Lessons From Neuropsychiatry

Constantine G. Lyketsos, M.D., M.H.S.

Neuropsychiatry is the field devoted to studying psychiatric manifestations of neurological conditions.[1] Working with and studying psychiatric symptoms in patients with known brain pathology seems a methodologically sound approach to investigating brain-behavior relationships. This lesion approach has for decades taught, and continues to teach, the field of neurology about the motor, sensory, visual, and auditory systems.

What have we learned so far about psychopathology from neuropsychiatry? This article is an attempt to distill my experience as a neuropsychiatrist on the question of what psychiatrists have learned from neuropsychiatry in the last few decades. These lessons arise out of my interactions with patients, a closer reading of the literature, my own research, and discussions with colleagues at Johns Hopkins and elsewhere.

As a field, psychiatry is searching for a structure to explain the emergence of the disturbances with which it concerns itself.[2] One of the most cogent and classical explanatory methods available to medicine, referred to as a "disease reasoning" by McHugh and Slavney,[3] is a top-down process whereby clinical phenomena (symptoms) that group together (syndromes) are understood as being caused by brain damage (broken part) of a specific pathology. The pathology emerges from complex causes, its etiology. The link between etiology and pathology is referred to as *pathogenesis*, while the link between pathology and syndrome is referred to as *pathophysiology*. These linkages are easy to follow conceptually in the case of left-sided stroke in which the *syndrome* might consist of aphasia and right-sided hemiparesis, the *pathology* might consist of ischemic necrosis of the left cerebral hemisphere, and the *pathogenesis* might consist of carotid artery occlusion. The pathophysiology explains the specific motor loss based on the specific area of the brain damaged, while the pathogenesis involves understanding the reasons for carotid occlusion in the patient at that time.

Neuropsychiatry affords a similar methodological approach that generates testable hypotheses about linkages between mental phenomena (e.g., depression) and brain pathology (e.g., left frontal infarct). However, when compared to motor and sensory phenomena, it is less intuitive to attribute psychopathological phenomena, such as depression, aggression, delusions, or dementia, to brain pathology, its location, and its etiology, in part because we tend to explain psychopathological phenomena with "meaningful connections."[2] Yet, not only is this link possible, it is likely based on decades of accumulated evidence. Therein lies the attraction of neuropsychiatry. Through experiments of nature, where a specific disease disrupts the brain, neuropsychiatrists are afforded the opportunity to investigate interactions between brain lesion, location, dysfunction, and asso-

Received April 27, 2006; accepted May 2, 2006. Dr. Lyketsos is Professor and Chair of the Department of Psychiatry, Johns Hopkins Bayview Medical Center, Baltimore, Maryland. Address correspondence to Dr. Lyketsos, 4940 Eastern Avenue, A4 Center, Room 458, Baltimore, MD 21224; kostas@jhmi.edu (E-mail).

ciated psychopathological manifestations. The lessons offered here are steps on the way toward this goal.

Lesson 1: Psychopathology Is About Circuits (Neuronal Networks), Not Brain Regions, and Not Just Neurotransmitters or Molecules

A common theme in neurological diseases is that dysfunction in specific brain circuits (neuronal networks), as opposed to specific areas or individual neurotransmitter systems, leads to specific types of psychopathology. This dysfunction might be *intrinsic* to the circuits, coming about as a result of damage within the key circuits, or *extrinsic* to the circuits, coming about as a result of loss of integrative activity in brain systems that link to or regulate the key circuits. The specific pathogenesis of the dysfunction is less important to the occurrence and type of psychopathology than the specific circuit(s) affected. Two key circuits closely associated with psychopathology are the "fronto-subcortical" circuits[4,5] and the limbic system. The ascending monoamine and cholinergic tracts regulate both these circuits so that dysfunction in monoamine tracts secondarily affects circuit functioning.

For example, patients with stroke or multiple sclerosis might manifest dementia, depression, or mania, when either specific cortical gray matter areas of the frontal lobes or the white matter connecting these areas to linked subcortical areas are damaged by infarct or degeneration. Similarly, patients with dementia due to fronto-temporal degeneration often develop motor findings characteristic of amyotropic lateral sclerosis (ALS), while a significant proportion of ALS patients develop fronto-temporal degeneration dementia. The pathology and etiology appears to be the same, but the development of motor as opposed to psychopathological symptoms (dementia), or both, depends on what brain circuit is affected.

Appreciation of the last point illuminates the high occurrence of psychopathology in patients with the rare disease transverse myelitis. Transverse myelitis is thought to be caused by immune reactions to viral infections in vulnerable people, leading to CNS immune activation and the local production of neurotoxic levels of Il-6. Transverse myelitis has traditionally been thought to affect only the spinal cord, leading to motor and sensory loss. Recent research identified high rates of cognitive and affective psychopathology in transverse myelitis patients. This psychopathology is less clinically obvious in light of the severe disability associated with spinal cord disease and because clinicians tend to attribute such affective psychopathology to psychological reactions to the motor-sensory disability. Nevertheless, the psychopathology is itself severely disabling, often more so than the motor disability. Its occurrence in a largely immune-mediated disease suggests that immune malfunction leading to spinal damage also damages brain circuits involved in affective psychopathology. This supports the idea we proposed a decade ago to explain the substantial elevation in rates of depression among patients who had HIV infection but were unaware of it,[6] namely that the immune system can cause affective psychopathology through effects on key brain circuits.

Damage to limbic and frontosubcortical circuits or to ascending monoamine and cholinergic tracts, no matter the cause, is likely to lead to psychopathology, such as dementia, depression, mania, or personality change. In areas where these circuits are tightly contiguous with each other, as in subcortical regions, local pathology might affect several circuits at once, giving rise to rather complex psychopathological presentations. This probably explains the paradox of how some patients develop more severe psychopathologies even though they only have a small but critical brain lesion (e.g., lacunar infarct on the thalamus).

Links between the cerebellum and fronto-subcortical circuits explain the recent observation of high rates of cognitive and affective psychopathology in patients with cerebellar degeneration or posterior fossa tumors.[7–9] In addition, damage to brain areas in the temporal or occipital lobes linked to these circuits and involved in auditory or visual processing have been associated with hallucinations.[10]

While the more damage to the brain the greater the likelihood of psychopathology, it is more probable that key circuits and/or their connections are more likely to be affected, rather than there being an additive effect on the probability of psychopathology. Regarding whether pathology is degenerative due to infarct or other causes, as long as the same circuit is damaged, the psychopathology is likely to be similar.

An interesting part of this lesson is that the *level* of circuit damage may explain variations in psychopathological phenotype across neurological diseases. Patients with Huntington's disease, HIV brain infection,

epilepsy, and bipolar disorder, all can display syndromes recognizable as "mania," and yet the form of the mania varies in its specifics. For example, patients with "AIDS mania," in whom the pathology probably lies in the caudate, have a different manic phenotype than patients with early HIV disease and mania related to bipolar disorder.[11] Similarly, patients with executive dysfunction syndrome[3] might manifest primarily disinhibition or apathy, or both at the same time, depending on which level of the "fronto-subcortical" circuits is damaged.[2]

Lesson 2: Accompanying Neurological Symptoms Do Not Account for the Appearance of Psychopathology; the Diseased Brain Does

Psychopathology is a parallel manifestation of brain disease to common "neurological" (e.g., motor, sensory, visual) symptoms. Depression in patients with Parkinson's disease, for example, likely arises from the underlying brain pathology or the consequences of medication treatment, as do the motor symptoms (both the bradykinesias and the dyskinesias) of the disease. Because this likelihood has not come to be appreciated, the understanding of psychopathology in patients with epilepsy has lagged behind that of Alzheimer's or Parkinson's disease. Early students of psychopathology associated with epilepsy classified it in relationship to the occurrence of its neurological manifestations (the seizures) instead of by using traditional syndromic approaches to classification, followed by attempts to relate psychopathological syndromes to the brain damage that led to the seizures. To this day, psychiatrists working in the epilepsy area tend to classify psychiatric syndromes as *pre-*, *peri-*, or *postictal*.[12]

While this approach provides a temporal explanation of the appearance of psychiatric symptoms, it fails to account for the etiopathogenesis of epilepsy and for the parallel psychiatric phenomena unleashed by the abnormal or damaged brain. Rather than approaching psychiatric phenomena in relation to seizures, the psychiatry of epilepsy would be better served by renewing the effort to understand differences in the brains of epileptic patients with and without psychopathology. Emerging brain-imaging modalities, such as diffusion tensor imaging, show great promise in advancing an understanding of circuit integrity in the living brain and could be used in the epilepsy field.

Lesson 3: Phenomenological Differentiation of Symptoms From General Psychiatry Cannot Be Readily Transported to Neuropsychiatry: DSM-IV Fits Part of the Story

The taxonomy articulated in DSM-IV only partly fits the psychopathology seen in neurological disease. Some conditions seen in neurological disease, such as post-stroke depression, phenomenologically resemble what is described in DSM-IV as major depression,[13] and the same may be true for depression after traumatic brain injury.[14] However, psychiatric disorders in several other conditions (e.g., Alzheimer's disease, HIV, Parkinson's disease, multiple sclerosis, Huntington's disease) do not fit well into the DSM-IV mold. Further, DSM-IV does not describe well certain other psychopathological conditions seen in neurological disease, such as apathy or executive dysfunction syndrome.[3] And DSM-IV, in its "atheoretical wisdom" that enumerates descriptions without explanations, does not differentiate conditions as physiological consequences of the brain disease versus "reactive" psychological states in brain damaged patients. As we move toward DSM-V, careful attention must be paid to the psychiatric phenomenology of patients with particular neurological diseases and to developing etiologic criteria that may link psychiatric syndromes to brain disease. Such criteria have already been proposed, drawing from clinical epidemiology.[15]

Lesson 4: The Value of Symptom-Targeted Psychopharmacotherapies Established in General Psychiatry Must Be Replicated in Individual Neurological Conditions

In other words, what works to reduce psychiatric symptoms in one neurological disorder may not work in another; replication is necessary. After a stroke, the efficacy of antidepressants for major depression, perhaps specifically of tricyclic antidepressants, is now established[16] and there is evidence that antidepressant therapy may prevent the onset of depression after stroke.[17] However, this is not the case with traumatic brain injury, multiple sclerosis, epilepsy, Alzheimer's, and Parkinson's disease. In the latter two, the value of antidepressants has not been unequivocally supported by randomized trials.[18,19] In fact, in Parkinson's disease the superiority of antidepressants over placebo for the treatment of depression is unproved, after several randomized trials.[20] In Alzheimer's disease, the data more clearly support

antidepressant efficacy, thanks to refinements in outcome assessment[21] necessary to demonstrate benefit. The lesson here is that what has been learned about symptom-targeted therapy in general psychiatry is not readily transferable to neuropsychiatry. Disease-specific study of treatment is necessary. Ultimately, effective therapy will only come about when disease-specific mechanisms are understood, leading to rational therapeutics.

Lesson 5: Available Therapies for Neuropsychiatric Phenomena Are Symptomatic; Different Therapies Will Be Needed to Address the Underlying Brain Damage

Existing treatments targeted at psychiatric symptoms in patients with brain disease have failed to reverse the brain damage, in part because they target specific symptoms that result from the loss of brain tissue. In Parkinson's and Alzheimer's disease, therapies exist that improve motor (L-dopa), cognitive (cholinesterase inhibitors), affective (antidepressants), or psychotic symptoms (antipsychotics). These therapies have been applied either empirically or out of evidence that specific symptoms arise with specific neurotransmitter disturbances. *None* of these treatments addresses the causes of the neurotransmitter deficits, namely progressive neuronal degeneration. In Alzheimer's disease, treatments that address more fundamental disease mechanisms do not resemble the symptomatic treatments. When brain damage is more severe, most of the mechanism-oriented therapies will likely not be successful after symptoms have started; in order to prevent brain damage, they will have to be applied before symptoms emerge. Generalizing this to schizophrenia means that our best bet to "cure" that disease is to prevent the "brain mis-wiring" that seems to underlie it. The field needs to move to understand the biological manifestations of pre- or early symptomatic phases of brain disease.

Lesson 6: Neurological Disease Is, for the Most Part, Neuropsychiatric Disease

Distinctions between neurology and neuropsychiatry are being blurred to the point of extinction. Even if nothing were learned about brain-behavior relationships from neuropsychiatry, we would still learn about the psychopathology of the neurological patients themselves. Psychiatric morbidity affects the great majority of these patients. Dementia, depression, delusions, and hallucinations are most troubling to patients and caregivers, and in general are even more troubling than motor, sensory, or other neurological symptoms. Disability is strongly linked to psychiatric symptoms and functional decline is often a consequence of their persistence. With millions of patients living with chronic neurological diseases (4.5 million Alzheimer's patients, 500,000 new stroke victims annually, over a million individuals with moderate or more severe traumatic brain injury every year, and millions of others with epilepsy, multiple sclerosis, etc.), the public health significance of caring for the psychiatric aspects of neurological disease is substantial. Developing a better understanding of the emergence of psychiatric disorders in neurological disease, and improving treatments for these conditions should be a major public health priority. Making sure that these millions of patients can access proper psychiatric care is critical to their well-being. As life expectancy after brain damage is steadily lengthened, planning for the growth in the number of cases with such conditions is also needed. Whether or not much is learned about other aspects of psychiatry, caring for these patients better is reason enough for this effort.

The Future

As neuroscience and psychology become more applied, as new tools become available to study the living brain, and as translational efforts take off in the next few decades, neuropsychiatry will continue to grow as a field rooted in the interface between neurology and psychiatry, as will caring for the patients seen at that interface. The basic sciences will bring better tools to help facilitate improved understanding of the etiopathogenesis of psychopathology in neurological disease, and continue to reap lessons about brain-behavior relationships. Concurrently, the clinical sciences should make a priority the development and study of treatments for psychopathology in neurological disease, and the educational oversight organizations, such as the American Board of Psychiatry and Neurology, and the Residency Review Commission of the Accreditation Committee for Graduate Medical Education, should modify educational activities, core competencies, and requirements to reflect advances in this area. This effort must also continue to

focus on these underserved patients themselves to be sure that what we learn is applied through secondary translation from best practices to widely used practices.

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