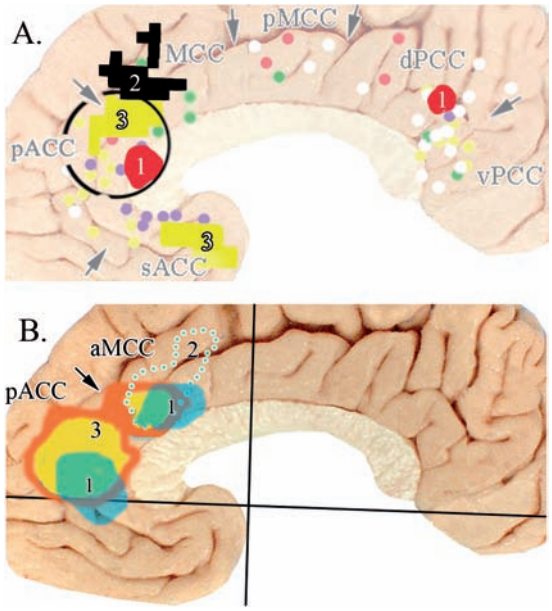

Fig. 26.2 Context of cingulate impairments in psychopaths. A. The opacity of Fig. 26.1 was reduced and medial surface alterations plotted in full from three studies: 1. Müller et al. (2003) reduced activity in criminal psychopaths while viewing pictures with emotional valence; 2. Sterzer et al. (2005) reductions to similar stimuli but in adolescents with conduct disorder; 3. Meyer-Lindenberg et al. (2006) vulnerability site in individuals with short allele of monoamine oxidase A gene and correlated impulsive aggression. B. Language involvement in psychopathy has been documented and structure/dysfunction overlaps in aMCC suggest a mechanism: 1. two sites from Kiehl et al. (2001) psychopathy study shown in next figure; 2. site of novel verb generation to noun lists (Raichle et al., 1994); 3. activation associated with syntactic errors (Kuperberg et al., 2008). Resolution of syntactic errors and the generation of action verbs are impaired in anterior midcingulate cortex (aMCC) in the psychopathic brain.

Figure 26.2A plots the following sites:

1 Müller *et al.* (2003) reported that activation of pACC (incorrectly reported as subgenual) and dPCC was reduced in criminal psychopaths contrasted with normals when viewing pictures from the International Affective Picture System.

2 Sterzer *et al.* (2005) evaluated children with severe conduct disorder and healthy control cases when viewing pictures with neutral or strong negative affective valence and reported a strong inactivation of dorsal aMCC. This finding may be pivotal to differentiating conduct disorder form criminal psychopathy as this region appears to be generally normal in the latter group.

3 Meyer-Lindenberg *et al.* (2006) evaluated allelic variation in the X-linked monoamine oxidase A gene that has been associated with impulsive aggression. They found that individuals with low expression of the variant gene were associated with increased risk of violent behavior and predicted pronounced reductions in the volume of cingulate cortex. Most importantly, blood oxygen level dependent (BOLD) signal reductions during stimulation with angry or fearful faces in men with the high carriers of the variant allele had a greater inactivation of two parts of ACC than did individuals with a low level of this variant. The overlap of inactivation sites 1 and 3 in the circle of high-emotional awareness suggests that this part of pACC is particularly vulnerable to monoamine oxidase A impairment and may contribute in a profound way to impaired processing of valenced information. Moreover, the deactivation of daMCC in adolescents with conduct disorder provides a means of segregating this disorder from individuals with psychopathic symptoms in terms of cingulate impairments.

Cingulate Subregional Inactivations in Psychopathy

Kent Kiehl extended his previous behavioral and psychophysiologic research in psychopaths by performing a functional magnetic resonance imaging (fMRI) study in criminal psychopaths, criminal non-psychopaths, and healthy controls as subjects encoded, rehearsed and retrieved neutral, and negative emotional words. Kiehl *et al.* (2001) aggregated the emotion conditions separately from the neutral conditions and showed that, in the negative emotion conditions, criminal psychopaths manifested reduced activity relative to non-psychopaths in three cingulate subregions, the left amygdala, parahippocampal gyrus, and anterior superior temporal gyrus. Importantly, the groups did not differ in BOLD activity during the processing of neutral

stimuli. The decreased activity in the amygdala is consistent with other evidence of amygdala dysfunction in psychopathy (Blair, 2005; Kiehl, 2006). The parahippocampal gyrus plays a key role in the processing of memories and has dense inter-connections with the amygdala. The anterior superior temporal gyrus has been implicated as functioning abnormally in other language-related studies in psychopathy.

Kiehl *et al.* (2001) is of particular interest in terms of reduced activations in three cingulate subregions. Their findings are summarized in Figure 26.3 with a modification of their figure coregistered to the eight subregion model to emphasize both the subregion inactivations they observed (blue) as well as those regions that have 'normal' rCBF (red ovals). This pattern of reduced rCBF shows alterations in pACC, aMCC, and vPCC. Interestingly, sACC, daMCC, pMCC, and dPCC have normal rCBF but this should not be interpreted to mean that information processing in these areas is necessarily intact.

Cingulate Structure/Dysfunction Correlates

Autonomic control and emotional information

A direct link between psychopathy and impaired autonomic output was shown by Patrick *et al.* (1994) during imagery of fearful scenes. Although their imagery experience seemed to appear similar to non-psychopaths, heart rate, and skin conductance was attenuated during this imagery. Birbaumer *et al.* (2005) showed that during the acquisition of fear, psychopaths failed to generate responses in pACC (likely area 24 mainly) that were characteristic of healthy controls. Psychopaths also failed to show conditioned skin conductance and emotional valence ratings although arousal ratings were normal. In another report, a general decrease in emotional responsivity has been reported (Day & Wong, 1996).

Significance, valence, and context-dependent sensation

Orienting responses are elicited by unpredictable, novel, or task-relevant stimuli. Skin conductance responses indicating a change in sweat gland activity in the palm of the hand are a relatively pure measure of sympathetic nervous system activity associated with arousal including orienting responses. Psychopaths manifest lower levels of skin conductance and show reduced skin conductance responses to a variety of aversive stimuli including loud noises, hypodermic needle injections, and viewing pictures of mutilated faces (Kiehl, 2006).

Psychopaths also manifest reductions in an event-related brain potential called error-related negativity (ERN; Dikman & Allen, 2000). This response occurs when mistakes are made during the execution of a task. The ERN appears to be specifically related to the unpleasant emotional response associated with realizing that one has made an error. The ERN is likely a combination of attention and affective processes and a growing body of evidence suggests that the MCC is responsible for generating the ERN.

Psychopaths appear to have a deficit in generating automatic emotional responses, including empathy (shared distress with others), in the differentiation between emotional and neutral stimuli, and in the cognitive processing of emotional stimuli, including the linkage between emotion and language.

A prominent feature of psychopathic behavior is an inability to detect the emotional significance of sensory information such as emotional words (Williamson *et al.*, 1991; Patrick *et al.*, 1994). At first, one might expect substantial overlap between this functional impairment and others discussed above in relation to ACC. However, this is where the frontal model of psychopathy fails as it presumes all information flows through prefrontal areas to cingulate cortex. Indeed, a pivotal intermediary exists whereby the entry of emotional information into the cingulate gyrus occurs in the vPCC. On the basis of a cytoarchitectural, connection and literature review, we concluded that the vPCC receives inputs from the orbitofrontal, middle temporal, and inferior parietal cortices and these contribute to assessing the self-relevance of emotional and non-emotional objects (Vogt *et al.*, 2006). Moreover, Chapter 13 proposes that context and particular features assist the vPCC in extracting information from multiple sensory spaces that are relevant to self. Indeed, this appears to be why both emotional and non-emotional tasks generate activity in vPCC but not in ACC, in addition to the fact that this region has the highest level of glucose metabolism in the brain. It is the continuous assessment of multiple sensory spaces using contextual cues for seeking self-relevant information via constant interactions with sACC that provides a vPCC gateway for emotionally relevant objects and circumstances to the cingulate gyrus. This intermediary system for access to premotor processing in the cingulate gyrus is impaired in the psychopathic brain.

The vPCC is in close communication with the sACC and likely assists in discriminating between emotional and non-emotional stimuli. The vPCC is heavily connected to memory structures in the medial temporal lobe and appears to serve a superordinate role in the evaluation of the personal significance and salience of exteroceptive stimuli. Thus, this impairment appears to be related to the diminished ability of psychopaths to discriminate between emotional and non-emotional stimuli. A further consequence of the functions of vPCC

is that is plays a role in coding the significance of words and linguistic concepts in terms of emotional significance.

Decision making, planning, and avoidance

Another feature of psychopathic behavior is an over focus on immediate goals that result in a lack of well-planned, long-term goals (Cleckley, 1976). These individuals fail to slow responses after making errors in a task involving punishment or reward and are unable to inhibit punishable responses. Avoidance learning impairments are a well-established consequence of cingulate lesions in experimental animal studies (Gabriel, 1993). In psychopaths, the ERN during error detection is reduced in this group and it is likely associated with impaired activity in aMCC. Thus, Kiehl *et al.* (2000) reported errors of commission during a go–nogo task with fMRI and showed activation of aMCC. Decision making, planning, fear activation, and avoidance behaviors are considered together here as part of the integrative premotor function of aMCC.

Bush *et al.* (2002) used a region-of-interest method to evaluate responses in a dorsal part of aMCC and showed that reduced rewards generated the greatest response in healthy individuals. This finding was extended in a study of single neuron responses before and after midcingulotomy lesions. Williams *et al.* (2004) showed that single neurons responded robustly to reduction in reward and predicted movements and associated behavioral responses were blocked with the lesion. As reduced rewards should generate a negative response, this finding supports the prediction that this region generates responses to negative-valenced events. Dikman and Allen (2000) evaluated the ERN in low-socialized subjects as a prodromal form of psychopathic individuals and compared them with a high-socialized group of healthy controls. Their task employed both reward and avoidance learning arms. The low-socialized group produced smaller ERNs during the punishment task than during the reward phase when compared with the high-socialized group. As the aMCC is pivotally involved in the ERN, responses during reward reduction, and avoidance behaviors, this result further suggests that psychopathic subjects have impaired activity in aMCC.

Finally, Nakata *et al.* (2008) used a go–nogo task with event-related fMRI and showed that aMCC (mainly area 32′) was active along with other premotor areas during the response inhibition trials. The daMCC includes part of the rostral cingulate premotor areas (rCPMAs) and area 32′ and their functions are thoroughly reviewed in Chapter 12 as is its involvement in attention-deficit/hyperactivity disorder. Thus, psychopathic deficits in decision making, planning, response inhibition, and avoidance may all have a substrate in a common impairment of aMCC.

Empathy and the pain neuromatrix

A lack of empathy in processing affective information is a pivotal feature of psychopathic behavior (Hare, 1993) and this may reflect dysfunction of aMCC. As discussed in detail below, empathy to another's painful response is generated in the same region that has high fear activation and is part of the pain neuromatrix; that is, is usually activated during noxious stimulation (Jackson *et al.*, 2005). Altered processing in this domain of psychopathic brain function could be associated with altered response inhibition and avoidance behavior as also noted above. In a cingulate context, therefore, a failure of empathy may be associated with impaired decision making, planning, and avoidance behaviors that are activated by the pain of others as well as one's own pain.

It is well established that MCC is the most frequently activated cingulate region in studies of acute pain processing (Vogt, 2005). The link between these activations and pain empathy suggest the site of a critical symptom in the psychopathic brain. Jackson *et al.* (2005) showed that aMCC is preferentially active while observing situations in which another individual is experiencing pain. Activity in the aMCC was correlated with the intensity of the participants' rating of the other person's pain. In another study, facial expressions of pain activated a similar region in observers (Botvinick *et al.*, 2005). Moreover, observing another's pain and feeling one's own pain evokes activity in aMCC, although in slightly different parts with some overlap (Morrison and Downing, 2007). Thus, networks that are engaged during the response to noxious stimuli activate a cingulate subregion that is similar to that when one observes the pain in others whether it is via facial expression or the objects known to produce pain such as knives or other noxious insults.

Mohr *et al.* (2005) reported three unique functions of cingulate subregions in terms of the external versus self-application of noxious tactile stimulation. The pACC was specifically active in relation to the certainty of pain onset, the aMCC was primarily activated in relation to externally applied stimuli, and the pMCC was activated mainly during self-administration of noxious stimuli. These findings support the concept that pain activation differs by cingulate subregion. In the present context, it is not surprising that an external application of pain would activate the same aMCC area that is involved in empathy. Consistent with the premotor planning hypothesis, as discussed in detail in Chapter 14, the aMCC is a pivotal premotor planning cortex that coordinates an individual's prediction of outcomes, anticipation of pain, and organization of nocifensive behaviors. It appears that empathy activation of the

aMCC prepares the observer to evaluate the level pf pain in another and provide for avoidance behaviors that will reduce the other person's pain as well as the pain of the individual observing the pain.

The cingulate 'empathetic premotor pain processing' module in aMCC is disrupted in the psychopathic brain as shown in blue in Figure 26.3. Emotional shallowness and callus attitudes to the states of others by psychopaths are reflected in the specific inability to interpret expressions of facial pain. Such impairment might assure that the psychopath cannot interpret the pain of their victim and could lead to multiple felony assaults. Such disordered emotional expression and hence behaviors are determined to a large extent by impairments in particular parts of the cingulate gyrus. Inactivation of aMCC in the psychopath impairs their empathetic responses to the pain expressed by their victims. A lack of this information prevents them from premotor planning to alleviate the pain of their victims that is mediated by external pain administration, interpretation of the victims face, and the selection of behaviors that would alleviate such expressions. Thus, the facial expressions of their victims fail to generate a pain avoidance response and an effort to relieve the pain of their victim. The focus in their cingulate gyrus continues as an effort to achieve personal goals in a deregulated limbic motor system including the CPMAs and its projections to the periaqueductal gray.

Language deficits

Psychopaths have a general deficit in semantic processing and of abstract information. The deficit in language appears to be for emotion-related words in particular. For example, while healthy controls respond faster and more accurately to letter strings that form positive or negative emotional words than letter strings that form neutral words, Williamson *et al.* (1991) reported that psychopaths did not show any difference in reaction time to emotional and neutral words. Consistent with this observation, psychopaths are not influenced by emotional word primes whereas healthy individuals are. They have difficulty recognizing and generating emotional prosody in speech. They have difficulty categorizing metaphors with emotional content and have a specific deficit in semantic judgments that involve emotional content. The study reporting three inactivation sites in the psychopathic cingulate cortex was based on the memorization, rehearsal and recognition of word lists with neutral and with emotional content (Kiehl *et al.*, 2001).

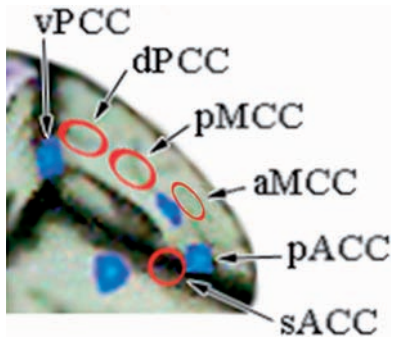

Fig. 26.3 Co-registration of Kiehl et al. (2001) inactivation sites to cingulate subregions (see also Fig. 26.4) in pregenual anterior cingulate cortex (pACC), anterior midcingulate cortex (aMCC), and ventral posterior cingulate cortex (vPCC). This pattern of decreased flow and 'normal' flow (red ovals) serve as the basis for assessing impairments in the flow of specific classes of information throughout the cingulate gyrus.

The ACC has been implicated in conspecific vocalization in monkeys including the separation call of infants (Müller-Preuss *et al.*, 1980) and it is known to receive auditory afferents (Vogt & Barbas, 1988). Ablations in the pACC severely disrupt conditioned and spontaneous vocalizations in monkeys (Aitken, 1981) and a detailed consideration of this functional part of pACC is presented in Chapter 15. Thus, a role in behaviorally relevant, emotional vocalization for this region is predicted for primates.

Hariri *et al.* (2003) observed that when subjects chose which of two verbal labels ('natural' – e.g., snake or 'artificial' – e.g., gun) matched a threatening pictorial target, compared with a condition in which subjects chose which of two pictorial threat stimuli matched a threatening pictorial target, pACC was activated. The verbal labeling condition was also associated with down-regulation of amygdala activity whereas the matching condition was associated with increased amygdala activity. Given the evidence of pACC dysfunction and the emotion-specific language impairment in psychopathy, these findings suggest that the typical modulatory effect of language on amygdala-mediated emotional responses is dysfunctional in psychopathy.

Kuperberg *et al.* (2008) used 'sentence violations' to evaluate BOLD responses including those associated with syntactic violations in sentence structure in a study of human language. They reported a large activation site in pACC as shown in Figure 26.2B (#3.). They suggested that attempts to determine actions described by verbs and arguments presented in a sentence were responsible for such activity. It was also considered that, as the button-pressing task was common to the 'non-violated sentence' condition, this activity was not responsible for the pACC response. As this activity is in pACC, one might assume that it is associated with the emotional motor aspects of language processing and may precede facial expression and other aspects of emotional output as predicted by the four-region neurobiological model outlined in Chapter 1.

Co-registration of the first two inactivation sites observed by Kiehl *et al.* (2001) to ACC in Figure 26.2B shows that these sites largely overlap.

By contrast, the generation of action verbs is also associated with the aMCC subregion. Raichle *et al.* (1994) used positron emission tomography (PET) to show activation of aMCC during the generation of verbs to noun lists and reduction in the signal with repetition of the task. The location of the novel activation site is shown in Figure 26.2B as #2. All three studies have an overlap in aMCC as shown in Figure 26.2B. Thus, verb generation in relation to skeletomotor output is differentiated from the behavioral output associated with emotional context.

Müller *et al.* (2003) observed reduced activity in dPCC criminal psychopaths while viewing pictures with emotional valence as shown in Figure 26.2A. A similar subregional activation has been generated with the auditory presentation of threat-related words (Maddock & Buonocore, 1997). Interestingly, the exact impairment in PCC in psychopaths is not yet resolved as Kiehl *et al.* (2001) inactivated the vPCC during performance of an affective memory task; either indicating critical differences in the task responses or variability in different populations of psychopathic subjects. It is possible that a third language-related symptom in psychopaths originates in the inactivation in dPCC.

Thus, inactivations in the psychopathic brain of pACC, aMCC, and dPCC appear to assure that both the contextual evaluation of emotional output and verbal actions are disrupted. Verbal links between action, expression, and emotional valencing appear to all be impaired in the psychopathic brain and are critically dependent on cingulate cortex.

These impairments can be understood within a developmental context. Werner and Kaplan (1963) maintain that the nature of experience is determined by the words or other symbolic mode of expression used to describe it. Symbolization is a structure-building, schematizing activity that promotes a developmental process. According to Werner's orthogenetic principle (1957), wherever development occurs it proceeds from a state of globality and lack of differentiation to a state of increasing differentiation, articulation, and hierarchic integration. Thus, the emotion-specific language impairment that psychopaths have is likely associated with relatively undifferentiated knowledge of their own emotions or the emotions of others and a concomitant relative failure to convert automatic, implicit emotional processes to consciously explicit emotional experiences. Moreover, this process of psychological development likely involves recruitment of cingulate subregions and their associated top-down modulatory effect on subcortical structures such as the amygdala (Lane, 2008). Thus, the emotion-specific language impairment in psychopathy is likely linked to the shallow emotions, lack of empathy, and callous interpersonal behavior of psychopaths.

Altered Information Flows into and Through the Cingulate Gyrus: An Information-Processing Impairment Theory of Psychopathy

Localization of impairments in cingulate subregions is an important step in understanding the structural substrates of psychopathic behavior. It is clear that disrupted behavior in psychopaths does not result from general impairments in attention or emotion or in global cerebral perfusion. The localized disruptions in cingulate functions shown with neuroimaging require a model of specific connection inactivations not currently available in this literature. Indeed, the psychopathology literature has not addressed specific pathway disruption in any system but focuses rather on global network functions and large structures (i.e., amygdala, insula, prefrontal cortex, etc.). We propose that disruptions in the cingulate gyrus are associated with impaired sensory processing, altered links to autonomic output, disorganization of input from the subjects of their repeated criminal activity, and impairments of processing of self-relevant information. Indeed, no studies address alterations in the flow of information within the cingulate cortex of the psychopathic brain.

It is striking how reduced processing in a few subregions could lead to the disruption of entire classes of cingulate circuitry. Indeed, there appear to be a number of inputs and intracingulate circuits that have reduced activity and others that may have normal blood flow but lack important afferent information from the impaired subregions. For example, the rCPMA is most profoundly impaired because of reduced activity in the gyral aMCC and altered inputs and this was confirmed by ERN studies (cited above). In contrast, the pMCC and the caudal CPMA (cCPMA) in the sulcus are relatively intact. It is the information input and properties of the cCPMA that shift the balance of motor activity toward a focus on immediate results and the former to emphasize failed responding to negatively valenced events. Thus, we look for two classes of circuits to explain psychopathic behavior; ones that are severely reduced and ones that are relatively normal but their output without the rostral affective output system produces abnormal behaviors.

The six-stage model of access and flow of valenced and context-dependent sensory information presented in Chapter 13 serves as a key to interpreting symptoms of the psychopathic brain. Two critical aspects of disrupted information flow include the following.

First, a reduced activity during the coding of valenced sensory stimuli from orbitofrontal (OFC), middle temporal gyrus (MTG), and interior parietal cortex (IP) to vPCC as shown in blue in Figure 26.4. Second, failure in coupling between autonomic output (blue dotted line, #1.) and events associated with emotional processing (blue solid lines #2. and #3.) are also shown. Subsequent alterations of outputs to the facial nucleus (motor nucleus of VII), basolateral and basal accessory nuclei of the amygdala (BL/BA), ventral tegmental area, lateral hypothalamus, periaqueductal gray (PAG) from ACC and to the BL/BA, nucleus accumbens, lateral hypothalamus, PAG, pontine nuclei, and the spinal cord from aMCC are shown with dashed lines. Finally, the flow of information into some subregions with apparently normal blood flow is also postulated for daMCC and sACC. One of the main outcomes of this information-processing model is that emotion is not processed as a singular and integrated construct as in holistic models but rather in small submodal codes that can be handled by aggregates of neurons. Although emotion, like pain, might be perceived as psychologically uniform, it appears unlikely that the brain can process such complex information as a single coded entity. The behavioral impairments in psychopathic individuals involving some but not all emotional functions support this view.

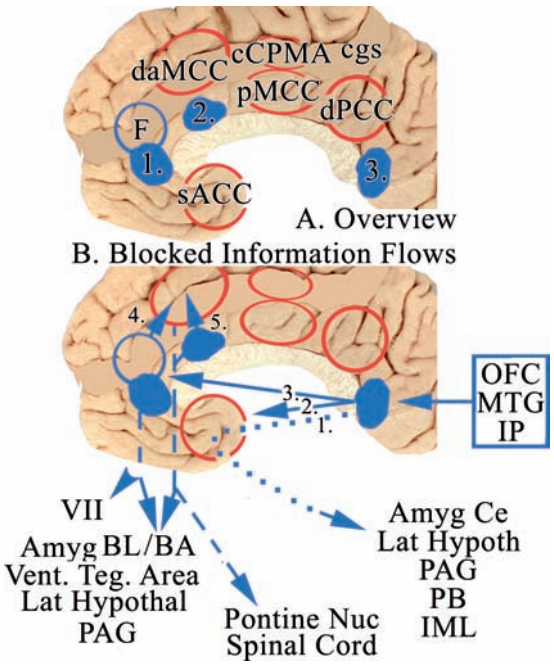

Fig. 26.4 A. Co-registration of the three sites of reduced blood flow (solid blue from Kiehl et al., 2001, and the subregion associated with the face and conscious emotional awareness F) to a postmortem case in which the subregions were identified histologically (red ovals for subregions of unchanged blood flow). B. Reduced blood flow is one reason to postulate disrupted processing in particular circuits shown with blue arrows: solid lines are cingulate sensory access from neocortical areas; dashed lines are impaired outputs; dotted line emphasizes disruption of the sensory-autonomic coding system through the subgenual anterior cingulate cortex (sACC) to autonomic regulatory structures.

Serial processing of emotion through cingulate cortex

Studies of cingulate functions, subregional localizations, and connections lead to the view that valenced and context-dependent sensory information must be processed through a series of intracingulate connections via a six-stage processing scheme that begins with entry of such sensory information to the vPCC as discussed in Chapter 13. It is an interesting fact that psychopaths have the sensory capability to identify some but not all differences in facial expression (Deeley *et al.*, 2006). Activity in the fusiform gyrus, a region involved in facial recognition and likely monitored by vPCC, shows an increase in BOLD signal when observing happy faces versus controls, while the activity in this region was reduced while observing fearful faces. Thus, a precursor signal for negative facial expression precedes the inactivation noted in valence coding of self-relevant information in vPCC. Indeed, the impairment in empathy, discussed above, may link to an early stage in facial distress cues that do not enter cingulate cortex. The concern here is the subsequent processing failure in cingulate cortex itself.

It is at the vPCC node in the six-stage circuit that context plays a particularly critical role in selecting among sensory information for coding in the cingulate gyrus and this leads to the view that emotion is processed according to submodalities. An important aspect of emotional relevance is the context in which an object or event occurs. The vPCC is active during context-dependent processing of visual stimuli (Bar & Aminoff, 2003). Although these investigators used the generic concept of retrosplenial cortex, the areas they activated were perisplenial and included both retrosplenial areas 29 and 30 and vPCC areas v23ab. Context from the visual system and emotional valence from sACC combine in vPCC for transmission of self-relevant objects and events into the cingulate gyrus for emotion-relevant processing and movements. As valences are assigned in ACC, the ACC stores those memories (George *et al.*, 1995, 1996; Mayberg *et al.*, 1999), regulates autonomic activity associated with emotion, and no non-emotion activity drives it (Vogt *et al.*, 2003). In this framework, the reciprocal connection between vPCC and ACC is very important. An important hypothesis for vPCC function suggests that it selects among emotion and non-emotion events and assesses their self

relevance with sensory context and interactions with ACC before further processing ensues. Thus, vPCC is a gateway for multisensory information processing and entry into the cingulate gyrus for processing as emotionally relevant information.

The pivotal role of vPCC/RSC impairment to psychopathic processing functions is critical because information for decision making, empathy, and language are disrupted at this pivtal node in the connection series to rostral parts of cingulate cortex. Indeed, the failure of pACC to activate along with vPCC almost guarantees that appropriate coding of context and significance cannot occur in the psychopathic cingulate cortex. The consequences of this organization in terms of cingulate information processing (Vogt *et al.*, 2003, 2006) are reflected in the following specific observations.

First, the link between emotion and autonomic output regulation does not occur uniformly throughout the cingulate gyrus but in ACC, with an emphasis on sACC, where direct projections to autonomic structures are well established as reviewed in Chapter 10. As shown in Figure 26.2, Meyer-Lindenberg *et al.* (2006) showed a vulnerability site in individuals with the short allele of monoamine oxidase A gene that is correlated with impulsive aggression in this region. As Figure 26.3 of the work of Kiehl *et al.* (2001) shows that sACC might have normal levels of blood flow in psychopaths, one must attribute the autonomic failure to pACC, the amygdala or their interaction.

Second, emotion-associated activity in PCC is extensive (Fig. 26.1) but, in contrast to ACC, there are many studies that show that non-emotional stimuli also activate this region (white dots in the figure). It is likely that this region is constantly engaged in surveying for context-relevant information via reciprocal connections with ACC where emotional information is stored. The vPCC appears to serve as a gateway whereby emotional information enters the cingulate gyrus based on valence and context coding for use in self-relevant processing and ultimate guidance of choices and premotor output.

Context-dependent sensory afferent failure: vPCC

Figure 26.4 shows the vPCC site (#3.) in blue that is inactivated in psychopaths as well as the correlated clusters of interest in a basal glucose metabolism study (Vogt *et al.*, 2006). These latter regions include the inferior parietal, orbitofrontal, and middle temporal cortices. All of these inputs are in blue as the entry of multisensory information via them into the cingulate gyrus is presumably blocked in the psychopathic brain. This information block further interferes with activity in intracingulate circuits to both divisions of ACC. The projection through sACC is emphasized with a dotted blue line that points to a key disruption in direct coupling of self-relevant information to the autonomic control division of sACC. Further disruptions of inflow into the rostral CPMA are via intracingulate inputs from the pACC face region (pathway #4.) and the gyral surface of aMCC (pathway #5.). Thus, self-relevant, valenced, and context-dependent information fails to enter the cingulate gyrus and does not guide cingulate motor outflow as proposed for normal individuals in Chapter 13. This fact in itself could account for a large part of why empathetic responses are weak in the psychopathic brain. One of the pivotal consequences of impaired self-relevant, cingulate input and flow through is disruption of cingulate output systems.

Altered output functions

One of the over-riding perspectives throughout this book is the pivotal role of ACC and MCC in regulating autonomic and skeletomotor outputs, respectively. Given the pivotal role of cingulate cortex in behavior, therefore, the specific impairments observed in the psychopathic brain can have devastating implications. Figure 26.3 shows that the superior parietal inputs reported previously (Vogt *et al.*, 2006; Chapter 13) are intact and drive the dPCC and caudal CPMA. Indeed, the intracingulate circuitry is also likely 'intact' as shown with the paired arrows (pathways #1., #2., and #3.). At this point it is a noteworthy fact that the rostral and caudal CPMAs have different functions and these assist in understanding the substrate of impaired skeletomotor function in psychopaths; that is, the over focus on short-term goals and inability to match behavior to achieve long-term goals. As discussed in Chapter 5, the rostral CPMA (also termed the rostral cingulate motor area) has long lead times between neuron discharges and coordinated movements, while neurons in the caudal CPMA have very short delays and are more easily driven by passive rather than active joint movements. Thus, the intact caudal CPMA to the exclusion of an adequately controlled rostral CPMA could account for the short-term focus of psychopathic behavior. It is also interesting that the daMCC, which is critically involved in Theory of Mind functions, is relatively intact and could provide a substrate for partial understanding of other's internal state and a limited use of this information to accomplish personal goals. The outputs of sACC and pMCC are summarized in Figure 26.5. It is unclear to what extent these outputs are disordered in the psychopathic brain, although they are certainly vulnerable.

One approach to evaluating impairments in psychopathic information processing is to consider cortical influences on autonomic regulation. The MCC and dorsomedial prefrontal cortex have autonomic regulatory functions that are mediated by direct neural

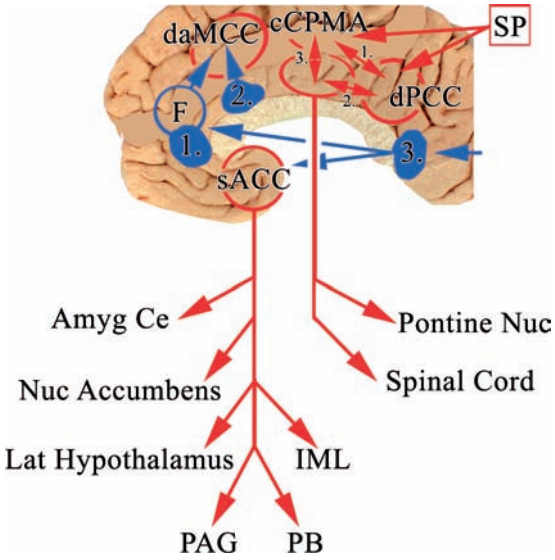

Fig. 26.5 Inflow from the superior parietal cortex (SP), intracingulate projections (#1., #2., #3.) and specific outputs to subcortical structures (vertical arrows) appear to be 'intact' as coded here in red. 'Intact' is used with reservation because the balance of long-term outputs from the rostral rostral cingulate premotor area (CPMA) is lacking and this drive of limbic motor systems can lead to an unregulated autonomic and skeletomotor outputs.

connections with subcortical visceromotor centers such as the lateral hypothalamus and periaqueductal gray as discussed in detail in Chapter 15. Lane *et al.* (2001) have observed a positive correlation between the high frequency, vagal component of heart rate variability and activity in the medial prefrontal area 10. Thus, these centers, when activated in conjunction with conscious emotional experience, have a tonic inhibitory effect mediated through the dorsal motor nucleus of the vagus, the nucleus ambiguus, and the nucleus of the solitary tract as discussed in Chapter 10.

Two other studies have examined the neural correlates of vagal tone during the performance of stressful cognitive tasks. Gianaros *et al.* (2004) observed a positive correlation between high-frequency-heart rate variability and sACC activity during the n-back memory task. Matthews *et al.* (2004) observed a positive correlation between this same parameter during the Counting Stroop task performed outside the scanner and sACC activity during the execution of the Counting Stroop task in the scanner. Differences in the correlation between vagal tone and the specific locus of brain activity may be due to differences in the tasks performed in the studies as the emotional stress in the latter two studies probably occurred as background feelings. Given the dense interconnections between prefrontal cortex and the sACC and that the latter structure has the most dense projections to subcortical autonomic centers such as the dorsal motor nucleus of the vagus and nucleus of the solitary tract, the sACC appears to be a final common pathway from the frontal lobe to regulate autonomic outputs.

Summary of the Role of Cingulate Cortex in the Functional Anatomy of Psychopathic Behavior

We are now in a position to link together the behavioral observations in psychopathy – the deficits in emotion-related language, negative-valenced facial responses, orienting, and emotional impairments – with the clinical behavioral and affective features of psychopathy through consideration of the underlying functional neuroanatomy. We have discussed the distinction between implicit and explicit emotional processes and the concept that the latter is modified with development. Specifically, through the use of language and other modes of symbolic representation as with facial expression, the capacity to experience discrete feelings in a complex and differentiated way develops over time. This capacity determines the extent to which a person can feel emotions oneself and appreciate the emotions that others have as well. One conclusion that we can reach is that psychopaths have impaired development of emotional awareness and the disruption in information processing in the cingulate gyrus remains throughout the life of an adult psychopath.

A second conclusion is that the behavioral and emotional features of psychopathy are inter-related. As we have seen above, the transmission of affective information from subcortical to cortical structures in the cingulate gyrus is associated both with the conscious instantiation of feeling AND the top-down modulation of visceromotor and skeletomotor expressions of emotion. Lower emotional awareness or emotional intelligence is characterized by impulsive behavior, an inability to delay gratification, and a tendency for action rather than contemplation. From this perspective, we can appreciate how deficits in vPCC, pACC, and aMCC may explain many of the clinical features of psychopathy.

It appears that there are two fundamental problems in the brain of psychopaths: an under-functioning amygdala and a deficit in those brain structures mediating the capacity for symbolic representation of emotion. These deficits will limit both implicit and explicit processes and the evidence from startle, memory, and imaging paradigms all suggest a primary deficit in amygdala functioning. As the amygdala plays a key role in emotional responses to both interoceptive and exteroceptive stimuli, and as it has substantial and reciprocal connections with the ACC, we can conclude

that psychopaths are deficient in their ability to generate emotional responses. Chapter 9 presents the case for ACC mediating amygdalar activity during extinction associated with faces coding for surprise. Impairment of pACC and aMCC functions in the psychopathic brain, therefore, suggests a loss of cortical control over the amygdala.

With regard to explicit processing, the emotion-related language impairment in psychopathy will limit the function of the vPCC as the gateway to other subsectors of the cingulate gyrus. The vPCC is involved in evaluating the personal or emotional significance of exteroceptive information. One may speculate that this is a key structure that participates in the language-driven development of the emotional schemata fundamental to the development of emotional awareness. The vPCC is densely connected to the sACC, and the two together evaluate the emotional significance of stimuli, the output of which is fed to autonomic, skeletomotor, and amygdalar structures. To the extent that this mechanism is deficient in evaluating the emotional significance of incoming information, it is to be expected that psychopaths fail to have insight into their own emotional experience as well as that of others. The cingulate-mediated failure of empathy must be a key to the relationships, behaviors and crimes of the psychopath.

References

Aitken, P. G. (1981) Cortical control of conditioned and spontaneous vocal behavior in rhesus monkeys. *Brain Lang 13*: 171.

Bar, M., & Aminoff, E. (2003) Cortical analysis of visual context. *Neuron 38*: 347–358.

Birbaumer, N., Veit, R., Lotze, M., Erb, M., Hermann, C., Grodd, W., & Flor, H. (2005) Deficient fear conditioning in psychopathy. *Arch Gen Psychiatry 62*: 799–805.

Blair, R. J. R. (2005) Applying a cognitive neuroscience perspective to the disorder of psychopathy. *Develop Psychopathol 17*: 865–891.

Botvinick, M., Jha, A. P., Bylsma, L. M., Fabian, S. A., Solomon, P. E., & Prkachin, K. M. (2005) Viewing facial expressions of pain engages cortical areas involved in the direct experience of pain. *NeuroImage 25*: 312–319.

Bush, G., Vogt, B. A., Holmes, J., Dale, A. M., Greve, D., Jenike, M. A., & Rosen, B. R. (2002) Dorsal anterior cingulate cortex: a role in reward-based decision-making. *Proc Natl Acad Sci USA 99*: 523–528.

Cleckley, H. (1976) *The Masl of Sanity* (5th ed.). St Louis, MO: Mosby.

Damasio, A. R. (1994) *Descartes' Error: Emotion, Reason and the Human Brain*. New York: G. P. Putnam.

Day, R., & Wong, S. (1996) Anomalous perceptual asymmetries for negative emotional stimuli in the psychopath. *J Abnorm Psychol 105*: 648–652.

Deeley, Q., Daly, E., Adze, S. S., Tunstall, N., Mezey, G., Beer, D., Apathy, A. A., Robertson, D., Giampieto, V., Brammer. M. J., Clarke, A., Dowsett, J., Fahy, T., Phillips, M. L., & Murphy, D. G. (2006) Facial emotion processing in criminal psychopathy. *Br J Psychiatry 189*: 533–539.

Dikman, Z. V., & Allen, J. J. B. (2000) Error monitoring during reward and avoidance learning in high- and low-socialized individuals. *Psychophysiology 37*: 43–54.

Farthing, G. W. (1992) *The Psychology of Consciousness*. Englewood Cliffs, NJ: Prentice Hall.

Gabriel, M. (1993) Discriminative avoidance learning: a model system. In: B. A. Vogt, M. & Gabriel, (Eds), *Neurobiology of Cingulate Cortex and Limbic Thalamus* (pp. 478–523). Boston: Birkhäuser Boston, Inc.

Gazzaniga, M., Ivry, R. B., & Mangun, G. R. (2002) Cognitive neuroscience—The Biology of the Mind. New York: Norton.

George, M. S., Ketter, T. A., Parekh, P. I., Herscovitch, P., & Post, R. M. (1996) Gender differences in regional cerebral blood flow during transient self-induced sadness or happiness. *Biol Psychiatry 40*: 859–871.

George, M. S., Ketter, T. A., Parekh, P. I., Horwitz, B., Herscovitch, P., & Post, R. M. (1995) Brain activity during transient sadness and happiness in healthy women. *Am J Psychiatry 152*: 341–351.

Gianaros, P., Van Der Veen, F., & Jennings, J. (2004) Regional cerebral blood flow correlates with heart period and high-frequency heart period variability during working-memory tasks: implications for the cortical and subcortical regulation of cardiac autonomic activity. *Psychophysiology 41*: 521–530.

Goleman, D. (1995) *Emotional Intelligence*. New York: Bantam Books.

Hare, R. D. (1991) *The Hare Psychopathology Checklist-Revised (PCL-R)*. Toronto, Ontario: Multi-Health Systems.

Hare, R. D. (1993) *Without Conscience: the Disturbing World of the Psychopaths Among Us*. New York: Pocket Books.

Hariri, A. R., Mattay, V. S., Tessitore, A., Fera, F., & Weinberger, D. R. (2003) Neocortical modulation of the amygdala response to fearful stimuli. *Biol Psychiatry 53*: 494–501.

Jackson, P. L., Meltzoff, A. N., & Decety, J. (2005) How do we perceive the pain of others? A window into the neural processes involved in empathy. *NeuroImage 24*: 771–779.

Kiehl, K. A. (2006) A cognitive neuroscience perspective on psychopathy: evidence for paralimbic system dysfunction. *Psychiatry Res 142*: 107–128.

Kiehl, K. A., Liddle, P. F., & Hopfinger, J. B. (2000) Error processing and the rostral anterior cingulate: an event-related fMRI study. *Psychophysiology 37*: 216–223.

Kiehl, K. A., Smith, A. M., Hare, R. D., Mendrek, A., Forster, B. B., Brink, J., & Liddle, P. F. (2001) Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. *Biol Psychiatry 50*: 677–684.

Kuperberg, G. R., Sitnikova, T., & Lakshmanan, B. M. (2008) Neuroanatomical distinctions within the semantic system during sentence comprehension: evidence from functional magnetic resonance imaging. *NeuroImage 40*: 367–388.

Lane, R. (2008) Neural substrates of implicit and explicit emotional processes: a unifying framework for psychosomatic medicine. *Psychosom Med 70*: 213–230.

Lane, R., Fink, G., Chua, P., & Dolan, R. (1997) Neural activation during selective attention to subjective emotional responses. *NeuroReport 8*: 3969–3972.

Lane, R., Reiman, E., Ahern, G., & Thayer, J. (2001) Activity in medial prefrontal cortex correlates with vagal component of heart rate variability during emotion. *Brain Cogn 47*: 97–100.

LeDoux, J. E. (1996) *The Emotional Brain*. New York: Simon and Shuster.

Maddock, R. J.U., & Buonocore, M. H. (1997) Activation of left posterior cingulate gyrus by the auditory presentation of threat-related words: an fMRI study. *Psychiatry Res 75*: 1–14.

Matthews, S. C., Paulus, M. P., Simmons, A. N., Nelesen, R. A., & Dimsdale, J. E. (2004) Functional subdivisions within anterior cingulate cortex and their relationship to autonomic nervous system function. *Neuroimage 22*: 1151–1156.

Mayberg, H. S., Liotti Manan, S. K., McGinnis, S., Mahurin, R. K., Jerabek, J. A., Tekell, J. L., Martin, C. C., Lancaster, J. L., & Fox, P. T. (1999) Reciprocal limbic-cortical function and negative mood; converging findings in depression and normal sadness. *Am J Psychiatry 156*: 675–682.

Meyer-Lindenberg, A., Buckholz, J. W., Kolachana, B., Hairi, A. R., Pezawas, L., Blasi, G., Wabnitz, A., Hones, R., Verchinski, R., Callicott, J. H., Egan, M., Mattay, V., & Weinberger, D. R. (2006) Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proc Natl Acad Sci USA 103*: 6260–6274.

Mohr, C., Binkofsli, F., Erdmenn, C., Büchel, C., & Helmchen, C. (2005) The anterior cingulate cortex contains distinct areas dissociating external from self-administered painful stimulation: a parametric fMRI study. *Pain 114*: 347–357.

Morrison, I., & Downing, P. E. (2007) Organization of felt and seen pain responses in anterior cingulate cortex. *NeuroImage 37*: 642–651.

Müller, J. L., Sommer, M., Wagner, V., Lange, K., Taschler, H., Röder, C. H., Schuierer, G., Klein, H. K., & Hajak, G. (2003) Abnormalities in emotion processing within cortical and subcortical regions in criminal psychopaths: evidence from a functional magnetic resonance imaging study using pictures with emotional content. *Biol Psychiatry 54*: 152–162.

Müller-Preuss, P., Newman, J. D., & Jürgens, U. (1980) Anatomical and physiological evidence for a relationship between the 'cingular' vocalization area and the auditory cortex in the squirrel monket. *Brain Res 202*: 307.

Nakata, H., Sakamoto, K., Ferretti, A., Perrucci, M. G., Gratta, C. D., Kakigi, R., & Romani, G. L. (2008) Somato-motor inhibitory processing in humans: an event-related functional MRI study. *NeuroImage 39*: 1858–1866.

Patrick, C. J., Cuthbert, B. N., & Lang, P. J. (1994) Emotion in the criminal psychopath: fear image processing. *J Abnorm Psychol 103*: 523–534.

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002) Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage 16*: 331–348.

Raichle, M. E., Fiez, J. A., Videen, T. O., MacLeod, A.-M., Pardo, J. V., Fox, P. T., & Peterson, S. E. (1994) Practice-related changes in human brain functional anatomy during nonmotor learning. *Cerebral Cortex 4*: 8–26.

Raine, A., Lencz, T., Bihrle, S., LaCasse, L., & Colletti, P. (2000) Reduced prefrontal grey matter volume and reduced autonomic activity in antisocial personality disorder. *Arch Gen Psychiatry 57*: 119–127.

Sterzer, P., Stadler, C., Krebs, A., Kleinschmidt, A., & Poustka, F. (2005) Abnormal neural responses to emotional visual stimuli in adolescents with conduct disorder. *Biol Psychiatry 57*: 7–15.

Vogt, B. A. (2005) Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci 6*: 533–544.

Vogt, B. A., & Barbas, H. (1988) Structure and connections of the cingulate vocalization region in the rhesus monkey. In J. D. Newman (Ed.), *The Physiological Control of Mammalian Vocalization* (pp. 203–225) New York: Plenum Press.

Vogt, B. A., Berger, G. R., & Derbyshire, S. W.J. (2003) Structural and functional dichotomy of human midcingulate cortex. *Eur J Neurosci 18*: 3134–3144.

Vogt, B. A., Derbyshire, S. W. J., & Jones, A. K. P. (1996) Pain processing in four regions of human cingulate cortex localized with coregistered PET and MR imaging. *Eur J Neurosci 8*: 1461–1473.

Vogt, B. A., & Pandya, D. N. (1987) Cingulate cortex of rhesus monkey. II. Cortical afferents *J Comp Neural 262*: 271–289.

Vogt, B. A., Vogt, L. J., & Laureys, S. (2006) Cytology and functionally correlated circuits of posterior cingulate areas. *NeuroImage 29*: 452–466.

Werner, H., & Kaplan, B. (1963) *Symbol Formation: an Organismic-Developmental Approach to Language and the Expression of Thought*. New York: Wiley.

Werner, H. (1957) The concept of development from a comparative and organismic point of view. In D. B. Harris (Ed.), *The Concept of Development: an Issue in the Study of Human Behavior*. Minneapolis: University of Minnesota Press.

Williams, Z. M., Bush, G., Rauch, S. L., Cosgrove, G. R., & Eskandar, E. N. (2004) Human anterior cingulate neurons and the integration of monetary reward with motor responses. *Nat Neurosci 7*: 1370–1375.

Yang, Y., Raine, A., Lencz, T., Bihrle, S., LaCasse, L., & Colletti, P. (2005) Volume reduction in prefrontal grey matter in unsuccessful criminal psychopaths. *Biol Psychiatry 57*: 1103–1108.