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Review article

Disruption of the ascending arousal system and cortical attention networks in post-stroke delirium and spatial neglect

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ABSTRACT

Delirium is an acute attention and cognitive dysfunction, adversely affecting functional outcomes and mortality. As many as half of hospitalized right brain stroke survivors may develop delirium. Further, about 50% of right stroke patients experience spatial neglect, impairing safety and recovery. In this review we explore the brain mechanisms, which may explain the high incidence of delirium and spatial neglect after right-brain stroke. We suggest that brain networks for spatial attention and arousal, composed of ascending projections from the midbrain nuclei and integrating dorsal and ventral cortical and limbic components, may underlie impairments in delirium and spatial neglect. We propose that lateralized deficits in spatial neglect may arise because cortical and limbic components of these functional networks are disproportionally impaired by right-brain strokes, and that spatial neglect may lower the threshold for developing delirium. An improved understanding of the brain basis of delirium and spatial neglect could provide a critical biomarker for initiating preventive care in stroke patients at high risk of hospital morbidity and loss of independence.

1. Introduction

In about 1 out of 5 patients, in-hospital care will be complicated by delirium (Fong et al., 2009; Inouye, 2006; Inouye et al., 2014). Delirium is an acute state of confusion, described as a sudden decline in attention, cognitive function and arousal, which is not better explained by other pre-existing conditions like depression, schizophrenia, dementia, or aphasia (Hales and Yudofsky, 2003; Inouye et al., 2014). The clinical profile of a delirious patient is familiar to many clinicians: the patient's attention is compromised. Patients are unable to sustain vigilance, their minds wander aimlessly, but they may suddenly and inappropriately focus on a single stimulus, which becomes a source of distraction (Mesulam, 2000; Mesulam and Geschwind, 1976; Mori and Yamadori, 1987). The stream of thought loses organization, and maintaining sequences of events becomes extremely effortful; tasks such as reciting the months of the year in backwards order are difficult or impossible (Horenstein et al., 1967; Mesulam, 2000). Patients may also appear drowsy, quiet, uncooperative, and unable to carry out goal-directed behaviors (Inouye et al., 2014; Mesulam and Geschwind, 1976). Other problems may include memory disturbance, disorientation, perseveration, perceptual distortions, anomia, and difficulty in writing or calculation (Mesulam, 2000; Mesulam and Geschwind, 1976; Mori and Yamadori, 1987). The clinical presentation of delirium can be classified into hypoactive and hyperactive on the basis of psychomotor behavior (Fong et al., 2009). The hypoactive subtype is associated with agitated, restless behavior, and hyper vigilance, with possible hallucinations and delusions. The hypoactive form is characterized by a decreased level of activity and alertness, and, therefore, may be frequently overlooked, or misdiagnosed as depression or dementia. Patients may also fluctuate between the two states.

Delirium is a morbid and dangerous complication after stroke, and efforts to improve understanding of its brain mechanisms may help to reduce its prevalence in this group. Delirium increases mortality, length of hospital stay, and adversely affects functional outcomes (Gustafson et al., 1991; Inouye et al., 2014, 1998; Khan et al., 2012; Kiely et al., 2010; Maldonado, 2013; McManus et al., 2009b, 2011; Oldenbeuving et al., 2011). It occurs in 10–27% of stroke survivors during the first critical weeks of recovery (Inouye et al., 2014; Langhorne et al., 2000; McManus et al., 2009a; Melkas et al., 2012; Rahkonen et al., 2000). This incidence may be nearly doubled when the right brain is damaged (Table 1). A substantial percentage of delirium cases may be preventable (up to 40%, Inouye et al., 2014). However, neural mechanisms are not yet being manipulated to prevent, manage, or treat delirium, because we lack detailed information about the brain correlates of this

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Table 1
Review of studies on delirium incidence after stroke showing greater risk for right-brain strokes.

Study	Participants	Delirium Assessment Method	Delirium Incidence	Delirium Incidence after a Right Brain Event (Spatial Neglect Co-morbidity Noted)
Caeiro et al. (2004)	218 (39% females) patients with ICH (48); SAH (28); & infarcts (142)	DRS[d]	13%	16% in right vs. 8% in left stroke (ns); left neglect predicted delirium ($p < 0.05$)
Dahl et al. (2010)	178 (65 females) patients with acute stroke	1) CAM[a] 2) DSM-IV[e] in CAM[1] positive patients 3) MDAS[f] for severity	10%	Hemianopsia (may include neglect) was a predictor of delirium OR = 12.3, 95% CI 2.8–54.3)
Dostović et al. (2009)	233 patients with ICH (36) or infarct (197); 57.6% of delirious patients were female	1) DRS-R-98[d] 2) DSM-IV[e]	25.3%	26.2% in right vs. 20.5% left ischemic stroke ($p < 0.001$); 42.9% in left vs. 27.8% right ICH ($p < 0.005$)
Dunne et al. (1986)	661 patients with stroke	Evidence of altered mental state	3%; 33% confused	Of 3% with acute delirium −almost exclusively right stroke
Gustafson et al. (1991)	145 (55 females) patients with ICH (8); infarct (113); TIA (21)	DSM-III-R[e]	48%	58% in left vs. 38% right stroke ($p < 0.05$)
Hénon et al. (1999)	202 (105 females) patients with ICH (25); infarct (177)	1) DSM-IV[e] 2) DRS[d]	24.3%	Right cortical lesion was a predictor of delirium ($\beta = 1.15$, $SE = 0.45$, $p < 0.05$)
Kostalova et al. (2012)	100 (47 females) patients with ICH or infarct	1) CAM-ICUcz[c] 2) DSM-IV[e] by a panel of experts	43%	51.2% in right vs. 37.4% in other stroke (ns)
Mori and Yamadori (1987)	41 (15 women) patients with right MCA infarct	1) Mini-Mental Status Exam 2) Staff neurologist examination	61% Acute Confusional State; 15% Acute Agitated Delirium	All right hemisphere MCA strokes
Naidech et al. (2015)	90 (39 females) patients with ICH	CAM-ICU[b]	28%	VLSM showed two right subcortical regions lesioned in delirium
Oldenbeuving et al. (2011)	527 (239 females) patients with ICH or infarct	CAM[a]	11.8%	OR = 2.0 for delirium in right vs. left stroke (95% CI 1.0-3.0)

[a] CAM = Confusion Assessment Method (Inouye et al., 1990).
[b] CAM-ICU = Confusion Assessment method for Intensive Care Units (Ely et al., 2001).
[c] CAM-ICUcz = Confusion Assessment method for Intensive Care Units in Czech (Mitasova et al., 2012).
[d] DRS (R-98) = Delirium Rating Scale (Trzepacz et al., 2001).
[e] DSM (III, III-R, IV) = Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1987, 1980); ICH − Intracerebral Hemorrhage.
[f] MDAS = Memorial Delirium Assessment Scale (Breitbart et al., 1997); OR − odds ratio; ns − not significant; SAH − Sub-Arachnoid Hemorrhage; TIA − Transient Ischemic Attack; VLSM − Voxelwise Lesion-Symptom Mapping.