Journal of the International Neuropsychological Society (2007), **13**, 595–605.

DOI: 10.1017/S1355617707070749

Cognitive sequelae in acute respiratory distress syndrome patients with and without recall of the intensive care unit

MICHAEL J. LARSON,[1,2] LINDELL K. WEAVER,[3,4] AND RAMONA O. HOPKINS[1,3,5]

[1]Psychology Department, Brigham Young University, Provo, Utah
[2]Department of Clinical and Health Psychology, University of Florida, Gainesville, Florida
[3]Department of Medicine, Pulmonary and Critical Care Divisions, LDS Hospital, Salt Lake City, Utah
[4]University of Utah School of Medicine, Salt Lake City, Utah
[5]Neuroscience Center, Brigham Young University, Provo, Utah

(RECEIVED October 26, 2006; FINAL REVISION January 6, 2007; ACCEPTED January 8, 2007)

Abstract

Some critically ill patients have dramatic recollections of the intensive care unit (ICU), whereas 23–50% have little or no recollection of their ICU stay. In addition, cognitive impairments are common following critical illness and ICU treatment. Little is known regarding the relationship between cognitive sequelae and ICU recall. We assessed recall of the ICU and its relationship to cognitive functioning at hospital discharge and 1 and 2 years after discharge in 70 consecutive acute respiratory distress syndrome (ARDS) patients. Seventeen patients (24%) had no recall of the ICU. Patients without ICU recall had increased rates of cognitive sequelae at hospital discharge and 1-year follow-up compared with the ICU recall group. Patients without ICU recall had a greater magnitude of cognitive impairments at hospital discharge, but not at 1- or 2-year follow-up. Profile analysis showed significant group differences in general intellectual functioning, executive function, processing speed, and spatial skills at hospital discharge, but not at 1- or 2-year follow-up. Estimated premorbid intelligence scores were inversely related to the magnitude of cognitive sequelae, suggesting greater "cognitive reserve" in patients with fewer cognitive decrements. (*JINS*, 2007, *13*, 595–605.)

Keywords: ARDS, Intensive care unit (ICU), Cognitive outcome, Cognitive reserve, Critical, Illness, Sequelae, Memory

INTRODUCTION

Advances in critical care have led to improved survival rates among those admitted to intensive care units (ICUs) where over 55,000 patients are hospitalized each day in the United States (Schmitz et al., 1998). Medical and surgical management of critical illnesses can, and frequently does, result in *de novo* cognitive impairments. Current data suggest that 25 to 78% of survivors of critical illness develop significant and persistent cognitive impairments (Gordon et al., 2004; Hopkins & Brett, 2005; Hopkins et al., 1999; Jackson et al., 2003). However, cognitive impairments following critical illness and ICU treatment are understudied and have received little attention in the neuropsychological literature.

Correspondence and reprint requests to: Ramona O. Hopkins, Ph.D., Division of Critical Care Medicine, LDS Hospital, 8th Avenue and C Street, Salt Lake City, UT 84143, USA. E-mail: ramona.hopkins@intermountainmail.com

In the general critically ill population, approximately 33% of medical ICU survivors have cognitive impairments at 6-months after hospital discharge (Jackson et al., 2003). Cognitive impairments in survivors of critical illness occur in memory, attention, concentration, processing speed, and visual spatial abilities (Hopkins & Jackson, 2006). Slow psychomotor speed and executive dysfunction have also been reported (Sukantarat et al., 2005). In specific ICU populations, such as patients with acute respiratory distress syndrome (ARDS), up to 78% of patients had unfavorable cognitive sequelae at hospital discharge (Hopkins et al., 1999), 45% at 1 and 2 years (Hopkins et al., 2005), and approximately 25% at 6 years (Rothenhausler et al., 2001). ARDS is characterized by severe acute lung injury, hypoxemia, and reduced total thoracic compliance (see Ashbaugh et al., 1967; Hopkins et al., 2005). ARDS can occur in response to direct or indirect insults to the lungs (e.g., sepsis, trauma, pneumonia) and requires aggressive care, including positive pressure ventilation and increased oxygen

concentrations with the risk of oxygen toxicity, barotraumas, and infection (The Acute Respiratory Distress Syndrome Network, 2000).

Some patients recovering from critical illness have dramatic recollections of the ICU and its associated treatments (Holland et al., 1997; Rundshagen et al., 2002), whereas 23 to 50% of ICU survivors do not recall their ICU experience (Bergbom-Engberg & Haljamea, 1989a; Capuzzo et al., 2001; Granberg et al., 1998; Jones et al., 2000). Possible contributing factors for lack of recall of the ICU and its associated treatments include traumatic stress, pain, hypoxia/anoxia, brain injury, and sedative/analgesic medications (McCartney & Boland, 1994; Skodol, 1999). However, studies suggest that sedation and analgesia do not fully prevent memory of unpleasant experiences in the ICU (Swaiss & Badran, 2004). When patients are able to recall memories of the ICU, these memories are predominately unpleasant and may lead to emotional morbidity, including depression, anxiety, agitation, and posttraumatic stress disorder (Goldman & Kimball, 1987; Schelling et al., 2000). The recollection of unpleasant memories persist well-beyond ICU discharge and can lead to difficulties in psychological and social functioning (Daffurn et al., 1994; Jones et al., 1994; Rundshagen et al., 2002; Schelling et al., 2000). To date, no studies have differentiated cognitive impairments in ICU patients with and without recall of their ICU stay.

The primary aim of this study was to examine cognitive sequelae in ARDS patients with and without recall of their ICU experience. We hypothesized that patients without recall of the ICU would have an increased rate and greater magnitude of cognitive impairment than those who recalled the ICU experience. Secondary aims were to examine the pattern of neuropsychological deficits in ARDS patients with and without ICU recall to determine whether patterns of deficits are stable over time. We also examined the relationships between estimated premorbid intellectual function, negative affect, and illness severity on cognitive performance.

METHODS

Acute respiratory distress syndrome survivors from a randomized clinical trial of higher tidal volume *versus* lower tidal volume ventilation management conducted from February 1994 to December 1999 were eligible for our study (Orme et al., 2003). Patients were invited to participate in an outcome study to assess cognitive function. A detailed description of the ventilation strategy has been published elsewhere (Orme et al., 2003). The inclusion criteria for the ventilation management study were as follows: tracheal intubation, ratio of arterial oxygen tension to inspired oxygen fraction (PaO_2/FiO_2) $\leq$ 150 mm Hg, pulmonary artery balloon occlusion pressure $\leq$ 18 mm Hg (when available), no clinical evidence of left atrial hypertension, diffuse infiltrates in three of four quadrants on chest radiographs, age $\geq$ 16 years, and presence of an ARDS risk factor (e.g., aspiration, multiple trauma, pancreatitis, pneumonia, sepsis). The exclusion criteria for the ventilation study were the following: disease states that were deemed to be rapidly terminal (e.g., liver failure, malignancy, acquired immune deficiency syndrome), traumatic brain injury, prior neurologic disease (e.g., stroke, dementia, multiple sclerosis), or enrollment in another ARDS study (e.g., NIH/NHLBI ARDS Network studies).

All ARDS survivors were evaluated for participation in our cognitive outcome study. There were 78 (65%) of the 120 patients in the ventilation study who survived. A total of 3 patients were excluded because of prior cognitive impairment, and 1 declined to participate, leaving 74 survivors who were enrolled in the cognitive outcome study. Of the 74 ARDS survivors, 3 died in the first year following hospital discharge from pulmonary fibrosis/cor pulmonale, liver failure, or diabetic complications. There were 5 survivors who declined to return for 1-year follow-up (busy schedules or not interested), resulting in 66 survivors who completed the 1-year evaluation. A total of 2 ARDS survivors died in the second year (bowel obstruction or cardiac failure) and 2 declined to return for the 2-year follow-up, resulting in 62 survivors who completed the 2-year evaluation. The LDS Hospital Institutional Review Board approved this study, and the study conformed to institutional and Federal guidelines for the protection of human subjects. Written informed consent was obtained before hospital discharge.

Figure 1 shows the timeline of measurements and data collection. Patient demographic and medical data were collected prospectively in an electronic medical record as part of routine clinical care. Data included length of stay, Acute Physiologic and Chronic Health Evaluation II (APACHE II) scores (Knaus et al., 1985), laboratory values (including glucose measurements), ventilator data, insulin doses, steroid therapy, and outcome data.

ICU Memory

Memory of the ICU was examined using semistructured interviews conducted within 1 week following ICU discharge. Interviews were conducted by a neuropsychologist (R.O.H.) and were tape recorded and transcribed. Three independent reviewers coded the transcribed interviews for number and type of events. Data were checked for accuracy, and all discrepancies were resolved by R.O.H. by consulting the original transcripts. Interviews elicited information in four primary areas: (1) overall memory of the ICU; (2) specific memories of the ICU experience, including intubation, restraints, pain, medication, visitors, and ability to speak; (3) dreams or hallucinations; and (4) the etiology of the ARDS. Patients were divided into "ICU recall" and "no ICU recall" groups based on their responses to questions about general and specific memories of the ICU, with patients who denied any memory of the ICU being classified into the "no ICU recall" group. Patients who recalled dreams, but no other portions of the ICU were also classified in the "no ICU recall" group.

https://doi.org/10.1017/S1355617707070749 Published online by Cambridge University Press

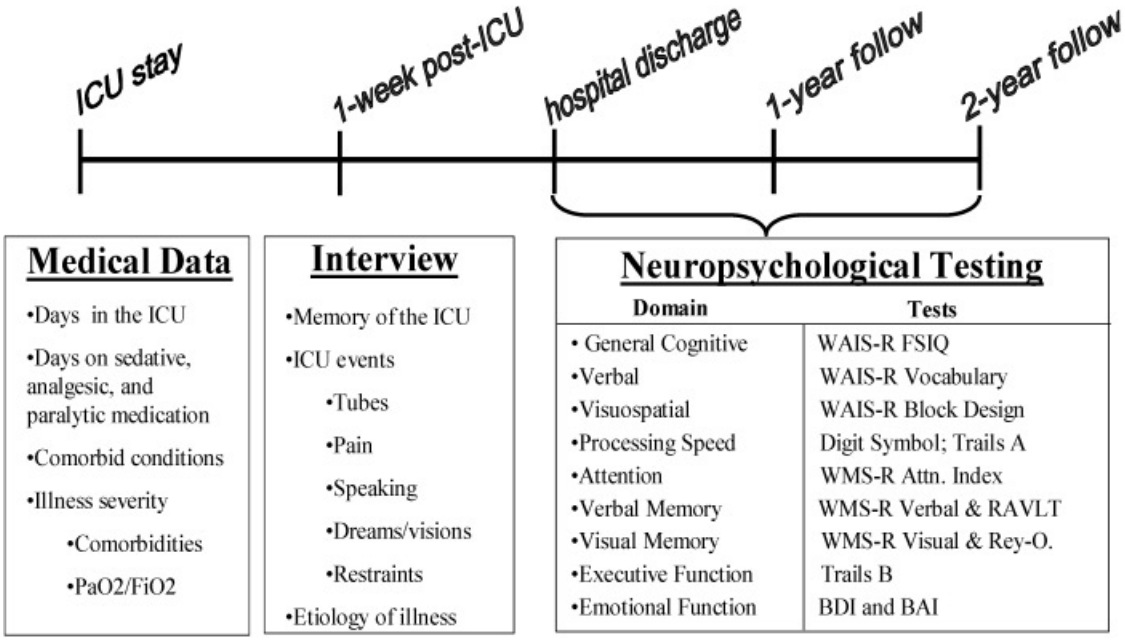

Fig. 1. Timeline of study procedures for all participants. WAIS FSIQ = Wechsler Adult Intelligence Scale-Revised Full-Scale IQ; ICU = intensive care unit; WMS-R = Wechsler Memory Scale-Revised; RAVLT = Rey Auditory Verbal Learning Test; Rey-O = Rey–Osterrieth Complex Figure; PaO_2/FiO_2 = ratio of arterial oxygen tension to fraction of inspired oxygen; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory.

Neuropsychological Tests

Standardized neuropsychological tests were administered to all survivors at hospital discharge, and at 1 and 2 years after hospital discharge and assessed general intelligence, attention, verbal and visual memory, processing speed, executive function, and visuospatial abilities (see Table 1 for the neuropsychological tests). We chose this test battery because of its sensitivity in detecting impairments in patients with critical illness or hypoxia (Gale & Hopkins, 2004; Gale et al., 2000; Weaver et al., 2002). The Oklahoma Premorbid Intelligence Estimation method (OPIE; Scott et al., 1997)

Table 1. Neuropsychological tests and cognitive domains

Cognitive domain	Neuropsychological tests	Calculation of index
Intellectual functioning	WAIS-R Full-Scale IQ	Heaton norms
Verbal	WAIS-R Vocabulary	Heaton norms
Spatial	WAIS-R Block Design	Heaton norms
Processing speed	WAIS-R Digit Symbol	(Digit Symbol + Trails A)/2
	Trail-Making Test A	
Executive function	Trail-Making Test B	Heaton norms
Attention	WMS-R Attention/Concentration Index	Standard
Verbal memory	WMS-R	(WMS-R Verbal Memory Index
	Verbal Memory Index	+ RAVL1 + RAVL 6 + RAVL Total)/4
	RAVL	
	Trial 1	
	Trial 6 (delayed recall)	
	Total of Trials 1 through 5	
Visual memory	WMS-R	(Visual Memory Index + ROCFD)/2
	Visual Memory Index	
	Rey–Osterrieth Complex Figure-Delay	

Note. WAIS-R = Wechsler Adult Intelligence Scale-Revised; WMS-R = Wechsler Memory Scale-Revised; RAVL = Rey Auditory Verbal Learning Test; RAVL1 = Rey Auditory Verbal Learning Test first trial; RAVL6 = Rey Auditory Verbal Learning Test recall trial; ROCFD = delayed recall raw scores from the Rey–Osterrieth Complex Figure. All scores were transformed to *Z* scores before averaging for domain scores. The Heaton norms referenced refer to the normative data from Heaton et al. (1991).

https://doi.org/10.1017/S1355617707070749 Published online by Cambridge University Press

was used to estimate premorbid intelligence. Depression and anxiety were assessed using the Beck Depression and Anxiety Inventories, respectively (BDI and BAI, respectively; Beck, 1987; Beck & Steer, 1993).

Raw test scores were converted to t (mean = 50; SD = 10) and Z scores (mean = 0; SD = 1) based on available normative data. When possible, scores took into account age, education, and sex. Normative data from Heaton et al. (1991) were used to convert the data from the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Block Design, Digit Symbol and Vocabulary) and Trail-Making Test (Parts A and B). Trials 1 and 6 of the Rey Auditory Verbal Learning Test (RAVL) were converted to t and Z scores using norms stratified by age and sex (Geffen et al., 1990). Delayed recall raw scores from the Rey–Osterrieth Complex Figure (ROCFD) were converted using normative data reported by Meyers & Meyers (1995). Conversion of the subtests from the Wechsler Memory Scale-Revised (WMS-R; Logical Memory and Visual Reproduction) used data provided in the manual (Wechsler, 1987). Because the normative data in the WMS-R manual are interpolated for ages 25–34 years, alternative norms were used for that age cohort (Mittenberg et al., 1992). After transforming neuropsychological test scores to t and Z scores, composite function indices were created by averaging these scores within each cognitive domain, as described below. Description and calculation of the cognitive domains are presented in Table 1.

Determination of cognitive sequelae was completed in a similar manner to previous studies (Hopkins et al., 2005; Jackson et al., 2003; Weaver et al., 2002; White et al., 2006) by using the *a priori* definition of cognitive sequelae being present when 2 or more cognitive test scores were > 1.5 SD or 1 test score > 2 SD below the normative population mean values using age, gender, and education corrected t scores (Heaton et al., 1991). Magnitude of cognitive sequelae was derived using the demographically corrected t scores and assigning a numeric value of 1 for each SD the t scores were >1 SD below the mean and summing the total number of SDs below the mean across all tests. In this convention, t scores ≥ 40 received a score of 0, scores > 1 SD below the mean (30 to 39) received a score of 1, scores > 2 SD below the mean (20 to 29) received a score of 2, scores > 3 SD below the mean (10 to 19) received a score of 3, and so on.

Statistical Analysis

Descriptive statistics were calculated for each interview category, demographic variable, medical variable, measure of depression and anxiety, and rate of neurocognitive sequelae. Independent-samples t tests were used to compare demographic variables between the ICU recall and no ICU recall groups. Noncontinuous data comparisons between groups used the Pearson's χ^2 statistic.

The primary outcome was the magnitude of neurocognitive sequelae. Repeated-measures analysis of variance (RMANOVA) was performed with impairment score and time as within-subjects factors and memory of the ICU as the between-subjects factor to test for group differences and examine cognitive sequelae over time. Significant main effects and interactions were decomposed using orthogonal Helmert contrasts and Bonferroni-corrected pairwise comparisons for between-group analysis at each time point (critical $p = .016$). Measures of effect size for all ANOVA analyses used partial eta squared (η^2).

Cognitive Domain Analyses

To reduce Type I error, tests that have been theoretically and empirically shown to assess similar cognitive functions were grouped together to create a single score (see Gale & Hopkins, 2004). Eight domain scores were calculated, each one representing a dependent variable: general intellectual functioning, verbal skills, spatial skills, processing speed, executive functioning, attention, verbal memory, and visual memory. Profile analysis examined the differences in the pattern of neuropsychological performance between the ICU recall and the no ICU recall groups at hospital discharge. A profile analysis is a repeated measures multivariate analysis of variance designed to compare two or more groups on a series of test scores (Stevens, 1996). A second multivariate RMANOVA with time (discharge, 1-year, and 2-year follow-up) added as a within-subjects factor was carried out to examine cognitive performance changes over time. Helmert contrasts were again used as a tool for decomposition of effects, and Greenhouse–Geisser corrected p values are reported for all within-subject effects with more than two levels of a factor to correct for possible violations of sphericity.

Finally, to examine the relationship between cognitive performance and measures of illness severity, negative affect, and demographic variables, we conducted three canonical correlations with the dependent variables of cognitive sequelae at hospital discharge, and at 1 and 2 years. For the first canonical correlation, demographic variables (age, education, sex, and OPIE score) were the independent variables. The second canonical correlation included measures of negative affect (BDI and BAI scores at 1 and 2 years), and the third included markers of illness severity (Charlson Comorbidity Index, APACHE II, PaO_2/FiO_2 ratio, mean multiple organ failure score, days in the ICU, and days in the hospital) as the independent variables. Using multivariate analyses, such as canonical correlation and profile analysis, reduces the potential for Type I error and provides a tool to look beyond single bivariate associations to examine possible contributors to cognitive sequelae.

RESULTS

Of the 74 ARDS patients, 4 patients declined to complete the structured interview, resulting in 70 patients (39 women) whose data were included in the analysis. The mean ± SD age was 45.3 ± 16.3 years (range, 16 to 77 years), and mean education level was 13 ± 2.4 years (range, 8 to 23 years).

https://doi.org/10.1017/S1355617707070749 Published online by Cambridge University Press

Recall of the ICU

Descriptive, medical, and emotional status data for all 70 ARDS patients by ICU recall group are provided in Table 2. On the semistructured interview, 17 patients (24.3%) had no recall of their ICU experience. Of these 17 participants, 10 were women, whereas 29 of the 53 patients who recalled memories of the ICU were women. Male-to-female ratio was not significantly different between groups, $\chi^2(1) = .09$, $p > .77$. There were more comorbid disorders in the no ICU recall group, and higher depression scores at 2-year follow-up for the ICU recall group (Table 2).

Of the 53 patients who could recall at least portions of their ICU experience, 34 (64%) recalled the etiology of their illness, 28 (53%) recalled feeding tubes or intravenous lines, and 36 patients (68%) recalled memories of visiting family and friends. Thirty-seven patients (70%) recalled treatment with mechanical ventilation; 90% described mechanical ventilation as an unpleasant experience. Thirty-three patients (62%) recalled restraints or being unable to move; all descriptions were unpleasant. Twelve patients (23%) had memories of being unable to speak. Vivid or real "dreams or hallucinations" were reported by 42 (79%) of the patients with ICU recall. Pain in the ICU was reported by 27 (51%) of patients. Patients were asked to rate their pain on a 10-point scale from "no pain at all" (a score of 0) to "intense pain" (a score of 10). The mean pain intensity rating was 7.5 ± 2.4.

Recall of the ICU and Rate of Cognitive Sequelae

At hospital discharge, cognitive sequelae were present in significantly more patients in the no ICU recall group (16/17; 94%) than those who reported recall of the ICU [34/53; 64%; $\chi^2(1) = 5.66$; $p < .02$]. Similar results were found at 1-year follow-up, where 11/16 (69%) of the no ICU recall group had cognitive sequelae and 18/47 (38%) of ICU recall group had cognitive sequelae ($p < .035$). Groups did not differ in the rate of cognitive sequelae at 2-year follow-up ($p > .25$), with 8/14 (57%) in the no ICU recall and 18/45 (40%) in the recall group.

Recall of the ICU and Magnitude of Cognitive Sequelae

Mean scores on the primary outcome and magnitude of cognitive sequelae at discharge and at 1-year and 2-year follow-up, are presented in Figure 2 as a function of group. Scores for magnitude of cognitive sequelae had roughly normal distributions on the Box-M test for homogeneity of variance [$F(6,2474) = 1.63$; $p < .13$]. The Levene's test was also nonsignificant [$F(1,49) = 2.35$; $p < .13$]. Results of the RMANOVA indicate main effects of group [$F(1,49) = 7.92$; $p < .01$; $\eta^2 = .14$] and interval after ARDS [$F(1,62) = 52.28$; $p < .001$; $\eta^2 = .52$]. The group-by-time interaction was not significant [$F(1,62) = 2.66$; $p > .10$; $\eta^2 = .05$]. All

Table 2. Descriptive information as a function of ICU memory group ($n = 70$)

	ICU recall ($n = 53$)		No ICU recall ($n = 17$)		Analysis		
	Mean	*SD*	Mean	*SD*	*t* score	*df*	*p* value
Age (years)	44.8	15.5	46.7	19.0	0.40	68	>.69
Average educational level (years)	13.1	2.6	12.8	1.8	−0.49	68	>.63
OPIE score	101.9	10.2	97.2	10.5	−1.61	68	>.11
Hospital length of stay (days)	39.7	23.4	35.5	16.3	−0.69	68	>.49
ICU length of stay (days)	34.2	21.8	31.6	16.7	−0.44	68	>.66
Duration of mechanical ventilation (days)	28.2	19.1	26.7	18.3	−0.28	68	>.78
APACHE II score	18.8	6.4	16.8	7.4	−1.08	68	>.28
Charlson Comorbidity Index	*.77*	*1.0*	*1.5*	*1.5*	*2.36*	*68*	*<.02*
Mean multiple organ failure score	7.2	3.8	7.4	3.3	0.14	68	>.89
Mean PaO_2 mm Hg	69.4	6.4	67.9	4.7	−0.89	66	>.38
Mean FiO_2 (%)	51.3	9.9	51.7	9.0	0.12	66	>.91
PaO_2/FiO_2 ratio	1.1	.34	1.1	.25	−0.14	66	>.89
Days receiving sedatives	21.0	16.0	16.6	10.3	−1.06	68	>.29
Days receiving narcotics	17.6	17.4	10.0	10.6	−1.69	68	>.10
Days receiving paralytics	5.2	6.9	3.2	3.0	−1.13	68	>.26
BDI score at 1 year	10.0	10.0	7.5	7.7	−0.90	61	>.37
BDI score at 2 years	*11.9*	*9.8*	*3.9*	*3.7*	*−3.0*	*57*	*<.01*
BAI score at 1 year	10.0	9.7	7.6	8.1	−0.89	61	>.38
BAI score at 2 years	10.7	9.4	6.4	7.9	−1.5	57	>.13

Note. ICU = intensive care unit; APACHE II = Acute Physiology and Chronic Health Evaluation; PaO_2 = arterial oxygen tension; FiO_2 = fractional inspired concentration of oxygen; PaO_2/FiO_2 = ratio of arterial oxygen tension to fraction of inspired oxygen; OPIE = Oklahoma Premorbid Intelligence Estimation; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory. Two participants were missing oxygen tension values.

https://doi.org/10.1017/S1355617707070749 Published online by Cambridge University Press

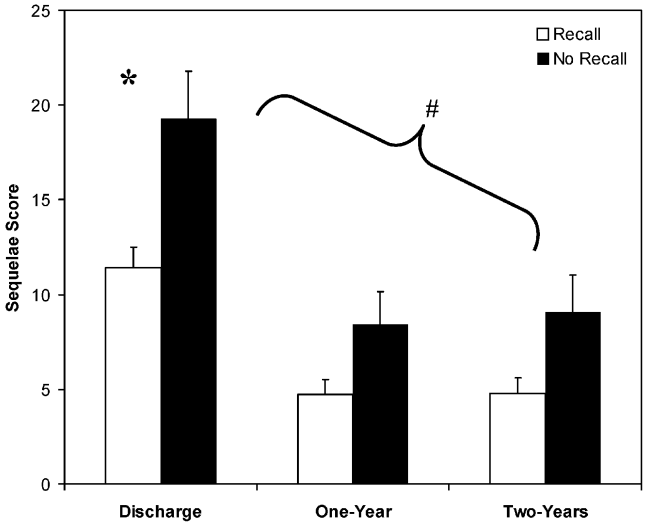

Fig. 2. Mean and standard errors for overall impairment scores by intensive care unit memory group and time. The asterisk indicates increased magnitude of sequelae in the non-recall group ($p < .001$) at hospital discharge. The pound sign indicates that both groups had significantly greater magnitude of sequelae at discharge compared to both follow-up periods.

ARDS patients experienced greater magnitude of cognitive sequelae at hospital discharge compared with 1- and 2-year follow-up [$F(1,49) = 60.02$; $p < .001$; $\eta^2 = .55$], with no differences between the 1- and 2-year measurements [$F(1,49) = 1.22$; $p > .28$; $\eta^2 = .06$]. Between-group comparisons for the ICU recall and no ICU recall groups indicated significant differences at hospital discharge [$t(68) = 3.15$; $p < .002$], but not at 1-year [$t(60) = 1.76$; $p > .08$] or 2-year [$t(57) = 1.84$; $p > .07$] follow-up (Figure 2).

Neuropsychological Domain Scores

Cognitive profile scores by domain at hospital discharge, and at 1- and 2-year follow-up by group are shown in Table 3. Age- and education-corrected scores for each measure used, along with between-group comparisons, are shown in Table 4. All domain scores had roughly normal distributions as evidenced by nonsignificant Box-M test for homogeneity of variance [Fs > 0.98; ps $> .50$] and Levene's test for all domain variables [Fs < 0.96; ps $> .33$]. Results of the profile analysis at hospital discharge show the profiles were not flat [$F(7,62) = 15.5$; $p < .001$; $\eta^2 = .64$], and parallel with no group by cognitive domain interaction [$F(7,62) = 0.55$; $p > .55$; $\eta^2 = .09$] (Figure 3). The ICU recall group had higher average Z scores, -0.87 ± 0.28 *versus* -1.20 ± 0.37 for the no ICU recall group. Mean Z scores for both groups were significantly below normal population values in all cognitive domains. The profiles were not level [$F(1,68) = 7.83$, $p < .007$; $\eta^2 = .10$], indicating significant differences in the between-group means. Significant domain differences were found for general intellectual functioning [$t(68) = 2.34$; $p < .02$], executive function [$t(68) = 2.61$; $p < .01$], processing speed [$t(68) = 2.03$; $p < .05$], and spatial skills [$t(68) = 2.12$; $p < .04$], with a trend toward better verbal memory in the ICU recall group [$t(68) = 1.85$; $p < .07$].

The next question of interest was whether domain performance changed over time. Results of the multivariate RMANOVA with cognitive domain and time as within-subjects factors and ICU recall group as the between-subjects factor indicated significant improvement in the cognitive domain profile of both groups with increased time after hospitalization [$F(2,56) = 60.83$; $p < .001$; $\eta^2 = .69$]. Both groups had significant cognitive improvement from hospital discharge to 1 and 2 years [$F(1,57) = 122.97$; $p < .001$; $\eta^2 = .68$], but no differences were found between 1 and 2 years [$F(1,57) = 2.68$; $p > .11$; $\eta^2 = .05$]. A significant main effect of group [$F(1,57) = 4.31$; $p < .04$; $\eta^2 = .07$] indicated the expected lower cognitive domain scores in the no ICU recall group when collapsed across all three time periods. The group-by-time, group-by-cognitive domain, and group-by-cognitive domain-by-time interactions were not significant [all Fs < 0.79; ps $> .61$].

Table 3. Mean ($\pm$ *SD*) cognitive domain Z scores by memory group

	ICU recall			No ICU recall		
	Discharge	1 Year	2 Years	Discharge	1 Year	2 Years
General	−0.93 (0.78)	−0.40 (0.89)	−0.29 (0.87)	−1.44 (0.53)	−0.87 (0.62)	−0.66 (0.82)
Verbal	−0.49 (0.79)	−0.37 (0.58)	0.86 (0.14)	−0.71 (0.62)	−0.37 (0.78)	0.92 (0.17)
Spatial	−0.86 (0.98)	−0.18 (0.95)	−0.07 (0.92)	−1.37 (0.64)	−0.38 (0.68)	−0.44 (0.79)
Processing speed	−1.32 (0.75)	−0.35 (0.87)	−0.32 (1.00)	−1.63 (0.70)	−0.77 (0.70)	−0.69 (0.79)
Executive	−1.34 (0.99)	−0.16 (1.08)	−0.03 (1.01)	−1.83 (0.87)	−0.52 (0.84)	−0.55 (1.07)
Attention	−0.85 (1.07)	−0.40 (0.89)	0.93 (0.19)	−1.25 (0.90)	−0.95 (0.99)	0.82 (0.23)
Verbal memory	−0.33 (0.87)	0.33 (0.88)	0.50 (1.12)	−0.85 (0.97)	−0.07 (0.61)	0.07 (0.54)
Visual memory	−0.63 (1.01)	0.97 (0.15)	1.01 (0.15)	−1.01 (0.85)	0.92 (0.17)	0.97 (0.18)

Note. ICU = intensive care unit.

https://doi.org/10.1017/S1355617707070749 Published online by Cambridge University Press

Table 4. Mean (± *SD*) for neuropsychological variables (*t* scores or standard index scores)

	ICU Recall			No ICU Recall		
	Discharge	1 Year	2 Years	Discharge	1 Year	2 Years
FSIQ[a,b]	91.2** (11.3)	99.6 (11.6)	101.2 (12.1)	85.4** (8.7)	93.1 (11.9)	95.4 (11.3)
VIQ	93.3** (12.7)	99.3 (12.1)	100.6 (11.9)	88.9* (11.5)	94.7 (11.3)	95.4 (11.7)
PIQ[a,b]	87.9** (10.4)	100.4# (11.7)	102.6 (12.3)	80.9** (8.6)	92.4 (12.9)	96.4 (13.0)
Digit Symbol[a]	37.7** (7.9)	46.4 (9.9)	46.5 (11.3)	32.6** (6.5)	42.8 (6.6)	44.4 (9.4)
Block Design[a]	41.6** (9.8)	47.9 (9.5)	49.3 (9.3)	36.3** (6.4)	46.3 (7.8)	45.6 (8.1)
Vocabulary	44.6 (7.9)	45.8 (8.0)	46.0 (8.3)	42.6 (6.2)	45.5 (6.3)	42.6 (7.1)
WMS-R Verbal	91.2* (12.2)	93.5# (11.5)	97.3 (14.2)	88.8 (12.9)	95.4 (13.4)	90.9 (12.7)
WMS-R Visual	95.1** (13.7)	101.3 (13.5)	104.2 (14.4)	92.4 (12.5)	96.6 (12.9)	97.4 (15.4)
WMS-R Attention[b,c]	86.6* (16.0)	94.0 (13.4)	94.5 (14.5)	80.5 (13.4)	86.0 (15.2)	84.1 (17.8)
ROCFD Delayed Recall	40.9** (14.3)	45.7# (8.9)	47.6 (8.9)	34.9** (10.7)	43.7# (11.7)	47.6 (10.1)
RAVL Trial 1[a]	51.8** (10.5)	57.2 (13.1)	57.4 (13.9)	41.3** (12.5)	52.2 (8.6)	55.2 (8.6)
RAVL Trial 5[b,c]	44.6** (15.3)	55.3 (14.1)	58.1 (18.7)	41.4 (12.7)	48.1 (7.2)	48.2 (8.1)
RAVL Delayed Recall[b,c]	44.7** (12.7)	53.9 (10.5)	55.7 (11.9)	39.2* (15.6)	49.4 (8.3)	49.4 (10.5)
Trail-Making Test A[a,b,c]	35.9** (10.6)	46.2 (9.6)	46.6 (10.5)	32.4* (9.8)	41.7 (10.4)	43.0 (10.4)
Trail-Making Test B[a]	36.6** (9.9)	47.9 (11.1)	49.6 (10.1)	30.1** (8.7)	44.6 (8.9)	44.5 (10.8)

Note. ICU = intensive care unit; FSIQ = Full-Scale IQ; VIQ = verbal IQ; PIQ = performance IQ; WMS-R = Wechsler Memory Scale-Revised; ROCFD = delayed recall raw scores from the Rey–Osterrieth Complex Figure; RAVL = Rey Auditory Verbal Learning Test. All differences between groups set at $p \leq .05$.
[a]Significant between-group differences at discharge.
[b]Significant differences at 1-year follow-up.
[c]Significant differences at 2-year follow-up.
*Differences between discharge and both 1-year and 2-year follow-up at $p \leq .01$.
**Differences between discharge and both 1-year and 2-year follow-up at $p \leq .001$.
#Differences between 1-year and 2-year follow-up at $p \leq .05$.

Correlational Analyses

A canonical correlation between the demographic variables and the magnitude of cognitive sequelae scores was .51; [Wilks' $\lambda = .71$; $\chi^2(12) = 22.1$; $p < .04$], accounting for 26% of the variance. Structural correlations between the individual variables and the canonical variate are shown in Table 5, with a cutoff of .35 used for interpretation (Tabachnik & Fidell, 2001). Only the OPIE score significantly contributed to the canonical variate of magnitude of cognitive

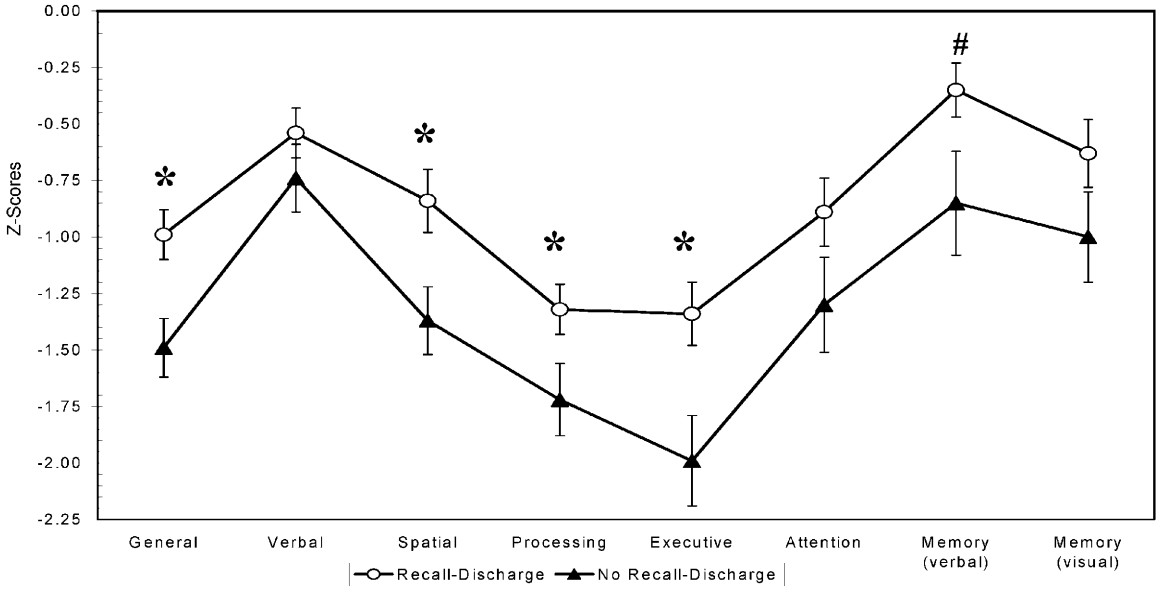

Fig. 3. Profiles of performance across cognitive domains by intensive care unit memory group. Asterisks indicate group differences $p < .05$. The pound sign indicates $p < .07$.

https://doi.org/10.1017/S1355617707070749 Published online by Cambridge University Press

Table 5. Structural correlations of demographic and sequelae variables with the canonical variate

Variables	Correlation with variate
Demographic set of variables	
Age	.16
Education	.08
Gender	−.03
OPIE score	.88
Neurocognitive sequelae variables	
Hospital discharge	−.60
One-year follow-up	−.79
Two-year follow-up	−.96

OPIE = Oklahoma Premorbid Intelligence Estimation.

sequelae, indicating that individuals with higher estimated premorbid intellectual functioning had a lower magnitude of cognitive sequelae. For depression, anxiety, and illness severity, no significant canonical correlations were found [$R_c = .43$; $\chi^2(12) = 22.5$; $p = .31$ and $R_c = .39$; $\chi^2(12) = 22.12$; $p = .39$, respectively], indicating that cognitive sequelae were not related to depression, anxiety, or indices of illness severity.

Finally, to examine the relationship between negative affect and ICU recall, we conducted point biserial correlations with BDI and BAI scores at discharge and at 1-year and 2-year follow-up. Depression score on the BDI at 2-year follow-up was associated with recall of the ICU [$r_{pb} = .37$; $p < .004$]. No other point biserial correlations reached statistical significance [$r_{pb} < .20$; ps $> .13$].

DISCUSSION

Approximately 24% of our prospectively identified ARDS survivors had no recall of their ICU experience, similar to rates between 23% and 50% found in other studies (Bergbom-Engberg & Haljamea, 1989a; Capuzzo et al., 2001; Granberg et al., 1998). Our data indicate both an increased rate and greater magnitude of cognitive sequelae in ARDS patients who did not recall their ICU experience. Patients with no ICU recall had a significantly higher prevalence rate of cognitive sequelae at hospital discharge and 1-year follow-up, but not at 2-year follow-up compared with patients with ICU recall. There was greater magnitude of cognitive sequelae in the no ICU recall group at hospital discharge. The magnitude of cognitive sequelae did not differ between the groups at 1- and 2-year follow-up.

Cognitive profile analysis indicates patients with no ICU recall were significantly worse than their counterparts on tests of general intellectual function, executive function, processing speed, and verbal memory. These results are in line with previous studies that report persistent impairments in cognitive performance following critical illness in ARDS (Rothenhausler et al., 2001) and medical ICU survivors (Jackson et al., 2003, 2004). However, this is the first study to report group differences in cognitive sequelae in patients with and without recall of their ICU experience.

Over 50% of patients who remembered the ICU recalled the etiology of their illness, feeding tubes or IV lines, mechanical ventilation, restraints or being unable to move, and vivid dreams. Nearly all of the patients who recalled ventilation and restraints described them as unpleasant experiences. These results are similar to studies that indicate adverse patient-reported memories of the ICU often include endotrachial suctioning (Leur et al., 2003), pain and discomfort (Simini, 1999; Turner et al., 1990), general fear and anxiety (Granberg et al., 1998; Hall-Lord et al., 1994; Turner et al., 1990), and fear and anxiety associated with nightmares and hallucinations (Bergbom-Engberg & Haljamea, 1989b; Green, 1996; Magarey & McCutcheon, 2005; McKegney, 1966). In our study, 79% of patients recalled enduring nightmares and hallucinations that were often described as vivid and lifelike, higher than prior reports (Bergbom-Engberg & Haljamea, 1989b; Green, 1996).

A difference in cognitive performance between ICU recall and nonrecall groups raises questions as to the specific contributing factors. There were no between-group differences for demographic variables; hospital length of stay; ICU length of stay; indices of illness severity; oxygen tension and inspiration variables; days receiving sedative, narcotic, or paralytic medications; or estimated premorbid intelligence levels, suggesting that these variables do not account for group differences in cognitive performance. However, the no ICU recall group had more comorbid disorders compared with those with ICU recall. Thus, it is possible that the increased number of comorbidities is associated with worse cognitive performance or that those with multiple comorbidities in this sample were more ill than their counterparts and, therefore, had more difficulty with recall and cognitive performance. Notably, other measures of illness severity did not differ between groups.

Other factors that were not specifically examined in the current study may contribute to decreased memory of the ICU experience and increased rate and magnitude of cognitive sequelae. Jones et al. (2000) propose a general nonspecific mechanism that is the result of several nonspecific factors, such as pain, sleep deprivation, metabolic disturbances leading to potential encephalopathy and delirium, as well as high doses of sedative and analgesic medication. Thus, the same mechanisms that play a role in impaired memory for events in the ICU may play a role in impaired cognitive function following critical illness and its treatment. In addition, hypoxia (whether due to anemia, hypotension, or oxygen desaturation), elevated cytokines and neurotoxic bacterial proteins from sepsis, hyperglycemia, other metabolic derangements, and inflammation likely contribute to poor cognitive functioning following critical illness (see Hopkins & Jackson, 2006). Reduced cognitive sequelae at follow-up may be the result of some degree of spontaneous recovery where the patient emerges from delirium, inflammation is reduced, medications are stabilized,

https://doi.org/10.1017/S1355617707070749 Published online by Cambridge University Press

and metabolic factors are controlled. These possibilities remain understudied in the immediate after-ICU time period. Studies to date indicate that cognitive function improves during the first 6 to 12 months after hospital discharge and remains consistent and disabling for up to 6 years after discharge (duration of the longest study; see Hopkins & Jackson, 2006), suggesting that while some recovery occurs initially, chronic cognitive impairments persist in many patients.

Relationship Between Cognitive Sequelae, Demographics, Severity of Illness, and Negative Affect

Overall magnitude of cognitive sequelae was significantly associated with the patient's estimated premorbid IQ in both groups. The ARDS patients with higher estimated premorbid intellectual functioning had a lower magnitude of cognitive sequelae. This finding is consistent with the hypothesis that a greater initial "brain capacity" or "cognitive reserve" (e.g., factors such as higher intelligence and higher educational and occupational attainment provide a buffer against brain dysfunction in the face of acquired central nervous system injury) in people with higher intellectual functioning results in decreased cognitive impairments after critical illness in such patients (Satz, 1993; Schmand et al., 1997). For example, an inverse relationship between higher premorbid intellectual function and frontal and parietal cerebral metabolism in patients with Alzheimer's disease is found (Alexander et al., 1997). Similarly, low educational and occupational attainment are related to an increased prevalence of Alzheimer's disease and subsequent rate of memory decline (Stern et al., 1995, 1999). A similar hypothesis of cognitive reserve could be generated in response to critical illness, although no studies have examined this question to date. Importantly, ICU recall and nonrecall groups did not differ in estimated premorbid intelligence. Thus, the relationship between magnitude of cognitive sequelae and premorbid intelligence cannot be accounted for by ability to recall the ICU.

The magnitude of cognitive sequelae did not correlate with indices of illness severity. In a review of the long-term effects of critical illness on cognitive function, Hopkins and Brett (2005) indicate that cognitive deficits appear to be independent of age and some markers of illness severity. Somewhat surprising, however, was the finding that cognitive deficits did not correlate with the latent component of depression and anxiety (i.e., negative affect), as the prevalence of depression and anxiety in ICU survivors ranges from 10 to 58% of patients (Al-Saidi et al., 2003; Angus et al., 2001; Hopkins et al., 1999; McCartney & Boland, 1994; Orme et al., 2003; Skodol, 1999). However, depression measured by the BDI at 2-year follow-up was related to ICU recall. This finding is consistent with previous studies that suggest the development of disorders of negative affect (e.g., posttraumatic stress disorder) following ICU stay is related to the number of unpleasant memories recalled (Schelling et al., 1998); however, other research suggests such a relationship may be primarily due to delusional memories, rather than factual recall (Jones et al., 2001). Research is needed to explicitly examine the relationship between depression and ICU recall.

Study Strengths and Limitations

The strengths of this study include the longitudinal prospective cohort study design, consistent follow-up times, high follow-up rates, detailed taped and transcribed ICU interviews regarding ICU recall, and a well-defined ARDS population. In addition, between-group comparisons used patients with the same illness and etiology, similar demographic variables (age, education, gender), illness severity, and duration in the hospital. A matched group such as this reduces the potential for spurious group differences.

The limitations of our study include the inability to measure premorbid cognitive and emotional function in each group. Therefore, we are unable to ensure that group differences are not the result of premorbid general group differences. In addition, we did not follow a control group of ICU survivors who did not have ARDS, thus the group differences in cognitive sequelae may be specific to ARDS and not generalize to other critically ill populations. Perhaps the different sedatives and narcotics, different doses of medications, and drug half-life may also have played a role in the group differences in cognitive sequelae. Finally, ICU recall was assessed by self-report. Self-reported recall may lead to unintentionally false reporting of memories; however, independent verification of each ICU memory is difficult given the number of consultations required with family members and medical providers as well as the times when no independent verification would be possible (e.g., when the patient was alone). However, previous investigations indicate self-reported ICU memories without independent verification are consistent across extended periods of time (Lof et al., 2006) and predict subsequent quality of life (Granja et al., 2005).

Our findings support emerging evidence that ARDS patients exhibit cognitive impairments following critical illness and ICU treatment. ARDS survivors with no ICU recall had worse initial cognitive outcomes that improved over time, compared with patients with ICU recall. It is unclear why patients with no ICU recall had worse cognitive outcome than patients with ICU recall. Additional research is required to elucidate the potential mechanisms for these differences. The inverse correlation of premorbid IQ estimates and cognitive sequelae potentially supports the hypothesis that initial cognitive reserve is associated with a lower rate of cognitive impairments after critical illness and ICU treatment. Neuropsychologists can play a key role in future research and assessment of critically ill patients regarding cognitive impairments, possible mechanisms, and potential interventions to prevent the observed cognitive impairments.

ACKNOWLEDGMENTS

This original research has not been published elsewhere and was sponsored by Deseret Foundation Grant numbers 300, 318, and 359 and NIH ARDS SCOR Grant no. HL50513. We thank Suzanne Stagg and Elizabeth Fong for transcribing the taped interviews.

REFERENCES

Alexander, G.E., Furey, M.L., Grady, C.L., Pietrini, P., Brady, D.R., Mentis, M.J., & Schapiro, M.B. (1997). Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: Implications for the cognitive reserve hypothesis. *American Journal of Psychiatry*, *154*, 165–172.

Al-Saidi, F., McAndrews, M.P., Cheunt, A.M., Tansey, C.M., Matte-Martyn, A., Diaz-Granadoes, N., & Herridge, M.S. (2003). Neuropsychological sequelae in ARDS survivors. *American Journal of Respiratory and Critical Care Medicine*, *167*, A737.

Angus, D.C., Musthafa, A.A., Clermont, G., Griffin, M.F., Linde-Zwirble, W.T., Dremisizov, T., & Pinsky, M.R. (2001). Quality-adjusted survival in the first year after the acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, *163*, 1389–1394.

Ashbaugh, D.G., Bigelow, D.B., Petty, T.L., & Levine, B.E. (1967). Acute respiratory distress in adults. *Lancet*, *2*, 319–323.

Beck, A.T. (1987). *Beck Depression Inventory Manual*. San Antonio, TX: Psychology Corporation.

Beck, A.T. & Steer, R.A. (1993). *Beck Anxiety Inventory Manual*. San Antonio, TX: Psychology Corporation.

Bergbom-Engberg, I. & Haljamea, H. (1989a). Assessment of patients' experience of discomforts during respirator therapy. *Critical Care Medicine*, *17*, 1068–1072.

Bergbom-Engberg, I. & Haljamea, H. (1989b). Patient experiences during respirator treatment—reason for positive-pressure ventilation treatment and patient awareness in the intensive care unit. *Critical Care Medicine*, *17*, 22–25.

Capuzzo, M., Pinamonti, A., Cingolani, E., Grassi, L., Bianconni, M., Contu, P., Gritti, G., & Alvisi, R. (2001). Analgesia, sedation, and memory of intensive care. *Journal of Critical Care*, *16*, 83–89.

Daffurn, K., Bishop, G.F., Hillman, K.M., & Bauman, A. (1994). Problems following discharge after intensive care. *Intensive Critical Care Nursing*, *10*, 244–251.

Gale, S.D. & Hopkins, R.O. (2004). Effects of hypoxia on the brain: Neuroimaging and neuropsychological findings following carbon monoxide poisoning and obstructive sleep apnea. *Journal of the International Neuropsychological Society*, *10*, 60–71.

Gale, S.D., Hopkins, R.O., Weaver, L.K., Walker, J.M., Bigler, E.D., & Cloward, T.V. (2000). Hippocampal atrophy following sleep apnea and carbon monoxide poisoning: Similarities and differences. *Journal of the International Neuropsychological Society*, *10*, 60–71.

Geffen, G., Moar, K.J., O'Hanlon, A.P., Clark, C.R., & Geffen, L.B. (1990). Performance measures of 16- to 86-year old males and females on the Auditory Verbal Learning Test. *Clinical Neuropsychologist*, *4*, 45–63.

Goldman, L.S. & Kimball, C.P. (1987). Depression in intensive care units. *International Journal of Psychiatry and Medicine*, *17*, 201–212.

Gordon, S.M., Jackson, J.C., Ely, E.W., Burger, C., & Hopkins, R.O. (2004). Clinical identification of cognitive impairment in ICU survivors: Insights for intensivists. *Intensive Care Medicine*, *30*, 1997–2008.

Granberg, A., Bergbom-Engberg, I., & Lunberg, D. (1998). Patients' experience of being critically ill or severely injured and cared for in an intensive care unit in relation to the ICU syndrome: Part I. *Intensive Critical Care Nursing*, *14*, 294–307.

Granja, C., Lopes, A., Moreira, S., Dias, C., Costa-Pereira, A., Carneiro, A., & JMIP Study Group. (2005). Patients' recollections of experiences in the intensive care unit may affect their quality of life. *Critical Care*, *9*, 96–109.

Green, A. (1996). An exploratory study of patients' memory recall of their stay in an adult intensive therapy unit. *Intensive and Critical Care Nursing*, *12*, 131–137.

Hall-Lord, M., Larsson, G., & Bostrom, I. (1994). Elderly patients' experiences of pain and distress in intensive care: A grounded theory study. *Intensive Critical Care Nursing*, *10*, 133–141.

Heaton, R.K., Grant, I., & Matthews, C.G. (1991). *Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographic Corrections, Research Findings, and Clinical Applications*. Odessa, TX: Psychological Assessment Resources.

Holland, C., Cason, C.L., & Prater, L.R. (1997). Patient's recollection in critical care. *Dimensions in Critical Care Nursing*, *16*, 132–141.

Hopkins, R.O. & Brett, S. (2005). Chronic neurocognitive effects of critical illness. *Current Opinions in Critical Care*, *11*, 369–375.

Hopkins, R.O. & Jackson, J.C. (2006). Long-term neurocognitive function after critical illness. *Chest*, *130*, 869–878.

Hopkins, R.O., Weaver, L.K., Collingridge, D., Parkinson, R.B., Chan, K.J., & Orme, J.F. (2005). Two year cognitive, emotional, and quality of life outcomes in acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, *171*, 340–347.

Hopkins, R.O., Weaver, L.K., Pope, D., Orme, J.F., Bigler, E.D., & Larson-Lohr, V. (1999). Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *American Journal of Respiratory Critical Care Medicine*, *160*, 50–56.

Jackson, J.C., Gordon, S.M., Hart, R.P., Hopkins, R.O., & Ely, E.W. (2004). The association between delirium and cognitive decline: A review of the empirical literature. *Neuropsychology Review*, *14*, 87–98.

Jackson, J.C., Hart, R.P., Gordon, S.M., Shintani, A., Truman, B., May, L., & Ely, E.W. (2003). Six-month neuropsychological outcome of medical intensive care unit patients. *Critical Care Medicine*, *31*, 1226–1234.

Jones, C., Griffiths, R.D., & Humphris, G. (2000). Disturbed memory and amnesia related to intensive care. *Memory*, *8*, 79–94.

Jones, C., Griffiths, R.D., Humphris, G., & Skirrow, P.M. (2001). Memory, delusions, and the development of posttraumatic stress disorder-related symptoms after intensive care. *Critical Care Medicine*, *29*, 573–580.

Jones, C., Griffiths, R.D., Macmillan, R., & Palmer, T.E.A. (1994). Psychological problems occurring after intensive care. *British Journal of Intensive Care*, *2*, 46–53.

Knaus, W.A., Draper, E.A., Wagner, D.P., & Zimmerman, J.E. (1985). APACHE II: A severity of disease classification system. *Critical Care Medicine*, *13*, 818–829.

Leur, J.P., Zwaveling, J.H., Loef, B.G., & Schans, C.P. (2003). Patient recollection of airway suctioning in the ICU: Routine versus minimally invasive procedure. *Intensive Care Medicine*, *29*, 433–436.

Lof, L., Berggren, L., & Ahlstrom, G. (2006). Severely ill ICU patients recall of factual events and unreal experiences of hospital admission and ICU stay–3 and 12 months after discharge. *Intensive Critical Care Nursing*, *22*, 154–166.

Magarey, J.M. & McCutcheon, H.H. (2005). 'Fishing with the dead'–Recall of memories from the ICU. *Intensive and Critical Care Nursing*, *21*, 344–354.

McCartney, J.R. & Boland, R.J. (1994). Anxiety and delirium in the intensive care unit. *Critical Care Clinics*, *10*, 673–680.

McKegney, F.P. (1966). The intensive care syndrome. *Connecticut Medicine*, *30*, 633–636.

Meyers, J.E. & Meyers, K.R. (1995). *Rey Complex Figure Test and Recognition Trial*. Lutz, FL: PAR Inc.

Mittenberg, W., Burton, D.B., Darrow, E., & Thompson, G.B. (1992). Normative data for the Wechsler Memory Scale-Revised. *Psychological Assessment*, *4*, 363–368.

Orme, J.F., Romney, J.S., Hopkins, R.O., Pope, D., Chan, K.J., Thomsen, G., Crapo, R.O., & Weaver, L.K. (2003). Pulmonary function and health-related quality of life in survivors of acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, *167*, 690–694.

Rothenhausler, H.B., Ehrentraut, S., Stoll, C., Schelling, G., & Kapfhammer, H.P. (2001). The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: Results of an exploratory study. *General Hospital Psychiatry*, *23*, 90–96.

Rundshagen, I., Schnabel, K., & Wegner, S.A.E. (2002). Incidence of recall, nightmare, and hallucination during analgosedation in intensive care. *Intensive Care Medicine*, *28*, 38–43.

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology*, *7*, 273–295.

Schelling, G., Stoll, C., Haller, M., Briegle, J., Manert, W., Hummel, T., Lenhart, A., Heyduck, M., Polasek, J., Meier, M., Perub, U., Bullinger, M., Schuffel, W., & Klaus, P. (1998). Health-related quality of life and post-traumatic stress disorder in survivors of the acute respiratory distress syndrome. *Critical Care Medicine*, *26*, 651–659.

Schelling, G., Stoll, C., Vogelmeier, C., Himmel, T., Behr, J., Kapfhammer, H.P., Rothenhausler, H.B., Haller, M., Durst, K., Drausneck, T., & Briegel, J. (2000). Pulmonary function and health related quality of life in a sample of long-term survivors of the acute respiratory distress syndrome. *Intensive Care Medicine*, *26*, 1304–1311.

Schmand, B., Smit, J.H., Geerlings, M.I., & Lindeboom, J. (1997). The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. *Psychological Medicine*, *27*, 1337–1344.

Schmitz, R., Lantin, M., & White, A. (1998). *Future needs in pulmonary and critical care medicine*. Cambridge: ABT.

Scott, J.G., Krull, K.R., Williamson, D.J.G., Adams, R.L., & Iverson, G.L. (1997). Oklahoma premorbid intelligence estimation (OPIE): Utilization in clinical samples. *Clinical Neuropsycholgy*, *11*, 146–154.

Simini, B. (1999). Patients' perceptions of intensive care. *Lancet*, *9178*, 571–572.

Skodol, A.E. (1999). Anxiety in the medically ill: Nosology and principles of differential diagnosis. *Seminars in Clinical Neuropsychiatry*, *4*, 64–71.

Stern, Y., Albert, S., Tang, M., & Tsai, W. (1999). Rate of memory decline in AD is related to education and occupation: Cognitive reserve? *Neurology*, *53*, 1942–1947.

Stern, Y., Alexander, G.E., Prohovnik, I., Stricks, L., Link, B., Lennon, M.C., & Mayeux, R. (1995). Relationships between lifetime occupation and parietal flow: Implications for a reserve against Alzheimer's disease pathology. *Neurology*, *45*, 55–60.

Stevens, J. (1996). *Applied multivariate statistics for the social sciences* (3rd ed.). Mahwah, NJ: Lawrence Erlbaum Associates.

Sukantarat, K.T., Burgess, P.W., Williamson, R.C.N., & Brett, S. (2005). Prolonged cognitive dysfunction after critical illness. *Anaesthesia*, *60*, 847–853.

Swaiss, I.G. & Badran, I. (2004). Discomfort, awareness and recall in the intensive care-still a problem? *Middle Eastern Journal of Anesthesiology*, *17*, 951–958.

Tabachnik, B.G. & Fidell, L.S. (2001). *Using multivariate statistics* (4th ed.). Needham Heights, MA: Allyn and Bacon.

The Acute Respiratory Distress Syndrome Network. (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *New England Journal of Medicine*, *342*, 1301–1308.

Turner, J.S., Briggs, S.J., Springhorn, H.E., & Potgieter, P.D. (1990). Patients' recollection of intensive care unit experience. *Critical Care Medicine*, *18*, 966–968.

Weaver, L.K., Hopkins, R.O., Chan, K.J., Churchill, S., Elliott, C.G., Clemmer, T., Orme, J.F., Thomas, F.O, & Morris, A.H. (2002). Hyperbaric oxygen for acute carbon monoxide poisoning. *New England Journal of Medicine*, *347*, 1057–1067.

Wechsler, D. (1987). *Wechsler Memory Scale-Revised*. San Antonio, TX: The Psychological Corporation.

White, J., Hopkins, R.O., Glissmeyer, E.W., Kitterman, N., & Elliott, C.G. (2006). Cognitive, emotional, and quality of life outcomes in patients with pulmonary arterial hypertension. *Respiratory Research*, *7*, 55.