Neurocognitive Deficits in a Cohort With Class 2 and Class 3 Obesity: Contributions of Type 2 Diabetes and Other Comorbidities

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Objective: This study examined the relationship between specific metabolic and vascular risk factors and cognition in adults with severe obesity.

Methods: A total of 129 adults (with BMI ≥ 35 kg/m²) underwent a baseline clinical evaluation and neuropsychological assessment. Regression analyses examined the relationship between cognition and medical factors (BMI, hemoglobin A1c, diabetes, hypertension, continuous positive airway pressure use, obstructive sleep apnea [OSA], and osteoarthritis).

Results: Diabetes was associated with deficits in overall cognitive performance and with deficits in the executive processing speed and verbal fluency domains. Hemoglobin A1c was inversely related to overall cognitive performance and deficits in the attention domain. Participants using continuous positive airway pressure to treat OSA had stronger learning and memory performance, whereas OSA was associated with reduced total learning. Elevated BMI together with diabetes diagnosis was associated with reduced verbal fluency and greater variability in sustained attention.

Conclusions: Obesity-associated comorbidities most notably appeared to have a greater relative influence on cognitive performance than BMI itself in adults with severe obesity. This likely reflects the fact that a very elevated BMI was ubiquitous and thereby probably exerted a similar influence among all adults in the cohort. Accordingly, in the context of severe obesity, diabetes and other comorbidities may have greater sensitivity to cognitive deficits than BMI alone.

Introduction
The prevalence of severe obesity has increased dramatically over the past 4 decades, resulting in increased mortality and higher prevalence of medical comorbidities, including type 2 diabetes and heart disease (1). Obesity is also associated with poor neurocognitive outcomes (2). We previously found not only that elevated BMI is associated with cognitive deficits in adults with obesity (3), but also that weight loss with bariatric surgery leads to cognitive improvements (4). Yet the pathophysiological bases for these adverse effects of obesity are not clearly understood. Elevated BMI alone is associated with reduced cognitive performance when examined in the context of otherwise healthy community samples (5). However, cognitive dysfunction also occurs secondarily among adults with medical disorders, including type 2 diabetes (6), hypertension (7), and other vascular etiologies and risk factors (8,9). It is also common in obstructive sleep apnea (OSA) (10), which is highly related to obesity and can be partially reversed with continuous positive airway pressure (CPAP) therapy (11).

Evidence of interactions between cognition and health-related factors, including hypertension and diabetes (12), is important to consider given the high prevalence of concurrent medical comorbidities in adults with chronic obesity. Although an interactive effect is not ubiquitous (13), diabetes commonly exacerbates adverse effects of elevated BMI on cognition and the brain (14). Yet studies often control for diabetes with minimal consideration for interactive effects with obesity (15).

Obesity-associated neuroinflammation can also contribute to cognitive decline, although exact mechanisms are not clear (16). Vascular etiologies in conjunction with obesity can also exacerbate cognitive deficits.

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Among patients with heart failure, both hypertension and obesity contributed to worse performance in attention, executive functions, and language (17). However, other studies have shown a less consistent impact of obesity using systematic comparison of vascular risk factors (8,18). Studies examining associations between obesity and other comorbidities on cognition have also yielded mixed results. We previously found that cognitive improvements associated with weight loss surgery were not attributable to reduced OSA (19). Despite research to support cognitive deficits secondary to OSA, disentangling the influence of obesity per se remains a challenge (20).

Although it is not surprising that comorbidities such as hypertension and diabetes are independently associated with cognitive deficits and that all are more prevalent among adults with elevated BMI (18), few studies have examined the influence of multiple medical comorbidities and severe obesity on cognitive function. Many studies are often epidemiological analyses of the general population, healthy community cohorts, or individuals with health conditions of wide-ranging severity. Unfortunately, such findings do not directly explain the reason for previously observed cognitive deficits among individuals with severe obesity. Several possibilities exist: (1) cognitive deficits may be a manifestation of obesity itself, (2) all of the comorbidities common with obesity may interact and contribute to cognitive deficits, or (3) the presence of a specific obesity-associated comorbidity is the primary factor driving cognitive deficits among some but not all individuals with obesity. To address this issue, the current study examined associations between vascular, metabolic, and clinical factors and cognitive performance in a cohort of adults with severe obesity. Consistent with our previous reports, we hypothesized that higher BMI values are associated with lower cognitive performance. We also hypothesized that various conditions linked to obesity (e.g., diabetes, hypertension) adversely impact brain function in individuals with severe obesity.

Methods
Study design
This current study employed data from the University of Florida’s Weight Loss Intervention Surgical Effects (WISE) Brain Stud (https://diabetes.ufl.edu/research/type-2-diabetes/wise-brain/). Funded by the National Institute of Diabetes and Digestive and Kidney Diseases, this longitudinal R01 study examines the effects of severe obesity on cognition and brain functioning to determine whether weight loss occurring after bariatric surgery contributes to improvements in cognition that can be attributed to specific metabolic, vascular, and neural changes occurring in the brain. The research described herein presents presurgical baseline data from a cohort of surgical and nonsurgical participants who are being followed prospectively in this larger study. Individual participant data are not available for review at this time as data are being collected as part of an active R01 study.

Participants
Individuals aged 20 to 75 years (with BMI ≥ 35 kg/m²) were eligible to participate in the study. Exclusion criteria included a total score < 20 on the Montreal Cognitive Assessment, history of neurological disorder or injury, severe psychiatric illness, unstable medical condition (e.g., cancer), and history of alcohol or substance abuse. A total of 129 patients were assessed at baseline; 65.9% met criteria for having class 3 obesity (BMI ≥ 40.0), whereas 34.1% met criteria for having class 2 obesity (BMI of 35.0-39.9). The sample included bariatric surgery candidates (n=88) and community dwellers with similar BMI levels who were not planning to have weight loss surgery. The community sample was recruited as controls for future analysis of postoperative changes in cognitive and brain functioning. Members from both groups reported a history of diet and exercise methods of weight loss but denied bulimia nervosa.

Procedures
The local institutional review board approved all study procedures, and all participants provided written informed consent prior to enrollment. Participants completed a medical history evaluation, a neuropsychological assessment battery, and self-report questionnaires. In addition, participants underwent a polysomnographic evaluation (if never assessed for OSA or not using CPAP therapy). A blood sample was collected for hemoglobin A1c (HbA1c) determination. Fasting plasma glucose was also obtained from medical records for surgical participants.

Measures
Demographic and medical history. History of hypertension, type 2 diabetes, osteoarthritis, apnea, and CPAP therapy; BMI; and pertinent demographic data were collected through a medical chart review and a background history questionnaire. Premorbid intellect was measured using the Barona Index (21), an equation that uses the demographic variables (e.g., age, sex, education) to estimate an individual’s intelligence quotient. Current depressive symptoms were reported via the Beck Depression Inventory, Second Edition (BDI-II) (22). Fasting plasma glucose and HbA1c levels, which indicate the average plasma glucose concentration, were measured along with type of antidiabetic medications used. Per medical standards, an HbA1c concentration ≥ 6.5% or plasma glucose level ≥ 126 mg/dL indicates diabetes (23).

Neuropsychological measures. All participants underwent a brief neuropsychological battery to assess various aspects of cognition, including attention, processing speed, memory, executive functioning, and verbal fluency. All measures used in the current study are well known for their strong psychometric properties. The domains and neuropsychological tests used are reported in Table 1.

Data analysis
Demographic and clinical characteristics were evaluated with descriptive statistics. χ² analyses were used to compare concurrence of diagnosis with various biomarkers or treatment, such as incidence of diabetes diagnosis (hereafter diabetes) and measured HbA1c levels or history of apnea among individuals using CPAP therapy versus nontreatment. Similar analyses were conducted to assess CPAP use, HbA1c levels, and prevalence of medical comorbidities across obesity class. For subsequent analyses, the two groups were pooled because bariatric surgery effects were not being examined. Missing cognitive and medical data were excluded listwise.

Means, SDs, and cognitive performance rates were calculated for all individual cognitive performances along with mean T-scores for overall cognition, attention, verbal fluency, processing speed, memory, and executive functioning domains. We used χ² analyses to determine whether cognitive performance in specific domains was significantly different from normative expectations. Scores below the 16th percentile (i.e., T-scores < 40) were considered below average.
Two sets of regression analysis (backward elimination) were used to study clinical risk factors as predictors for various aspects of cognition. Overall cognitive domain composite scores were used in the first set of analyses, in which all raw data for included neuropsychological measures assessing cognition were transformed into T-scores (mean = 50; SD = 10) using well-established normative data to control for age, education, and sex. Only age-corrected norms were available for Stroop and Adaptive Rate Continuous Performance Test (ARCPT) measures; thus, education and sex were entered as covariates at the final step of regression analysis. Although all measures were controlled for age, additional t tests helped to assess potential group differences between young (ages 20-40) and older (41+) adults. Given recognized associations between depression and cognition, we also controlled BDI-II total scores. The second set of analyses examined within-domain individual neuropsychological test performances. Potential explanatory variables included BMI, HbA1c, and history of hypertension, diabetes, CPAP use, apnea, and osteoarthritis. Fasting plasma glucose was evaluated in a separate analysis because data were available only for 30 presurgical participants.

### TABLE 1 Neuropsychological test measures

| Test measure                  | Test description                                                                                                                                                                                                 |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Attention**                | Computerized measure of vigilance and sustained attention; participants respond through a single keystroke when a specific combination of letters appears on the screen. Indices examined included inconsistency, final ISI (i.e., the minimum interval between stimulus items at which participants can maintain 80% accuracy), and sensitivity a’ (i.e., accuracy in detecting hit targets). |
| ARCPT inconsistency, ARCPT final ISI, ARCPT sensitivity a’ |                                                                                                                                                                                                                   |
| **Processing speed**         | Assessment of visual search speed requiring participants to draw a continuous line through 25 consecutive numbered circles; performance is measured by overall completion time.                                      |
| TMT part A                   |                                                                                                                                                                                                                   |
| **Stroop word reading, Stroop color naming** | Measure of selective attention, cognitive speed, and response inhibition; the test includes two baseline trials lasting 45 seconds each. Trial 1 (word reading) consists of 100 randomly arranged words (red, green, and blue) that participants must quickly read aloud. In trial 2 (color naming), the participants quickly name color patches. |
| **Memory**                   | Measure of learning and recall of a 16-item word list; after the initial learning phase, participants are asked to recall the list after a 20-minute delay. Indices examined included total recall (trials 1-5) and long delay free recall. |
| CVLT-II total recall, CVLT-II long delay |                                                                                                                                                                                                                   |
| **Executive functioning**    | Assessment uses colored words in which the word and the color do not match; this test provides a measure of cognitive inhibition in terms of the ability to inhibit a prepotent response (reading the word) in favor of naming the ink color. |
| Stroop                       | Participants required to draw a continuous line through consecutive numbers and letters, alternating the order each time a connection is made (1-A-2-B-3-C, etc.); unlike part A, this task introduces the added cognitive demand of mental set-shifting. |
| TMT part B                   |                                                                                                                                                                                                                   |
| **Verbal fluency**           | Speeded word retrieval based on letter cues; performance is based on total number of correct responses.                                                                                                        |
| Letter fluency (COWAT)       |                                                                                                                                                                                                                   |
| Animal fluency               | Rapid word generation for a semantic category; performance is based on total number of correct responses.                                                                                                       |
| **Overall cognition**        | Composite score generated using aggregate data from the above individual domains.                                                                                                                                  |
Results

Demographic and clinical characteristics
The majority of patients met criteria for severe obesity, and a significant proportion of the total sample reported diagnosis of hypertension (57.4%), diabetes (35.7%), apnea (42.6%), and osteoarthritis (34.9%). The sample as a whole reported minimal to mild depressive symptoms on the BDI-II (mean = 10.59; SD = 8.90). Participants had up to four comorbidities, and the majority of participants had at least one comorbidity (83.5%). Additional demographic and clinical data are presented in Table 2.

Correlation and cross-tabulation analyses were performed to characterize the study sample and examine relationships between medical variables of interest. Fasting glucose among surgical participants was positively associated with HbA1c ($r = 0.86; P < 0.001$) and diabetes ($r = 0.58; P < 0.001$). Diabetes and HbA1c were also strongly associated ($r = 0.76; \chi^2_{1,100} = 58.01; P < 0.001$). However, only 4 of 46 participants with diabetes exhibited HbA1c levels below the standard cutoff (HbA1c level $< 6.5$), whereas 88.2% of participants with diabetes showed elevated HbA1c levels despite control with diet or medication. Metformin (56%) and insulin (28%) were the most commonly used anti-diabetic medications. Seven individuals with no record of diabetes had elevated HbA1c levels ($\geq 6.5$). Additionally, the hypertension rate was 81.1% for individuals with elevated HbA1c levels, indicating a strong association between variables ($r = 0.38; \chi^2_{1,102} = 14.95; P < 0.001$). Osteoarthritis was also significantly higher among individuals with elevated HbA1c levels (51.4%) versus normal status (29.2%; $r = 0.22; \chi^2_{1,102} = 4.94; P < 0.05$).

Despite a strong association between CPAP use and sleep apnea, there was not a complete correspondence between diagnosis and treatment because only 51.9% of those with apnea reported using CPAP intervention ($r = 0.55; \chi^2_{1,128} = 38.34; P < 0.001$). There was also a higher than expected number of individuals with apnea who were also diagnosed with diabetes ($r = 0.17; \chi^2_{1,129} = 3.82; P = 0.05$). No other associations were found for other clinical variables.

Neurocognitive performance
All cognitive domain scores were in the average range but below expectancy based on the participants’ estimated premorbid intelligence (Barona T-score: mean = 52.55, SD = 5.76). Global cognition was 0.41 SD below premorbid estimates ($t_{21,124} = 1.20, P = 0.04$) and in two individual test scores contributing to these domains (ARCP sensitivity $t_{115} = -2.14, P = 0.04$; memory: $t_{115} = -2.04, P = 0.04$) and in two individual test scores contributing to these domains (ARCP sensitivity $t_{115} = -2.14, P = 0.04$; memory: $t_{115} = -2.04, P = 0.04$) and in two individual test scores contributing to these domains (ARCP sensitivity $t_{115} = -2.14, P = 0.04$; memory: $t_{115} = -2.04, P = 0.04$) and in two individual test scores contributing to these domains (ARCP sensitivity $t_{115} = -2.14, P = 0.04$; memory: $t_{115} = -2.04, P = 0.04$) and in two individual test scores contributing to these domains (ARCP sensitivity $t_{115} = -2.14, P = 0.04$; memory: $t_{115} = -2.04, P = 0.04$). Participants did not exhibit severe neurocognitive disturbances (i.e., scores greater than 2 SDs below the normative mean); deficits for individual cognitive domains ranged from −0.25 to −1.15 SDs. Statistically significant deficits ($P < 0.05$) relative to premorbid estimates were evident for the verbal fluency, memory, processing speed, and executive functioning domains.

Cognitive performance did not differ significantly between younger and older participants across most cognitive domains or individual test scores. Age-associated differences were evident in two cognitive domains (attention: $t_{115} = -2.14, P = 0.04$; memory: $t_{115} = -2.04, P = 0.04$) and in two individual test scores contributing to these domains (ARCP sensitivity $t_{115} = -2.14, P = 0.04$; memory: $t_{115} = -2.04, P = 0.04$) and in two individual test scores contributing to these domains (ARCP sensitivity $t_{115} = -2.14, P = 0.04$; memory: $t_{115} = -2.04, P = 0.04$) and in two individual test scores contributing to these domains (ARCP sensitivity $t_{115} = -2.14, P = 0.04$; memory: $t_{115} = -2.04, P = 0.04$). However, for each of these measures, older participants performed better than younger participants, indicating that older age was not associated with greater obesity-related cognitive deficits (Table 3).

Across the sample, performance was greater than 1 SD below the normative average in two cognitive domains: processing speed ($t_{115,124} = 12.03; P < 0.01$) and executive functioning ($t_{115,126} = 4.62; P < 0.05$). Individual test performances contributing to these domains were also significantly lower than expected, although there were also decrements for various outcomes on the ARCP, CVLT-II, and letter fluency measures.

Clinical factors associated with cognitive performance
Regression analyses were performed to assess relationships between BMI, each comorbidity, and neurocognitive performance (Table 4). In the first analysis, we examined the relationship of clinical factors with the overall cognition composite and performance within each cognitive domain. The same clinical factors were also examined relative to individual neuropsychological test performances that contributed to each domain score.

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**TABLE 2 Demographic and clinical characteristics of total sample**

|                          | Total sample (N = 129) |
|--------------------------|------------------------|
| Age, mean ± SD, y        | 45.65 ± 12.41          |
| Female sex, %            | 73.6                   |
| Education, mean ± SD, y  | 13.72 ± 2.53           |
| White race, %            | 64.3                   |
| Number of comorbidities, %|                        |
| 0                        | 17.1                   |
| 1                        | 24.0                   |
| 2                        | 20.9                   |
| 3                        | 20.2                   |
| 4                        | 17.9                   |
| Hypertension, %          | 57.4                   |
| BMI, mean ± SD           | 45.42 ± 8.28           |
| Obesity class, %         |                        |
| With class 2 obesity     | 34.1                   |
| With class 3 obesity     | 65.9                   |
| Type 2 diabetes, %       | 35.7                   |
| Controlled with diet, %  | 19.6 (9)               |
| On oral antidiabetic medication, % | 43.5 (20)         |
| On insulin only, %       | 15.2 (7)               |
| On oral antidiabetic medication and insulin, % | 17.4 (8)           |
| Not reported, %          | 10.9 (6)               |
| Fasting plasma glucose, mean ± SD, mg/dL | 120.5 ± 54.03  |
| HbA1c, mean ± SD         | 6.44 ± 1.46            |
| Normal, % (n)            | 63.4 (64)              |
| Elevated, % (n)          | 36.6 (37)              |
| CPAP use, %              | 25.0                   |
| Sleep apnea, %           | 42.6                   |
| Arthritis, %             | 34.9                   |

Continuous variables reported as means ± SD and categorical variables reported as percentages. T-scores have a mean of 50 and an SD of 10. CPAP = continuous positive airway pressure.
Diabetes and HbA1c were the clinical factors associated with performance in the majority of cognitive domains. HbA1c was associated with overall cognitive performance ($\beta = -0.44; P = 0.002$). BMI was significantly associated with reduced performance in the verbal fluency domain only. The relationships between clinical factors and performance in each cognitive domain are described below.

### Attention
HbA1c was associated with performance in the attention domain ($\beta = -0.29; P = 0.03$). Fasting plasma glucose in surgical participants was also related to attention ($\beta = -0.49; P = 0.01$). An analysis of ARCPT subindices indicated that the inconsistency index score was related to BMI ($\beta = -0.31; P = 0.02$) and that the final interstimulus interval was related to blood HbA1c levels ($\beta = -0.38; P = 0.004$). No associations were found for accuracy in detection of targets (sensitivity a').

### Processing speed
Diabetes was associated with slower performance in the processing speed domain ($\beta = -0.21; P = 0.05$). Secondarily, diabetes was associated with speed of both word reading ($\beta = -0.23; P = 0.05$) and color naming ($\beta = -0.23; P = 0.03$) on the Stroop task. Completion time of the Trail Making Test: Part A was not significantly associated with any clinical factor.

### Memory
Performance in the memory domain was associated with CPAP use ($\beta = 0.38; P = 0.006$). Participants who used a CPAP had stronger CVLT-II total learning ($\beta = 0.39; P = 0.006$) and long delayed recall scores ($\beta = 0.22; P = 0.04$). Sleep apnea was inversely related to CVLT-II total learning ($\beta = -0.30; P = 0.03$). BMI and other comorbidities were not significantly associated with learning or memory performance.

### Executive functioning
Diabetes was associated with reduced performance in the executive domain ($\beta = -0.23; P = 0.03$) and weaker executive performance on the Trail Making Part B task ($\beta = 0.21; P = 0.04$). Performance on the Stroop Color-Word inhibition trial was not associated with any clinical variables.

### Verbal fluency
Elevated BMI was associated with lower verbal fluency performance ($\beta = -0.24; P = 0.02$). In a secondary analysis, semantic fluency (animal naming), but not letter fluency performance, was most strongly associated with diabetes ($\beta = -0.25; P = 0.02$).

### Discussion
The current findings provide further evidence of a relationship between obesity and reduced cognitive performance. In this cohort of adults with class 2 and class 3 obesity, deficits in cognitive performance were found relative to the normative population and participants' own premorbid intelligence. These deficits did not appear to be age-associated because most participants were between the age of 30 and 55, and older participants did not perform worse for any cognitive outcomes when the cohort was dichotomized at 40 years of age.
These results reinforce previous findings showing that elevated BMI is associated with reduced cognitive performance and extend past findings to individuals with severe obesity. Although we did not observe, nor expect, severe cognitive dysfunction among participants, overall cognitive performance was approximately 0.5 SD below estimated premorbid intellect for the sample, and a significant proportion exhibited performance in the executive and processing domains that was greater than 1 SD below normative levels.

Consistent with the study hypotheses, comorbid conditions were significantly associated with cognitive performance. Diabetes was most strongly and consistently associated with neurocognitive performance for both the total cognitive composite score and specific cognitive domains. The diabetes measure with the strongest association to these cognitive domains varied. Diabetes diagnosis was most strongly associated with reduced overall cognitive performance and deficits in the executive, processing speed, and verbal fluency domains, whereas elevated HbA1c levels were associated with reduced attentional performance. The exception was the memory domain because OSA diagnosis and CPAP use were most strongly associated with learning and memory recall.

Thus, comorbidities occurred in the context of severe obesity with a restricted BMI range, and the results must be interpreted in this context. Notably, BMI was not among the clinical factors associated with overall cognitive performance, nor were deficits in the executive, processing speed, and memory domains. Yet, elevated BMI was associated with variability in sustained attention on the ARCPt. Its association with reduced verbal fluency performance is also noteworthy because these tasks require sustained attention or response generation with effortful demands that may be more taxing with greater BMI even in the context of severe obesity. Given that obesity is disproportionately higher with lower income and education, limited vocabulary can influence verbal fluency scores; however, this is unlikely for this cohort because Barona values were not significantly related to BMI or verbal fluency. Additionally, most investigations into the relation between socioeconomic status and/or education and cognitive function have not controlled for confounding health and behavioral factors.

Comparisons between participants with class 2 and class 3 obesity failed to show differences on any of the cognitive measures. Although, counter to our original hypotheses, the extent of BMI elevation may be less determinant of the severity of cognitive deficits in the context of severe obesity than the impact of comorbidities, particularly diabetes. This should not be interpreted as an indication that elevated BMI did not affect cognitive performance. Very elevated BMI was ubiquitous in the cohort, with a mean BMI of 45, and the influence of BMI on cognitive performance was likely relatively consistent such that the added adverse impact of comorbidities was evident. Therefore, among adults with severe obesity, BMI may be a less sensitive indicator of cognitive dysfunction than the presence of comorbidities, such as diabetes.

That diabetes was the factor most strongly associated with both overall cognitive performance and deficit across multiple cognitive domains is not surprising. There is mounting evidence that diabetes plays a significant role in brain pathophysiology and in the development of stroke, other cerebrovascular disturbances, Alzheimer disease, and neurodegeneration. Diabetes can affect the brain in a number of different ways. Insulin resistance causes alterations in the liver-brain axis that result in the production of toxic lipids and ceramides, which in turn can cause oxidative stress, neuroinflammation, and possibly cell death and neurodegeneration (30). Insulin resistance also causes endothelial damage, which can alter blood-vessel integrity and cause other vascular abnormalities (31). In addition to increased risk of stroke among people with uncontrolled diabetes, microvascular disturbances often occur, resulting in the accumulation of cerebral white-matter lesions (32) and subsequent cognitive dysfunction (33). These pathophysiological mechanisms may account for the observed associations between diabetes and cognitive deficits in the attention, executive, processing speed, and verbal fluency domains. These cognitive functions tend to be particularly vulnerable to microvascular and hemodynamic alterations that affect cerebral white matter and frontal-subcortical systems (34).

The observed relationship between OSA and verbal learning performance supports past findings that chronic sleep apnea contributes cognitive and brain dysfunction (35). Participants who used CPAP therapy for OSA actually had stronger verbal learning and delayed recall on the CVLT-II. This finding is also consistent with previous findings of CPAP adherence being associated with improved learning and memory (36). It is possible that adverse cognitive effects of OSA were mostly mitigated by CPAP therapy or that participants who adhered to CPAP therapy had stronger premorbid cognitive ability that contributed to better CPAP adherence (37,38). Hypertension could also contribute to similar adverse effects on the brain (39,40), although in the current

### TABLE 4

| Cognitive domain and test measure | Clinical variable | β |
|----------------------------------|------------------|---|
| Overall cognition                | HbA1c            | −0.44** |
| Attention                        | HbA1c            | −0.29* |
| ARCPt inconsistency             | BMI              | −0.31* |
| ARCPt final ISI                 | HbA1c            | −0.38** |
| ARCPt sensitivity a'            |                  | ns |
| Processing speed                 | Diabetes         | −0.21* |
| Trail Making Test: part A       |                  | ns |
| Stroop word reading             | Diabetes         | −0.23* |
| Stroop color naming             | Diabetes         | −0.23* |
| Memory                           | CPAP             | 0.38** |
| CVLT-II total recall            | CPAP             | 0.39* |
| CVLT-II long delay              | CPAP             | 0.22* |
| Executive functioning           | Diabetes         | −0.23* |
| Stroop color and word           |                  | ns |
| Trail Making Test: part B       | Diabetes         | −0.21* |
| Verbal fluency                   | BMI              | −0.24* |
|                                  | Diabetes         | −0.21* |
| Letter fluency                   |                  | ns |
| Animal fluency                   | Diabetes         | −0.25* |

T-scores have a mean of 50 and an SD of 10. Normative data used to adjust for age, education, and sex for Trail Making Test, CVLT-II, and verbal fluency measures. For Stroop and ARCPt measures, only age-corrected normative data used; thus, education and sex entered as covariates into regression models (final step).

P < 0.05.

**P < 0.01.

IsI = interstimulus interval; ARCPt = Adaptive Rate Continuous Performance Test; CVLT-II = California Verbal Learning Test, Second Edition; ns = not significant at P < 0.05 level or below.
study, hypertension was not associated with deficits in any cognitive domain. When hypertension has been examined in clinical populations consisting of more severe forms of cerebrovascular or cardiovascular disease (e.g., heart failure), its adverse impact on cognition and the brain is often masked by other etiological factors, such as the presence of systemic hypoperfusion (41). In the current study, almost all participants with a diagnosis of hypertension were pharmacologically treated and had relatively well-controlled blood pressure. Osteoarthritis was also not found to contribute to obesity-associated deficits in this cohort, although it causes systemic inflammation (42), which can affect cognitive functioning.

Several factors may explain why these certain cognitive functions are particularly vulnerable to these pathophysiological processes: (1) Processing-speed deficits result from reduced neural transmission efficiency secondary to white-matter damage (41); (2) Highly metabolic frontal-subcortical systems responsible for attention executive functions, processing speed, and working memory are more vulnerable to hypoperfusion (41,43); (3) Executive-attention and controlled “top-down” processes are more susceptible to effortful demands and involve the integration of multiple cognitive skills (44) compared with “bottom-up” cognitive functions such as perception; and (4) Obesity and its comorbidities tend not to cause focal abnormalities, and thus certain brain functions (e.g., language, memory, and sensory-perceptual functions) that are more topographically restricted may be less common with vascular cognitive impairment and metabolic disturbances.

There are several limitations regarding conclusions that can be drawn from this study. The reported results came from cross-sectional analyses of baseline cognitive functioning. Causality cannot be inferred based on the observed associations between the clinical factors and cognition. Although medical record and detailed medical history data were available on all clinical measures, the diagnoses of hypertension, OSA, and arthritis were coded categorically. For example, an OSA diagnosis was determined on the basis of medical record review, self-report, and polysomnogram results when possible. However, not all participants had data from each of these three sources, which could have resulted in some imprecision in the determination of OSA severity. Data were not available regarding date of onset of medically diagnosed obesity, so it is not possible to determine the extent to which duration of or age at onset of obesity contributed to the observed relationships.

Although, intuitively, one might expect BMI to be strongly associated with cognitive performance, the fact that this was not the case for most cognitive domains is not surprising in light of considerations discussed earlier. However, it is possible that other methods for quantifying obesity (e.g., waist circumference and body-fat composition) could prove to be more sensitive to cognition. Unfortunately, these measures were not consistently available in the study. Finally, it should be emphasized that to some extent, the data collected were constrained by the standard clinical procedures employed by the bariatric surgery team. Additional laboratory measures would have been of analytic interest but could not be obtained routinely. For example, HbA1c levels were determined from acquired blood samples, and fasting glucose values were available for few participants. However, fasting insulin values were not available, so a homeostatic model assessment index could not be obtained in a sufficient number of participants to enable examination of the contribution of insulin resistance (homeostatic model assessment of insulin resistance), which might provide greater sensitivity to obesity-associated cognitive deficits. Despite known drawbacks (45), obtaining this metric in future studies would be beneficial.

Conclusion

Compelling evidence of cognitive deficits among adults with severe obesity in the current study provides support for and extends past findings of a relationship between elevated BMI and reduced cognitive performance. The deficits observed in the study cohort were greatest with respect to executive functioning and cognitive processing speed relative to both normative data and premorbid intelligence. As expected, comorbidities known to be common with severe obesity were very prevalent in the study cohort. Type 2 diabetes was the comorbidity most strongly and consistently associated with cognitive deficits, whereas OSA was associated with learning and memory performance. Counter to expectation, BMI was not significantly associated with overall cognitive performance or with deficits in most cognitive domains. This is probably attributable to the restricted range of BMI in this sample of adults with class 2 and class 3 obesity. Nonetheless, this finding suggests that in the context of severe obesity, the presence of comorbidities, such as diabetes, takes on greater significance by adversely affecting cognitive functioning.

The current study is only one step toward disentangling these complex influences. Although the association of diabetes or other comorbidities with cognitive deficits gives clues to possible underlying pathophysiological mechanisms, other types of data are needed to adequately address these questions. Incorporating neuroimaging methods along with cognitive measures may help this effort. Multimodal neuroimaging is well suited in this regard, making it possible to simultaneously measure alterations in cerebral neural response with functional magnetic resonance imaging, abnormal cerebral metabolite concentrations with magnetic resonance spectroscopy, reductions in cerebral blood flow with magnetic resonance imaging methods (such as arterial spin labeling), and the existence of neuroinflammation (based on concentrations of extracellular free water) with diffusion imaging. As longitudinal data become available from the current study cohort following bariatric surgery, we will also be able to examine causal relationships to a greater extent by determining the relationship between improvements in BMI, diabetes status, and other comorbidities and changes in cognition. We will also examine changes that occur in the brain following bariatric surgery by analyzing data from multimodal neuroimaging.

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Individual participant data will not be available because the data are still being collected as part of an active R01 study and are thus restricted for sharing.

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