

# The American Journal of Psychiatry

## Residents' Journal

August 2015

Volume 10

Issue 8

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### IN THIS ISSUE



This issue of the *Residents' Journal* focuses on the topic of **Biological Psychiatry**. In an editorial, Adarsh S. Reddy, M.D., Ph.D., discusses the importance of understanding the biological underpinnings of psychiatric illnesses. Matthew E. Hirschtritt, M.D., M.P.H., examines evidence for and against a causal mechanism linking traumatic brain injury (TBI) and criminality in youths, with discussion on the neurobiology of TBI. Gopalkumar Rakesh, M.D., investigates the neurobiology of consciousness and its relevance and application in psychiatry. Amy E. Curtis, M.D., presents a review of white matter dysfunction central to the neurodevelopment of schizophrenia. Alecia Vogel-Hammen, M.D., Ph.D., provides important information on resting state functional connectivity. Julio M. Bernardi, M.D., examines optogenetic applications in psychiatric research. Lastly, Janet Charoensook, M.D., presents a review of the book *Brain on Fire: Month of Madness*, about a rare neuro-immunological illness that manifested with prominent psychosis.

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# Biological Psychiatry

Adarsh S. Reddy, M.D., Ph.D.

Major advances were made in the phenomenological descriptions of psychiatric illnesses at the turn of the previous century. Defining specific criteria for illness, an idea adopted from various medical syndromes, which further augmented the identification of major psychiatric syndromes, was done in the landmark publication of the Feighner criteria (1). Despite limited understanding of the biological underpinnings of psychiatric illnesses, serendipity has been gracious to psychiatry. The fortuitous discovery of lithium, antipsychotics, stimulants, antidepressants, and ECT essentially moved psychiatric patients from the asylums to an outpatient/inpatient type of setting. Despite our seemingly remarkable progress, much remains to be learned. Reverse engineering of drugs has led to improvements in side-effect profile and pharmacokinetic and pharmacodynamic parameters. However, there is little change in terms of our fundamental understanding of the illnesses and their treatments.

One of the fundamental limitations of our understanding of psychiatric illnesses stems from our limited understanding of the complexities of the brain and the genetic heterogeneity of diseases with complex inheritance. All hope is not lost in psychiatry, as tremendous advances have been made in our

It might serve the resident well to be familiar with some of the current approaches to understanding the biological bases of mental illnesses.

understanding of brain structure, function, and development (2). New tools for imaging and rapid sequencing of genetic information, along with the computational power to support processing of massive amounts of data and online collaborations, have accelerated progress in this area. The National Institute of Mental Health has implemented the Research Domain Criteria, whose goal is to “develop, for research purposes, new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures” (3). Future advances in psychiatry might largely depend on progress in such an understanding. Hence, it might serve the resident well to be familiar with some of the current approaches to understanding the biological bases of mental illnesses. It has been recognized that psychiatry residency programs must consider mod-

ifying their curricula (4). Granted that some findings may need revision with better understanding of illnesses, they might still provide a theoretical framework that forms a basis for good clinical practice.

One of the goals of this issue of the *Residents' Journal* is to introduce the reader to certain concepts that have gained traction in the field. While the art of the practice of psychiatry might remain fundamentally unchanged, the science might not be.

Dr. Reddy is a fourth-year resident in the Department of Psychiatry at Washington University, St. Louis, and the Guest Section Editor for this issue of the *Residents' Journal*.

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# Traumatic Brain Injury and Juvenile Criminal Behavior

Matthew E. Hirschtritt, M.D., M.P.H.

Traumatic brain injury (TBI) is defined by a physical injury to the head directly associated with at least one of the following symptoms: decreased level of consciousness, amnesia, skull fracture, neurological or neuropsychiatric abnormality, or an intracranial lesion (1). There is no universally accepted grading of TBI severity; however, most published research operationalizes TBI severity by duration of loss of consciousness (LOC) and/or Glasgow Coma Scale (GCS) score, with “mild” TBI resulting in no LOC to minimal LOC and a GCS score  $\geq 13$ , “moderate” TBI resulting in less than an hour of LOC and a score between 9 and 12, and “severe” TBI resulting in hours of LOC and a score  $\leq 8$  (2). Evidence from multiple epidemiologic samples demonstrates an annual incidence rate of TBI among children and adolescents (0–20 years) of 691 per 100,000 treated in emergency departments and 74 per 100,000 treated in inpatient settings; nine per 100,000 cases result in death (3).

In comparison, rates of TBI among youths involved in the juvenile justice system are significantly higher. A meta-analysis suggests that the prevalence of TBI among juvenile offenders is approximately 30% and is more commonly reported in this population compared with nonoffending youths (pooled odds ratio=3.37) (4). Although it is possible that TBI in and of itself leads directly to impaired judgment and impulsivity that predispose youths to criminal behavior, there is evidence to suggest that in some cases a predisposition to risky behavior may lead to TBI, which acts as a mediator in the path toward criminal behavior.

The purpose of the present review is to summarize the evidence for and against a causal mechanism linking TBI and criminality in youths. In this con-

text, it is crucial to first appreciate the neuropsychological and neurobiological sequelae of TBI in youths.

## NEUROBIOLOGY OF TBI

The observed histopathologic effects of TBI are thought to be the result of mechanical trauma that precipitates traumatic hematomas, leading to vasospasm and ischemia (5). Simultaneously, angular or rotational acceleration of the head leads to stretching and tearing of white matter brain tissue and diffuse axonal injury (DAI) (6). In combination, these effects may lead to disrupted axonal transport and neuronal circuits. However, the long-term effects of TBI depend on the severity and frequency of the insulting injury; whereas mild TBI may have few long-term neurocognitive sequelae, repetitive mild or severe TBI carries a higher risk of permanent axonal and cytoskeletal alterations and accumulation of abnormal protein aggregates (5, 6).

Advances in neuroimaging have revealed short- and long-term effects of TBI in youths. Among structural modalities, diffusion tensor imaging (DTI) has been particularly useful, as it illustrates the location, orientation, and directionality of white matter tracts in the brain that may be disrupted by TBI. Numerous studies have demonstrated DAI in brain regions that subservise executive functioning and impulse control. For example, in a study comparing children exposed to mild-to-moderate TBI with control subjects, the DTI examinations of TBI-exposed children demonstrated disruption of inferior frontal, superior frontal, and supracallosal white-matter tracts (7). Exploratory analyses revealed significant differences in the degree of disruption of these tracts between youths with moderate TBI and controls

but not mild TBI and controls, suggesting a dose-dependent relationship between severity of the physical trauma and integrity of white-matter axonal tracts (7). Subsequent DTI-based studies among youths with TBI have demonstrated disruption of white-matter tracts in the corpus callosum (8), orbito-frontal white matter, cingulum bundles, and uncinate fasciculi (9). These studies have found strong correlations between the degree of DAI in frontal cortical regions and measures of executive function and working memory (7) and between DAI of the corpus callosum and measures of processing speed (8).

Neuropsychological findings among youths with mild-to-moderate TBI reflect damage to frontal polar and orbito-frontal regions, including social dysfunction, such as decreased self-esteem, loneliness, maladjustment, and social isolation (10), as well as decreased executive functioning skills (11). Of these postinjury deficits, impairments in executive functioning (the regulation of cognitive processing) are particularly relevant to risk of criminal behavior. Specifically, numerous studies demonstrate that youths who have experienced moderate-to-severe TBI show decreased working memory, inhibition, planning, metacognition, social cognition, and behavioral regulation (11).

## TBI AND CRIMINALITY IN YOUTHS: A CAUSAL RELATIONSHIP?

Taken together, these neuroimaging and neuropsychological findings appear to support the concept that TBI in childhood or adolescence leads to increased risk for disinhibited behavior and subsequent involvement in the juvenile justice system. Further supporting this conclusion, cross-sectional studies support a dose-dependent re-

relationship between frequency of self-reported TBI and degree of violence in offenses (12, 13) and between severity of TBI and age at first offense (13). In addition, incarcerated youths, compared with nonincarcerated youths, report high rates of previous TBI in cross-sectional studies (14). Other studies suggest potential mediators of this relationship. For example, among adolescent offenders, higher-frequency TBI is associated with elevated risk of psychological disorders and problematic substance use (15), both of which may lead to involvement in the juvenile justice system. Similarly, among incarcerated adolescents, increasing severity of TBI (as measured by length of loss of consciousness) is associated with increased self-reported alcohol use (13). Specifically, substance use may be a more robust mediator linking TBI and criminal behavior in childhood victims of TBI compared with adolescents (12, 16). The few longitudinal studies that have examined the relationship between early TBI and later criminal behavior demonstrate that increased severity and earlier age at onset of TBI in childhood or adolescence are strongly associated with increased risk of offending behavior (antisocial behavior or involvement in petty crime) in adulthood (17). Childhood TBI history remains a risk factor for criminal behavior in young adulthood, even when controlling for preinjury substance dependence and criminal behavior (16).

However, TBI may be only one among many factors leading to criminality. Early studies have demonstrated that incarcerated youths with TBI have greater preinjury risk factors for criminality, including medical issues, cognitive delay, behavioral dysfunction, neurodevelopmental skills (e.g., gross and fine motor skills, visual processing), family disruption, decreased socioeconomic status, and poorer verbal and nonverbal skills (18). Furthermore, these risk factors, as well as prenatal exposures such as poor maternal diet or smoking, may lead to dysfunction of brain circuitry that is believed to be involved in empathy, threat sensitivity, and decision making (19), leading to increased risk-taking behavior. Further supporting the concept that delinquent

adolescents may be predisposed to risk-taking behavior that predates their TBI, a survey (20) among parents of delinquent (N=316) and nondelinquent (N=427) adolescents demonstrated that the most common mechanism of TBI among nondelinquent adolescents was sporting accidents (20.2%). In contrast, among delinquent adolescents, sporting accidents, falls, motor vehicle accidents, and fights were each roughly equally likely to be causes of TBI (each about 10%–13%).

### LIMITATIONS AND FUTURE DIRECTIONS

A complete understanding of the relationship between juvenile criminality and TBI is hampered by several limitations. First, despite the importance and timeliness of this topic, there are only nine to 10 studies available that have examined this association (4, 14), in large part because of the sensitive nature of the information and the challenges of working with doubly vulnerable research subjects (both youths and prisoners). Second, the available studies use vastly different definitions of TBI, ranging from any head injury to injuries that resulted in LOC of a certain minimum length (14). This heterogeneity of TBI criteria creates challenges when aggregating results among studies because

different types of head injuries may lead to diverse behavioral sequelae. Third, few studies have defined the severity or frequency of TBI, instead relying on a yes/no response to measure for a history of TBI. Those few studies that have measured severity by LOC have yielded results suggesting that incarcerated youths tend to have more severe TBI compared with nonincarcerated controls (14). Fourth, most studies use self- or parental reports, which are subject to recall bias. Fifth, there are no published studies, to our knowledge, that have integrated neuroimaging findings among incarcerated youths with TBI, limiting our ability to correlate differences in neural architecture with behavioral outcomes.

From these limitations arise at least three corresponding areas for methodologic improvement and future research directions. First, researchers should clearly define mechanism, severity, and frequency of TBI in subsequent studies involving juvenile offenders. Second, birth cohorts should be examined for behavioral, cognitive, and emotional development before and following TBI to better delineate the causal pathway between TBI and juvenile criminality. Third, use of neuroimaging, especially DTI and functional modalities, should be integrated into these studies to correlate neural findings with behavioral outcomes.

### KEY POINTS/CLINICAL PEARLS

- Traumatic brain injury (TBI) is more common among youths involved in the juvenile justice system than the general pediatric population; the estimated rate of TBI in this population is as high as 30%.
- The neurobiologic effects of TBI depend on the severity of impact; in general, TBI is characterized by hematomas and diffuse axonal injury (DAI), leading to disrupted axonal transport and neuronal circuits.
- Evidence supporting a direct causal relationship between TBI in youths and criminality include the high prevalence of executive functioning deficits among youths with TBI, a dose-dependent relationship between frequency of self-reported TBI and degree of violence in offenses, and between severity of TBI and age at first offense. In addition, TBI is associated with increased risk of disruptive behavioral disorders and substance use, which increases risk of criminality.
- However, a direct causal relationship between TBI and criminality among youths has not been established; specifically, adolescents may be predisposed to risk-taking behavior that predates their TBI because of environmental (e.g., violence at home) and biological (e.g., genetic loading for risk-taking behavior) factors.



## CONCLUSIONS

In summary, TBI is more prevalent among juvenile offenders compared with nonoffending youths, and there is epidemiologic and neurobiological evidence to suggest that TBI itself may predispose to criminal behavior. Specifically, neurobiological changes secondary to TBI have been shown to lead to increased risk taking and disinhibited behavior, and TBI is more common among juvenile offenders compared with nonoffenders. However, various other risk factors, such as low socioeconomic status, may simultaneously predispose youths to both TBI and criminality. Identifying the mechanism underlying the relationship between TBI and youth criminality will inform primary and secondary preventive efforts to protect this vulnerable population, including targeted interventions to prevent criminal behavior in at-risk youths and to decrease risk of re-offense in incarcerated youths.

Dr. Hirschtritt is a second-year resident in the Department of Psychiatry, University of California, San Francisco.

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# Neurobiology of Consciousness: Relevance and Application in Psychiatry

Gopalkumar Rakesh, M.D.

Consciousness is defined as the entirety of what makes us human beings. Although it evades a universal definition, multiple attempts to define it have focused on domains as described by the terms “awareness” and “wakefulness.” Awareness is a qualitative measure of consciousness, while wakefulness is a quantitative measure of consciousness (1). Neurobiological definitions have focused on assessing brain activity using various modalities: imaging brain activity while resting, measuring EEG when awake as opposed to the same measurement during sleep or in vegetative patients. An anatomical definition would detail the brain areas synchronizing to create a net of consciousness, whereas a physiological definition details cycles of thalamo-cortical brain activity in the gamma band frequency (2). A distinction needs to be made between awareness of the environment, perception of stimuli from the environment, and perception regarding self and thinking that precedes volitional activity.

In neuroscience there are two schools of thought regarding the neurobiology of consciousness: the holistic approach and the neuronal specificity approach. The holistic approach postulates that all neurons in the brain contribute toward creating consciousness, whereas the neuronal specificity hypothesis postulates that there is one particular area or group of neurons that is responsible for creating consciousness.

## HISTORY OF CONSCIOUSNESS RESEARCH

In 1929, Hans Berger demonstrated the ability to read brain electrical activity from the surface of the scalp using surface electrodes; this would later be-

come the EEG and give us a powerful tool to distinguish brain activity between being awake and being asleep. In the 1950s, Kleitman and his colleagues in Chicago discovered that sleep itself has an internal architecture and comprised different stages, which were further detailed by measuring with EEG. Seminal work by Moruzzi and Magoun (3) in 1949 demonstrated the existence of a group of neurons in the upper brain tegmentum and central thalamus controlling wakefulness, which came to be known as the ascending reticular activating system (ARAS) (Figure 1). Subsequent studies have reinforced evidence that the ARAS does play an important role in mediating arousal and wakefulness. Sherrington showed, by studying cats, that lesions at the midbrain level cause a decorticate posture and lesions at the level of the pons cause a decerebrate posture.

## DISORDERS OF CONSCIOUSNESS

Some disorders of consciousness are coma, vegetative state, minimally conscious state, akinetic mutism, and catatonia. Coma is a disorder of consciousness characterized by the absence of any arousal or wakefulness, although reflexes are usually present. The underlying pathology is usually a complete dysfunction of the ascending reticular activating system and the cortex, which can broadly be a result of metabolic abnormalities or brain injury (4). Vegetative state occurs when the patient regains some degree of wakefulness but lacks awareness. The individual may have a few sleep-wake cycles and can open his or her eyes but does not have any cognitive function. It is a progression of comatose patients who fail to regain

normal function, but it is not essentially irreversible. Persistent vegetative state is defined as a vegetative state that has been present for a month. The chance of recovery decreases as the time spent in the vegetative state increases. Patients in a vegetative state usually show reflex or spontaneous eye opening and breathing. They can occasionally be awake with their eyes open, sometimes showing spontaneous roving eye movements and occasionally moving trunk or limbs; at other times their eyes are shut, and they appear to be asleep (4). Minimally conscious state (MCS) has been defined as a condition with impaired consciousness but definite behavioral evidence of self- or environmental awareness that can be demonstrated. Patients follow simple commands, show gestural/verbal responses irrespective of accuracy, can perform intelligible verbalization, show some purposeful behavior that is contingent due to appropriate environmental stimuli, and are nonreflexive. Purposeful behavior can include smiling/crying, vocalizations, reaching or touching objects, and pursuit eye movements (5). Akinetic mutism is characterized by deficits in arousal, movement, speech, initiation, and spontaneity. The individual’s eyes can be drawn to stimuli and demonstrate alertness. Some causes can be frontal lobe damage, thalamic stroke, and infectious/physical lesions.

The term “locked-in” syndrome was introduced by Plum and Posner to reflect the quadriplegia and loss of speech. The defining feature of the locked-in syndrome is the relative preservation of cognition.

Catatonia is a clinical syndrome characterized by a constellation of symptoms such as mutism, stupor, posturing, waxy flexibility, catalepsy, grimacing,

negativism, and mannerisms. Although not essentially a disorder of consciousness, it does have an association with patients being nonresponsive as part of negativism and mutism. A single brain imaging study found changes in activation in the right medial and lateral orbitofrontal cortices, as well as in the right posterior parietal cortex in catatonic patients. A predominant GABAergic deficit seems to be the underlying pathophysiology of catatonia (6). It would be interesting to study how much catatonic patients remember about events that occurred when they were catatonic. Further research would be needed to elucidate whether neural circuits mediating consciousness, especially the ARAS, are involved in mediating the process of catatonia.

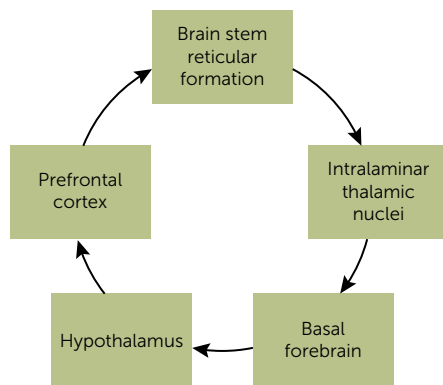
## NEUROBIOLOGY

### Neurobiology of Consciousness

Multiple studies have implicated the ARAS to play an important role in arousal. The ARAS is an intricate network of neurons that connects a portion of the brainstem: the reticular formation, intralaminar thalamic nuclei, basal forebrain (which receives cholinergic projections from the ARAS and plays an important role in REM sleep), hypothalamus (involved in sleep-wake transition), and cerebral cortex. Neurotransmitter-wise, it comprises a group of cholinergic nuclei in the upper brainstem and basal forebrain, noradrenergic nuclei, especially the locus ceruleus, the histamine projection from the posterior hypothalamus, and probably dopamine and serotonin pathways that arise from the brainstem. Much of the activity exerted by these pathways is mediated by the thalamus, which can be regarded as the apex of the ARAS, as well as a critical synaptic relay for most sensory and intracerebral pathways (7).

A diffuse tensor imaging study (DTI) of the ARAS mapped it to begin in the reticular formation at the level of the mid-pons, ascending through the periaqueductal gray of the midbrain through the anterior commissure and terminating on the hypothalamus (8). This study found DTI parameters to be equal in both hemispheres for both gen-

**Figure 1. Ascending Reticular Activating System Connections**



ders (8). Another study assessing white matter connections using tractography of the intralaminar thalamic nuclei found connections to reticular formation (where the ARAS starts), pedunclopontine nucleus, hypothalamus, basal forebrain, primary sensorimotor, primary motor cortex, and basal ganglia (9). This resonates with published research implicating areas such as the basal ganglia that play an important role in the cortico-basal ganglia-thalamic circuits that play a central role in motivation, planning, and goal-directed behaviors. Other studies have found alterations in the ARAS fractional anisotropy (which is a measure of neuronal integrity) in patients with traumatic brain injury and cerebral hemorrhage (10).

### NEUROBIOLOGY UNDERLYING DISORDERS OF CONSCIOUSNESS

**Coma.** PET studies have shown gray matter cortical metabolism to be within 50%–70% of normal range. White matter axonal injury could also account for observed pathology (2).

**Vegetative state.** Diffuse decrease in cerebral blood flow is observed, and overall cortical metabolism is within 40%–50% of normal range. Preserved brainstem function is also found (2).

**Minimally conscious state.** Few studies elucidating neurobiology exist, and global reduction in cortical metabolism with islands of preserved activity is present.

**Locked-in syndrome.** Isolated lesions of midbrain and absence of reduced cortical metabolism is observed, as well as disruption of corticospinal and corticobulbar pathways.

**Akinetic mutism.** The underlying pathology is bilateral injury to the medial frontal lobes and anterior cingulate cortex from a mass lesion or anterior cerebral infarct. It can also be caused by bilateral injury to the basal ganglia, thalamus, or midbrain (11).

**Catatonia.** GABAergic deficit in psychosis or affective disorders can also be caused by encephalitis or structural lesions.

## DEFAULT MODE NETWORK

In the last several years, what has become robustly associated with consciousness research has been the default mode network. The default mode network is a group of brain structures that are active when an individual is at rest or daydreaming and not focused on performing a particular task. This concept was proposed in the early 2000s by Raichle et al. (12). Functional imaging studies done in individuals at rest/daydreaming have shown activity in the medial temporal lobe, medial prefrontal cortex, posterior cingulate cortex, ventral precuneus, and parietal cortex (medial, lateral, and inferior). This network of activity is absent in newborns and is present in children aged 9–12 years, showing dynamic changes with age (13). A potential change in default mode network functional connectivity between these regions in disorders of consciousness has been shown in multiple studies. A recent systematic review of resting state studies done in patients with disorders of consciousness, such as coma, vegetative state, and minimal conscious state, showed marked decrease in functional connectivity in regions mediating the default mode network. This review also included PET studies that showed a global reduction in blood flow to these affected regions, as well as a demonstrated relationship between the degree of connectivity and degree of impairment in consciousness (14).

Synchronized phase-locked low-amplitude brain activity in the gamma frequency band coordinated by the intralaminar nuclei of the thalamus with back-and-forth cycling between the thalamus and cortex has also been postulated to mediate consciousness. The thalamo-cortical circuit, which recruits more brain regions to form widespread activation, is what sustains consciousness. It is only reasonable to think that this circuit utilizes the neuronal structure of the ARAS for mediation of its effects.

## RATING SCALES

The most widely used scale for diagnosis and assessment of consciousness has been the Glasgow Coma Scale, which has three domains of assessment: eye opening, verbal response, and motor response. A total score ranging from 3 to 14 is calculated on this scale, with recording of scores on individual items as well. A good rating scale for catatonia is the Bush Francis Catatonia Rating Scale, which has 22 items with a range of 0–66.

## IMPLICATIONS FOR CLINICAL APPLICATIONS AND FUTURE DIRECTIONS OF RESEARCH

A possible proposition is that consciousness as an entity being the opposite of unconsciousness has clear neurobiological underpinnings. This would also encompass the neurobiology of what distinguishes thoughts and actions mediated by the “self” as opposed to thoughts brought by an external source, which would be relevant in mediating treatment for schizophrenia (15). Research in this direction would also be able to explain why the concept of self is altered and why patients report that actions performed or thoughts they have are not their own (16). In obsessive-compulsive disorder, where insight into the illness is important for treatment response and prognosis, consciousness research could reveal new treatment modalities (17). Electrical modulation of consciousness can be a part of treatment for coma, minimally conscious state, and vegetative state in the future just as

## KEY POINTS/CLINICAL PEARLS

- Some disorders of consciousness are stupor, coma, akinetic mutism, minimally conscious state, persistent vegetative state, conversion disorder and catatonia.
- Neurophysiological theories behind consciousness include activation of the ascending reticular activating system and thalamo-cortical oscillations.
- Some drugs that can be used in patients with disorders of consciousness are zolpidem, dopamine agonists, modafinil, and selective serotonin reuptake inhibitors.
- Modulation of consciousness using brain stimulation techniques as well as correlation of consciousness to resting state networks on imaging are two avenues with scope for research in the future.

ECT is currently used to treat catatonia. A systematic review provided detailed summaries of patients with modulation of disordered states of consciousness with deep brain stimulation of the ARAS by implanting electrodes in the thalamic nuclei (18). It has also opened up research into the use of medications that promote neurogenesis and modulate glutamate and GABA to promote recovery in these patients. There has been substantial evidence recommending use of zolpidem in patients with vegetative state or minimally conscious state. Other drugs such as baclofen, lamotrigine, selective serotonin reuptake inhibitors, tricyclic antidepressants, methylphenidate, and modafinil are also being examined for the same purpose. Dopaminergic agents, such as amantadine, levodopa, and apomorphine, have been implicated to promote recovery in akinetic mutism in isolated case studies (19). What has been interesting has been the large number of psychotropic medications being used to promote recovery in these disorders. However, we lack greater levels of evidence for approved clinical application. That would be an endeavor for the future to see how these drugs span out along with the use of brain stimulation techniques like deep brain stimulation and ECT to modulate consciousness.

Dr. Rakesh is a second-year resident in the Department of Psychiatry, Duke University Medical Center, Durham, N.C.

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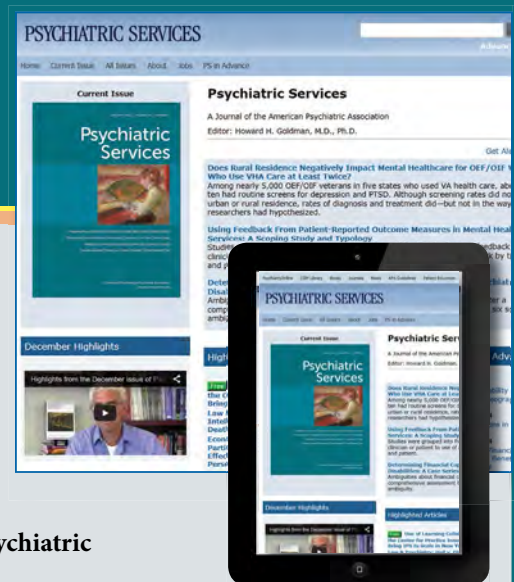
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# White Matter Dysfunction Central to Neurodevelopment of Schizophrenia: A Review of Emerging Literature

Amy E. Curtis, M.D.

Schizophrenia is a complex disorder with an associated congregation of symptoms resulting in severe global functional impairment. Despite recent studies supporting genetic heterogeneity in predisposition to schizophrenia (1), expanding evidence has emerged supporting a common neurodevelopmental pathway with white matter dysfunction at the epicenter. It is apparent that white matter abnormalities exist in early schizophrenia, though the question remains whether these changes reflect primary pathophysiology or stem secondary to cortical impairments (2). Historically, imaging studies have focused on gray matter pathology in exploring the etiology and progression of schizophrenia, with more consistent evidence for cortical changes compared with white matter structural abnormalities (2–4). However, findings in the early stages of schizophrenia suggest that frontal lobe gray matter deficits may be driven by white matter alterations, and a common causal pathway may be promoting these changes (3).

White matter is becoming an increasing focus of research, as it serves as the physical structure for functional connectivity in the brain, with newer neuroimaging methods sensitive to subtle changes in white matter connectivity (5–6). Such emerging techniques include magnetic resonance spectroscopy to measure microstructure and CNS metabolism, a particular measure of MRI to quantify myelination known as relaxometry, magnetization transfer imaging to approximate connectivity through proton interaction in free water, and combination techniques such as joint magnetization transfer ratio and diffusion tensor spectroscopy to explore

both axon and myelin abnormalities (7–8). Diffusion tensor imaging (DTI) is a particularly sensitive tool in measuring progression of white matter degeneration and is now one of the most widely used neuroimaging biomarkers for schizophrenia (3). DTI is an *in vivo* MRI tool that provides a proxy for white matter “connectivity,” with reductions in its fractional anisotropy measure correlating to decreased white matter integrity in diseases such as multiple sclerosis and the leukodystrophies (5, 7). Fractional anisotropy estimates the proportion of water diffusion along the longest axis of movement and gauges white matter fiber coherence (5). As these measures are also sensitive to subtle white matter alterations in schizophrenia, they have opened new doors in investigating the illness as a neurodevelopmental process with an element of disconnectivity at its core (5). Structured by developmental stage of illness, the present review serves to summarize evidence of white matter dysfunction and its essential contribution to the pathogenesis of schizophrenia.

## EARLY DEVELOPMENT

With synthesis of a wide array of research including data stemming from neuroimaging, genetic analyses, histological and postmortem morphology, and biochemical processes, numerous white matter alterations have shown a significant role in the etiology of schizophrenia (2). Specific deficits discovered in white matter include reductions in volume, myelin composition abnormalities, changes in gene expression, and altered oligodendrocyte density (2). Altered connectivity can reflect a variety

of phenomena associated with white matter disruption in schizophrenia, including impaired control of plasticity and resulting disintegration of neural systems, disruption of white matter integrity, and deviation of neuronal connections to structural targets (9). In examining the normal trajectory of white matter development over time, it is interesting to note the overlap between ages of peak development and that of onset of schizophrenia and prodromal symptoms, specifically in those tracts associated with higher-order functions rather than motor and sensory information (3).

Risk factors have been shown to play a role across both genetic and clinical risk groups, with implications for impact on white matter trajectories and cortical circuits at critical time points (6). The link between environmental insults and resulting white matter pathology may stem from their excitotoxic effects on oligodendrocytes (7), with possible variation in clinical outcome or symptom severity depending on the level of disruption. A recent review by Peters et al. (6) suggests a type of two-hit hypothesis, with evidence supporting disrupted development of white matter during adolescence with later modulation by stressors, including inflammation, neurotoxicity, abnormal aging effects, or medications. An example of one such stressor that has been consistently implicated in activation and progression of psychosis is cannabis exposure. A recent systematic review exploring the effect of cannabis use in early development of schizophrenia found evidence for an additional impact of drug exposure on preexisting white matter dysfunction, strengthening support for

**TABLE 1. Location of White Matter Abnormalities in Psychosis by Disease Stage<sup>a</sup>**

High-Risk	First Episode	Chronic
Right internal capsule	Joint of external plus internal capsule	External plus internal capsule
Corpus callosum	Corpus callosum	Forceps major/minor
Cingulum	Cingulate bundle	Cingulum radiations
Inferior fronto-occipital fasciculus	Inferior fronto-occipital fasciculus	Inferior fronto-occipital fasciculus
Inferior longitudinal fasciculus	Inferior longitudinal fasciculus	Inferior longitudinal fasciculus
Superior longitudinal fasciculus	Superior longitudinal fasciculus	Superior longitudinal fasciculus
Medial temporal lobe	Temporal/occipital lobe white matter	Superior/middle temporal white matter
Parahippocampal cingulum	Frontal/parietal lobe white matter	Inferior frontal white matter
	Left inferior frontal gyrus	R deep frontal white matter
	Fornix	Fornix
	Posterior thalamic radiation	Anterior/posterior thalamic radiations
	Corona radiata	Uncinate fasciculus
		Lingual/insular white matter

<sup>a</sup> The DTI findings presented are taken from data reported by Melicher et al. (4), Peters et al. (6), Lyu et al. (11), Karlsgodt et al. (12), Jacobson et al. (13), Canu et al. (14), Katagiri et al. (17).

a two-hit neurodevelopmental theory of pathogenesis (5).

### HIGH-RISK STATE

Important inferences can be made from studying individuals at elevated genetic and/or clinical risk for psychosis, where factors related to vulnerability can be differentiated. Large genetic studies have consistently found that a variety of white matter phenotypes are heritable, with nearly every white matter tract exhibiting moderate to high heritability throughout the lifespan (10). Unaffected siblings of patients with first-episode schizophrenia may also share white matter changes, as well as cognitive deficits, indicating a genetic vulnerability to the illness (11). Evidence of white matter alterations have become apparent even prior to development of psychosis in adolescents at high clinical risk (3), with early fractional anisotropy changes predictive of later functional and cognitive outcomes (12). Decreased fractional anisotropy has been found even in children aged 11–13 with sub-clinical psychotic symptoms, specifically within the inferior fronto-occipital fasciculus, cingulum, and inferior longitudinal fasciculus (13).

Those at ultra-high risk of psychosis have exhibited DTI alterations intermediate between first-episode patients and healthy participants, with more pronounced alterations in the high-

risk population who convert to schizophrenia (14). Interestingly, other disorders with psychotic components share similar white matter abnormalities to those of schizophrenia. For example, early prodromal individuals and those diagnosed with schizotypal personality disorder have shown disruptions in the corpus callosum genu resembling patients with chronic schizophrenia, though more widespread abnormalities manifest as psychosis progresses (15). Similarly, while white matter alterations are present in both bipolar disorder and schizophrenia, the pattern of abnormalities differs greatly, with bipolar disorder favoring subcortical myelin compared with the intracortical deficits in schizophrenia (16). This may explain the difference in clinical manifestations of both diseases, as the episodic nature of bipolar disorder may reflect the more efficient repair system of subcortical myelin (16). Another longitudinal study exploring white matter in individuals with prodromal symptoms found that those who did not eventually meet criteria for psychosis experienced resolution of structural deficits over time, suggesting that vulnerability to illness is a dynamic process with potential to be modified early by treatments (17).

### ILLNESS ONSET

Studying individuals in early phases of schizophrenia allows for research into

core pathology with minimal impact of confounding variables such as age, medical comorbidities, medication effects, and illness progression. Early evidence for white matter alterations in schizophrenia has suggested structural abnormalities; however, these findings were regional and inconsistent between studies (3, 4). More recent developments in imaging imply more subtle and widespread alterations of white matter microstructure in schizophrenia (2, 4–5). A recent study by Melicher et al. (4) exploring white matter changes in early stages of psychosis found extensive alterations in most major tracts, including the corpus callosum, superior and inferior longitudinal fasciculi, the posterior thalamic radiation, and the inferior fronto-occipital fasciculus. The authors hypothesized that while previous studies showed inconsistent, localized changes in white matter tracts, these regionalized findings may have stemmed from underpowered studies with increasing sample size revealing more extensive anomalies (4). In studies comparing individuals with adolescent and adult-onset schizophrenia, more severe white matter alterations were present in adolescent patients and could stem from delayed maturation of white matter (18). Investigating white matter trajectory at different stages of the disease, another systematic review showed a sharper slope of white matter volume reductions in early stages of schizophrenia, high-

lighting more pronounced changes in the preclinical phases of illness (14).

## IMPACT OF PHARMACOTHERAPY AND FUTURE DIRECTIONS

In addition to evidence supporting incremental degeneration of white matter in development and progression of psychosis, promising areas of research suggest that this decline could be mitigated by pharmacologic agents early in the course of illness (16). More recent data has indicated that antipsychotics may increase fractional anisotropy over time (19), with a promyelinating effect through direct impact on oligodendrocytes (7) and potential for modification of white matter decline early in the disease course (16). The influence of antipsychotics on white matter may be mediated through effect on glial cells (2), with findings of greater impact of atypical medications on increase in intracortical myelin and white matter volume (16). However, the known effects of medications on white matter can complicate study of DTI changes even in early phases of disease due to established confounds of drug exposure.

Exciting new treatment prospects have surfaced based on insights into other illnesses featuring white matter pathology, such as multiple sclerosis, where common models of pathogenesis have emerged (20). Future explorations into psychosis etiology may involve monitoring the longitudinal course of illness, with early white matter modulation in high-risk individuals having potential to delay disease onset or reduce duration of untreated symptoms

(14). Newer data suggest that use of joint imaging and genetic markers at disease onset could aid in disease prognosis (10). The use of white matter data to predict conversion to psychosis is a relatively new area of study with conflicting findings, considering difficulties in diagnostic heterogeneity and the potential confound of medication effects in early illness course (6). However, the use of white matter data as biomarkers to estimate illness progression or treatment response has promising implications, and future studies might focus on intervening at critical neurodevelopmental windows to slow or even prevent progression of schizophrenia.

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## KEY POINTS/CLINICAL PEARLS

- In addition to gray matter changes, white matter abnormalities are becoming increasingly evident in schizophrenia.
- Newer neuroimaging techniques such as diffusion tensor imaging have advanced the study of white matter changes in many diseases, including schizophrenia.
- White matter dysfunction occurs early in schizophrenia disease course, with patterns changing over time with illness progression and treatment impact.
- Newer studies may explore use of white matter alterations as biomarkers to predict treatment response or to identify vulnerable neurodevelopmental windows.



# A Brief Introduction to Resting State Functional Connectivity

Alecia Vogel-Hammen, M.D., Ph.D.

Resting state functional connectivity (RSFC) MRI uses measures of the intrinsic activity of the brain to better understand neural function and how this function may change across development or in different neurologic or psychiatric illnesses. The power of this technique is just starting to be realized. The present review is of the basics of what constitutes RSFC MRI and what it measures, with brief discussion of some applications in psychiatry.

## THE DEVELOPMENT OF RSFC MRI

MRI produces images by measuring differences in the relaxation states of protons activated by pulses of electromagnetic energy. The difference in both the amount of energy produced in different types of tissues and the time to return to the baseline state after stimulating with magnetic energy allows us to identify different types of tissue (i.e., bone, fat, blood, fluid) and produce the MRI images with which we are all familiar (for a basic review of MRI physics, see reference 1). Standard structural MRI imaging produces a static image of the structure of the organ under study. However, there is clearly more to the brain than just the structure.

In the 1990s, those interested in brain function demonstrated that MRI could also be used to study brain function, in a technique appropriately termed functional MRI (fMRI) (see reference 2 for a review of fMRI and reference 3 for a historical perspective). It was known that oxygenated hemoglobin has different relaxation properties than deoxygenated hemoglobin, and, by carefully tuning the magnetic pulses in the MRI, physicists could measure the difference between the two, the blood-

oxygen-level-dependent (BOLD) signal. This signal allowed neuroscientists to see parts of the brain getting more oxygenated hemoglobin, which was demonstrated experimentally to correspond to increased neuronal activity. Thus, fMRI allowed one to see evoked neural activity, or activity in the brain that was related to a particular stimulus. With careful experimental design, fMRI has allowed for progress in understanding what parts of the brain are active during not only simple but also complex tasks, such as interpreting complicated perceptual information, directing attention, making decisions, and performing complex mental functions such as arithmetic.

fMRI has also been used to better understand what our brain is doing when we are at “rest,” not participating in any specific task (4). Task-evoked fMRI primarily focuses on the activity produced in response to a particular stimulus the experimenter has decided to study. Yet, we have known for at least 20 years that there are not only the changes in BOLD signal during tasks but also slower changes that continue at rest and even underneath the task-based activity (5). Initially, it was thought that these slow signals were just noise, or perhaps related to changes in vascular perfusion. However, studies by Biswal et al. (5) demonstrated that related parts of the brain (e.g., both motor strips) had correlated changes in the slow, resting state BOLD signal, referred to as resting state functional connectivity (Figure 1).

Subsequent work since the mid-2000s has shown that not only do contralateral regions have correlated RSFC signals, but regions thought to be part of the same network also have correlated resting-state BOLD signals (6). For ex-

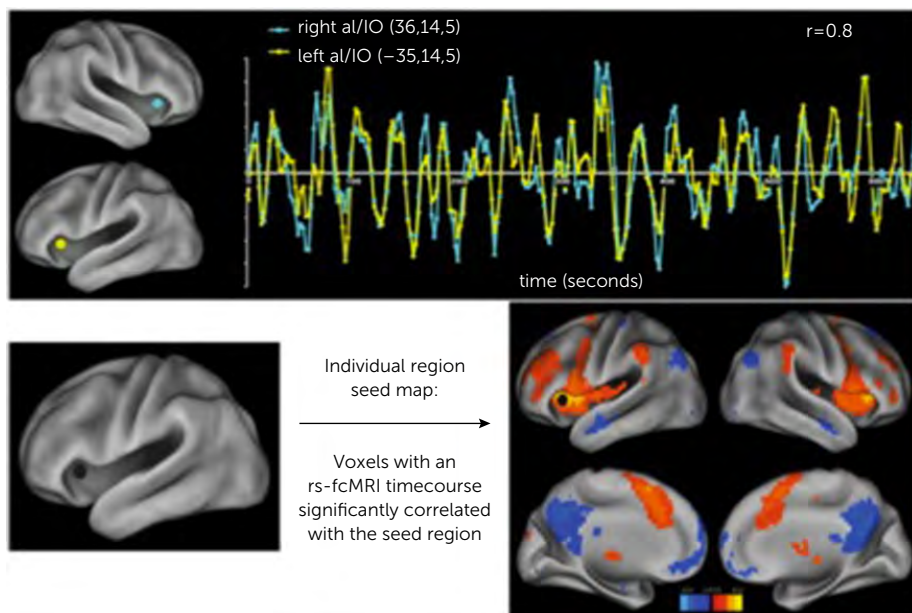
ample, there is a group of brain regions often active at rest with decreased activity during tasks termed the “default mode network.” These regions also have highly correlated RSFC signals (7). The same is true for brain regions that are commonly used for directing attention to environmental stimuli or for organizing task sets (8).

Overall, the pattern seems to be that regions commonly activated together have correlated RSFC time courses (2). In other words, it seems that RSFC may reflect the Hebbian phenomenon of regions that “fire together, wire together,” in that the patterns of activity useful for tasks are repeated in these low-amplitude resting state signals. However, it is important to know that RSFC does not reflect actual “wiring.” There are brain regions with highly correlated resting-state signals that do not have direct anatomical connections (2). RSFC rather seems to reflect a history of common activation, the underpinnings of which are still under study.

## RSFC MRI METHODS

There are a number of ways to measure RSFC. Initial studies in RSFC simply focused on a small part of the brain, typically just a sphere of voxels from the MRI scan, and extracted the low-frequency BOLD signal, measured for at least 3 minutes while at rest, and compared this time course to the RSFC time course extracted from another sphere of voxels in the brain, calculating the correlation (i.e., see references 5, 7, 8 [also see Figure 1]). This allowed researchers to determine that some regions had positively correlated time courses, some regions had no correlation in their time course, and some had negatively corre-

**FIGURE 1. Resting State Functional Connectivity (RSFC) Defined by Correlations in the Slow Time Course of Blood-Oxygen-Level-Dependent (BOLD) Signal Present at Rest<sup>a</sup>**



<sup>a</sup> The top panel shows the BOLD signal in the right and left anterior insula/ frontal operculum (al/fO) regions over about 10 minutes. The BOLD signal is often strongly correlated (in this case with an  $r$  of 0.8) in contralateral regions. The bottom panel shows how these can be used to make a seed map, as the correlation between the BOLD signal from the left al/fO is calculated for every voxel in the brain; voxels with significant positive correlations are shown in warm colors, and voxels with significant negative correlations are shown in cool colors. Figure modified with permission from *Neuropsychology Review* (Vogel et al., "Development of the brain's functional network architecture"). Copyright © Neuropsychol Rev, 2010.

lated time courses. This same idea can be broadened to take the time course from a region in the brain and to calculate how correlated the time course of that "seed" region is with every voxel in the MRI scan that is located in the brain. This results in a "seed map" that reveals what parts of the brain are highly positively and negatively correlated with the given region of interest (Figure 1). One of the first such analyses using seed maps demonstrated the close relationships between regions of the default mode network, a group of regions that are commonly activated at rest and are now thought to be related to self-referential neural processing, as well as future planning and imagery (7).

Alternately, more complicated mathematical techniques can be used to identify groups or networks of regions as defined by RSFC (6). As mentioned above, it is thought that regions with highly correlated RSFC are more commonly activated at the same time. In other words, if parts of the brain have similar, or related, functions, they should have correlated RSFC. Given this presupposi-

tion, computational and graph analytic methods can be used to divide parts of the brain into groups of related regions based on the strength of their RSFC correlations. This can be done either at the level of an individual voxel (the unit of measurement of MRI images) or at a regional level. Common techniques for these types of analysis are independent components analysis, which uses factor analytic techniques to group voxels or regions, and graph theoretic techniques, including InfoMap, which uses a minimization function and random walk generator to identify communities in a larger network of regions. All of the grouping techniques have strengths and weaknesses that are beyond the scope of this introductory review (see reference 6 for a detailed review), but suffice it to say that each of these techniques allows the researcher to identify communities of regions that underlie the basic functions of the human brain, including not only sensorimotor systems but cognitive control systems, attention systems, and emotional processing systems. Extension of these techniques to whole-brain

analyses have allowed for the division of the entire brain into communities of related regions, allowing for a finer and task-independent method of mapping the brain (6).

In addition to the capabilities of RSFC to better understand brain systems, there are significant methodological benefits in using RSFC. One such benefit is that it does not require subjects to perform any task (9). This prevents confounds of differences in subjects' ability to perform certain tasks, which is often a problem in psychiatric illnesses that affect cognitive abilities, such as schizophrenia, depression, and attention deficit hyperactivity disorder (ADHD), and prevents biases created by task design (10). As RSFC is not task dependent, it is also easier to generalize across study sites and compile very large data sets (11).

## RSFC MRI IN PSYCHIATRIC ILLNESS

Many major psychiatric illnesses have been the subject of RSFC studies, touched upon here in brief. RSFC studies of schizophrenia have added further support to the view that there is an essential disconnection between important brain networks in this disorder (12), specifically in the fronto-parietal cognitive control network (13), which may allow for new avenues of research into the etiology of and potential interventions for this illness. ADHD has been the subject of much study, with evidence that there is both delayed maturation and decreased connectivity within regions of the default mode network and other cognitive control networks (14), differences that may even be able to differentiate between ADHD subtypes (15). A number of RSFC studies have implicated changes in connectivity between cortical control and limbic networks in the pathology of major depressive disorder (16), and some have found that RSFC patterns may be related to treatment response in major depressive disorder (17). RSFC has also provided interesting new avenues of investigation for developing an underlying framework of psychiatric disorders (i.e., see reference 18).

## KEY POINTS/CLINICAL PEARLS

- Resting state functional connectivity (RSFC) MRI is a newer imaging technique that allows researchers to get more information regarding what regions of the brain communicate with each other most frequently.
- There are multiple ways to analyze RSFC MRI data, from looking at correlations in the signal between pairs of regions to looking at correlations across the brain, or across large groups of regions, and each technique has its own benefits and drawbacks.
- Changes in resting state functional connectivity have been seen across development, as well as in a number of psychiatric illnesses, and may lead to better understanding of psychiatric diagnosis and treatment.

## CONCLUSIONS

Overall, RSFC has many potential benefits for better understanding typical brain functioning both in adults and across development (9), as well as in a variety of psychiatric disorders. RSFC allows one to see the most common history of coactivation of regions across time and thus defines networks of brain regions, the level at which most psychiatric illness are likely to occur, and allows us to define these networks in large data sets (11). RSFC has already started to play a role in our understanding of psychiatric illness and will only continue to provide more information in the future.

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The author thanks Dr. Adarsh Reddy, for encouragement and editorial support, as well as her graduate thesis mentors Dr. Brad Schlaggar and Dr. Steve Petersen for guidance in RSFC MRI research.

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# Optogenetic Applications in Psychiatric Research

Julio M. Bernardi, M.D.

The ability to experimentally manipulate the CNS in a temporal, spatial, and cell-type specific fashion has been an open challenge in neuroscience research for many years. Optogenetics is a relatively new and rapidly evolving set of techniques first described in 2005, increasingly being used to probe the mechanisms of several psychiatric disorders in experimental animals. In their seminal work, Boyden et al. (1) transfected mammalian neurons with a modified bacterial transmembrane ion channel called channelrhodopsin-2 (ChR2). ChR2 is a member of a vast family of light-sensitive proteins called opsins. ChR2 transiently opens in response to light stimulation allowing cations to flow inside the cell. When expressed in neurons, ChR2 allows precise temporal and spatial control of cell firing by delivering pulses of light to the CNS (2).

Since then, other bacterial light-sensitive proteins have been engineered for neuroscience applications. Halorhodopsin is a chloride pump that is activated by yellow light allowing hyperpolarization and silencing of neuronal activity. Other recent developments include opsins with different activation wavelengths, allowing two different neuronal populations to be controlled at the same time, and opsins that are activated for long periods of time after a brief pulse of light allowing manipulations of overall cell excitability of entire neuronal populations rather than directly controlling action potential firing (3).

One of the greatest strengths of this method is the precise targeting of genetically well-defined neuronal populations, which cannot be achieved by standard electrical stimulation methods. Opsins such as ChR2 are usually delivered to the brain using a virus such as adenovirus-associated virus (AAV) that

can infect neurons (3). The sequence of the opsin gene can be flanked with DNA sequences that are recognized by an enzyme called Cre recombinase (Cre) and then packaged in an AAV construct. When this virus is injected in the brain, only neurons expressing Cre will be able to activate the flanked opsin gene through Cre-mediated splicing and thus express the opsin protein in the target cell line.

Many different transgenic mouse lines expressing Cre have been developed, allowing optogenetic control of many different cell types, such as dopaminergic neurons, pyramidal cortical cells, or specific subtypes of GABAergic neurons. Excitingly, optogenetic tools are already being used to further our understanding of psychiatric disorders.

## APPLICATIONS

### Anxiety Disorders

The amygdala is essential for anxiety behavior, but more precise delineation of amygdala circuitry function has been elusive until recently. ChR2 stimulation of pyramidal neuron terminals from basolateral amygdala (BLA) ending in the lateral central amygdala (CEA) reduces anxiety in mice, whereas activating BLA inputs to the medial CEA drive anxiety behavior (5). Furthermore, activation of BLA afferents to ventral hippocampus increases anxiety, and inhibition of these inputs decreases anxiety (5). These studies underscore that activation of different cell populations in the same anatomical region can often have opposing effects on behavior.

### Mood Disorders

Serotonergic circuits are classically implicated in the neurobiology of depressive disorders. Recent research impli-

cates the ventral tegmental area (VTA) dopaminergic system as well. Optogenetic stimulation of VTA dopaminergic neurons produced antidepressant-like effects in the forced swim test, which is an animal behavior model for depression (6).

Another way of modeling depressive behavior in rodents is by exposing the animals to the social stress of repeatedly interacting with a larger and more dominant mouse. Mice exposed to this social stress are either resilient or develop a depression phenotype with decreased interest for sugar intake and social interaction (7). Phasic stimulation of VTA dopamine neurons in susceptible mice increased depressive-like behaviors, while phasic stimulation in resilient mice converted them to susceptible mice. Inhibition of VTA neurons projecting to the medial prefrontal cortex also induced the stress-susceptible phenotype in resilient mice (8). These results implicate the VTA dopaminergic circuitry in the pathogenesis of depressive disorders.

### Addiction

The VTA has also been strongly implicated in addictive disorders. Phasic but not tonic optogenetic stimulation of VTA dopaminergic neurons induce conditioned place preference in mice (9), meaning that the animals prefer to stay in a chamber where they received the stimulation versus a chamber where they received a neutral stimulus. Mice will also repeatedly press down a lever to obtain optogenetic stimulation on their dopaminergic VTA neurons (10). Most drugs of abuse activate VTA dopamine cells, and these studies provide causal evidence that activation of this pathway is crucial for the development of addictive disorders.



## Schizophrenia

Gamma oscillations are periodic changes in membrane potential synchronized across large numbers of neurons, giving rise to the gamma band in EEG recordings. They have been postulated to allow information transfer between distant brain regions (11) and to be important for cognitive function, supporting stimulus processing, attentional control, and short-term memory (12), which are functions known to be impaired in schizophrenia.

Extensive research shows that gamma band oscillations are decreased during a variety of cognitive tasks in schizophrenia patients when compared with controls (13). Fast-spiking parvalbumin neurons are GABAergic interneurons widely distributed in the brain that are thought to be drivers of gamma oscillations (14). Optogenetic techniques allowed this hypothesis to be tested. When fast-spiking neurons in mice were tagged with Chr2 and optically stimulated in a broad range of different frequencies, gamma band EEG power increased irrespective of the frequency of stimulation, providing the first causal evidence that fast-spiking neurons drive gamma oscillations in vivo.

*N*-methyl-D-aspartate (NMDA) antagonists such as ketamine can replicate many of the symptoms of schizophrenia in normal subjects (15), and this is the basis of the NMDA receptor hypofunction hypothesis. Linking the gamma oscillation hypothesis and the NMDA hypothesis is the fact that fast-spiking neurons express NMDA receptors, which activate them. It is postulated that hypofunctional NMDA receptors in fast-spiking neurons can contribute to the symptoms of schizophrenia by disrupting gamma oscillations, and administration of NMDA antagonists can indeed disrupt gamma rhythms (16).

One study tested this hypothesis more directly by comparing the response to optogenetic stimulation of fast-spiking neurons in control mice versus mice with a partial knockout of the NR1 subunit of the NMDA receptor (17). Chr2 stimulation drove gamma oscillation in both controls and mutant mice, but NMDA-deficient mice gener-

ated significantly less gamma oscillations in vivo than controls.

## Autism

The excitation/inhibition hypothesis states that alterations in the dynamic equilibrium of excitatory and inhibitory inputs to cortical neurons can cause faulty information processing and might underlie social deficits found in autism (18). To study this hypothesis, Yizhar et al. (19) used the step function opsin. When step function opsin was expressed in pyramidal neurons in the medial prefrontal cortex, it increased the excitation/inhibition ratio in that region. Conversely, expressing step function opsin in postsynaptic GABA neurons decreased the excitation/inhibition ratio in the medial prefrontal cortex. Increasing the excitation/inhibition ratio led to a profound disruption in social behavior in the mice. Decreasing the excitation/inhibition ratio did not have the same effects, indicating that an elevated excitation/inhibition ratio might impair information processing more than the opposite imbalance.

## FUTURE APPLICATIONS AND LIMITATIONS IN PSYCHIATRY

Optogenetic methods could be used in the future as a substitute for electrical deep-brain stimulation (DBS) treatment of severe psychiatric disorders. DBS induces a local electric field that nonspecifically influences all neuronal types and crossing fibers in the target area where the electrode is placed, potentially leading to unwanted side effects and decreased efficacy, since both neurons stimulating and inhibiting the desired effect could be activated. This limitation

might be one of the reasons why DBS has had limited success in the treatment of severe psychiatric illnesses to date.

Currently, it is not possible to achieve the same level of precise genetic control of channelrhodopsin expression that is possible in mice, since this depends on using transgenic mice lines. Further research could bypass this problem by using viral vectors designed to target a genetically or cell-surface receptor-defined neuron population.

Viral transfection methods commonly used to express opsins in the CNS also would pose a risk of mutagenesis or neurotoxicity if used in human subjects, and more research is needed to demonstrate that CNS viral delivery can be performed safely in humans.

In terms of the current limitations of optogenetics as a research method, light delivery requires invasive surgery and mechanical disruption of brain tissue, which might be a confounding factor in the interpretation of studies. Furthermore, optic stimulation leads to very precise synchronized discharge of a large number of neurons, a state that rarely if ever occurs in vivo. This could be mitigated by next-generation devices that deliver patterned illumination to the brain, allowing optical control of individual neurons in real time (20).

Dr. Bernardi is a fourth-year resident in the Department of Psychiatry, Washington University in Saint Louis.

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## KEY POINTS/CLINICAL PEARLS

- Optogenetics is an expanding set of tools that are revolutionizing basic and translational neuroscience research.
- Expression of light-sensitive channels (opsins) in neurons allows investigators to control cell firing using pulses of light.
- Optogenetic techniques have been used to probe the underlying neural circuitry of several animal models of psychiatric disorders, including autism, mood disorders, schizophrenia, and addiction.

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# TEST YOUR KNOWLEDGE

## Test Your Knowledge Has Moved

Our Test Your Knowledge feature, in preparation for the PRITE and ABPN Board examinations, has moved to our Twitter ([www.twitter.com/AJP\\_Res-Journal](http://www.twitter.com/AJP_Res-Journal)) and Facebook ([www.facebook.com/AJPResidentsJournal](http://www.facebook.com/AJPResidentsJournal)) pages.

We are currently seeking residents who are interested in submitting Board-style questions to appear in the Test Your Knowledge feature. Selected residents will receive acknowledgment for their questions.

Submissions should include the following:

1. Two to three Board review-style questions with four to five answer choices.
2. Answers should be complete and include detailed explanations with references from pertinent peer-reviewed journals, textbooks, or reference manuals.

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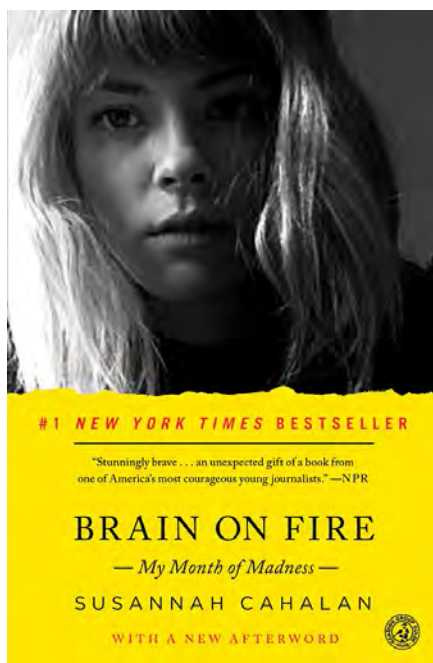
## Brain on Fire: My Month of Madness

Reviewed by Janet Charoensook, M.D.

In my first year of psychiatry training, attending psychiatrists had expounded that psychiatric illnesses are usually diagnoses of exclusion. This is especially true when the first presentation appears to be that of a possible serious mental illness. I recommend Susannah Cahalan's New York Times' Bestseller, *Brain on Fire: My Month of Madness*, about a rare neuro-immunological illness that manifested with prominent psychosis. Cahalan, a New York Post journalist, chronicles her account of struggling with a mysterious illness that landed her in NYU Hospital's Epilepsy Unit. Her everyday life unravels when she becomes obsessed with the idea that her apartment was infested with bedbugs, misses important deadlines at work, and starts throwing out precious personal possessions. She becomes paranoid, perseverative, and impulsive while

periodically experiencing severe migraines, nausea, paresthesias, and seizures. Cahalan describes the details of her experience in a lyrically aesthetic style in a cadence that moves the story forward. She explains the confusion she felt at the oddity of these experiences: the disorganized, bizarre behavior, labile mood, and the development of a very distorted perception of her hometown. She provides her own unique perspective on the puzzling experiences of her illness.

Psychiatrists are often inundated with their patients' insistent resolve that they are not mentally ill. This, then,



by Susannah Cahalan. New York, Simon and Schuster, 2012, 288 pp., \$10.99.

is commonly discounted as having “no insight.” This novel forebodes psychiatrists to take heed in being too quick to label such patients as “seriously mentally ill.” Cahalan’s story should move psychiatrists to better appreciate the patient’s own perspective and avoid making assumptions too hastily. She also posits a chilling, yet profound, question, “If it took so long for one of the best hospitals in the world to get to this step, how many other people were going untreated

... condemned to a life in a ... psychiatric ward?” Each individual’s experience of illness, particularly psychiatric, is unassailably dissimilar from the next individual’s. Cahalan’s story is especially fascinating because she articulates the events, not only from her perspective but from the perspective of her treating physicians, a bevy of neurologists, psychiatrists, and internists. She reviews the progress notes that were written about her, including hospital film footage trying to recollect the events, and gains wonderfully in-depth insight into her condition. She succinctly describes the panicked disarray that her family and friends are thrown into as they struggle with her illness. For those who are interested in a more detailed medical account of the anti-N-methyl-D-aspartate-receptor encephalitis she struggled with, this text is not for you.

I highly recommend this account of a young woman’s ordeal with a rare, autoimmune encephalitis that not only puzzled her and her family but also the many physicians who treated

her. As a resident physician, especially, it is important to learn both the common diagnoses and the “zebras.” Psychiatric diagnoses are important and must be wholly certain because they affect multiple facets of a person’s life.

Dr. Charoensook is a second-year resident in the Department of Psychiatry, University of California Riverside, Riverside, Calif.

# Residents' Resources

Here we highlight upcoming national opportunities for medical students and trainees to be recognized for their hard work, dedication, and scholarship.

*\*To contribute to the Residents' Resources feature, contact Hun Millard, M.D., M.A., Deputy Editor (hun.millard@yale.edu).*

## OCTOBER DEADLINES

Fellowship/Award and Deadline	Organization	Brief Description	Eligibility	Contact	Website
The Group for the Advancement of Psychiatry (GAP) Fellowship  <b>Deadline:</b> October 1, 2015	GAP	Each Fellow: Attends four GAP meetings over 2-years; becomes a member of one of the working GAP committees; collaborates with other fellows on a plenary presentation to the general GAP membership; learns about group process in their GAP committee and with their fellowship group; and benefits from close interaction with peers and mentors.	PGY 2 or later at an accredited psychiatry residency program in the United States or Canada; have at least 2 years of training ahead (e.g., PGY-1 or 3, or first year of a 2-year fellowship).	e-mail: Frda1@airmail.net or telephone: 972-613-0985	<a href="http://ourgap.org/">http://ourgap.org/</a>
Geriatric Mental Health Foundation's Honors Scholarships  <b>Deadline:</b> October 1, 2015	American Association for Geriatric Psychiatry (AAGP)	Provides residents 1-year membership to AAGP; registration and travel costs to attend the AAGP Annual Meeting; Participation in an academic project related to geriatric psychiatry under the supervision of an assigned mentor.	PGY 1, 2, or 3 at an accredited psychiatry residency program	e-mail: main@AAGPonline.org or telephone: 703-556-9222	<a href="http://www.aagponline.org/">http://www.aagponline.org/</a>
Geriatric Mental Health Foundation's General Scholarships  <b>Deadline:</b> October 1, 2015	AAGP	Provides medical students 1-year membership to AAGP; registration and travel stipend to attend the AAGP Annual Meeting; voluntary participation in an academic project related to geriatric psychiatry under the supervision of an assigned mentor.	Medical students in a LCME or COCA accredited medical school.	e-mail: main@AAGPonline.org or telephone: 703-556-9222	<a href="http://www.aagponline.org/">http://www.aagponline.org/</a>

## NOVEMBER DEADLINES

Fellowship/Award and Deadline	Organization	Brief Description	Eligibility	Contact	Website
APA/Lily Psychiatric Research Fellowship  <b>Deadline:</b> November 17, 2015	APA	This fellowship provides funding for 2 postgraduate psychiatry trainees, under the supervision and guidance of his/her mentor to design and conduct a research study on a major research topic.	APA RFM; Received M.D. or D.O. degree; Completed residency training in general psychiatry or child psychiatry prior to time fellowship commences; Not already an established investigator.	psychresearch@psych.org	<a href="http://www.psychiatry.org/researchers/research-training-and-career-distinction-awards/psychiatric-research-fellowship">http://www.psychiatry.org/researchers/research-training-and-career-distinction-awards/psychiatric-research-fellowship</a>
American Psychiatric Foundation (APF) Schizophrenia Research Fellowship  <b>Deadline:</b> November 17, 2015	APF	A 1-year psychiatric research fellowship for three postgraduate psychiatry trainees specifically to focus on research and personal scholarship. Minimal time (less than 15%) will be devoted to teaching, patient care, consultation, or other duties. The protection of time for research should be assured by the department chairman.	Received M.D. or D.O. degree; Completed residency training in general psychiatry or child psychiatry prior to time fellowship commences; Not already an established investigator.	Marilyn King e-mail: schizophr-nia@psych.org or telephone: 703-907-8653	<a href="http://www.psychiatry.org/researchers/research-training-and-career-distinction-awards/schizophrenia-research-fellowship">http://www.psychiatry.org/researchers/research-training-and-career-distinction-awards/schizophrenia-research-fellowship</a>



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questions based on the article's content. Limited to 1,500 words, 15 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3-4 teaching points.

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- 6. Review Article:** A clinically relevant review focused on educating the resident physician. Limited to 1,500 words, 20 references, and one figure. This

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- 7. Drug Review:** A review of a pharmacological agent that highlights mechanism of action, efficacy, side-effects and drug-interactions. Limited to 1,500 words, 20 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3-4 teaching points.
- 8. Letters to the Editor:** Limited to 250 words (including 3 references) and three authors. Comments on articles published in *The Residents' Journal* will be considered for publication if received within 1 month of publication of the original article.
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