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NEUROLOGICAL DIGRESSION

Why is delirium more frequent in the elderly?

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Abstract
An aging-related reduction in the brain's functional reserve may explain why delirium is more frequent in the elderly than in younger people insofar as the reserve becomes inadequate to cover the metabolic requirements that are critically increased by stressors. The aim of this paper is to review the normal aging-related changes that theoretically compromise complex mental activities, neuronal and synaptic densities, and the neurocomputational flexibility of the functional reserve. A pivotal factor is diminished connectivity, which is substantially due to the loss of synapses and should specifically affect association systems and cholinergic fibres in delirious patients. However, micro-angiopathy with impaired blood flow autoregulation, increased blood/brain barrier permeability, changes in cerebrospinal fluid dynamics, weakened mitochondrial performance, and a pro-inflammatory involution of the immune system may also jointly affect neurons and their synaptic assets, and even cause the progression of delirium to dementia regardless of the presence of co-existing plaques, tangles, or other pathological markers. On the other hand, the developmental growth in functional reserve during childhood and adolescence makes the brain increasingly resistant to delirium, and residual reserve can allow the elderly to recover. These data support the view that functional reserve is the variable that confronts stressors and governs the risk and intensity of and recovery from delirium. Although people of any age are at risk of delirium, the elderly are at greater risk because aging and age-dependent structural changes inevitably affect the brain's functional reserve.

Keywords Aging · Brain · Delirium · Functional reserve

Introduction

In 2006, Speciale et al. [1] raised the question as to whether delirium, an "enormously impactful syndrome" [2] and a subject of semantic and research confusion [3, 4] since it was first described more than two thousand years ago, is a marker of brain fragility due to aging. This question was partially answered by the European Delirium Association and American Delirium Society [5], which established that delirium "is unquestionably a marker of [brain] vulnerability". However, the relationship between brain vulnerability and aging has not been addressed with as much resolution probably because it is considered obvious given the phenomenology of aging, and so how aging may make the brain more susceptible to delirium is still a matter of speculation.

The aim of this paper is to consider the changes that occur in the brain during normal aging. It is assumed that these changes reduce the brain's functional reserve, thus causing the fragility that may evolve into delirium more frequently in the elderly than in the young. In hospitalised subjects, the risk of delirium may increase from 3% in the young to 14% and 36% in the elderly aged 64–74 years and over [6]: i.e. about 2% per year after the age of 65 years [7].

Functional reserve and delirium

According to most experts, delirium is a confusional syndrome ("an acute disorder of attention and cognition") [8] that develops because of the action of various stressors on fragile brain structures and their connections. Stressors act on nerve and glial cell systems via metabolic mediators, such as low energy levels following hypoxia, hypoglycemia and respiratory chain impairments, endo- and exotoxins, antibodies and autoantibodies, unbalanced ions, pH and osmolarity, drugs, and undue quantities of substantial metabolites and hormones.

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It is probably the balance between stressor strength and brain resilience that governs the risk and intensity of and recovery from delirium. Intuitively, brain resilience depends on the brain's functional reserve, which diminishes with aging: as summarised by Inouye et al. [9] "delirium may serve as a marker of the vulnerable brain with diminished reserve capacity".

The brain's functional reserve has been defined as "the remaining capacity [of the brain] to fulfil its physiological activity, [particularly] in the context of disease […] or impairment" [10] of the brain itself and any organ or body system influencing its metabolism. Functional reserve is due to the interaction of complex mental activities, neural and synaptic densities, and neurocomputational flexibility [11], and may depend on the balance between brain connectivity and adaptive plasticity [12, 13], and the brain structures and energy available at any given moment. This suggests that the increased vulnerability of the elderly to delirium is because they have less functional reserve than the young [14]. According to the homeostenosis theory of the aging-related decline in reserve [15], which "matches the observation that the typical organ does not lose visible function so much as it loses measurable reserve" [16], delirium emerges when the reserve can no longer compensate for the effect of stressors. This view fits the conclusions of a meta-analysis of functional magnetic resonance imaging (fMRI) studies that the risk of delirium is related to the reduced structural connectivity of fragile networks, whereas the onset and course of clinical signs follow incidental dysfunctions of residual networks [17–19]. The question raised by Speciale et al. [1] may therefore be fully answered by considering aging-related structural and functional changes in the brain. Intuitively, the most relevant of these are changes in neuritic wiring and connectivity, cerebral blood flow (CBF), the blood-brain barrier (BBB), the dynamics of cerebrospinal fluid (CSF), the respiratory chain, and native immunity, which may also represent the postulate for some of the hypotheses concerning the origin of delirium [4, 20, 21]. Moreover, as might be expected, the effect of aging on functional reserve may be potentiated by the severity of concomitant diseases, pre-existing cognitive impairment, and reduced vision and hearing [22].

Aging-related brain changes, functional reserve, and delirium (Tables 1 and 2)

Connectivity

Brain shrinkage is a gross outcome of normal aging. The extent of the shrinkage was long debated until Fotenos et al. [23] used magnetic resonance imaging (MRI) to measure brain volume in 362 non-demented subjects aged 18–93 years and found that, after adjusting for head size, it was inversely related to age and was 0.22% per year (0.40% in the elderly). This study confirmed the findings of a previous study of 465 healthy subjects aged 18–79 years that revealed grey matter attenuation, particularly in the anterior cingulate, central, and angular gyri [24]. Shrinkage is due to cellular and sub-cellular changes, such as shortening dendritic branches [25], the loss of dendritic spines [26] and synapses [27], the shrinkage of large pyramidal neurons [28], the contraction of axonal fields [29], and centrum ovale re-modelling leading to a 45% loss of myelinated axons by the age of 80 years [30]. Although less dramatic than once believed [31, 32] and variably distributed [33, 34], these changes concur with lesions conventionally attributed to pathology (β-protein deposits in neuropil and vessel walls, neuronal and glial phospho-tau tangles, α-synuclein and TDP43 protein immunoreactive neurons, senile plaques [35], hippocampal sclerosis, micro-infarcts, and microbleeds) to reduce neuronal connectivity [36], energy metabolism [37], and neurotransmitter levels [4, 20]. Salthouse [38] looked for a relationship between cognitive decline and age-dependent changes, particularly MRI hyperintensities, and found that at most it was only weak. However, although this conclusion is in line with the concept of an asymptomatic burden of structural changes in brains that have aged cognitively well, as suggested by observations in the oldest old [39], it does not argue against the possibility that the changes may become symptomatic because of the action of stressors that absorb the functional reserve. In this regard, the interactions between changes and stressors may be expressed by the stressor-to-synapse ratio, which is expected to increase with aging.

Table 1 Aging-related brain changes

A. Morpho-functional changes peculiar to aging
1. Reduced
   a. Neural connectivity due to shortening dendritic branches, with the loss of dendritic spines and synapses, the contraction of axonal fields, and the loss of myelinated axons, all revealed by decreased neurotransmitter and neurohormone levels
   b. Cerebral blood flow due to micro-vessel stiffening, reduced vessel density, and deficient autoregulation
   c. Respiratory chain efficiency
2. Increased blood-brain barrier permeability following changes in neurovascular components
3. Remodelled
   a. Cerebrospinal fluid dynamics, with an increased fluid-to-brain volume ratio
   b. Immunosurveillance leading to the pro-inflammatory status of microglia and macrophages

B. Incidental structural lesions common to diseases
a. Protein overload in cells, the neuropil, and vessel walls, with neuritic dystrophy and degeneration
b. Micro-infarcts and micro-bleeds

Table 2 Principal targets of morpho-functional changes in aging brain and their delirium-related effects (→)

A. Nerve cell systems
Associative thalamo-cortical and fronto-thalamic fibres
Brainstem activation system
Resting- and task-positive networks
Hypothalamic-pituitary-adrenal axis
Cholinergic systems
Melatonin-related systems
→ Decreased connectivity
B. Parenchymal vessels
Wall structure and neurovascular units: endothelium, smooth muscle fibres, basement membrane, astrocytes, pericytes, microglia, and nerve cell terminals
→ Inadequate blood flow and increased blood-brain barrier permeability
C. Plexus and ventricles
Ependyma, plexus vessels, and water pumps
→ Changes in cerebrospinal fluid dynamics
D. Respiratory chain
Mitochondria in nerve and glial cells, endothelia, and ependyma
→ Reduced efficiency
E. Immune system
Microglia and macrophages
→ Pro-inflammatory changes

There has been a long debate about which brain structures are the most vulnerable. Meynert [40] and Bonhoeffer [41] attributed delirium to the fragility of the thalamic and association systems supporting sensory perceptions, whereas Lipowski [42] and Plum and Posner [43] regarded delirium as a state of altered consciousness, thus implying that the main target was the brainstem activating system. Later, based on a longitudinal study of 100 delirious subjects (27 of whom were demented), Leonard et al. [44] maintained that delirium was the consequence of a thalamus-mediated cortical impairment, consistent with the slowing of electroencephalographic tracings [45, 46] and a global reduction in CBF [47, 48], whereas McLott et al. [49] speculated that post-operative delirium was related to abnormalities in thalamic inputs to the amygdala, hypothalamus, and periaqueductal grey matter. However, diffusion tensor imaging MRI (DTIMRI) allowed Cavallari et al. [50] to show that inter-hemispheric and fronto-thalamo-cerebellar networks were the most involved in patients with post-operative delirium. Trzepacz [51], who analysed functional and imaging studies of psychiatric patients and delirious patients sharing the same symptoms, reached more varied conclusions and suggested that the right or left prefrontal cortex, the anterior and right thalamus, or the right basilar mesial temporoparietal cortex may cause the core symptoms of delirium (e.g. disorientation, cognitive and language defects, a disordered sleep-wake cycle, disorganised thinking), whereas the ancillary symptoms (delusions, hallucinations, illusions, affective lability) depend on the causative disease. On the other hand, theories about the brain being organised into opposing resting- and task-positive networks [52] gave Sanders [53] the idea that delirium is due to abnormalities in their functional relationships. The structures active at rest include the postero-medial cortex, the medial pre-frontal cortex, and temporo-parietal junctions, whereas those activated by tasks include the posterior cingulate gyrus and the precuneus, dorso-, and ventrolateral pre-frontal cortex; the insula; and supplementary motor areas. Using fMRI, Choi et al. [54] found that rest- and task-activated structures were not functionally opposed in delirious subjects as they were in normal subjects and patients after recovery. Furthermore, some subcortical structures (the intralaminar thalamus, the striatum, the tegmentum, and the basal nucleus) were variably involved.

Changes in neurotransmitter balance, the sleep-wake cycle, and stress response dynamics have also been considered in the search for the more fragile structures. Reactions to stress start from the hippocampus and hypothalamus and, via the autonomic nervous system and pituitary gland, force the adrenal glands to increase noradrenaline and cortisol secretion (hence the definition of the hypothalamic-pituitary-adrenal [HPA] axis) to provide the body and mind with anti-stress support [55, 56]. In the limbic system (CA1 and CA3 hippocampus, dentate gyrus, basolateral amygdala) and medial pre-frontal and orbital frontal cortex (the most widely studied in laboratory animals for the presence of specific receptors), glucocorticoids may foster dendritic circuitry and modulate neurogenesis, but become neurotoxic over time. The shrinkage of the hippocampus, amygdala, and frontal cortex in the normal elderly and demented patients has been attributed to chronic stress and cortisol neurotoxic activity, but neurodegeneration could modify the cortisol set-up [57], increase diurnal cortisol secretion [58], and cause abnormal stress responses. On these grounds, MacLullich et al. [59] speculated that delirium may be due to stress responses that become harmful after HPA axis dysregulation possibly caused by inflammatory mediators.

Acetylcholine, dopamine, glutamine, GABA, serotonin, noradrenaline, tryptophan, phenylalanine, and histamine levels are decreased in the normal elderly [4, 20], and unbalanced in delirious patients [60]. Delirium is most frequently associated with reduced acetylcholine levels, excess dopamine, noradrenaline, and/or glutamate release, or uneven amounts in serotonin, histamine, and γ-aminobutyric acid [19]. However, cholinergic deficiency [61] has so far been the most widely accepted because of the confusional state caused by anti-cholinergic drugs and the possibility of

recovery by means of cholinergic agents. A variant hypothesis based on an imbalance between cholinergic and adrenergic neurotransmitters has been suggested by Itil and Fink [62], who maintained that hyperactive forms are due to a prevalence of noradrenergic systems. A dopamine to acetylcholine imbalance might also be involved [51], as suggested by the existence of delirium due to opioids and drugs that promote dopamine release, and the anti-delirium efficacy of neuroleptic drugs that compete with dopamine. Guo et al. [63] have even suggested that glutamate-glutamine cycle dysfunction may explain post-surgical delirium. Multiple defects may lead to contrasting effects [64] as in the case of the susceptibility to delirium of Parkinsonian patients who have a prevalence of cholinergic over dopaminergic and monoaminergic neurons. In comparison, the normal elderly can rely on fewer striatal dopamine receptors balancing residual nigral neurons [65–67]: this lasting balance can appropriately support extrapyramidal functions under basal conditions, but it cannot easily combat stressors such as fever, infections, and neuroleptics.

The reduced duration, continuity, and quality of sleep in the old age [68, 69] all increase the risk of delirium. They are associated with lower levels of melatonin and structural changes in the networks supporting the sleep-wake cycle by means of circadian melatonin release [70], although this might be increased in hypoactive delirious patients [71]. Among the involved structures, Zhong et al. [72] listed the retinal-hypothalamic tract, the suprachiasmatic and galaninergic ventrolateral preoptic nuclei regulating the melatonin clock, orexinergic neurons in the hypothalamus, brainstem monoaminergic nuclei, hemispheric white matter, and the prefrontal cortex. However, sleep deprivation is supposedly responsible for so many dysfunctions [73, 74] that it may contribute to causing delirium [75] before becoming one of its leading symptoms.

Blood flow

CBF decreases with age [76] and, according to Amin-Hanjani et al. [77], who analysed MRI angiograms of 325 healthy subjects aged 18–84 years, and Zhang et al. [78], who used arterial spin labelling MRI (ASL-MRI), the reduction amounts to 2.6 mL/min and 0.38–0.45% every year. Aging also affects CBF autoregulation: i.e. the ability to compensate for blood pressure fluctuations and provide the brain with constant rates of oxygen and glucose by means of arterioles that shrink and expand in response to nervous and chemical inputs [79]. Aging could affect the neurons that regulate vascular tone (bipolar nerve cells in sub-cortical white matter and projections from the locus coeruleus, raphe, tegmentum, and nucleus basalis) [80, 81], and also affect autoregulation as a result of structural alterations in arterioles and capillaries, such as the attenuation of the endothelium with loss of mitochondria, changes in connective tissue and smooth muscle fibres, the thickening of basement membranes, microglia and pericyte proliferation, the decreased expression of water channels in astrocytic feet [82, 83], and β-protein overload. Additional modifications such as vessel tortuosity and collagenosis, string segments in the white matter [84], hyalinisation of vessel walls due to arteriolosclerosis and lipo-hyalinosis [85, 86], and the enlargement of perivascular spaces following an increased pulse rate indicate wall stiffening [87], which impairs the elastic reservoirs of pulse energy [88] and contributes to slowing CBF [79, 89]. These changes may be relevant to brain reserve insofar as they increase the risk of tissue hypoxia, metabolic stress, and nerve cell death [90] when blood pressure drops critically and, in the absence of autoregulation, prevents CBF from fulfilling tissue metabolic requirements. An additional risk may come from vessel density, which decreases with aging [91] despite attempts of capillary regrowth and repair [82], and the characteristics of some intraparenchymal vessels: for example, a narrowing lumen of long penetrating arteries might predispose to chronic periventricular hypoxia, which can be revealed by MRI as leukoaraiosis. Nevertheless, the weight of MRI hyperintensities as a risk marker of delirium in selected surgical patients [92–94] has been questioned [95]. Likewise, an association between delirium and global or regional CBF abnormalities revealed by ASL-MRI before surgery proved to be doubtful [96], although low levels of cerebral oxygen saturation have been found to predict delirium after cardiac surgery in aged, neurologically impaired, or chronically hypoxic subjects [97].

Blood-brain barrier

Aging-related capillary changes affect the efficacy of the BBB, a neurovascular unit consisting of endothelial cells lying on a membrane surrounded by astrocytic feet, pericytes, nerve cell terminals, and microglia [98]. The tight junctions between endothelial cells, and cell-specific functions allow the BBB to act as an intercellular gate for water-soluble molecules and trans-cellular transfer machine for lipophilic agents, molecules carried by proteins, and substances that cross cells via receptors and vesicles [99–101]. In addition, astrocytes mediate metabolic traffic between blood and neurons [102], whereas pericytes control capillary flow [103]. Any changes in the neurovascular unit affect its functional coupling and lead to inaccurate permeabilities that challenge brain tissue and interstitial fluids with abnormal concentrations of ions, metabolites, and substances that otherwise remain or are transferred outside the brain. Erickson and Banks [104] have drawn attention to the reduced expression of proteins carrying glucose and insulin into the brain and β-protein outwards, and the increased intracerebral diffusion of plasma proteins through

inter-cellular clefts. β-protein overload may also contribute to BBB breakdown [105].

The CSF-to-plasma albumin ratio has usually been used to follow the increase in BBB permeability during aging [106]. A dynamic contrast-enhanced MRI study of 113 cognitively normal subjects aged 21–83 years by Senatorov et al. [107] found that the increase begins in mid-life, and Chen et al. [108] have calculated that, in comparison with young barriers that can stop proteins with a molecular weight of >91.9 kDa, elderly barriers can be crossed by heavier molecules of up to 120 kDa. Some capillaries are more vulnerable to permeability failure than others, thus suggesting where BBB dysfunction may start. Montagne et al. [109] measured the MRI gadolinium blood-to-brain transfer constant in 24 non-demented subjects aged 23–91 years and found that BBB permeability increases with age in the capillaries of CA1 and the dentate gyrus of the hippocampus, but not in the capillaries of CA3 or other regions. According to Nation et al. [110], hippocampal BBB permeability is even more compromised in subjects with mild cognitive impairment and a CSF load of sPDGFRβ, a growth factor involved in angiogenesis but also a marker of pericyte damage. This suggests that pericytes might be the first victims of BBB breakdown, although it is the whole unit that suffers structural modifications during aging. Erdö et al. [111] have reviewed the literature on this point and listed a loss of endothelial cells, a reduction in the number of endothelial mitochondria and the expression of tight junction proteins (occludin, claudin, immunoglobulin), a thickening of the basement membrane coupled with decreased laminin content and increased collagen IV and agrin, abnormal bodies and larger mitochondria in the cytoplasm of pericytes, astrocytosis with glial fibrillary acidic protein overexpressed in astrocytic feet, and amoeboid microglia expressing pro-inflammatory mediators. Similar changes have been reproduced in models of BBB breakdown. Varatharaj and Galea [112] have reviewed studies of the pro-inflammatory effects of lipopolysaccharides on cell cultures and laboratory animals, and indicated abnormalities in transporters, prostaglandins, cytokines, tight junctions, astrocytes, and endothelial surfaces. Acharya et al. [113] reported that flurane anaesthetics can damage the proteoglycans and sialoproteins contained on the endothelial surfaces of laboratory animals and increase BBB permeability to plasma proteins. These changes were much more severe and lasted longer in older animals, which suggests that fluranes may be involved in post-surgical delirium in the elderly.

Cerebrospinal fluid

Aging-related changes in CSF have been attributed to oxidative damage and atrophy of the ependymal cells covering plexus and ventricles, and degeneration of the plexus vascular stems [114]. Each of the various components of CSF dynamics [115] is susceptible to senescence: its formation rate (500–600 mL/day is filtrated and secreted via the choroid plexus, ependyma, BBB, arachnoid surface, and modulated by endocrine mechanisms), pressure (100 cm H_2O), flow (pulsatile from the plexus to subarachnoid spaces), turnover rate (up to 4-fold daily), volume (160 mL inversely related to turnover and intra-cranial blood volume), composition (99% water, with a very low protein content), sleep-related recycling via perivascular spaces and interstitial glymphatic networks, and reabsorption by lymphatic and venous streams. Combined with brain shrinkage, the overall effect of senescence on these parameters is an increase in the CSF-to-brain volume ratio [116, 117], which reflects reduced CSF formation (−50%), turnover, recycling, and reabsorption, and increased protein and glucose content with higher osmolarity [118]. Ventricular enlargement can also be magnified by hypoxia because of the over-expression of aquaporin 4, a water channel of pericapillary astrocytes that pumps water from the blood into interstitial spaces and may increase CSF water content [119, 120].

The findings of experimental studies [121, 122] indicate that aged CSF and changes in the BBB obstruct the adequate delivery of nutrients (glucose, vitamins, peptides, nucleosides, growth factors, etc.) to tissues via interstitial fluids and the total removal of harmful metabolites [123]. Particular attention has been paid to β-protein, which accumulates in grey matter during aging, particularly in subjects with Alzheimer's disease. This apparently neurotoxic accumulation is probably due to an imbalance in the activity of RAGE (a receptor for advanced glycation end products) and LRP-1 (low-density lipophilic receptor-associated protein 1), which reside in plexus epithelia and capillary endothelia [124]. The former moves β-protein from the blood into interstitial fluids and CSF, and the latter does the opposite [125, 126]. Aging increases the expression of RAGE and decreases that of LRP-1 [127], and thus drives β-protein turnover towards accumulation. The generation of β-protein is stimulated by aging-related chronic hypoxia, glucose deprivation [128–130], and sleep dysfunctions [131, 132], and its neurotoxicity may be strengthened by the aging-related decreased expression of transthyretin, a protein that is secreted by plexus and binds and blocks β-protein [114, 133].

Respiratory chain

Aging impairs cellular respiration because of a mitochondrial dysfunction that lessens ATP production by 8% every ten years, and even more in sedentary, overweight subjects [134]. Furthermore, mitochondria cross reduced antioxidant defences and accumulate reactive oxygen species, thus leading to oxidative stress and the generation of mitochondrial DNA mutations, a loss of efficient energy metabolism, and metabolic changes that progress to cell degeneration and

apoptosis. Harman [135] suggested that this process, which induces muscle volume to shrink from mid-life onwards, was the basic mechanism of aging but it is now regarded as just part of the involution of various interactive cell pathways [136]. However, it has been suggested that delirium is related to oxidative neuronal stress because oxygen saturation and catalase levels are consistently lowered in delirious post-operative patients [137, 138]. Neurons are particularly vulnerable to mitochondrial impairment and anaerobic metabolism, and the consistently increased lactate levels in elderly brains due to mitochondrial involvement may be a marker of aging in general [139]. The hypoxic vulnerability of neurons is related to the fact that they depend on oxidative phosphorylation to satisfy their energy needs. A review by Grimm and Eckert [140] describes neurons as life-long cells that cannot retain the mitochondrial assets received at birth because of the failure of mitochondrial functions of paramount importance, such as fusion and fission dynamics, debris autophagy, and the ability to increase energy production when required. It is possible that mitochondrial vulnerability to aging is greater in the neuronal compartments that require more energy, particularly the synaptic terminals and axons at the level of the nodes of Ranvier, which suggests that mitochondrial aging is a critical event that consistently affects neuronal connectivity.

Little is known about the mitochondrial aging of glial cells or its neuronal effects, but Jiang and Cadenas [141] have reported increased energy production by astrocytes at the expense of neurons, which suggests that aging is associated with a detrimental change in the previously protective neuro-centred functions of astrocytes.

Microglia and macrophages

The word "inflammaging" was coined by Franceschi et al. [142] to define the pro-inflammatory state of the immune system induced by life-long antigen pressure and stress [143], which can generate an immuno-senescence that favours the onset of aging-related diseases. This generalised involution also affects microglia (the resident immune cells that protect the brain against organic intruders) by eventually allowing them to develop a neurotoxic pro-inflammatory phenotype. According to Cornejo and von Bernhardi [144] and many others who have studied the subject [145–147], aging microglia are characterised by molecular changes (an increased expression of pro-inflammatory cytokines, inflammatory and toll-like receptors and signalling, a decreased expression of anti-inflammatory cytokines and the activation of inhibitory factors, and the overproduction of reactive oxygen species) that make them abnormally primed and unfit to do their work. The morphology and dynamics of senescent microglia are in line with changes in their younger functions [148, 149] as they show an increased propensity for proliferation and enlargement. Their cytoplasm is fragmented, and the residual processes are thicker, less ramified, and poorly reactive to extra-cellular signals of injury. These changes lead to exaggerated inflammatory responses and simultaneously impaired ability to catch and phagocyte intruders [150]. Two additional phenotypes (rod-shaped and dark microglia) have been described in elderly humans [151] and mice [152], but it is doubtful that they are pertinent to normal aging. Unlike microglia, brain macrophages derived from circulating monocytes become more anti-inflammatory and less prone to proliferation; however, they are functionally like aging microglia as they do not activate phagocytosis as effectively as when they were young [153]. In addition, a senescent BBB may interfere with their ability to cross vessel walls, which normally occurs at venule level. Conversely, increased BBB permeability allows plasma albumin to enter astrocytes and over-activate neurotoxic cytokines [107], particularly in patients whose peripheral inflammation is responsible for further endothelial and perivascular cell involvement [154]. Perry and Holmes [155] have underlined the role of β-protein and misfolded proteins in microglial priming, whereas Safaiyan et al. [156] have observed microglia that become senescent after accumulating membrane debris from myelin turnover.

"Inflammaging" implies that aging-related inflammation can promote delirium, and so cytokines capable of mediating the detrimental effect of stressors on the brain (and possibly modifying the release of neurotransmitters [157] and activating the HPA axis) [55, 158, 159] may be markers of delirium. Peripheral inflammation and infections are powerful humoral and cell-mediated stressors that reach the brain via the blood and the vagus nerve and stimulate innate immune cells to produce pro-inflammatory cytokines [160, 161]. Interleukin-6 (IL-6) may be the best peripheral marker of delirium as it is not only detectable in plasma and CSF samples from delirious post-surgical and post-stroke patients [158, 162–167], but also in brain tissue together with markers of astroglial and microglial activation [168]; however, plasma and CSF C-reactive protein, tumour necrosis factor α, IL-1α and 1ß, IL-8, IL-10, and soluble IL-1 and IL-6 receptor antagonist levels may be equally important [169–174]. On the other hand, these diagnostic markers have no predictive value as they are undetectable before the onset of delirium [175].

Comments

This overview argues that senescence involves many entwined changes that deplete the structural and metabolic resources supporting cerebral functions and reserves, thus making the brain increasingly vulnerable to the progression of stress to a state of delirium without precluding recovery. The relationships between these magnitudes can be transformed into the proportion *delirium : recovery = stressor : reserve*, which indicates that functional reserve and stressor

strength are factors that act in opposition to each other to govern not only the individual risk and severity of delirium, but also the prospect of recovery, thus explaining why the aim of treating delirium is to weaken stressors and strengthen reserve.

If a decreasing reserve predisposes to delirium, residual reserve and the capacity to resist stressors may not only partially explain differences in individual resilience, but also allow the brain to recover. This was first pointed out by Meynert [40], who coined the word "amentia" to connote confusion as the clinical hallmark of delirium and underline the fact that, unlike dementia, delirium is not necessarily irreversible. Nevertheless, despite residual reserve, delirium can increase the risk of incident dementia [176, 177], accompany long-term cognitive decline [178], and worsen the severity of pre-existing dementia [179, 180]. Davis et al. [181, 182] have investigated whether the acceleration of cognitive decline in later life induced by delirium is influenced by the tangles, plaques, Lewy bodies, micro-infarcts, and micro-bleeds associated with aging that may cause late-onset dementia. Their study of 987 brain donors (mean age at death 90 years, median follow-up 5.2 years, 279 with delirium) showed that the conversion of delirium to dementia is not influenced by the burden of the lesions conventionally associated with dementia; they concluded that "additional […] pathologic processes [should] specifically relate to delirium", and suggested inflammation as one of these. A complementary study by Erten-Lyons et al. [183] investigated the progression of brain disease and atrophy in 71 elderly subjects and the authors concluded that the burden of Alzheimer-type and vascular lesions does not justify the amount of brain atrophy in patients with mild cognitive impairment and dementia, thus suggesting the involvement of other factors. These findings may argue against the conventional view that there is a continuum between normal aging and late-onset Alzheimer's disease based on the progression and increasing burden of plaques and tangles in both conditions [184] and support the pathogenic role of aging-related and stressor-mediated structural changes that are accelerated and increased by particularly severe, recurrent, and long-standing delirium. In other words, stressors may not only drain functional reserve and lead to the onset of delirium but, depending on their severity and the duration of delirium, simultaneously increase the burden of common aging-related changes in CBF, BBB, CSF dynamics, the respiratory chain, immunosurveillance, and, finally, connectivity. One example of the multiple consequences of even a single stressor on the aging brain is COVID-19 encephalopathy [185, 186].

The difficulty of assigning these changes a recognisable dimension is due to the difficulty of assessing and following them during life to identify traits that are comparable with those of dementia. However, some instrumental data have been obtained from delirious patients that are consistent with recovery or ongoing neurodegeneration. Yokota et al. [47] used xenon-enhanced computed tomography to measure CBF in delirious patients, and found that it was significantly reduced at the level of the frontal, temporal, and occipital cortex; the thalamus; and basal ganglia, but normalised after delirium regression, and Choi et al. [54] found that fMRI abnormalities involving the connections between the dorsolateral, prefrontal, and posterior cingulate cortex can disappear after recovery, although van Montfort et al. [16] used the same experimental design and found that functional abnormalities persisted. Sharshar et al. [187] have reported that MRI perivascular hyperintensities in the white matter of patients with septic shock had a poor outcome that was attributed to abnormally increased BBB permeability. Morandi et al. [188] studied the structure of corpus callosum and internal capsule white matter in 47 delirious patients by means of DTI-MRI and found that reduced fractional anisotropy values indicating white matter disruption persisted for a long time in association with worse cognitive scores. Similar changes were found by Cavallari et al. [189] in the periventricular, frontal, and temporal white matter of 25 subjects presenting cognitive decline one year after post-operative delirium. Prolonged delirium may be responsible for reduced frontal lobe and hippocampal volume [190], and worse global cognition and executive function scores after three and 12 months [5]. According to van Munster et al. [191], increased plasma levels of astrocytic protein S100 may be a marker of brain tissue damage in delirious patients.

Concluding remarks

Although elderly subjects are at much higher risk of delirium than the young, children and adolescents are also at high risk. A review by Hatherill and Flisher [192] has described prevalence rates of 17–66% among referrals from paediatric intensive care units, and others have reported rates of 4–29% and 13–44% [193, 194]. The size of the intervals has been attributed to methodological differences in diagnostic procedures [194, 195], but a complementary explanation might be age, given that delirium occurs more frequently in children aged <5 years and its prevalence peaks at 56% [196] before the age of two years [194, 196]. The reduction in the prevalence of delirium as children and adolescents become older indicates that the ongoing organisation of neuronal hierarchies in myelinogenetic cycles, and the maturation of barrier and ependyma, blood flow autoregulation, native immunity etc., allows functional reserve to increase during brain development as much as it decreases during aging following the onset and progression of structural and functional changes. Taken together, these data show a U-shaped distribution of brain vulnerability to delirium in relation to age, which reflects the availability of functional reserve and supports the relevance of its pathogenic role in lifetime delirium.

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Declarations

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