CHAPTER 11

The Cingulate Cortex as Organizing Principle in Neuropsychiatric Disease

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Chapter contents

Humans have a behavioral repertoire that far exceeds that of even our closest animal relatives. Humans are unsurpassed in their ability to monitor, adapt to, and modify their environment which includes not only the natural world but also the complex social structures that characterize the human species. Thus, while every animal can adapt to changes in the environment (and many animals operate in social systems), humans are unique in the degree to which they can problem-solve and engage in multiple complex goal-oriented behaviors in an ever-changing natural (and man-made) environment.

These unique behavioral and adaptive qualities have been traditionally associated with the much larger frontal lobe of the human brain, which includes greatly expanded prefrontal and anterior cingulate cortices. These regions have extensive connections throughout the brain that implicate them in nearly all neurological systems (motor, sensory, cognitive, emotional, autonomic, and homeostatic/drive processes). While its role in each of these systems is not completely understood, the prefrontal cortex appears to be important for the integration of multiple streams of information about the internal and external environment. Selection among internally represented "goals" in the process of determining a course of action appears to result from decisions made in cingulate cortex based on information flow between these connected structures. The operations of the prefrontal region are referred to as executive functions that allow humans to have their unique behavioral and adaptive capabilities. However, these same processes, when dysfunctional, can also

generate unique behavioral and adaptive disturbances.

When adaptive disturbances occur in functions associated with neural processes with a clear underlying neuroanatomy (e.g., language, cognition, and/or sensorimotor integration), they have classically fallen under the purview of behavioral neurology. However, when such disturbances affect an individual's experience of and ability to monitor behavior and emotions, processes with a less well-described neurobiology at present, they have been referred to as mental or psychiatric disease. This classification recognizes the effect these disturbances have on the substance of what it means to be human, that is, disturbance of the *psyche* or "mind," but also suggest a difference in etiology and biology. As the study of the mechanisms and neuroanatomy of psychiatric disease has progressed, however, this division between neurology and psychiatry has become more semantic than pathophysiologic. In short, it is likely that psychiatric disease generally results from a neuronal disturbance located in or involving connections with the prefrontal cortex, via its heavy projections through anterior cingulate cortex (ACC), to a distributed network of brain regions.

As the neurobiological investigation of psychiatric disease has progressed, the importance of the cingulate cortex in the pathophysiology of mental illness has been consistently demonstrated. Specifically, the critical role of the ACC has been clearly identified for a number psychiatric illnesses based on structural and functional neuroimaging. While these data do not suggest that the cingulate cortex is the "source" of psychiatric illness *per se*, it is strongly suggested that the various subdivisions of the cingulate cortex are key modulators of function within various distinct but integrated neurological systems involved in these diseases. Further, it also appears the cingulate cortex may provide a central common pathway for integrating and connecting various nodes of neural networks that underlie regulation and integration of mood, thought, and behavior.

Goals of this chapter

In this chapter, we review the phenomenology of several common psychiatric diseases and highlight how phenomenological variability within and between diagnoses point to the involvement of multiple, integrated neurological systems in the pathophysiology of mental illness. Based on this, we suggest that neural network models provide an excellent framework for understanding and further exploring the neurobiology of psychiatric disease. Using a proposed neural network model for psychiatric disease, we highlight the unique role of the cingulate gyrus in the normal and abnormal regulation of mood, thought, and behavior. This is then related to data (explored in detail elsewhere in this book) supporting the role of the cingulate cortex in various psychiatric illnesses. We conclude that the cingulate gyrus serves as a critical node in neural networks involved in psychiatric health and disease and suggest further investigation of the cingulate cortex and its integral role in these networks as a path for enhancing our understanding of psychiatric disease as a neurobiological disturbance. The specific goals of this chapter are to:

1. Emphasize the need for sophisticated models of psychiatric diseases based on the phenomenological similarities and differences within and between these illnesses.
2. Present a model of neuropsychiatric disease based on a developing model for depression.
3. Highlight the critical role of the cingulate gyrus in this model and the important role different subdivisions play in various functions related to the regulation of mood, thought, and behavior.
4. Discuss the role of the cingulate gyrus in neuropsychiatric diseases with an emphasis on the primary role of different subdivisions in specific illnesses.

Phenomenology of Neuropsychiatric Disease

The diverse phenomenology of psychiatric disease suggests a neurobiology involving multiple distinct but interrelated neural systems. While psychiatric illnesses are characterized by "mental" disturbances including mood, thought, and behavioral abnormalities, these conditions also involve disruption of multiple adaptive and homeostatic processes such as sleep, drive, appetite, autonomic function, and sensorimotor activity. Mood disorders such as depression, for example, are characterized by prominent disturbances of emotion and cognition but are also associated with dysfunction of motor systems (e.g., slowing of motor responses), energy, motivation, sleep, and appetite. Anxiety disorders are defined by the presence of emotional anxiety and intrusive/ruminative thoughts but also include disturbances of sleep, appetite, and autonomic functioning. Schizophrenia and other psychotic disorders involve disturbances of thought and emotional regulation, but also involve disruption of motor function and integration of sensory stimuli. Alzheimer's Dementia (AD) is defined by cognitive disturbance but is commonly associated with behavioral abnormalities similar to those seen in other neuropsychiatric conditions (e.g., apathy, disinhibition, psychosis, depression), as well as sleep and appetite disturbances and psychomotor activity changes. In children, attention-deficit/hyperactivity

disorder (ADHD) is characterized by a disturbance in attention as well as disruptions in psychomotor activity and emotional regulation.

Beyond this, there can be significant symptomatic differences within a single mental illness across subjects. One patient with Major Depressive Disorder (MDD), for example, may have decreased sleep, decreased appetite, decreased mood reactivity, and dramatically slowed psychomotor functioning (i.e., "melancholic depression"), while another may show opposite changes in sleep, appetite, activity, and emotional reactivity (i.e., "atypical depression") (American Psychiatric Association 2000). Similar symptomatic variations are seen in schizophrenia (e.g., paranoid versus catatonic subtypes), obsessive–compulsive disorder (OCD; e.g., with and without comorbid tics) and generalized anxiety disorder (with some patients showing a predominance of "psychic" anxiety such as worry, ruminations, irritability while others experience mostly "somatic" anxiety such as tension, gastrointestinal distress, sleep disturbance).

Further, there are clear differences in treatment response among patients with the same psychiatric disease. Some patients with depression respond well to psychotherapy (Beck, 1991), while others appear to require some form of pharmacologic or other somatic treatment. Among patients receiving somatic interventions, some respond to treatments that modulate serotonergic function while others only seem to respond to treatments targeting multiple neurotransmitter systems; others only achieve an antidepressant response with interventions with widespread neurophysiological effects (e.g., electroconvulsive therapy) (Thase and Rush, 1997). In schizophrenia, most patients with predominant "positive symptoms" (i.e., hallucinations and delusions) respond well to treatments that block dopamine receptor binding (Johnstone *et al*., 1978); however, "negative" symptoms (such as poor motivation, cognitive disturbances, and poor social relatedness) appear less responsive to dopaminergic modulation (Carpenter, 1995). Most patients with OCD show significant symptom reduction with medications that modulate serotonergic transmission (Vaswani *et al*., 2003), but few patients achieve full remission with such treatments (Pallanti *et al*., 2002).

In addition to variability in symptoms and treatment response within a particular psychiatric disease, there is significant overlap between conditions. Depressed patients may experience significant anxiety without meeting diagnostic criteria for a distinct anxiety disorder; some patients may become psychotic during their mood episodes. Psychotic patients may experience depressive symptoms; alternatively, patients with schizophrenia may present with apathy, amotivation, and low energy (symptoms which overlap with the common presentation of depression) without meeting criteria for a mood episode. Other patients may meet criteria for schizoaffective disorder which commonly presents with distinct major mood episodes superimposed on a chronic psychotic condition. Patients with certain personality disorders may experience mood, thought, and behavior disturbances that overlap with multiple other diagnostic entities without meeting formal criteria for any of them. In addition to symptomatic similarities between different illnesses, treatments that work for one condition are often useful in treating the same or similar symptoms in another condition. Serotonin reuptake inhibitors have efficacy in treating depression, anxiety, and mood lability in some neurologic conditions. Atypical neuroleptics have shown efficacy for treating schizophrenia and bipolar mania; these medications may also be useful for treatment-resistant depression and anxiety disorders.

In considering this variability and similarity within and among psychiatric illnesses, it is important to recognize that psychiatric diseases are *syndromal* conditions comprised of multiple symptoms that typically "track together". In the absence of a clear neurobiological basis for a particular condition, such a classification is useful for diagnostic and research purposes. However, there is no reason to expect that a particular psychiatric disease (based on this classification system) will necessarily correspond to a specific neurobiological disturbance. Rather, it is more likely that each illness will be associated with multiple abnormalities in several neural systems, with certain abnormalities taking predominance and resulting in the "core" symptoms of the illness. These same neural systems may be involved in a number of psychiatric diseases, but the degree to which one or another system is disturbed determines the phenomenological expression in a particular individual and the diagnosis assigned.

Given this, distinct unidirectional neurochemical or neuroanatomical models are clearly inadequate for describing the neurobiology of psychiatric disease. While the monoaminergic neurotransmitter systems have been implicated strongly in multiple (if not all) psychiatric illnesses, no single disruption within these systems fully explains the phenomenology of any particular illness. This is not surprising since the monoamines likely function within a larger system that involves other neuromodulators (e.g., glutamate, GABA, CRF, substance P, and immune factors), key second messenger systems and other intracellular processes. Further, it is likely that important *where* neuromodulation occurs within the brain. A growing database from autopsy, brain lesion, and neuroimaging studies implicate multiple brain regions, mostly involving frontal cortical and subcortical regions, in the pathophysiology of nearly all psychiatric diseases. These brain regions

often have significant overlap between illnesses; for example, the prefrontal cortex and hippocampus have been implicated in depression, schizophrenia and several anxiety disorders. Consistent with the phenomenology of psychiatric diseases, these neuroanatomical findings show significant similarities between illnesses and striking differences within particular illnesses. Thus, nuances in anatomical variability and patterns of connectivity may be critical in determining symptomatic differences and differential response to treatment. Useful models of psychiatric disease will need to appropriately account for these findings.

Neural Network Models of Neuropsychiatric Disease

Neural network models offer one approach for developing appropriately sophisticated models of neuropsychiatric disease. Neural network modeling is based on the premise that widely distributed brain regions are structurally and functionally connected such that the coordinated activity of these brain regions *as a system* is required for normal regulation of mood, thought, behavior, sensorimotor, autonomic, and drive functions. In neural network models, less emphasis is placed on how a particular region functions in isolation, but rather on how several brain regions function together. Rather than specifically attempting to model a particular psychiatric disease, neural network models attempt to model how the brain is involved in specific processes (e.g., affective regulation versus motivation) and how each of these might be more or less disturbed in a particular illness (Phillips *et al.*, 2003a, 2003b). This information is then applied back to disease models to test the findings and further extend the model. Neural network models are useful for explaining the multi-dimensional phenomenology of neuropsychiatric disease; further, these models may also be useful in guiding treatment development. Although findings from animal studies and human "lesion" cases (e.g., psychiatric complications of stroke) have assisted the development of neural network models in psychiatry, advances in neuroimaging have played an increasingly dominant role.

The application of neural network modeling to Parkinson's Disease (PD) provides a good example of the usefulness of this approach in the study and treatment of neuropsychiatric conditions. In PD, loss of dopaminergic neurons in the substantia nigra results in decreased regulation of striatal-thalamic motor pathways which leads to the complex motor symptoms of the illness (tremor, bradykinesia, rigidity); thus, dysfunction of a single node in the network (substantia nigra) can result in diverse functional disturbances via downstream effects throughout the network. While function can, to some degree, be restored in PD patients by increasing dopaminergic tone throughout the system, not all patients respond well to such treatment and many develop treatment limiting side effects. However, based on a neural network understanding of PD, symptomatic improvements can also be achieved by modulating function of other critical nodes within the operative network. To this end, specific surgical interventions, such as lesioning of the globus pallidus (Vitek *et al.*, 2003) or modulation of the subthalamic nucleus or internal globus pallidus through deep brain stimulation (The Deep Brain Stimulation for Parkinson's Disease Study Group 2001) can result in dramatic improvements in motor functioning in PD patients. Thus, by conceptualizing PD within a neural network framework as opposed to a disease limited to decreased dopamine in the basal ganglia, the symptomatology is better explained and improved treatment strategies have been developed.

An example of a proposed neural network model in psychiatry is shown in Figure 11.1. This model was largely developed from investigations in depression (discussed in detail in Chapter 24) and provides a framework for a more general discussion of neural systems involved in regulation of mood, thought, and behavior. The location and functional classification of brain regions within this model are based primarily on structural and functional neuroanatomical data derived from human and animal studies. The brain regions depicted in the top of the figure include dorsolateral portions of the prefrontal cortex, premotor areas of the frontal cortex, association cortices in the parietal cortex, hippocampus and portions of the anterior, middle and posterior cingulate cortex. These brain regions have been most consistently implicated in sensorimotor integration, attention, memory, and other cognitive functions, and they are largely externally focused and receive little direct input about the organism's internal state. Therefore, these areas may serve to obtain and integrate information about the external environment and to control the behavior of the organism in the external world. The brain regions shown in the bottom of the figure include the subgenual cingulate cortex, insula, hypothalamus, and brain stem nuclei (e.g., dorsal raphé nuclei, locus coeruleus, and ventral tegmental area). These areas primarily serve to regulate autonomic function and other homeostatic processes (such as sleep, appetite, and libido); they also receive, integrate, and respond to information about the internal milieu; as such, these brain areas are largely internally focused receiving little direct information about the external world. By providing information about the internal state, these brain regions literally convey the "feelings" of emotion (Damasio, 1996). The middle brain regions in the figure include the ventromedial prefrontal cortex, orbitofrontal cortex, pregenual

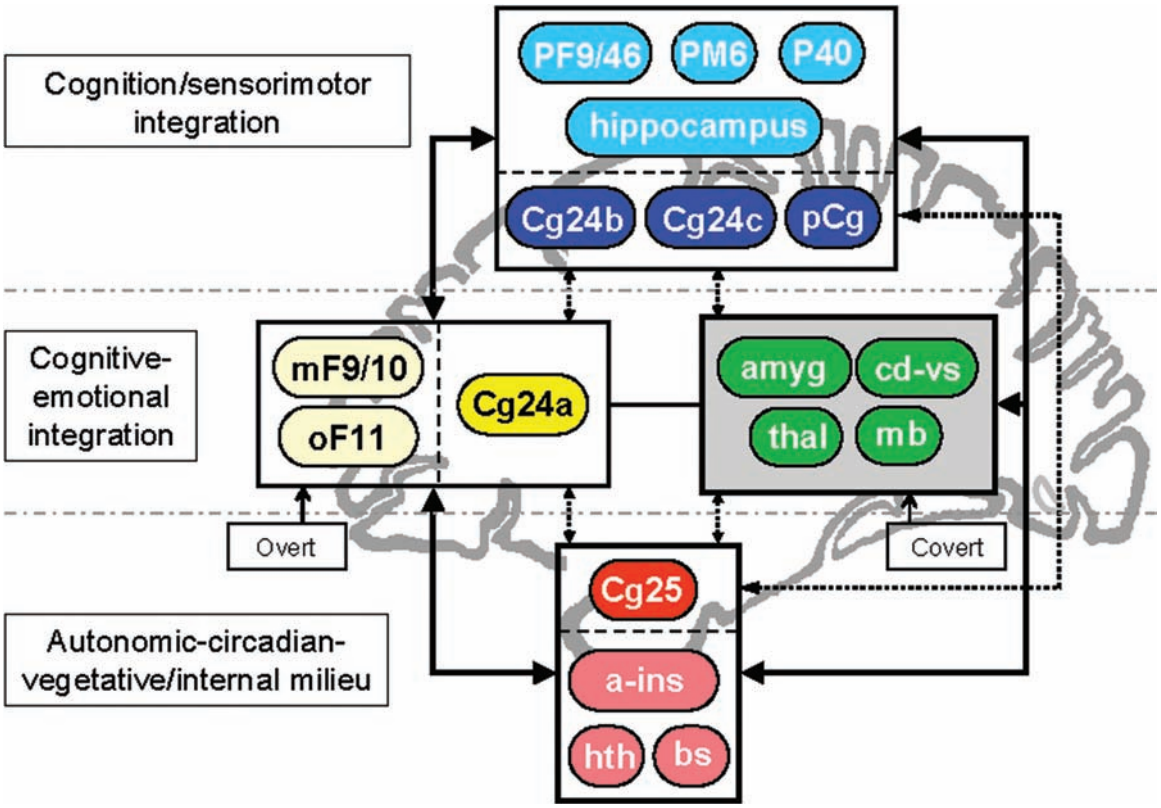

Fig. 11.1 A proposed neural network model of mood regulation. PF9/46, dorso-lateral prefrontal cortex; PM6, premotor cortex; P40, parietal cortex; Cg24b/Cg24c, anterior midcingulate cortex; pCg, posterior cingulate cortex; mF9/10, medial prefrontal cortex; oF11, orbitofrontal cortex; Cg24a, pregenual anterior cingulate cortex; amyg, amygdala; cd-vs=caudate-ventral striatum; thal, thalamus; mb, midbrain nuclei; Cg25, subgenual cingulate cortex; a-ins, anterior insula; hth, hypothalamus; bs, brain stem nuclei.

anterior cingulate, amygdala, basal ganglia, and various midbrain structures. These areas are largely involved in integrating and managing information from "above" and "below" and are therefore implicated in implicit and explicit cognitive-emotional processing. Importantly, despite these broad classifications, there is much cross-talk between the brain regions within each of these areas. The normal functioning of the system as a whole results in normal regulation of mood, thoughts, and behavior.

This model is not presented as the definitive model for all neuropsychiatric disease (or even depression) and further study will likely modify it significantly. As this and other neuroanatomical models are extended, they will necessarily incorporate effects of various neurotransmitter and other neuromodulatory systems operating within this neuroanatomical framework. However, this model does provide a useful example of how such models are developing as a way of better understanding psychiatric illnesses. Further, it provides a basis for exploring the role of the cingulate gyrus in the pathophysiology of psychiatric disease.

The Cingulate Gyrus in Neuropsychiatric Disease

Based on its extensive structural connectivity (described in detail in Chapters 1 and 4-7), the cingulate gyrus is expected to be a key component of neural systems involved in the regulation of mood, thought, behavior, and autonomic/drive functions. In each of the three major subdivisions of the above proposed network, a specific portion of the cingulate gyrus is involved. Generally speaking, each portion of the cingulate cortex has connections with nearby prefrontal/frontal cortex, specific deeper cortical/subcortical structures, and other divisions of the cingulate cortex. Even without other information about the function of the cingulate gyrus, such connectivity would suggest the cingulate gyrus serves an integrative function, coordinating inputs from "above" (e.g., prefrontal cortical) and "below" (e.g., basal ganglia and midbrain). Functional imaging data support such a role. In the more dorsal regions of the network, the midcingulate cortex (MCC) is involved in conflict monitoring

(Botvinick *et al.*, 1999; Bush *et al.*, 1998; Kerns *et al.*, 2004). The pregenual anterior cingulate cortex (pACC) in the middle part of the model also appears to be involved in conflict monitoring but with a greater emphasis on conflicts involving emotion (Whalen *et al.*, 1998). The subgenual ACC (sACC), in the most ventral part of the model, likely functions in emotional processing, autonomic function, and has been associated with the experience of negative mood (George *et al.*, 1995; Kimbrell *et al.*, 1999; Liotti *et al.*, 2000).

It is not surprising then that the cingulate gyrus appears to be involved in the pathophysiology of many neuropsychiatric diseases. Abnormalities in various divisions of the cingulate gyrus have been implicated in depression (Chapter 24), OCD (Chapters 27 and 28), ADHD (Chapter 12), PTSD and panic disorder (Chapter 21), central neuropathic and functional pain conditions (Chapters 19 and 23), chronic stress disorders (Chapters 21, 22, and 23), schizophrenia (Chapters 30 and 31), Parkinson's Disease (Chapter 31) and Alzheimer's Disease (Chapters 34 and 35). For most of these conditions, subdivisions of the ACC have shown the most consistent abnormalities. Supporting its role in neuropsychiatric illness, ablative lesion of the aMCC has potential efficacy as an "end-stage" treatment for a number of severe treatment-refractory neuropsychiatric conditions including OCD, depression and chronic pain conditions. Such interventions are discussed in more detail in Chapters 18 and 27. Table 1 highlights portions of the cingulate cortex implicated in various neuropsychiatric diseases.

These associations strongly support a role for various components of the cingulate cortex in cognitive and emotional processing generally, with more specific dysfunction of the ACC and aMCC in certain neuropsychiatric disorders. As above, however, the cingulate cortex may not be the actual locus of disease in these conditions. Instead, cingulate cortex dysfunction *per se* is more likely to be associated with specific symptoms of the illness (as opposed to being associated with the "disease state" in toto), such as cognitive dysfunction in schizophrenia, rumination in OCD, apathy in AD, or sadness in depression. In some cases (e.g., Parkinson's Disease), the primary disease process may not even involve the cingulate cortex directly; instead, cingulate dysfunction may be an epiphenomenon of some more widespread abnormality. (By analogy, nearly all cases of Gullain-Barre Syndrome [GBS] are associated with leg weakness which is associated with symptoms of disturbed gait or inability to walk; however, leg dysfunction itself is clearly not the cause of GBS.) Alternatively, primary cingulate cortex dysfunction could be etiologically important for a particular illness, but only when one of several necessary conditions is also present, for example, poorly filtered auditory input could result in hallucinations only when combined with impaired conflict monitoring by the aMCC. It is also possible that the cingulate cortex itself is not dysfunctional at all in psychiatric disease but is merely responding (in a normal way) to overall system abnormalities; in this sense, cingulate dysfunction may actually represent an attempt at an adaptive response to ongoing system dysfunction. Beyond this, certain cingulate abnormalities in disease (such as static hyperactivity of the sACC in treatment-resistant depression, see Chapter 24) may be the result of long-term adaptive changes such that the normal (cingulate) adaptive response becomes maladaptive. As such, interpreting the role of the cingulate cortex in psychiatric disease may actually depend on the time point in the disease process at which this is being assessed (discussed in more detail in Chapter 24).

TABLE 11.1 Association of Specific Cingulate Cortex Subdivisions with Psychiatric Diseases

Cingulate region	Psychiatric disease(s) and other conditions
sACC	Depression, familial mood disorders, PTSD, AD, PD
pACC	Depression, OCD, PTSD, ADHD, AD
aMCC	Depression, schizophrenia, OCD, pain disorders

sACC, subgenual anterior cingulate cortex; pACC, pregenual anterior cingulate cortex; aMCC, anterior midcingulate cortex;. OCD, obsessive–compulsive disorder; PD, panic disorder; ADHD, attention-deficit hyperactivity disorder.

It is possible (indeed likely) that for each neuropsychiatric disease associated with cingulate cortex dysfunction, a different mechanism is operating. However, another important consequence of conceptualizing psychiatric disease within a neural network framework is that even if cingulate cortex dysfunction is not etiologically related to a particular psychiatric disorder, the cingulate cortex may serve as a useful target for treatment development. By analogy, the subthalamic nucleus may not be etiologically important in Parkinson's Disease but it does serve as a very useful therapeutic target for deep brain stimulation based on its pattern of connectivity. In depression, high frequency deep brain stimulation of the white matter adjacent to the sACC has shown very promising results in treating profoundly treatment-refractory depression (Mayberg *et al.*, 2005).

This conceptualization of the role of the cingulate gyrus in neuropsychiatric disease provides a stronger framework for understanding the similarities in phenomenology seen among otherwise distinct illnesses, as well as phenomenological differences within illnesses. For example, diseases that may not involve pACC and sACC dysfunction as *primary* disruptions, may show

downstream secondary dysfunction of these regions, but perhaps only in certain patients. Thus, some patients with AD, PD, PTSD, or chronic pain conditions may also show apathy or sadness as comorbid symptoms, while others may not. Similarly, all patients with depression show mood disturbance and/or anhedonia (likely associated with ACC dysfunction), but sleep and appetite changes may differ significantly between patients. Beyond this, one can imagine more complex neural network abnormalities developing over time. A chronic pain patient, for example, may not develop depression until later in the illness. However, once depression develops, this may further modulate the neural processing of pain via acquired and sustained functional abnormalities in the ACC (see Chapters 23 and 24).

Thus, even though cingulate cortex *dysfunction* may not be etiologically important for all neuropsychiatric diseases, further study of the role of the cingulate cortex in neuropsychiatric illness may help to further clarify the functional neuroanatomy of these illnesses as well as identify potential targets for therapeutic manipulation.

Cingulate Cortex Dysfunction as Central to the Neurobiology of Neuropsychiatric Disease

Neuropsychiatric diseases most likely represent multilevel dysfunction within neural systems involved in the regulation of mood, thought, behavior, and homeostatic/drive processes. Based on its high degree of connectivity throughout the brain, the cingulate cortex has been implicated in several of these systems and most neuropsychiatric conditions. Indeed, given its strong structural and functional connections with other cortical and subcortical brain regions involved in cognitive and emotional processing, it would be surprising if a particular neuropsychiatric disease was not associated with cingulate cortex dysfunction at some level. That said, it is unlikely that cingulate cortex abnormalities are pathophysiologically causative for most neuropsychiatric disorders. Instead, as a particular syndrome progresses, specific subdivisions of the cingulate cortex may become involved directly through downstream connections with other affected regions, or by simply attempting to compensate for dysfunction throughout the network resulting from the primary disease process. As these cingulate cortex subdivisions become involved, dysfunction in these regions will typically be associated with characteristic behavioral disturbances associated with specific symptoms or symptom clusters.

Thus, while cingulate cortex dysfunction may not be causative for the majority of neuropsychiatric conditions, a better understanding of its role in these conditions is clearly necessary to develop more sophisticated models of these illnesses. On one level, these models will help explain and guide further research into the neurobiology of mental illness. Beyond this, these models can guide the development of novel interventions such as therapeutic focal neuromodulation.

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