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2

Depression and Dementia
An Introduction to Systems Neuroscience and Psychiatry

How will a conceptual understanding of neurosciences, genetics, epigenetics, and gene–environment interactions help us better understand psychiatric disorders? On the surface, current clinical diagnosis and management of psychiatric disorders may not appear to require understanding concepts such as "the central reward system" or "central nervous system (CNS) plasticity." Nonetheless, we believe that psychiatrists and other mental health professionals must be equipped with knowledge to adapt to a changing landscape in diagnosis and treatment. Over the next several decades, we believe that brain research will have a major impact on how we think about psychiatric disorders and how we develop treatment strategies, aiming at more mechanism-based therapies and rehabilitative strategies targeted toward correcting specific defects in brain function. Thus, a firm knowledge base in the neuroscientific underpinnings of the field will be required in order to adapt to a changing clinical environment. This may not be obvious to current psychiatrists or students entering the field, but it will become clear as emerging advances in neuroscience take root.

The purpose of this chapter is to describe how a conceptual understanding of clinically relevant basic sciences, including neuroscience and genetics, will be essential for understanding tomorrow's diagnostic systems and treatments. For illustrative purposes, we will focus on two groups of disorders: major depression and the dementias. Depressive disorders are among the most common illnesses that psychiatrists treat. Alzheimer's disease is the most common cause of dementia and one of the best-characterized neuropsychiatric illnesses in terms of neural mechanisms. The scientific advances in understanding molecular, cellular, and systems neuroscience mechanisms in Alzheimer's disease are highly instructive and can lead to better ways to conceptualize the mechanisms contributing to primary psychiatric disorders.

SOME BASIC CONCEPTS ABOUT SYSTEMS NEUROSCIENCE AND PSYCHIATRY

Certain evolutionarily ancient brain regions such as the amygdala and nucleus accumbens (parts of the "limbic system") are primarily involved in processing and

integrating information related to emotion and motivation. These regions receive information about our external and internal worlds and generate responses that help us quickly assess a situation by attaching meaning to the incoming information. Other interconnected brain regions, particularly those in the more recently evolved areas of neocortex, are primarily involved in cognitive processing and allow us to think consciously and to plan and execute decisions. In these examples, a collection of specific brain regions are directly connected to each other and constantly talking with each other, forming a brain system (or network). Some brain structures belong to several brain systems—for instance, the hippocampus is involved in emotional processing as well as cognitive and motivational brain systems. On the other hand, individual brain systems do not operate in isolation. The emotional processing brain systems, for example, require cognitive processing brain systems in order for a person to become conscious of emotions (called "feelings" in the words of Antonio Damasio), learn from emotions, and even control emotions via top-down processing. Thus, emotional systems interact closely with cognitive systems that involve brain regions such as the prefrontal cortex, parietal cortex, and temporal cortex.

In addition to the emotional and cognitive processing systems, pathways related to reward and motivation are involved in determining and regulating a person's feelings and actions. People change their behaviors depending on how rewarding a particular behavior is and the perceived costs associated with the behavior. If we like the way something feels, we take steps to prolong that feeling. If we enjoy the taste of a certain food, we want to eat more of it. If we do well in the stock market, we want to continue investing in stocks. Interestingly, if we suddenly do poorly in the stock market, we may have a response that is out of proportion to our loss. Such decisions are often emotionally and not cognitively driven. Bad outcomes or perceived bad outcomes can have a big impact on behavior and tend to trigger centers in the brain that process negative emotions such as fear and anxiety. Sometimes this is appropriate and we take defensive action, but at other times it is inappropriate and leads to bad decisions and interpersonal problems.

The symptoms associated with clinical depression involve abnormal functioning of systems underlying emotional processing, cognition, and reward. While we classify these disorders as "mood problems," it is important to realize that defects occur across all aspects of the mind, including cognition and motivation. When these systems aren't working in concert, the human brain reacts with a range of symptoms that can include sadness, decreased interest in everyday surroundings and activities, poor concentration and inattention, appetite and sleep changes, poor energy and motivation, and, at times, lack of will to live and suicidal thoughts. A depressive syndrome does not reflect abnormalities in one or a few brain structures or in one or a few neurotransmitter systems; it reflects a complex and distributed multi-network problem. This is discussed in more detail in Chapter 5.

There are likely to be many different reasons for malfunctions in these brain systems. Some people have a genetic makeup that makes it hard to perturb these particular brain networks; such people are highly resilient and not prone to depression, even in the face of adverse life circumstances. Others have brains that are wired

in such a way that even slight perturbations can lead to significant disruption and, therefore, to changes in behavior. There is little doubt that genes contribute significantly to the predisposition to becoming depressed. Some families have higher risks for depression than other families. These risks may involve small effects of many common genes or possibly larger effects of rarer genetic variants. Various factors that disrupt brain systems are discussed in Chapter 9.

DEPRESSION

The DSM-IV diagnosis "major depression" refers to a broad and heterogeneous category of disorders and is a term that is somewhat parallel to the term "cancer." When told that a friend has cancer, we want to know what kind of cancer because that can have a huge impact on treatment and life expectancy. Similarly, when a patient has a history of depression, clinicians should want to know what kind of depression, because the answer to this question has a huge impact on treatment decisions and the likely course of the illness. Our current diagnostic system lumps many types of dysfunction under the heading of "major depression." While this simplifies clinical practice, it creates major difficulties for understanding the underlying biology of the disorders and for devising the most effective treatment strategies for individual patients. We will give a few examples of the heterogeneity below.

Some patients with depression seem to have a "pure" form of the illness—a type of depression that runs in their families and seems to be independent of other psychiatric illnesses or major environmental stressors. A young adult with this type of "pure" depression may experience the onset of severe depressive symptoms over a period of several weeks that interfere with school, work, and relationships. This person's family history may reveal a similar illness in close family members who might each have responded well to the same therapeutic approach—for example, bupropion in combination with cognitive behavioral therapy. In such cases, it is likely that the patient will respond to the same treatment as well. The particular group of genes that this person inherited may result in fragility in the smooth functioning of the neural systems involved in emotional processing and mood regulation. In theory, bupropion and psychotherapy help to re-establish healthy activity, connectivity, and interactions of these systems, leading to clinical improvement.

There are data strongly suggesting that individuals with these types of highly familial major depressive disorders have significant changes in brain structure and function. For example, a recent study by Brad Peterson and colleagues at Columbia University demonstrated that there is substantial thinning (more than 25% thinning) in certain areas of the right parietal cortex in persons whose families have multigenerational major depression. This right-sided cortical thinning in areas involved in cognition correlated with problems in focusing attention and visual memory (cognitive defects) and familial risk for depression (an emotion-based illness). These recent findings build upon earlier work in familial depression demonstrating structural changes in areas of subgenual anterior cingulate cortex that are part of an emotional processing network, changes that include a loss of glial cells in the region. These findings

suggest that some of the genetic abnormalities predisposing to depression may be associated with significant structural changes in the brain. Such changes influence the connectivity within and across specific brain systems, and it is likely that these changes in connectivity contribute to risk for mood disorder. As we will discuss in subsequent chapters, it is currently unclear how the changes in brain structure and function arise and whether they are actually causal changes or the consequence of illness, although studies in children and adolescents increasingly suggest that at least some of the brain changes antedate significant clinical symptoms. The important point is that these changes are associated with a specific form of depression and are not necessarily found in other forms of depression.

A different clinical scenario might involve a patient who developed cocaine dependence as a teenager. This patient was seen in the emergency room on several occasions with severe, short-lived depressive symptoms time-linked to coming off cocaine highs. Each time, his symptoms were dramatic and involved significant suicidal ideation, but resolved over several hours without specific intervention. After several years of cocaine addiction, the patient again was seen in the emergency room with severe depressive symptoms, but this time the symptoms did not resolve as quickly as before when he came off his high. His clinical presentation included a full spectrum of depressive symptoms, including thoughts of suicide. He was admitted to the hospital, but his depressive symptoms persisted for several days. With resolution of his suicidal thoughts, the patient was transferred to a residential treatment program for management of his chemical dependency. After 3 weeks of cocaine abstinence and group therapy, depressive symptoms resolved. Although he continued to have a strong desire to use cocaine, he began to develop insight into his addiction and the connection between his cocaine dependence and his mood symptoms. He stayed clean for 3 months before relapsing. During those 3 months, he did not experience depressive symptoms.

This person demonstrates two types of depressive syndromes that are every bit as severe as the symptoms observed in the individual with familial major depression. The earlier presentations to the emergency room resulted from pharmacologic withdrawal from cocaine. This withdrawal acutely disrupted one or more of the neural systems related to mood regulation; it likely involved abnormal function of the dopamine transmitter system that is involved in motivational processing and is a prime target for drugs of abuse like cocaine. The disruption was acute and time-linked to the short-term effects of coming off the cocaine high. While severe, the depressive symptoms lasted for only several hours. This syndrome would not qualify for a diagnosis of major depression, but it does illustrate that perturbation of neural systems can acutely cause a depression-like picture. The longer-lasting depressive picture that occurred several years later was likely related to a longer-term dysregulation of the patient's central reward system as a result of persistent cocaine dependence. In this case, the depressive syndrome lasted several weeks but gradually resolved after several weeks of behavioral treatment and abstinence from cocaine.

In earlier terminology championed by Eli Robins and Sam Guze at Washington University-St. Louis, this more persistent depressive syndrome would be referred to as a "secondary depression." This means that the depression occurred subsequent to the onset of an addictive disorder and thus was "secondary" in time to the cocaine dependence. Importantly, cocaine dependence was already running its course prior to the onset of persistent mood symptoms and was thus having a significant impact on brain networks, including those involved in mood regulation and cognition. Note, however, that the term "secondary depression" does not imply causality; it indicates only that the depressive syndrome occurred at some point in time after the onset of drug abuse. In contrast, a "primary" depression is one that arises in the absence of a preexisting psychiatric or serious medical disorder. We believe this distinction is useful conceptually because it helps to differentiate subtypes of depression, including separating depression in the context of cocaine dependence from the highly familial ("primary") mood disorder described previously. This also highlights the possibility that the neural pathways leading to depression and dysfunction may be different. In the examples presented, the "primary" depressions likely involve prominent changes in emotional processing systems (e.g., abnormal function and perhaps cell loss in subgenual cingulate cortex, neocortex, and amygdala), while the "secondary" depression occurred in the context of cocaine-induced changes in motivation/reward systems. We would further argue that treatments for the different types of depression should be tailored to the underlying brain dysfunction. Failure to recognize this may be a contributing factor to the overall weak remission rates observed in recent large-scale clinical effectiveness trials such as STAR*D, where early age of onset and high psychiatric and medical comorbidity were predictors of worse outcomes.

Although the cocaine-dependent patient's depressive symptoms resolved, his craving for cocaine did not, and he returned to the use of cocaine several months after discharge from the residential treatment center. Several years later, he once again was hospitalized for treatment of depressive symptoms and cocaine addiction. This time, however, his depressive symptoms did not resolve after several weeks of abstinence. After another month of treatment for his drug addiction in a residential facility, he was able to remain abstinent for years; however, his depressive symptoms were more persistent. Eventually, this depressive disorder responded to a combination of medications, psychotherapy, and lifestyle changes, including diet, exercise, and abstinence from drugs. Based on what we are learning about the biology of drug addiction, it is likely that this patient's long-term substance dependence led to structural and functional changes in his central reward system as well as in his emotional processing and cognitive systems. Such changes required pharmacologic, psychological, and lifestyle interventions to help the neural systems regain function.

Contrast these two scenarios with the depressions frequently observed in individuals with bipolar disorder, an illness characterized by episodes of both mania and depression. Although a person with bipolar depression is likely to have abnormalities in brain systems that overlap with those involved in the previous two cases, these abnormalities result from neural mechanisms that cause bipolar disorder, an illness that typically runs in families and at times presents with depression and psychotic features. The causes of bipolar disorder are not known, but mood stabilizers, as

opposed to antidepressants, are the initial drug category of choice for treatment. Appropriate treatment might involve a mood stabilizer coupled with antipsychotic medication and, when appropriate, talk therapy and education about the importance of good sleeping habits and other routines that help circadian rhythms stay on track. Interestingly, there is evidence that bipolar disorder tends to worsen over time in some individuals, with more frequent episodes of illness and shorter periods of wellness between episodes. This led Robert Post and colleagues to propose that a "kindling" or behavioral sensitization phenomenon occurs in these individuals, and they conducted trials of anticonvulsant medications as "anti-kindling" mood stabilizers. It also appears that conventional antidepressant medications may worsen the course of bipolar disorder, leading to greater instability in some individuals. Thus, it is likely that the brain biology of bipolar disorder differs from the depression scenarios outlined previously. Note also that bipolar disorder is a form of "primary" mood disorder that probably shares some, but not all, mechanisms with primary major depression. For example, subjects with bipolar disorder have shrinkage and cell loss in subgenual cingulate cortex, but they clearly have illness features that differ from non-bipolar mood disorders.

These are only a few of the different "types" of depression routinely encountered in clinical practice. Other examples include depressions arising in the context of personality disorders (e.g., borderline personality disorder or somatization disorder) or serious medical illnesses (e.g., cardiac illnesses, cancer, or diabetes). The symptoms of these disorders are all similar, but the underlying brain mechanisms are likely to be different. Furthermore, appropriate treatments are likely to vary as a function of the cause of the syndrome, not the clinical phenotype. Patients in our examples usually experienced weeks of the symptoms listed in DSM-IV; however, the triggers for their symptoms were different and even changed over time within the same individual depending on other variables (e.g., the duration of cocaine abuse). From a neuroscience perspective, clinical symptoms result from abnormal functioning of specific brain networks. Treatments, on the other hand, fall into two broad categories: rehabilitative treatments and cause-based treatments. Rehabilitative treatments are not specific to the etiology of the illness; they decrease symptoms by influencing the brain in a manner that bypasses or minimizes the dysfunctional system. For instance, certain psychotherapies teach people methods to minimize depressive symptoms by training them to think differently. This new learning may establish or reestablish brain circuits that promote clinical improvement. A cause-based treatment would directly fix the broken circuitry. Current antidepressants and mood stabilizers are not cause-based therapies. Rather, these drugs likely work by enhancing function in certain dysfunctional systems even though the primary defects in the malfunctioning circuits aren't actually fixed. The key point we want to emphasize is that DSM-IV "major depression" is an extremely heterogeneous set of disorders. We don't yet know whether the neural circuitry involved in depression is the same or different across illness subtypes. What seems highly likely is that the neural pathways leading to depression can vary according to subtype, and this has practical implications for how we think about diagnosis and treatment. We believe that lumping all depressions together makes no more sense than lumping all cancers or dementing illnesses together. To make these latter points more vivid, we will turn our attention to recent advances in understanding the pathobiology of dementing illnesses—advances that graphically highlight how brain network dysfunction drives clinical presentation, while effective treatment strategies target causal molecular mechanisms.

DEMENTIAS

Much progress has been made in understanding Alzheimer's disease. In contrast to primary psychiatric disorders, the term "Alzheimer's disease" refers to a specific pathology-based diagnosis that cannot yet be definitively confirmed until examination of the brain at autopsy. Thus, when Alzheimer's disease is suspected clinically, it is diagnosed as "dementia of the Alzheimer's type" (DAT), reflecting uncertainty about the underlying pathological process. The clinical phenotype and course of DAT are well described, and the structural abnormalities in the brain underlying Alzheimer's disease are well characterized. Another well-defined dementia is known as behavioral variant frontotemporal dementia (bvFTD). Recent studies of DAT and bvFTD are providing information that is clarifying the relationship between clinical presentation (phenotype) and cause (molecular mechanisms). In this section, we will briefly review the clinical picture of both dementias. In addition, we will discuss recent information pertaining to two brain networks—the *default* system and the *emotional-salience* system—and the ways in which these neural networks appear to contribute to illness. Core neural systems like these are called "intrinsic connectivity networks" (ICNs) by some neuroscientists, and these ICNs appear to process specific types of information. Measuring biomarkers in individuals thought to show indications of a dementing illness can also provide information that is likely to have a direct impact on treatment. We believe that the information learned from clinical phenotypes, neural systems, and causes of these two dementias has substantial implications for understanding other psychiatric disorders. While we note that the descriptor "ICN" is used by some by not all neuroscientists, we prefer this terminology and will use it throughout the book. Others refer to these networks as "resting state connectivity networks" or "functional connectivity networks."

Dementia of the Alzheimer's Type

DAT is characterized by gradual deterioration in many brain functions, including memory, thinking, executive function (decision making), learning, and personality. It is a disorder that becomes increasingly common with aging: about half the population over age 85 exhibits symptoms of DAT. The brains of persons with DAT have characteristic structural changes that involve the accumulation of two polypeptides (proteins): beta-amyloid and hyperphosphorylated *tau*. Beta-amyloid accumulates outside of cells and forms a visible microscopic structure called an amyloid plaque. *Tau* is a protein involved in the function of microtubules that are involved in the efficient trafficking of molecules within neurons. Hyperphosphorylated *tau*

accumulates inside neurons and destroys their ability to transport materials from the cell body to distant parts of the cell (synaptic terminals). The accumulated *tau* forms pathological "tangles" inside neurons. Both plaques and tangles eventually interfere with neuronal function and intercellular communication. Interference with function leads to neuronal loss and the clinical symptoms of DAT.

Certain specific brain regions appear to be involved earlier than others in the course of DAT, and this information provides clues about how clinical symptoms develop and evolve. These brain regions include the hippocampus, areas near the hippocampus such as the entorhinal cortex, and neurons in the precuneus, a region of neocortex located toward the back of the brain near the posterior cingulate gyrus (see Appendix for structural brain maps that indicate the anatomical location of these areas). These structures overlap with brain regions that make up a neural network called the "default" system, which is a collection of broadly distributed brain regions that are functionally connected. Using neuroimaging techniques such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), investigators have shown that brain activity in each of the structures involved in the default system correlates highly with each other (Fig. 2-1 and Table 2-1). This default ICN is most active when a person isn't focusing on a particular task (hence the name "default" network). At such times, structures in the default system are all humming together in correlated activity and processing largely internal (intra-self) information, including memories, emotions, and overall state of well-being (Table 2-2). Interestingly, the default system uses a lot of energy when other regions of the brain are "resting," and the regions of the default ICN are among the most energy-demanding areas in the human brain. It appears that the heavy energy demand in the default system makes these brain regions particularly susceptible to the earliest damage in DAT. Furthermore, there is evidence that the demands of ongoing synaptic activity may be a key factor rendering these regions vulnerable to amyloid deposition, and current thinking highlights synaptic dysfunction as a

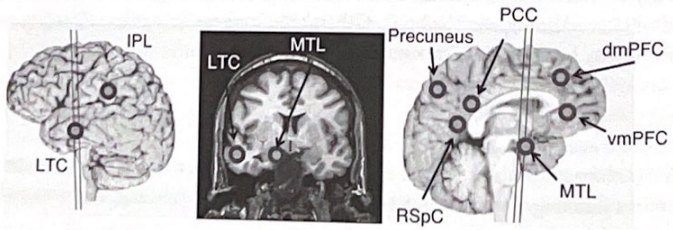

Figure 2-1 Key nodes of the default mode network. The figure depicts key structures involved in the default mode network as defined by Marc Raichle, Randy Buckner, and others. The highlighted regions include the lateral temporal cortex (LTC), inferior parietal lobule (IPL), precuneus, retrosplenial cortex (RSpC), posterior cingulate cortex (PCC), dorsomedial PFC (dmPFC), ventromedial PFC (vmPFC), and medial temporal lobe (MTL), including the hippocampus. The lines through the brain reconstructions indicate the approximate location that is shown in the radiologic image. (Adapted from Damasio, 2005, with permission.)

Table 2-1 Default Network: Key Structures

Medial temporal lobe
Hippocampus
Entorhinal and parahippocampal cortex
Lateral temporal cortex
Dorsomedial prefrontal cortex
Ventromedial prefrontal cortex
Posterior cingulate, precuneus, and retrosplenial cortex
Inferior parietal lobule

prime driver in the pathogenesis of Alzheimer's disease. The key point is that the regions involved early in DAT appear to be the same regions involved in a specific brain network. It is logical to propose that malfunction of this network drives at least the early clinical manifestations of DAT. A principle evolving from this work is that when dysfunction/degeneration occurs within a specific network, it tends to spread within the network, perhaps as a result of coordinated neural activity within the system.

Behavioral Variant Frontotemporal Dementia

bvFTD is much less common than DAT. It also tends to occur in younger people, with age of onset typically between 50 and 60 years. The most obvious symptoms involve profound changes in social behavior. For example, a well-mannered person may gradually demonstrate behaviors that are grossly inappropriate, like telling obscene jokes in public settings or becoming overly friendly and even sexually inappropriate with strangers. These new-onset behaviors are embarrassing to family and friends but are not usually recognized by the individual. Other changes may accompany these inappropriate behaviors, including changes in eating habits, sex drive, and speech. Cognitive tasks become more difficult, and changes in memory and thinking similar to those found in persons with DAT develop.

A recent report by William Seeley and colleagues suggested that the brains of people with bvFTD demonstrate a breakdown in a specific ICN known as the "emotional-salience system" (Table 2-3 and Fig. 2-2). This system involves several limbic and cortical brain regions that help to process emotions and meaning (Table 2-4). The cause

Table 2-2 Default Network: Internally Focused Functions

Autobiographical memories
Encoding and retrieval
Mood and motivation state
Mental simulations
"Remembering" the future
Social interactions
Conceiving perspectives of others (theory of mind)

Table 2-3 Emotional-Salience Network: Key Structures

Frontal and anterior insula cortex
Anterior cingulate cortex
Orbital fronto-insular cortex
Frontopolar cortex
Temporal polar cortex
Extended amygdala
Ventral striatopallidum
Ventral tegmental area/substantia nigra
Hypothalamus and periaqueductal gray

of the breakdown in the emotional-salience system may involve abnormalities in specific proteins. These include a protein called TDP-43 (TAR DNA-binding protein 43), another that is an abnormal form of *tau*, and yet another called FUS (fused in sarcoma). The form of *tau* involved in bvFTD differs from the hyperphosphorylated *tau* seen in DAT. It is important to note, however, that on rare occasions, the protein abnormalities associated with DAT, leading to the formation of plaques and tangles, can cause the clinical syndrome of bvFTD. This suggests that amyloid and hyperphosphorylated *tau* can, in some individuals, selectively attack the emotional-salience system instead of the default system. Interestingly, such patients have a

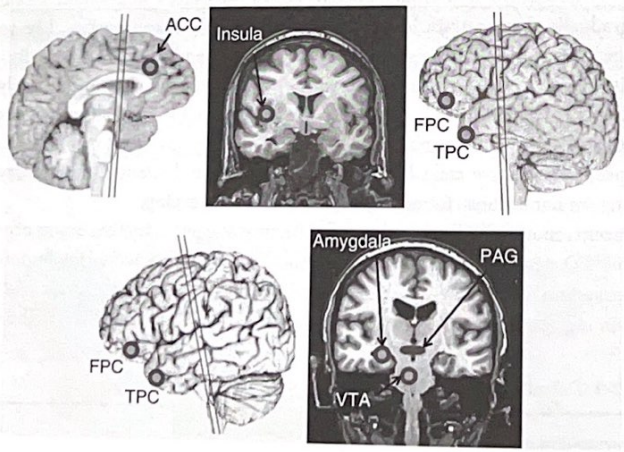

Figure 2-2 Key nodes of the emotional-salience system. The figure depicts key structures involved in the emotional-salience network as defined by William Seeley and colleagues. Highlighted regions include the anterior cingulate cortex (ACC), insular cortex, frontopolar cortex (FPC), temporal polar cortex (TPC), amygdala, periaqueductal gray area (PAG), and ventral tegmental area (VTA). The lines through the brain reconstructions indicate the approximate locations that are shown in the radiologic images. (Adapted from Damasio, 2005, with permission.)

Table 2-4 Emotional-Salience Network Function

Conflict monitoring
Interoceptive awareness
Autonomic nervous system processing
Reward processing

clinical syndrome that is indistinguishable from bvFTD caused by TDP-43, FUS, or the non-DAT form of *tau*. Why would the emotional-salience system be more vulnerable to plaque and tangle pathology in some individuals (resulting in bvFTD) while the default system is more vulnerable in other individuals (resulting in DAT)? We don't yet know, but a key finding seems to be that once pathology attacks a particular ICN, it seems to percolate throughout that ICN and lead to characteristic clinical features that reflect the function of the ICN.

Importantly, in both DAT and bvFTD, the phenotype of the dementia (i.e., the clinical manifestation of the disorder) appears to be defined by the specific neural networks that are being disrupted. The clinical phenotype does not always define the biochemical cause of that disruption. Most but not all persons with DAT have amyloid plaque and *tau* tangle pathology. There are now brain-imaging techniques that are able to demonstrate amyloid accumulation in humans during life (using Pittsburgh Compound B [PIB] to label amyloid, for example), and this work has the potential to allow earlier identification of individuals at high risk for DAT and perhaps early intervention. Studies using PIB are already demonstrating changes in resting-state default-mode connectivity in elderly individuals who are cognitively normal. How and whether these early changes drive a progression to dementia will be an important consideration going forward. In addition, DAT appears to be associated with decreased levels of amyloid and increased levels of *tau* in cerebrospinal fluid (CSF), changes that can be assessed by lumbar puncture, a relatively simple clinical procedure. These changes, like amyloid deposition in the brain, may occur prior to the onset of clinical symptoms. We are not far away from the time when physicians will be able to use imaging procedures and CSF biomarker studies to determine whether a phenotypic DAT is associated with amyloid plaques in the brain and diminished CSF amyloid. This information will allow physicians to determine whether an individual's DAT is likely caused by amyloid and abnormal *tau*. When such changes are identified prior to any symptoms, it may be possible to delay or prevent the development of clinical DAT. In fact, treatments are currently being tested that are directed at eliminating the initial accumulation of pathological levels of amyloid (i.e., the proposed cause of the disorder). If amyloid accumulation is the proximal cause of the destruction of the default system (something that is still not certain), then the clinical manifestations of the illness may be halted or perhaps even prevented by decreasing amyloid formation or by increasing its elimination. This cause-based mechanistic treatment is in contrast to current symptomatic treatments for DAT. Support and education can help families and patients handle the illness

better—a form of rehabilitative treatment. Cholinesterase inhibitors may influence one brain system that allows for short-term stabilization of symptoms, but these medications certainly do not treat the actual cause of the disorder.

It should also be possible to apply imaging and biomarker procedures to people with bvFTD and use the results as the basis for rational treatments. For example, if a patient with bvFTD shows amyloid plaques on imaging and decreased amyloid in the CSF, it is likely that the etiology of that patient's bvFTD is amyloid-based instead of being caused by the other proteins more typically associated with bvFTD. This would suggest that anti-amyloid therapy would be helpful in this particular patient with bvFTD, something that could not have been predicted on the basis of the clinical picture alone. In this example, the clinical phenotype would be bvFTD; however, the imaging and biomarker modifiers would suggest that the etiology of this particular case of bvFTD involves amyloid and hyperphosphorylated *tau*. Eventually, it may be possible to measure levels of other abnormal proteins in CSF or plasma, such as TDP-43. With such measurements, physicians will have a more specific understanding of the cause of the clinical syndrome. The clinical phenotype predicts the current and future clinical course of the illness, but the biomarker data suggest the underlying pathology.

Will these types of advances ever be applicable to the depressive disorders or other psychiatric illnesses? We clearly know the clinical phenotype in depression. As more is learned about the different causes of depression, we should be able to be more specific in terms of treatments. Akin to DAT and bvFTD, the clinical phenotype will be determined by the specific brain networks involved in the primary pathophysiology, while the cellular, synaptic, and molecular mechanisms leading to abnormal function will likely be the targets for specific treatment approaches. One can also imagine that specific rehabilitative efforts (i.e., behavioral, lifestyle, and psychotherapeutic strategies) could be directed toward restoring function in the disrupted brain networks involved.

Similarly, progress in understanding DAT and bvFTD should lead to optimism about understanding disorders such as schizophrenia and bipolar disorder. For physicians to understand the clinical ramifications of this progress, we suggest that psychiatrists and mental health professionals must understand the neuroscience underlying these advances. We will continue to develop this theme throughout this book.

Points to Remember

The clinical phenotype (i.e., signs and symptoms of a disorder) reflects the nature of the neural networks that are involved in the illness.

There are many causes of dysfunction in specific neural networks. Borrowing from advances in the dementing illnesses, it appears that specific clinical disorders and pathology can attack specific brain systems. The reason that certain brain systems are vulnerable to attack is not yet clear. Networks with high activity and high energy utilization may be particularly vulnerable in illnesses like DAT.

The more specific the knowledge of a particular cellular and molecular cause, the more specific the pharmacologic treatment can be.

Understanding basic principles of neural networks, molecular sciences, and clinical diagnoses will be essential for keeping up to date with specific treatments.

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