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Assessing the Influence of Obesity on Longitudinal Executive Functioning Performance in Patients with Obstructive Sleep Apnea Syndrome

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Abstract

Objective—To investigate longitudinal performance on an executive functioning task among individuals with obstructive sleep apnea syndrome (OSAS) and the impact of obesity on performance.

Methods—Participants completed the Trail Making Test Part B (TMT-B), which is an executive functioning task that measured cognitive flexibility, at baseline, 3, 6, and 12-month follow-ups. Hierarchical linear modeling (HLM) analyses were used to assess participants' initial performance on the task, as well the trajectories of growth on the task across time points. Additionally, body mass index (BMI) was included in the estimations of fixed and random effects as a predictor of performance.

Results—There were no significant differences between obese and non-obese individuals on the cognitive flexibility task at baseline. However, obese and non-obese individuals differed significantly in their linear and quadratic rates of growth across time points.

Conclusions—This study suggests that obese and non-obese individuals may differentially respond to Continuous Positive Airway Pressure (CPAP) treatment (as related to cognitive flexibility). Future research should examine the impact of weight loss on the neuropsychological sequelae of obese individuals with OSAS.

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Keywords

Obesity; Obstructive Sleep Apnea Syndrome; Neuropsychological Deficits; Executive Functioning; Hierarchical Linear Modeling

Introduction

The prevalence of obesity has increased substantially over the past four decades, and is currently considered one of the foremost causes of preventable death in the United States [1]. More than two thirds of adults in the United States are now classified as overweight or obese, which has led to predictions that obesity will cause the first decline in life expectancy in the past 100 years [2]. The risk of death associated with obesity is primarily a result of associated health complications, including type 2 diabetes, hypertension, cardiovascular disease, certain types of cancer, and sleep-disordered breathing [3].

Obstructive sleep apnea (OSAS) affects 2% of middle-aged women and 4% of middle-aged men in the United States [4]. Obesity is present in approximately 70% of individuals with OSAS and is considered the most prominent and only reversible risk factor. Though the underlying mechanisms pertaining to the association between obesity and OSAS are somewhat unclear, it is hypothesized that increased weight decreases the size of the upper airway, and thus, increases the propensity for apnea events [5].

Considering the prevalence of obesity in patients with OSAS, some investigators have analyzed the impact of weight loss as a treatment. Veasey et al. [6] found that a sufficient amount of weight loss through dietary modification can result in significant improvement in OSAS symptomatology among overweight and obese individuals. These investigators acknowledged that improvements in weight loss programs are warranted. At present, Continuous Positive Airway Pressure (CPAP) is considered the most effective and preferred treatment for OSAS [7]. The CPAP device provides positive air pressure to the upper portion of the airway, which prevents it from collapsing during sleep, and thus, reduces or completely eliminates nocturnal respiratory disturbances. The decrease or absence of upper airway collapse results in minimized sleep fragmentation and nocturnal hypoxemia [8].

Untreated OSAS is associated with several neuropsychological deficits, including impaired executive functioning [9 – 14]. Additionally, a growing body of literature suggests that obesity is related to negative neurocognitive outcomes, including executive dysfunction, independent of other health problems [15 – 17]. Strauss, Sherman, and Spreen [18] described executive functions as a set of complex processes mediated by the frontal lobe of the brain. Broadly, they allow persons to respond adaptively to their environment, particularly in novel situations. Executive dysfunction may manifest as a collection of problems in everyday life, such as difficulty with decision-making, problems following through and shifting plans, difficulty in circumstances involving different aspects of memory (e.g., remembering to carry out a goal directed activity at a later time), and poor organizational ability, among others.

Taken together, the studies assessing executive functioning in obese persons and OSAS patients suggest both are related to deficits in this domain of cognitive functioning. The specific aspects of executive functioning that may be impacted by both obesity and OSAS are the following: cognitive flexibility, planning, and problem solving. Considering the evidence that obesity is independently associated with executive functioning impairments, the current study hypothesized that obese participants would demonstrate poorer performance on the executive functioning task at baseline compared to non-obese participants. Additionally, it was hypothesized that obesity status would be a significant predictor of performance on the executive functioning task following CPAP treatment.

Methods

Participants

Three hundred participants were recruited to participate in a randomized clinical trial, referred to as Project Breathe [19]. Project Breathe aimed to identify methods to increase adherence to CPAP treatment and assessed the neuropsychological functioning of participants over time. Participants for Project Breathe were recruited from the Sleep Center at National Jewish Health and were between the ages of 30 to 80 years. All participants were diagnosed with mild to severe OSAS and had no previous history of CPAP treatment.

Procedure

After consenting to participate in the study, participants completed the Mini Mental Status Exam (MMSE) and the Alcohol Use Disorders Identification Test (AUDIT) to further determine their eligibility to participate in the study. Participants who scored less than 26 out of 30 on the MMSE and/or greater than or equal to 8 on the AUDIT were informed that they would not be able to participate, and they were paid \$25.00 for their time.

Participants completed baseline assessments, which included measures of cognitive functioning, mood, daytime sleepiness, sleep-related functional outcomes, and psychological constructs of behavior change principles. The outcome measure of interest in the present study was the Trail Making Test (TMT; [20]), Part B (TMT-B). The American National Adult Reading Test (AMNART; [21]) and the Beck Depression Inventory-II (BDI-II; [22]) were used to assess differences between obese and non-obese individuals on estimated premorbid intelligence and depressive symptoms. These assessments were administered at baseline, 3, 6, and 12-month follow-up visits. Participants were paid \$50.00 for each follow-up visit. Data from baseline, 3, 6, and 12-month follow-ups were used in the present study.

Measures

American National Adult Reading Test (AMNART; [21])—The AMNART was used as an estimate for premorbid IQ in the present study. Schwartz and Saffran ([23]; cited in [21]) demonstrated that predicted IQ from the AMNART highly correlated with the Wechsler Adult Intelligence Scale (WAIS) Intelligence Quotient (IQ) measures when controlling for the impact of education: $r = .72$ for the Verbal Intelligence Quotient, $r = .51$ for the Performance Intelligence Quotient, and $r = .72$ for the Full Scale Intelligence Quotient (FSIQ). These investigators also found that the premorbid IQ of patients with

Alzheimer's Disease (AD) was no different than the scores of normal controls, whereas the current IQ of the patients with AD was consistently lower. In similar analyses, Grober and Sliwinski [21] found that estimated premorbid IQ exceeded current IQ by at least 10 points in patients with dementia, but did not differ for non-demented participants. As the AMNART is a measure of premorbid IQ, these results highlight its construct validity. It would be expected that persons with dementia would perform more poorly on a measure of current IQ (i.e., the WAIS) than a measure that assesses their IQ prior to the onset of dementia.

BDI-II [22]—The BDI-II is a 21-item self-report measure of depressive symptoms. The BDI-II reflects the diagnostic criteria for Major Depressive Disorder outlined in the *Diagnostic and Statistical manual of Mental Disorders, Fourth Edition, Text Revision* [24]. The BDI-II was adapted from an earlier version of the instrument and is one of the most widely used instruments for assessing the severity of depressive symptoms [25], which include the following: sadness, pessimism, past failure, loss of pleasure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts, crying, agitation, loss of interest, indecisiveness, worthlessness, loss of energy, changes in sleeping, irritability, changes in appetite, concentration difficulty, tiredness or fatigue, and loss of interest in sex. Each item has a list of four statements that are organized in increasing severity regarding a particular symptom of depression, and participants choose one statement that matches their experience in the past two weeks. The BDI-II is appropriate to use with individuals ages 13 to 80 years.

TMT [20]—Participants completed the TMT at four separate time points: baseline, 3, 6, and 12-month follow-ups. The TMT consists of two parts, (A) and (B), which cumulatively test attention, visual-motor speed, and mental flexibility. The TMT-A involves connecting 25 encircled numbers that are randomly scattered on the page in consecutive order. The TMT-B is similar; however, it also has 25 encircled letters, and the examinee is required to alternate between numbers and letters in the proper order. Scoring is based on the time in seconds required to complete the task, and less time is indicative of better performance. Whereas the TMT-A assesses attention, the TMT-B is commonly used as a test of cognitive flexibility, as it requires divided attention and alternating sequencing [18]. The TMT has demonstrated adequate test-retest reliability for Part A ($r = .79$) and high test-retest reliability for Part B ($r = .89$) in a large sample of individuals aged 15-83-years over a period of 11 months [26].

Adherence—Adherence to CPAP was measured using electronic monitoring equipment. Participants received either a modem that attached directly to their CPAP device and automatically downloaded their usage data, or a microchip that could be removed, and the data were manually downloaded at follow-up visits. Adherence was measured as the amount of time the CPAP device was turned on and the amount of time the mask was properly positioned on the face and maintaining the appropriately prescribed pressure.

Hierarchical Linear Modeling (HLM) Analyses

HLM was used to evaluate growth trajectories on the TMT-B task over time. Using HLM, at level 1 each participant's performance is modeled by a starting point (intercept) and an

individual growth rate (slope), both of which then become the outcome variables at level 2. There were four time points (baseline, 3, 6, and 12 month follow-ups). Hence, the time scores were coded as 0, 1, 2, and 4. Observations at multiple time points for each individual are nested within the person [27]. A series of HLM models were estimated to address the questions of interest in this study. These models were tested on and based on the same dataset in order to explore the optimal pattern (i.e., linear or quadratic) of growth for the construct and the impact of personal characteristics on the trajectory. The first, and simplest, model estimated was the unconditional linear model where no Level 2 predictors were involved. This model was specified as follows:

$$\text{Level 1 Model: } TRAILS_{ti} = \pi_{0i} + \pi_{1i} * (TIME_{ti}) + e_{ti}$$

$$\begin{aligned} \text{Level 2 Model: } \pi_{0i} &= \beta_{00} + r_{0i} \\ \pi_{1i} &= \beta_{10} + r_{1i} \end{aligned}$$

$$\text{Mixed Model: } TRAILS_{ti} = \beta_{00} + \beta_{10} * TIME_{ti} + r_{0i} + r_{1i} * TIME_{ti} + e_{ti}$$

In order to determine what type of growth trajectory fit the data best, an unconditional quadratic growth model was also estimated to compare model fit. The unconditional quadratic growth model was specified as follows:

$$\text{Level 1 Model: } TRAILS_{ti} = \pi_{0i} + \pi_{1i} * (TIME_{ti}) + \pi_{2i} * (TIME_{ti}^2) + e_{ti}$$

$$\begin{aligned} \text{Level 2 Model: } \pi_{0i} &= \beta_{00} + r_{0i} \\ \pi_{1i} &= \beta_{10} + r_{1i} \\ \pi_{2i} &= \beta_{20} + r_{2i} \end{aligned}$$

$$\text{Mixed Model: } TRAILS_{ti} = \beta_{00} + \beta_{10} * TIME_{ti} + \beta_{20} * TIME_{ti}^2 + r_{0i} + r_{1i} * TIME_{ti} + r_{2i} * TIME_{ti}^2 + e_{ti}$$

Unconditional linear and quadratic growth models were then tested with a chi square difference test of deviance to determine if the quadratic model makes significant contribution to model fit compared with the linear model. The quadratic growth model was chosen, as it provided a better fit according to the chi-square difference test, $\chi^2(7, N = 78) = 33.07, p < .01$. After concluding that the quadratic model provided a better fit, a conditional quadratic growth model was estimated, which explored if obesity status as a Level 2 predictor had a significant impact on the Level 1 starting point and growth parameters. Age was included as a covariate in the model. This model was specified as follows:

$$\text{Level 1 Model: } TRAILS_{ti} = \pi_{0i} + \pi_{1i} * (TIME_{ti}) + \pi_{2i} * (TIME_{ti}^2) + e_{ti}$$

$$\begin{aligned}\text{Level 2 Model: } \pi_{0i} &= \beta_{00} + \beta_{01} * (OBESITYS_i) + \beta_{02} * (AGEATTIM_i) + r_{0i} \\ \pi_{1i} &= \beta_{10} + \beta_{11} * (OBESITYS_i) + \beta_{12} * (AGEATTIM_i) + r_{1i} \\ \pi_{2i} &= \beta_{20} + \beta_{21} * (OBESITYS_i) + \beta_{22} * (AGEATTIM_i) + r_{2i}\end{aligned}$$

$$\begin{aligned}\text{Mixed Model: } TRAILS B_{ti} &= \beta_{00} + \beta_{01} * OBESITYS_i + \beta_{02} * AGEATTIM_i \\ &+ \beta_{10} * TIME_{ti} + \beta_{11} * OBESITYS_i * TIME_{ti} + \beta_{12} * AGEATTIM_i * TIME_{ti} \\ &+ \beta_{20} * TIMESQ_{ti} + \beta_{21} * OBESITYS_i * TIMESQ_{ti} + \beta_{22} * AGEATTIM_i * TIMESQ_{ti} \\ &+ r_{0i} + r_{1i} * TIME_{ti} + r_{2i} * TIMESQ_{ti} + e_{ti}\end{aligned}$$

Results

Participant Characteristics

At the time of this study a total of 120 participants had completed the larger study from which the data were obtained. Of those 120 participants, 78 met the inclusion criterion for this study, which included average CPAP usage of at least four hours a night across the 12 months of their involvement in the larger project. The sample was 74% white, 12% black or African American, 3% American Indian, 3% Asian, and 8% identified as “Other.” The sample was comprised of 61 males and 17 females, and the mean age of participants at baseline was 52-years ($SD = 8.53$). The average years of education among participants was 15.74-years ($SD = 2.96$). The mean BMI among participants was 31.88 ($SD = 6.86$), and 60% of participants met the criteria for obesity (i.e., BMI ≥ 30 kg/m²). The study sample was representative of the general population in terms of most demographic characteristics; however, there were differences in sex and obesity status. The sample consisted of more males than females and a greater number of obese individuals. This is not surprising given that both being male and obese are risk factors for the development of the OSAS [5]. Thus, while the sample was less representative of the general population with regard to sex and obesity status, they were representative of the population of individuals with OSAS. Psychosocial characteristics of the obese and non-obese groups are presented in Table 1.

Preliminary Analyses

Preliminary analyses were conducted to determine if psychosocial variables predicted obesity status in order to clarify if any of these variables needed to be included as covariates in the HLM models. A logistic regression was performed to assess the effects of sex, age, level of depression, level of anxiety, years of education, and income on obesity status. Age was the only variable that added significantly to the model/prediction ($p < .01$). Specifically, increasing age was associated with a decreased likelihood of being obese. Results of the logistic regression are presented in Table 2. As age significantly predicted obesity status, it was included as a covariate in the HLM models.

HLM Analyses

Prior to running HLM analyses, the data were also checked to determine if they met the HLM assumptions. The data met all assumptions, with the exceptions of homogeneity of Level 1 random errors and multivariate normal Level 2 random errors. Heterogeneity of

variance can indicate several problems, including the omission of one or more meaningful Level 1 predictors, random predictors may have been treated as fixed, errors may have been made in coding the data, and the data may be non-normal [27]. Heterogeneity of variance due to misspecification of the Level 1 model can bias estimates of Level 2 coefficients [27]. Additionally, the Level 2 random errors did not meet the multivariate normality assumption, which can bias the estimation of the fixed effects, and can lead to unreliable confidence intervals and hypothesis tests for fixed effects [27]. Since the data did not meet all of the HLM assumptions, the parameter estimates with robust standard errors were used in the final analyses of the results.

The estimated parameters of the unconditional linear model are presented in Table 3. The average TMT-B score at baseline was 69.11 seconds, which differed significantly from zero ($p < .001$). The estimated mean growth rate was -0.54 from baseline through the 12-month follow-up; however, this was not significant ($p > .05$), indicating that there was not significant growth over time. There was significant variation in initial status on the TMT-B task between participants ($p < .001$), but there was not significant variation in linear growth rates among participants ($p > .05$).

The estimated parameters of the unconditional quadratic model are presented in Table 4. The average TMT-B score at baseline was 72.25 seconds. The mean linear growth rate among participants was -7.04 , which was statistically significant ($p < .001$), demonstrating that there was significant decline over time on the TMT-B task, where lower scores represent improved performance. Specifically, participants' scores decreased at an average rate of 7.04 seconds on the TMT-B task every three months. The average quadratic growth rate among participants was 1.57, which was significant ($p < .01$), indicating that there was significant quadratic growth on the TMT-B task every three months. Specifically, despite the linear decline, participants' scores increased at an average rate of 1.57 seconds on the TMT-B task across time points. The negative linear growth, combined with positive quadratic growth, indicates an overall trend of improved scores initially, followed by a slight deterioration in improvement over time. There was significant variation in initial status $\chi^2(76) = 513.29, p < .01$, linear growth rate $\chi^2(76) = 106.21, p < .05$, and quadratic growth rate $\chi^2(76) = 107.17, p < .05$ on the TMT-B task among participants. This indicated that modeling individual growth rates as a function of person-level variables (i.e., obesity status) was warranted.

The estimated parameters for the quadratic model predicting TMT-B scores from baseline obesity status, while controlling for age, are presented in Table 5. There were no statistically significant differences between obese and non-obese participants on the TMT-B task at baseline ($p > .05$). While not statistically significant, results indicate that on average obese individuals took 6.6 seconds longer to complete the TMT-B task at baseline compared to non-obese participants. There were significant differences in linear growth rates between obese and non-obese participants ($p < .05$), such that obese participants' linear rate of change decreased significantly faster than that of non-obese participants. Specifically, obese individuals' performance decreased at an average rate of 10.75 seconds every three months compared to non-obese participants. Additionally, there were significant differences in quadratic growth rates between obese and non-obese participants ($p < .01$) over time, such

that obese participants' scores accelerated (i.e., stopped improving) faster than non-obese participants at an average rate of 2.79 seconds across time points. Predicted and log predicted model estimated means on TMT-B performance by group, across time points, are presented in Table 6 and represented graphically in Figure 1 and Figure 2, respectively.

Discussion

This study aimed to elucidate the relationship between obesity and executive functioning, specifically cognitive flexibility, in individuals with OSAS. First, it was hypothesized that obese participants would demonstrate poorer performance on the executive functioning task at baseline compared to non-obese participants. Second, it was hypothesized that obesity status would be a significant predictor of performance on the executive functioning task. While the results do not provide evidence to support the first hypothesis, they do demonstrate that obesity status is a significant predictor of performance on the executive functioning task, and thus, support the second hypothesis.

The results demonstrate that the overall linear and quadratic growth rates on the cognitive flexibility task among the sample were significant, such that performance improved with CPAP treatment, and the acceleration of improvement slowed and slightly deteriorated over time. While this pattern in response to treatment may be expected, the results further demonstrate that obese and non-obese participants differed significantly on rates of linear and quadratic growth from baseline to 12-month follow-up. Specifically, obese individuals' growth rate decreased at a faster rate than that of non-obese participants. As lower scores on the TMT-B task are indicative of better performance, these results indicate that obese individuals' scores improved at a faster rate than non-obese individuals initially. However, there were also significant differences in quadratic growth rates between obese and non-obese individuals, such that obese individuals' improvements deteriorated at a significantly faster rate than non-obese participants across time points.

Taken together, the results from this study illustrate that obesity status has an impact on OSAS patients' response to CPAP treatment, such that obese individuals seem to improve at a faster rate initially, but this effect is partially offset by obese individuals' higher rate of deterioration in improvement over time compared to non-obese patients. These results provide important implications regarding the treatment recommendations for obese individuals with OSAS. Obese individuals seem to respond positively to CPAP in terms of improvements in cognitive flexibility; however, their increasingly slowed down performance compared to non-obese individuals suggests that their improvement may regress relatively faster, perhaps because obesity is independently associated with cognitive dysfunction. It seems warranted to also recommend weight loss as part of the treatment plan, and appears that more efforts need to be made to identify effective weight loss programs specifically tailored to individuals who are both obese and have OSAS.

Though the results from this study are informative and potentially influential in terms of OSAS treatment recommendations, they need to be viewed in light of several limitations. First, OSAS severity among participants was not taken into consideration in this study. As OSAS severity can differentially impact cognitive dysfunction [6], participants' OSAS

severity level could have confounded the results. Further, it is possible that duration of illness, comorbid medical conditions, and sleep fragmentation could have impacted participants' cognitive performance. Inclusion of these variables was beyond the purview of this study; nevertheless, the results should be considered in the context of this limitation. Additionally, only one unique aspect of one cognitive domain was analyzed in this study. Therefore, it is not clear whether or not the results found in this study generalize beyond executive functioning, specifically cognitive flexibility, to other aspects of cognition. Finally, although BMI is widely used to measure obesity, it is not a highly sensitive measurement in that it does not differentiate between fat mass and lean mass, nor does it indicate the distribution of fat. Alternative measures of obesity such as waist-to-hip ratio or waist circumference, which measure abdominal obesity, should at least be used as a supplement to BMI in future research.

Future studies in this area should extend this research by determining if obesity status impacts the growth rate of OSAS patients treated with CPAP on multiple domains of cognitive functioning. For instance, researchers could assess the growth rates of obese and non-obese individuals with OSAS on a full battery of neuropsychological tests. Additionally, more research needs to be done to both develop and examine the efficacy of weight loss programs geared specifically to obese individuals with OSAS. Moreover, these studies should examine the impact of weight loss on cognitive functioning and whether or not it has a positive impact on cognition in obese individuals with OSAS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Predicted model estimated means of TMT-B performance across time points by group

Figure 2.

Log predicted model estimated means of TMT-B performance across time points by group