Consciousness, Functional networks and Delirium screening

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Abstract

Consciousness, the medium of sentient thought, requires integrity of functional networks and their connectivity. In health, they function as a co-operative but mutually exclusive paradigm of introspection versus external awareness subserved via the Default Mode Network and Task Positive State respectively. Higher thinking is segregated according to need, but this relationship is impacted in disorders of consciousness. In delirium, a disturbance of consciousness, the Default Mode Network is pathologically co-activated and functional cortical connectivity is compromised. Inversion of this functional network relationship in conjunction with cortical disconnectivity, we argue, is central to the mechanism of delirium. The corollary of divided networks is that internal and external drivers become indistinguishable, and an experiential singularity follows where reality and delusion merge and the notion of self is effaced. Clinical tools may exploit the neurobiology of delirium to improve diagnosis and an example of such a screening instrument is provided. After all, if delirium is just disorganized electricity then clinical instruments that reflect this neurobiology offer exciting research opportunities with potential for therapeutic gains in detection, diagnosis, and management.

Introduction

Delirium is a common consequence of an encounter between illness and frailty in the hospital setting. Delirium is considered to represent a change in attention associated with cognitive disturbance [1] or, more variably, a disturbance of consciousness [2]. The ICD-10 characterizes this impairment as a ‘clouding of consciousness (i.e., reduced clarity of awareness of the environment). Conversely, DSM V is less explicit regarding the role of consciousness disturbance but its contribution is alluded to in

terms of loss of awareness. This is at odds with earlier iterations of DSM criteria, which are clear in the involvement, if not the centrality, of consciousness and its dissolution in delirium. The fluctuating fortunes of consciousness in delirium diagnostic criteria are owed, no doubt, to impediments in its objective assessment [3]. Alternative features, such as reduced attention, are considered almost a surrogate for disturbance of consciousness and may account for its displacement from certain diagnostic criteria. Whether or not this approach is biologically sound is less clear. Other cardinal features are often used to inform the diagnosis, including disorientation to time, place or person, and disturbance of sleep-wake cycle. Psychomotor disturbance, emotional disruption, perceptual abnormalities and delusions may also accompany the condition, with fluctuation only making more elusive what is otherwise a great masquerader. Despite criticisms of diagnostic criteria, both the DSM and ICD, by the inclusion of cognitive impairment provide a classic means for distinguishing between other conditions that share psychiatric manifestations, such as psychosis. Emphasis on inattention also helps discriminate delirium from dementia, except when both diagnoses collide. The elephant in the room, or hallucination in the hospital bed, is the role that consciousness has to play. This impedes progress concerning our understanding and recognition of delirium and is unable to be reconciled by diagnostic criteria. If clinical criteria and neurobiology are unable to unravel the foundations of consciousness, as it pertains to delirium, then perhaps attempting to understand consciousness from first principles may shed light on this enigma. For this, we must contemplate what consciousness represents at a fundamental level. Consciousness is described as the state in which all waking thoughts are marshalled. Indeed, there is no sentient thought, in the totality of description of symptoms that has not been impacted by delirium. For instance,

patients report their state of mind as being ‘on the threshold between awareness and unawareness’ [4] with all the disorganization of thought across all domains of contemplation a predictable response. Thus, disturbance of consciousness is not just a convenient description applied to delirium but must be axiomatic to its diagnosis. Yet, disturbance of consciousness, as part of delirium, has not been operationalized at a clinical level, resulting in under-diagnosis of this potentially serious condition. Instead, physicians rely on symptoms of delirium to *diagnose* delirium but such approach poses diagnostic circularity. Without a reliable measurement of consciousness, conceptualization and identification of delirium remain superficial. To this extent, the premise that consciousness and its disturbance are central to delirium, presents opportunities for research enquiry. For instance, thought in consciousness exists as a duality, not necessarily of a Cartesian dimension [5] where the thought is a non-physical entity that emanates from a physical substance, but in terms of a division according to functional properties. Consciousness embodies the mutually exclusive functions of introspection and readiness for action, binary states, which are subserved by two large-scale functional brain networks, the Default Mode Network (DMN) and Task Positive State (TPS), respectively. These functional networks allow segregation of sequential planning for action reflection and are thought to represent an evolutionary advantage, particularly in novel situations [6]. Conversely, disruptions of the functional networks are implicated in disorders of consciousness, such as delirium, with loss of reciprocity between states. This article presents an overview of the physiology of functional networks, their role in consciousness, and their disturbance in delirium. In particular, the clinical features of delirium, as they relate to the underlying neurobiology of conscious disturbance, together with opportunities in development of diagnostic instruments, will be explored.

Consciousness and Functional Networks

As discussed, functional networks critical to consciousness encompass the DMN, which supports the function of self-reflection, or repose of the mind. DMN is paired with its functional antonym of action intention, TPS. Structurally, the DMN includes posterior cingulate and medial prefrontal cortices. Functionally, benefits of stimulus independent thought in DMN are numerous: positive constructive daydreaming, future planning, creativity, attentional cycling, and dishabituation [7], as well as offline memory consolidation [8], creative incubation and the generation of original ideas [9], future event simulation [10] and problem solving. TPS, on the other hand, comprises the dorsolateral, ventrolateral prefrontal and pre-supplementary motor areas, and is responsible for external awareness and, more tangibly, is of benefit to navigation in the physical world [11]. Reciprocal innervation of the DMN and task positive networks characterizes the physiological and sentient states. DMN and TPS function are anticorrelated, or mutually exclusive states, that would seem to follow the Heisenberg principle. In other words, the more we know about one state at any point in time, the less we know of the other. So, at an experiential level, one can be in an attitude of reflection or action intention but not in both simultaneously [12]. Cognitive processing requires that these functional networks connect properly between brain regions (i.e., functional connectivity) and interact dynamically to optimize cognitive capacity. Functional network relationships and connectivity integrity, measured using functional magnetic resonance imaging (fMRI), are integral to cognition and awareness of self in relation to the environment; in other words, are pivotal to consciousness [13, 14, 15]. This can be appreciated schematically with a representation of the ‘universe of consciousness’ (see figure 1) [12]. How DMN/TPS uncoupling relates to other features of delirium has not been explored yet. Salient

features, such as loss of tenacity, or sustained attention and hypervigilance are notable considerations. The task positive state activates during attention, demanding tasks to provide ‘external awareness’. These functions are characteristically compromized, in terms of the clinically measureable ability to focus, shift, and sustain attention in delirium. It is conjectured that TPS activity is also impaired, but has not been studied.

Unfortunately, imaging in delirium is a challenge owing to behavioural disturbance and movement artefacts that reduce both the feasibility and accuracy of MRI. Additionally, concomitant CNS disease, and in particular co-existent white matter disease, observed in Korsakoff’s syndrome, may confound interpretation [16]. Undertaking long and exacting studies in patients who are most frequently frail and suffering from disorganized thinking also presents ethical barriers. Hence, there are only a handful of neuroimaging studies in delirium and only one that has explored the role of functional networks, with the action of TPS implied [17]. Nevertheless, the findings from this study, together with supporting literature from other fields, shall form the basis of this review in which we highlight the critical role of functional networks in delirium and their relation to the clinical features of this confusional state.

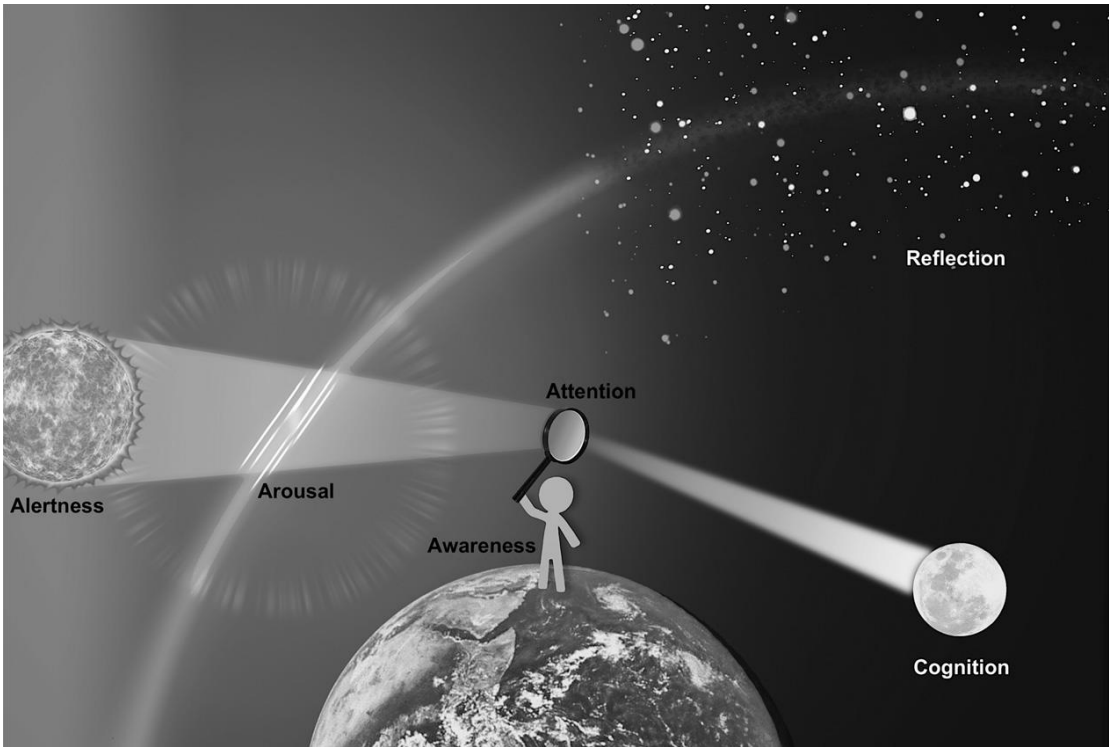

Fig. 1. The Universe of consciousness shows the relationships between the components of consciousness: (i) the level of consciousness is modulated by alertness; (ii) the content of consciousness is filtered by arousal and consists of awareness of self and the environment; (iii) consciousness, focused by attention, can switch between task positive cognition and reflection.

Default mode networks in pathology and delirium

Default mode networks are highly coherent and functionally distinct brain circuits [18] that interact dynamically with each other in order to mediate sensorimotor and cognitive functions, such as consciousness, memory, or attention [19,20]. Disruptions of resting state networks have been linked to cognitive decline [21], depression [22] and schizophrenia [23]. Failure of striatal inhibition of DMN has been implicated in pathologically intense self-reference symptoms observed in schizophrenia [24, 25] and behavioral variant frontotemporal dementia [26]. Alzheimer's disease (AD)

shares some of the cognitive, behavioral and psychiatric manifestations of delirium, not to mention reciprocal risk. DMN hypometabolism [27] and reduced DMN connectivity [28] that affect even unaffected carriers of familial AD [29] are characteristics of AD that make it a candidate biomarker [30]. DMN disconnectivity tends to reverse on AD treatment with cholinesterase inhibitors [31]. Paradoxically, connectivity overload within the DMN results in compensatory load shifting, which may instigate downstream neuronal dysregulation [32].

Specifically, the DMN is known to functionally subserve internally-driven cognitive operations (e.g., self-referential, language, and memory processes [33, 34]). Importantly, however, this network also plays a critical role in cognitive processes that are engaged during stimulus-directed tasks, as it dynamically interacts with task-related networks. To date, only a single study has examined resting state functional connectivity in patients with delirium [17]. Fourteen patients underwent functional MRI, both during and after an episode of delirium, compared with a control group. Functional connectivity of the dorsolateral prefrontal cortex was found to be inversely proportional to task positive activity of the posterior cingulate cortex in healthy controls. In delirium, however, a positive correlation between DMN and TPS regions was observed simultaneously. Choi et al. propose that loss of independence between the DMN and TPS suggests an underlying mechanism for reduced clarity of awareness, or clouding of consciousness [17]. This finding resonates with the clinical picture of a patient with delirium: inattentive, unable to complete simple tasks, disorganized in thought and lacking agency [35]. These clinical features of delirium would appear to be task independent (clinical abnormalities are present whether at rest or during task). Therefore, if functional networks are implicated then it can be conjectured that reciprocity is also lost during task activity although this has yet to be

demonstrated. The authors also noted that a healthy anticorrelation between functional networks did not resume, even after apparent clinical recovery according to improvement in delirium rating scores. This is an important finding and reflects similar loss of connectivity after recovery from propofol-induced coma [36]. Whether the recovery time of functional relationships provides prognostic clues would be an interesting research line of enquiry as apparent clinical recovery still often confers a poor prognosis and risk of dementia [37, 38].

In addition to these qualitative changes, a quantitative reduction in functional connectivity between subcortical regions was also reversibly reduced during delirium [17]. This finding has also been observed in EEG-derived functional connectivity, with desynchronization with respect to alpha band following post cardiac surgery delirium [39], which is speculated to contribute to attentional deficits [40,41]. Decrease in alpha power has also been described in the vegetative state [42]. As well as attention, disconnectivity may also be impacting consciousness level, which may be important in delirium when arousal or alertness diminish, such as hypoactive states. The disconnection syndrome has also been observed in subcortical vascular cognitive impairment [43,44] and psychiatric disorders, such as schizophrenia and bipolar disorder [45]. Indeed, there is a suggestion that hallucinations, as part of delirium and schizophrenia, may share disturbed small world networks. Hub region targeted attacks of brain network also contribute to global disconnectivity and widespread cognitive impairment identified in Alzheimer's' disease, all the while in a conscious state. Altered consciousness in delirium, through disrupted functional network relationships, would, in the context of a disconnection disorder, provoke a ground zero for cognition. This may account for why the confusion is 'an incomprehensible experience' to the sufferer [46]. Furthermore, and in keeping with

delirium being a form of madness [46], it can be argued that the cognitive void created by consciousness clouding and disconnectivity syndrome is intruded by psychiatric symptoms, as is commonly observed [47]. Often, patients feel the simultaneous juxtaposition of past, present and imagination merge into an unpleasant experiential singularity [47]. It is arguable that more networks are affected in delirium and yet it seems reasonable to hypothesize that a breakdown in networks involved in attention, self-reference and whole brain integration would, in and of themselves, be sufficient to account for the protean manifestations of delirium. Alternatively, as was observed by Hughlings Jackson, when higher-order thinking breaks down, primitive central nervous system drive takes over [48].

One may argue that functional disturbance in delirium might be non-causal and merely an epiphenomenon. However, reduced anticorrelation between the DMN and task-positive networks has been observed in other disorders of consciousness, such as in propofol-induced loss of consciousness and vegetative state [13, 14] in addition to disconnectivity [39]. Overall, the relationship between paired networks of DMN and TPS, and subcortical functional disconnection are likely to play a role in the neurobiology of delirium.

Implications for clinical practice

To date, there have been at least 24 delirium scales and 11 screening tools developed for diagnostic purposes [49], all relying on the clinical symptoms of delirium for diagnosis. Perhaps the prolific output of scales and dependence upon ancillary features of delirium are effect and cause of this diagnostic circularity. However, the presentation of delirium can be varied with a spectrum of psychomotor subtypes that has the ability to confound even experienced practitioners. The Confusion Assessment Method, which was developed by an expert panel and derived from

DSM-III-R criteria [50], is perhaps the most widely used in a research or clinical context [51]. This instrument relies upon training of the rater for optimum results. Also, psychomotor properties have shown both reduced sensitivity when used by nurses. Lower specificity has also been demonstrated when the instrument has been used in the presence of psychiatric comorbidity [52]. The Delirium Rating scale (and DRS-R-98) performs well and is perhaps the reference standard when it comes to estimating severity [53, 54]. Use of this instrument is, however, limited to psychiatric populations, and for those with psychiatric training. The 4AT is straightforward, brief to administer, and exploits simple questions that relate to most of the core features of delirium, such as counting months of the year backwards for attention [55, 56] generating a score consistent with the presence or absence of delirium. What these, and all other delirium screening/ diagnostic tools, rely on are the findings of cognitive impairment, particularly inattention. Whilst cognitive dysfunction is recognized as a core feature of delirium, there is no consensus on how this should be determined. Psychiatric symptoms (e.g., delusions and hallucinations) are well described in delirium as is psychomotor disturbance, and these symptoms are often included in delirium screening. However, inclusion of these items favours recognition of more florid forms of delirium, so-called hyperactive delirium, which is not usually a diagnostic problem at a clinical level. Most inconsistently conceptualized and applied to delirium screening is the disruption of an imprecise construct of consciousness content that inhabits a mercurial continuum between alertness and coma [57]. Therefore, diagnosis of delirium would be most desirable if it captured not just the symptoms, but also clinical features that most closely reflected the underlying neurobiology. An understanding of functional networks in health and disease forms a foundation of any approach to exploring the fundamental clinical features of delirium.

In health, consciousness is characterized by network integrity and intact connectivity. Observable and testable tenets of an intact state of consciousness would thus comprise: (1) dynamic networks that interact freely; (2) preserved reciprocal innervation between networks; and (3) integrity of cortical connectivity. Clinically, this would be demonstrated by reflective thought in the medium of awareness (DMN) that is followed by congruent action (TPS). Conversely, in delirium, any clinical tool that mirrors: (1) disturbance in the ability to alternate between DMN and TPS; (2) loss of reciprocal innervation; and (3) disconnectivity syndrome would reflect biology of delirium in the medium of consciousness disturbance. There may be ways of specifically testing DMN, such as application of the self-referential and theory of mind [58], the ability to intuit mental states to oneself and others, and mnemonic facilitation hypothesis [59, 60]. However, these may be beyond the reach of the delirious patient, owing to limited attention span and inadequate cognitive reserves required for such tasks. The point of departure from a sustained task as de facto mind wandering might be a more straightforward way of assuming engagement of the DMN [61]. Therefore, any candidate instruments for use in the context of delirium would need to be relatively simple (as otherwise the high prevalence of prior dementia in delirium would result in false positives) and short (to avoid non-completion in the context of inattention).

From this premise, our multiprofessional group (neuropsychologist, geriatrician, physician and registered nurse) developed from first principles and through an iterative process the Simple Query for easy evaluation of consciousness (SQeeC) [62]. The first question, ‘Name a place you would like to visit that you have never been before’ examines the reflective state subserved through the DMN. The second question ‘How would you get there’ was reasoned to exploit task positive

cognition. This query was refined by an expert group and tested in a hospitalized acute medical/geriatric population of 100 patients against consultant geriatrician clinical opinion and standard screening. The SQeeC showed a sensitivity of 83% and specificity of 81%, respectively. Whilst these are encouraging results, what is more salient from a proof of principle perspective is that virtually no patients who were able to answer the SqeeC correctly were delirious (negative predictive value of 97%). This result suggests to our group that intact functional networks as part of the construct of consciousness and reflected in simple directed questions, if proven to be intact, must reflect a non-delirious state. From cogito ergo sum to tibi conscientia demonstrat ergo non deliriaire (you demonstrate thought and so are not delirious). Our group argue that this hitherto most elusive part of delirium screening, around consciousness, is measureable and may yet prove to be the most insightful. Further development and testing of instruments that are intended to reflect the neurobiology of delirium and their neurophysiological correlates are required. To date, delirium has been described and diagnosed primarily in terms of observable symptoms and their measurement. This, as we have discussed, has resulted in a form of diagnostic circularity. If delirium can be conceptualised as a disorder of consciousness, functional networks, which are important in the maintenance of awareness, must be compromized in the delirious patient. To this end, further development of clinical tools, which converge on the true essence of delirium in terms of functional networks, are required.

Further studies

Greater understanding of the neurobiology of delirium may inform the development of improved diagnostic tools and more efficacious treatments to follow. Functional analysis of patients with delirium remains in its infancy, with practical,

methodological, and ethical challenges remaining [63]. Careful selection of patients, streamlined protocols, and psychotropic agents that are neutral to functional properties may optimize the research outputs within an ethical paradigm. The interrelationship between functional and structural CNS architecture is paramount; most commonly delirium is caused by a problem outside of the brain and yet global or focal brain lesions are important in causality. The ability for functional studies to test existing theories in relation to pathogenesis, aberrant stress response, neurotransmitter hypothesis, microglial activation, and/or inflammatory cascade will be key to unlock the prospect of evaluating targeted therapies [64]. How neurophysiology relates to risk of delirium would be valuable to quantify and the attenuation of neurobiology in response to preventative and treatment strategies may define more precise management plans. Any and all of such studies need to be planned in the context of vulnerability factors, such as dementia, which have a direct effect on neurophysiology and with an appreciation of the heterogeneous nature of causation.

Conclusion

Consciousness, the medium of sentient thought, requires integrity of functional networks and their connectivity. In health, these networks function as a co-operative, but mutually exclusive, paradigm that helps segregate higher thinking according to need. When consciousness is disturbed, such as in delirium, the DMN is pathologically co-activated and functional cortical connectivity is compromised. Internal and external drivers become indistinguishable, and an experiential singularity follows where reality and delusion merge, and the notion of self is effaced. There is conceptual and neurophysiological evidence to support functional network disruption and cortical disconnectivity as central to the mechanism of delirium. Clinical tools

may exploit the neurobiology of delirium and an example of such a screening instrument is provided. Clinical instruments that reflect the cardinal neurobiology of delirium offers exciting research opportunities with potential for gains in detection, diagnosis, and therapeutics.

References

[1] American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Press.

[2] American Psychiatric Association (2000): Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Press.

[3] European Delirium Association; American Delirium Society.
The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. BMC Med 2014; 12:141.

[4] Laitinen H. Patients' experience of confusion in the intensive care unit following cardiac surgery. Intensive Crit Care Nurs 1996; 12(2):79-83.

[5] Stanford Encyclopedia of Philosophy (online): Descartes and the Pineal Gland.

[6] Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC , Raichle ME et al. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA 2005; 102:9673–9678

[7] Schooler J. W , Smallwood J, Christoff K, Handy T. C, Reichle E. D, Sayette M. A. Meta-awareness, perceptual decoupling, and the wandering mind. Trends Cogn Sci 2011; 15:319–326

[8] Wang K, Yu C, Xu L, Qin W, Li K, Xu L. Offline memory reprocessing: involvement of the brain's default network in spontaneous thought processes. PLoS ONE 2009; 4:e4867 10.1371.

[9] Mayseless N, Eran A, Shamay-Tsoory SG. Generating original ideas: The neural underpinning of originality. Neuroimage 2015; 116:232-9.

[10] Baird B, Smallwood J, Mrazek M. D, Kam J. W, Franklin M. S, Schooler J. W. Inspired by distraction mind wandering facilitates creative incubation. Psychol. Sci. 2012; 23 (10): 1117-1122.

[11] Provost JS, Monchi O. Exploration of the dynamics between brain regions associated with the default-mode network and frontostriatal pathway with regards to task familiarity. Eur J Neurosci 2015; 41(6):835-44.

[12] Eeles EM, Pandy S, Ray JL. Delirium: a disorder of consciousness? Med Hypotheses 2013; 80(4):399-404.

[13] Boveroux P, Vanhaudenhuyse A, Bruno MA, Noirhomme Q, Lauwick S, Luxen A, et al. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. Anesthesiology 2010; 113(5):1038-53.

[14] Vanhaudenhuyse A, Noirhomme Q, Tshibanda LJ, Bruno MA, Boveroux P, Schnakers C et al. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Brain 2010; 133(Pt 1):161-71.

[15] Qin P, Wu X, Huang Z, Duncan NW, Tang W, Wolff A et al. How are different neural networks related to consciousness? Ann Neurol 2015; [Epub ahead of print]

[16] Segobin, S., Ritz, L., Lannuzel, C., Boudehent, C., Vabret, F., Eustache, F., Beaunieux, H. and Pitel, A.-L. Integrity of white matter microstructure in alcoholics with and without Korsakoff's syndrome. Hum Brain Mapp 2015; 36: 2795–2808.

[17] Choi SH, Lee H, Chung TS, Park KM, Jung YC, Kim SI et al. Neural network functional connectivity during and after an episode of delirium. Am J Psychiatry 2012; 169(5):498-507.

[18] Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995; 34:537–541.

[19] Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity.J Neurophysiol 2008; 100(6):3328-42**.**

[20] van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 2010; 20(8):519-34.

[21] Sun Y, Yin Q, Fang R, Yan X, Wang Y, Bezerianos A et al. Disrupted functional brain connectivity and its association to structural connectivity in amnestic mild cognitive impairment and Alzheimer's disease. PLoS One 2014; 7; 9(5):e96505.

[22] Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc Natl Acad Sci USA 2010; 107(24):11020-5.

[23] Manoliu A, Riedl V, Zherdin A, Mühlau M, Schwerthöffer D, Scherr M et al. Aberrant dependence of default mode/central executive network interactions on anterior insular salience network activity in schizophrenia. Schizophr Bull 2014; 40(2):428-37.

[24] Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. Annu Rev Clin Psychol 2012; 8:49-76.

[25] Li M, Deng W, He Z, Wang Q, Huang C, Jiang L et al. A splitting brain: Imbalanced neural networks in schizophrenia. Psychiatry Res 2015; 232(2):145-53.

[26] Buhour MS, Doidy F, Laisney M, Pitel AL, de La Sayette V, Viader F et al. Pathophysiology of the behavioral variant of frontotemporal lobar degeneration: A study combining MRI and FDG-PET. Brain Imaging Behav 2016; [Epub ahead of print]

[27] Liguori C, Chiaravalloti A, Sancesario G, Stefani A, Sancesario GM, Mercuri NB et al. Cerebrospinal fluid lactate levels and brain [18F]FDG PET hypometabolism within the default mode network in Alzheimer's disease. Eur J Nucl Med Mol Imaging. 2016 May 25. [Epub ahead of print]

[28] Chen Y, Yan H, Han Z, Bi Y, Chen H, Liu J et al. Functional Activity and Connectivity Differences of Five Resting-State Networks in Patients with Alzheimer's Disease or Mild Cognitive Impairment. Curr Alzheimer Res 2016;13(3):234-42.

[29] Chhatwal JP, Schultz AP, Johnson K, Benzinger TL, Jack C, Jr, Ances BM, et al. Impaired default network functional connectivity in autosomal dominant Alzheimer disease. Neurology 2013; 81:736–744.

[30] Sui X, Zhu M, Cui Y, Yu C, Sui J, Zhang X, et al. Functional Connectivity Hubs Could Serve as a Potential Biomarker in Alzheimer's Disease: A Reproducible Study.Curr Alzheimer Res 2015; 12(10):974-83.

[31] Blautzik J, Keeser D, Paolini M, Kirsch V, Berman A, Coates U, Reiser M, Teipel SJ, Meindl T. Functional connectivity increase in the default-mode network of

patients with Alzheimer's disease after long-term treatment with Galantamine.Eur Neuropsychopharmacol 2016; 26(3):602-13.

[32] Jones DT, Knopman DS, Gunter JL, Graff-Radford J, Vemuri P, Boeve BF et al. Alzheimer's Disease Neuroimaging Initiative. Cascading network failure across the Alzheimer's disease spectrum. Brain 2016 Feb;139 (Pt 2):547-62.

[33] Burianova H, McIntosh AR, Grady CL. A common functional brain network for autobiographical, episodic, and semantic memory retrieval. Neuroimage 2010; 1;49(1):865-74.

[34] Buckner RL, Carroll DC. Self-projection and the brain. Trends Cogn Sci 2007; 11(2):49-57.

[35] Rapazzini P. Functional interrelationship of brain aging and delirium. Aging Clin Exp Res 2015; 28(1):161-4.

[36] Lee, H, Mashour, GA, Noh, GJ, Kim, S, Lee, U. Reconfiguration of network hub structure after propofol-induced unconsciousness. Anesthesiology 2013;119: 1347–59.

[37] Eeles EM, Hubbard RE, White SV, O'Mahony MS, Savva GM, Bayer AJ.Hospital use, institutionalisation and mortality associated with delirium. Age Ageing 2010; 39(4):470-5.

[38] Davis DH, Barnes LE, Stephan BC, MacLullich AM, Meagher D, Copeland J et al; MRC Cognitive Function and Ageing Study. The descriptive epidemiology of delirium symptoms in a large population-based cohort study: results from the Medical

Research Council Cognitive Function and Ageing Study (MRC CFAS). BMC Geriatr. 2014; 14:87.

[39] van Dellen E, van der Kooi AW, Numan T, Koek HL, Klijn FA, Buijsrogge MP et al. Decreased functional connectivity and disturbed directionality of information flow in the electroencephalography of intensive care unit patients with delirium after cardiac surgery. Anesthesiology 2014; 121(2):328-35.

[40] Klimesch, W, Doppelmayr, M, Russegger, H, Pachinger, T, Schwaiger, J Induced alpha band power changes in the human EEG and attention. Neurosci Lett. 1998; 244*:*73–6.

[41] Başar, E, Başar-Eroglu, C, Karakaş, S, Schürmann, M. γ, α, δ, and θ oscillations govern cognitive processes. Int J Psychophysiol 2001; 39 241–8.

[42] Lehembre, R, Marie-Aurélie, B, Vanhaudenhuyse, A, Chatelle, C, Cologan, V, Leclercq et al. Q Resting-state EEG study of comatose patients: A connectivity and frequency analysis to find differences between vegetative and minimally conscious states. Funct Neurol 2012; 27: 41–7.

[43] Zhou X, Hu X, Zhang C, Wang H, Zhu X, Xu L et al. Aberrant Functional Connectivity and Structural Atrophy in Subcortical Vascular Cognitive Impairment: Relationship with Cognitive Impairments. Front Aging Neurosci 2016; 2;8:14.

[44] Ding W, Cao W, Wang Y, Sun Y, Chen X, Zhou Y et al. Altered Functional Connectivity in Patients with Subcortical Vascular Cognitive Impairment--A Resting-State Functional Magnetic Resonance Imaging Study. PLoS One 2015; 16;10(9):e0138180.

[45] Skåtun KC, Kaufmann T, Tønnesen S, Biele G, Melle I, Agartz I et al. Global brain connectivity alterations in patients with schizophrenia and bipolar spectrum disorders. J Psychiatry Neurosci 2016; 41(3):150159.

[46] Liposki ZJ (1990). Delirium Acute confusional states. Oxford University Press; New York.

[47] Bhat R (2005). Psychotic symptoms in delirium. Psychosis in the Elderly. In Hassett A, Ames D, Chiu E, editors. Taylor and Francis Group, London and New York, pp135-148.

[48] Hughlings-Jackson J (1958): Evolution and dissolution of the nervous system (Croonian Lectures), in The Selected Writings of John Hughlings Jackson, vol 2. In Taylor J, editor. New York, Basic Books, pp 45–75.

[49] De J, Wand AP. Delirium Screening: A Systematic Review of Delirium Screening Tools in Hospitalized Patients. Gerontologist 2015; 55(6):1079-99.

[50] Inouye SK, Van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the Confusion Assessment Method. Annals of Internal Medicine 1990; 113:941-8.

[51] Neufeld KJ, Nelliot A, Inouye SK, Ely EW, Bienvenu OJ, Lee HB et al. Delirium diagnosis methodology used in research: a survey-based study. Am J Geriatr Psychiatry 2014; 22(12):1513-21.

[52] Grover S, Kate N. Assessment scales for delirium: A review. World J Psychiatry 2012 22;2(4):58-70.

[53] Trzepacz P. T, Baker R. W, Greenhouse J. A symptom rating scale for delirium. Psychiatry Research 1988; 23, 89–97.

[54] Trzepacz PT, Mittal D, Torres R, Kanary K, Norton J, Jimerson N. Validation of the Delirium Rating Scale-revised-98: Comparison with the delirium rating scale and the cognitive test for delirium. Journal of Neuropsychiatry & Clinical Neurosciences 2001; 13, 229–242.

[55] Bellelli G, Morandi A, Davis DH, Mazzola P, Turco R, Gentile S, Ryan T, Cash H, Guerini F, Torpilliesi T, Del Santo F, Trabucchi M, Annoni G, MacLullich AM. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. Age Ageing 2014;43(4):496-502.

[56] O'Regan NA, Ryan DJ, Boland E, Connolly W, McGlade C, Leonard M, Clare J, Eustace JA, Meagher D, Timmons S. Attention! A good bedside test for delirium? J Neurol Neurosurg Psychiatry 2014;85(10):1122-31.

[57] Eeles E, Bhat RS (2016). Delirium. Textbook of Geriatric Medicine and Gerontology 8th edition. In Fillit HM, Rockwood K, Young JB, editors, pp903-908. Elselvier.

[58] Buckner RL, Carroll DC. Self-projection and the brain. Trends Cogn Sci 2007; 11(2):49-57.

[59] Konishi M, McLaren DG, Engen H, Smallwood J. Shaped by the Past: The Default Mode Network Supports Cognition that Is Independent of Immediate Perceptual Input. PLoS One 2015; 10(6):e0132209.

[60] Spreng RN, Grady CL. Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. Journal of cognitive neuroscience 2010; 22:1112–1123.

[61] Durantin G, Dehais F, Delorme A. Characterization of mind wandering using fNIRS. Front Syst Neurosci 2015; 26; 9:45.

[62] Lin HS, Eeles E, Pandy S, Pinsker D, Brasch C, Yerkovich S. Screening in delirium: A pilot study of two screening tools, the Simple Query for Easy Evaluation of Consciousness and Simple Question in Delirium. Australas J Ageing 2015; [Epub ahead of print]

[63] Slooter and Groot (2014). Neuroimaging of Delirium. PET and SPECT in Psychiatry. In Dierckx RAJO, Otte A, de Vries EFJ, van Waarde A, den Boer JA, editors. Pp463-470. Part IV. Pp463-470. Springer Berlin Heidelberg.

[64] van Gool WA, van de Beek D, Eikelenboom P.
Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet 2010; 27; 375(9716):773-5.