The Neuropsychological Course of Acute Delirium in Adult Hematopoietic Stem Cell Transplantation Patients

Leigh J. Beglinger1,*, James A. Mills1, Stacie M. Vik1, Kevin Duff2, Natalie L. Denburg1, Michelle T. Weckmann1, Jane S. Paulsen1, Roger Gingrich1

1Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA
2Department of Neurology, University of Utah, Salt Lake City, UT, USA

*Corresponding author at: Department of Psychiatry, University of Iowa Carver College of Medicine, MEB 1-321, Iowa City, IA 52242-1000, USA.
Tel.: +1-319-335-8765; fax: +1-319-353-3003.
E-mail address: leigh-beglinger@uiowa.edu (L.J. Beglinger).
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Abstract

Although delirium is a common medical comorbidity with altered cognition as its defining feature, few publications have addressed the neuropsychological prodrome, profile, and recovery of patients tested during delirium. We characterize neuropsychological performance in 54 hematopoietic stem cell/bone marrow transplantation (BMT) patients shortly before, during, and after delirium and in BMT patients without delirium and 10 healthy adults. Patients were assessed prospectively before and after transplantation using a brief battery. BMT patients with delirium performed more poorly than comparisons and those without delirium on cross-sectional and trend analyses. Deficits were in expected areas of attention and memory, but also in psychomotor speed and learning. The patients with delirium did not return to normative “average” on any test during observation. Most tests showed a mild decline in the visit before delirium, a sharp decline with delirium onset, and variable performance in the following days. This study adds to the few investigations of neuropsychological performance surrounding delirium and provides targets for monitoring and early detection; Trails A and B, RBANS Coding, and List Recall may be useful for delirium assessment.

Keywords: Bone marrow transplantation; Cognition; Cancer; Attention; Delirium

Introduction

Delirium, or acute confusional state, is a disturbance of consciousness caused by at least one medical condition and characterized by a rapid onset, fluctuating course, and change in cognition (APA, 2000). Although the above definition is the currently accepted clinical depiction of delirium, emerging research and criticisms have sparked an expanding view with better operationalization of the cognitive criteria and an appreciation for the continuum of severity of delirium (for detailed discussion, please refer to Watt, Koziol, & Budding, in press). There is gathering evidence of multifactorial causes of delirium (Gagnon, Allard, Masse, & DeSerres, 2000; Lawlor et al., 2000), including altered neurotransmission of any number of agents (e.g., acetylcholine, dopamine, serotonin) leading to widespread cortical dysfunction (Fann, Alfano, Roth-Roemer, Katon, & Syrjala, 2007; Trzepacz, 2000), inflammatory processes caused by infection or disease, and even cell injury or apoptosis (Murray et al., in press; van Gool, van de Beek, & Eikelenboom, 2010). Delirium is a common medical comorbidity in up to 60% of older and critically ill patients (Pandharipande, Jackson, & Ely, 2005). Up to 40% of cancer patients experience delirium (Stiefel & Holland, 1991) and the incidence climbs to as high as 85% in patients with late-stage and terminal cancer (Breitbart, Bruera, Chochinov, & Lynch, 1995). Unfortunately, delirium is poorly recognized in cancer patients, perhaps due to the common presentation of hypoactive delirium, with as many as two thirds undiagnosed (Breitbart, Bruera, Chochinov, & Lynch, 1995; Fann & Sullivan, 2003; Inouye, 1994). Early detection and proper treatment of delirium is critical because delirium has been associated with several negative outcomes, such as a significantly increased risk of...
Cognitive disturbance is a defining feature of delirium. However, there is a paucity of literature characterizing the acute neurocognitive profile of delirium. Textbooks of neuropsychology either fail to describe delirium as its own syndrome or provide a cursory description of the differences between delirium and dementia (Watt, in press). Although this is an important distinction, very little guidance is provided beyond noting that attention is more impaired in delirium and memory is more impaired in dementia. There is an emerging interrelationship between delirium and Alzheimer disease, whereby each may increase the risk for the other through pathophysiological changes in brain structure and function (such as alterations of the blood–brain barrier through the pro-inflammatory cytokine release), that is largely overlooked or missed in texts and clinical training (Di Bona et al.; Fong et al., 2009). In the majority of empirical studies, a brief screening instrument is used to assess cognition in delirious patients, such as the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). Although the MMSE is clearly useful in the quick assessment of medical patients, it does not provide detailed information about which cognitive domains are affected. Such information has obvious utility for differential diagnosis of other conditions (i.e., delirium vs. aphasia), for making recommendations based on cognitive strengths and weaknesses and for the detection of milder cases of delirium, as even subsyndromal delirium is associated with a poorer long-term outcome (Cole, You, McCusker, Ciampi, & Belzile, 2008). Subsyndromal delirium represents a kind of borderline zone whereby patients experience milder, though still abnormal, symptoms or fewer symptoms than would be needed for a delirium proper diagnosis and highlights the important role of detailed neuropsychological assessment in tandem with thorough medical workup for possible early intervention (von Gunten & Mosimann; Watt, in press).

A small number of studies have more fully explored the cognitive changes associated with delirium. In a study comparing older medical/surgical patients with delirium to those with Alzheimer’s disease and controls, Brown and colleagues (2009) found evidence of impaired visual perception (as well as general cognition) in the delirious patients. Using the cognitive test for delirium (CTD) in 100 palliative care inpatients, Meagher and colleagues (2007) found that cognition is globally reduced, with most notable impairments in attention and vigilance, comprehension, and visuospatial skills. Leonard and colleagues (2008) found the same areas of impairment using the CTD; importantly, they found that greater cognitive impairment on the CTD was more indicative of irreversible delirium (i.e., delirium preceding death) than other “classic signs” of delirium such as psychomotor agitation and psychosis, further indicating the importance of cognitive assessment in delirious patients.

Some older studies have identified language abnormalities in delirium, including confabulation and writing impairments (Chedru & Geschwind, 1972; Wallesch & Hundsalz, 1994). Fann and colleagues (2005) examined the clinical features and course of delirium in hematopoietic stem cell/bone marrow transplantation (BMT) patients, where delirium is a common complication (Beglinger et al., 2006; Fann, Roth-Roemer, Burtoning, Katon, & Syrjala, 2002). Patients undergoing BMT probably have multiple predisposing conditions leading to increased vulnerability for delirium, such as the use of opiates and anticancer drugs, infections and their medicinal treatments post-transplantation, and sleep deprivation during hospitalization. Fann and colleagues (2005) found three factors representing delirium symptoms: Psychosis behavior, cognition, and mood consciousness. Importantly, changes in cognition, specifically attention, memory, and working memory, began 4 days prior to the onset of delirium, increased for 7–10 days after delirium onset and then resolved.

Taken together, prior studies have found evidence of cognitive impairment in patients with delirium, specifically reduced attention and working memory, visuoperceptual deficits, and language abnormalities, and these cognitive changes appear to be early and sensitive indicators of impending delirium. However, the prior studies have relied on limited measures of cognitive performance (e.g., global measures of cognition, Delirium Rating Scales). Although older literature characterized delirium primarily as a psychiatric disorder with an emphasis on agitation and psychotic symptoms, newer research reflects a gathering appreciation for the central role of altered cognitive processes in delirium and the common presentation of hypoactive delirium (Watt, in press). Additionally, the studies showing global cognitive dysfunction in delirium failed to fully examine the core underlying processes that may be driving impaired cognition, particularly the foundational components of attention and working memory which are needed for all other types of neuropsychological performance. Characterization of cognition before, during, and after an acute delirium using the standard neuropsychological tests is needed. A more thorough understanding of the course of delirium and how it looks on traditional neuropsychological tests has diagnostic and treatment implications.

Therefore, the aim of this paper is to describe the cognitive performance of patients during their acute period of delirium compared with patients who did not experience delirium and healthy comparisons and to examine the cognitive prodrome and recovery from delirium in BMT patients. We hypothesize that BMT patients with delirium will perform more poorly than...
both BMT patients without delirium and healthy comparisons on all cognitive tasks, but that differences will be most notable on measures of attention and working memory.

Materials and Methods

Patients and Procedures

The protocol and all study procedures were approved by the University of Iowa Institutional Review Board. Fifty-four patients were recruited from the University of Iowa Blood and Marrow Transplantation Program between 2004 and 2008, where they were being treated with an allogeneic (patient receives donor cells) or autologous (patient receives their own treated cells) bone marrow or peripheral blood transplant. Participants enrolled in one of the two studies during this time examining the cognitive and the psychiatric sequelae of BMT, particularly in those patients who experienced delirium. Additionally, 10 healthy comparisons were recruited during the second study matched for the age and gender of the delirious participants. Most comparisons were family members or friends of the BMT patients and thus were well-matched to the stressful conditions the patients experienced. All participants provided written informed consent and were financially compensated for their participation. Participants were assessed at a pretransplantation visit with a 90-min screening battery that assessed cognitive and psychiatric functioning, delirium, and demographic and medical information (see below). During their inpatient stay, participants completed testing twice weekly until discharge or up to 4 weeks post-transplant with a briefer battery to monitor for delirium. For more details, see Beglinger and colleagues (2006, 2007). Comparison participants were tested on the same schedule as the BMT participants to simulate “pre-transplant” and “inpatient” visits. All assessments were conducted by a trained research assistant or neuropsychologist. Alternate forms of tests were not used so that “cognitive rebound” could be examined, which has been linked with the long-term outcome in other patient samples (Duff et al., 2007; Newman et al., 2001).

Measures

Medical history. A semi-structured clinical interview was used to gather the following information: Demographics (age, gender, education, handedness, employment, and marital status); history of diagnosis (date and specific diagnosis); past treatment (medications/procedures); other significant medical history; family history; cognitive history (current complaints and onset); and psychiatric history (current complaints and onset). A chart review was conducted to obtain medical comorbidity information prior to transplant using the Hematopoietic-Cell Transplantation-specific Comorbidity Index (Sorror et al., 2005).

Neuropsychological functioning. The following neuropsychological tests were administered at baseline to assess the areas most prone to dysfunction in patients who underwent BMT and to provide information for completing the delirium measures. (1) The Modified MMSE (3MS) is an expanded version of the MMSE, which assesses global cognitive functioning on a 100-point scale (Teng & Chui, 1987). (2) Trail-Making Test Parts A and B (Reitan, 1955) are the measures of visual scanning, psychomotor speed, working memory, and set shifting. (3) The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph, Tierney, Mohr, & Chase, 1998) is a brief screening battery of tests measuring attention, language, visuospatial/constructional abilities, and immediate and delayed memory. (4) The Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999) provides an estimate of Full-Scale IQ based on two subtests (Vocabulary and Matrix Reasoning). (5) A visual analog scale of thinking clarity, which ranges from 1 (“clear thinking”) to 100 (“trouble with thinking”), and the patient draws a line to represent his/her current cognition.

The following tests were also given twice weekly during the inpatient stay to measure neuropsychological status and assist with delirium assessment: Trail-Making Test, 3MS, and the RBANS List Learning, Coding, Fluency, List Recall, and List Recognition subtests.

Delirium assessment. The Delirium Rating Scale (DRS) and DRS-Revised (DRS-R; Trzepacz, Baker, & Greenhouse, 1988; Trzepacz et al., 2001) are the scales of delirium severity based on all available information from patient interview, family, and nurses’ reports, cognitive tests, and medical reports, measured over a 24-h period (DRS cutoff > 12; DRS-R cutoff = 15 for severity or =18 total score). The Memorial Delirium Assessment Scale (MDAS) (Breitbart et al., 1997) measures delirium presence and severity and can be administered multiple times in 1 day (cutoff ≥ 8). These scales have been validated in cancer patients.
Statistical Analyses

Cross sectional and trend analyses between groups. Neuropsychological tests were administered and scored according to their respective manuals and converted to z-scores based on their published norms. Patients who surpassed the cutoff value on the DRS/DRS-R or MDAS at any point up to 1 month after transplantation were coded as having delirium. Cross-sectional analyses were conducted using ANCOVAs controlling for sex to examine group differences on the eight cognitive tests at baseline and the final visit. We chose to include sex as a covariate due to possible sex-related differences on neuropsychological test performances (the norms used to calculate z-scores do not account for sex). Neuropsychological performance trends were examined for the three groups (comparison, BMT-delirium, and BMT-no delirium) using a mixed model. The model included a group by visit interaction, adjusted for sex, and allowed for correlations in repeated measurements of the same subjects utilizing an autoregressive moving-average correlation structure. Trend plots were produced for each neuropsychological measure from the adjusted estimates of the mean z-score for each group at baseline and the next four repeat visits. Differences in group trends were tested using appropriate linear contrasts. The Satterthwaite approximation was used to estimate the degrees of freedom in all F-tests in the longitudinal analysis (Brown & Prescott, 1999).

Delirium prodrome and recovery. A prodromal/post-dromal plot was created for patients with delirium. The visit in which delirium was first identified ("delirium onset") was used for all participants, regardless of the actual visit number or number of days post-transplant. Average scores on neuropsychological measures from the repeated battery (3MS, Trails A, Trails B, RBANS: List Learning, List Recall, List Recognition, Fluency, Coding) are presented from three visits before to three visits after the delirium onset visit.

Results

Participant Characteristics

A total of 64 participants consented to participate in the two studies. Ten of these served as comparisons and 54 were patients who had a BMT. Two BMT participants in the delirium group did not experience a delirium episode during the 4 weeks following transplant (but did at a later date) and have been excluded from this analysis. The majority of the remaining 52 BMT patients were men (65%), had lymphomas or leukemias (60%), and received myeloablative therapy (94%). A greater number of patients received an autologous transplant (n = 30, 58%) than an allogeneic (n = 22; 42%) transplant. The majority received their stem cells from peripheral blood (75%) versus bone marrow harvesting. Patients who underwent an autologous BMT received high dose, multiagent chemotherapy for myeloablative therapy. Allogeneic BMT patients mostly received total body irradiation and high-dose chemotherapy or the Busulfan-based high-dose chemotherapy. The average age, level of education, and baseline WASI IQ between the three groups (comparison, BMT-delirium, and BMT-no delirium) did not differ (see Table 1 for patient characteristics).

More than one third of patients (37%) undergoing BMT had an episode of delirium in the first month after transplantation. For most patients (84%), delirium took place in the first 2 weeks after transplantation. The average number of days to the onset of delirium, as defined by exceeding the cutoffs on formal delirium measures, was 11.6 (SD = 6.9) days after transplantation. The majority of participants had a delirium episode that lasted for only one study visit (12 of 19 or 63%), four had delirium for two visits, two for three visits, and only one person experienced persistent delirium across four sessions. Three participants with delirium across multiple visits had scores that fell below the delirium threshold in between delirium visits (i.e., nonconsecutive delirium episodes). In most cases, these scores were still elevated but not meeting the cutoff. There was no evidence of an association between transplant type, \( \chi^2(1) = 0.14, p = .71 \), cell type, \( \chi^2(1) = 0.69, p = .41 \), diagnosis, \( \chi^2(1) = 6.40, p = .17 \), or baseline medical comorbidity, \( \chi^2(1) = 0.75, p = .39 \), and the occurrence of delirium.

Cross-Sectional Analyses

Raw means and standard deviations for every visit are presented in Table 2. ANCOVAs for each of the eight tests at the baseline did not show any group differences. However, five of the eight measures showed group differences at visit 4. Post hoc comparisons revealed that, in all cases, the delirium group performed significantly more poorly than comparisons: Trails A \( t = 4.5; p < .0001 \), Trails B \( t = 2.9; p = .005 \), List Learning \( t = 3.8, p = .0005 \), List Recall \( t = 3.7; p = .0005 \), and Coding \( t = 2.6; p = .01 \). The delirium group was worse than the no delirium BMT group on two measures: List Learning \( t = 2.5; p = .02 \) and List Recall \( t = 2.6; p = .01 \). BMT patients without delirium were different from comparisons on three measures: Trails A \( t = 3.6; p = .0008 \), Trails B \( t = 2.7; p = .009 \), and Coding \( t = 2.6; p = .01 \).
Performance Trends by Group

Trend plots of the $z$-scores for each measure are presented in Fig. 1 for the three groups. Mixed model analyses revealed group differences on the following tests: Trails A, $F_{(2,62.5)} = 5.36, p = .007$; RBANS List Learning, $F_{(2,77.2)} = 6.03, p = .0037$; List Recognition, $F_{(2,54.4)} = 4.07, p = .0225$; and Semantic Fluency, $F_{(2,46.2)} = 6.49, p = .003$. Post hoc testing showed that the delirium group was different from comparisons on all of the above tests: Trails A, $F_{(1,60.7)} = 10.69, p = .002$; List Learning, $F_{(1,75.8)} = 10.94, p = .001$; List Recognition, $F_{(1,52.9)} = 5.45, p = .02$; Coding, $F_{(1,68.6)} = 5.62, p = .02$; Semantic Fluency, $F_{(1,45.1)} = 12.51, p = .001$; and different from BMT patients without delirium on List Learning, $F_{(1,80)} = 6.46, p = .01$, and Semantic Fluency, $F_{(1,44.7)} = 8.50, p = .006$.

Delirium Profile

The prodromal/post-dromal plot for each neuropsychological measure is presented in Fig. 2, where zero is the delirium onset visit, and three visits before and after delirium onset are also presented. Patients with delirium consistently demonstrated lower than average scores on each measure throughout the post-transplantation period, with the lowest level of performance taking place on or after the delirium visit. Trails B, List Recall, and Coding $z$-scores show a considerable decrease from the second visit to the first visit before delirium ($z = -0.80$ to $-1.30$, $z = -0.55$ to $-1.0$, and $z = -0.42$ to $-0.81$, respectively). Three measures, List Learning, Coding, and Fluency, continued to decline after delirium onset. Five of the eight measures showed a second dip or worst performance two visits after delirium onset (~7 days after delirium onset): Trails B, List Recall, List Learning, Coding, and Fluency.

Discussion

In this sample of 52 patients undergoing BMT, over one third experienced delirium in the 4 weeks following the procedure. Not surprisingly, patients with delirium performed more poorly than healthy comparisons on every test administered. When their entire cognitive course was plotted and compared with both comparison groups, four of the eight neuropsychological measures were significantly different in a trend analysis of their performance trajectories across five visits. At the end of the study period (2 weeks post-transplant), five of the eight tests showed group differences. Deficits were most pronounced on the measures of psychomotor speed, learning and memory, and attention/working memory. As a group, the patients with delirium did not return to normative “average” ($z = 0$) on any of the tests during this period of observation, nor did they return to their baseline levels of performance for most tasks, despite having mean estimated IQ in the average range.

Table 1. Demographic characteristics of participants ($N = 62$)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>$N$</th>
<th>Range</th>
<th>Delirium (n = 19; mean [SD])</th>
<th>No Delirium (n = 33; mean [SD])</th>
<th>Comparison (n = 10; mean [SD])</th>
<th>$F$-value</th>
<th>$p$-value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>62</td>
<td>21–69</td>
<td>53.3 (12.4)</td>
<td>52.9 (10.3)</td>
<td>58.6 (6.0)</td>
<td>1.36</td>
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<td>Education (years)</td>
<td>62</td>
<td>11–24</td>
<td>14.9 (3.7)</td>
<td>14.2 (2.5)</td>
<td>14.4 (2.2)</td>
<td>0.26</td>
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<tr>
<td>WASI IQ</td>
<td>62</td>
<td>67–128</td>
<td>102.4 (14.1)</td>
<td>104.3 (12.5)</td>
<td>105.7 (13.4)</td>
<td>0.24</td>
<td>ns</td>
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<tr>
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<tr>
<td>Men</td>
<td>39</td>
<td></td>
<td>11</td>
<td>23</td>
<td>5</td>
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<tr>
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<td>8</td>
<td>10</td>
<td>5</td>
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<td>None (comparison)</td>
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<td>—</td>
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<td>11</td>
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<td>0</td>
<td>3</td>
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</table>

Note: WASI = Wechsler Abbreviated Scale of Intelligence.
Table 2. Means and standard deviations of neuropsychological tests by group for each visit

<table>
<thead>
<tr>
<th>Test</th>
<th>BL Visit</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
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<tr>
<td>Trails A***</td>
<td>30.1 (6.6)</td>
<td>36.1 (11.7)</td>
<td>34.2 (12.2)</td>
<td>30.9 (9.2)</td>
<td>34.8 (10.6)</td>
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<tr>
<td>Trails B*</td>
<td>72.3 (28.2)</td>
<td>90.9 (44.4)</td>
<td>87.4 (37.8)</td>
<td>54.4 (14.9)</td>
<td>87.1 (41.1)</td>
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<tr>
<td>RBANS List Learning**</td>
<td>27.3 (3.0)</td>
<td>25.5 (5.3)</td>
<td>25.4 (5.2)</td>
<td>27.6 (2.9)</td>
<td>26.4 (7.4)</td>
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<tr>
<td>RBANS List Recall**</td>
<td>6.2 (2.5)</td>
<td>4.9 (3.1)</td>
<td>4.3 (2.8)</td>
<td>6.3 (1.6)</td>
<td>5.3 (3.0)</td>
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<tr>
<td>RBANS List Recognition</td>
<td>19.4 (0.8)</td>
<td>19.0 (1.1)</td>
<td>19.4 (0.7)</td>
<td>19.0 (1.1)</td>
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<tr>
<td>RBANS Coding*</td>
<td>46.3 (7.2)</td>
<td>42.4 (10.4)</td>
<td>41.7 (10.6)</td>
<td>45.7 (5.0)</td>
<td>39.2 (11.4)</td>
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<tr>
<td>RBANS Semantic Fluency</td>
<td>19.0 (3.8)</td>
<td>18.2 (4.3)</td>
<td>20.7 (5.1)</td>
<td>18.3 (3.0)</td>
<td>18.2 (4.4)</td>
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<td>3MS Total</td>
<td>94.3 (3.7)</td>
<td>92.8 (5.2)</td>
<td>94.2 (4.8)</td>
<td>95.6 (2.3)</td>
<td>94.8 (2.9)</td>
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</table>

Notes: BL = baseline; ND = bone marrow transplant-no delirium group; D = bone marrow transplant-delirium group; C = healthy comparisons; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; 3MS = Modified Mini-Mental Status Exam.

*p < .05, group differences at visit 4.
**p < .01, group differences at visit 4.
***p < .001, group differences at visit 4.
Fig. 1. Plots of neuropsychological performances by the three groups across five sessions. Scores shown are standardized $z$-scores using published normative data (i.e., $z = -1.0$ equals performance 1 SD below the mean).
Fig. 2. Plots of neuropsychological performances by the patients who experienced delirium. On the x-axis, visit 0 indicates the first point at which patients were identified with delirium, regardless of the actual visit number. To the left of visit 0 are the three visits immediately preceding the delirium onset and to the right are the three visits following the delirium onset. Lower z-scores on the neuropsychological tests reflect poorer performance and higher scores on the MDAS and DRS reflect more severe symptoms of delirium.
Moreover, patients with delirium had a more impaired cognitive trajectory over that same period on List Learning and Recognition than a peer group matched for the BMT (i.e., patients who did not experience delirium). In the subgroup of patients with delirium, we standardized delirium onset by placing everyone on the same plot, regardless of the actual visit of delirium onset, so performance before and after delirium could be elucidated. Results indicated that performances declined on most tests the visit prior (2–5 days) to delirium onset, declined sharply with delirium onset and then were variable in the 10 days following onset. This study adds to the few prospective investigations on neuropsychological performance surrounding acute delirium and provides a target for monitoring and early detection of delirium. Trails A and B and RBANS Coding and List Recall may be useful measures for delirium assessment, as they showed the largest normative impairments and cross-sectional group differences.

Consistent with prior research (Fann, Roth-Roemer, Burington, Katon, & Syrjala, 2002), we found the timing of delirium onset to be, on average, almost 12 days after transplantation. This time frame suggests several possible etiological factors underlying delirium in this population. First, there are nadir effects from the conditioning therapy that patients undergo prior to BMT, like GI mucositis with medicinal interventions to counteract the mouth pain, esophageal reflux, and diarrhea. Second, cytokine release from tissue injury like tumor necrosis factor alpha and interleukin 1B may cause inflammation which predisposes the patient (or lowers their threshold) for delirium (van Gool, van de Beek, & Eikelenboom, 2010). Third, increased transfusion requirements occur during this time frame, with most transfusions performed at night, with premedications and interrupted sleep blocks causing sleep deprivation. Relatedly, sleep medications may last into the next day and interact or overlap causing cognitive impairment. Finally, multiple antibiotics are given, most in a prophylactic mode, that can cause symptoms of delirium (e.g., a common one, Vfend, causes visual hallucinations with some frequency). Many of the above factors may be percolating several days before delirium onset and cause the types of cognitive impairment we identified up to a week before delirium was identified. With awareness of the timing of these subtler symptoms of dysfunction, treatment staff may be able to identify and treat potentially reversible causes of delirium, such as sleep-related issues.

Previously published studies have identified specific areas of neuropsychological dysfunction associated with delirium, specifically reduced attention and working memory, visuoperceptual and language deficits (Chedru & Geschwind, 1972; Fann et al., 2005; Meagher et al., 2007; Wallesch & Hundsalz, 1994). However, the prior studies have relied on limited measures of cognitive performance, such as DRSs or mental status exams. Our results, using a neuropsychological screening battery, confirm prior findings of the importance of attention and working memory. Over the entire study period, patients with delirium were most different from healthy comparisons on Semantic Fluency, List Learning, List Recognition, and Trails A. For Trails A, List Recognition, and Fluency, comparison performance improved over time while the performance of delirium patients declined; this is especially apparent between the first two visits. We see a practice effect for the healthy comparisons on every test administered during the study. Performances in the delirium group declined between the first two visits, then remained flat or are variable. An exception is in the List Learning and Recall plots; both the BMT no delirium and delirium groups had increasing performance suggesting good recovery of immediate and delayed memory over time. In a subset of this sample, we previously found that RBANS List Learning and List Recall were two of the domains of greatest recovery by 100 days post-BMT (Beglinger et al., 2007). These findings indicate that memory is an area of early recovery both post-BMT and post-delirium. In the patients who did not experience delirium, Trails A, Trails B, Fluency, and Coding, performance was relatively stable for the first few visits before trending up at the third repeat visit. List Learning and Recall performance for these subjects continually increased from one visit to the next. These plots should be viewed cautiously, however, as the number of patients experiencing delirium differs from one visit to the next, depending on when in the study participants had delirium onset.

In addition to differing from healthy comparisons, the patients with delirium also performed below patients undergoing BMT who did not experience delirium, an important distinction in determining whether the cognitive impairments found in the delirium group are accounted for solely due to transplant- and cancer-related factors. Differences between the delirium and nondelirium groups are evident on seven of eight tasks in Fig. 1. There were statistically significant differences in the trends on the List Learning and List Recognition plots. In each case, the nondelirium group had a faster rate of increase than the delirium group (p = .013 and .013, respectively); on List Recognition, the delirium group actually declined over time. In contrast, performances on Semantic Fluency were unexpected. The delirium group outperformed the nondelirium group at four of the five visits and the comparison group at the first two visits. It is unclear why this task did not separate the two BMT groups, but it was the least impaired task in the delirium group and the only speeded task without a graphomotor component. Measures with a writing component have been sensitive in delirious patients in previous research (Chedru & Geschwind, 1972) and may be more taxing and thus better able to distinguish subtler defects compared with measures that only have an oral component. Additionally, the RBANS fluency task measures semantic fluency, which may be less sensitive to delirium group differences than a measure of phonemic fluency. Taken together, these findings converge with prior research demonstrating that attention, working memory, memory, and language are the critical features of the neuropsychological
profile of delirium. We also show that the measures of psychomotor speed and learning are abnormal, two areas that have not been traditionally highlighted in the literature.

Examination of the plots in Fig. 2 representing the course of delirium provide information about which cognitive domains may be most sensitive to underlying cerebral dysfunction. At the visit in which delirium was first identified, mean scores on four tasks were abnormal: Trails B \((z = -1.8)\), Coding \((z = -1.4)\), Trails A \((z = -1.1)\), and List Recall \((z = -1.0)\). This suggests that complex attention, processing speed, visual scanning, writing, and immediate memory are deficient during delirium. The other three neuropsychological tasks were below normal (List Learning, Recognition, and Semantic Fluency all at \(z = -0.7\)). Four of the tasks showed a decline up to two visits, or 5–7 days, before patients met the threshold for delirium: Trails B, List Recall, Coding, and Trails A. These results indicate that measures of attention, learning, psychomotor speed, and scanning may be useful indicators of impending delirium. This is consistent with the view that delirium represents multifactorial cognitive dysfunction and is not simply a disorder of attention. More recently, delirium and other disorders of impaired consciousness have been conceptualized as a network of distributed and interrelated neuropsychological processes (e.g., attention, executive functions), working as an integrated system through subcortical gating (Schiff & Plum, 2000). If one of the primary processes is abnormal, downstream effects may be observed in other neuropsychological domains. The above results suggest that these primary areas of dysfunction may be detected with the standard neuropsychological tests. Measures of memory and language, while abnormal during delirium, may not be sensitive to the prodromal phase. Two visits after delirium identification, an interesting second dip in performance occurred on several measures (Trails B, List Learning and Recall, Coding) indicating that deficits may persist or worsen in these domains. Fann and colleagues (2005) also found continuing decline in the measures of attention and working memory for 7–10 days after delirium onset in their BMT sample. These converging findings about the persistence of delirium should alert the treatment team to the need for extra monitoring in the 2 weeks following delirium identification, a time which may hold clinical significance (e.g., discharge planning).

The three delirium measures (DRS Total, DRS Severity, and MDAS) were all sensitive to impending delirium, with mild increases in scores shown at each of the three visits prior to the identified delirium, with the largest increase between the visits adjacent to delirium onset (i.e., visits \(-1\) and 0). However, the delirium measures also showed an equal decline (i.e., “recovery”) in symptoms in the visit immediately following delirium onset (+1) and a near return to baseline by three visits post-delirium. The neuropsychological profile suggests that the delirium postdrome conferred more cognitive morbidity than these scales indicate. Semantic Fluency, Trails B, and Coding all remained substantially lower after delirium than they had in the prodromal phase, suggesting that more detailed cognitive testing may be necessary as delirium is resolving to tease out the full extent of cognitive deficits. For example, Coding remained between 1.3 and 2 SD below average at all post-delirium visits. Coding is both a quick and a complex test of multiple skills (attention, memory, writing, processing speed) making it a good candidate for delirium screening. Based on our findings, we recommend adding a version of Coding to delirium screenings and assessments for both research and clinical evaluation.

Although it was not an aim of this study to characterize neuropsychological performance in patients undergoing a BMT who did not experience delirium, our data also shed light on the cognitive changes that occur immediately after BMT. There is emerging literature on the cognitive sequelae associated with BMT. It is not surprising that patients who undergo the intensive preparative regimens associated with BMT (e.g., total body irradiation, high-dose chemotherapy) would have cognitive morbidities. Several studies have demonstrated mild impairments in BMT patients both before the transplantation and up to many years after (Meyers et al., 1994; Parth, Dunlap, Kennedy, Ordy, & Lane, 1989; Peper et al., 2000; Syrjala, Dikmen, Langer, Roth-Roemer, & Abrams, 2004). We have previously shown that BMT is associated with mild, diffuse cognitive impairments pre-transplantation, particularly on the Trail-Making Test and List Recall (Beglinger et al., 2007). The larger sample presented here confirms our earlier findings. The BMT-no delirium group remained consistently between 0.5 and 1 SD below the normative average on Trails B, Coding, and Semantic Fluency throughout the whole study. Importantly, despite using the same test form, there was a lack of practice effect in the BMT group across the five test sessions—a different trajectory from the healthy comparisons indicating that these are treatment-related impairments. The implication of these results is that patients undergoing BMT may display processing speed and executive deficits even without the presence of delirium, which could be important for patient care and recommendations (e.g., patients may need assistance following complicated medical plans or may need additional time to process informed consent documents).

This study adds to the existing literature by providing a prospective examination of the course of delirium, from 10 days prior to delirium onset to 10 days post-delirium identification. Given the difficulty of repeat testing in critically ill and frail patients, the relatively large sample size is also a strength. However, there are important limitations to be noted. First, the number of patients in the delirium group is small and sample sizes dropped even further for some of the visits before and after delirium onset. Second, although the battery used in this study was an improvement over prior studies in that multiple domains were assessed with validated neuropsychological measures, more work is needed to fully elucidate the cognitive
profile. For example, more thorough examination of language (e.g., naming, comprehension) and visual perception is needed. Results should be considered preliminary and should be validated both with larger samples and with other types of patients, as cancer patients overrepresent the hypoactive subtype of delirium and cognitive deficits may be different in hyperactive patients. Finally, the follow-up period to examine the cognitive sequelae of delirium was relatively short in these patients. We have previously presented 100-day follow-up data on a subset of these patients (Beglinger et al., 2007), but longer follow-up is needed in future studies.

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Conflict of Interest

None declared.

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