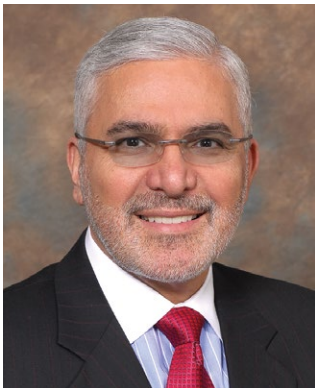
Psychiatry is Neurology: White matter pathology permeates psychiatric disorders



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Ask neurologists or psychiatrists to name a white matter (WM) brain disease and they are very likely to say multiple sclerosis (MS), a demyelinating brain disorder caused by immune-mediated destruction of oligodendrocytes, the glial cells that manufacture myelin without which brain communications would come to a standstill.

MS is often associated with mood or psychotic disorders, yet it is regarded as a *neurologic* illness, not a *psychiatric* disorder.

Many neurologists and psychiatrists may not be aware that during the past few years, multiple diffusion tensor imaging (DTI) studies have revealed that many psychiatric disorders are associated with WM pathology.[1]

Most people think that the brain is composed mostly of neurons, but in fact the bulk of brain volume (60%) is comprised of WM and only 40% is gray matter, which includes both neurons and glial cells (astroglia, microglia, and oligodendroglia). WM includes >137,000 km of myelinated fibers, an extensive network that connects all brain regions and integrates its complex, multifaceted functions, culminating in a unified sense of self and agency.

The role of the corpus callosum

Early in my research career, I became interested in the corpus callosum, the largest interhemispheric WM commissure connecting homologous areas across the 2 cerebral hemispheres. It is comprised of 200 million fibers of various diameters. Reasons for my fascination with the corpus callosum were:

The studies of Roger Sperry, the 1981 Nobel Laureate who led the team that was awarded the prize for split-brain research, which involved patients whose corpus callosum was cut to prevent the transfer of intractable epilepsy from 1 hemisphere to the other. Using a tachistoscope that he designed, Sperry discovered that the right and left hemispheres are 2 independent spheres of consciousness (ie, 2 individuals) with different skills.[2] Cerebral dominance (laterality) fully integrates the 2 hemispheres via the corpus callosum, with a verbal hemisphere (the left, in 90% of people) dominating the other hemisphere and serving as the "spokesman self." Thus, we all have 2 persons in our brain completely integrated into 1 "self."[2] This led me to wonder about the effects of an impaired corpus callosum on the "unified self."

Postmortem and MRI studies conducted by our research group showed a significant difference in the thickness of the corpus callosum in a group of patients

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Table 1

High-yield diffusion tensor imaging terms

Measurement	Definition
Fractional anisotropy (FA)	Values range between 0 (water motion random) and 1 (directional selectivity of water movement)
Mean diffusivity (MD)	Average molecule motion, regardless of direction
Axial diffusivity (AD)	Molecule movement parallel to axons
Radial diffusivity (RD)	Molecule movement perpendicular to axons

Table 2

Psychiatric disorders and symptoms reported to have white matter pathology

Schizophrenia[7]
Bipolar disorder[8]
Major depressive disorder[9]
Obsessive-compulsive disorder[10]
Anxiety disorders[11]
Autism spectrum disorder[12]
Alcohol use disorders[13]
Substance use disorders[14]
Borderline personality disorder[15]
Antisocial personality[16]
Psychopathy[17]
Conduct disorder[18]
Oppositional defiant disorder[19]

with schizophrenia vs healthy controls, which implied abnormal connectivity across the left and right hemispheres.[3]

I then conducted a clinical study examining patients with tumors impinging on the corpus callosum, which revealed that they developed psychotic symptoms (delusions and hallucinations).[4] This study suggested that disrupting the integrity of the callosal inter-hemispheric fibers can trigger fixed false beliefs and perceptual anomalies.[4]

A 'dysconnection' between hemispheres

I translated those observations about the corpus callosum into a published hypothesis[5] in which I proposed that Schneider's First-Rank Symptoms of schizophrenia of thought insertion, thought withdrawal, and thought broadcasting—as well as delusional experiences of "external control"—may be due to a neurobiologic abnormality in the corpus callosum that disrupts the flow of ongoing bits of information transmitted from the left to the right hemisphere, and vice versa. I proposed in my model that this disruption leads to the verbal left hemisphere of a psychotic patient to describe having thoughts inserted into it from an alien source, failing to recognize that the thoughts it is receiving are being transmitted from the disconnected right hemisphere, which is no longer part of the "self." Similarly, impulses from the right hemispheric consciousness are now perceived by the patient's verbal left hemisphere (which talks to the examining physician) as "external control." Thus, I postulated that an abnormal corpus callosum structure would lead to a "dysconnection" (not "disconnection") between the 2 hemispheres, and that anomalous dysconnectivity may generate both delusions and hallucinations.[6]

Two decades later, my assumptions were vindicated when DTI was invented, enabling the measurement of WM integrity, including the corpus callosum, the largest body of WM in the brain. ***Table 1*** defines the main parameters of WM integrity, anisotropy and diffusivity, which measure water flow inside WM fibers.

Table 3

Neuroprotective and promyelination effects of prolactin

Enhances and sustains neurogenesis
Protects from damage caused by seizures
Protects against glutamate neurotoxicity
Protects the retina from degeneration
Stimulates immune response
Protects against apoptosis
Promyelination effects: Repairs white matter damage by stimulating the proliferation of oligodendrocytes, the main source of myelin in the brain (and the number of which declines in schizophrenia and related psychoses)
If women who have multiple sclerosis (MS) become pregnant, their MS may go into remission as their prolactin rises dramatically. The remission will continue during lactation, and relapse occurs when they wean their babies and prolactin drops precipitously

Source: References 22,23

During the past 15 years, many studies have confirmed the presence of significant abnormalities in the myelinated fibers of the corpus callosum in schizophrenia, which can be considered a validation of my hypothesis that the corpus callosum becomes a dysfunctional channel of communications between the right and left hemisphere. Subsequently, DTI studies have reported a spectrum of WM pathologies in various other cerebral bundles and not only in schizophrenia, but also in other major psychiatric disorders (***Table 2,***[7-19] ***page 8***).

The pathophysiology of WM pathology in many psychiatric disorders may include neurodevelopmental aberrations (genetic, environmental, or both, which may alter WM structure and/or myelination), neuroinflammation, or oxidative stress (free radicals), which can cause disintegration of the vital myelin sheaths, leading to disruption of brain connectivity.[6,7] Researchers now consider the brain's WM network dysconnectivity as generating a variety of psychiatric symptoms, including psychosis, depression, mania, anxiety, autism, aggression, impulsivity, psychopathy, and cognitive impairments.

It is not surprising that WM repair has become a therapeutic target in psychiatry and neurology. Among the strategies being investigated are inhibiting the Nogo-A signaling pathways[20] or modulating the Lingo-1 signaling.[21] However, the most well-established myelin repair pathway is prolactin, a neuroprotective hormone with several beneficial effects on the brain (***Table 3***[22,23]), including the proliferation of oligodendroglia, the main source of myelin (and the number of which declines in schizophrenia). Antipsychotics that increase prolactin have been shown to increase WM volume.[24,25] It has even been proposed that a decline in oligodendrocytes and low myelin synthesis may be one of the neurobiologic pathologies in schizophrenia.[26] One of the 24 neuroprotective properties of the second-generation antipsychotics (SGAs) is the restoration of WM integrity.[27] It's worth noting that WM pathology has been found to be present at the onset of schizophrenia before treatment, and that SGAs have been reported to correct it.[28]

In conclusion, psychiatric disorders, usually referred to as "mental illnesses," are unquestionably neurologic disorders. Similarly, all neurologic

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disorders are associated with psychiatric manifestations. WM pathology is only 1 of numerous structural brain abnormalities that have been documented across psychiatric disorders, which proves that psychiatry is a clinical neuroscience, just like neurology. I strongly advocate that psychiatry and neurology reunite into a single medical specialty. Both focus on disorders of brain structure and/or function, and these disorders also share much more than WM pathology.[29]

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