BRAIN IMAGING AND COGNITIVE FUNCTION IN SURVIVORS OF CRITICAL ILLNESS: A PILOT STUDY

by

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(Under the Direction of Steven R. H. Beach)

ABSTRACT

Critically ill patients are at high risk of developing serious neurological dysfunctions including delirium and long-term cognitive impairment (LTCI). A growing body of evidence has shown that critical illness and its treatment can lead to de novo cerebral atrophy including white and grey matter abnormalities, delirium, and neurocognitive decline. This phenomenon is a major public health issue that effects literally millions of ICU patients each day. Cerebral atrophy is manifested in some LTCI patients over the first several months following their ICU discharge, yet no systematic or well-designed, prospective imaging studies have been conducted to date. Interestingly, of seven small studies of post-ICU LTCI performed to date, none have found a relationship between severity of illness and the development of LTCI, and none have included functional magnetic resonance imaging (fMRI), voxel based morphometry (VBM) nor diffusion tensor imaging (DTI) in evaluations of neurological dysfunction. After adjusting for severity of illness and age, delirium has been shown to be a strong independent predictor of the risk of LTCI amongst ICU survivors. The current study is a prospective, case-control pilot investigation designed to examine a cohort of ICU patients with and without delirium via magnetic resonance imaging (MRI). Cases and controls were scanned at hospital discharge and at 3-month follow-up. Results suggested a complex relationship between delirium, brain function

and anatomy. Specifically, at 3-month follow-up, cases exhibited significantly lower levels of blood oxygen level (BOLD) response compared to controls, even while controlling for time-1 group differences. Moreover, cases also displayed evidence of grey and white matter atrophy, expansion of the cerebral ventricles, and attenuated axonal fractional anisotropy (FA) compared to non-delirious patients. The extent of this neurological degradation was also highly correlated with several neuropsychological measures. Clinical and theoretical implication of these data as well as future directions and questions in delirium research are discussed. This data set is planned to be used to design a larger cohort study as a competitive supplement to an ongoing NIH-sponsored R01 entitled BRAIN ICU (Bringing to light the Risk factors And Incidence of Neurological dysfunction in ICU survivors) which is being conducted between 2007 and 2011 at Vanderbilt University Medical Center (VUMC).

INDEX WORDS: Critical Illness, Delirium, Long-Term Cognitive Impairment, Neuroimaging, fMRI, ICU, LTCI

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DEDICATION

I would like to dedicate my dissertation to my mother Susan Bakewell, and step-father Peter Bakewell, the greatest professors I have ever had.

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INTRODUCTION & BACKGROUND

In older individuals, the quality of one's life has increasingly become the coin of trade compared to survival alone [1]. Recent evidence suggests that critical illness may pose substantial risks for long-term declines in cognitive functioning and has the potential to severely impact the quality and independence of one's life. Of the 55,000 intensive care unit (ICU) patients who are treated daily in the United States, approximately 40% require mechanical ventilation [2]. Patients who are ventilated for three or more days represent only 4 to 10% of hospital admissions yet appear to account for the use of 30 to 50% of an ICU's resources [3]. Demographic data suggest that approximately 60% of all days spent in the ICU are patients who are 65 years of age or older [4]. With the burgeoning number of elderly individuals in the current population, these statistics take on vital importance when considering the accumulating data which links critical illness to cognitive decline. Although the total number of hospital beds has been reduced in the United States over the last 15 years, the number of critical care beds has increased by 26% over the last 2 decades [2]. Unfortunately, it is only in the last decade that researchers and clinicians have begun to document the neurocognitive decline associated with this vulnerable population, despite the fact that neurologic organ dysfunction has been studied extensively in other populations [5]. Additionally, other lines of investigation suggest that CNS degradation is not only linked to declines in quality of life, but is also an independent predictor of mortality [6].

Clinical Presentation of LTCI

Critical illness frequently results in de novo neurocognitive impairments. Estimates suggest that 25 to 78% of patients suffer from a clinically significant decline in cognitive functioning following stays in the ICU and that in many cases this decline may be permanent [7].

Although the specific mechanism or mechanisms by which the neurological degradation occurs remain under investigation, it is clear that the development of delirium, i.e. an acute cerebral dysfunction, is a major precursor to post ICU cognitive decline. In reviewing the studies which have examined this phenomenon, it is a challenge to draw conclusions since most reports to date vary widely in terms of their population of interest, prospective or retrospective reports, as well as their operational definition and quantification of cognitive decline. Nonetheless, 10 studies are reviewed below that have examined patient's neurocognitive impairments following ICU treatment [8-18]. These investigations include two studies in general ICU patients, five studies in ARDS patients, and one study a piece in respiratory and acute lung injury patients. The majority of these reports assessed participants within the first year of hospital discharge; however, three investigations have assessed patients within a longer time frame. Two studies examined participants approximately two years following discharge, and two others tested individuals at six years post ICU.

The studies listed above report widely varying levels of cognitive impairments. This is likely due at least in part to differences in methodological procedures such as the psychometric properties for neuropsychological assessment instruments, the study's definition of cognitive impairment, the length of time to follow up and the type of population studied. The importance of these methodological differences must be taken into account when comparing the reported rates of cognitive impairment. For example, Hopkins et al. [10] observed that 78% of patients

were experiencing clinically significant impairment in cognitive functioning at hospital discharge. This percentage then decreased to 46% at one year follow up. Conversely, Rothenhausler et al. [16] reported that only 26% of patients continued to suffer from cognitive declines 6 years after discharge which may be due to the study's operational definition and measurement of cognitive impairment. This retrospective cohort study found that only 21 of the original 46 ICU survivors returned to full-time employment. Furthermore, all of the patients classified as having neurocognitive impairments were considered "disabled" as defined by the German government. The second long-term ARDS longitudinal follow up study by Suchyta et al. [17] reported that the 30 ICU survivors were impaired with regard to executive functioning, attention, concentration, memory and fine motor ability with a mean assessment time of 6.2 years of post ARDS recovery. These studies highlight the long-term cognitive consequences of critical illness and strongly suggest that the neurological degradation may indeed be permanent. This is in particular believed to be so in geriatric populations, especially when suffering from preexisting conditions such as mild cognitive impairment (MCI), traumatic brain injury (TBI) or dementia. Whatever the specific mechanism of the ICU related cognitive decline, these preexisting risk factors appear to compound patient's neurocognitive losses, hastening the pace of dementia. This phenomenon has also been documented for at risk populations; however, these studies have not examined the specific impact of critical illness.

Clinical Associations

Although preexisting risk factors such as TBI or MCI have been found to interact with ICU related cognitive decline, a number of potentially deleterious variables have consistently yielded no associated risk. Specifically, data suggest that there is no link with ICU long-term impairment and patient's scores on acute physiology and chronic health evaluation (APACHE-II), their

length of time in the ICU, on mechanical ventilation, total days under sedation, narcotic and paralytic medication or tidal volume [15, 16, 18-20]. Although it is counter intuitive to assume that neuropsychological dysfunction is not yoked to the level of patient severity, these data provide evidence that this is indeed the case [cf. 9]. Ruling out these potentially confounding variables has been an important step in furthering our understanding of ICU delirium and neurological degeneration. In doing so it allows investigators and clinicians alike to focus their attention on uncovering potential causal variables in order to reduce the likelihood and prevalence of neurocognitive decline in the critically ill.

Patient Age

Of the studies mentioned above [8-18], most have examined adult patients who were either young or middle-aged (mean age = 54; SD = 11). In these studies, age of participant is not significantly related to level of cognitive impairment ($r = .262$; ns; [16]). In a multivariate analysis, Jackson et al. [15] examined the individual contribution of age in predicting the overall outcomes of patient's cognitive measure and found that age did not significantly contribute to the proportion of variance accounted for. At time of discharge, there is a moderate relationship between decline in executive abilities and age, although this relationship loses significance at two month follow up [9]. Other evidence does however suggest that patient's global mental status, visuospatial / constructional ability and visual memory may decline more rapidly for patients over the age of 60 following ICU treatment [15]. Although all of the studies mentioned above enrolled elderly patients (defined as over the age of 65), only one study contained participants with a mean age over 65 [13]. This is unfortunate given that the elderly account for nearly half of all critical care admissions and more than half of all days spent by patients in the ICU [4]. Most studies which have examined neurocognitive outcomes excluded patients with

known preexisting or comorbid cognitive impairments. Given that approximately 37% of patients in the ICU meet these exclusion criteria, this constitutes a sizable proportion of the population of interest. In this regard, it would be helpful for future research to include patients with premorbid impairments in order to help paint a more accurate picture of ICU delirium and long-term cognitive decline.

Etiology & Proposed Mechanisms

Delirium, a central nervous system perturbation, can result from multiple physiological and pharmacological factors. An exhaustive description of the possible causes of delirium is beyond the scope of this document. Therefore, the introduction will continue to focus on the mechanisms most likely to be related to delirium in the ICU.

Several theories have been proposed to explain ICU delirium. Certain lines of reasoning suggest that cognitive confusion is simply a naturally endogenous state related to medical illness [21, 22] in particular for frail individuals. With regard to sedatives and analgesics, there may be a common mechanism for linking both cognitive impairment and delirium [23-25]. Unfortunately, the mechanism underlying delirium is not likely to be due to a single factor; rather, it is more likely to be multivariate [26], due to interactions between patient characteristics and precipitating factors such as critical illness and its treatment. At the time of this writing, no studies have specifically examined potential causal mechanisms related to ICU delirium and long-term cognitive impairment. This question is therefore ripe for investigation and will likely involve interdisciplinary collaboration.

Sedatives and Analgesics

Related to this, evidence is mounting that various sedatives and analgesics may play a role in the length and severity of delirium, and ultimately may contribute to ICU related cognitive decline [27]. For example, using a prospective, nested case-control design, Marcontonio and colleagues [28] found a significant relationship between the development of delirium and benzodiazepines and meperidine use. Additionally, Dubois and coworkers [29] reported that opiates (morphine and meperidine), when administered intravenously or via an epidural catheter may be linked with the development of delirium for individuals being treated in medical or surgical ICU settings. Pandharipande, Ely and colleagues (2006) have examined the temporal relationship between delirium and the administration of sedatives and analgesics [30]. This study found that lorazepam was an independent risk factor for the onset of delirium. Fentanyl, morphine, and propofol demonstrated associated trend with higher, but not statistically significant, odds ratios. These types of investigations require repeated cognitive assessments and the ability to assess potential risk factors to which a patient is exposed. This must be completed in-between cognitive assessments in order to elucidate which factors pose an associated risk with a transition or change in cognitive status (i.e. from normal to delirium, to coma, and back to normal, etc). Investigations such as these have raised serious concern regarding a potentially putative role for these medications in the development of delirium.

Regarding the use of medications for the management of delirium, Ely and colleagues [31, 32] therefore recommend that they only be administered after attempts have been made to modify potential environmental contributors to delirium listed under the current document section heading titled “The Management of Delirium.” Conversely, it is important to note that delirium may be an expression of an acute, potentially life-threatening condition requiring urgent

medical attention. In these cases delirium may be a result of sepsis, shock, metabolic derangements, hypoxia, hypercarbia or hypoglycemia. The American Food and Drug Administration has not officially approved any medications for the treatment of acute delirium. Therefore, anti-delirium agents have been recommended to be used with caution [32, 33], and in the smallest doses possible and for the shortest period deemed necessary [32]. All anti-delirium medications have psychoactive properties which may actually cloud the patient's consciousness and increase the potential for long-term cognitive impairment.

In particular, the use of benzodiazepines has been discouraged due to the likelihood of over sedation [27, 34], exacerbation of confusion, and respiratory suppression. It is unfortunate that benzodiazepines remain the most commonly prescribed sedative agent in the ICU since they accumulate residually and may lead to prolonged delirium long after the drugs have been discontinued. Elderly patients with underlying dementia may be at elevated risk for this reaction as they have the potential to lead to increased confusion and agitation. Accordingly, it has been advised to utilize other sedation agents which do not target GABAergic circuits [35].

For example, initial reports from a recent randomized, prospective study in cardiac surgical patients demonstrated that dexmedetomidine (an α2 agonist) sedation during sternal closure was correlated with only an 8% postoperative occurrence of delirium [36]. This is markedly lower than the typical base rate of 50% which is associated with propofol or various benzodiazepines [37, 38].

Dexmedetomidine imitates stage 3 and stage 4 sleep by acting in the locus coeruleus region [39]. Given that sleep deprivation is an associated delirium risk factor, α2 agonist mediated sedation may help to reduce delirium by promoting endogenous sleep mechanisms. Before this practice is accepted as doctrine however, further investigations and replications are

required on a larger scale to affirm the initial positive outcomes. Ely and colleagues [35] recently completed a large, randomized, prospective, blind trial designed to evaluate the prevalence, duration, and severity of delirium in critically ill patients sedated with either benzodiazepines or α2 agonist (dexmedetomidine).

At present, haloperidol is the most widely prescribed anti-psychotic agent for delirium. The Society for Critical Care Medicine (SCCM) guidelines list it as the drug of choice for the management of delirium (SSCM, 2001). Although its effectiveness is based solely on sparse, level C outcome data, it does not suppress the respiratory drive and works as a dopamine receptor antagonist. Specifically, it is hypothesized to reduce the overt positive symptoms associated with delirium and psychosis by acting on mesocortical areas rich in D2 receptors resulting in relative sedation. In the non-ICU setting, the recommended starting dose of haloperidol has been listed at 0.5 to 1.0 mg orally or intramuscularly, repeating doses at 20 to 30 minute intervals until appropriate behavioral modification has occurred [40]. Conversely, in the ICU recommended dosages are listed as beginning with 5 mg every 12 hours (oral or intravenous) [32, 34, 41]. The optimal effect is typically achieved at approximately 20 mg/day [32, 34, 42].

This dosage aims to reach a theoretical therapeutic window of approximately 60% D2 receptor blockage while averting total D2 receptor obstruction which may result in parkinsonian symptomatology, along with other undesirable side effects [43]. In everyday clinical practice higher levels of haloperidol are frequently used as a result the unintentional removal of endotracheal tubes, central lines or in some cases aortic balloon pumps. Regrettably, there is a paucity of data to guide empirical dosage recommendations of haloperidol, chlorpromazine and droperidol as none of these agents have been sufficiently investigated in ICU settings [32].

Clinical guidelines suggest that patients can often be medicated with much lower doses of haloperidol once acute delirium has passed [44].

Regarding the potential benefits of haloperidol, in a retrospective analysis of critically ill patients receiving mechanical ventilation, Skrobik and colleagues presented data which suggest that the anti-psychotic may have reduced mortality rates, although regrettably, delirium was not specifically assessed in these patients [45]. Other evidence has brought to bear the possibility that D4, 'atypical' neuroleptic agents such as risperidone, may also benefit delirious patients in the ICU [46]. Although the exact psychoactive mechanism is not wholly understood, atypical antipsychotics are thought to impact all of the monoamines [47]. This has the potential to be of particular clinical use especially in hypoactive/mixed cases of delirium. In the future, prospective, randomized, controlled trials with sufficient power are needed to provide clinicians and researchers with empirically-based guidelines in order to prevent and treat delirium.

Delirium as a Causal Mechanism for Cognitive Decline

Certain lines of inquiry have speculated that delirium is indicative of a more subtle dementia which may not become apparent to either patients or clinicians even at the time of hospital discharge. In particular, for 'frail' populations [48], minor incidents may result in major impacts which could lead to cognitive decline and functional disabilities [49]. ICU induced delirium may in fact qualify as just such an 'incident.' In this regard, delirium could represent the precipitating factor which causes patients to cross a critical threshold eventually resulting in irreparable cognitive decline. Consistent with this prediction, a number of studies suggest that like other diseases of the CNS [50], the neurodegeneration linked to Alzheimer's disease may be present, possibly even for decades prior, to the manifestation of observable functional impairment. In this view, neurocognitive functioning may teeter on a neurodegenerative cliff until a precipitating

event, in this case, a stay in the ICU, pushes it over a vital threshold, resulting in long-term cognitive impairment.

Other studies have suggested that a common pathogenic mechanism may underlie Alzheimer's disease and delirium [22]. Of particular interest are the inflammatory processes, such as elevated levels of cytokines (IL-1) which may contribute both to delirium and Alzheimer's disease [51, 52]. Change in an individual's potential for neuroplasticity may also serve as a mediator for neurological atrophy and cognitive declines [53, 54]. Not surprisingly, reduction in neuronal tissue is closely linked to dementia and cognitive impairments [54-57]. An alternative line of reasoning suggests that delirium is related to the degradation of vital sub cortical structures such as the brain stem and thalamus [58] along with mnemonic (i.e. hippocampus) and executive structures such as the prefrontal and parietal cortices (see Figure 2). This makes intuitive sense when considering that critical illness survivors often suffer from losses in attention and memory as well [19, 59].

Neurocognitive Impairment Following Delirium

Mounting evidence suggests that delirium may be the causal link between critical illness and enduring neurocognitive declines. Unfortunately, the majority of studies examining this relationship have been conducted in non-ICU populations. These data are likely to be relevant nonetheless. To date, nine studies have assessed the association between delirium and cognitive decline in non-ICU patients. From these studies, when compared to controls, patients diagnosed with delirium were much more likely to experience a significant decline in cognitive functioning at follow up. At this point in the discussion, it is important to highlight an essential distinction between dementia and delirium. Whereas dementia and cognitive impairment tend to be

relatively stable conditions, delirium is characteristic of rapidly fluctuating changes in consciousness [60].

A study which examined hip fracture patients, when excluding individuals with dementia, found that delirious participants were nearly two times as likely to suffer from cognitive impairments at two-year follow up compared to non-delirious controls [61]. Another investigation, which examined hospitalized geriatric patients in community housing observed that individuals who experienced delirium had poorer Mini Mental Status Examination (MMSE) scores at 6 months and suffered from greater cognitive declines during the 18 months following hospitalization, when compared to non-delirious controls [62]. Furthermore, patients in this study were matched case-wise by highest hospital MMSE score, suggesting that the observed cognitive decline in delirious patients cannot be accounted for by premorbid cognitive impairment. McCusker et al. [63] reported that hospitalized elderly patients admitted to emergency services had MMSE scores five points below patients without delirium. Furthermore, to account for potential alternative explanations, the authors of this study controlled for premorbid dementia, overall functioning, comorbid disease, and illness severity, suggesting once again that delirium may be the critical factor impacting patient's cognitive outcomes. In a separate study examining individuals in geriatric nursing homes [64], while also accounting for premorbid cognitive impairments, investigators reported that patients, who developed delirium while hospitalized, demonstrated significant cognitive declines when compared to controls.

Four additional studies report greater occurrence of dementia following delirious episodes while hospitalized in elderly patients. Specifically, when investigating a sample of geriatric patients hospitalized for acute delirium, 14 individuals, immediately following remission of their dementia and an additional 14 patients were diagnosed as demented at two-

year follow-up [65]. This proportion of patients suffering from dementia was significantly higher than that in a typical geriatric population with no demented episodes. In a separate sample, individuals who were 85 years or older, who suffered an episode of delirium, were significantly more likely to be diagnosed with dementia at three-year follow-up than were individuals without delirium, when excluding patients with a prior history of dementia,. Specifically, rates of dementia climbed from 5.6% with no delirium to 18.1% per year compared to those with delirium [66]. Finally, Koponen et al. [67] observed that one third of psychiatric patients hospitalized for delirium had evidence of cognitive decline.

To the best of our knowledge, only one study to date has assessed long-term cognitive outcomes in the critically ill [59]. In this study, a trend suggested that length of delirium duration was related to depth of cognitive decline. This study differed from previous reports in that the population was significantly younger (mean age = 53.2).

Neuroimaging

At present, research has only recently begun to employ neuroimaging techniques to answer important questions regarding the nature of the underlying neurological substraights associated with ICU delirium and cognitive impairment. Neuroimaging has the potential to be a powerful tool that could allow investigators to answer a wide range of questions related to post-ICU cognitive decline. Traditional structural imaging techniques such as computerized tomography (CT) as well as magnetic resonance imaging (MRI) have already shed light onto the nature of the white and grey matter degradation that appears to be occurring in certain ICU patients [67-70]. Newer methods of neuroimaging are allowing researchers to shed light onto not only anatomical changes in the brain, but functional and molecular signatures as well. An early CT study reported atrophy surrounding the cerebral ventricles in elderly psychiatric patients experiencing delirium

compared to matched controls [68]. Furthermore, the degree of atrophy was related to patient's MMSE scores. Patients in these studies also displayed cerebral infarctions and hemorrhages in frontal and parietal regions [67-70]. Another study which examined the effects of electroconvulsive shock therapy (ECT) in delirious patients found white matter abnormalities and lesions in the basal ganglia [71].

Further evidence suggests that there are major neuroanotomical changes which occur in patients experiencing prolonged delirium, diminished level of consciousness, alerted state of mental status, or confusion [69]. In one study, CT scanning revealed that 61% of critically ill patients who suffered from these conditions were found to have either gross white and grey matter atrophy, white matter lesions/hyperintensities, cortical and sub cortical lesions and ventricular enlargement [69]. Additionally, Hopkins et al. [55] observed similar findings when employing MRI to examine anatomical changes associated with poor cognitive outcomes in ARDS patients. In this study, structural lesions were found in the brain stem (pons), posterior parietal cortex, atrophy in the medial temporal lobe (hippocampus), and significant white matter intensity changes in cortical and subcortical white matter tracts [55].

A longitudinal investigation by Buckner and colleagues [72] examined potential mechanisms underlying neurophysiological changes associated with the conversion from mild cognitive impairment (MCI) to Alzheimer's disease. In a series of studies Buckner and colleagues employed multi-modal neuroimaging techniques to examine molecular (i.e. amyloid protean plaque formation) signatures in Alzheimer's disease patients. They then demonstrated that these changes mirrored metabolic abnormalities for individuals possessing the apoE 4 allo protein which they proposed leads to grey matter atrophy in the medial temporal/hippocampal region and posterior parietal cortex. Not surprisingly, grey matter degradation in these regions of

interest was also observed to correlate with functional Blood Oxygen Level Dependent (BOLD) declines in activation for these known mnemonic regions, while engaged in memory tasks.

Additionally, the brain's primary arousal mechanism, the Ascending Reticular Activating System (ARAS) may also play an important role in the modulation of delirium [73]. Excitatory projections originating in the myelencephalon innervate the midbrain and cortex directly and are hypothesized to be critically involved in general attention [73, 74]. As many anesthetic agents are thought to act in the brainstem region, it is possible that perturbation of the ARAS circuit may lead to fluctuating in arousal, sensoration perception, attention and executive function. Excitatory pontine afferents may therefore be involved in maintaining an equilibrium between top down regulation via cortical structures and bottom up arousal levels originating in the brain stem (see Figure 2). For individuals with preexisting neuronal degradation, transient interference in either or both areas could have the potential for major neurocognitive disruption. Gross longitudinal changes in brain physiology are known to impact metabolic cellular mechanisms [72, 75, 76]. If such changes persist for a sufficient length of time, either hyper or hypo metabolic modifications can lead to apoptosis, grey matter atrophy and axonal degradation. Once again, patients with prior CNS deterioration or insults may be particularly at risk for this hypothesized deleterious mechanism depicted in Figure 2. Although this model of ICU linked cognitive impairment remains highly speculative [77], the hope is that it may generate novel hypothesis for the investigation of potential explanations for ICU delirium and long-term cognitive decline.

Premorbid Risk Factors for Delirium

It is clear that ICU delirium is related to emerging cognitive impairment; however, many questions remain regarding the specific mechanism by which ICU delirium may lead to cognitive

decline. It is important to emphasize that although delirium is indicative of emerging cognitive impairment, it is not the case that all patients who experience delirium have preexisting cognitive conditions. Jackson et al. demonstrated this in two studies [19, 59] which excluded patients who suffered from suspected dementia prior to their admittance to the ICU. Of the remaining sample, nearly one third of individual's in the ICU who were suffering from delirium had cognitive impairments 6 months later. Once again, this suggests that although there does appear to be a kindling effect for cognitive decline in individuals who present with preexisting dementia, this condition does not explain ICU delirium for a sizable percentage of the patient population.

It is also important to note that although delirium is often discussed as though it is a unitary construct, in fact there exists a great deal of heterogeneity regarding the presentation and course of the condition. In reality, delirium is a dynamic state characterized by both hypoactive as well as hyperactive behaviors. Moreover, it is common in ICU populations for patients to oscillate frequently between these states, painting a complex clinical picture [78]. Between these two extremes, the level of delirium can fluctuate widely as well. Given the heterogeneity of this construct, it is not surprising that debate continues to exist regarding the conceptualization and measurement of delirium's duration and severity [79-81]. It is clear however, and generally agreed upon, that a spectrum of severity exists and that variables such as duration, etiology, delirium subtype as well as the level of severity itself will likely prove to be important factors for predicting long-term neuropsychological outcomes. To date, only one study has examined this relationship explicitly. Jackson et al. [59] found that after controlling for other variables, the greater the duration of time that patient's were classified as delirious, the more likely they were to suffer long-term cognitive impairments following stays in the ICU. To summarize, although

the quantification of delirium duration is relatively straight forward, several challenges remain regarding the measurement of delirium itself as well as its severity.

Environmental Variables and Delirium

Several recent studies have identified a long list of potential risk factors for the development of delirium [82-85] with certain variables emerging as potential 'high-risk' conditions. In particular, patients who possess three or more individual risk factors appear to be at elevated risk compared to controls [82-85]. Although several demographic variables cannot be modified (e.g. age, socioeconomic status, etc.), others have potential to serve as useful points of intervention. For example, the use of specific types of sedatives and analgesic medications [84-91] appear to be good candidates. In line with this reasoning, benzodiazepines and meperdine have been shown to be related to the development of delirium in ICU patients [35, 85, 86]. Additionally, benzodiazepines, narcotics and as other psychoactive agents have been reported to correspond with 3 to 11 fold increases in the prevalence of delirium [30, 35]. Recent survey data indicate that lorazepam is frequently administered in the ICU for the treatment of delirium and may be prescribed at over 50 mg/day. Finally, other reports suggest that preventing fluid and electrolyte disturbance, gastrointestinal bleeding [58] and alcohol abuse [82] may also represent important clinically modifiable conditions related to the development of ICU delirium. Given that delirium appears to be a causal variable related to the development of cognitive impairment, the identification and modification of these risk factors is paramount to the prevention and treatment of adverse cognitive outcomes.

The Management of Delirium

Despite the growing body of data linking negative neurocognitive outcomes with the development of delirium, there remains a paucity of information regarding the clinical management of acute delirium [32]. Pharmacological management of delirium has been recommended only after correction for non-pharmacological factors such as hypoxemia, metabolic derangement, and inability of the patient to sleep [92, 93]. Environmental interventions (e.g. sleep, mobilization, hydration & orientation) were found to reduce the occurrence of delirium from 15% to 9% in a non-ICU prospective study [94]. No studies to date have accurately assessed the effectiveness of haloperidol in treating ICU delirium, despite being the most widely prescribed neuroleptic agent [92]. Overall, very little data exist regarding empirically based recommendations for the treatment of delirium despite the enormous public health and economic implications [94] as delirium remains a serious, and all too common, complication in critical illness.

Clinical Awareness of Cognitive Impairment

Recent reports suggest that individuals recovering from critical illness rarely have the opportunity for neurocognitive rehabilitation. Hopkins et al. [19] found that although 42% of ARDS survivors enrolled in general rehabilitation therapy, only 12% participated in cognitive rehabilitation. Neuropsychological decline appears to be grossly under recognized by both intensive care and rehabilitation professionals. Unfortunately, this oversight is not restricted to critically ill patients alone. One study suggested that between 35 to 90% of physicians fail to either recognize or accurately assess potential neurocognitive impairment in non-ICU settings [95]. Furthermore, cognitive dysfunction is rarely evaluated in the critically ill [59] and is likely to go unnoticed in approximately half of all cases [96]. These unsettling statistics are at least in

part likely to be due to the subtlety by which neurocognitive impairment may manifest itself, especially if patients are alert, oriented and appear to be mentally intact overall. The education of medical care providers with regard to neuropsychological decline is therefore imperative. Raising the awareness of physicians and nurses alike to this issue is of vital importance. In light of the paucity of relevant data regarding rehabilitation for neurocognitive impairments, this will ideally stimulate future research on the topic with the goal that such interventions for the critically ill can eventually be realized.

ICU Diagnosis and Monitoring of Sedation and Delirium

Delirium is a dynamic state characterized by change in mental status. Specifically, it is associated with inattention and an altered level of consciousness [60]. The Society of Critical Care Medicine (SCCM) suggested in its 2002 guidelines for sedation and analgesia that all critically ill patients should be monitored for level of sedation and delirium concurrently [97]. Unfortunately, evidence has repeatedly shown that neither nurses nor physicians are able to consistently diagnose delirium using clinical judgment alone. For this reason, it is necessary to employ well-validated and reliable, yet brief assessment tools to monitor patient's level of consciousness. A streamlined two-step process designed to track sedation and delirium has been recommended [92].

In step one, the ICU attendant should assess an individual's level of consciousness using an objective and reliable assessment instrument. This is recommended in order to avoid over sedation and to insure that the patient can be removed from mechanical ventilation as soon as possible. These instruments provide a common language by which a treatment team can communicate when discussing the treatment of patients in the ICU. The most commonly used scale is the Ramsay, which has been employed for decades in both clinical practice as well as

scientific research [97, 98]. Additionally, the Richmond Agitation Scale and the Sedation Agitation Scale are also considered reliable and valid measurements of critically ill patient's verbal reports as well as their reactions to physical stimuli [99-101] and are increasingly employed in ICU settings around the world [102, 103].

Following this broad assessment of the patient's arousal, the second step in monitoring individuals in the ICU is to assess patients who respond to verbal stimuli for delirium. In 2001, Ely and colleagues [102, 104, 105] published the first non-verbal instruments designed to specifically assess delirium for intubated patients. The Intensive Care Delirium Screening Checklist has a high sensitivity (99%) and moderate specificity (64%) and is frequently employed as a screening instrument [105]. Alternatively, the Confusion Assessment Method for the ICU (CAM-ICU) has a sensitivity and specificity of approximately 95% with an inter-rater reliability (Kappa) of 0.96 [102, 104]. The CAM-ICU was specifically designed for bedside use by nurses or physicians. Therefore, it is quite easy to implement, requires minimal training and on average only takes 1 minute to administer. Furthermore, it incorporates four key features derived from the Diagnostic and Statistical Manual IV definition of delirium [106]. These features are: 1) change in mental status from baseline or fluctuating course of mental status; 2) inattention; 3) disorganized thinking; and 4) altered level of consciousness. According to the DSM IV and the CAM-ICU definitions, a patient is considered delirious when both conditions 1 and 2 are present along with either condition 3 or 4. The CAM-ICU has been translated into several languages and more information is available at www.icudelirium.org .

Summary

A growing body of literature is helping to increase awareness in clinicians and researchers alike regarding the importance of delirium and long-term cognitive impairment in the critically ill.

Although the relationship between delirium and neurocognitive decline is well documented in non-ICU populations [57], it is becoming evident that a analogous relationship appears to exist for the critically ill. Several causal models have been proposed to elucidate potential mechanisms for this phenomenon, unfortunately however, none have emerged as clear winners. One finding which has come to light however is that delirium in the ICU can no longer be thought of as harmless. Rather, it appears to pose serious risks for patient's long-term and immediate health. Until more detailed data are available to explain the pathway in which ICU delirium leads to neurocognitive decline, it will likely be necessary to appeal to neuroscience and gerontology to provide further clues for how to overcome this widespread and devastating public health issue.

METHODS

Statement of the Problem the Study Will Address

Survivors of the ICU experience brain injury acutely as delirium and chronically as LTCI. Delirium occurs in up to 80% of critically ill medical and surgical patients, is independently associated with increased length [107] and costs of ICU stay [108] and six-month mortality, and leads to development of subacute cognitive impairment at hospital discharge [59]. LTCI, which contributes to poor quality of life and limits functional recovery as well, persists in 1 out of every 2 survivors for at least 2 years [19]. The severity of most ICU survivors' LTCI is functionally equivalent to mild/moderate dementia [8, 10, 14, 16, 19, 59, 109]. Anecdotal reports have shown that cerebral atrophy is manifested in some LTCI patients over the first several months [110], following their ICU discharge, yet no systematic or well-designed, prospective imaging studies have been conducted to date. There is an unmet need to determine risk factors for the development of post-ICU LTCI and to characterize the nature of the brain injury. Interestingly, of seven small studies of post-ICU LTCI performed to date, none has found a relationship

between severity of illness and the development of LTCI, and none have included brain imaging. After adjusting for severity of illness and age, data suggest that delirium is an independent predictor of the risk of LTCI amongst ICU survivors [7, 59]. Thus, the current proposal is a pilot investigation to study a prospective cohort of ICU patients with and without delirium via MRI, and to correlate these in-hospital and 3-month follow-up MRI results with the development of LTCI. The hope is to use these data to plan a larger cohort study as a competitive supplement to our upcoming NIH-sponsored R01 entitled BRAIN ICU (Bringing to light the Risk factors And Incidence of Neurological dysfunction in ICU survivors) conducted between 2007 and 2011.

Hypotheses and Specific Aims

AIM 1: To characterize MRI abnormalities in ICU survivors who had delirium (cases) as compared to controls who did not. It was hypothesized that patients who had delirium would manifest abnormalities in the frontal lobe, hippocampus, or parietal lobe. To test this hypothesis, 8 previously mechanically ventilated medical or non-cardiac surgical patients were studied (4 who had delirium and 4 who did not) in the current pilot case-control investigation. Brain MRI scans were obtained prior to hospital discharge and at 3 months following ICU admission.

AIM 2: To correlate the development of brain atrophy over a 3-month period in ICU survivors with the severity of LTCI following ICU admission. It was hypothesized that atrophy in the frontal lobe, hippocampus, and/or parietal lobe would correlate with neuropsychological test scores. To test this hypothesis, MRI data were compared with severity of neuropsychological test scores measuring cognitive function in multiple domains.

Background and Significance

Critical illness is characterized by multi-system organ dysfunction [111, 112] a syndrome of failure of the central nervous, respiratory, renal, endocrine, cardiovascular, hepatic, gastrointestinal, and other organ systems. Despite major advances in management of this syndrome, little is known about the causes and pathophysiology of the most valued organ, the brain.

The most common phenotypic manifestation of acute brain dysfunction is delirium, which occurs in 60 to 80% of mechanically ventilated medical and surgical ICU patients [111, 113, 114] and 50 to 70% of non-ventilated medical ICU patients [115, 116]. During the ICU stay, delirium is acutely associated with complications of mechanical ventilation including nosocomial pneumonia, self-extubation, and reintubation [116, 117]. ICU delirium predicts a 3- to 11-fold increased risk of death at 6 months, even after controlling for relevant covariates [110, 118].

A thorough review of the literature further reveals that delirium may lead to LTCI [57], but more in-depth study is warranted (which is the purpose of the current NIH-sponsored R01, BRAIN ICU). There have now been 7 cohorts of over 350 medical and surgical ICU survivors—exclusive of traumatic brain injury and cardiac surgery patients—indicating a 50-80% risk of developing an acquired or accelerated form of LTCI that is functionally equivalent to mild/moderate dementia [8, 10, 14, 16, 19, 59, 109]. Using standard criteria for defining neuropsychological abnormalities and excluding patients with detectable baseline deficits, Hopkins et al.[19] determined that ~1 in 2 patients had LTCI at 2 years following recovery from ARDS. In a separate series of 15 ARDS survivors who underwent brain CT, significant atrophy, brain lesions, or both were found in over 50% when compared to gender- and age-matched controls [55]. The findings included significantly enlarged ventricles and ventricle-to-brain ratios

(an indirect index of neuronal cell loss and atrophy) compared to matched controls [55]. Interestingly, in both anoxic and traumatic brain injury the extent of LTCI appears to parallel the degree of morphologic abnormalities [119, 120]. As preliminary studies in ARDS have shown, the more extensively studied anoxic and traumatic brain injury patients' changes in critical anatomic structures such as the hippocampus and frontal lobes generally evolve over weeks to months following acute neurological injury [120-122]. Although delirium appears associated with LTCI, there are no prospective studies to date of MRI among survivors of the medical or surgical ICU with concomitant collection of objective delirium and LTCI evaluations.

Premliminary Reports

Delirium can be reliably and rapidly detected using the Confusion Assessment Method for the ICU (CAM-ICU), a well-validated, brief, bedside assessment [113, 118, 123]. Following one of the first studies of post-ICU LTCI [59], a pilot investigation was recently completed with 67 consecutive, ventilated, medical ICU patients to assess the relationship between delirium and LTCI. After adjustment for age and education using normative data, 38 of 67 patients (57%) demonstrated marked deficits in domains of memory (especially visual), executive function, processing speed, and visuo-spatial construction, with more sporadic deficits in language and attention/concentration [59]. Patients with cognitive impairment at 3 months had been delirious an average of 1.6 days longer during their ICU stay (Figure 3). After adjustment for pre-existing cognitive impairment, APACHE II scores, and coma duration, every day spent delirious in the ICU increased the risk of long-term cognitive impairment by 35% (adjusted OR 1.35; $P = 0.037$). A commonality among these studies and those previously referenced is that none have found an association between severity of illness scores and the development or severity of LTCI. This consistent finding speaks against the notion that LTCI is merely a marker of the severity of acute

illness. These data support the design of the current study, and highlight the need for these pilot data of delirium and LTCI coupled with brain imaging. Anecdotally, there are several examples that also strongly support the study aims. For instance, a 49 year-old executive who was admitted to the Vanderbilt medical ICU with sepsis and ARDS and experienced 16 days of ICU delirium underwent brain MRI 32 months after ICU admission (Figure 1), which demonstrated profound brain atrophy relative to ventricular size, with a ventricle-to-brain ratio that is 2.9 standard deviations above normative controls. She also experienced a decline in her Wechsler Full Scale Intelligence Quotient [124] from 139 pre-admission to 106 six months after admission to 118 thirty-two months following ICU discharge. This case illustrates the type of structural abnormalities that were hypothesized to occur in the brains of critically ill delirious patients. The current study aims to provide the data for a competitive supplement to a recently-funded, 5-year cohort study of delirium and LTCI in ICU survivors.

Research Design and Methods

The current study is a case-control study of adults discharged from the medical or non-cardiac surgical ICU who were monitored daily for delirium and who are co-enrolled in the IRB-approved, NIA-sponsored BRAIN-ICU study. After obtaining informed consent and enrollment, ten ICU survivors were given MRIs at discharge and 3 months following ICU admission. Based on the published literature [33, 57], 3 months was hypothesized to be sufficient time for atrophy and ventricular enlargement to occur in response to neuronal cell loss. Data were collected prospectively at enrollment, including delirium via the CAM-ICU [113, 123] Acute Physiology and Chronic Health Evaluation (APACHE) II score [125], age, and gender. Daily data collection included pulse oximetry and arterial blood pressure measurements (as recorded in the electronic medical record) as well as sedation scale and delirium assessment (CAM-ICU) data. Table 1

outlines the procedures and chronological sequence of events that patients experienced. Patients were consented and enrolled upon ICU discharge (in order to differentiate cases from controls) and then underwent initial imaging prior to hospital discharge. 3 months later, repeat imaging and neuropsychological testing was conducted.

Imaging

A thorough yet efficient protocol was developed for the brain fMRI testing prior to hospital discharge and 3 months post-ICU admission (Table 2) to determine if there were functional changes in the brain's of study patients. Table 3 depicts the number of patients who were enrolled in each cell of the study. The protocol started with structural studies that use high-resolution 3D brain MR images to measure tissue volumes of critical structures (e.g., hippocampus, etc.) that are theorized to be affected in the cases (delirium patients) [126, 127]. Using both block and event-related fMRI paradigms, the Simon arrow test [128, 129], a visual "oddball" paradigm and the n-back [130] were then employed to assess executive function and working memory, during the fMRI in accordance with well-established protocols [131]. Diffusion-weighted images were obtained for those patients who were able to remain in the scanner for an additional 5 minutes in order to detect underlying changes in white matter fractional anisotropy.

All MRI imaging was performed using a Philips Achieva 3T MRI scanner (Philips Medical Systems, Inc., Best, The Netherlands). Informed consent was obtained prior to scanning in accordance with Institutional Review Board guidelines. Scanning included a two dimensional, T1-weighted high-resolution image set covering the whole brain (256x256, FOV = 240mm, 4.5mm thick/0.5mm gap, 30 axial slices), and T2* weighted gradient-echo, echo planar BOLD

fMRI scans (64x64, 3.75mmx3.75mm, FOV = 240mm, 4.5mm thick/0.5mm gap, TE = 35 ms, TR=2s, 200 volumes per series).

Neuropsychological Testing

A neuropsychologist conducted cognitive performance testing at three month follow up to determine the association of cognitive function with morphologic changes, functional changes (fMRI), and ischemic lesions from diffusion imaging. The LTCI battery emphasized executive function and visual memory, 2 domains particularly susceptible to neuropsychological decline following delirium in the studies to date [59]. The battery also thoroughly assessed domains of cognitive function plus pre-morbid intelligence using the following tests (which took 60-90 min to complete): (1) Executive Function – Trail Making B [132]; Stroop Interference Test [133], and Category Fluency [132] ; (2) Mental Processing Speed – Digit Symbol Coding [124]; (3) Global Cognitive Functioning – Extended Mini Mental State (3MS) [134]; (4) Memory; Visual Memory - Faces Test (Immediate, Delayed, and Recognition Trials) [135] and Rey-Osterrieth Complex Figure - Delayed Recall [136]; Verbal Memory - Rey Auditory Verbal Learning Test [136]; (5) Attention/Concentration – Trail Making A [132] and Digit Span [135]; (6) Visuo-Spatial Construction – Rey-Osterrieth Complex Figure – Copy [136]; (7) Pre-morbid Intelligence (to calculate baseline intellect) – American National Adult Reading Test [137]. The tests are highly sensitive to the presence of even mild forms of cognitive impairment and have well-described population norms as well as excellent validity and reliability. This same battery of tests has been used by the Vanderbilt ICU delirium research team in hundreds of ICU survivors to date over the past 4 years.

Study Population Description

Ten ICU survivors enrolled in the BRAIN-ICU cohort study were originally planed to be studied at two time points. Due to budgetary constraints and the expiration of one case patient, only four cases and four controls were studied at two time points. Patients were determined to be cases who were delirious for at least 2 days. Previous work has indicated that this is the median duration of delirium. Patients were determined to be controls when they had not experienced delirium during their ICU stay. Both cases and controls were enrolled in the same imaging and neuropsychological testing protocols.

Inclusion Criteria

All adult survivors of the medical and non-cardiac surgical ICU already enrolled in the BRAIN-ICU and who met none of the exclusion criteria listed below were enrollment into the study. Adults (≥18 years old) in the medical or surgical ICUs were enrolled within 2 days of ICU discharge.

Exclusion Criteria

Patients were excluded if they met any of the following 5 criteria: (1) prior ICU admission within 2 months of current stay requiring mechanical ventilation >3 days, thus limiting the surrogate's ability to assess the patient's current baseline cognitive function; (2) blind, deaf, or unable to speak English, as these conditions precluded the ability to perform delirium and cognitive testing; (3) absolute or relative contraindications for MRI at the time of enrollment or reasonably anticipated in the next 3 months (e.g., presence of ferromagnetic material or devices thought to be subject to damage from MRI, or intractable claustrophobia); (4) pregnancy or planned pregnancy in the next 6 months; (5) cognitive or other neurodegenerative disease that prevented

patients from living independently at baseline (e.g., mental illness requiring institutionalization, acquired or congenital mental retardation, known brain lesions, traumatic brain injury, acquired immune deficiency syndrome, cerebrovascular accidents with resultant moderate to severe cognitive deficits or ADL dependency, Parkinson's disease, Huntington's disease, Alzheimer's disease, moderate to severe dementia of any etiology). All patients were screened for pre-existing cognitive impairment using the Clinical Dementia Rating (CDR) scale [138, 139], which has strong concurrent validity based on correlations between the scale and neuropsychological and pathological data, including Alzheimer's disease [140-143], as well as robust inter-rater reliability (with agreement between raters of >80%) [144, 145]. Patients with a CDR score >1.0 (i.e., those with moderate or severe dementia) were also excluded.

Aim 1: To characterize MRI abnormalities in ICU survivors who had delirium (cases) as compared to controls who did not. (1) For MRIs, intra and inter-patient analyses was performed along with comparing the cases (delirious patients) versus controls (non-delirious patients). Using intra-patient analysis, each patient's initial MRI data was compared to his/her 3-month imaging data. Then, using inter-patient analyses, MRI data was compared between cases and controls both initially, at 3 months, and at 3 months versus baseline. For each of these paired analyses, an established protocol was followed for spatially smoothing and temporally normalizing data for each imaging series into a statistical parameter map, from which activation maps were constructed and then t-values (applicable to Student *t* tests)[146] were calculated for a given patient's series of images. Finally, using Student *t* tests, differences were assessed within patients and between groups to determine statistical significance ($P < 0.001$, uncorrected for multiple comparisons). (2) Student *t* tests were also used to assess differences between groups

according to brain volumes after employing correctional measures [147] to permit reliable gray-white differentiation.

Aim 2: To correlate the development of brain atrophy over a 3-month period in ICU survivors with the severity of LTCI following ICU admission. (1) Long-term cognitive impairment was quantified by calculating a composite cognitive score representing a summary of neuropsychological performance across all domains and serving as an index of overall cognitive functioning. Additionally, average T-scores for the individual domains of the battery was calculated for both groups. Statistical analysis was then performed using Student *t* tests to assess mean change in test scores between the cases and controls to determine differences. Both within patients and across groups, the composite cognitive score and the average T-scores for individual domains were then correlated with imaging parameters of interest from Aim 1. (2) For each brain region of interest (ROI), activation and volumetric measurements for fMRI, respectively, were examined for relationships between different cognitive domains and MRI data.

Human Subject Research Considerations

All study materials were collected and recorded solely for research purposes. The socio-demographic, clinical, and outcomes information collected during this investigation were obtained from multiple sources, including subjects directly, the electronic medical record, observational data, and the BRAIN-ICU study database. These data were recorded on case report forms designed specifically for the study and entered into a secure electronic database, using direct electronic transfer when possible and manual entry when necessary (e.g., neuropsychological tests results). All data were secured by password-only access for the purpose of confidentiality. A main source of data for the ICU and ward hospitalization was an electronic chart abstraction utilizing the patient's electronic medical record. Permission was requested of all

subjects to abstract medical record information. Progress notes, bedside nursing notes, and "flowsheet" charting were also used to collect data. All of the remaining data were derived from the interactions with the patient in the form of the physicians' and neuropsychologist's examinations and interviews.

Potential Risks to Subjects

All nursing interactions from which delirium data was derived as well as clinical data acquisition (except as noted in the subsequent two paragraphs) were standard of care at our institution. There were no known major risks with MRI scans. Claustrophobia and the presence of pre-existing, ferromagnetic material were exclusion criteria. The risks associated with participation in neuropsychological testing was minimal. During screening, the patient and family may have been inconvenienced because of the need to answer questions regarding presence of pre-existing cognitive impairment. The possibility exists that a subject experienced a degree of emotional discomfort related to learning about the existence or severity of cognitive deficits.

Adequacy of Protection Against Risks

Exhaustive efforts have been taken to prevent loss of anonymity. The study database contains identifiable data (addresses, date of birth, phone numbers, admission dates, etc.). This was required to coordinate completion of the 3-month follow-up components of the protocol. For this reason, there were several layers of security to protect privacy. Confidential patient information collected as part of this study has been stored at Vanderbilt University Medical Center in the office of the Principal Investigator, Dr. E. Wesley Ely. Electronic data was entered into password-encrypted electronic files where only the PI and co-investigators knew the passwords. The file server was accessed by username and password, neither of which were recorded

anywhere to prevent discovery. Virus scanning software ran on the server daily. The server is part of the larger VUMC network that is insulated from the larger internet by a firewall. Data on the server was stored on a redundant array (RAID level 5) of disks. The server was password protected and physical access to the server is limited by locked doors. Server power was protected by the use of an APC model 1000 UPS. Data was protected by daily backups to cartridge tape. Monthly backup tapes were stored in a secure off-site location. All hard copy data, such as neuropsychological testing battery, were stored in a locked filing cabinet, with data for each patient being contained in an individual folder identified only by study ID number. These data were collected only by Study Personnel and entered by Study ID only in a password-protected database. Access was permitted only to the investigators and the study personnel who conducted the testing. All databases were stored on secure servers that were password protected. A separate key was also stored in a separate locked filing cabinet in a different location than office of the Principal Investigator, that contains the names and contact information of study patients. This key linked these patients to their assigned study ID numbers, and has only been used by study staff to identify patients in order to contacting them at follow-up intervals. All study personnel who were required to access patient files (e.g. to score cognitive tests, enter data, etc.) obtained IRB approval and have completed Human Protection Training. Additionally, the author of this dissertation has obtained official UGA IRB approval to analyze these data (UGA IRB Project Approval Number: 2008-10410-0). Trained healthcare workers and supplies were on hand for the possibility to treat the extremely rare occurrence of side effects or potentially adverse reactions associated with MRIs. Additionally, doctors were available during the scan to provide any needed care. The data collection team met extensively with Vanderbilt radiologists and patient surgeons to plan the sequence of testing procedures.

Participant Recruitment

The current study focused on a population composed of 10 patients. Of these, one expired, and one declined to participate in the three month follow-up. Therefore the final analysis consists of a sample size of 8. Baseline demographic and other data obtained at the time of hospital discharge found no statistically significant differences between groups with regard to age (51.9 vs. 53.3 yrs, $p = 0.61$) or severity of illness as measured by APACHE II (26.2 vs. 25.5, $p = 0.67$). Statistically significant differences did however exist between cases and controls on measures of depression and mental status at the time of hospital discharge which is consistent with previous accounts [59]. The average number years of education was significantly lower for the cases versus the controls group (10.3 vs. 12.0 yrs, $p = 0.05$). The duration of mechanical ventilation was similar between the cases and the controls (median, 6 days [interquartile ranges, 4–11 for cases] vs. 5 days [3 to 9], $p = .81$). The length of stay in the ICU for cases vs. control patients was 11.9 days (9–14 days) vs. 11.4 days (9–13 days), $p = 0.91$. The length of stay in the hospital for cases vs. control patients was 20 days (15–26 days) vs. 22 days (18–28 days), $p = 0.45$. Discharge characteristics were very similar between the groups. Most cases (3 out of 4) went to another healthcare facility (rehabilitation), and one went home directly. These proportions were exactly the same for the controls.

In this case-control study, eight adult survivors of the medical and non-cardiac surgical ICU already enrolled in the BRAIN-ICU study of acute lung injury and who met none of the exclusion criteria were enrolled into this study. The BRAIN-ICU study sought to enroll consecutive adult ICU patients in order to develop biochemical markers for the development of LTCI. Adults (≥18 years old) in the medical or surgical ICUs were enrolled within 2 days of ICU discharge. The study and all its components was developed in keeping with published ethical

conduct standards for the American Thoracic Society [148]. Informed consent guidelines were followed in accordance with Vanderbilt University Medical Center institutional review board. The attending medical and/or surgical team was fully informed of the nature of the study and any risks and benefits. Study coordinators visited the ICUs daily, following IRB-approved and HIPAA-compliant procedures to identify candidates for enrollment. Once a potential participant was identified, the coordinator or investigator approached the patient regarding possible participation in the study.

Functional MRI (fMRI) Image Analyses

Images were reoriented, realigned (residual motion < 1 mm in all planes), normalized to a T1 template from the Montreal Neurological Institute [149] and smoothed using a 7 mm full-width at half maximum gaussian kernel within the SPM5 software suite (http://www.fil.ion.ucl.ac.uk/spm). The data was then high pass filtered using the default 128 second cutoff period in order to correct for signal drift. SPM5 was used to calculate statistical parametric maps using the general linear model (GLM) with no grand mean scaling and SPM's canonical hemodynamic response function.

Group statistical parametric maps were used to calculate t-test statistics at the $p < 0.001$ level (uncorrected for multiple comparisons) in a fixed effects analysis [150] with a cluster size extent threshold of 8 voxels in order to reduce false positive activations [151]. Coordinates for the most significant voxels within active regions are reported along with z-scores in the results section. Anatomical locations were determined at the group level using automated anatomical labeling [152] and are displayed on the MNI canonical composite T1 brain [149]. To calculate region of interest (ROI) data, signal intensity was averaged across the ROI for each participant [153].

Voxel Based Morphometry (VBM) Image Analyses

After reconstruction, the scan data were resampled to isotropic 1 mm voxels, aligned visually to the AC-PC plane using BRAINS software [154] and reformatted to the axial plane. VBM was performed using custom Matlab scripts, implemented according to the methods described by Ashburner and Friston, and Good et al. [155, 156]. The AC-PC aligned SPGR data were resampled to 1.5 mm voxels and segmented to extract grey matter (GM) maps. GM maps were then spatially normalized to the GM prior probability template using a 12 parameter model including nonlinear basis functions within SPM5. The normalized scans were smoothed using an isotropic spatial filter with a full width half maximum of 12 mm to help adjust for individual differences in gyral anatomy. The smoothed normalized GM maps were subjected to statistical parametric mapping on a voxel-by-voxel basis using a general linear model as implemented in SPM5.

Diffusion Tensor Image (DTI) Analyses

Diffusion-encoded images were acquired parallel to the AC/PC line, with a single-shot echo-planar sequence: 128 x 128 acquisition matrix, 1.71 x 1.72 x 4 mm; reconstructed to 0.86 x 0.86 x 4 mm; 40 axial slices; 220-mm field of view; TE 62 ms; TR 7390 ms; flip angle 90 degrees; slice gap 0 mm; 3 averaging per slice; b-factor of 600 s mm x 2. With the baseline image and no diffusion weighting [0, 0, 0], diffusion-weighted images were acquired from six different directions. Magnitude Fourier-transformed images were transferred in Phillips PAR/REC format and then converted into Neuroimaging Informatics Technology Initiative (NIfTI) readable form, using in-house written Matlab (MathWorks Inc., Natick, MA, USA) routines. The diffusion-weighted images were then corrected for any spatial distortions induced by eddy currents, using a modified SPM5 algorithm, designed to minimize mutual information between the diffusion-

unweighted and -weighted images. After the generation of diffusion tensor matrices from sets of diffusion images, (anisotropic diffusion coefficient) ADC maps were generated in accordance with the methods described by (Basser and Pajevic, 2000).

DTI images were coregistered with the high-resolution T1 images. The T1 images, in native space, were then transformed into T1 Montreal Neurological Institute (MNI) templates, and the coregistration and normalization parameters were applied to the ADC map. Finally, these normalized ADC data were smoothed using a Gaussian kernel of 10 mm full width at half maximum. The ADC values were then compared between the cases and the controls, using the two sample t-test within SPM5. Results of the statistical analyses were expressed with a threshold of uncorrected $P < 0.001$ and 8 contiguous voxels, without global normalization, considering the ADC maps to represent the images with absolute values.

RESULTS

Patient Characteristics

On average, participants were 55.7 years old, with 11.6 years of education. Over half had impairment in activities of daily living, and most had preexisting cognitive impairment. During hospitalizations, 89% of participants were rated as moderately ill, and 11% as mildly ill. All cases had over 2 days of continuous delirium according the CAM-ICU criteria. During delirium, an average score of 18.1 on the MMSE indicates significant cognitive impairment. Mean scores on the forward and backward digit span and vigilance tests indicate substantial impairments in attention. The cause of delirium on medical record review was felt to be multifactorial in the majority of cases, with the most common contributing factors being medications, infection, dehydration, metabolic derangements, hypoxia, and immobility.

Functional MRI Results

The results of fMRI Simon arrow task revealed wide-spread activation differences in the frontal and parietal cortices of cases compared to controls (Table 4 and Figure 4). These differences represent significantly smaller signal intensities for patients who experienced delirium. Peek differences were observed in the posterior cingulate cortex (PCC; x = +/-4, y = -52, z = 33; t = 8.16) for cases compared to controls. This was a medium size cluster (131 voxels) that could be seen in both hemisphere's of the cortex (left sided activation cluster = 78 voxels). Results also revealed activation differences in the anterior cingulate cortex (ACC), visual cortices bilaterally, and a small cluster in the rolandic operculum (cluster size = 11 voxels). The results of the fMRI visual N-back task revealed significant differences primarily in the prefrontal cortex for cases compared to controls (Table 5 and Figure 5). Peek differences were observed in the dorsal lateral prefrontal cortex (DLPFC; x = +/-40, y = 21, z = 31; t = 7.96) for cases compared to controls. Cases also exhibited significantly lower signal intensities in the PCC, the left precentral gyrus, the right dorsal parietal cortex, and medial parietal cortices. Most of the clusters were of medium to smaller size, with the largest observed in the dorsal posterior parietal region.

Voxel Based Morphometry Results

GM densities in the whole brain were calculated using a critical significance threshold $p < 0.001$, uncorrected for multiple comparisons at the voxel level and minimum cluster size of 8 contiguous voxels. Areas of GM reduction in cases included the cingulate, hippocampus, hypothalamus and distributed regions in the prefrontal cortex, (Table 6 and Figure 6). Peek differences were observed in the hippocampus (x = -18, y = -30, z = 9; t = 8.01) for cases compared to controls. Delirious patients also exhibited significant differences in grey matter volumes in the posterior and anterior cingulate cortices, as well as the thalamus. Cluster size

differences were relatively small, with the greatest volume difference being observed in the hippocampus. Group differences in white matter volumes (WM) revealed marked decreases in volumes for cases compared to controls in both the corpus callosum (CC) and the anterior cingulum bundle (aCB) (Table 7 and Figure 7). Peek differences were observed in the corpus callosum at (CC; x = +/-5, y = -50, z = 33; t = 7.22) for cases compared to controls. Delirious patients also displayed significantly lower white matter volumes bilaterally in the anterior cingulum bundle. Group differences in cerebral spinal fluid (CSF) volumes suggested increases in CSF volume for cases compared to controls surrounding the lateral ventricles (LV) and the 3rd ventricle (Table 8 and Figure 8). Peek differences were observed in the lateral ventricles (LV; x = +/-19, y = -3, z = 22; t = 6.18) for cases compared to controls. The cluster sizes were relatively small ranging from 53 voxels in the right ventricle to 11 voxels at the 3rd ventricle.

Diffusion Tensor Imaging Results

Qualitative fractional anisotropy differences were observed between cases and controls; however, since only half of the patients were able to complete the scanning protocol in order to acquire DTI data, it was not possible to conduct a quantitative statistical analyses. In the right anterior cingulum bundle (CB), mean FA values in patients and control subjects were 0.445 and 0.488, respectively; in the left anterior CB, they were 0.471 and 0.535, respectively (Figure 9). Although these numbers appear to be quite similar, it is important to note that the standard deviations of FA values are typically quite small (e.g. in the range of 0.005%); unfortunately it was not possible to calculate standard deviation estimates in the current sample due to the low number of patients completing the DTI protocol. FA values in the right and the left posterior CB appeared to be quite similar (0.502 and 0.503 respectively), suggesting meaningful differences in anisotropy may not have been present in those regions.

Region of Interest Results

Delirious participants had significant ($p < 0.05$) decreases in regional blood flow ratios in the DLPFC and PCC (Figure 10). There was a trend towards significant differences in the hippocampus ($p = 0.067$) for cases compared to controls. A fourth ROI analysis was conducted in the brainstem that did not yield any statistically significant differences between groups for either of the behavioral tasks.

Behavioral Results

Behavioral data collected in the scanner were primarily used as regressors to optimize fMRI analyses. These data were entered into SPM's GLM equation used to produce statistical brain maps. Specifically, the experimenter recorded patient's responses (i.e. correct vs. in-correct) and reaction times to the Simon arrow and n-back tasks via the hand response pads. Using behavioral data as predictors for fMRI results allows one to more accurately account for brain activation that is associated with a participant's responses; said another way, behavioral regressors make fMRI results more sensitive and provide additional assurance that the patterns of brain activation that are observed covary with what the patient was physically doing while inside the scanner.

Clinical Measures

Neuropsychological test results are depicted in Table 10. The mean raw test scores for the cases and control patients are presented in Table 10. All case patients demonstrated RBANS age normed impairment on at least one measure, four demonstrated memory impairment on at least two measures, and three on three or more measures. Sedation scale scores (Richmond Agitation Sedation Scale) was worse (although not significantly so) for cases than the controls (2.8 vs. 2.0, $p = .32$), as were mean scores on the Glasgow Coma Scale (GCS; 8.3 vs. 10.9, $p = .26$). At three

month follow up, the mean BDI score for the cases was significantly higher (i.e., more depressed) than the mean score of the controls (24.1 vs. 8.0, $p < 0.03$) , and 3 out of 4 of the cases met criteria for clinically significant depression compared to only 1 control respectively. Significant differences were also observed in quality-of-life scores (Short Form Health Survey) between groups at follow up for Mental Component Summary (40.2 vs. 50.7, $p < 0.05$) but not for the Physical Component Summary (34.9 vs. 35.1, $p = 0.91$).

Correlational Results

Correlational analysis was performed between neuropsychological age-normed T scores and ROI functional signal intensity values during both the Simon arrow and n-back tasks. A correlational region of interest analysis was performed in the dorsal lateral prefrontal cortex (DLPFC), the posterior cingulate cortex, the hippocampus and the brainstem for each of the behavioral tasks (See Figure 11). Digit Span was used as a measure of working memory. The switching condition of the Trails B was used as a measure of executive functioning and Word Lists Delayed Recall was used to measure semantic memory retrieval. Correlational analyses revealed a statistically significant ($r = 0.93$; $p < .001$) relationship between signal intensity in the left dorsal lateral prefrontal cortex (DLPFC) during the Simon arrow task and individual scores on RBANS subtest Trails B, age normed T-scores at three month follow up. An additional highly significant relationship was observed between the functional signal in the left posterior cingulate cortex (PCC) during the n-back task and individual scores on RBANS subtest Digit Span and age normed T-scores at three month follow up ($r = 0.88$; $p < 0.004$). A third analyses revealed a statistically significant ($r = 0.91$; $p < 0.01$) relationship between signal intensity in the left hippocampus during the n-back task and individual scores on RBANS subtest Digit Span, age normed T-scores three month follow up.

Correlational analysis was also performed between neuropsychological test scores and the three types of segmented brain matter, grey matter (GM), white matter (WM) and cerebral spinal fluid (CSF) volumes. Higher left dorsal lateral prefrontal cortex (DLPFC) GM density correlated with greater executive functioning ability ($r = 0.61$, $p < 0.05$); a trend towards significance was observed between hippocampal GM volume and Digit Span scores ($r = 0.56$, $p = 0.08$).

DISCUSSION

Results of the current study revealed a striking picture of neurological degradation across imaging modalities in delirious patients compared to controls. Most notably, these differences were related to declines in specific cognitive abilities as measured by a formal neuropsychological assessment. Furthermore, the losses in patient's cognitive abilities appear to be related to functional and morphological changes in the brain. The following section will attempt to integrate and interpret these findings with what is currently known about ICU delirium and related neurocognitive decline.

In order to understand delirium and its long-term consequences, it is necessary to explain acute brain dysfunction at the neurological level. Delirium research has only recently begun to employ neuroimaging techniques. The studies discussed below help provide a precedent and context from which to interpret the MRI results reported above. At present, only a handful of neuroimaging studies have evaluated delirious patients [157-159]. These investigations, along with the present study, have provided the first clues that delirium may manifest via widespread brain dysfunction rather than localized disruption [77, 160]. Broadly speaking, the data from the current study replicate and extend these findings.

fMRI: Functional Neuroimaging and Delirium

The results of the functional neuroimaging data suggested that several parts of the brain may become less active during attention and memory tasks for ICU patients who experienced delirium compared with those who did not. Additionally, areas which demonstrated reduced functional activity also showed signs of grey matter atrophy at 3-month follow-up.

In order to understand these results, it is useful to place them in the context of what neuroimaging work has been conducted with delirious patients. Recent advances in functional neuroimaging have offered a much needed window into the effects of delirium on the brain. The first of these studies was reported by Yokota et al. [157]. Using xenon-enhanced CT to measure blood flow during and after acute delirious states, this study [157] reported that delirious patients experienced a 42% reduction in overall cerebral blood flow (CBF). Furthermore, there were even greater decreases in subcortical and occipital regions [157]. This overall decrease in CBF suggests that *acute* delirium may indeed manifest via widespread brain dysfunction rather than localized disruption [77, 160]. It is important to note that the Yokota study examined *acutely* delirious patients where as the present investigation scanned participants several days after acute delirium subsided. Additionally, although the current study did not measure perfusion directly, functional MRI has been used as a proxy for cerebral metabolism and integrity [161-164]. Global hypoperfusion had the potential to cause several of the long-term changes associated with prolonged delirious states, including autophagy [165, 166], LTCI [167, 168] and loss of tissue [69]. More recently, Fong et al. [158] used single photon emission computed tomography (SPECT) to examine geriatric patients during and after *acute* delirious episodes. Like the Yokota et al. [157] study, their results indicated wide-spread hypoperfusion with marked decreases in

regional cerebral blood flow (rCBF) in the occipital lobe and brainstem. In a recent case report, Kitabayashi and colleagues [159] scanned a patient suffering from delirium tremens. Consistent with the Fong [158] and Yokota [157] investigations, Kitabayashi et al. [159] also described a reduction in blood flow for multiple areas of the brain.

In the current study, although there were no statistically significant changes in the BOLD response in the brainstem area, this is in many ways not surprising in light of the previous neuroimaging investigations of ICU delirium. In particular, the tasks that were used in the current study were not designed (nor expected) to activate the brainstem regions. A major difference between the Yokota, Fong and Kitabyashi investigations is that patients were imaged *during* acute delirious states. This was not the case for the current study. Consistent with the hypotheses that sedatives and analgesics bring about delirium by acting on the brainstem [169-172], these data make sense that the ARAS may have indeed exhibited relatively normal activity during both baseline and three month scanning time points.

VBM: The Neuroanatomical Correlates of Delirium

Several reports have documented long-term cognitive and behavioral sequelae of delirium (i.e. declines in intellectual functioning) [19, 59, 173] and these are presumably attributable to underlying cellular changes in the brain; however, to the best of the author's knowledge, the data presented in the current study represent the first attempt to systematically quantify volumetric cerebral differences associated with ICU delirium. VBM measures in the current pilot data set suggested that key neuroanotomical structures exhibited significantly reduced structural densities in gray and white matter regions associated with executive functioning and memory. Specifically, compared to controls, cases displayed lower grey matter volume in the dorsal lateral

prefrontal cortex, the dorsal anterior cingulate, the posterior cingulate cortex and the hippocampus, even when controlling for overall gray matter volume and time one group differences. Interestingly, controls exhibited reduced blood oxygen level dependent response at time one in these same regions. In order to better understand and interpret these results in light of the pertinent literature, several imaging studies are reviewed below and compared to the current data.

A number of studies have used CT or MRI to examine lesions or other structural abnormalities associated with delirium [55, 71, 174-184]. Frank hemorrhage or ischemia may cause delirium. In these examples [175-184], delirium is more likely to have been an effect rather than the cause of a stroke. Other studies, however, suggest in many instances delirium may have a more insidious relationship and perhaps predictive relationship to grey and white matter lesions [55, 71, 174]. An early CT study reported atrophy surrounding the cerebral ventricles in elderly psychiatric patients experiencing delirium compared to matched controls [68]. Furthermore, the degree of atrophy was related to patients' Mini Mental-State Examination (MMSE) scores. In line with the results from the current study, this study [68] also reported that patient's had evidence of cerebral infarctions and hemorrhages in frontal and parietal regions. Conversely, some reports [184] have found little or no association between delirium and neuropathology. It is important to note however that neither of these investigations [184] and [68] employed quantitative analytic techniques (e.g., VBM) to report the degree of atrophy.

As post-ICU syndrome and delirium related LTCI have gained increasing attention in the critical care literature, other reports have also begun to support the notion that suggest that major neuroanotomical changes may indeed occur in patients suffering from prolonged delirium [55,

174]. For example, CT scans revealed that 61% of critically ill patients were found to have either gross white and grey matter atrophy, white matter lesions and hyperintensities, cortical and subcortical lesions, and ventricular enlargement [55]. In an early study, Figile et al. [71] observed that delirious patients undergoing electroconvulsive shock therapy (ECT) exhibited white matter abnormalities and lesions in the basal ganglia compared to controls. These reports have provided essential descriptions for potential links between anatomical changes and delirium [55, 174]. It is the hope that data from the current study can replicate and extend these findings in order to better understand, treat and prevent ICU delirium and the associated LTCI.

DTI: White Matter Tractography

DTI results from the participants who were able to remain in the scanner long enough to acquire these data revealed marked declines in fractional anisotropy for white matter tracks in the frontal lobe. These findings appear to correspond with the general clinical presentation of post-ICU patients suffering from LTCI. Additionally, degradation of axonal tissue is not only consistent with the handful of delirium studies which have gathered neuroradiological data, it is also internally in-line with the voxel based morphometry segmentation analysis of white matter from the current participants. Each of these topics will be examined in the following sections.

Most notably, in two studies Alsop and colleagues [55, 174] reported that the majority of critically ill patients who were examined exhibited white matter lesions as well as hyperintensities in cortical regions, many of which were either located in, or connected to the frontal lobe. Another study [71] found that ECT related delirium was associated with white matter abnormalities and lesions in the basal ganglia. Hopkins et al. reported similar findings [55] and suggested that these positive neuroradiological results were most closely linked to

deficiencies in processing speed. Broadly speaking this fits with a large neuropsychological literature which has observed relationships between axonal volume and processing speed deficits [185-187].

Despite the potential importance of these findings, these results also raise several questions. For example, at present, the causal mechanism for white matter decline following ICU delirium remains elusive. Along with other neurological changes (e.g. gray matter and white matter), it is a case of chick and the egg; that is does degradation in grey matter lead to losses in white matter density or vice versa? Or is it possible that a third unnamed variable (e.g. global hypoperfusion) is the causal factor for both? Such questions are difficult to answer at the present time and may be more feasibly examined via animal models.

Within the current data, in many ways it is not surprising to find potentially meaningful differences in diffusion anisotropy coefficients in the same regions which exhibited statistically significant declines in white matter volume. Stated another way, voxel based morphometry segmentation routines identified differences in case's white matter volumes in virtually identical regions to those that showed FA differences. Additionally, these overlapping tendencies in the data (i.e. functional loss of prefrontal white matter tracts) provides validating support for this interpretation of the data as proof of principal. Regardless, these data should nonetheless be interpreted with caution and as preliminary given the small sample size and the nature of fixed effects analyses. Future delirium studies examining the same outcome variables will provide much needed replication and extension of these findings and will determine to what degree the current results can be generalized to larger ICU populations.

There are several conclusions that can be drawn from these data. The most important however may be information that can be quickly and readily applied to what is currently known about ICU delirium and how this state may be a red flag to physicians that brain damage is occurring. Sedatives and analgesics appear to represent the leading modifiable iatrogenic risk factors for transitioning from normal cognitive functioning to delirium in the ICU [84-86, 88-91]. Marcantonio et al.[91] reported an association between benzodiazepines and meperidine and delirium and Pandharipande colleagues [171, 188, 189] recently reported that the administration of benzodiazepines was a strong independent predictor for the development of delirium in both surgical and trauma ICU patients. These studies have also suggested that alternative agents which do not impact the CNS directly (i.e. somatic agents such as dexmedetomidine or other muscle relaxants) may be much safer alternatives [35]. Additionally, Dubois et al. [86] have shown that narcotics (morphine and meperidine) may be associated with delirium in medical and surgical ICUs and Inouye [84] concluded that benzodiazepines, narcotics, and other psychoactive drugs are associated with a 3- to 11-fold increased relative risk for delirium. Taken together, all of these studies suggest that delirium in ICU patients may be an alarm signal for CNS organ dysfunction. The data in the current study provide clues to the nature of the functional and anatomical degradation that may occur when delirium persists for a sufficient length of time.

Unfortunately, it remains the case that even today in ICUs around the world, patients are still frequently subjected to prolonged and massive exposure to sedatives and analgesics [84-86, 88-91]. In fact, recent survey data [44] suggest that lorazepam remains the treatment of choice for delirium and is frequently administered in excess of 50 mg/day by a the majority of current

ICU professionals. Over 90% of ventilated patients receive benzodiazepines and opiates [107, 190] to improve oxygenation, alleviate agitation, and prevent removal of support devices. Unfortunately, the quantity and dosing intervals are largely based on "clinical judgment" [44] rather than evidence based guidelines. It is common to find both young and old patients in a state of drug-induced suspended animation [191]. Considering the role of age as a susceptibility factor to the development of long-term cognitive impairment, it is also striking that physicians rarely modify the quantity or dosing intervals of these drugs based on a patients' age. This flies in the face of evidence that, for many drugs, aging results in reduced or altered metabolism [192, 193]. It is clear that large doses and extended use of sedatives and analgesics often result in over sedation that may be reduced but not eliminated through the use of clinical protocols [191, 194-197].

Past studies of the relationship between sedatives, analgesics and outcomes have used total drug dose to estimate exposure [198-200]; however, it has been recognized for over 2 decades that drug responses for essentially all medications exhibit inter-individual variability, often marked, when drug dosage alone is considered. This is because the associated drug level leading to a response is determined by the interaction of genetic, environmental, age, and disease factors modulating drug disposition including distribution to the brain and other organs. By contrast, there is frequently a better quantitative relationship between a drug's plasma concentration and its effects. In healthy volunteers and critically ill patients, for example, a relationship exists between levels of sedation induced by short-term midazolam and morphine infusions and their plasma concentrations [201-203]. Accordingly, the understanding of the association between drug exposure, delirium and LTCI may be enhanced by further examination of plasma levels of psychoactive drugs to which the patient is exposed. These are important

questions to answer but would require much larger samples in order to understand the effects of these agents in the context of neuroimaging.

Study Limitations

There are several limitations for the current study, the most obvious being the sample size. Because the sample size is so small (even by neuroimaging standards) it only allows one to draw very preliminary conclusions. This is in particular the case given the way that the data were analyzed using a fixed rather than a random effects analysis. Despite this, it is important to note that random effects (i.e. multi-level modeling) have only recently become the norm in neuroimaging studies. Most PET, SPECT and fMRI experiments conducted prior to 2000 employed fixed effects analyses [204].

In theory, the implication of a fixed effects analyses is that these data are less readily generalized to a larger population [204]; however, fixed effects analysis do not rule out the ability to interpret results regarding the participants in the *current* study. Said another way, it is not the case that the results reported here are unlikely to be true for the patients who were scanned. Rather, any conclusions that can be drawn from the current data should be applied with caution to other ICU populations.

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TABLES

Table 1

Sequence of Study Procedures			
	ICU	Hospital	3-Month Follow-

	Discharge	Discharge	Up
Consent/enrollment	X		
Baseline demographics	X		
Clinical data collection	X		
MRI		X	X
Neuropsychological testing		X	X

Table 2

Sequence of MRI Procedures

MRI Procedures	
Test	Duration
Anatomical	7 min
fMRI: Simon Arrow	20 min
fMRI: N-Back	13 min
DTI	5 min
Total duration	~45 min

Table 3

Study Sample Size By Cell		
	Cases	Controls
Post Discharge	4	4
3 Month	4	4

Follow-Up		
Totals	8	8

Table 4

Brain Regions Significantly Less Active for Cases than for Controls During Simon Arrow Task After Partialing Out Time 1 Scans Via ANCOVA.

Region	Broadman area	L/R	X	Y	Z	Voxels	T score	P value
Cases Time 2 > Controls Time 2								
PCC	31	R	4	-52	33	131	8.16	> 0.001
PCC	31	L	-6	-50	32	78	7.98	> 0.001
ACC	32	L	-8	12	39	38	6.32	> 0.001
VC	18	R	11	-96	7	82	6.21	> 0.001
VC	18	L	-16	-98	8	23	6.01	> 0.001
RO	44	L	-36	25	43	13	5.55	> 0.001

Note: Coordinates listed at peak activation at 0.001 threshold; Peak Signal Difference for Cluster; Voxels list number of significant voxels in each activation cluster; Voxel size after spatial normalization = 2 x 2 x 2; L = left; R = right L = left; R = right; PCC = Posterior Cingulate Cortex; ACC = Anterior Cingulate Cortex; VC = Visual Cortex; RO = Rolandic Operculum

Table 5

Brain Regions Significantly Less Active for Cases than for Controls During N-Back Task After Partialing Out Time 1 Scans Via ANCOVA.

Region	Broadman area	L/R	X	Y	Z	Voxels	T score	P value
Cases Time 2 > Controls Time 2								
DLPFC	9	L	-40	21	31	42	7.96	> 0.001
DLPFC	9	R	43	27	33	50	7.90	> 0.001
PCC	32	L	-10	-52	32	55	7.00	> 0.001
Precentral Gyrus	6	L	-32	-3	49	60	6.70	> 0.001
Dorsal Parietal	7	R	24	-63	42	190	7.89	> 0.001
Medial Parietal	39/40	L	-37	-54	37	113	6.69	> 0.001
Medial Parietal	39/40	R	36	-55	38	59	6.13	> 0.001

Note: Coordinates listed at peak activation at 0.001 threshold; Peak Signal Difference for Cluster; Voxels list number of significant voxels in each activation cluster; Voxel size after spatial normalization = 2 x 2 x 2; L = left; R = right L = left; R = right; PCC = Posterior Cingulate Cortex; DLPFC = Dorsal Lateral Prefrontal Cortex

Table 6

Regions of Reduced Grey Matter Volumes in Cases Compared to Controls at 3 Month Follow Up After Partialing Out Time 1 Scans Via ANCOVA.

Region	Broadman area	L/R	X	Y	Z	Voxels	T score	P value
Cases Time 2 > Controls Time 2								
Hippocampus	27	L	-18	-30	9	88	8.01	> 0.001
PCC	31	R	5	-50	33	80	7.22	> 0.001
PCC	31	L	-6	-48	30	42	6.29	> 0.001
ACC	32	L	-7	10	35	10	5.98	> 0.001
Thalamus	--	L	-21	-24	10	10	5.88	> 0.001

Note: Coordinates listed at peak activation at 0.001 threshold; Peak Signal Difference for Cluster; Voxels list number of significant voxels in each activation cluster; Voxel size after spatial normalization = 2 x 2 x 2; L = left; R = right L = left; R = right; PCC = Posterior Cingulate Cortex; ACC = Anterior Cingulate Cortex

Table 7

Regions of Reduced White Matter Volumes in Cases Compared to Controls at 3 Month Follow Up After Partialing Out Time 1 Scans Via ANCOVA.

Region	Broadman area	L/R	X	Y	Z	Voxels	T score	P value
Cases Time 2 > Controls Time 2								
CC	--	--	0	27	7	198	8.58	> 0.001
CC	--	--	0	9	21	52	7.89	> 0.001
aCB	--	L	-10	9	38	48	6.77	> 0.001
aCB	--	L	-10	9	30	70	6.87	> 0.001
aCB	--	R	9	10	38	22	5.88	> 0.001

Note: Coordinates listed at peak activation at 0.001 threshold; Peak Signal Difference for Cluster; Voxels list number of significant voxels in each activation cluster; Voxel size after spatial normalization = 2 x 2 x 2; L = left; R = right L = left; R = right; CC = Corpus Callosum; aCB = Anterior Cingulum Bundle

Table 8

Regions of Increased Cerebral Spinal Fluid Volumes in Cases Compared to Controls at 3 Month Follow Up After Partialing Out Time 1 Scans Via ANCOVA.

Region	L/R	X	Y	Z	Voxels	T score	P value
Cases Time 2 > Controls Time 2							
LV	R	19	-32	18	44	6.18	> 0.001
LV	L	-19	-33	17	53	6.19	> 0.001
3rd Ventricle	--	0	-43	-31	11	5.91	> 0.001

Note: Coordinates listed at peak activation at 0.001 threshold; Peak Signal Difference for Cluster; Voxels list number of significant voxels in each activation cluster; Voxel size after spatial normalization = 2 x 2 x 2; L = left; R = right L = left; R = right; LV = Lateral Ventricle

Table 9

Neuropsychological Assessment

	Cases		Controls	
	M	SD	M	SD
RBANS				
Immediate memory index	65.8	3.0	67.9	2.7
List learning	14.1	7.2	20.7	8.1
Story memory	11.7	5.1	13.7	5.2
Delayed memory index	67.2	3.8	70.2	3.3
List, story, and figure	13.2	4.1	20.2	2.2
List recognition	18.9	3.1	21.9	1.1
Visuoconstructional index	68.9	3.3	72.9	3.4
Figure copy	8.5	4.4	8.9	4.1
Line orientation	14.3	4.7	16.3	4.2

Attention index	75.2	3.0	79.2	2.7
Digit span	4.5	2.3	8.5	2.1
Coding	30.6	10.1	36.6	9.4
Language index	88.2	3.2	90.2	2.9
Picture naming	7.1	1.5	8.4	3.5
Semantic fluency	16.5	5.5	19.5	5.1
Total	67.9	3.1	72.9	2.7

FIGURES

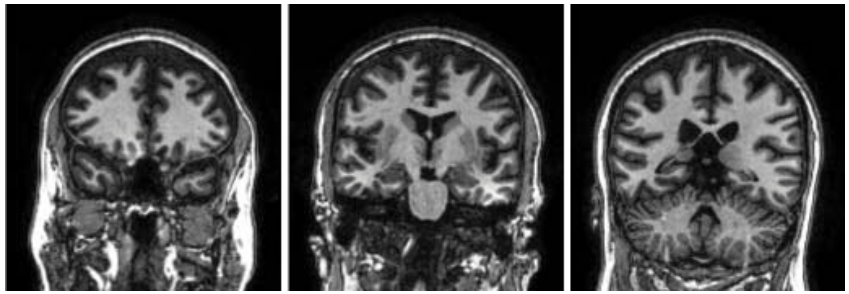


Figure 1 T1-weighted brain MRI scan slices 32 months following ICU admission demonstrating marked atrophy and enlarged ventricles.

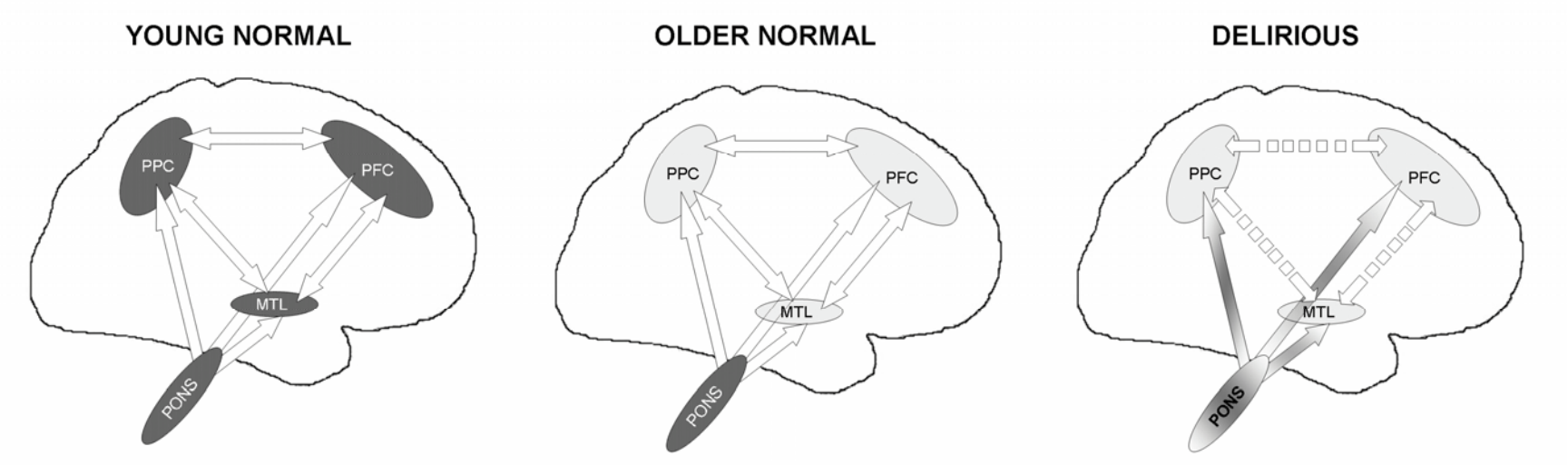


Figure 2. Duration of Delirium by Cognitive Impairment

Critical Consciousness Circuit – C3 - Delirium in critical illness is related to grey and white matter degradation in the CNS. Disruption of this critical circuit in key brain regions for cognition depicted below may result in the decoupling of functional connectivity leading to long term cognitive impairment. **1) YOUNG NORMAL:** In healthy individuals there is normal and consistent connectivity between the PPC, MTL and PFC. This circuit is innervated, activated and maintained by the ARAS arising from the brainstem via the thalamus; **2) OLDER NORMAL:** Elderly individuals begin to show signs of grey matter atrophy in the PPC, MTL and PFC. Although functional connectivity between these regions remains intact, the strength of the connections is no longer as robust as it once was in the healthy CNS. This circuit continues to be activated and maintained via the ARAS; **3) DELIRIOUS:** Individuals treated in the ICU are subject to a number of medical and pharmacological challenges which may disrupt normal CNS connectivity. Serious

illnesses such as sepsis, ARDS, and ALI as well as sedative and analgesic medications commonly prescribed in the ICU have the potential to weaken functional links between the cortical regions depicted above. This is particularly likely for processes impacting the ARAS. Fluctuations in activation arising from the brainstem may be sufficient in elderly individuals to cause a disruption which may surpass a critical threshold of functional connectivity necessary to maintain normal consciousness. In combination with exposure to other ICU related threats to cognitive function, prolonged decoupling of this circuit may lead to deleterious neurodegenerative consequences such as excitotoxicity. Over time this has the potential to result in apoptosis and long term cognitive impairment. **Note:** PPC = posterior parietal cortex; PFC = prefrontal cortex; MTL = medial temporal lobe; ARAS = Ascending Reticular Activating System

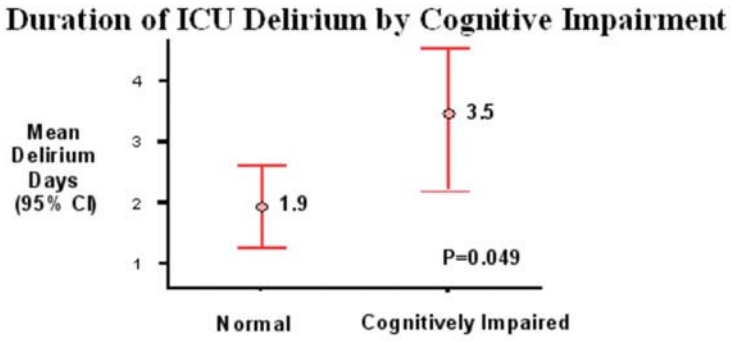


Figure 3. Patients with cognitive impairment at 3 months are delirious an average of 1.6 days longer during their ICU stay (unpublished data).

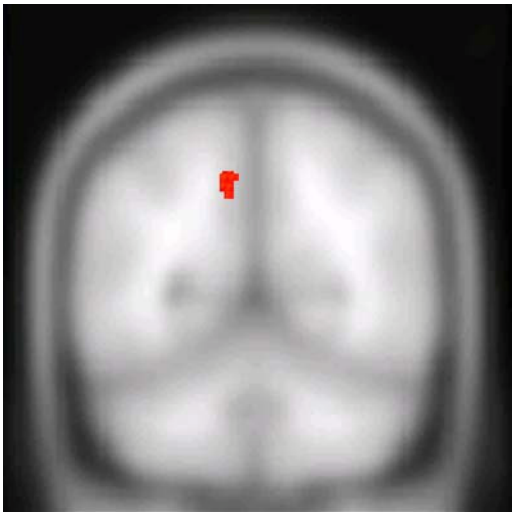


Figure 4. Cases exhibited decreased BOLD response compared to controls in several brain regions including the posterior cingulate cortex (shown) while engaged in the Simon arrow visual attention task at three month follow-up.

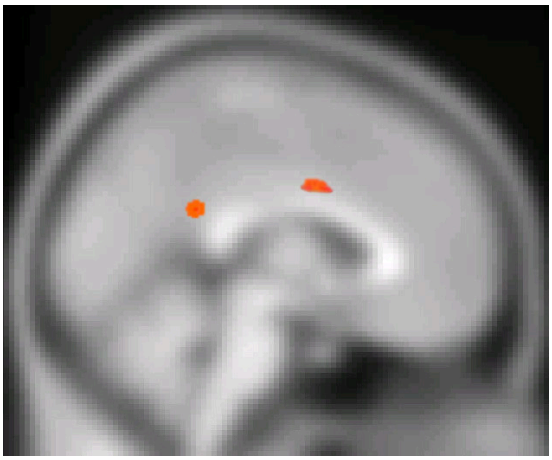


Figure 5. Cases exhibited decreased BOLD response when compared to controls in several brain regions including the anterior and posterior cingulate cortex (shown) while engaged in the working memory n-back task at three month follow-up.

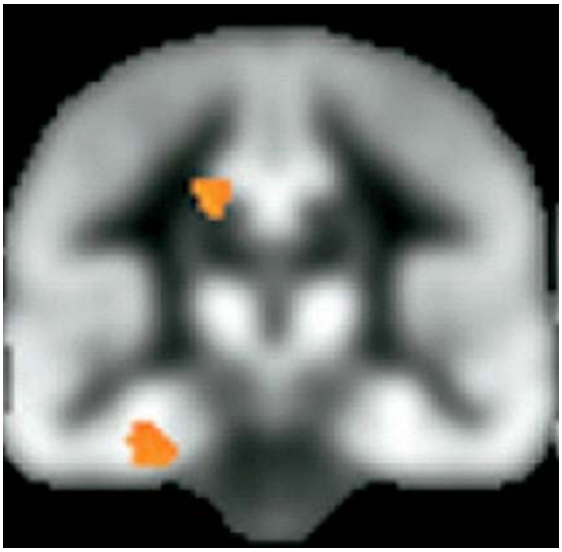


Figure 6 .Cases exhibited decreased grey matter densities in several brain regions when compared to controls at three month follow-up. Axial view reveals reduced grey may matter densities for cases in the hippocampus and cingulate cortex. B) Coronal view depicts grey matter loss in the hippocampus and the cingulate gyrus.

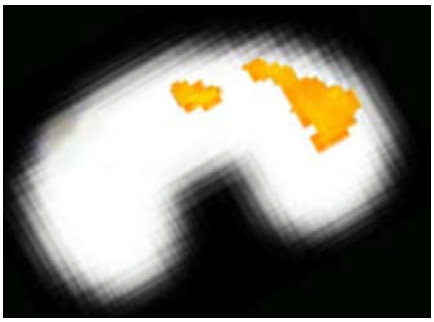


Figure 7. Cases exhibited decreased white matter volumes in several brain regions including corpus callosum and anterior cingulum bundle (shown) when compared to controls at three month follow-up.

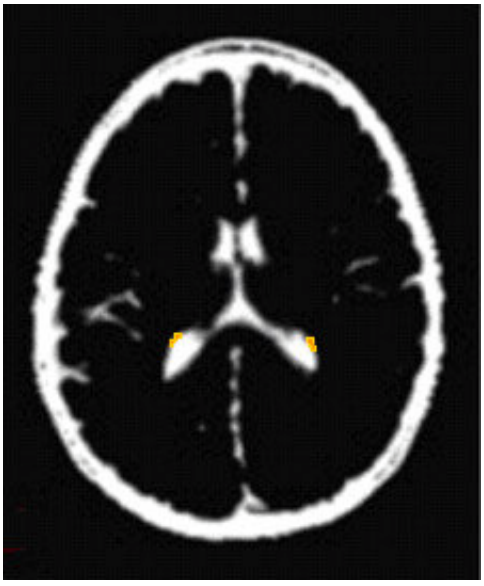
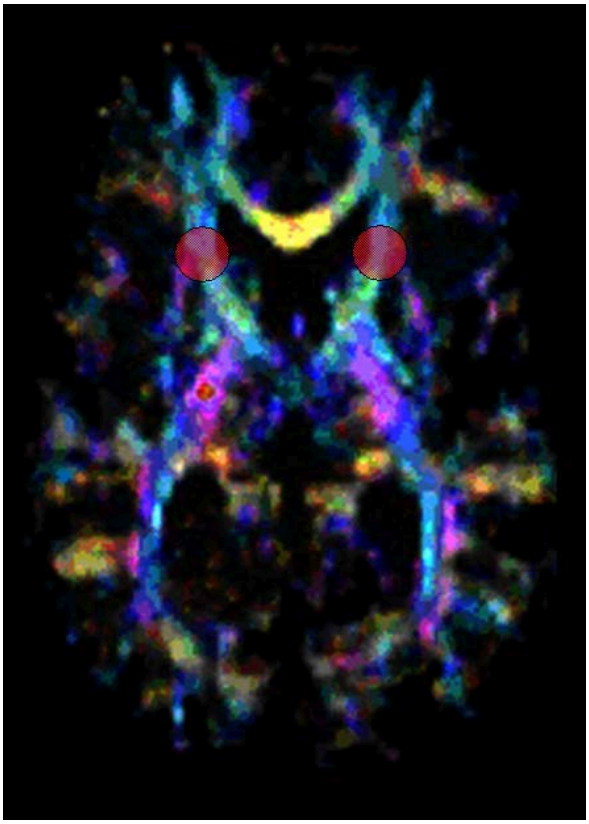


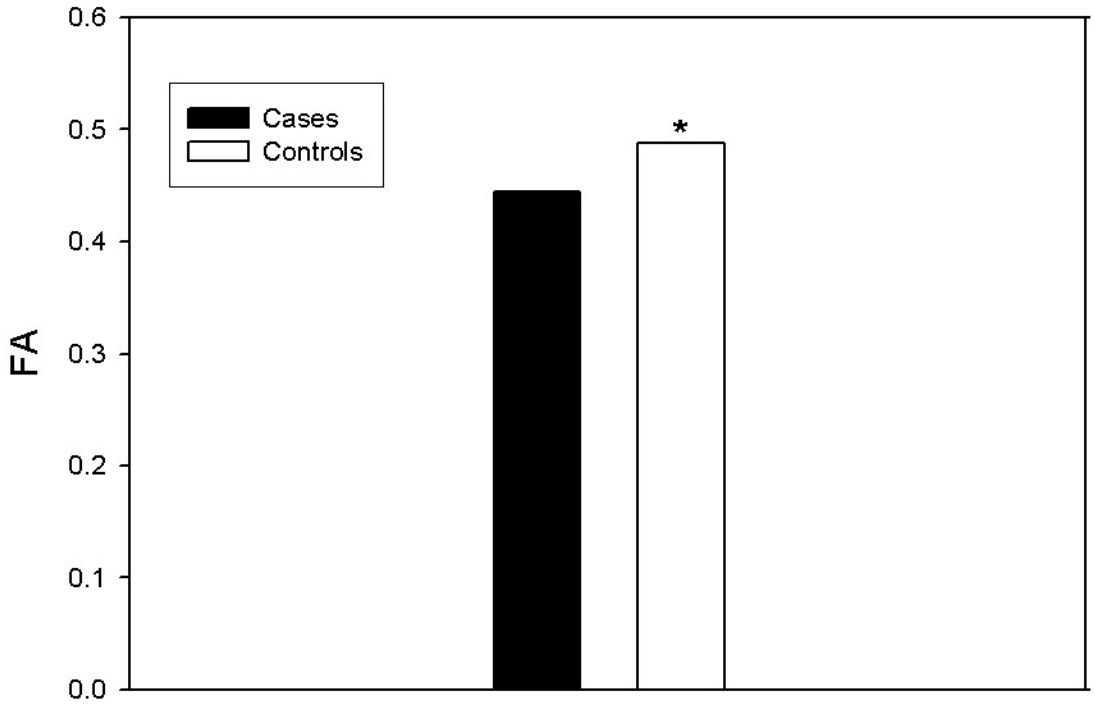
Figure 8. Voxel based morphometry segmentation routines within SPM5 enable the ability to visualize cerebral spinal fluid (CSF) volumes. Cases exhibited increased CSF volumes in the lateral as well as the 3rd ventricle when compared to controls at three month follow-up.

Figure 9

A)



B)



A) Diffusion tensor imaging (DTI) visualizes fractional anisotropy (FA), or diffusion of water molecules through white matter tracts. Yellow = medial/lateral diffusion; Blue = anterior/posterior diffusion; Red = superior/inferior diffusion. Red circles indicate the location of the statistical tests. B) Compared to controls, cases exhibited lower FA values bilaterally in the anterior cingulum bundle (aCB) at three month follow up.

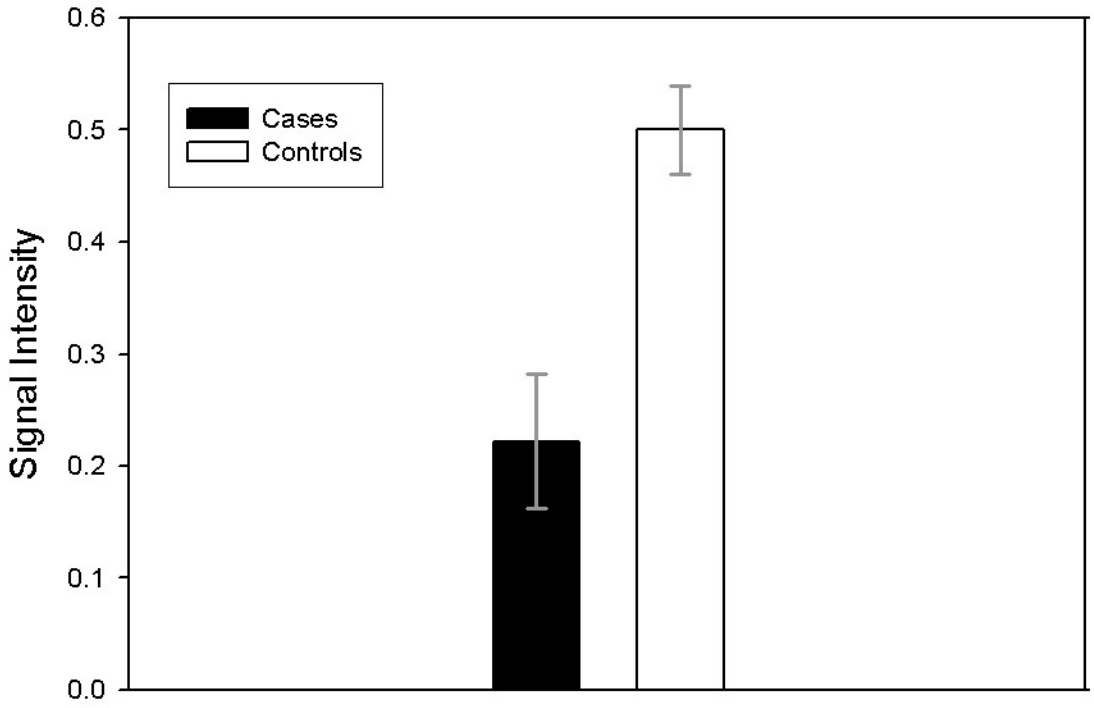
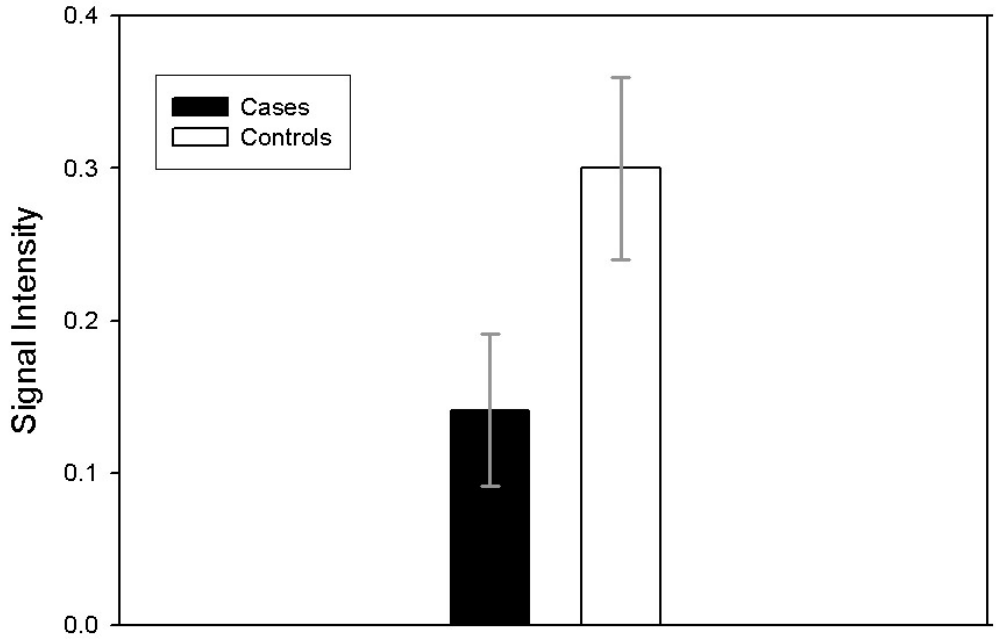


Figure 10 A. Cases exhibited lower signal intensity compared to controls in several brain regions at three month follow up. A) Cases had lower signal intensity in the dorsal lateral prefrontal cortex (DLPFC) while engaged in the Simon arrow visual attention task. B) Cases had lower signal intensity in the posterior cingulate cortex (PCC) while engaged in the n-back working memory task. C) A trend was observed for lower signal intensity in the hippocampus in cases compared to controls for the n-back task. D) No statistically significant differences were observed between cases and controls in the brain stem for the Simon arrow task.


0.4
0.3
0.2
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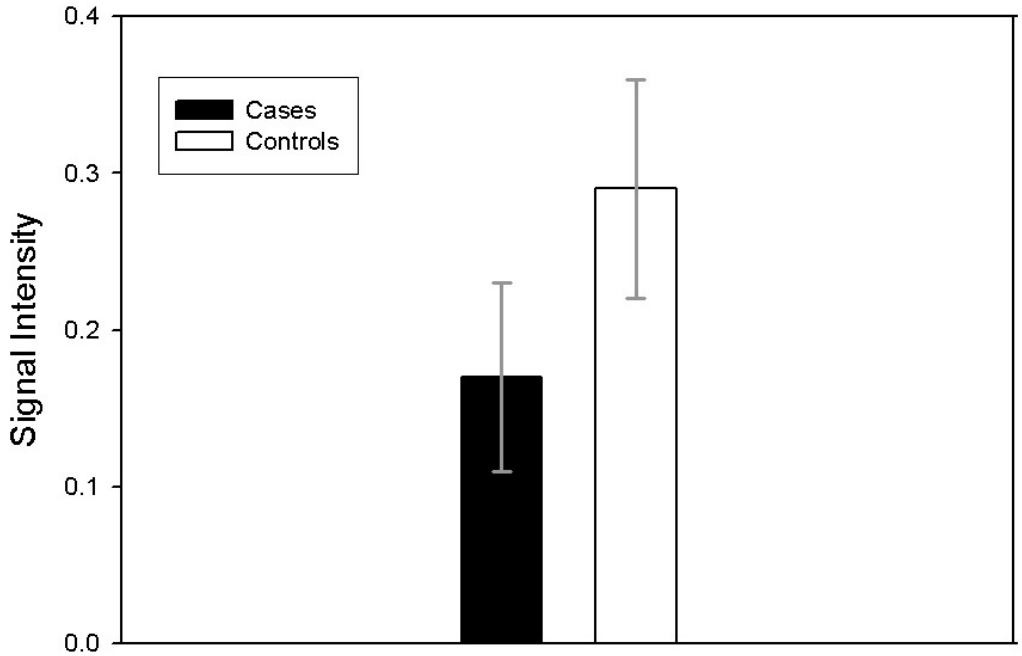
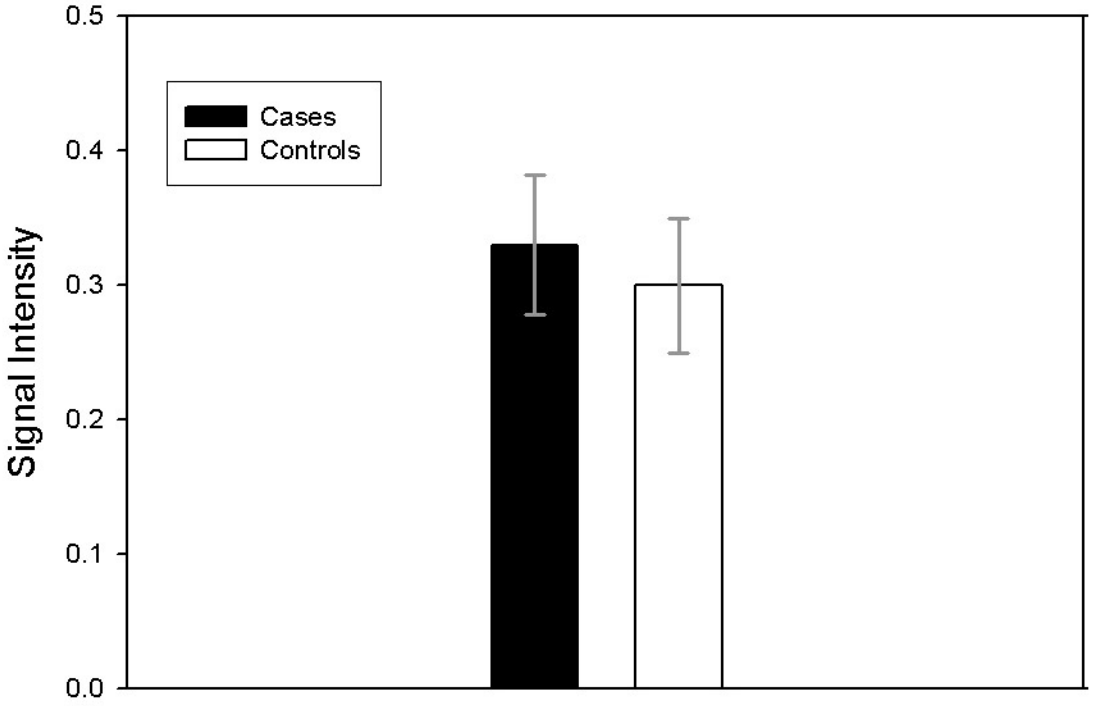
Signal Intensity
Cases
Controls

B)


0.4
0.3
0.2
0.1
0.0
Signal Intensity
Cases
Controls

C)



D)

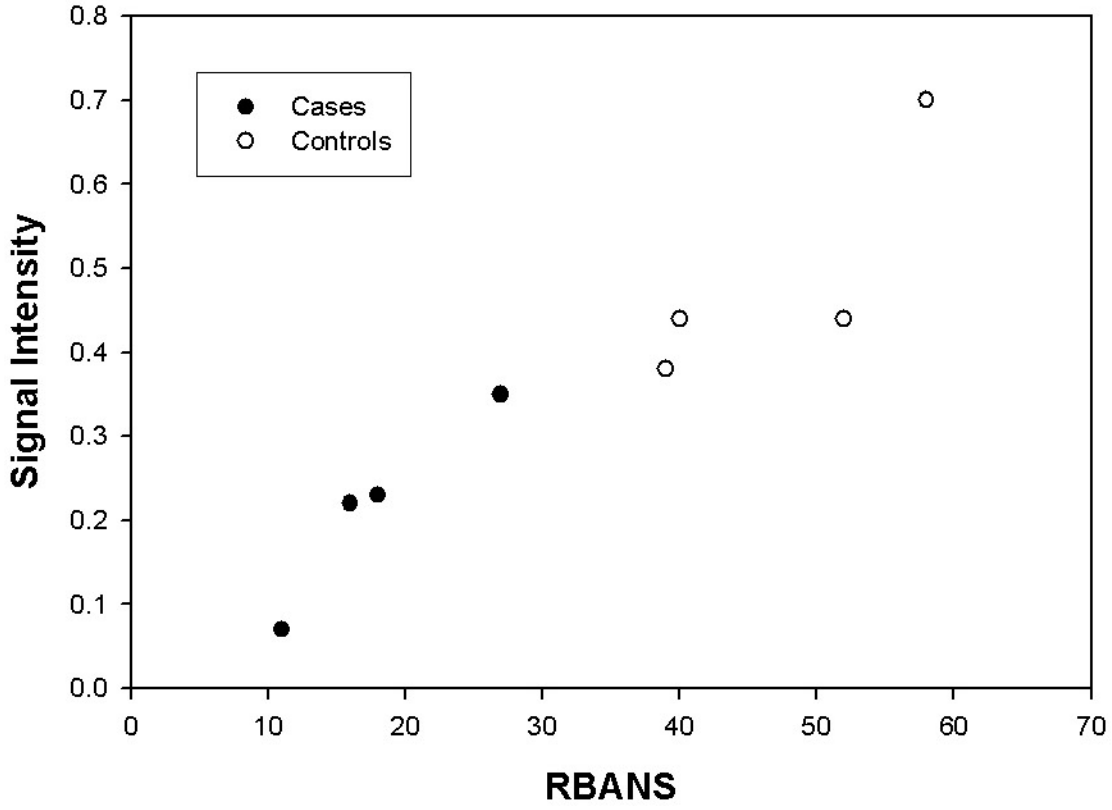
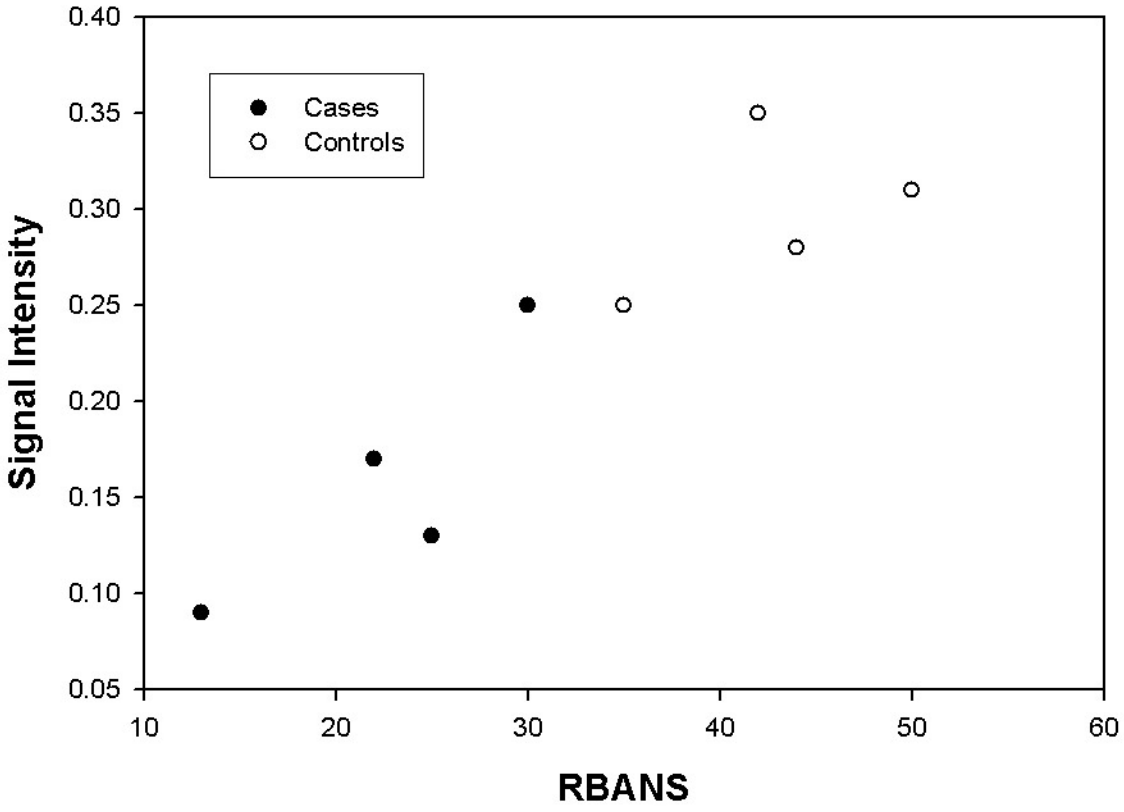
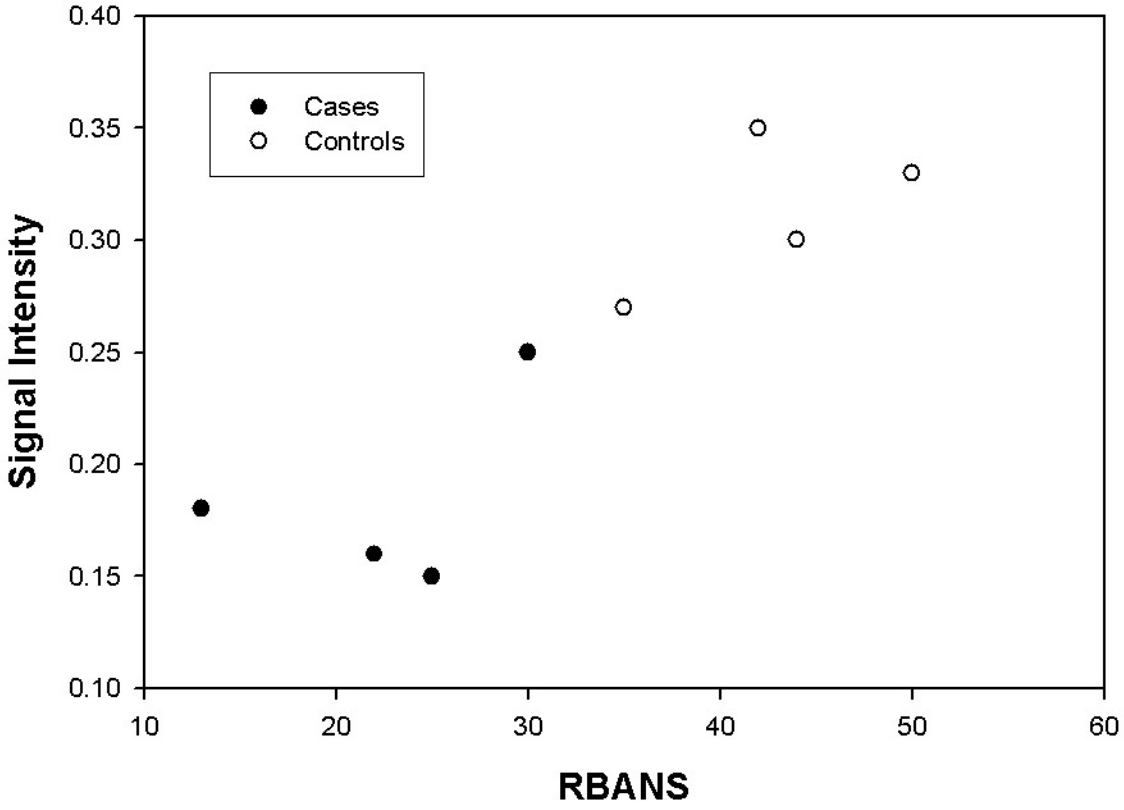


Figure 11 A. Correlational analyses revealed a statistically significant ($r = 0.93$; $p < .001$) relationship between signal intensity in the left dorsal lateral prefrontal cortex (DLPFC) during the Simon arrow task and individual scores on RBANS subtest Trails B, age normed T-scores at three month follow up.



B) Correlational analyses revealed a statistically significant ($r = 0.88$; $p < 0.004$) relationship between signal intensity in the left posterior cingulate cortex (PCC) during the n-back task and individual scores on RBANS subtest Digit Span, age normed T-scores at three month follow up.



C. Correlational analyses revealed a statistically significant ($r = 0.91$; $p < 0.01$) relationship between signal intensity in the left hippocampus during the n-back task and individual scores on RBANS subtest Word Lists, age normed T-scores three month follow up.