Interrelationship Between Delirium and Dementia

Review Article

The Role of Neuroimaging in Elucidating Delirium Pathophysiology

David C. Alsop, 1 Michael A. Fearing, 2 Keith Johnson, 3 Reisa Sperling, 4 Tamara G. Fong, 5 and Sharon K. Inouye 6

1Department of Radiology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts.
2Geriatric Research, Education, and Clinical Center (GRECC), VA Boston Healthcare System and Harvard Medical School, Boston, Massachusetts.
3Departments of Radiology and Neurology, Massachusetts General Hospital, Boston.
4Department of Neurology, Brigham and Women’s Hospital, Boston, Massachusetts.
5Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts.
6Division of Gerontology, Beth Israel Deaconess Medical Center, Harvard Medical School, and Aging Brain Center, Hebrew SeniorLife, Boston, Massachusetts.

Understanding of delirium pathogenesis remains limited despite improved diagnosis, and elucidation of risk factors and prognosis. Major advances in neuroimaging offer the possibility of probing the mechanisms and networks involved in delirium and hence improving understanding of this often devastating syndrome. This review describes the current literature of imaging studies in delirium and related conditions, introduces some of the newer capabilities of neuroimaging with magnetic resonance imaging, positron emission tomography, and single photon emission computed tomography, and discusses how these techniques may be applied to the study of delirium. Despite considerable challenges in patient recruitment, study design, intersubject variability, and scanner and contrast agent availability, imaging offers great potential for the identification and clarification of pathogenic mechanisms of delirium and its long-term sequelae.

TARGET QUESTIONS FOR NEUROIMAGING STUDIES OF DELIRIUM

Delirium is an acute confusional state characterized by decline in attention and cognition. It is a syndrome defined by its clinical features (1), rather than its histopathologic or molecular effects. Since delirium arises predominantly in older persons during hospitalization, where comorbidity can confound many diagnostic tests, studies of clinical populations have yielded only modest insights into the mechanisms of delirium to date. In the absence of defined mechanisms, delirium may appear to be a nonspecific syndrome of a vulnerable brain. As it has for other pathologies, neuroimaging may enable the definition of delirium as a regional pathology of the brain, as a global deficit in flow or metabolism, or as a deficiency in one or more neurotransmitter systems. Hence, the first target question is: 1. What abnormalities of brain function are responsible for the state of delirium?

While most cases of delirium may result from a final
common pathway of disordered brain function, the factors that initiate delirium are typically multifactorial, including systemic illnesses, extracranial processes, or injury that need not originate in the brain. The capabilities of these diverse factors for inducing delirium must be mediated by a pathway into the brain, such as the blood–brain barrier, requiring either high permeability of the inciting factors or a compromised blood–brain barrier (2). Thus, the second target question is: 2. How do extracranial factors associated with delirium reach the brain?

Considerable progress has been made at defining risk factors for delirium, including both vulnerability and precipitating factors identified in epidemiologic studies (1). Neuroimaging may permit the investigation of brain-specific risk factors including structural abnormalities (i.e., periventricular white matter disease, atrophy), incipient dementia, amyloid deposition, and cholinergic dysfunction. The third target question is: 3. What brain-specific factors predict an elevated risk of delirium?

Delirium is associated with numerous negative outcomes including longer hospital stay, reduced cognitive function, increased institutionalization, and death. Considerable evidence indicates that delirium itself, above and beyond the precipitating factors, contributes to reduced cognitive function and may initiate or accelerate incipient dementia (1). This raises the fourth target question: 4. Does delirium result in permanent effects on the brain?

After reviewing the existing literature on neuroimaging in delirium, we will consider some of the newer neuroimaging techniques available, and how they may be used to address these four questions.

**IMAGING STUDIES OF DELIRIUM**

**Structural and Lesion Studies**

Several studies have used x-ray computed tomography (CT) or magnetic resonance imaging (MRI) scanning to search for lesions or other indicators of structural abnormality in the brains of patients with delirium. In one CT study (3), an increase in the incidence of abnormal brain findings (hemorrhage, hematoma, space-occupying lesion, infarct) in elderly emergency room patients with delirium was noted, but such findings were present in less than half of the delirium cases. In a different emergency room population study (4), abnormal head scans were not predictive of delirium. The authors note that serious medical disease was much more predictive of delirium incidence. These studies suggest that brain lesions visible on CT may contribute to reduced cognitive function and may initiate or accelerate incipient dementia. Incidence of delirium following antidepres- sant (5) or electroconvulsive therapy (6) was reported as highly correlated with the presence of basal ganglia and subcortical white matter changes.

While the evidence for a relationship between abnormal MRI or CT structural scans and the occurrence of delirium in a general population is limited, a number of case reports or small case series describe delirium in response to focal lesions. One report of delirium following an infarct in the basal forebrain that resolved following cholinesterase in-

**Cerebral Blood Flow Studies**

Because anatomic imaging is often inconclusive in cognitive and psychiatric disorders, imaging methods sensitive to the level of activity in the brain are frequently evaluated for further characterization. Measurements of cerebral blood flow (CBF) are appealing because they can be performed with clinically available imaging systems and because blood flow is typically correlated with metabolic indicators of brain activity such as glucose utilization. Thus, these modalities may allow detection of regional or global blood flow changes that might be associated with delirium.

Single photon emission computed tomography (SPECT) measures CBF using a radioactive tracer. A substantial number of SPECT studies of delirium or related conditions have been reported (see Table 1). It should be noted that there is variation across the reports in etiology of delirium, radioisotope used, and processing of scans. Frequently, SPECT scans are interpreted visually by an experienced radiologist or by quantitative comparison to a control region.

While many of the SPECT references are case reports, combination of these reports and the larger studies suggest some recurring themes. First, delirium is mostly associated with a decrease in blood flow. Increased blood flow is reported in some studies, but these studies involve either direct brain insult from surgery or a known infectious or inflammatory component, especially hepatitis or cirrhosis. Second, in those studies where scanning is repeated after symptom resolution is observed, a recovery of blood flow is usually seen. Third, regional flow deficits may be present, but do not appear to be consistent across study participants. Parietal and frontal deficits are probably the most commonly reported.

One limitation of most SPECT studies is that absolute measurement of blood flow is not performed. Thus, while fairly sensitive for localized changes, SPECT studies are usually not capable of detecting global flow changes. One study performed with Xenon-enhanced CT for blood flow measurement in 10 patients during and after delirium (16) demonstrated a 42% globally decreased flow during delirium with possibly greater decreases in subcortical
Limitations of Existing Studies

Previous studies have not fully addressed any of the target questions we raised. While regional findings of anatomic, diffusion MRI, or CBF abnormalities were sometimes found, they lacked the specificity and reproducibility required to demonstrate a regional or neurotransmitter basis for delirium. Little additional understanding of the mechanisms for inducing delirium was achieved, and no study addressed permanent damage following delirium. In addition, neuroimaging-based risk factors for delirium were not addressed in any of these studies.

NEWER TECHNIQUES WITH POTENTIAL FOR THE STUDY OF DELIRIUM

Newer neuroimaging techniques may offer powerful methods to elucidate the pathophysiology of delirium and to directly address our target questions. The current literature suggests that anatomical imaging findings in delirium may be subtle or absent. Newer imaging and analysis methods may be helpful to either detect subtle anatomical changes or to provide different information with greater sensitivity to delirium. Since most of these newer techniques are not readily available for clinical assessment of delirium, making them available, at least for research studies, is an important priority.

Volumetric Analysis

Imaging studies of anatomy and brain atrophy have been greatly improved in the past decade. Improved image contrast and robustness to motion can be achieved with optimized timing, surface coil arrays, and motion correction strategies. Perhaps the biggest advance, however, has been in postprocessing (19,20). Careful statistical methods for analysis of structural images have been honed for detecting subtle changes in volume over time, as can occur in

Table 1. SPECT Cerebral Blood Flow Studies in Delirium and Related Conditions

<table>
<thead>
<tr>
<th>Reference (Ref. No.)</th>
<th>No. of Patients/Controls</th>
<th>Cause of Onset</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bogousslavsky et al. (10)</td>
<td>1/0</td>
<td>Right thalamic infarction</td>
<td>Right frontal hypoperfusion</td>
</tr>
<tr>
<td>Shih et al. (46)</td>
<td>1/0</td>
<td>Drug withdrawal</td>
<td>Left frontotemporal hypoperfusion</td>
</tr>
<tr>
<td>Kohira et al. (47)</td>
<td>1/0</td>
<td>Hepatic encephalopathy</td>
<td>Cerebellum, basal ganglia, cortical hyperperfusion</td>
</tr>
<tr>
<td>Doyle and Warden (48)</td>
<td>1/0</td>
<td>Cardiomyopathy</td>
<td>Right temporal-occipital hypoperfusion</td>
</tr>
<tr>
<td>Ohta et al. (49)</td>
<td>1/0</td>
<td>Portal-systemic encephalopathy</td>
<td>Bilateral parietal hypoperfusion</td>
</tr>
<tr>
<td>Kamijo et al. (50)</td>
<td>1/0</td>
<td>Barbiturate withdrawal</td>
<td>Diffuse bilateral decrease</td>
</tr>
<tr>
<td>Pittcock et al. (51)</td>
<td>1/0</td>
<td>Transplant immunosuppression</td>
<td>Bilateral frontal, parietal, temporal hypoperfusion</td>
</tr>
<tr>
<td>Ikeda et al. (52)</td>
<td>6/0</td>
<td>Hepatic encephalopathy</td>
<td>Diffusely decreased cortical perfusion; in 4 participants recovery after liver transplant</td>
</tr>
<tr>
<td>Jalan et al. (53)</td>
<td>8/0</td>
<td>Oral amino acid loading in cirrhosis</td>
<td>Bilateral temporal lobe, left superior frontal gyrus, and right parietal and cingulate gyrus decrease</td>
</tr>
<tr>
<td>Trzepacz et al. (54)</td>
<td>6/6</td>
<td>Cirrhosis</td>
<td>Right basal ganglia and bilateral frontotemporal hypoperfusion</td>
</tr>
<tr>
<td>Strauss et al. (55)</td>
<td>10/9</td>
<td>Hepatic encephalopathy</td>
<td>Frontal and basal ganglia hypoperfusion</td>
</tr>
<tr>
<td>O’Carroll et al. (56)</td>
<td>10/10</td>
<td>Cirrhosis</td>
<td>Basal ganglia and occipital increase</td>
</tr>
<tr>
<td>Yazgan et al. (57)</td>
<td>12/8</td>
<td>Hepatic encephalopathy</td>
<td>Anterior cingulate decrease</td>
</tr>
<tr>
<td>Catafau et al. (58)</td>
<td>13/13</td>
<td>Hepatic encephalopathy</td>
<td>Bilateral thalamic hypoperfusion</td>
</tr>
<tr>
<td>Fong et al. (59)</td>
<td>22/6</td>
<td>Multiple etiologies in hospitalized medical patients</td>
<td>Prefrontal hypoperfusion. Striatal and medial temporal perfusion was higher in more impaired participants</td>
</tr>
<tr>
<td>Ogasawara et al. (60)</td>
<td>5/12</td>
<td>Subdural hematoma</td>
<td>Parietal hypoperfusion in 6</td>
</tr>
<tr>
<td>Goğoz et al. (61)</td>
<td>6/44</td>
<td>Cardiac surgery</td>
<td>Frontal hypoperfusion in 5</td>
</tr>
<tr>
<td>Gunaydin et al. (62)</td>
<td>7/43</td>
<td>Cardiac surgery</td>
<td>Reversible parietal hypoperfusion in 3 of 6</td>
</tr>
</tbody>
</table>

Note: SPECT = single photon emission computed tomography.

structures and occipital cortex compared to other brain regions. Such changes would be largely missed in relative flow studies and are consistent with delirium being, at least in part, a global brain dysfunction (17). Globally reduced blood flow could represent a causal mechanism in some cases of delirium or a marker for some of the conditions that can precipitate delirium (e.g., toxic–metabolic derangements). Evaluation of global alterations in flow would also be useful to investigate the coupling between brain function and blood flow, which might be altered in delirium, such as with cholinergic deficiency (18).

Thus, regional and global CBF studies with SPECT, or possibly other imaging modalities, can provide a sensitive means to evaluate pathophysiologic changes associated with delirium, both acutely and evolving over time. Caution must be taken in interpreting CBF studies of delirium since elderly persons are prone to vascular disease, which can affect both CBF and brain activity, and alterations of neurotransmitter activity frequently associated with delirium may directly affect vascular regulation. The use of serial scans in matched patients with and without delirium may help to address these issues.

Limitations of Existing Studies

Previous studies have not fully addressed any of the target questions we raised. While regional findings of anatomic, diffusion MRI, or CBF abnormalities were sometimes found, they lacked the specificity and reproducibility required to demonstrate a regional or neurotransmitter basis for delirium. Little additional understanding of the mechanisms for inducing delirium was achieved, and no study addressed permanent damage following delirium. In addition, neuroimaging-based risk factors for delirium were not addressed in any of these studies.
Alzheimer’s disease. Less than 1% changes in brain volume can be detected within participants, and only slightly higher standard deviations occur in smaller, automatically defined regions. Such techniques could be useful to test for accelerated rates of atrophy following delirium, which would indicate permanent damage. High levels of delayed atrophy have been observed in other insults, such as brain trauma (21). Measures of brain volumes would help to address our questions about brain-specific risk factors for delirium (Question 3), since high levels of atrophy may be predictive of delirium, perhaps representing the onset of incipient dementia. In addition, detection of accelerated brain atrophy following delirium could demonstrate the nature of permanent damage from delirium (Question 4) and, if regionally specific, may provide input for defining the physiologic basis of delirium (Question 1). Because atrophy is a nonspecific indicator of degeneration, its diagnostic value will be limited unless a strong regional specificity is demonstrated.

**Blood Oxygen Level Dependent (BOLD) Technique**

In addition to structural imaging, MRI has made major advances in functional assessment of the brain. Perhaps most widely known is the blood oxygen level dependent (BOLD) technique for imaging of brain activity changes (22). This technique permits the imaging study of brain responses to different stimuli or task activities. While this technique generally requires a controlled and cooperative patient population, clinical studies in Alzheimer’s disease (23) and other dementias (24) have been successfully performed. The magnitude of BOLD activation in temporal lobe structures during memory tasks can used to predict conversion from mild cognitive impairment to Alzheimer’s disease. BOLD studies might be used as a predictor of risk or vulnerability for delirium (Question 3), or as an indicator of performance over time in long-term follow-up studies after delirium (Question 4). Because BOLD studies can detect altered brain activity in response to stimuli, they offer a different window into the delirious state than resting studies such as SPECT and PET. High requirements of patient cooperation in BOLD studies may limit the use of BOLD to studying the neural substrates of confusion and other cognitive symptoms of delirium, which could contribute to our understanding of the delirious state (Question 1).

**Arterial Spin Labeling**

Another MRI technique capable of imaging brain activity change is the arterial spin labeling blood flow MRI method (25). This technique measures blood flow and can provide a resting blood flow measure (26), as in the SPECT studies reviewed in the previous section, and can also quantify modulations of flow over seconds to hours (27). Arterial spin labeling can be performed as part of a standard MRI scan so that both anatomical and blood flow information can be obtained. It is particularly well suited to measuring the effect of pharmacologic challenges (28) and its use in conjunction with neurotransmitter modulators, such as scopolamine or donepezil, is intriguing for assessing the contribution of neurotransmitter function to the risk of delirium (Question 3), or for assessing long-term changes after delirium (Question 4).

**Diffusion Tensor Imaging**

Another exciting MRI technique is diffusion tensor imaging (29). Diffusion MRI is sensitive to the random motion of water within tissue. In acute stroke, diffusion decreases rapidly and is highly sensitive to early injury to tissue (30). Diffusion changes can be reversible, and there have been some signs of delirium-related symptoms in participants with diffusion lesions in the splenium of the corpus callosum (13). Many of the recent developments in diffusion imaging relate to measuring the directionality of diffusion in white matter (31). Diffusion is much faster along axons than perpendicular to them. Because MRI tends to measure diffusion along one direction at a time, the images appear different with the direction chosen. The direction of greatest diffusion in a region can be used to determine the direction of fiber tracts. Computerized methods can be used to define fiber tracks anatomically and potentially derive measures related to connectivity between brain regions. Additionally, a measure of the dependence of diffusion on direction, or anisotropy, has been used as an indicator of brain connectivity. Decreases in white matter integrity and connectivity have been identified with diffusion tensor imaging in Alzheimer’s disease (32), schizophrenia (33), and geriatric depression (34). With its high sensitivity, diffusion tensor imaging may prove useful to identify chronic pathologic changes associated with delirium (Question 4), which may contribute to the associated longer-term cognitive impairment.

**Blood–Brain Barrier Imaging**

MRI can also be used to assess blood–brain barrier integrity. The blood–brain barrier plays a critical role in protecting the brain from systemic disease and dysfunction. Delirium, however, is frequently initiated by conditions outside the brain. The health of the blood–brain barrier prior to and during delirium could be an important factor in pathogenesis. Inflammatory cytokines and other potentially neurotoxic agents enter the brain when the blood–brain barrier is disrupted (35). MRI with routine paramagnetic contrast is an indicator of blood–brain barrier disruption. While aging, and most likely delirium, are not associated with sufficient contrast uptake to readily detect visually, the subtle blood–brain barrier disruption associated with aging (36), and possibly a more severe disruption associated with delirium, are potentially measurable with contrast-enhanced MRI (36–38). Quantitative analysis of serial images must be used for greatest sensitivity to small concentrations of contrast. This modality may offer important clues about the pathophysiologic initiation of delirium (Question 2).

**Amyloid Imaging**

Recent research in the neurochemistry of amyloid plaques has resulted in the development of the benzothiazole class of compounds, which specifically bind to individual amyloid plaques in mouse models of Alzheimer’s disease (39). These compounds cross the blood–brain barrier...
and have now been labeled with radioisotopes for use as in vivo molecular probes. One such compound, known as Pittsburgh Compound B, has been tested in animal models of Alzheimer’s disease, in human Alzheimer’s disease post mortem brain tissue, in living healthy older participants, and in patients with a clinical diagnosis of Alzheimer’s disease (40). Pittsburgh Compound B binds primarily to fibrillar forms of amyloid and has been found to be highest in neocortical regions, especially frontal, temporal, and parietal cortices. Interestingly, recent reports have also found evidence of neocortical Pittsburgh Compound B retention in a subset of cognitively intact older participants (41), consistent with autopsy reports of amyloid deposition in a small proportion of healthy older individuals. Amyloid PET imaging is an important modality to explore in patients exhibiting prolonged delirium, as early Alzheimer’s disease pathology may be a significant contributing factor. Moreover, this modality will facilitate follow-up studies to detect increased amyloid deposition over time following a delirium episode. This technique could help to elucidate the brainspecific risk factors for delirium (Question 3), and the relationship between delirium and subsequent occurrence or acceleration of dementia (Question 4).

**PET and SPECT Imaging**

PET and SPECT offer a number of exciting new possibilities for the characterization of delirium. Besides more traditional glucose utilization and flow imaging, which can be used to determine the presence and severity of dementia before and after delirium, newer tracers for imaging of neurotransmitters, such as cholinergic receptor activity (42) and dopaminergic function (43), are now available. Since neurotransmitter dysfunction is likely an important part of the physiologic basis of delirium, the ability to image neurotransmitter function could be an invaluable tool for clarifying the pathophysiology of delirium (Question 1). Many of these agents require special chemistry or cyclotron facilities as well as considerable planning and recruitment, moderate to large sample sizes, and considerable imaging and clinical infrastructure. Advances in imaging speed and sensitivity, such as are made possible with high field strength and parallel imaging MRI, may help make studies in this clinical population more feasible. Despite their challenges, these studies will represent a major advance in understanding the pathophysiology of delirium and its long-term sequelae.

**Table 2. Conducting Neuroimaging Studies in Delirious Older Persons: Challenges and Potential Solutions**

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Potential Solution(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient enrollment and recruitment</td>
<td>Assembly of cohorts of eligible patients by skilled recruitment staff</td>
</tr>
<tr>
<td>Patient selection</td>
<td>Match for age, comorbidity, delirium risk</td>
</tr>
<tr>
<td>Comparable delirium and nondelirium patients</td>
<td>Control for precipitating insults, or select sample with uniform insults (e.g., similar surgical type)</td>
</tr>
<tr>
<td>Differing insults precipitating delirium</td>
<td>Control for precipitating insults, or select sample with uniform insults (e.g., similar surgical type)</td>
</tr>
<tr>
<td>Scanning procedures</td>
<td>Comfort procedures, padding, minimize scan time</td>
</tr>
<tr>
<td>Patient discomfort</td>
<td>Scan patients with mild delirium; use relaxation music, hand massage</td>
</tr>
<tr>
<td>Motion artifact</td>
<td>Supervision by medical personnel during procedure</td>
</tr>
<tr>
<td>Patient risk (acute illness)</td>
<td>On-call staff, and assurance of adequate neuroimaging infrastructure</td>
</tr>
<tr>
<td>Scheduling of scan during delirium or postdelirium timeframes</td>
<td>On-call staff, and assurance of adequate neuroimaging infrastructure</td>
</tr>
<tr>
<td>Interpretation and analysis procedures</td>
<td>Use of state-of-the-art equipment, software, and well-trained staff</td>
</tr>
<tr>
<td>Determination of changes due to delirium</td>
<td>Sequential scans before, during, and after delirium, with control for interscan events</td>
</tr>
</tbody>
</table>

**Future Prospects for Neuroimaging Studies of Delirium**

While existing and newer imaging modalities hold great promise for the study of delirium, progress is impeded by the many challenges posed by studying acutely-ill older persons with delirium (See Table 2). Some potential solutions to these challenges are indicated. One approach to avoiding these challenges is by the imaging study of animal (44) or human (45) models of delirium. Definitive clinical imaging studies of delirium are likely to require careful planning and recruitment, moderate to large sample sizes, and considerable imaging and clinical infrastructure. Advances in imaging speed and sensitivity, such as are made possible with high field strength and parallel imaging MRI, may help make studies in this clinical population more feasible. Despite their challenges, these studies will represent a major advance in understanding the pathophysiology of delirium and its long-term sequelae.

**Acknowledgments**

This work is an adaptation of a presentation at “The Interface of Delirium and Dementia,” a conference organized by the Aging Brain Center, Hebrew SeniorLife, April 10, 2006, in Waltham, Massachusetts. Authors acknowledge support from the Education Core of the Massachusetts Alzheimer’s Disease Research Center (P50AG005134), a conference grant from the Alzheimer’s Association, the National Institute on Aging R21AG025193 (SKI) and K24AG00949 (SKI), the National Institute of Neurological Disorders and Stroke 5F32NS047431 (TGF), and the Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife.

Address correspondence to David Alsop, PhD, Department of Radiology, Ansin 226, Beth Israel Deaconess Medical Center, 330 Brookline Ave., Boston, MA 02215. E-mail: dalsop@bidmc.harvard.edu

**References**


Received July 6, 2006
Accepted September 19, 2006
Decision Editor: Luigi Ferrucci, MD, PhD

Editor Nominations

Journal of Gerontology: Psychological Sciences

The Gerontological Society of America’s Publications Committee is seeking nominations for the position of Editor of the Journal of Gerontology: Psychological Sciences, the Society’s journal on the psychological science of aging.

The position will become effective January 1, 2008. The Editor makes appointments to the journal’s editorial board and develops policies in accordance with the scope statement prepared by the Publications Committee and approved by Council (see the journal’s General Information and Instructions to Authors page). The Editor works with reviewers and has the final responsibility for the acceptance of articles for the journal. The editorship is a voluntary position. Candidates must be dedicated to developing a premier scientific journal.

Nominations and applications may be made by self or others, but must be accompanied by the candidate’s curriculum vitae and a statement of willingness to accept the position. All nominations and applications must be received by April 2, 2007. Nominations and applications should be sent to the Publications Committee, Attn: Patricia Walker, The Gerontological Society of America, 1030 15th Street, NW, Suite 250, Washington, DC 20005-1503.