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The network model of delirium

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ABSTRACT

The coordinated function of brain networks underlies consciousness, attention and reality testing, all of which are impaired in delirium. The default-mode network, salience network, frontoparietal control network and dorsal attention network are brain networks with integral roles in the maintenance and modulation of the aforementioned functions. Multiple lines of evidence point to their dysfunction in delirium. The convergence of neurotransmitter changes, neuroendocrine and inflammatory stressors on brain networks disrupts bottom-up and top-down attentional control. Neuroimaging and neuroanatomy correlates are potentially consistent with this hypothesis. Overall, this model appears to have significant utility in connecting the seemingly disparate precipitants of delirium while accounting for the clinical manifestations of the syndrome.

Introduction

Delirium is a functional brain disorder, as there are no specific findings on conventional neuroimaging studies or pathological specimens which clearly correlate with the clinical syndrome. This has been a significant reason for our poor understanding of exactly what delirium is. Functional brain imaging studies with functional magnetic resonance (fMRI) and positron emission tomography (PET) have begun to provide insights into brain dysfunction which arises from problems in the coordinated function of the neural network rather than discrete pathological lesions. Therefore, a functional perspective has the potential to shed light on the nature of delirium. Sanders [1] and Rapazzini [2] have previously proposed the idea of changes in brain network connectivity being responsible for delirium.

Functional imaging studies have reinforced the general idea that the cortex and subcortical gray matter are more usefully viewed as a collection of discrete modules, or nodes, that network together [3]. Various combinations of nodes are recruited to perform the diverse functions which the brain is capable of. Multiple functional brain networks have been identified which significantly influence attention, but several appear to be especially important: the default-mode network (DMN) [4], the dorsal attention network (DAN) [5], the salience network (SN) [6,7], and the frontoparietal control network (FPCN) [8] (Table 1). Because inattention is the core cognitive symptom of delirium, these brain networks are suspected to be dysfunctional in delirium.

Brain network function and inattention

The function of individual brain networks is an evolving area, but general themes describing the function of these networks have emerged. The DMN is more active when 'task-activated' areas of the brain are quiet [4]. Its activity constitutes the baseline state of conscious awareness which includes broad, low-level awareness of multiple internal and external stimuli [11]. When no deliberate thinking is occurring it allows for some awareness of mostly irrelevant external sensory data (to permit detection of unexpected salient stimuli) while mostly allowing for an unstructured stream of internal thoughts to meander along. For more deliberate mental tasks such as imagination or planning the future, the DMN is required, but it is co-opted by the FPCN and directed more intentionally. Consciousness itself may arise largely from the coordinated function of the nodes of the DMN in particular, and thus any disruption of its function could lead to an altered state of consciousness. This is seen physiologically each night when we sleep [11,12], but also in altered states of consciousness due to anesthesia or brain injury [13]. Thus, the integrity of the DMN as a standalone network seems to be an important determinant of the level of consciousness and awareness of the environment.

The dorsal attention network (DAN) is activated when externally focused attention is required. When attention is directed externally the DMN is suppressed while the DAN is activated. Conversely, the DAN is suppressed in the absence of external stimuli,

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Table 1
Brain networks involved in attention, their components, and symptoms of delirium which likely result from their dysfunction.

Network	Components	Normal Functions	Network dysfunction leads to	Refs.
Default-Mode Network	1. Medial prefrontal cortex 2. Posterior cingulate cortex 3. Inferior parietal lobule 4. Lateral temporal cortex 5. Hippocampal formation	Active when subjects are at rest, such as in a quiet room with eyes closed, not engaged in any specific task (the 'default-mode'). Increased activity with tasks of mental simulation and self-referential thought and 'mind-wandering'. Suppressed when attention focused on specific stimuli or tasks in the external environment.	– Altered level of consciousness – Disorganized thinking	[4,9]
Frontoparietal Control Network	1. Dorsolateral prefrontal cortex 2. Anterior inferior parietal lobule	Deliberate ('top down') control of attention. Works with elements of the salience network.	– Inattention (reduced sustained attention) – Perceptual disturbances	[6,9]
Salience Network	1. Anterior insula 2. Anterior cingulate cortex 3. Amygdala 4. Ventral striatum 5. Substantia nigra/ventral tegmental area 6. Thalamus	Receives input about reward (ventral striatum/VTA), emotion (amygdala), pain and other senses (thalamus), autonomic activity (AI), cytokine and cortisol levels (ACC). This allows the SN to monitor and prioritize homeostatically important information (grabs attention 'bottom up'). The SN may act as a switch between DMN and DAN modes of attention. The SN along with input from the FPCN can activate the DAN to recruit focused attention towards homeostatically significant stimuli in the external environment.	– Inattention (distractibility) – Perceptual disturbances – Agitation	[3,6,9]
Dorsal Attention Network	1. Intraparietal sulcus 2. Frontal eye fields 3. Superior parietal lobule 4. Middle temporal motion cortex	Activated when attention is focused on a specific external task or stimulus. Activity is anticorrelated with the default mode network.	– Inattention	[9,10]

while the DMN remains active. This reciprocal activity, termed anticorrelation, is essential for efficient deployment of attention towards different tasks or spheres of interest, and avoids interference from irrelevant brain activity [14].

Christoff et al. view attention management in terms of constraints on attention [9]. Unconstrained attention allows DMN activity to proceed spontaneously (day-dreaming in a quiet room). External stimuli can constrain attention further ("automatic constraints", e.g. your eye is automatically drawn to the bright pink car that drives by) and this occurs by SN activation of the DAN and suppression of the DMN (this is also referred to as 'bottom-up' attentional control). Conscious constraints can similarly focus attention ("deliberate constraints", e.g. "I need to stop thinking about that movie and focus on this boring lecture") and this occurs by FPCN-mediated suppression of the DMN and reinforcement of the SN/DAN (this is also referred to as 'top-down' attentional control). The FPCN and SN, therefore, can work together (either cooperatively or antagonistically) to guide attention, bottom-up and top-down.

Importantly, the SN appears to be a hub which mediates switching between different modes of attention [3,7,15,16]. The SN is in the unique position of gathering information from sensory systems regarding internal and external stimuli which may have motivational significance (e.g. reward, pain, fear, anxiety, arousal, stress, etc.). The SN is a sentinel which monitors these streams, developing context for incoming sensory data, and then prioritizing the most homeostatically relevant and allocating finite attentional resources accordingly. The SN exists at a convergence point for multiple stress signals [16]. This is especially interesting as it relates to delirium, because the brain network which receives such a wide variety of stress signals also has a significant role in switching between unfocused attention (uncoupled DMN activity), automatically focused attention (SN/DAN interactions) and deliberately-focused attention (SN/FPCN/DAN interactions). Therefore, this leads logically to the possibility that perturbation of SN function is a critical aspect of inattention in delirium (Fig. 1). Dysfunction of the SN has also been postulated to contribute to other neuropsychiatric problems [16,17].

It is well recognized that stress signals from illness can fundamentally influence brain function. 'Sickness behaviours' are behaviour changes which classically occur in an organism with acute infection (e.g. fatigue, poor concentration, sleep disturbances, etc.), and provide clear evidence for this [18,19]. They are mediated by a variety of neuroendocrine changes, especially cytokine release and HPA axis activation. Sickness behaviours are typically viewed as adaptive, promoting rest, energy conservation, healing, etc. This is probably true in the context of a healthy organism with an acute and reversible illness (e.g. acute infection). However, they may also provide the substrate for neurobehavioural changes which, when poorly regulated or taken to extremes, resemble many of the symptoms of delirium, which are decidedly maladaptive. Interestingly, inflammatory cytokines have been shown to act on brain areas which are nodes in the salience network [20,21].

Delirium is frequently precipitated by inflammation or drugs. Infection resulting in systemic cytokine changes may result in behaviour changes via the SN as noted above. Dementia is a known significant risk for delirium, likely due to a propensity towards exaggerated neuroinflammation [22,23] and baseline changes in brain networks [24–26]. Sanders suggest that some drugs may influence inhibitory tone within brain networks, which may reduce their connectivity and function [1]. Opioids, benzodiazepines and anticholinergics, among others, have the potential to alter thalamic and striatal function [27], which may disrupt SN function and DMN/DAN switching/anticorrelation. One thing which appears to be common among many drugs with a high potential to precipitate delirium is their ability to significantly impact on one or another