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Critical Illness Acquired Brain Injury: Neuroimaging and Implications for Rehabilitation

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Objective: The increasing likelihood of surviving critical illness has resulted in a large and growing number of individuals transitioning from medical and surgical intensive care units (ICUs) to their homes. Many ICU survivors develop pervasive morbidities in physical, psychological, and cognitive functioning that adversely impact day-to-day functioning, ability to return to work, and quality-of-life. These individuals have been extensively studied with neuropsychological test batteries, but relatively little research has been conducted using neuroimaging. This paper reviews neuroimaging findings in survivors of critical illness treated in medical or surgical ICUs. ***Methods:*** We assessed the relationships between abnormalities on neuroimaging and cognitive outcomes and discussed the implications for rehabilitation. ***Results:*** There are limited imaging studies in ICU survivors. These studies use a wide range of modalities including magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), fluid attenuated inversion recovery (FLAIR), and diffusion weighted imaging. Structural abnormalities in survivors of critical illness include cortical and subcortical lesions, white matter hyperintensities (WMHs), and generalized and focal atrophy. These abnormalities persist months to years after ICU discharge and are associated with cognitive impairments.

Impact and Implications
This review describes approaches to the rehabilitation of memory and executive dysfunction in survivors of critical illness. In particular, it offers insights into the relevance of neuroimaging for rehabilitation and seeks to elucidate the ways, both now and in the future, that neuroimaging can influence clinical practices. Future directions in both clinical and research arenas should focus on robustly building bridges between neuroimaging and cognitive rehabilitation and using rehabilitation to increasingly inform the development of rehabilitation related interventions.

Keywords: neuroimaging, critical illness, cognitive impairments, cognitive rehabilitation

Introduction

Over 800,000 people in the United States develop a critical illness (e.g., sepsis, acute respiratory distress syndrome [ARDS]) each year that requires admission to an intensive care unit (ICU) with the use of life-sustaining treatments (Wunsch et al., 2010). Advances in the treatment of critical illness have decreased mortality, resulting in a large and growing number of survivors (Iwashyna, Cooke, Wunsch, & Kahn, 2012). These survivors are at increased risk of developing morbidities known as postintensive care syndrome (PICS; Elliott et al., 2014; Needham et al., 2011).

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These pervasive morbidities occur in physical (Needham, Dinglas, Bienvenu et al., 2013; Needham, Dinglas, Morris et al., 2013), psychological (Davydow, Desai, Needham, & Bienvenu, 2008; Davydow, Gifford, Desai, Bienvenu, & Needham, 2009; Davydow, Gifford, Desai, Needham, & Bienvenu, 2008; Jackson et al., 2014; Wade, Hardy, Howell, & Mythen, 2013), and cognitive functioning (Hopkins et al., 2005). Such morbidities adversely affect survivor's day-to-day functioning, ability to return to work, and quality-of-life (Hopkins et al., 2005; Needham, Dinglas, Bienvenu et al., 2013).

Cognitive impairment following critical illness is a topic of intense research, and a recent landmark *New England Journal of Medicine* study demonstrated that almost one third of 871 critical illness survivors developed cognitive impairment similar in severity to Alzheimer's disease or moderate traumatic brain injury. Cognitive impairments in ICU survivors are rapid in onset, are present at ICU discharge, and occur in a variety of cognitive domains. Deficits are pronounced in areas of memory, executive functioning, and attention (Wilcox et al., 2013). For many patients, impairment improves over time, as a multicenter study found that 36% of the 174 survivors of acute lung injury at 6 months and 25% at 12 months had significant cognitive impairment (Needham, Dinglas, Morris et al., 2013). In other patients, impairment persists years after hospital discharge.

Neuroimaging studies in critically ill populations have documented cortical and subcortical lesions, generalized and focal atrophy (neuronal loss) in the hippocampus and superior frontal lobes and white matter lesions (Gunther et al., 2012; Hopkins, Gale, & Weaver, 2006; Morandi et al., 2010; Morandi et al., 2012; Suchyta, Jephson, & Hopkins, 2010). In order to utilize neuroimaging data in the development of rehabilitation plans and strategies for use with survivors of critical illness it is essential to understand the location of damage in the brain and mechanisms of neural injury. This article describes neuroimaging in survivors of critical illness (defined as medical or surgical critical illness and patients who require mechanical ventilation—studies done with neuro and trauma ICU cohorts were excluded), mechanisms of brain injury, the relationship between neuroimaging findings and cognitive outcomes, and the implications for rehabilitation. Part of our purpose in writing this article is aspirational—that is, we recognize that currently in many cases, the translation of neuroimaging findings into rehabilitation interventions may be neither practical nor intuitive, although in some cases it is. Our hope is that we will introduce readers to a paradigm that we believe will increasingly be realized in upcoming years—one in which clinicians will indeed rely on neuroimaging findings for treatment planning and for the implementation of targeted interventions.

Cognitive Outcomes of Critical Illness

Available data demonstrates that cognitive impairments are prevalent and persistent in survivors of critical illness. Survivors of critical illness have cognitive impairment, which is variable in occurrence (Guerra, Linde-Zwirble, & Wunsch, 2012; Iwashyna, Ely, Smith, & Langa, 2010; Wolters, Slooter, van der Kooi, & van Dijk, 2013) depending on the population evaluated and the cognitive tests utilized (Wolters et al., 2013). A recent systematic review of ~25 prospective investigations in critically ill cohorts found the prevalence of cognitive impairment in ICU survivors ranges from 11%–62% (Wolters et al., 2013). Cognitive impairment often persists years after the critical illness (Hopkins et al., 2005; Rothenhausler, Ehrentraut, Stoll, Schelling, & Kapfhammer, 2001) and rarely fits a narrowly defined pattern, with deficits observed across a wide array of cognitive domains (Guerra et al., 2012; Iwashyna et al., 2010; Wolters et al., 2013). There is little evidence that the etiology of the critical illness predicts the type or nature of cognitive impairment or dysfunction (Guerra et al., 2012; Iwashyna et al., 2010; Wolters et al., 2013) There is some evidence that a subset of patients experience progressive cognitive decline which may be a result of (a) the direct effects of critical illness; (b) the effects of treatment for the critical illness; (c) factors such as older age or comorbid diseases (e.g., cardiovascular disease, diabetes); and/or (d) undiagnosed preclinical dementia (Guerra et al., 2012; Wilcox et al., 2013).

Mechanisms of Brain Injury

Multiple mechanisms appear to be associated with cognitive impairment in survivors of critical illness including hypoxia, hypotension, glucose dysregulation, and inflammation. (Wilcox et al., 2013). A longer duration of hypoxemia is associated with cognitive impairments in ICU survivors (Hopkins et al., 2005). Similarly, a prospective multicenter study found hypoxemia was independently associated with cognitive impairment at 12 months (Mikkelsen et al., 2012). Hypoxia damages the brain through several biochemical mechanisms including (a) reperfusion and reoxygenation injury; (b) excitotoxic cell damage due to calcium influx and subsequent excitatory amino acid neurotransmitter release (e.g., glutamate); (c) glucose dysregulation; and (d) inflammation. The above mechanisms can result in cellular death via apoptosis (programed cell death) or necrosis (Johnston, Nakajima, & Hagberg, 2002). Generalized brain atrophy and enlargement of the temporal horns of the lateral ventricles is associated with hypoxemia (Hopkins, Gale et al., 2006).

The brain is extremely sensitive to changes in blood glucose (Hansen, 1985; Pulsinelli, Jacewicz, Levy, Petito, & Plum, 1997). Current data indicate that hypoglycemia causes neuronal death (Auer & Siesjo, 1993) and cognitive dysfunction in healthy individuals (Allen et al., 2015). Glucose dysregulation (hypoglycemia, hyperglycemia, and blood glucose variability) during critical illness is associated with cognitive impairments in ICU survivors (Duning et al., 2010; Hopkins et al., 2010).

Inflammation causes brain injury due to production of substances such as tumor necrosis factor alpha and interleukins, such as interleukin-6 (Bone, 1991). Data from rodents demonstrates that inflammation induces programed cell death in the hippocampus, a brain structure critical for memory (Semmler, Okulla, Sastre, Dumitrescu-Ozimek, & Heneka, 2005). Critically ill patients with sepsis have increased markers of neuronal injury such as S100B (glial-derived cytokine) and neuron-specific enolase can cause brain atrophy (Lindlau et al., 2015; Salerno, Marik, Daskalakis, Kolm, & Leone, 2009) and cognitive impairment (Nguyen et al., 2006). The above mechanisms may further interact with other risk factors such as older age and comorbid illness to exacerbate cognitive impairments in ICU survivors.

Depression, which occurs in up to a third of ICU survivors, may be another contributor to cognitive impairment (Jackson et al., 2014). Among depressed individuals, cognitive complaints are common. Often, these complaints do not reflect the presence of

fundamental neuropsychological deficits but rather the fact that depression can be expressed through problems with attention, memory, and motivation.

Neuroimaging Review

Neuroimaging studies were identified by searching PubMed using medical subject headings or text key words ("brain imaging" OR "neuroimaging" OR "fMRI" OR "diffusion tensor imaging") AND cross-referenced with ("critical care" OR "critical illness" OR "critically ill patients" OR "ICU survivors" OR "survivors of ICU"). Limitations were applied regarding language (English language only) and human subjects. In addition, studies were identified from the reference lists of the selected journal articles and personal files. While we believe that we have engaged relevant literature on neuroimaging and critical illness, our goal in this article was not to conduct a systematic review.

Structural Imaging

Twenty-two studies were identified that used structural imaging, including 11 in medical or surgical ICU patients, eight in patients with sepsis or septic shock (four case studies) and three in patients with acute lung injury (one case study; Table 1). Most of these studies were performed in the first 6 months after discharge. An early computed tomography (CT) study in 10 septic patients found normal brain CT scans in 66% of patients (Jackson, Gilbert, Young, & Bolton, 1985); however, on autopsy widely distributed neuropathological abnormalities were found in all patients. A study found that 37% of patients with sepsis had abnormalities on neuroimaging which predicted new focal neurologic deficits (Rafanan et al., 2000). Bilateral white matter lesions (Hollinger, Zurcher, Schroth, & Mattle, 2000) or white matter hyperintensities also occur in patients with sepsis (Piazza, Cotena, De Robertis, Caranci, & Tufano, 2009; Sharshar et al., 2007). A study of 71 septic patients identified new cerebral infarcts in 29% and white matter lesions in 21% of the patients (Polito et al., 2013). Hollinger and colleagues used serial imaging in a patient with septic encephalopathy and showed that white matter lesions increased in size over the first week and remained present at 4 weeks (Hollinger et al., 2000).

Critically ill patients without sepsis had variably high rates of lesions and atrophy on CT and MRI (Fugate et al., 2010; Suchyta et al., 2010; Sutter et al., 2015). Atrophy and WMHs are common findings in ICU populations (Luitse, van Asch, & Klijn, 2013; Suchyta et al., 2010). A study of 146 ICU patients found that 89% of patients who underwent MRI scans for acute onset of brain dysfunction (e.g., altered mental status) had multiple abnormalities including white matter lesions, acute infarcts, and intracerebral hemorrhage that were associated with poor outcomes (Sutter et al., 2015). Brain atrophy (focal and/or general) is common in survivors of critical illness (Balachandran et al., 2009; Luitse et al., 2013; Purmer et al., 2012; Suchyta et al., 2010) and may manifest as ventricular enlargement (Brown et al., 2015). Unfortunately, neither clinical or patient characteristics predicted brain abnormalities (Salerno et al., 2009).

Quantitative Imaging

Nonspecific damage such as gyral atrophy and passive increase in ventricular volumes is best documented using quantitative MRI analyses (Bigler, 2001). Five studies used quantitative MRI (qMRI), four of which found significant generalized atrophy, ventricular enlargement, sulcal widening, and hippocampal atrophy in survivors of critical illness (Gunther et al., 2012; Hopkins, Gale et al., 2006; Jackson et al., 2009; Lindlau et al., 2015; Morandi et al., 2010). Semmler et al. (2013) reported critically ill patients with sepsis had greater hippocampal atrophy compared to nonseptic patients and healthy controls (Semmler et al., 2013), but there were no differences in volume of gray matter, white matter, or cerebrospinal fluid.

Diffusion tensor imaging (DTI) is sensitive to white matter integrity allowing quantitative assessment of white matter pathways (Huisman et al., 2004). A single study in critically ill patients utilized diffusion tensor imaging (DTI). White matter disruption (lower fractional anisotropy) was identified in the genu and splenium of the corpus callosum and anterior limb of the internal capsule at hospital discharge and 3 months' postdischarge were found in 47 critically ill patients with delirium (Morandi et al., 2012).

Functional MRI

A recent study (Jackson et al., 2015) utilized functional MRI (fMRI) to investigate neural activation patterns associated with a working memory task. Patients completed an N-Back task, a behavioral measure of working memory, during fMRI 3 months after hospital discharge. Increased activation during the working memory task occurred in the fronto-parietal network (left and right inferior parietal, left precentral, right middle frontal, left superior parietal, right superior occipital, left and right middle frontal, and left supplementary motor areas) was noted, while decreased activation was evident in medial brain regions including the superior medial frontal gyrus and left posterior cingulate gyrus (Jackson et al., 2015). Patients performed very poorly on the N-Back task and displayed more errors than individuals with mild cognitive impairment (Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005) and Parkinson's disease (Miller, Price, Okun, Montijo, & Bowers, 2009).

Structural Abnormalities and Cognitive Impairments

Eight studies evaluated the relationship between neuroimaging and cognitive functioning in ICU survivors (Table 2). A study in 15 ARDS survivors found 53% of survivors had atrophy and/or lesions on brain CT scans and 30% of survivors had cognitive deficits compared with healthy controls (Hopkins, Gale et al., 2006). A case study described a young, healthy ARDS sepsis survivor with a 33-point decline from a pre-ICU intelligence that correlated with white matter lesions and brain atrophy 4 years' postillness (Jackson et al., 2009). A small prospective longitudinal study of eight delirious ICU patients found white matter lesions in 70% of the patients and one patient had significant atrophy (Morandi et al., 2010). While 75% of these patients had severe cognitive impairment at hospital discharge and at 3-month follow-up, no relationship was found between brain abnormalities and cognitive impair-

Table 1
Neuroimaging Findings in Critical Illness

Study	Study design	Sample characteristics	*n*	Imaging type	Significant findings/conclusions
			Structural imaging		
Structural lesions					
Jackson et al., 1985	Retrospective cohort with postmortem brain evaluation	Septic encephalopathy	12 (8 with autopsy)	CT	Brain CT normal in 88%, one patient had a hypodense area in the parietal-occipital region Autopsy data: 100% patients were abnormal; 50% with micro-abscesses 38% with central pontine myelinolysis 13% cerebral hemorrhage 5% with astrocyte proliferation
Hollinger et al., 2000	Case study	Septic encephalopathy	1	CT and MRI	Initial CT with several nonenhancing hypodense areas in white matter on Day 2 MRI 1 week later several areas of hyperintense lesions with evidence of cytotoxic edema MRI at 3 weeks with cortical enhancing lesions CT at 4 weeks, regressive WM hypodensity with ring like enhancements
Rafanan et al., 2000	Retrospective cohort	Medical ICU patients	230 patients 297 CT scans	CT	37% with new CT findings: 49% ischemic stroke 15% intraparenchymal hemorrhage 13% with cerebral edema 9% with hemosiderin 7% with anoxia 7% other findings Presence of neurologic deficit differed between groups of normal CT vs. abnormal CT ($p < .001$) and seizures ($p < .01$)
Finelli & Uphoff, 2004	Case study	Sepsis	1	MRI	Abnormalities in the midbrain, cerebellum, bilateral temporal lobes, basal ganglia, thalamus, internal capsule, and adjacent white matter
Sharshar et al., 2007	Prospective cohort	Septic shock	9	MRI	78% patients with abnormalities 22% with ischemic stroke 56% with white matter lesions Follow-up MRI indicating progression of white matter lesions at 90 days (one patient) MRI findings correlated with outcome
Balachandran et al., 2009	Retrospective cohort	Medical ICU patients	42	CT	40% with abnormalities: 47% with diffuse atrophy 35% with small vessel ischemic changes 12% with cerebral infarcts 6% intracranial hemorrhage

Table 1 (*continued*)

Study	Study design	Sample characteristics	*n*	Imaging type	Significant findings/conclusions
Piazza et al., 2009	Prospective case study	Septic shock	4	CT and MRI	CT normal on all 4 patients at admission MRI on 2 patients were normal at admission 2 patients with frontal, cortical and subcortical hyperintense foci on MRI day 20, cytotoxic edema excluded by DWI 2 patients with normal MIR on day 20
Salerno et al., 2009	Retrospective cohort	Medical ICU patients	123	CT	21% with abnormal CT findings in patients with neurologic dysfunction 50% with ischemic lesions, 17% with tumor, 8% with hemorrhage, 31% with other
Suchyta et al., 2010	Retrospective cohort	Medical and surgical ICU patients	64	CT and MRI	40 patients with CT imaging to assess neurologic changes, 6 with MRI and 18 with both CT and MRI: 65% with atrophy 48% with WMHs 42% with lesions 18% with focal hemorrhage 10% with encephalomalacia
Morandi et al. 2010	Prospective cohort	Medical ICU patients with shock or acute respiratory failure	8	CT and MRI	CT in individuals with delirium: 88% of patients had normal scans; 13% with mild atrophy MRI 75% abnormal 100% with neurological impairment of which 75% had WMHs Grade 1 (33%); Grade 2 (33%); Grade 3 (33%)
Purmer et al., 2012	Prospective cohort	Medical and surgical ICU patients	175	CT	Abnormal CT findings in 55% of medical patients 46% with ischemic lesions 9% with hydrocephalus 3% with hematomas*
Luitse et al., 2013	Case study	Septic encephalopathy	1	CT	Day 5: Abnormal hypodensity of complete white matter Week 4: periventricular and deep white matter hyperintensities
Polito et al., 2013	Prospective cohort	Septic shock	71	MRI	48% of patients had abnormal findings on MRI 62% had ischemic lesions/ strokes 44% had leukoencephalopathy 18% had mixed lesions

(*table continues*)

Table 1 (*continued*)

Study	Study design	Sample characteristics	*n*	Imaging type	Significant findings/conclusions
Brown et al., 2015	Prospective cohort	Medical and surgical ICU patients	2386 of which 28 with critical illness, 10 with imaging	MRI	Significantly increased ventricular size in all patients compared with patients with noncritical illness hospitalization ($p = .02$) No significant differences for WMH volumes, visual grade, infarct presence or sulcal widening comparing patients with critical illness to patients with noncritical illness hospitalization
Sutter et al., 2015	Retrospective cohort	Medical and surgical ICU patients	146	MRI	89% had abnormal MRI findings 51% of patients had new abnormalities 41% had WMHs 40% acute cerebral infarcts 7% cerebral hemorrhage. Apparent diffusion coefficient (ADC) values were significantly higher in patients with WMHs ($p = .001$). Unfavorable outcome was associated with brain abnormalities ($p = .029$
		Quantitative neuroimaging			
Hopkins, Gale et al., 2006	Retrospective cohort	Acute respiratory distress syndrome Healthy controls	15 15	15 CT and 9 MRI	ARDS patients had significantly larger ventricular volumes ($p = .02$) and ventricle-to-brain ratio ($p = .008$) when compared with controls
Jackson et al., 2009	Case study	Acute respiratory distress syndrome	1	CT and MRI	CT normal on day 28, MRI showed WMHs on Day 31 Marked atrophy and ventricular enlargement at 3.5 years posthospital discharge
Gunther et al., 2012	Prospective cohort at 2 centers	Medical ICU patients	47	MRI at hospital discharge and 3 months postdischarge	Longer duration of delirium associated with larger ventricle-to-brain ratios at discharge ($p = .05$) Duration of delirium associated with superior frontal lobe atrophy at discharge ($p = .03$) and 3 months ($p = .02$) and smaller hippocampal volumes at discharge ($p < .001$) adjusted for age and sepsis

Table 1 (*continued*)

Study	Study design	Sample characteristics	*n*	Imaging type	Significant findings/conclusions
Semmler et al. 2013	Prospective cohort at 2 centers	Septic patients	25	MRI outcome measured at a range of 6 to 24 months	Left ($p < .01$) and total hippocampal volumes ($p < .05$) were smaller for septic patients compared with healthy controls
		Nonseptic ICU survivors and Healthy controls	19		Hippocampal volume in nonseptic ICU survivors was between that of sepsis patients and healthy controls
			31		There were no differences for grey matter, white matter, intracranial or cerebral spinal fluid volumes between any of the groups
Lindlau et al., 2015	Prospective cohort	Medical and surgical ICU survivors	20	MRI measured at a range of 6 to 24 months	Reduced hippocampal and total white matter volumes
		Healthy controls	30		Procalcitonin correlated with hippocampal volume ($p = .016$) Interleukin-6 correlated with hippocampal volume ($p = .03$) C-reactive protein was associated with grey matter volume ($p = .018$) Markers of illness severity were not associated with any brain volume
		Diffusion tensor imaging			
Morandi et al., 2012	Prospective cohort at 2 centers	Medical ICU patients	47	Diffusion tensor MRI at hospital discharge, and 3-month follow-up postdischarge	Longer duration of delirium associated with white matter disruption ($p = .02$ to .04 depending on white matter location)
		Functional imaging			
Functional brain imaging Jackson et al., 2015	Prospective cohort	Respiratory failure or shock	47	fMRI at hospital discharge and 3 months, cognitive outcomes at 12 months	80% completed fMRI at hospital discharge and 91% at 3 months There was increased activation on a working memory task in the fronto-parietal network (left and right inferior parietal, left precentral, right middle frontal, left superior parietal, right superior occipital, left and right middle frontal and left supplementary motor areas). There was decreased activation in medial brain regions (superior medial frontal gyrus and left posterior cingulate gyrus).

Note. * Data are presented for critically ill medical patients only as they are comparable with critically ill patients from other studies. Data from patients with subarachnoid or intracerebral hemorrhage, traumatic brain injury, or neurosurgical intervention are not included in table.

Table 2
Relationship Between Neuroimaging and Cognitive Outcomes

Study	Study design	Sample characteristics	*n*	Imaging type	Cognitive outcome
Morandi et al., 2010	Prospective cohort	Critically illness with delirium	8	CT and MRI	100% of patients with neurocognitive impairment: 75% with abnormal MRI Severe impairments in memory, executive function and attention at 3 months. No correlation between MRI and neurocognitive findings.
			Quantitative neuroimaging		
Hopkins, Gale et al., 2006	Retrospective cohort	Acute respiratory distress syndrome compared to healthy controls	15	15 CT and 9 MRI	No association between brain volumes and neurocognitive function
Jackson et al., 2009	Case study	Acute respiratory distress syndrome	1	CT and MRI	Intellectual decline post-ICU compared with pre-ICU
Gunther et al., 2012	Prospective cohort at 2 centers	Medical ICU patients	47	MRI at hospital discharge and 3 months post-discharge	Greater ventricle-to-brain ratio associated with worse neurocognitive outcome at 12 months ($p = .04$); executive function associated with thalamic and cerebellar volumes ($p = .02$); superior frontal lobe volumes associated with worse visual attention ($p = .003$) No association between hippocampal volumes and neurocognitive function
Semmler et al., 2013	Prospective cohort at 2 centers	Septic patients	25	MRI outcome measured at a range of 6 to 24 months	Septic patients were impaired compared with healthy controls for attention, working memory, verbal memory, alertness, visual-spatial abilities, psychomotor speed, verbal fluency and executive function. Patients had cognitive and memory impairments and hippocampal atrophy. There were no differences in cognitive function for patients with sepsis compared with nonseptic ICU survivors.
		Nonseptic ICU survivors	19		Left hippocampal atrophy was associated with impairment verbal learning and memory
		Healthy controls	31		
Brown et al., 2015	Prospective cohort	Medical and surgical ICU patients	2386 of which 28 with critical illness, 10 with imaging	MRI	Hospitalization was associated with increase in ventricular size increased by at least 1 grade and was significantly different than participants with noncritical illness hospitalization ($p = .02$) Hospitalization was associated with cognitive decline ($p > .001$) and with the number of hospitalizations ($p > .001$) Worse memory was associated with larger ventricular size and a small decline in cognitive function with WMH volumes Significant greater decline in executive function for patients with critical illness when compared to patients with noncritical illness hospitalization ($p = .046$) No other differences were found for language, and memory between patients with critical illness and noncritical illness

Table 2 (*continued*)

Study	Study design	Sample characteristics	*n*	Imaging type	Cognitive outcome
			Diffusion tensor imaging		
Morandi et al., 2012	Prospective cohort at 2 centers	Medical ICU patients	47	Diffusion tensor MRI at hospital discharge, and 3 months postdischarge	White matter disruption associated with worse neurocognitive outcomes (verbal fluency and attention; $p = .05$)
			Functional brain imaging		
Jackson et al., 2015	Prospective cohort	Respiratory failure or shock	47	fMRI at hospital discharge and 3 months, cognitive outcomes at 12 months	Impaired working memory (key component of executive function) at 3 months. fMRI activation patterns during a working memory task at 3 months did not predict cognitive outcomes at 12 months

ment (Morandi et al., 2010). Semmler et al. (2013) found left hippocampal atrophy in a group of ICU survivors was associated with impairments in attention, working memory, verbal memory, alertness, visual-spatial abilities, psychomotor speed, verbal fluency, and executive function. Ventricular enlargement was associated with worse memory and white matter lesions were associated with slightly worse cognitive function in survivors of critical illness (Brown et al., 2015).

Quantitative and Functional MRI and Cognitive Impairments

Two studies assessed the relationship between quantitative imaging and cognitive function (Gunther et al., 2012; Morandi et al., 2010). Longer duration of delirium correlated with atrophy at hospital discharge and 3 months and greater brain atrophy at 3 months was associated with worse cognitive outcome at 12 months. Morandi and colleagues found white matter disruption lower fractional anisotropy in the corpus callosum and internal capsule at hospital discharge and at 3 months was associated with cognitive impairment at 12 months (Morandi et al., 2012). A single study assessed functional imaging and its relationship to neurocognitive function (Jackson et al., 2015). The fMRI activation patterns during the working memory task did not predict cognitive outcomes at 12 months (Jackson et al., 2015).

Summary of Neuroimaging

The above studies demonstrate that critical illness is frequently associated with neuroimaging abnormalities. Brain structural abnormalities are diverse and included gray and white matter lesions, global and focal atrophy, and hemorrhage. Functional imaging may provide information regarding real time cognitive functioning but additional studies are needed (Carey & Seitz, 2007; Hodics, Cohen, & Cramer, 2006). Not all survivors of critical illness have imaging abnormalities, even when cognitive impairment is present. While imaging can be a useful diagnostic and predictive tool, it has limitations in identifying subtle structural or functional abnormalities that may cause significant cognitive impairments.

Implications of Neuroimaging for Rehabilitation

As noted above, critical illness results in cognitive impairments and in neuroimaging abnormalities which are associated with cognitive and behavioral changes in critically ill populations that persist years after the illness (Gunther et al., 2012; Hopkins, Gale et al., 2006; Jackson et al., 2009; Lindlau et al., 2015; Semmler et al., 2013). Research has evaluated the effectiveness of cognitive rehabilitation and evidence strongly supports the use of wide-ranging cognitive rehabilitation strategies to improve cognitive functioning in individuals with acquired brain injury (Levine et al., 2011; Neundorfer et al., 2004; Weber, Woods, Kellogg, Grant, & Basso, 2012). Information regarding the effects of rehabilitation following critical illness is limited, especially the use of neuroimaging findings to guide rehabilitation strategies. However, data from other brain-injured populations pertaining to the prognostic value of neuroimaging may be helpful in this regard. A study of 135 individuals with mild traumatic brain injury found structural abnormalities predicted unfavorable outcome at 3 months (Yuh et al., 2013). Neuroimaging findings are also used to predict cognitive outcomes following anoxic brain injury (Els, Kassubek, Kubalek, & Klisch, 2004; Wijdicks, Hijdra, Young, Bassetti, & Wiebe, 2006; Wu et al., 2009). For example, widely distributed abnormalities on FLAIR imaging (Greer et al., 2011) and reduced whole brain apparent diffusion coefficients on diffusion weighted imaging are associated with poor outcomes following anoxic brain injury (Wu et al., 2009). Importantly, neuroimaging findings have been used to develop algorithms to determine outcomes following anoxia (Kandiah, Ortega, & Torbey, 2006). Such algorithms may be used to target rehabilitation to maximize cognitive outcomes.

Early data in other forms of chronic brain injury suggest that functional neuroimaging may be able to track changes in the brain associated with cognitive and physical rehabilitation. (Patel, Spreng, & Turner, 2013) The ability to monitor changes would allow individualized therapies, tailored to meet a specific patient's needs. Stroke rehabilitation may potentially be done more effectively and with better outcomes if it is guided by findings from neuroimaging, though questions exist (Seitz, 2010; van Vliet, Carey, & Nilsson, 2012). The ability to predict outcomes using neuroimaging may lead to more personalized rehabilitation thera-

pies and better outcomes in ICU survivors. Insights from neuroimaging could provide valuable prognostic information that could contribute to the development of focused therapies for ICU populations (Stinear, 2010). Finally, the efficacy of cognitive rehabilitation interventions on cognitive functioning can be effectively evaluated using neuroimaging, as some studies historically have done (Belleville & Bherer, 2012). Data available from neuroimaging is a much "harder" outcome than self-report questionnaires or even objective neuropsychological testing and can provide a scientific basis for determining the impact of a therapy and the magnitude or persistence of its effects (Belleville & Bherer, 2012). For example, diffusion tensor imaging or DTI, referenced earlier in this article, allows for the calculation of fractional anisotropy (FA), which is a useful measure of brain connectivity and structural integrity (Grieve, Williams, Paul, Clark, & Gordon, 2007). Greater brain connectivity (or other outcomes such as decreased whole brain atrophy over time) could be important goals of a cognitive rehabilitation and can only be measured via neuroimaging.

Cognitive Rehabilitation in ICU Populations

Correspondence has been observed between neuropsychological findings and neuroimaging—that is, patients display cognitive deficits on tests of memory and executive ability which are associated with abnormalities in hippocampal and frontal brain regions, problems that are potentially remediable. Cognitive rehabilitation is increasingly a standard approach to the treatment of acquired brain injuries and involves interventions designed to reinforce, strengthen, or reestablish previously learned behaviors, or establish new patterns of cognitive activity or compensatory mechanisms in impaired cognitive domains (Stuss, Winocur, & Robertson, 2008). Interventions to prevent cognitive impairments in critically ill patients have yet to be identified but appear promising for use with ICU survivors.

While between a third and half of ICU survivors have cognitive impairment, few patients are referred for rehabilitation, and if they are referred, it is primarily to receive physical rehabilitation only (Hopkins et al., 2005). There are two studies that have utilized cognitive rehabilitation in ICU survivors. In the first of these, Jackson and colleagues performed 12 weeks of combined cognitive and physical therapy in 21 ICU survivors (eight controls and 13 patients who received the intervention) using a combination of telemedicine and in-home cognitive, physical, and functional rehabilitation over a 3-month period after hospital discharge (Jackson et al., 2012). At 3-month follow-up, the intervention group demonstrated significantly improved cognitive functioning on a measure of executive function (tower test) when compared with controls (median [interquartile range]: 13.0 [11.5–14.0] vs. 7.5 [4.0–8.5]; adjusted $p < .01$). Intervention group patients also reported better performance in day-to-day functioning (functional activities questionnaire) at 3 months when compared with controls, 1.0 [0.0−3.0] versus 8.0 [6.0–11.8], adjusted $p = .04$; Jackson et al., 2012).

In the second study, a total of 87 critically ill patients were randomized to usual care, early once-daily physical therapy, or early once-daily physical therapy plus cognitive stimulation which focused on memory, attention, and problem solving (all therapy was delivered during inpatient hospitalization; Brummel et al., 2014). A subset of patients also received outpatient cognitive therapy after hospital discharge as well. At 3-months, cognitive, functional, and health-related quality of life outcomes were assessed but no differences existed between these groups with regard to patient functioning in these domains. In both of these investigations, an approach known as goal management training (GMT) was employed, consistent with findings—both empirical and theoretical—that suggest that metacognitive approaches are most effective in treating executive dysfunction symptoms (Jackson et al., 2012). The aforementioned studies have targeted executive dysfunction, as this is a domain that, along with memory, has been shown to be commonly impaired after critical illness (Wilcox et al., 2013). Due to the prominence of executive and memory decrements in ICU survivors, we will engage issues related to their rehabilitation in the paragraphs below.

While cognitive rehabilitation was begun early after ICU discharge in these two studies, the ideal timing of cognitive rehabilitation is unknown in the critically ill population. In other populations such as individuals with TBI, evidence suggests that early postinjury rehabilitation may be injurious. Late physical rehabilitation (5-weeks postinjury) improves memory impairment at 3 months compared with early rehabilitation (1-week postinjury) by reducing inflammation (Piao et al., 2013) and acute exercise downregulates brain-derived neurotrophic factor which may disrupt recovery after brain injury (Griesbach, Hovda, Molteni, Wu, & Gomez-Pinilla, 2004). Research is needed to determine the optimal timing of cognitive rehabilitation in critically ill populations.

Cognitive Rehabilitation Interventions for ICU Populations

Cognitive rehabilitation may one day prove to be useful in an ICU context but significant barriers to employing it with people who are often delirious and acutely ill remain. Moreover, the types of cognitive impairment individuals may eventually have been very hard to determine in a critical care setting, where the dysfunction that characterizes patients often changes dramatically depending on their medical status. For these reasons, implementing targeted therapies beyond simple interventions aimed at orientation and reality testing is difficult indeed. As such, our article focuses largely on treating individuals after hospital discharge, when the true nature and extent of their problems can be determined.

Interventions to rehabilitate cognitive impairments after critical illness are needed for a variety of reasons—partly because they appear to be effective based on their use with other populations (Cicerone et al., 2005; Cicerone et al., 2011; Zoccolotti et al., 2011) and because efforts to prevent the development of cognitive impairment in ICU survivors have proven to be largely ineffective. One key target for rehabilitation is executive dysfunction, shown to be commonly impaired in ICU survivors (Jackson et al., 2003; Pandharipande et al., 2013). Evidence from a wide array of patient populations supports the use of cognitive rehabilitation for executive dysfunction (Cicerone et al., 2005; Cicerone et al., 2011; Zoccolotti et al., 2011) with one review recommending that cognitive rehabilitation become the standard of care (Cicerone et al., 2011). Metacognitive approaches are widely used and among the most effective interventions used to treat executive dysfunction. Goal management training (GMT) is the most popular and has the

strongest evidentiary support. GMT is a stepwise intervention that uses self-awareness and self-monitoring techniques to train patients to "STOP" and monitor ongoing behavior and regain cognitive control when behavior becomes incompatible with intended goals (Levine et al., 2011). GMT has been studied in patients with executive dysfunction due to TBI (Levine et al., 2000), stroke (Manly, Hawkins, Evans, Woldt, & Robertson, 2002), frontal lobe injuries (Levine et al., 2011), and in a small number of ICU patients (Jackson et al., 2012).

Survivors of critical illness frequently have significant memory deficits (Hopkins et al., 2005). A number of interventions may be effective for impaired memory including environmental adaptations, internal strategies, and errorless learning. Environmental adaptations may include the use of technological devices (e.g., "smart" phones), however such devices may be "lost" as a direct result of impaired memory. Other environmental adaptations include planners or the use of post-it notes. Internal strategies involve the use of mnemonics and other self-generated techniques or strategies that serve to enhance memory. A key problem with internal strategies is that patients must remember to use them and this is often problematic due to the underlying memory disorder. Finally, errorless learning involves learning without mistakes. Errorless learning is often employed for individuals with memory impairments (Wilson & Kapur, 2008) such as those observed in ICU populations.

Computer-assisted retraining programs typically focus on one of two approaches: (a) task-specific, with training targeting a specific cognitive deficiency; or (b) hierarchical, with interventions following a sequenced progression from basic to more complex cognitive abilities, with the goal of improving overall cognitive functioning (Chen, Thomas, Glueckauf, & Bracy, 1997; Gontkovsky, McDonald, Clark, & Ruwe, 2002). A significant advantage of computerized training programs is the flexibility and ease with which training can be tailored to particular patient need in terms of complexity, speed, and nature of the task, as well as ability to closely monitor performance outcomes. This advantage applies equally to video games, which are distinct from computerized programs in that they are significantly more immersive and often three-dimensional. As with computerized training, the use of video games remains a subject of controversy, though recent evidence suggests that they may have benefits that include increased cognitive control (Anguera et al., 2013). For ICU survivors, who are often physically debilitated, the ability to engage in training at home may be a significant added benefit.

As a brief aside, cognitive rehabilitation will likely not be optimally effective among individuals whose primary neuropsychological difficulties are driven by depression, which can contribute to problems with attention and concentration and memory among others. For such individuals, making appropriate differential diagnoses is of paramount importance as it may be that psychotherapy or medication management can effectively alleviate depression symptoms and, in turn, reduce cognitive complaints.

Conclusions

Neuroimaging of patients with critical illness demonstrates diverse and global abnormalities and included cortical and subcortical lesions, white matter hyperintensities (WMHs), and atrophy in brain structures including the hippocampus and superior frontal lobes. These abnormalities have been demonstrated using a wide range of imaging techniques both clinical and more experimental including MRI, CT, DTI, and fMRI. These abnormalities have been associated with cognitive dysfunction in small subsets of patients. The numbers of patients undergoing neuroimaging of a sort that generates clinical reports is admittedly low and certainly many patients do not have neuroimaging abnormalities, but still present with cognitive deficits. Cognitive deficits may be prolonged and persistent, affecting quality of life and ability to return to functional status (e.g., living independently, returning to previous employment) and rehabilitation or otherwise improving these deficits is a public health priority.

Guidance in the development and implementation of cognitive rehabilitation in survivors of critical illness may be derived from many sources (e.g., treatment guidelines, the guidance of experts, research data) and one of these sources is likely neuroimaging. Future directions in both clinical and research arenas should involve the utilization of findings from neuroimaging in the quest to make cognitive rehabilitation more effective, recognizing that the world in which neuroimaging is consistently used in the ways proposed here only exists in the future and is not yet fully realized, though we believe that it will be. Structural and functional imaging following critical illness in conjunction with neuropsychological testing may prove more useful in predicting outcomes and guiding rehabilitation, though questions about how to best utilize and integrate the data remain. Recent data suggests that the addition of neuroimaging findings to a prognostic outcome model can improve prediction by two fold (Yuh et al., 2013). Such prognostication may allow stratification of patients for therapies that will work most successfully. Sequential imaging could further aid in rehabilitation planning and prognostication by identifying late developing lesions or resolution of lesions (Hopkins, Fearing, Weaver, & Foley, 2006; Pulsipher, Hopkins, & Weaver, 2006). Sequential imaging may also allow for alteration of rehabilitation plans based on subsequent neuroimaging. The future of neuroimaging in predicting long-term outcome and guiding rehabilitation in ICU survivors is in its infancy with much potential. Randomized trials will be necessary for future rehabilitation recommendations.

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