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Neuropsychological profiles of an elderly cohort undergoing elective surgery and the relationship of cognitive performance with delirium

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Abstract

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Dr. Fong contributed to the conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically. Dr. Hsieh substantially contributed to the analysis and interpretation of data, drafting the article and revising it critically for important intellectual content. Dr. Wong contributed to the conception and design, acquisition of data, analysis and interpretation of data and revising the article critically. Dr. Tommet contributed to the analysis and interpretation of data and revising the article critically. Dr. Jones contributed to the conception and design, analysis and interpretation of data and revising the article critically. Dr. Schmitt contributed to the acquisition of data, analysis and interpretation of data and revising the article critically. Ms. Puelle contributed to the acquisition of data, analysis and interpretation of data and revising the article critically. Dr. Saczynski contributed to the analysis and interpretation of data and revising the article critically. Dr. Marcantonio contributed to the conception and design, acquisition of data, analysis and interpretation of data and revising the article critically. Dr. Inouye contributed to the conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically as well as obtaining funding and administrative support.

Conflict of Interest: All the co-authors fully disclose they have no financial or personal conflicts of interest. The co-authors also declare they have no potential conflicts from the three years prior to submission of this manuscript.

Background/Objectives—To examine the baseline (preoperative) neuropsychological test performance in a cohort of elderly individuals undergoing elective surgery and the association between specific neuropsychological domains and post-operative delirium.

Design/Setting/Participants—An ongoing prospective cohort study of elderly patients (n=300) scheduled for elective (non-cardiac) surgery.

Measurements—Neuropsychological testing, including standardized assessments of memory, divided and sustained attention, speed of mental processing, verbal fluency, working memory, language, and an overall measure of premorbid cognitive functioning, was obtained 2-4 weeks prior to surgery. The relationship of the individual neuropsychological tests and delirium status was examined using linear regression, adjusting for age, gender and education.

Results—After adjustment, patients who developed post-operative delirium performed significantly lower pre-operatively on measures of speed of mental processing and divided attention (Trails Making Test B, mean difference=17.55, $p=0.02$), category fluency (animal naming, -1.94, $p=0.01$), sustained visual attention (Visual Search and Attention, -3.19, $p<0.001$) and working memory with new learning and recall, (HVLT-R Total, -0.53 to -0.79, $p<0.01$).

Conclusion—Lower performance scores on tests evaluating the areas of complex attention, executive functioning, and rapid access to verbal knowledge or semantic networks are seen at baseline in patients who later develop delirium. Future studies to better understand how the identified cognitive profiles may predispose individuals towards developing delirium may help pave the way to greater understanding of the mechanisms of delirium.

Keywords

Neuropsychological profiles; elderly; cognitive performance; delirium

Introduction

Delirium is a serious post-operative complication especially prevalent among older persons associated with increased mortality, poor recovery, extended hospitalizations, higher hospital costs, post-discharge institutionalization, and persistent cognitive deficits (1, 2). A number of studies have identified baseline risk factors – such as age, sensory impairment, severe illness, pre-existing co-morbidities, metabolic disturbances, alcohol abuse – that contribute to development of post-operative delirium but these studies focused on medical and not specific neurocognitive factors (3-5). However, pre-operative dementia among older patients is a well-established independent risk factor for post-operative delirium (6). Pre-existing cognitive impairment has been included in validated clinical prediction rules for delirium (4, 5) and is associated with prolonged delirium after hip surgery (7).

While it is widely accepted that cognitive impairment is a risk factor for delirium, most prior studies have used only brief tests of global cognitive function, such as the Mini-Mental State Examination (MMSE) or the Telephone Interview for Cognitive Impairment (TICS) (3-5). These global diagnostic tests lack specificity as to which individual cognitive domains underlie the impairment. Cognitive impairment is also present during acute delirium, with inattention as a key feature (1). In more severe cases, global impairments can occur, yet

whether performance on specific cognitive domains at baseline is associated with development of delirium has not been examined. Few previous studies have examined specific neurocognitive domains at a pre-operative baseline and their association with post-operative delirium. In one small study of 80 patients undergoing coronary artery bypass surgery, pre-existing executive dysfunction was independently associated with increased risk for developing delirium (8). Thus, the aim of the current study was to extend previous findings by examining baseline (pre-operative) domain-specific neuropsychological characteristics of older individuals without dementia who did and did not develop delirium following major elective surgery. We hypothesized that since inattention is such a prominent impairment in delirium, patients with impairments in attention and frontal executive functioning at baseline would be more vulnerable to developing delirium than patients without these impairments.

Methods

Study Population

The Successful Aging after Elective Surgery (SAGES) Study has been described in detail previously (9). In brief, the study is an ongoing prospective observational study of patients aged 70 years and older scheduled for major elective (noncardiac) surgery with an anticipated hospital length of stay of at least two days. The elective surgeries included in the study were total hip or knee replacement, laminectomy, lower extremity arterial bypass, open abdominal aortic aneurysm repair, and colectomy. Exclusion criteria were active delirium pre-operatively, dementia diagnosis or baseline education-adjusted Modified Mini-Mental State (3MS) score ≤ 69 , terminal condition, legal blindness, severe deafness, severe mental illness, or documented alcohol abuse. Dementia screening occurred at three levels: 1) Initial medical record screening for documented dementia, dementia evaluation or treatment; 2) Telephone recruitment where participants were asked if they had ever been given a diagnosis of dementia or Alzheimer's disease (AD); and 3) Baseline enrollment interview, which included capacity assessment for informed consent, and the Modified Mini-Mental (3MS). Any evidence of pre-existing dementia based on any of these screening evaluations was adjudicated by a team of three clinicians to determine enrollment eligibility. This study was based on the first 300 participants enrolled from two Harvard-affiliated hospitals, Beth Israel Deaconess Medical Center (BIDMC) and Brigham and Women's Hospital (BWH). Written informed consent was obtained from all participants, according to procedures approved by the Institutional Review Boards of BIDMC, BWH and Hebrew SeniorLife (HSL), all located in Boston, Massachusetts.

After study enrollment, patients completed a 75-minute interview in their homes prior to surgery, which included a standardized battery of neuropsychological tests, as well as assessments of demographics and functional status. Patients were also interviewed daily during their surgical hospitalization to assess delirium status.

Measures

The neuropsychological battery used in SAGES has been described previously (9). The measures included the Visual Search and Attention Test (VSAT) (10), Hopkins Verbal

Learning Test-Revised, (HVL-T-R) (11), Digit Span Forward and Backward (12), Category Fluency (animal naming) (13), Phonemic F-A-S Fluency Tasks (13), Boston Naming Test (14), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Digit Symbol Substitution Test (12) and the Trail-Making Tests (Trails) A and B (15). The battery also included the Wechsler Test of Adult Reading (WTAR) (12), a test of single word reading that measures verbal intellect and peak cognitive functioning (Appendix Table 1). Theoretically, a person's performance on the WTAR should not change significantly with age-related pathology.

Delirium status was determined from two sources: patient interview and medical record review. Patients received a standardized interview daily during their hospitalization by a trained interviewer. The interview consisted of a brief cognitive screen, digit span testing, Delirium Symptom Interview (DSI), and rating of the 10-item Confusion Assessment Method (CAM). We used an adapted DSI that includes a brief patient interview about the presence or absence of eight key delirium features, and these answers were used to help inform the CAM rating. The CAM is a 10-item instrument and corresponding diagnostic algorithm that defines delirium as present if a patient exhibits an acute change or fluctuation in symptoms, inattention, and either disorganized thinking or an altered level of consciousness (16).

Delirium was also assessed from a review of the patient's hospital records using a validated chart review method, which included adjudication of all chart-documented confusion by a panel of delirium experts (SKI, BW, ERM) (17). A patient was considered to have delirium during hospitalization if the patient fulfilled CAM criteria for delirium during any daily interview or if the patient's medical record indicated delirium (17).

Other study variables to characterize the cohort included the Charlson comorbidity index, 3MS score and any functional impairment in Instrumental Activities of Daily Living (IADLs) or Activities of Daily Living (ADLs) (18, 19).

Statistical Analysis

The statistical analysis involved a series of unadjusted and adjusted linear regression models with mean values for individual neuropsychological tests scores as the outcome and delirium status as the key co-variable of interest. The adjusted models also controlled for age, gender, and education. Mean differences between non-delirious and delirious patients for each neuropsychological test were normalized to a mean of 0 and standard deviation of 1; all test results are thus presented on a common scale.

We report standardized mean differences as a guide to the interpretation of differences in neuropsychological test scores. To compute standardized mean differences, we use the standard deviation for each of the neuropsychological tests obtained from a control sample of primary care patients (n=119). Participants are classified as impaired on a test if their score represents performance worse than one standard deviation of the primary care control group, using the mean and standard deviation from the control group to define a normative distribution for this sample.

Results

The average age for the 300 study participants was 76.9 ± 5.0 years old, and the majority was white (95%), married (63%) and female (55%). On average, patients had 15.0 ± 2.9 years of education. Most had mild impairments on functional scales at baseline, with 7-8% reporting any ADL impairments and 23-32% reporting any IADL impairments. Cognitive test scores were generally high, with 3MS scores averaging 93.2 out of 100. Thus, prior to surgery, the cohort represents a highly educated, generally healthy group of community-dwelling older individuals with little or no cognitive or functional impairment. Delirium, as defined by CAM and medical record criteria, occurred in 82 of 300 patients (27%). Delirium incidence did not vary by type of surgery (Chi-squared = 2.2, $p=0.331$). Among 253 patients undergoing orthopedic surgery, 26% developed delirium; among 16 undergoing vascular surgery, 38% developed delirium; and among 31 undergoing gastrointestinal surgery, 35% developed delirium.

Standardized differences in neuropsychological test scores between non-delirious and delirious patients are presented in Figure 1. In the analysis for this figure only, scores for Trails A and B, were reversed such that higher values indicate better performance to better align with all other measures. In both adjusted (for age, gender and education) and unadjusted models, patients who developed delirium had significantly poorer pre-operative performance on measures of speed of mentation and divided attention (Trails B), sustained visual attention (VSAT), new learning and recall (HVLt-R Total) and category fluency (animal naming), all $p < 0.05$ (Figure 1). Differences in peak lifetime verbal intellect (WTAR) did not reach statistical significance, but there was a trend towards lower performance in the delirious group (Figure 1).

The neuropsychological test scores and distribution of impaired patients are presented in Table 1, overall and stratified by delirium status. For Trails A and B, a higher score indicates worse performance; for all other measures, a lower score indicates worse performance. Mean differences in performance on the various neuropsychological tests between patients who became delirious and those who did not were determined. More patients in the group that developed post-operative delirium had impaired performance on Trails B (mean score 128.7, 12% impaired vs. non-delirious mean score 111.1, 8% impaired; higher score indicates worse performance) (Table 1). The mean difference in Trails B scores between non-delirious and delirious patients was $+17.55$, $p=0.02$. More patients who developed delirium also had impaired performance in category fluency (mean score 19.9, 15% impaired vs. non-delirious mean score 21.8, 11% impaired) and VSAT (mean score 40.7, 27% impaired vs. non-delirious mean score 43.9, 14% impaired) (Table 1). This represents a mean difference in category fluency scores of -1.94 , $p=0.01$ and in VSAT scores of -3.19 , $p < 0.001$. Finally, more patients who developed delirium had impaired performance on HVLt-R – Total (mean score 19.8, 15-24% impaired vs. non-delirious mean score 21.9, 12-14%). This represents a mean difference in HVLt-R scores of -0.53 to -0.79 , $p = 0.01$.

Discussion

Patients who developed post-operative delirium demonstrated weaker performance at baseline on tests examining the ability to maintain sustained attention, particularly in complex situations. Specifically, those patients who later developed delirium were less capable of dividing their attention between tasks and sustaining attention for prolonged activities as reflected by their weaker performance on Trails B and VSAT. In addition, the ability to learn new information was more likely to be impaired on pre-operative neuropsychological testing in the group that later developed delirium, as demonstrated by their weaker performance on the HVLT-R, particularly trials 2 and 3. These impairments reflect difficulties in registration and maintaining attention, as these patients were unable to focus their attention on new material or tasks and to encode the material or tasks into memory. Given that inattention is a key feature of delirium, this finding may suggest that baseline dysfunction in attention-based cognitive tasks may predispose to development of delirium. It should be noted, however, that the “higher order” attentional deficits detected by neuropsychological testing are distinct from the basic attentional deficits seen in acutely delirious patients (1).

The group who developed delirium also demonstrated poorer performance when tested on category fluency, i.e., naming as many animals as possible within one minute, indicating impaired semantic memory and executive functioning at baseline. Organizing items into memory by category facilitates retrieval and underlies performance on categorical fluency tests. Such categorical fluency impairment in the setting of intact letter/phonemic fluency suggests emerging difficulties accessing semantic knowledge rapidly. This discrepancy between category versus semantic fluency suggests more difficult access to semantic networks or disruptions in the integrity of semantic networks – and has been shown to predict the development of neurodegenerative diseases affecting language and semantic systems (20). Categorical fluency, and in particular semantic fluency, becomes disordered specifically in Alzheimer's dementia, likely as a result of alterations in semantic networks, with different dimensions, fewer common links and associations of atypical strength (21). Dementia is well established as one of the strongest risk factors for delirium (4, 6). However, even in our study population essentially free of dementia, it is possible that mild deficits in the categorical fluency domain indicate early vulnerability that can predispose patients toward the development of delirium. Furthermore, there was a trend in the delirium group towards lower performance on the WTAR, a test considered to be a measure of peak lifetime verbal intellect and a marker of cognitive reserve (22). As shown previously, lower cognitive reserve is also a risk factor for delirium (22, 23).

To date, only a few previous studies have examined the cognitive profiles of older patients prior to undergoing elective surgery. Jankowski et al. found that memory impairment as measured by the Auditory Verbal Learning Test efficiency score predicted the development of delirium in elderly patients without dementia undergoing elective total hip/knee arthroplasty (24). Rudolph et al. found that mildly impaired cognitive performance (1.5 SD below the mean) pre-operatively on two executive function tests (Visual Verbal Learning Test and Stroop Color-Word Test) was associated with an over two-fold increased risk for

delirium among elderly patients undergoing noncardiac surgery (RR 2.2, 95% CI 1.4-3.6) (25).

This study has important strengths, including the large, well-characterized cohort, and the standardized administration of a complete neuropsychological test battery in patient's homes prior to surgery by well-trained staff. The neuropsychological battery was completed and analyzed blinded to the patient's delirium status. Delirium was assessed using state-of-the-art methods, by a well-trained experienced team and with adjudication of all results by expert clinicians (9). Incidence of delirium in our study sample (27%) is comparable to rates in non-cardiac surgery populations reported in the literature (1). Importantly, this study helps to characterize the baseline neuropsychological profile of a patient at risk for delirium, which includes specific impairment in complex attention (divided and sustained), executive functioning and rapid access to verbal knowledge or semantic networks. While global cognitive dysfunction has been well established as a risk factor for delirium (2-6), this study extends previous work in identifying specific cognitive domains – fronto-executive and early semantic that are associated with increased risk for delirium in non-demented older persons. The cognitive battery administered in the current study covers a broader range of cognitive functions, and importantly, includes the Trailmaking Tests, which several studies have shown to be highly correlated with functioning in daily life, including driving (26), financial decision-making (27), and medication management in patients with Parkinson's disease (28).

Several caveats about this study are worthy of mention. The cohort used in this study is highly educated with little cognitive impairment at baseline, and thus, the results from this study may not be generalizable to all geriatric populations. Moreover, surgery types included were limited to elective orthopedic, vascular and general surgery procedures, and applicability to other types of surgery will need further examination. These are, however, the most common types of elective surgery performed in older adults, and it was not logistically feasible to perform this study in patients undergoing emergency surgery. This study enrolled patients scheduled for surgery at 2 hospitals in one geographical area; thus, generalizability of the findings to other settings will need to be verified in future studies. Finally, this study was intended to be descriptive, that is, to provide the detailed correlations between neuropsychological tests and delirium. Predicting delirium based on specific neuropsychological test results was not an intended part of this study.

The study findings hold important implications and suggest promising avenues for future investigation. Characterizing the preoperative neuropsychological profile may allow cognitive training interventions for delirium prevention, targeted to the high-risk areas identified in this study. For example, pre-operative interventions such as computer training protocols or other behavioral training programs that boost brain “fitness” (29, 30) might strengthen attentional systems, working memory and perhaps bolster cognitive reserve to protect against the deleterious effects of surgery or other stressors (30). Thus, this study may lay the groundwork for future delirium prevention trials targeted at preoperative attention and executive functioning domains.

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Appendix

Elements of Financial/ Personal Conflicts	Tamara G. Fong		Tammy T. Hshieh		Bonnie Wong		Doug Tommet		Richard N. Jones		Eva M. Schmitt	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X		X		X
Grants/Funds		X		X		X		X		X		X
Honoraria		X		X		X		X		X		X
Speaker Forum		X		X		X		X		X		X
Consultant		X		X		X		X		X		X
Stocks		X		X		X		X		X		X
Royalties		X		X		X		X		X		X
Expert Testimony		X		X		X		X		X		X
Board Member		X		X		X		X		X		X
Patents		X		X		X		X		X		X
Personal Relationship		X		X		X		X		X		X

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Figure 1.

Standardized differences in neuropsychological test scores between non-delirious and delirious patients. Higher scores equate to better test performance for all tests (Trails A and B scores are reversed for consistency). All scores adjusted for age, gender and education. VSAT = visual search and attention test; HVLTR = Hopkins Verbal Learning Test – Revised; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; WTAR = Wechsler Test of Adult Reading

* Please refer to Appendix Table 1 for detailed information regarding each neuropsychological test.

Table 1

Neuropsychological Test Results by Delirium Status

	Overall Cohort N=300		No Delirium N=218		Delirium N=82	
	Score (SD)	N (%) impaired	Score (SD)	N (%) impaired	Score (SD)	N (%) impaired
Trail-making Test A	42.3 (15.4)	24 (8)	42.0 (15.9)	18 (8)	43.1 (13.9)	6 (7)
Trail-making Test B	115.9 (57.3)	30 (10)	111.1 (54.8)	18 (8)	128.7 (61.8)	12 (15)
FAS Fluency	34.7 (12.7)	45 (15)	35.4 (13.3)	32 (15)	32.9 (11.1)	13 (16)
Category Fluency	21.3 (6.0)	37 (12)	21.8 (6.3)	25 (11)	19.9 (5.1)	12 (15)
VSAT	43.0 (9.5)	52 (17)	43.9 (9.4)	30 (14)	40.7 (9.5)	22 (27)
HVLT-R – Trial 1	5.4 (1.7)	38 (13)	5.6 (1.7)	26 (12)	5.0 (1.5)	12 (15)
HVLT-R – Trial 2	7.5 (2.0)	46 (15)	7.7 (2.0)	30 (14)	7.0 (1.9)	16 (20)
HVLT-R – Trial 3	8.4 (2.1)	50 (17)	8.6 (2.0)	30 (14)	7.8 (2.2)	20 (24)
HVLT-R – Discrimination	9.8 (1.9)	34 (11)	9.9 (1.9)	22 (10)	9.8 (1.8)	12 (15)
HVLT-R – Delayed Recall	7.3 (2.8)	25 (8)	7.4 (2.7)	17 (8)	6.8 (2.8)	8 (10)
Digit Span Forward	6.4 (1.3)	78 (26)	6.5 (1.3)	55 (25)	6.3 (1.2)	23 (28)
Digit Span Backward	4.6 (1.2)	45 (15)	4.7 (1.3)	34 (16)	4.5 (1.0)	11 (13)
Boston Naming Test	13.4 (2.0)	30 (10)	13.5 (2.0)	18 (8)	13.0 (2.1)	12 (15)
RBANS Digit Symbol Substitution	35.8 (9.8)	36 (12)	36.3 (9.9)	27 (12)	34.2 (9.2)	9 (11)
WTAR	38.0 (9.5)	44 (15)	38.6 (9.2)	29 (13)	36.3 (10.0)	15 (18)

SD = standard deviation; VSAT = visual search and attention test; HVLT-R = Hopkins Verbal Learning Test – Revised; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; WTAR = Wechsler Test of Adult Reading. For Trails A and B, a higher score indicates worse performance; for all other measures a lower score indicates worse performance.

* Please refer to Appendix Table 1 for detailed information regarding each neuropsychological test.

Appendix Table 1
SAGES Neuropsychological Test Battery with Cognitive Domain Correlates

Test	Description	Scoring	Domain(s) tested
Trail-making Tests A and B	Participant must connect a sequence of alternating numbers and letters	Time (seconds) to completion, maximum 300 seconds. Lower score (time) is better	Executive function, visual spatial function, processing speed
Phonemic F-A-S Fluency	Participant must generate as many words in one minute as possible beginning with a given letter over three trials (e.g., "F", "A", "S")	Number of items, higher is better	Executive function, semantic memory, language
Category Fluency	Participant must generate as many words in one minute as possible from a semantic category (e.g., "animals")	Number of items, higher is better	Executive function, semantic memory, language
Visual Search and Attention Test	Four timed visual cancellation tasks where participant must cross out letters and symbols identical to a target	Number of items, 200 total (100 per side, left and right)	Executive, visual spatial function
Hopkins Verbal Learning Test - Revised	A list of words is read to the participant, who is asked to repeat the list back over multiple learning and delayed recall trials	Number of items, 0-28 per trial, higher is better	Verbal episodic memory
Digit Span Forward/Backward	Participant is asked to repeat a string of digits forward and in reverse order	Number of correct trials, 0-14, higher is better	Attention
Boston Naming Test	Participant is presented with drawings of common objects, which then must be named correctly	Number of correct items, 0-15, higher is better	Confrontation naming, language
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Digit Symbol Substitution	Using a key provided, the participant matches symbols to numbers as quickly as possible while being timed	Number correct items, 0-160 total index score	Executive function, visual spatial function, processing speed
Wechsler Test of Adult Reading	Participant is presented with 50 irregularly spelled words on individual word cards and asked to pronounce each word	Number of correct items, 0-50, higher is better	Peak life-time intelligence