Delirium

Delirium as a disorder of consciousness

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Delirium is a common clinical phenomenon, often described as a disorder of consciousness. Delirium is commonly under recognised. The usual response to under recognition is to exhort practitioners to do a better job, but perhaps under recognition should instead be seen as a daily pragmatic challenge to how delirium is conceptualised. Here we retain the view that delirium is a disorder of consciousness, but propose a more multidimensional approach to this key feature. We argue that delirium can be recognised through evaluating arousal, attention and temporal orientation. We suggest that this approach can be validated by testing whether it leads to better delirium identification, accounts for the characteristic clinical disturbances, explains why delirium is common in the extreme age groups and why in later life its boundaries often blend with dementia.

A troop of newly graduated recruits parades on final review. The march past is a portrait of symmetry, save for one young soldier, whose mother nevertheless beams from the stands: ''Look! They're all out of step but my boy John''. Such misplaced parental pride finds a modern day counterpart in the routine exhortation by delirium specialists—including ourselves—for other physicians to get in step with the expert when assessing the mental state of their patients. While physician education is important, part of the pervasive under recognition of delirium must reflect the teaching—that is, how delirium is described and discussed. Here we review some current thinking about what constitutes delirium, propose an alternate operational approach and consider some implications of this synthesis.

THE CURRENT DEFINITION OF DELIRIUM AND SOME ANTECEDENTS

Can it still make sense to ask ''what is delirium''? The fourth edition of the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association[1] defines delirium as a disturbance of consciousness and a change in cognition that develops acutely (table 1).

Support for delirium as a disordered level of consciousness can be found from Hughlings Jackson and was explicit in Lipowski's advocacy for the study of delirium that has so informed modern thinking.[2–5] But DSM-IV displaced DSM-III-R,[6] in which delirium was grounded in Geschwind's influential account of it as a disorder of global attention.[7 8] What is more, some influential textbooks continue to distinguish between what DSM-IV calls ''delirium with psychomotor retardation'' (and which they term the ''acute confusional state'') and ''delirium with psychomotor agitation'' which they term simply ''delirium''.[9 10]

The persistence of this confusion about delirium seems to us to stem from its description being rooted in the experience of particular types of patients at particular historical periods, which now have become less relevant in the face of population ageing. The first modern proposals of what delirium is and how it might be defined have proceeded neither from a model nor from a systematic characterisation of the patients who most commonly suffer from delirium.[11] Now, however, we have enough empirical studies of delirium to allow a model to be proposed and debated. Any new model of delirium should not just account for its characteristic features, but should lend insight into why delirium is under recognised, why it is common in the extreme age groups, why in late life its boundaries can blend with dementia and whether delirium with psychomotor agitation should be grouped with delirium with psychomotor retardation.

PSYCHOPATHOLOGY OF DELIRIUM: AROUSAL, TEMPORAL ORIENTATION AND ATTENTION

In the late 1990s, two reviews of delirium psychopathology noted that it was remarkably under studied.[12 13] The commonest symptoms were disorientation (especially temporal disorientation) (78–100%), clouding of consciousness (65–100%) and impairments in attention/vigilance (62–100%). Disorganised thinking was present in 95%, and memory deficits (62–90%) and diffuse cognitive deficits in 77% of people with delirium.[12 13] Subsequent studies, constrained by instruments that look for these deficits,[14–16] have added comparatively little to the record. An exception is a prospective phenomenological study of 50 elderly people, most of whom reported—a few dispassionately—a sense of being trapped in incomprehensible experiences.[17] Being confused meant that time and place were dissolved, so that past and present, as well as different places, seemed to coexist.[17]

To build on this evidence base, we can also consider ''clouding of consciousness'', classically defined as ''states of reduced wakefulness or awareness that in their minimal form may include hyperexcitability and irritability alternating with drowsiness''.[5] When delirium is defined in relation to disturbed levels of consciousness, impaired arousal is obviously essential. Arousal can be graded, but it is not readily conceptually reduced. Likewise, while arousal can clearly influence attention and while there are different types of attentional impairment, attention too is similarly difficult to reduce further. By contrast, other features are reducible—for example, disorganised thinking can be referable to a variety of other impairments in delirium, including arousal, attention, time perception and memory difficulty.

In addition to arousal and attention, we argue that temporal disorientation is essential, not just because it is common in delirium but because ''time ordered-ness'' is integral to conscious experience.[18] Some might argue that disorientation results from memory impairment and the consequent failure to update knowledge about time and environment. Most people with memory impairment are not temporally disoriented however[19]; more likely, disorientation is due to faulty encoding of the temporal order of information.[20] Disorientation to time may represent impaired time perception, a facet of which has so eloquently been captured in the phenomenological studies of delirium.[17]

PROPOSAL FOR AN ALTERNATE CONCEPTUALISATION OF DELIRIUM

We recognise that some part of the difficulty of operationalising criteria for delirium, conceptualised as a disorder of

Table 1 Diagnostic and Statistical Manual (DSM-IV) criteria for delirium[1]

A	Disturbance of consciousness (ie, reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.
B	A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.
C	The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D	DSM-IV distinguishes between delirium due to general medical conditions, substances (intoxication or withdrawal), multiple aetiologies and others. Thus D criterion varies with aetiology.

consciousness, simply reflects the at-times impenetrable semantic problems in describing fundamental aspects of everyday human conscious experience. Still, delirium must be faced. Based on the frequency of their occurrence and their relative irreducibility, we think it reasonable to suggest that delirium can be operationalised as an acute disturbance in consciousness, characterised by impairments in arousal, time perception and attention.

OPERATIONALISING THE ASSESSMENT OF CONSCIOUSNESS IN DELIRIUM BY MEASURING AROUSAL, TIME PERCEPTION AND ATTENTION

Arousal presents comparatively little difficulty in measurement, especially hypoarousal, which can be graded on a continuum of alertness through lethargy, drowsiness, stupor and coma.[21] Measuring hyperarousal is more problematic. There is no readily available scale, and the term ''hyperarousal'' is often used interchangeably with ''inattentiveness'' and ''distractibility''. The measurement problem becomes easier to resolve when arousal is defined as responsiveness to sensory stimuli and motor activity.[22] Hyperarousal then has clear behavioural anchors, making it more measurable.

Current theories of attention explicitly distinguish between arousal and attention, and suggest a critical role for the noradrenergic system in mediating the influence of arousal on attention.[23] A revealing primate study for example, contrasted phasic locus coeruleus (LC) firing (in response to stimulation) with the level of tonic LC activity.[24] An inverted U-shaped curve was demonstrated, such that too low or too high a state of tonic LC firing (corresponding to differences in arousal) altered phasic LC firing (corresponding to variability in attention). Similar findings come from functional MRI studies in human subjects.[25] Thus hyperarousal is not only distinct from inattentiveness, but can be seen as a cause of it. In consequence, we propose that both hypoarousal and hyperarousal should be measured and rated separately.

Clinically, temporal orientation is often measured using instruments such as the Mini-Mental Status Examination.[26] The Temporal Orientation Test,[27] which includes a question on time of day, is likely better for this purpose than the Mini-Mental Status Examination.[26]

Even though impaired attention is a striking clinical feature of delirium, problems of ''attention'', writ large, are ubiquitous in neuropsychiatric disorders.[28] Not all attentional tests perform equally well, but it is not clear whether any particular form of attentional impairment is specific to delirium. In perhaps the only systematic study of attention in delirium, only Digit Span Backwards, a test of both attention and working memory, and aspects of the Digit Cancellation Test, a test of sustained visual attention and divided attention, were significant independent predictors of delirium.[29] Considering the historical importance of measuring attention in delirium, this is a surprisingly narrow foundation for the weight that it is expected to carry. For future studies, Digit Span Backwards and months backwards are each easy to do.[21] The picture recognition attention screening task from the Confusion Assessment Method for the Intensive Care Unit is also feasible, even though it requires copies of the pictures to hand.[30]

POSSIBLE MECHANISMS FOR DISORDERED AROUSAL, TIME PERCEPTION AND ATTENTION

Arousal arises from a brainstem ''ascending arousal system'', which is reciprocally innervated with specific thalamic nuclei that in turn transmit sensory information to the cortex.[31] Levels of cerebral blood flow or metabolism are seen as correlates of both hypoarousal[5] and hyperarousal.[32] Arousal appears to be modulated by acetylcholine (ACh), γ-amino butyric acid (GABA) and monoamines. ACh released by laterodorsal and pedunculopontine tegmental neurons, in their projections through the thalamus and basal forebrain into the cortex, plays a prominent role in arousal.[33] This network is also associated with EEG activation during wakefulness and the generation of paradoxical sleep.[31] In contrast to the role of ACh in learning in the hippocampus, this perhaps better explains the profound sleep–wake cycle disturbance that is seen in delirium.

A role for reciprocally controlled[22] tonic sensory and muscle spindle activity in maintaining a state of wakefulness[34] might also be relevant to the clinical picture of delirium. This is seen in sharp relief clinically when epidural anaesthesia reduced by about half the need for general anaesthesia in a randomised double blind trial.[35] Interestingly, in both young children and older adults epidural anaesthesia also causes significant sedation.[36]

Time perception, arguably central to human conscious experience, has been the focus of models in psychology, philosophy and neuroscience.[37–43] In animals, the range of processed time scales spans at least 12 orders of magnitude.[42] Most theories of time perception address short time durations, in the range of milliseconds to seconds, and many do not make explicit the difference between timing and time awareness. Timing can only be observed in an animal that is acting or behaving, making it possible to infer that perhaps the animal has some notion of duration judgment. By contrast, time awareness is how humans perceive time[44]; there is no way for us to tell if other animals perceive time as we do.

Broadly, timing theories can be classified as those that propose timers and those that instead attempt to model timing on cognitive or neuronal processes. Most timer based theories propose the existence of an internal clock or pacemaker.[37 45–48] As timing cannot be studied independently of an animal acting in its environment, models that hypothesise the existence of some sort of independent ''organ of time'' are intractable. For our purposes, and recognising that many processes must be involved, the oscillator–comparator model seems to provide a relevant and testable starting point.[49 50] In this model, cortical timing expectations are compared with the actual sensory input timing, to experience time passing, and whether it seems shorter or longer than expected.

Similarly, mechanisms in humans that are relevant for navigating in space—processes that are continuous and automatic—could also be relevant for timing. By such processes, an observer accounts for changes in the spatial relationship between self and objects in the environment that result from one's own movements.[51] Spatial updating likely relies on an egocentric representation of space,[51] wherein the location of each object is encoded with respect to the observer. (The contrast is allocentric representa-

tion, in which object locations are encoded in an external reference frame.) The egocentric reference frame is likely to be influenced by vision (extrapersonal space) and proprioceptive information from the hand (peripersonal space).[52] Egocentric tasks activate a bilateral (R>L) frontoparieto network.[53–55] If this were to occur simultaneously with cognitive acts, then larger scale integration could form the basis of subjective awareness of time.[39] Note too that there is a good foundation for considering subjective time awareness to be related to personal identity.[56] An egocentric frame of reference—taking a first person perspective—is also considered to be the basic constituent of ''minimal self'', which underlies every cognitive process that deals with perceptual experiences.[57]

Attention consistently activates areas in the posterior parietal cortex, the anterior cingulate gyrus and the frontal and supplementary eye fields.[58] Of particular interest, work on attentional orienting to time shows preferential activation of the left inferior parietal lobule and the left inferior lateral premotor cortex,[59 60] a pattern notably similar to that found in motor attention studies.[61–63] Although the regions activated in attention and egocentric representation frames show many similarities, there are equally relevant differences. Compared with the egocentric representation frame, attention appears to activate a relatively narrower area in the posterior parietal cortex. Additionally, it activates the anterior cingulate cortex, which the egocentric representation frame does not. In consequence, perhaps timing, attention and action share a broadly similar network, in which the integration of a large scale, bilaterally represented parietofrontal network is associated with timing (and time awareness when it includes internal cognitive acts). The network would also be relevant in motor attention and visuospatial attention.

SYNTHESIS

Impairments in mechanisms that underlie arousal, time perception and attention impair consciousness, and thereby result in delirium. This conceptualisation seems to offer the following advantages, offered as hypotheses: as it defines the concept and measurement more clearly, it should result in better delirium identification and by yielding a more multidimensional, yet not over inclusive, account of delirium psychopathology and phenomenology and should offer better sensitivity and specificity; by proposing a better mechanistic account, it should predict new risk factors, and; it allows for a metaphorical understanding of delirium, which should make teaching easier.

Three other items—disorganised speech, fluctuations in consciousness and mobility—can each be reduced to the proposed core features that arise from considering delirium as a disorder of consciousness. The assessment of disorganised speech in delirium is often unreliable, probably because of the many ways in which speech can be disorganised. It is not just a matter of ''drifting off'' in the middle of a sentence, which is easily referable to inattention. People with delirium and disorganised speech sometimes slur their words, confuse their order or lack the phoneme discrimination even to formulate them—probably reflecting impaired arousal and/or impaired time awareness.[64] Likewise, fluctuation in consciousness is better understood in terms of arousal for circadian arousal levels in older adults, which reduce through the day after peaking in the morning.[65] It also likely reflects varying levels of sensory stimulation, and impaired signal/noise ratios, through impaired ACh mechanisms. If the basis of timing is in our navigation of space, this could explain the navigation problems commonly seen in delirium.

Impairments in mechanisms of arousal, time and attention could predict the following risk factors: sarcopenia; drugs that affect arousal (anticholinergics, monoaminergic and GABAergic agents); increased sensory stimulation; impairments in vision and proprioceptive information, especially from the hand and; damage to the egocentric representation frame. Note that damage to just the frontal lobe may not be sufficient to produce delirium, as arousal and time perception are not impaired.

Clearly, some risk factors, such as visual impairment, are known. The evidence for others, especially hand proprioception, is not clear, although a deeply considered argument for why hand function should impinge on consciousness has been made.[66] Delirium is associated more with late onset Alzheimer's disease and vascular dementia than with early onset Alzheimer's disease or frontotemporal dementia.[67] Even so, while seen with posterior hemispherical strokes,[68] there is no association with regional brain syndromes.[69] This conceptualisation would also suggest that impairments may range from peripheral (for example musculature) (through the brainstem) to central (frontoparietal cortex). The hypothesis would be that, in elderly people, the risk of delirium increases as the number of deficits along this continuum increases. Moreover, the clinical picture would be determined by which mechanism is most impaired. Thus hypoactive delirium is likely to be associated with greater peripheral impairment (sarcopenia, drugs that impair arousal) relative to central impairment of parietofrontal networks and vice versa. This conceptualisation is likely to lead to better recognition of delirium as it recognises the multidimensional nature of the disturbance of consciousness; identifies simple methods of measuring the three dimensions allowing for evaluating both acuity of onset and fluctuations; provides a framework to identify risk factors and; provides a metaphor for delirium. This should also address the common complaint that disordered consciousness in delirium is difficult to operationalise.[70]

While mental activity alone could produce a sensation of time, it is not anchored to the here and now: time perception instead emerges out of ''minimal self''.[71] Minimal self is the consciousness of oneself as an immediate subject of experience, unextended in time, including the sense of self-ownership and sense of self-agency. We propose that delirium, not unlike dreams, is the unanchored narrative self, leaving the ship lost at sea. Dementia can be seen as the disintegration of both minimal self and narrative self, where both the anchor and the ship are crumbling. This might well give delirium in dementia a distinctive phenomenology, although this remains to be clarified. Likewise, the state of development of self and of time perception might explain why delirium is not rare in children.

Just as delirium has many precipitants, there is unlikely to be a single mechanism that accounts for its many manifestations. By considering arousal, time perception and attention, we are considering the perceptual world, the body and the mind. Delirium in this sense is likely not usefully reducible—instead of being seen as a specific neurotransmitter deficit, it might more usefully be conceived of as the failure of a high order function in a complex system that is close to ''system failure''.[72] This metaphor at least allows us to understand why we must embrace the many aspects of patients' disordered states if we are to better be in step with their care.

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