

# Executive Function and Depression as Independent Risk Factors for Postoperative Delirium

Patrick J. Smith, M.A.,\* Deborah K. Attix, Ph.D.,† B. Craig Weldon, M.D.,‡ Nathaniel H. Greene, B.S.,§  
Terri G. Monk, M.D., M.S.,||

**Background:** Postoperative delirium has been associated with greater complications, medical cost, and increased mortality during hospitalization. Recent evidence suggests that preoperative executive dysfunction and depression may predict postoperative delirium; however, the combined effect of these risk factors remains unknown. This study examined the association among preoperative executive function, depressive symptoms, and established clinical predictors of postoperative delirium among 998 consecutive patients undergoing major noncardiac surgery.

**Methods:** A total of 998 patients were screened for postoperative delirium (n = 998) using the Confusion Assessment Method as well as through retrospective chart review. Patients underwent cognitive, psychosocial, and medical assessments preoperatively. Executive function was assessed using the Concept Shifting Task, Letter-Digit Coding, and a modified Stroop Color Word Interference Test. Depression was assessed by the Beck Depression Inventory.

**Results:** Preoperative executive dysfunction ( $P = 0.007$ ) and greater levels of depressive symptoms ( $P = 0.049$ ) were associated with a greater incidence of postoperative delirium, independent of other risk factors. Secondary analyses of cognitive performance demonstrated that the Stroop Color Word Interference Test, the executive task with the greatest complexity in this battery, was more strongly associated with postoperative delirium than simpler tests of executive function. Furthermore, patients exhibiting both executive dysfunction and clinically significant levels of depression were at greatest risk for developing delirium postoperatively.

**Conclusions:** Preoperative executive dysfunction and depressive symptoms are predictive of postoperative delirium among noncardiac surgical patients. Executive tasks with greater complexity are more strongly associated with postoperative delirium relative to tests of basic sequencing.

POSTOPERATIVE delirium occurs in 5–15% of patients after noncardiac surgery<sup>1,2</sup> and is associated with a 3-

to 11-fold increase in mortality during the subsequent 6 months.<sup>3–5</sup> Accordingly, there is an increasing need to examine clinical risk factors of delirium to identify individuals in need of prophylactic intervention.<sup>2</sup> Although risk factors for postoperative delirium vary between studies, preoperative age, depression, alcohol use, medical comorbidities, and cognitive impairment appear to confer a greater risk of postoperative delirium.<sup>6</sup>

Recent evidence suggests that preoperative cognitive and psychosocial dysfunction may predict postoperative delirium among individuals without clinically significant impairments.<sup>7,8</sup> Although it is well recognized that individuals with compromised cognitive ability preoperatively (e.g., dementia)<sup>9,10</sup> are at greater risk of delirium, recent evidence suggests that decrements in higher-order cognitive functions, such as executive function, may predict postoperative delirium in the absence of frank cognitive impairment.<sup>7</sup> Similarly, subclinical levels of depression may predict delirium after major noncardiac surgery, independent of traditional risk factors.<sup>8</sup> A companion article in this issue by Greene *et al.* suggests that the combination of preoperative depression and executive dysfunction has the highest positive predictive value for postoperative delirium, relative to the presence of either risk factor by itself.<sup>11</sup>

Executive dysfunction has been variably defined as difficulty carrying out complex tasks, inability to successfully engage in problem-solving behaviors, and difficulty engaging in independent, purposeful actions.<sup>12</sup> Compromises in processing speed and in complex sequencing and reasoning, are common among those with executive deficits. Executive dysfunction is common among individuals with depression<sup>13,14</sup> and is associated with greater cardiovascular risk factors<sup>14</sup> regardless of cardiac acuity.<sup>15,16</sup> In addition, white matter degradation has been prospectively associated with greater severity of executive dysfunction<sup>17,18</sup> and depressive symptoms.<sup>19</sup> Furthermore, recent studies reporting that depression predicts postoperative delirium have demonstrated that the severity of executive dysfunction parallels depression severity, underscoring the need to clarify this potentially confounding relationship.<sup>8</sup> Despite recent findings demonstrating a relationship between executive dysfunction, depression, and delirium, few studies have examined the independent predictive abilities of these interrelated factors on delirium, or considered them along with clinical variables known to increase delirium risk.

This article is featured in "This Month in Anesthesiology."  
Please see this issue of ANESTHESIOLOGY, page 9A.

\* Graduate Student, Department of Psychiatry and Behavioral Sciences, Division of Medical Psychology, † Associate Professor, Department of Psychiatry and Behavioral Sciences, Division of Medical Psychology, and Department of Medicine, Division of Neurology, ‡ Associate Professor, Departments of Anesthesiology and Pediatrics, § Medical Student, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, || Professor, Department of Anesthesiology, Duke University Medical Center, and Durham Veterans Affairs Medical Center, Durham, North Carolina.

Received from the Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina. The sample was recruited at the University of Florida, Gainesville, Florida. Submitted for publication September 17, 2008. Accepted for publication December 18, 2008. Supported by Grant K01-AG19214 from the National Institute on Aging, Bethesda, Maryland, the Anesthesia Patient Safety Foundation, Indianapolis, Indiana, and the I. Heermann Anesthesia Foundation, Inc., Gainesville, Florida.

Address correspondence to Dr. Smith: Department of Psychiatry and Behavioral Sciences, Box 3119, Duke Medical Center, Durham, North Carolina 27710. smith562@mc.duke.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

## Materials and Methods

### *Patient Sample*

After approval by the University of Florida Institutional Review Board in Gainesville, Florida, patients were enrolled in a previously reported trial examining predictors of postoperative cognitive decline.<sup>20</sup> Patients were approached for participation at Shands Hospital (Gainesville, Florida) between February 1, 1999, and January 31, 2002, and gave written informed consent before participation. Inclusion criteria included adult age (at least 18 yr) and a scheduled hospital admission as an inpatient for a minimum of 2 days after noncardiac surgery. Notably, patients with a mini mental status exam score of 23 or less<sup>21</sup> or a history of dementia or any disease of the central nervous system were excluded. Patients with current or past history of psychiatric illness of thought disorders, bipolar disorder, or substance abuse disorders were also excluded, as were patients with current major depression requiring psychiatric management or current or past electroconvulsive therapy. Individuals undergoing active pharmacologic management by a psychiatrist (including tranquilizers and/or antidepressants) were also excluded.

### *Preoperative Evaluation*

All subjects were interviewed within 14 days of surgery to obtain information regarding demographic status, medical history, education, and employment status.<sup>20</sup> Current medications, alcohol use, smoking history, and surgical and psychiatric histories were also recorded. Severity of postoperative pain was assessed using the numerical rating scale for pain, which rates pain on a 0–10 scale, with 0 indicating no pain and 10 indicating severe pain.<sup>22</sup> Medical comorbidities were indexed using the Charlson comorbidity score, which provides a weighted index, including both the number and the seriousness of comorbid medical conditions.<sup>23</sup>

### *Delirium*

Delirium status was assessed with chart review and/or the Confusion Assessment Measure.<sup>24</sup> Results did not differ substantively among delirium assessment methodologies. The Confusion Assessment Method diagnostic algorithm was used to define the presence or absence of delirium at each assessment, monitored up to 8 days postoperatively. Delirium was defined as the presence of both (1) acute onset and fluctuating course and (2) inattention, as well as either (3) disorganized thinking, or (4) altered level of consciousness.

### *Neuropsychological Performance*

Neuropsychological performance was assessed using a standardized battery of cognitive measures that have been previously reported.<sup>20</sup> The following instruments were used in this analysis.

**Concept Shifting Task.** Concept Shifting Task<sup>25</sup> part C, based on the Trail Making Test, requires patients to draw consecutive lines alternating back and forth between the numbers 1 through 8 and the letters A through H. This task is simpler than the Trail Making Test because the sequence involves fewer letters/numbers and because the stimuli occur in a straightforward, circular array. The score is the time in seconds required for completion.

**Letter-Digit Coding.** Letter-Digit Coding,<sup>26</sup> based on the Digit-Symbol Substitution subtest of the Wechsler Adult Intelligence Scale III, requires rapid sequencing of digits and letter symbols. This task also is simpler than the Digit-Symbol Substitution subtest on which it is based because the pairs of letters and numbers may be easier to encode than pairs of digits and abstract symbols. In this task, the subject is given a key grid of numbers and corresponding letters and a test grid with letters and empty boxes. The subject fills in as many of the empty boxes with the numbers that correspond to the printed letters in 1 min.

**Modified Stroop Interference Task.** Modified Stroop Interference Task<sup>27</sup> is based on the Stroop Test. In the word trial, the subject reads words, all of which are colors (*e.g.*, blue, green), printed in black ink. In the color trial, the subject next identifies colors that appear as colored rectangles. Finally, in the color/word trial, the subject must rapidly identify the printed color that the color words (*e.g.*, blue, green) are printed in, which requires suppressing the reading of the color word. It is the time to complete this third response inhibition trial that is used for analysis.

### *Depression*

Depressive symptoms were assessed using the Beck Depression Inventory (BDI).<sup>28,29</sup> The BDI is a standardized 21-item self-report questionnaire consisting of symptoms and attitudes related to depression, including items such as self-dislike, suicidal ideation, insomnia, and sadness. The items are summed with total scores ranging from 0 to 63, with higher scores indicating higher levels of depression. The BDI has been shown to be a valid and reliable measure of depression severity with robust psychometric properties among patient and normal populations, across a wide range of age groups.<sup>30</sup>

### *Statistical Analysis*

**Data Reduction.** To characterize the sample and those who did *versus* did not develop delirium, preoperative demographic and background differences between delirium groups were evaluated using *t* tests for continuous variables and chi-square tests for categorical variables. For analysis of executive function as a potential predictor, a composite Z-score of executive function was created for each individual. Use of a composite minimized both the number of statistical tests in the

present analysis and type-I error inflation due to significant intercorrelations between executive function measures ( $r \geq 0.56$ ,  $P < 0.0001$ ).<sup>31</sup> First, subject scores for each measure were transformed to Z-scores using the sample mean and SD. All three z-scores were then summed to form the executive function composite. Before calculating the Z-scores, we ensured that the direction of each individual test Z-scores reflected the same level of performance, *i.e.*, the higher the Z-score the better the performance. The composite score is calculated as the sum of the Z-scores for each individual measure, combined within individuals. This unit-weighted composite was then used as a predictor variable in the primary logistic regression model described below.

**Data Analysis.** General linear modeling equations using SAS programming (Cary, NC) were used for all analyses. Sample size determination has been previously reported.<sup>20</sup> Briefly, the current study from which these data were drawn was powered for the purposes of examining differences in postoperative cognitive decline between elderly and middle-aged/younger patients, and data on delirium were collected as a secondary endpoint. Assuming a 40% rate of mild preoperative depressive symptoms among nondelirious patients<sup>8</sup> and a two-sided test at  $\alpha = 0.05$  for this secondary analysis, we determined that we would have a power of 80% to detect a difference of 24% in the proportion of delirious patients exhibiting mild preoperative depressive symptoms. Using Beck's criteria,<sup>28</sup> we observed a 27.3% difference in the presence of mild depressive symptoms among individuals who developed delirium postoperatively.

The primary analysis consisted of a logistic regression. To avoid inflation of type-I error rates associated with step-wise regression, all covariates were selected *a priori* and were entered simultaneously.<sup>32</sup> Covariates included age, years of education, Charlson comorbidity scale, alcohol consumption (drinks per week), pain, and depressive symptoms. These covariates were chosen because they are empirically validated predictors of delirium.<sup>6</sup> As a secondary analysis, the predictive ability of individual executive measures was examined in both unadjusted and adjusted analyses. Exploratory analyses were conducted to examine the additive effects of executive dysfunction and clinically significant depression. Continuous predictors were standardized using the sample SD. This rescaling preserves the continuous nature of the predictor but places the regression coefficient on a clinically meaningful scale.

## Results

### Patient Characteristics

Complete patient data were available for 998 subjects. As previously reported,<sup>20</sup> 1,496 were assessed for eligibility, with 267 refusing to participate and 165 not meet-

**Table 1. Demographic and Clinical Characteristics of Patient Sample**

	Delirium (n = 35)	No Delirium (n = 961)	P Value
Age, yr*	63.9 (15.5)	50.5 (16.8)	< .001
Education level, yr*	13.0 (3.1)	13.5 (2.6)	0.26
Alcohol intake, units/week*	2.0 (4.2)	1.1 (3.3)	0.107
Pain*	2.3 (3.0)	2.4 (3.1)	0.814
BDI*	8.8 (5.1)	6.9 (6.7)	0.092
Charlson Comorbidity Score*	3.0 (2.0)	1.5 (1.9)	< 0.001
Executive factor*			
Concept Shifting, s	43.4 (21.3)	33.9 (16.5)	0.013
Letter Digit Coding, correct	28.0 (7.7)	34.1 (8.4)	< 0.001
Stroop, s	61.4 (23.2)	47.6 (15.6)	< 0.001
Additional descriptive comparisons			
History of stroke, n (%)	2 (5.7)	34 (3.5)	0.496
History of heart disease, n (%)	10 (28.6)	95 (9.9)	< 0.001
History of hypertension, n (%)	12 (34.3)	323 (33.5)	0.927
History of depression, n (%)	11 (31.4)	142 (14.8)	0.007
Benzodiazepines, n (%)	7 (20.0)	74 (7.7)	0.009
BMI, kg/m <sup>2</sup>	28.4 (6.1)	30.9 (10.2)	0.138

Values represent mean (SD) unless otherwise indicated.

Variables selected for inclusion in primary regression model.

BDI = Beck Depression Inventory; BMI = Body Mass Index.

ing inclusion criteria. In addition, 66 patients did not have complete delirium data. Participants in the final sample ranged in age from 18 to 90 yr (mean age = 51.0 yr, SD = 17.0) and reported 13.5 yr of education (SD = 2.6), and the majority of participants were female (63.4%) and of European descent (89.3%). Consistent with inclusion criteria, patients in our sample exhibited minimal levels of depressive symptoms (mean BDI = 6.9, SD = 6.6). Based on the level of depressive symptomatology endorsed (using Beck's criteria<sup>28</sup>), 74.4% of the patients endorsed minimal, 19.7% endorsed mild, 4.6% endorsed moderated, and 1.3% endorsed severe symptoms of depression. Delirium occurred in 3.5% of patients and was more common among individuals 65 yr of age or older (n = 21, 8.0%; chi-square = 21.24,  $P < 0.001$ ). We did not observe any differences in rate of postoperative delirium between inhalational *versus* intravenous anesthesia ( $P = 0.457$ ), intraoperative use of nitrous oxide ( $P = 0.539$ ), or body mass index ( $P = 0.138$ ).

As shown in table 1, patients who developed delirium were older ( $P < 0.001$ ), exhibited greater medical comorbidities ( $P < 0.001$ ), had a greater prevalence of heart disease ( $P < 0.001$ ), and had a higher rate of Benzodiazepine use ( $P = 0.009$ ) relative to their nondelirious counterparts. Patients were also assessed specifically for a history of depression. Patients who developed postoperative delirium were also more likely to report a history of depression ( $P = 0.007$ ). Patients developing postoperative delirium exhibited poorer performance on all executive function tasks at baseline: Concept Shifting ( $P = 0.013$ ), Letter-Digit Coding ( $P < 0.001$ ), and Stroop ( $P < 0.001$ ).

**Table 2. Results of Multivariable Linear Regression Model Predicting Postoperative Delirium**

Predictor (SD)	Odds Ratio for Delirium* (95% Confidence Interval)
Age (17)	1.847 (1.106–3.086)†
Education (2.6)	1.055 (0.730–1.525)
Charlson (2)	1.377 (1.020–1.861)†
Alcohol (3.3)	1.141 (0.881–1.479)
Pain (3.1)	0.936 (0.636–1.377)
Beck depression (6.6)	1.370 (1.000–1.876)†
Executive function composite	1.231 (1.058–1.433)‡

\* Adjusted for age, education (years), comorbidity (Charlson Comorbidity Index), alcohol consumption, pain, and Beck Depression Inventory. Values are scaled using the standard deviation (SD) of the predictor variable. † Significant at  $P \leq 0.05$ . ‡ Significant at  $P \leq .01$ .

### Predictors of Postoperative Delirium

Regression analyses were then conducted to investigate the independent contributions of selected predictors when considered simultaneously. After adjustment for *a priori* selected covariates (see table 1 for variables included), older age ( $P = 0.019$ ), greater medical comorbidities ( $P = 0.036$ ), higher levels of depressive symptoms ( $P = 0.049$ ), and poorer executive function ( $P = 0.007$ ) continued to predict postoperative delirium (table 2).

### Executive Function Predictors of Delirium

*Post hoc* examination of the predictive ability of individual executive function measures is shown in table 3. As shown, all executive function measures were predictive of delirium in unadjusted analyses ( $P < 0.013$ ). After adjusting for age, education, medical comorbidities, alcohol consumption, pain, and depressive symptoms, poorer performance on the modified Stroop task was the only index of executive function that predicted postoperative delirium ( $P = 0.006$ ).

### Additive Effects of Depression And Executive Dysfunction

Exploratory analyses were conducted to assess the additive effects of clinically significant depression among

**Table 3. Results of Multivariable Linear Regression Model Predicting Postoperative Delirium**

Predictor (SD)	Odds Ratio for Delirium (95% CI)	
	Raw	Adjusted*
Concept Shifting (16.4)	1.326 (1.094–1.606)‡	1.116 (0.854–1.458)
Letter Digit Coding (8.4)	2.007 (1.438–2.801)‡	1.432 (0.920–2.229)
Stroop Color Word (15.1)	1.823 (1.433–2.319)‡	1.559 (1.138–2.136)‡

\* Adjusted for age, education (years), comorbidity (Charlson Comorbidity Index), alcohol consumption, pain, and Beck Depression Inventory. ‡ Significant at  $P \leq 0.01$ .

individuals exhibiting executive dysfunction. Clinically significant depression was defined on the basis of previously established clinical cut-offs ( $BDI \geq 14$ ), and executive dysfunction was defined as 60 s or more for completion of the modified Stroop task (corresponding to the 20th percentile of the sample performance, approximately). Delirium risk was defined as low (neither executive dysfunction nor depression), moderate (either executive dysfunction or depression, but not both), or high (both executive dysfunction and depression). Results demonstrated that the prevalence of delirium increased with risk, such that individuals at low, moderate, and high risk exhibited delirium rates of 2.8%, 4.7%, and 12.0%, respectively ( $\chi^2 = 5.78$ ,  $P < 0.016$ ).

## Discussion

These findings parallel those obtained by Greene *et al.*<sup>11</sup> in the companion article found in this issue. In the current sample, we again found that poorer executive function and higher levels of depressive symptoms were associated with an increased incidence of postoperative delirium among patients undergoing major noncardiac surgery. We also found that, consistent with previous studies, greater age and medical comorbidities were also associated with an increased risk of delirium in addition to the independent risk introduced by executive and affective factors. Secondary analysis suggested that the association between executive function and incidence of delirium was strongest on tasks associated with greater complexity, such as the Stroop Color Word Test. In contrast, performance on executive tasks with limited sequencing requirements, such as the Concept Shifting and Letter-Digit Coding tasks, were not associated with increased delirium risk.

Our findings in a robust sample of approximately 1,000 patients of various ages are similar to those of Greene *et al.*<sup>11</sup> We specifically demonstrate that executive function and depressive symptoms contribute unique information in assessing delirium risk among noncardiac surgical patients, independent of age and comorbidity effects. Although these studies varied in the diversity of executive tasks administered and analytical strategies, both found executive task complexity to be an important determinant of its predictive strength.

Our finding that poorer executive function was associated with increased likelihood of delirium is consistent with previous studies demonstrating an association between preoperative cognitive impairment and postoperative delirium. In a systematic literature review, Dasgupta and Dumbrell<sup>6</sup> found that preoperative cognitive impairment was a consistent predictor of postoperative delirium across numerous patient samples. Moreover, the relationship between cognitive impairment and delirium was predictive across studies, regardless of

other variables considered. Recent studies among cardiac patients indicate that decrements in higher-order cognitive functions, such as executive function, may predict postoperative delirium even among patient samples without cognitive compromise. Rudolph *et al.*<sup>7</sup> recently found that executive dysfunction was associated with a greater incidence of delirium among 80 cardiac patients undergoing coronary artery bypass grafting or coronary artery bypass grafting-valve surgery. Notably, this association remained after controlling for other domains of cognitive function, including memory and general mental status, indicating that the effects are specific to the domain of executive function.

Our finding that greater levels of depressive symptoms may be associated with increased risk of delirium is consistent with previous findings among older adults.<sup>8,33,34</sup> McAvay *et al.*<sup>33</sup> found that higher levels of depression, indexed using the Geriatric Depression Scale, were associated with increased delirium incidence among 412 individuals aged 70 yr or older participating in the Delirium Prevention Trial. Galanakis *et al.*<sup>34</sup> reported similar findings among individuals aged 60 or older, demonstrating that higher levels of depression predicted delirium after adjustment for clinical predictors such as age and previous cognitive impairment. Similarly, Leung *et al.*<sup>8</sup> found that greater preoperative depression levels were associated with an increased incidence and longer duration of postoperative delirium among older individuals undergoing major, noncardiac surgery. Results of the present analysis therefore extend existing findings by demonstrating that preoperative depressive symptoms may predict postoperative delirium independent of age and that executive dysfunction and depression independently increase the risk of delirium among noncardiac surgical patients.

Our finding that depressive symptoms predicted postoperative delirium is notable given that individuals currently undergoing psychiatric treatment or reporting a history of severe depression requiring electroconvulsive therapy treatment were excluded from our study sample, consistent with previous studies.<sup>35</sup> It is possible that patients in our study not actively receiving treatment for depression may have had a recent history of major depression, or may have been actively experiencing sub-threshold depressive symptoms during their preoperative assessments. This is consistent with previous studies demonstrating that the majority of depressed individuals will experience recurring episodes throughout their lifetimes.<sup>36,37</sup> Subclinical depression is defined as depressive symptomatology of either insufficient frequency or severity to meet diagnostic criteria for major depressive disorder.<sup>38</sup> Subclinical levels of depression, although less severe, have garnered recent attention as emerging evidence suggests that subclinical levels of depression may predict later episodes of full-blown depressive disorders<sup>36</sup> and have been shown to predict postoperative

delirium in some studies.<sup>8</sup> It is therefore not surprising that individuals exhibiting depressive symptoms preoperatively showed a greater vulnerability for developing delirium postoperatively in our sample, despite the exclusion of individuals undergoing active treatment for depression. Given the restricted range of depressive symptoms in our sample due to our exclusion of severely depressed individuals, we suspect that future studies incorporating patients with greater levels of depression will find similar, if not stronger, associations with delirium. Our findings provide evidence that subclinical depression represents a significant risk factor for delirium, which is compelling.<sup>39</sup>

Our findings also provide preliminary evidence that tasks of executive function with greater complexity may have enhanced predictive utility relative to tasks relying more heavily on straightforward sequencing abilities. As an illustrative point among patients in the current sample, a 10-s slower score on the modified Stroop task conferred an increased risk of delirium comparable to an increase of 8 yr in age (odds ratios = 1.531 [1.275–1.839] and 1.534 [1.238–1.900], respectively), controlling for the covariates included in our primary analyses. This finding is not surprising given that executive dysfunction has been shown to mediate age-related cognitive deterioration<sup>40</sup> and overlaps substantially with basic sequencing skills in some samples.<sup>12</sup> The degree of complexity varies across executive measures, with some tasks tapping more basic attentional processes and others drawing upon more complex reasoning, inhibition, or sequencing skills. There is evidence to suggest that the more complex executive tasks require the synthesis of information from multiple brain systems, including cortical and subcortical areas associated with attention, working memory, and speed of processing.<sup>41</sup>

In our study, the results of exploratory regression analyses of the separate measures revealed that the more complex response inhibition task was the only executive measure that remained an independent predictor among the other risk factors of depression, age, and comorbidities. In contrast, the simpler, more straightforward tasks did not remain as independent predictors. It is interesting to note that the methodology used by Greene *et al.* also identified the executive task with greater complexity as the most predictive of postoperative delirium.<sup>11</sup> In that study, the investigators considered all of the executive measures simultaneously to identify which measure was most predictive, and also found that the task with the most complexity was independently related to delirium, as was depression. Further study of which executive tasks best predict delirium across studies is necessary to improve instrument selection for use in clinical samples.

Delirium is associated with significant reductions in global cerebral blood flow and systemic neurotransmitter dysfunction.<sup>42</sup> Although the pathophysiology of de-

lirium is multifactorial, the  $\gamma$ -Aminobutyric Acid, acetylcholine,<sup>43</sup> and serotonin neurotransmitter systems appear to be principally involved.<sup>44</sup> Recent evidence suggests that dysregulation in the homeostasis of tryptophan, the precursor to serotonin, may play a critical role in the pathogenesis of postoperative delirium.<sup>45</sup> Because abnormalities in the regulation of serotonin have been consistently linked with depression,<sup>46</sup> this may have important implications for elucidating the depression and delirium relationship. Future studies should examine the pathophysiologic mechanisms responsible for postoperative delirium and interventions to prevent its occurrence.<sup>47</sup>

It is also possible that occult white matter damage to the frontal-striatal areas of the brain predisposes some patients to develop delirium. It is not inconceivable that such mild white matter decrements could manifest preoperatively by decreased executive performance and/or greater levels of depression. This hypothesis is supported by the conclusion from recent coronary artery bypass grafting studies that the executive dysfunction and delirium relationship may be mediated by severity of atherosclerosis.<sup>7</sup> Furthermore, abnormalities in the frontal-striatal circuitry have been previously shown to predict delirium among depressed individuals after electroconvulsive therapy<sup>48</sup> and are associated with executive deficits in a variety of patient populations.<sup>49,50</sup> Again, the relationship between these factors and their independent and joint effects on delirium warrant further study.

Results from the current study should be viewed with the following limitations in mind. First, our enrollment criteria excluded individuals with a history of specific psychiatric illnesses as well as patients under psychiatric care; therefore, it is possible that our analyses of depressive symptoms were underpowered due to a restricted range of depressive symptoms in our sample. Therefore, our finding that depressive symptoms may predict postoperative delirium despite the limited range under examination underscores the need for future studies to investigate this relationship; this association may be stronger among samples with more inclusive recruitment practices. However, even in this restrictive sample, the relationship between depressive symptoms and the development of postoperative delirium emerged clearly. In addition to the significance of current symptomatology to delirium risk, it is also interesting that those who developed delirium were also 2.5 times more likely to report having had a history of depression than those that did not develop delirium (31.4% *vs.* 14.8%, odds ratio = 2.65,  $P = 0.007$ ). Our enrollment criteria also excluded individuals with cognitive impairment (defined as mini mental status exam < 23), restricting the range of our executive function variable in a similar manner. It is unclear, for example, how the executive measures used in our study would have functioned in a sample incorporating individuals with significant cognitive impairment or dementia. Second, the observed rates of delirium

differed between our findings and those of Greene *et al.*,<sup>11</sup> most likely due to differences in patient populations. Finally, our multivariate model included more covariates than ideally preferred given the small number of delirium cases in our study. However, it has been recommended by authorities in this area that *a priori* selected modeling is preferable to stepwise techniques,<sup>32</sup> and recent simulation studies have demonstrated that this reduced number of events per variable provides adequate model estimates in some circumstances.<sup>51</sup>

In summary, poorer executive function and greater levels of depressive symptoms were associated with a greater incidence of postoperative delirium after major noncardiac surgery. Moreover, these effects persisted after adjustment for established risk factors of delirium. Secondary analyses indicated that the vulnerability to delirium exhibited on executive tasks may only be evidenced on tests associated with greater complexity. Future studies should systematically examine the predictive ability of individual executive measures to establish the most reliable and valid instruments by which to identify at-risk individuals preoperatively. Further study of the predictive ability of executive function measures among cognitively impaired patients is also warranted, as our sample excluded individuals with cognitive compromise or dementia. Furthermore, future studies should examine the effects of prophylactic interventions among patients exhibiting executive dysfunction to prevent postoperative delirium.

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