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Update on the Neuropathogenesis of Delirium

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Abstract
Delirium has been considered a syndrome of generalized dysfunction of higher cortical functions due to its breadth of symptoms and associated diffuse slowing on electroencephalogram. Advances in neuropsychiatry have revealed differences between brain regions, including the hemispheres, which may underlie the constellation of symptoms among different psychiatric disorders. For example, different neural pathways are involved in major depression and obsessive-compulsive disorder, including lateralization to one or the other hemisphere. In this article the author proposes that delirium, too, involves particular neural pathways and that lateralization to the right may be relevant. Structural and functional neuroimaging reports and recent neuropsychological studies support this lateralization. Prefrontal cortices, anterior and right thalamus, and right basilar mesial temporoparietal cortex may play a significant role in subserving delirium symptoms and may be the 'final common pathway' for delirium from a variety of etiologies. The final common pathway may be responsible for certain 'core symptoms' (disorientation, cognitive deficits, sleep-wake cycle disturbance, disorganized thinking, and language abnormalities), while other symptoms (delusions, hallucinations, illusions, and affective lability) may occur depending on the etiology causing delirium. An imbalance in the cholinergic and dopaminergic neurotransmitter systems is most commonly implicated in causing delirium, and could both account for delirium symptoms and be consistent with the neuroanatomical pathways being implicated.

Is Delirium a Diffuse Disorder of Brain Pathways?

Little is known about the neuropathogenesis of delirium in comparison to its epidemiology, risk factors and associated morbidity and mortality. There are many terms used to denote delirium, including 'acute brain failure', 'encephalopathy', and 'acute confusional state'. Delirium is felt to represent a generalized dysfunction of higher cerebral cortical processes [1]. Supporting this notion, electroencephalograms (EEGs) in delirious patients characteristically show diffuse slowing of the dominant posterior rhythm, consistent with widespread cortical dysfunction. Delirium involves deficits in a variety of cognitive functions (not just attention) as well as other neuropsychiatric symptoms such as disturbances in affect, thinking, language and sleep-wake cycle. Psychotic

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symptoms occur to a lesser extent (delusions and hallucinations).

Characteristic features that distinguish delirium from other disorders include its temporal onset (acute to abrupt) and a tendency for symptom severity to fluctuate during a 24-hour period. Lewy body dementia mimics some features of delirium – prominent visual hallucinations and fluctuating symptom severity – otherwise these characteristics are quite unique to delirium. Interestingly, Lewy body dementia is a rapidly progressive dementia involving severe degeneration of nucleus basalis and related basal forebrain cholinergic nuclei that may underlie its cognitive and other delirium-like features. However, it also involves extrapyramidal symptoms similar to Parkinson's disease and pathological abnormalities similar to Alzheimer's dementia.

In this paper, I will provide evidence to suggest that specific neuronal pathways and neurotransmitter systems are responsible for causing delirium – beyond the generally accepted concept of it being a generalized, and perhaps nonspecific, impairment of higher cortical functions accompanied by a diffuse disturbance of cortical EEG activity. The brain is a highly specialized and complex organ with different regions devoted to primary motor, sensory and autonomic functions, secondary association areas and tertiary association areas. Not all of these areas are equally impaired in delirium. There is also evidence for lateralization of many brain functions and even of some neurotransmitter activities that supports the potential for specificity of symptom profiles in delirium even when the brain shows generalized abnormalities on EEG.

Delirium as a Disorder of Specific Brain Pathways: Role of Symptoms

The specific neuronal pathways that cause delirium are unknown. Because a variety of physiological and/or structural abnormalities can cause delirium, it is suggested that particular brain regions or circuits affected by these many different etiologies may constitute a 'final common pathway' for the syndrome of delirium. A careful study of symptoms may suggest which are 'core symptoms' common to delirium across etiologies. For example, a recent principal component analysis of delirium symptoms using the Delirium Rating Scale (DRS) found that 7 of 10 items were 'core' symptoms of delirium which were common to two groups of delirious elderly – those with and without a concomitant dementia [2]. If in fact 'core' symptoms can be identified through phenomenology studies across etiologies, then the neural circuits subserving these symptoms can be located.

There are a few studies since the 1960s that have described the prevalence of delirium symptoms in different patient samples [reviewed in 3, 4], though their methodologies varied and some did not use standardized rating instruments. It might be expected that core symptoms should be the most prevalent. Cognitive impairment is the most common symptom noted in studies, though it was assessed under different headings. Disorientation ranged from 78 to 100%, attention deficits from 62 to 100%, memory deficits from 62 to 90%, and diffuse cognitive deficits occurred in 77%. 'Clouded consciousness', a poorly defined concept that probably includes cognitive impairment, was noted in 65–100%. That cognitive deficits would be part of the core symptoms of delirium is consistent with current DSM-IV categorization of delirium as a cognitive disorder.

In addition, disorganized thinking processes (95%), language abnormalities (47–93%), and sleep-wake cycle disturbances (49–96%) are commonly found, which suggests they also may be core symptoms. The brain regions that subserve thinking processes, language, and different components of cognition are therefore implicated in delirium (frontal, temporal, parietal cortices and their subcortical connections).

On the other hand, less commonly occurring symptoms may indicate involvement of their related brain regions only under certain circumstances. For example, psychotic symptoms are less common, with delusions in 18–62%, visual hallucinations in 30–77%, auditory hallucinations in 4–15%, and illusions in 9–23%. Affective lability occurred in 43% in one study. Thus, though delirium seems to indicate 'acute brain failure' of multiple higher cortical functions – often accompanied by generalized EEG slowing – studies suggest that not all brain regions seem equally affected. The occurrence of noncore symptoms may depend on the etiology of the delirium. Perhaps various combinations of etiologies of delirium in individual patients cause different neurochemical or physiological imbalances that alter the expression of delirium.

By applying known brain-behavior relationships for neuropsychiatric symptoms, one can implicate certain brain regions and neurotransmitters in causing delirium symptoms as is done for other psychiatric disorders. For example, delusions in schizophrenics appear related to abnormalities in temporolimbic circuits and abnormal dopamine in the mesolimbic system. Patients with seizures of the temporal lobes also have delusions as well as a

variety of hallucinations (especially visual). In Alzheimer's dementia, Cummings et al. [5] showed that persecutory delusions were associated with neuropathological abnormalities in the mesial prefrontal cortex and with cholinergic deficits. Vaphiades et al. [6] studied patients with infarcts of the central visual pathways and found that agitated delirium accompanied by visual hallucinations was related to lesions involving the mesial aspect of the occipital, hippocampal and parahippocampal region. Such data support the notion that delusions in delirium are related to dysfunction of frontal and/or temporolimbic circuits and hallucinations in delirium are related to temporo-occipital circuits.

Mesial orbitofrontal and basal forebrain lesions have been implicated in causing disorientation to time in stroke patients [7], which was distinguished from their short-term memory problems. Basal forebrain nuclei are important cholinergic nuclei. Disorientation to time is almost ubiquitous in delirium.

Sleep-wake cycle disturbances in delirium – especially when the circadian cycle is severely fragmented – implicate involvement of the hypothalamic suprachiasmatic nucleus and brainstem nuclei that produce REM oscillations. Evidence is conflicting as to whether sleep-wake cycle disturbance precedes the onset of other symptoms of delirium.

Delirium as a Disorder of Specific Brain Regions: Lesion Studies

Delirium is a brain disorder affecting areas of the brain serving behavior, thought and cognition. Any primary motor or sensory abnormalities appear only as a result of the specific underlying medical problem (e.g. stroke, tumor, liver insufficiency); focal neurological signs have not been found to be part of the delirium syndrome. This implies that the brain regions involved in causing delirium are areas other than those involved in supporting primary motor and sensory functions.

Brain regions involved in personality, mood and affect, cognition, thinking and language include prefrontal cortex (PFC), temporal-limbic structures, anteromedial thalamus, and the tertiary association polymodal sensory cortex (at the temporoparietal occipital junction). Alterations in neurotransmission from reticular formation and basal forebrain nuclei also affect the function of these brain regions. Though certain brain regions are associated with specific functions, lesions in connected structures distanced from them can also cause dysfunction of those regions ('diaschisis'). For example, a small lesion (e.g. a lacune) in subcortical regions can cause PFC dysfunction by altering neurotransmission along thalamic-prefrontal-basal ganglia circuitry. A case of delirium caused by a right anterior thalamic stroke was associated with a defect in regional cerebral blood flow in the right PFC [8]. Though specific brain regions have individual functions, their brain activities are also affected by activities of related circuits and networks. For example, it is hypothesized that limbic structures express neuronal activity via a summation of individual activities expressed as a pattern based on a group of interconnected regions, and it is the pattern that is important. Thus, delirium may involve several brain regions or functional circuits that are known to serve behavior and cognition.

The use of structural and functional brain imaging of patients with delirium of different etiologies may offer clues about which brain regions are most important, as has been shown in other psychiatric disorders. Studies of major depression patients show a relationship between hypofunction of left PFC and severity of depression and studies of obsessive-compulsive disorder show a relationship between hyperfunction of the right caudate and orbitofrontal cortex with severity of obsessive-compulsive symptoms. In major depressive disorder the same pattern of hypofrontality exists for primary or secondary (e.g. stroke, Parkinson's) depression cases, suggesting that either physiological or structural causes appear to use a final common neural pathway. In fact, the anatomical location of the stroke predicts depression vulnerability and severity in poststroke depression patients, accounting for about 70% of the variance in Hamilton depression scale scores, such that the proximity to the left anterior pole has the highest association with depression. Similarly, though delirium results from a wide variety of structural or physiological insults, certain anatomical pathways may play a more important role than others.

Imaging studies of metabolic (hepatic encephalopathy) and structural (traumatic brain injury, stroke) causes of delirium support the hypothesis that certain neural pathways are particularly important. Though research is still limited by small sample sizes or case series reports, MRI, CT, SPECT and PET scans show that frontal cortex, anteromedial thalamus, right basal ganglia, right posterior parietal cortex and mesial-basal temporo-occipital cortex are particularly important [1, 9]. This is not to suggest that delirium can only occur after structural damage to these regions; rather, these regions may represent the most vulnerable or the 'final common' neural pathways for causing delirium symptoms resulting from many different struc-

tural or physiological effects on the brain. When brain lesions or dysfunction directly affect these regions, the resultant delirium may be particularly severe and prolonged, as has been described after strokes to the posterior parietal cortex. Other lesions or physiological dysfunctions may cause neurochemical or metabolic effects on these important pathways, or may produce a diaschisis situation.

Attention is one of the cognitive deficits in delirium. Attention has several components – including span, space/environment, concentration, and freedom from distractibility – and several brain regions are involved. Interestingly, the same anatomic areas involved in attention have been cited in brain scan reports of delirium – frontal and right posterior parietal cortices, and thalamus. The thalamus is particularly important for nonselective attention ('arousal'), which is a cholinergic function mediated through both nicotinic and muscarinic (probably M_2 subtype) receptors. [Note that the thalamus also 'drives' the cortical EEG where acetylcholine (Ach) is responsible for maintaining the waking EEG pattern and anticholinergic drugs interfere to cause diffuse slowing on EEG. Anticholinergic drugs are a common cause of delirium.] Nondominant posterior parietal cortex is important for spatial attention and maintaining concentration; strokes of this area cause intense, prolonged delirious states. PFC is very important for attention, with the right side relevant to visuospatial attention, and the orbitofrontal cortex is important for freedom from distractibility.

Brain scan reports suggest that the right hemisphere is particularly important in delirium, both subcortical and cortical. Unfortunately, cognitive testing in many studies of delirious patients have used the Mini Mental State Exam which assesses more left-sided language and cognitive functions. Two recent studies using neuropsychological tests in delirium found that impairment of visuospatial attention and visual memory – both right-sided cognitive functions – alone were sufficient to distinguish delirious from demented or other psychiatric patients [10, 11], even though many cognitive functions were also impaired. Other studies support the lateralization of important neural circuits in delirium to the right hemisphere. A study of delirium incidence among psychiatric patients (not medical-surgical patients) found that bipolars had a significantly higher rate of delirium [12], suggesting an inherent predisposition to delirium. Because lesions of the right anterior cortex and subcortical pathways have been implicated in the bipolar disorder, in contrast to depressed patients, this lateralization to the right side might suggest a neurological vulnerability toward delirium. Also, 'Bell's mania' has been described since the 1800s as a rare form of nonmedical delirium caused by extremely severe mania. Goldberg [13] has noted cognitive laterality differences between the PFC such that the right side processes novel situations whereas the left processes familiar contexts. Delirious patients may have more difficulty processing novel situations than familiar ones, though both types of processing can be impaired.

Dopamine (DA) activity is also lateralized such that the left PFC is normally higher than the right side. If right hemisphere pathways are relatively more dysfunctional in delirium, then a shift in the hemispheric balance of DA activity may result in cognitive and behavioral symptoms. Similarly, studies of major depression after stroke suggest that serotonin laterality may be related to the relationship between anatomy and incidence of poststroke depression (i.e. greater serotonin dysfunction on the left side).

Neurochemistry and the Neuroanatomy of Delirium

Though a number of neurotransmitter systems has been suggested as playing a role in delirium, the predominant hypothesis for which there is the most evidence involves underactivity of the cholinergic system [14]. The Ach hypothesis is probably not separable from DA because these two neurotransmitters interact closely with each other in the brain, often reciprocally. Insufficient Ach is implicated in many causes of delirium – metabolic, pharmacological, and structural – and cholinergic agents reverse delirium [14]. DA excess also can cause delirium, including from dopaminergic medications, cocaine intoxication and ECT [3, 15]. DA (D2 receptor subtype)-blocking medications treat delirium. DA-blocking medications may temporarily rebalance the ratio of Ach and DA activity until the underlying causes of delirium are fixed. In addition, D2 blockade increases Ach release. DA's role is more regulatory in the CNS, allowing or inhibiting functions of other neurotransmitters. Ach serves multiple CNS functions including mood, motor activity, REM sleep, thalamic EEG rhythm, attention, memory, and other cognitive abilities; Ach deficiency has been implicated in causing delusions and hallucinations. Thus, abnormalities of Ach and/or of its regulation by DA could be responsible for delirium symptoms.

DA and Ach neurons also interface in the PFC with different laminar distributions. Layers I, III and V stain densely for cholinergic fibers in human brain [16]. DA has a bilaminar distribution in human PFC with D2 receptors

in layer V and D1 receptors in layers I, II and III [17, 18]. PFC layers II and III are association layers and make corticocortical projections between hemispheres (II) and within hemispheres (III). Layers V and VI have corticothalamic projections. Thus, there are opportunities for Ach and DA to interface with each other in these layers and also to affect information flowing from PFC to thalamus and to other cortical sites where higher level association information is being shared. For example, D2 blockade at PFC layer V might alter neurotransmission to the thalamus. The thalamus drives EEG rhythm, is interconnected to many brain regions and when its anteromedial portions are lesioned is associated with delirium. Thus, knowledge about cytoarchitecture, neural connectivity, and neurochemistry will eventually assist in clarifying the 'final common pathway' to delirium symptoms.

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