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SCIENTIFIC INVESTIGATIONS

# Cognitive profiles in obstructive sleep apnea: a cluster analysis in sleep clinic and community samples

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**Study Objectives:** Although cognitive dysfunction is a recognized consequence of untreated obstructive sleep apnea (OSA), the deficit pattern is heterogeneous. Understanding this heterogeneity may identify those at risk of cognitive deficits and guide intervention strategies. To facilitate understanding, we examined whether distinct profiles of neuropsychological performance were present in OSA and, if so, how they are related to other OSA features.

**Methods:** We studied sleep clinic (n = 121) and community (n = 398) samples with moderate-severe OSA (apnea-hypopnea index ≥ 15 events/h). Attention and memory were assessed using the Cognitive Drug Research system. Sleep was assessed using polysomnography in the clinic sample and dual channel (flow, oximetry) portable monitoring in the community sample. Latent profile analysis was used to determine structure of cognitive clusters. Discriminant function analysis was used to examine associations between nocturnal and diurnal features of OSA and profile membership.

**Results:** Both samples were best characterized by a 3-profile solution: (1) strong thinkers (performed well across most domains and showed greater cognitive reserve); (2) inattentive fast thinkers (strong processing speed but poor ability to maintain attention); and (3) accurate slow thinkers (strengths in maintaining attention but poor processing speed). Profile membership was associated with mean overnight oxygen saturation and cognitive reserve in the clinic sample and the presence of cardiovascular disease and/or diabetes in the community sample.

**Conclusions:** These findings help explain the diversity of outcomes in previous studies of cognitive dysfunction in OSA by demonstrating that individual differences in cognitive reserve, nocturnal oxygen saturation, and comorbidities affect how cognition is impacted by OSA.

**Keywords:** OSA, cognition, cognitive reserve, attention, memory, comorbidity

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**BRIEF SUMMARY**

**Current Knowledge/Study Rationale:** Although cognitive dysfunction is a recognized consequence of untreated obstructive sleep apnea, the deficit pattern is heterogeneous. Understanding this heterogeneity may help identify those most at risk of cognitive deficits and guide intervention strategies.

**Study Impact:** There are separable cognitive profiles in obstructive sleep apnea in both clinic and community samples, and cognitive reserve, overnight oxygen saturation, and comorbid cardiovascular disease and/or diabetes are among the most important factors affecting cognitive performance in those with obstructive sleep apnea. Accounting for cognitive reserve, oxygen saturation, and comorbidity in studies examining cognition in OSA through study recruitment or analyses is crucial, as these factors impact the type and severity of cognitive impairment.

## INTRODUCTION

Obstructive sleep apnea (OSA) is one of the most common, underacknowledged, untreated, and costly disorders in high-income countries. Global prevalence for moderate to severe OSA is estimated at 435 million individuals between the ages of 30 and 69 years.[1] Moreover, the combined direct and indirect costs of OSA in advanced economies is high.[2] In addition to direct health care costs, individuals with OSA experience more motor vehicle accidents, occupational injuries, work absenteeism, disruptions to mood, and cognitive deficits than individuals without sleep apnea.[3–6] Aspects of cognition affected in OSA include attention, memory, executive function, psychomotor speed, language abilities, and visuospatial function.[7–10]

Although cognitive problems are a recognized accompaniment of OSA,[7] there is substantial heterogeneity between individuals and populations.[11–13] To explain this heterogeneity, previous research has explored factors proposed to affect disease expression in OSA. This has included exploration of nocturnal features (sleep disturbance and blood gas abnormalities),[14,15] diurnal symptoms (fatigue, sleepiness, and poor mood),[16] comorbidity (obesity, cardiovascular, and psychiatric),[11] and individual resilience factors (cognitive reserve, level of physical activity, and age).[12,13] The results from these analyses have been

mixed, with some papers showing the integral nature of certain factors, for example, hypoxia, to cognitive dysfunction and others not.[17] It has been suggested that these heterogeneous results may be caused by differing methods used to measure cognition and risk (eg, comorbidity), individual differences in resilience (eg, cognitive reserve), and/or the influence of OSA-related features such as sleep-related hypoxemia. As yet, the notion of examining OSA in terms of separable cognitive profiles and examining the features associated with membership of such profiles has not been explored (**Table S1** in the supplemental material is a review of the literature).

To do so could be important, because the existence of different profiles of cognitive performance among patients with OSA could explain some of the reported heterogeneity in the literature regarding the relationship between OSA severity and its clinical features, including cognitive function. When assessing disease severity and impact, failure to account for underlying cognitive profile could lead to an incorrect estimate of disease impact on individuals, particularly those with vulnerable or resilient predispositions.[18] For example, those with more severe OSA (eg, apnea-hypopnea index [AHI] > 30 events/h or greater oxygen desaturation) may demonstrate less marked cognitive problems if they also have high levels of resilience (ie, high cognitive reserve). In support of this notion, previous studies have found that individuals with OSA who are of high intelligence and/or education level performed similarly on attentional tests to individuals without OSA and who did not meet mild cognitive impairment criteria, whereas those with low intelligence or education were vulnerable to attention problems and mild cognitive impairment.[12,19] However, no previous studies have explored the influence of underlying cognitive resilience on the relationship between OSA severity and degree of cognitive dysfunction and whether some of the previously documented heterogeneity in this relationship could be explained by it.

To address this deficiency, we decided to determine whether distinct profiles of cognitive performance were present across individuals with OSA and, if present, to describe how they related to factors thought to impact cognition in OSA (such as age, depression, and body mass index) and whether cognitive reserve modified these impacts. We hypothesized (1) that there would be different profiles of cognitive performance separable by different patterns of performance across cognitive domains, because past studies show individuals with OSA are heterogeneous in terms of cognitive resilience and daytime symptomatology[20] and (2) that those with greater cognitive resilience would be less cognitively vulnerable to more severe OSA. To explore if such profiles differ according to whether individuals with OSA present to a clinic with overt symptoms or exist, often asymptomatically, in the wider community, we conducted analyses in 2 samples: 1 from a sleep clinic and 1 from a community cohort.

# METHODS

## Participants

Two samples of individuals with moderate to severe untreated OSA (AHI ≥ 15 events/h) were studied: a sleep clinic sample and a community sample. People using continuous positive airway pressure (CPAP) or other effective treatments for their OSA were excluded from the study.

### *Sleep clinic sample*

Participants were consecutively recruited patients diagnosed with OSA, who attended the sleep clinic and underwent level 1 polysomnography (PSG) at the West Australian Sleep Disorders Research Institute Sir Charles Gairdner Hospital, Western Australia, Australia, between March 2009 and July 2011. Cognitive testing was performed in 151 individuals. Of the 151 with cognitive testing, 121 had an AHI ≥ 15 events/h (range, 15–154 events/h; mean ± SD, 42.4 ± 25.5 events/h).

### *Community OSA sample*

Participants were individuals from the Busselton Healthy Ageing Study, a longitudinal study of community-dwelling adults, randomly selected from the Busselton (Western Australia, Australia) shire electoral roll, who were born between 1946 and 1964. Participants completed detailed clinical and cognitive assessments and questionnaires, provided blood samples, and were offered an in-home unattended overnight screening study using dual-channel portable device (Apnealink, ResMed, San Diego, CA).[21] Validation studies have demonstrated that ApneaLink is sensitive (66–100%) and specific (88–100%) compared with level 1 PSG at an AHI ≥ 15 events/h.[22,23] Of the 5,107 individuals enrolled in the Busselton Healthy Ageing Study, 2,129 completed an ApneaLink study, of whom 398 had an AHI ≥ 15 events/h (range, 15–89 events/h, mean ± SD, 24.8 ± 11.8 events/h) and had completed cognitive assessment. Participants were not excluded for other comorbid sleep disorders.

The University of Western Australia Human Research Ethics Committee approved the community study (RA/4/1/2203), and both the University of Western Australia and Sir Charles Gairdner Hospital human research ethics committees approved the clinic study (RA/4/20/4356). All participants gave written, informed consent.

## Measures

### *Demographic details*

Both samples responded to questions about their age, sex, self-reported daytime sleepiness (Epworth Sleepiness Scale),[24] self-reported depression symptoms (Depression Anxiety and Stress Scale-21),[25] and self-reported comorbidities as part of a wider set of demographic and sleep questionnaires. Questionnaires were completed the evening of the sleep study for the clinic sample and within 2 weeks of the ApneaLink study for the community sample.

For this study, comorbidities that commonly occur together and seem to have some similar disease processes (OSA, diabetes, and cardiovascular disease [CVD])[26–28] were summed, and each participant was given a comorbidity score, ranging between 0 (no OSA, CVD, or diabetes) and 3 (OSA, CVD, and diabetes). This comorbidity score included OSA because we also examined the number of profiles in a healthy sample (**Table S2**).

### Sleep recording details

The sleep clinic sample underwent full overnight level 1 PSG (Compumedics E-Series, Compumedics, Melbourne Australia), and the sleep studies were scored using Compumedics PSG 3 software. Equipment placement, sleep staging, and event scoring were completed by experienced sleep technologists according to American Academy of Sleep Medicine standards.[29] The alternative hypopnea rule was used for scoring (≥50% decrease in nasal airflow with a ≥3% oxygen desaturation).

The community sample was administered a dual-channel (oximetry and nasal pressure) ApneaLink device as part of the Busselton Healthy Ageing Study. Participants were instructed how to apply and operate the ApneaLink devices and returned them the following day when data were downloaded and scored with the automated ApneaLink software (version 8.00). The sleep study was judged acceptable if it was ≥4-h duration, and both flow and oxygen saturation data were present for ≥90% of the recording time.

### Cognition

Attention and memory were assessed using instruments known to be sensitive to cognitive dysfunction in individuals with OSA.[7–10]

**Cognitive Drug Research System:** The Cognitive Drug Research System is a 20- to 30-minute, computerized battery of cognitive assessments measuring important aspects of attention, short-term memory, and episodic long-term memory.[30,31] The Cognitive Drug Research System has good reliability and validity[32] and has previously been used to assess subtle cognitive changes in OSA.[33,34] The system assesses immediate and delayed word recall; simple and choice reaction time; digit vigilance; spatial and numeric working memory; and delayed word and picture recognition. Five-factor scores are derived from these assessments: power of attention (speed of correct responses in attention tasks), continuity of attention (accuracy in attention tasks over time), quality of working memory (accuracy in short-term working memory tasks), quality of episodic memory (accuracy in word recall and word and picture recognition), and speed of memory (time taken to correctly retrieve information in working and episodic recognition tasks). For power of attention and speed of memory, lower scores indicate better performance, whereas for the other factor, higher scores indicate better performance. More information on these tasks and calculation of these scores can be found in Edgar et al.[35]

Normative data for the Cognitive Drug Research System factor scores were used to create standardized residuals controlling for the effects of age, sex, and education (K. Wesnes, personal communication, July 2018). High positive scores indicate higher than average performance for individuals of the same age, sex, and years of education. Large, negative scores indicate lower than average performance. These standardized scores were used as the indicators in the latent class analysis. Not controlling for these factors may have created profiles that differ because of education, age, or sex rather than underlying differences in the level of cognitive function across individuals with OSA; the latter is the intended purpose of this study. Regarding age effects, a healthy control sample was also examined to rule out that the profiles may represent normal cognitive aging (**Table S2**).

However, it was not our aim to examine differences between those with and without OSA but rather to examine within-OSA variations to better understand how these might, in turn, influence the variable relationships between disease severity and cognitive dysfunction observed in this disorder.

**National Adult Reading Test:** The National Adult Reading Test is a widely used task to estimate cognitive reserve.[36] Two people with the same brain changes, perhaps as a function of OSA, may perform differently on cognitive tasks if one has greater resilience to help them to compensate for those brain changes.[37] As such, individuals with higher cognitive reserve are expected both to perform better on cognitive tasks and to be more resilient to the impact of brain changes on those same cognitive tasks. The participant reads aloud 50 English words with irregular spellings (eg, drachm, aisle, campanile). Crawford's equation was used to convert raw National Adult Reading Test error scores into predicted intelligence quotient scores, which is used as an index of cognitive reserve.[38]

## Statistical analyses

Statistical analyses were performed using Mplus for Windows, Version 8.0 (Muthen and Muthen, Los Angeles, CA) and SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY).

### Missing values

Little's missing completely at random statistic demonstrated that missing data were missing completely at random in the sleep clinic [$\chi^2(9) = 3.97$, $P = .914$] and community samples, [$\chi^2(10) = 16.39$, $P = .089$]. Because Mplus software can analyze data with missing values, these were not replaced. Guidelines recommend that a sample size of $2^m$ can be used (where m = number of clustering variables)[39] for latent profile analysis (LPA), and as such, the samples sizes were sufficient.

### Latent profile analysis

LPA was used to classify individuals with OSA into cognitive profiles in the 2 samples separately. LPA assumes that a heterogeneous group of individuals are comprised of a set of distinct, homogenous subgroups or profiles. LPA identifies latent (ie, unobserved) profiles of people on the basis of scores on a set of indicator (ie, observed) variables. Profiles are determined that account for the shared variance among the indicator variables. LPA assesses the symptom profile of an individual in the sample on each indicator and then probabilistically assigns them to a profile. The first step in LPA is to determine the optimal number of profiles.

The optimal number of profiles was established by assessing (1) statistical fit (Akaike information criterion, sample size–adjusted Bayesian information criterion, Vuong-Lo-Mendell-Rubin likelihood ratio test, and the bootstrap likelihood ratio test); (2) the number of individuals in each profile; (3) the latent class posterior probabilities for most likely class membership; and (4) inspection of the profiles (the 1-profile solution is presented in the supplemental material for both samples). The indicators were age- and education-standardized scores on power of attention, continuity of attention (accuracy over time), quality of working

memory, quality of episodic memory, and speed of memory from the Cognitive Drug Research System cognitive test battery.

One-way analysis of variance and Bonferroni corrected post hoc analyses were used to describe group differences in cognition, separately for each sample (clinic and community).

Discriminant function analyses were used to assess for predictors of profile membership using demographic and sleep variables in each sample (clinic and community). Discriminant function analyses was used to assess the degree to which theoretical predictors of profile membership could predict to which profile a participant belongs. Hypothesized predictors, selected a priori, of profile membership, for the sleep clinic sample, were cognitive reserve, age, daytime sleepiness (Epworth Sleepiness Scale), sex, body mass index, depression symptoms, AHI, mean level of nocturnal arterial oxygen saturation ($SaO_2$), and an interaction term: mean $SaO_2$ by cognitive reserve. Predictors, selected a priori, for the community sample included these same variables with the addition of number of comorbidities (diabetes, obesity, and CVD). Predictors were entered in a stepwise fashion to determine which would contribute significantly to each model. The disease severity measure, AHI, as moderated by premorbid IQ was examined as a potential variable. It showed no association to group membership and was not retained.

## RESULTS

### Descriptive results

Descriptive statistics for the clinic and community samples for demographics, cognition, sleep, and mood are presented in **Table 1**.

### Latent profile analysis

To establish the presence and number of cognitive profiles in individuals with OSA, LPAs were conducted as outlined previously. The fit statistics are presented in **Table 2** for both the sleep clinic and community samples. For the clinic sample, the Akaike information criterion and Bayesian information criterion were lowest for 3- and 4-profile solutions, suggesting good fit; however, the Vuong-Lo-Mendell-Rubin likelihood ratio test and bootstrap likelihood ratio test supported a 2- or 3-profile solution. For the community sample, the Akaike information criterion and Bayesian information criterion were lowest for 3, 4, and 5 profiles, suggesting good fit, whereas the Vuong-Lo-Mendell-Rubin likelihood ratio test and bootstrap likelihood ratio test supported a 2-, 3-, or 4-profile solution. Taken together, these statistics suggested agreement for a 3-profile solution for the clinic and community samples. The LPA was repeated in a healthy general population sample, also from the Busselton Healthy Ageing Study, to ensure the 3 profiles were not typical of healthy aging. The results indicated that a 2-profile solution best fit the healthy sample, thus suggesting that the 3-profile solution is specific to individuals with OSA (results are provided in the supplemental material).

In addition to examining the fit statistics, we inspected class counts (n presented in **Table 3**), posterior probabilities for class membership, and inspection of the profiles; each supported a 3-profile solution in each sample. **Figure 1** and **Figure 2** present 2 and 4 solutions for the clinic and community sample, respectively, and the 3-profile solution is presented for the clinic (**Figure 3A**) and community (**Figure 3B**) samples.

### Profile differences in cognition

The profiles identified by the LPA were then assessed for between-profile differences (**Table 4**).

#### *Sleep clinic sample*

There were between-profile differences in power of attention, continuity of attention, quality of working memory, speed of memory, and cognitive reserve but not for quality of episodic

**Table 1**—Descriptive statistics for the clinic and community samples.

| Category of Descriptive | Specific Descriptive | Sleep Clinic Sample (n = 121) | Community Sample (n = 398) |
|---|---|---|---|
| Demographics | Age | 53.94 ± 12.27 | 60.00 ± 5.53 |
| | Body mass index | 33.98 ± 7.60 | 30.54 ± 5.66 |
| | Sex (% male) n | 52.9% (64) | 61% (n = 245) |
| Mood | Depression | 5.55 ± 4.96 | 3.96 ± 5.64 |
| | Anxiety | 4.14 ± 3.23 | 2.67 ± 3.93 |
| | Stress | 6.29 ± 4.68 | 6.50 ± 6.84 |
| Sleep | AHI | 42.43 ± 25.52 | 24.75 ± 11.83 |
| | Average $SpO_2$ | 92.21 ± 3.20 | 93.43 ± 2.89 |
| | Epworth Sleepiness Scale | 9.96 ± 4.78 | 6.50 ± 3.89 |
| Cognitive assessments | Premorbid IQ | 105.07 ± 9.21 | 103.79 ± 8.91 |
| | Power of attention | −0.34 ± 1.24 | −0.52 ± 1.24 |
| | Continuity of attention | −0.24 ± 1.27 | −0.08 ± 1.01 |
| | Quality of working memory | 0.31 ± 0.96 | 0.52 ± 0.71 |
| | Quality of episodic memory | 0.49 ± 1.02 | 0.28 ± 0.94 |
| | Speed of memory | −0.55 ± 1.32 | −0.86 ± 1.35 |

**Table 2**—Fit indices for 1–4 profiles for the clinic sample and 1–6 profiles for the community sample.

| No. of Profiles | Sleep Clinic Sample | | | | | Community Sample | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | AIC | BIC (n adjusted) | ΔBIC (Relative to k-1 Profiles) | VLMRLRT (*P* Value) | BLRT (*P* Value) | AIC | BIC (n adjusted) | ΔBIC (Relative to k-1 Profiles) | VLMRLRT (*P* Value) | BLRT (*P* Value) |
| 1 | 1,875.45 | 1,871.99 | N/A | N/A | N/A | 5,723.71 | 5,731.84 | N/A | N/A | N/A |
| 2 | 1,707.01 | 1,699.33 | −172.66 | .008 | <.001 | 5,147.11 | 5,164.19 | −567.65 | <.001 | <.001 |
| 3 | 1,640.15 | 1,628.44 | −70.89 | .017 | <.001 | 5,018.91 | 5,044.94 | −119.25 | <.001 | <.001 |
| 4 | 1,621.76 | 1,606.03 | −22.41 | .580 | .667 | 4,945.82 | 4,980.80 | −64.86 | .047 | <.001 |
| 5 | N/A | N/A | N/A | N/A | N/A | 4,866.63 | 4,910.56 | −70.24 | .003 | <.001 |
| 6 | N/A | N/A | N/A | N/A | N/A | 4,907.57 | 4,960.44 | −49.88 | .290 | .667 |
| 7 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |

A significant *P* value indicates that the model with k-1 profiles is a better fit to k profiles. AIC = Akaike information criterion, BIC = Bayesian information criterion, lower AIC and BIC indices indicate better fit, ΔBIC = change in BIC as number of profiles increases, BLRT = bootstrap likelihood ratio test, N/A = not applicable, VLMRLRT = Vuong-Lo-Mendell-Rubin likelihood ratio test, a smaller *P* value suggests that the model with k profiles is a better fit to k-1 profiles.

**Table 3**—Raw means and standard deviations on Cognitive Drug Research System factors for 3 profiles in the clinic and community samples, respectively (standardized means are presented in Figure 1 and Figure 2).

| Latent Profile | Power of Attention (ms)[a] | Continuity of Attention (Maximum 95)[b] | Quality of Working Memory (Maximum 2.0)[b] | Quality of Episodic Memory (Maximum 400)[b] | Speed of Memory (ms)[a] | Premorbid Intelligence[b] |
|---|---|---|---|---|---|---|
| Sleep clinic sample | | | | | | |
| Strong thinkers (n = 46) | 1,176.36 (137.92) | 92.59 (1.02) | 1.96 (0.05) | 204.65 (56.48) | 3,625.06 (730.42) | 112.88 (6.89) |
| Inattentive fast thinkers (n = 54) | 1,178.07 (105.56) | 87.64 (5.26)[c] | 1.77 (0.18)[c] | 199.42 (52.29) | 3,733.65 (637.74)[d] | 110.10 (8.85) |
| Accurate slow thinkers (n = 21) | 1,339.20 (154.45) | 89.67 (3.79)[e] | 1.63 (0.47)[e] | 177.94 (53.95) | 5,312.92 (865.01)[e] | 104.98 (8.00)[e] |
| Community sample | | | | | | |
| Strong thinkers (n = 267) | 1,233.84 (128.78) | 91.57 (2.09) | 1.94 (0.06) | 182.74 (47.25) | 4,191.55 (697.28) | 105.04 (7.70) |
| Inattentive fast thinkers (n = 97) | 1,220.90 (114.17)[d] | 86.14 (4.99)[c] | 1.73 (0.19)[c] | 165.75 (47.26)[c] | 4,282.73 (569.83)[d] | 102.14 (10.56) |
| Accurate slow thinkers (n = 34) | 1,406.66 (188.84)[e] | 90.66 (3.12)[f] | 1.68 (0.36)[e] | 167.70 (51.37)[e] | 6,174.96 (1358.95)[e] | 98.71 (10.36)[e] |

[a]Lower scores indicate better performance. [b]Higher scores indicate better performance. *P* < .001 for [c]strong thinkers > inattentive fast thinkers; [d]inattentive fast thinkers > accurate slow thinkers; [e]Strong thinkers > Accurate slow thinkers; [f]accurate slow thinkers > inattentive fast thinkers.

memory. **Table 4** shows omnibus and post hoc results, **Figure 3A** shows cluster scores, and **Table 3** shows raw means and standard deviations.

### *Community sample*

There were differences across the profiles for power of attention, continuity of attention, quality of working memory, quality of episodic memory, speed of memory, and cognitive reserve. **Table 4** provides omnibus and post hoc results, **Figure 3B** provides cluster scores, and **Table 3** provides raw means and standard deviations.

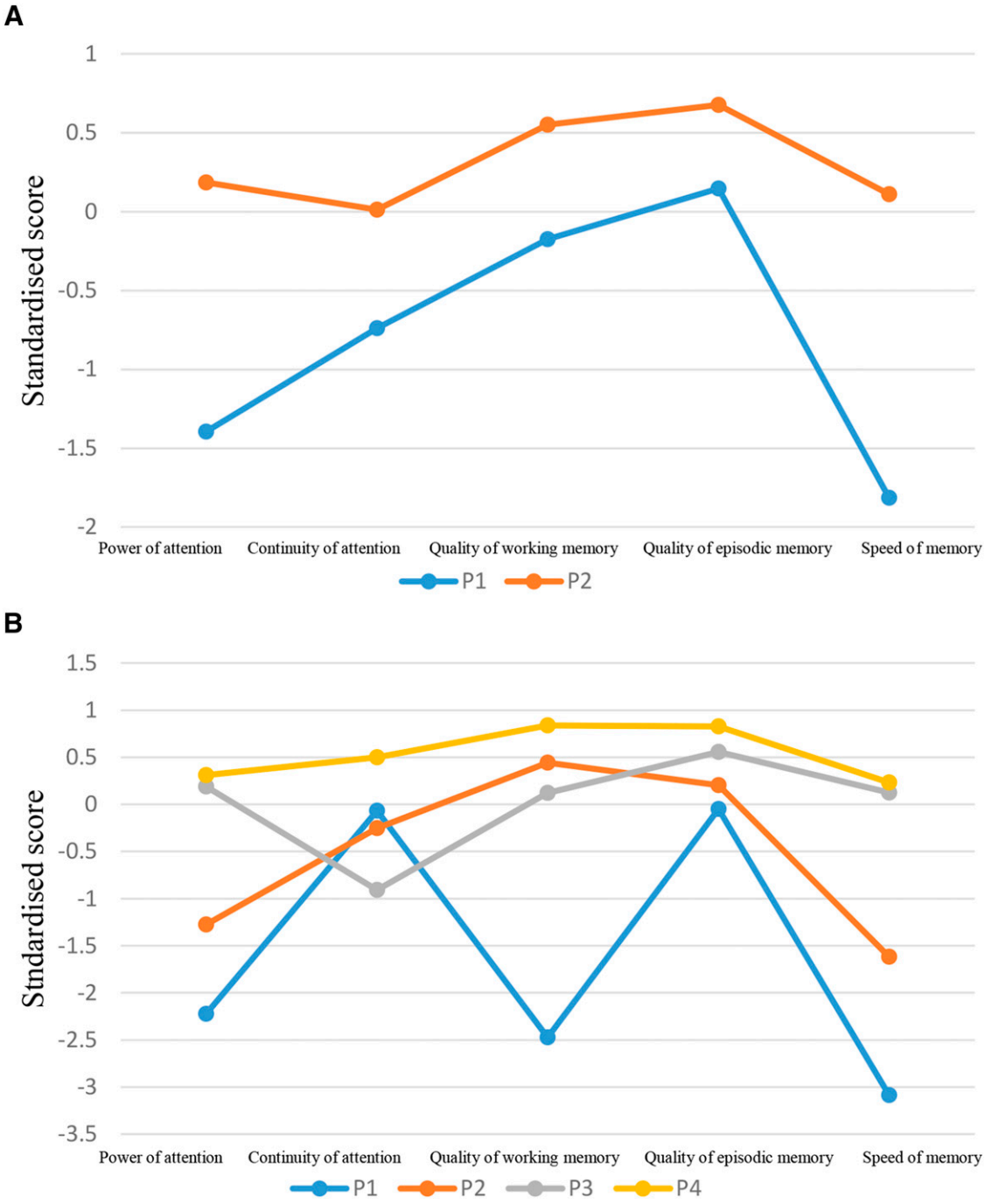
Consideration of these differences across both the clinic and community samples allowed the tentative naming of the profiles. One profile showed an advantage across most cognitive domains, including cognitive reserve (profile label: strong thinkers), another demonstrated problems in maintaining attention over longer time periods but relatively preserved attention and memory speed (profile label: inattentive fast thinkers), and the third showed slowed thinking but maintenance of accuracy across tasks (profile label: accurate slow thinkers). **Figure 4** presents a summary of these profiles.

## Profile differences in demographic and sleep variables

### *Sleep clinic sample*

Box's M indicated that the assumption of equality of covariance matrices had not been violated (*P* = .120) for the discriminant function analysis and that the proportion of variance explained in this model was 39%, with 42.1% of all cases correctly classified into their profile. Only the interaction term, mean $SaO_2$, moderated by cognitive reserve, was a significant predictor of profile membership, with having both the lowest $SaO_2$ combined with the lowest reserve being predictive of being in the accurate slow

**Figure 1**—Profile solutions for the clinic sample.



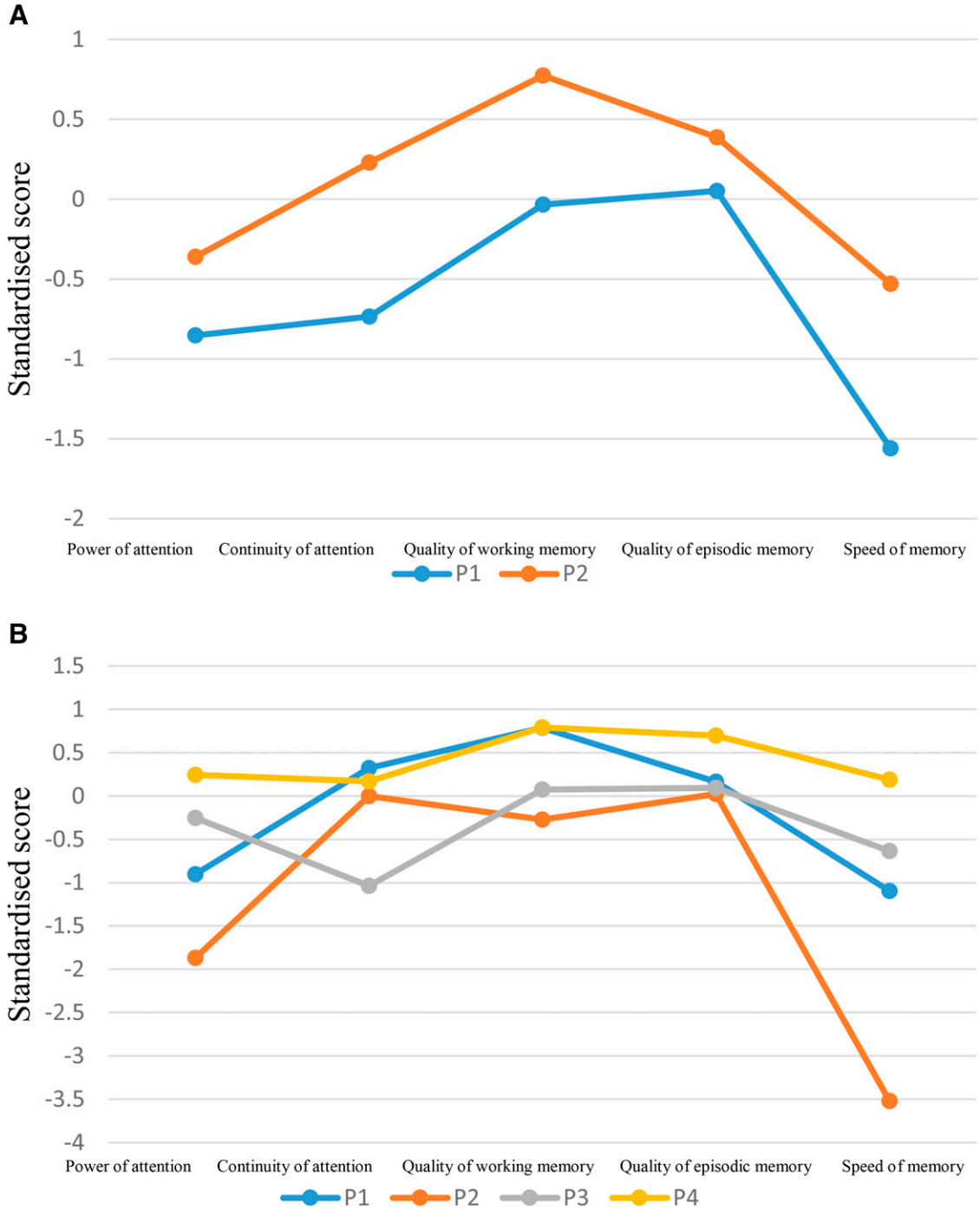

Two-profile **(A)** and 4-profile **(B)** solutions for the clinical sample. The fourth profile appears to replicate profile 2, and fit statistics provided mixed agreement for model fit.

thinkers profile. Those with the highest cognitive reserve who also had the highest mean nocturnal $SaO_2$ were predicted to have preserved cognition (strong thinkers). **Table 5** provides raw means and standard deviations.

### *Community sample*

Box's M indicated that the assumption of equality of covariance matrices had not been violated ($P$ = .732) for the discriminant function analysis and that the proportion of variance explained in this model was 22%, with 67.1% of all cases correctly classified. Only the number of comorbidities was a significant predictor of profile membership, with those with the most comorbidities being predicted to be accurate slow thinkers, whereas those with no comorbidities other than OSA were predicted to be strong thinkers. **Table 5** provides raw means and standard deviations.

**Figure 2**—Profile solutions for the community sample.

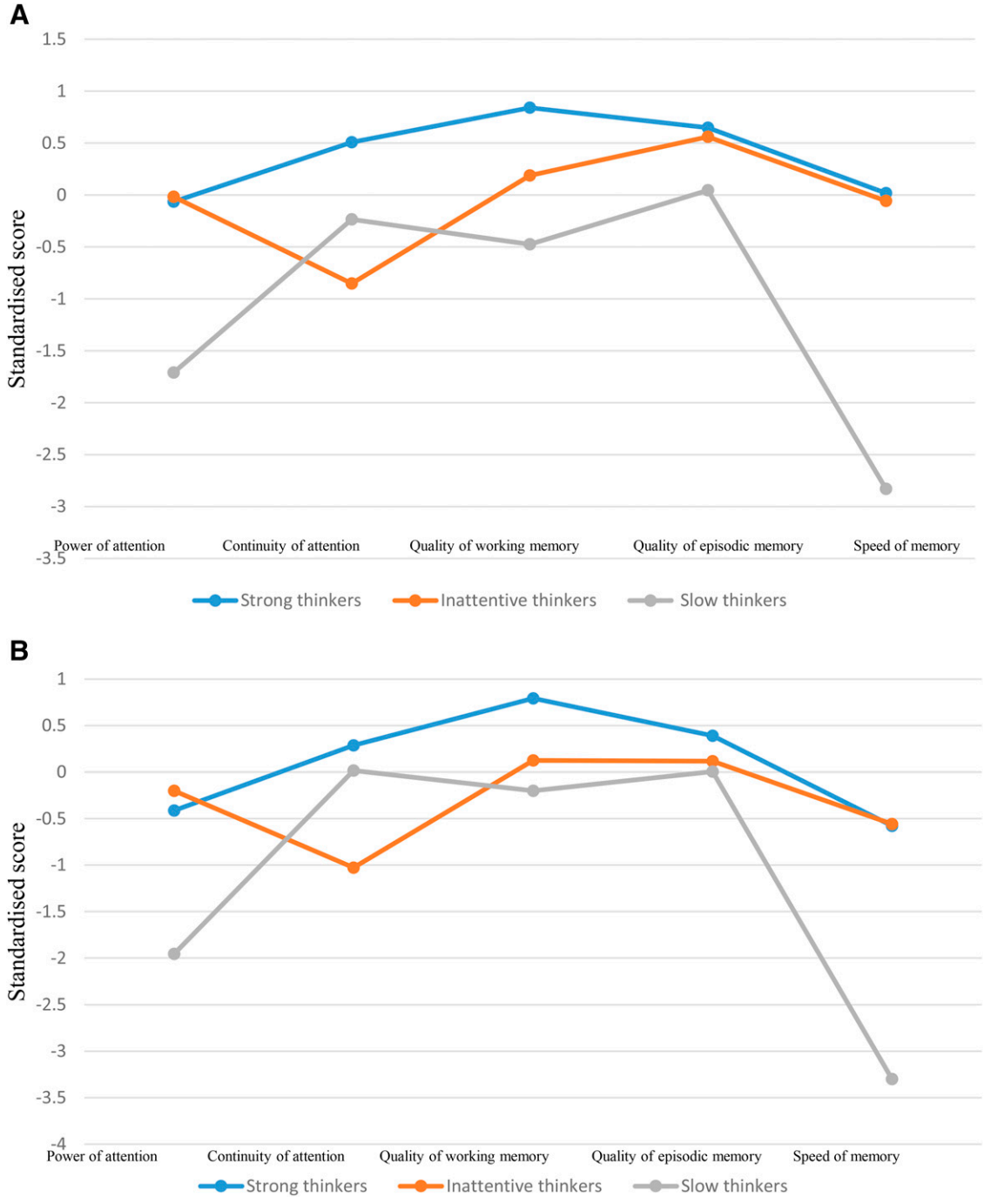



Two-profile **(A)** and 4-profile **(B)** solutions for the community sample. The fourth profile appears to replicate the third profile, and fit statistics provided mixed agreement for model fit.

## DISCUSSION

The same 3 distinct cognitive profiles in individuals with moderate-severe OSA were found in both a sleep clinic and a community sample: (1) strong thinkers, characterized by generalized cognitive strength, including greater cognitive reserve; (2) inattentive fast thinkers, characterized by problems in being able to organize information well and maintain attention over longer time periods but with preserved attention and processing speed; and (3) accurate slow thinkers, characterized by slowed thinking but satisfactory capacity to maintain attention.

**Figure 3**—Three cognitive profiles in the sleep clinic and community samples.




Three profiles provided best fit statistically and practically.

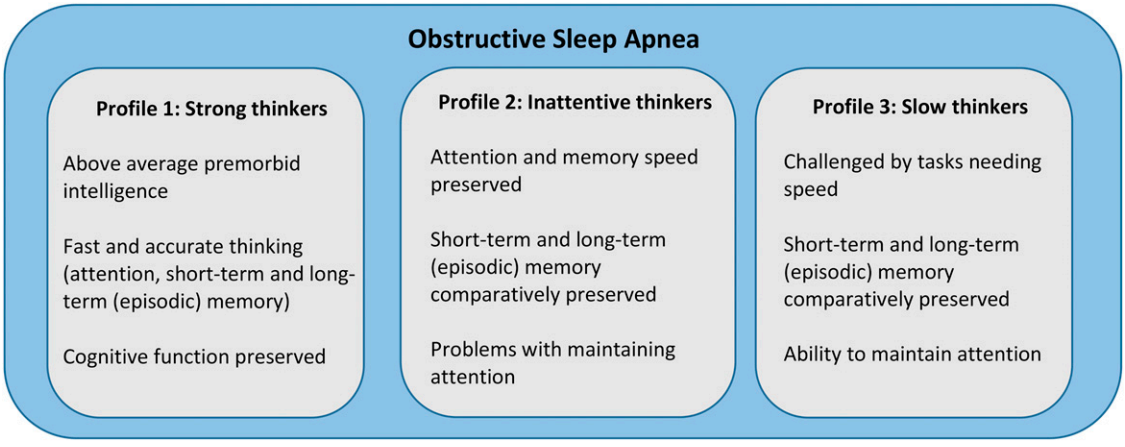
## Factors affecting cognition in OSA: cognitive reserve, $SaO_2$, comorbidity, and age

In the clinic sample, greater cognitive reserve (a measure of cognitive resilience to insult and injury) moderated the impact of mean $SaO_2$ on cognition, and this interaction was thus a predictor of cognitive profile: strong thinkers, who had both greater cognitive reserve and higher mean oxygen saturation, also had better overall cognitive function. Critically, this difference between profiles in cognitive reserve and mean $SaO_2$ was found despite controlling for the effect of cognitive reserve on the cognitive scores of each individual. This, taken with the findings from the discriminant function analysis, suggest that greater cognitive reserve modifies the impact of OSA on cognition, acting as a resilience factor to prevent decline in the presence of more severe oxygen desaturation, at least as evidenced in the sleep clinic sample. This is consistent with past literature exploring the relationship between cognitive reserve and current cognitive function in those with OSA.[12,40]

**Table 4**—Profile differences in cognition in the clinic and community samples for the omnibus and post hoc tests.

| Cognitive Domain | *F* Test | Post hoc |
|---|---|---|
| Sleep clinic sample | | |
| Power of attention | $F(2,118) = 22.70$, $P < .001$ | Strong > inattentive fast > accurate slow |
| Continuity of attention | $F(2,118) = 21.54$, $P < .001$ | Strong > accurate slow > inattentive fast |
| Quality of working memory | $F(2,117) = 20.75$, $P < .001$ | Strong > accurate slow > inattentive fast |
| Quality of episodic memory | $F(2,113) = 2.49$, $P = .090$ | Not significant |
| Speed of memory | $F(2,114) = 129.87$, $P < .001$ | Strong > inattentive fast > accurate slow |
| Cognitive reserve | $F(2,118) = 9.08$, $P < .001$ | Strong > inattentive fast > accurate slow |
| Community sample | | |
| Power of attention | $F(2,395) = 38.65$, $P < .001$ | Inattentive fast > strong > accurate slow |
| Continuity of attention | $F(2,395) = 109.13$, $P < .001$ | Strong > accurate slow > inattentive fast |
| Quality of working memory | $F(2,394) = 90.84$, $P < .001$ | Strong > accurate slow > inattentive fast |
| Quality of episodic memory | $F(2,390) = 5.55$, $P < .004$ | Strong > accurate slow > inattentive fast |
| Speed of memory | $F(2,390) = 162.37$, $P < .001$ | Strong > inattentive fast > accurate slow |
| Cognitive reserve | $F(2,395) = 10.27$, $P < .001$ | Strong > inattentive fast > accurate slow |

**Figure 4**—Summary of 3 cognitive phenotypes in the sleep clinic and community samples.




However, these factors did not impact cognitive profile membership in the community sample, where, instead, greater numbers of comorbidities predicted profile membership. In this sample, accurate slow thinkers had higher rates of comorbidity and poorer cognition, whereas strong thinkers had OSA but with low rates of CVD or diabetes. Past research shows that comorbidity affects cognitive dysfunction in OSA; for example, Borges et al showed that individuals with OSA, but without comorbidity, performed within the normal range on executive function tests.[11]

Cognition is known to decline in healthy aging[41] and is affected by OSA, and rates of OSA increase with increasing age.[42] For these reasons, it was critical to remove the impact of age on cognitive scores, via standardization, before exploring for profiles. However, age may also be a proxy measure of how long an individual has had OSA; thus, removing age may also have removed variance associated with how long someone has been affected by OSA. Being able to measure the length of time of exposure to OSA may facilitate clarification of the separable contribution of age and exposure time on cognition in OSA.

Taken together, this research supports the notion that resilience factors (eg, cognitive reserve), risk factors (eg, number of comorbidities and age), and nocturnal features (eg, nocturnal $SaO_2$) contribute to the cognitive dysfunction seen in OSA. For researchers or clinicians wanting to assign a cognitive profile to individuals with OSA, measures of cognitive reserve (eg, years of education, occupational history, or a reading task such as the National Adult Reading Test), nocturnal $SaO_2$, and comorbidities would be necessary, and cognitive tasks assessing speed and accuracy would be desirable. However, full cognitive assessment will provide the best way to characterize those with OSA in these terms, facilitating individualized care and tracking of changes in cognition across time.

### Factors unrelated to cognitive profiles: body mass index, sex, mood, sleepiness, and disease severity

There was no relationship in either the clinic or community samples between body mass, sex, mood, sleepiness, or overall disease severity of OSA and these different profiles or to

**Table 5**—Raw means and standard deviations for demographic and sleep factors for 3 profiles in the clinic and community samples, respectively.

| Latent Profile | BMI | Age | Sex (% Male) | Depression (Maximum 42) | Anxiety (Maximum 42) | Stress (Maximum 42) | ESS (Maximum 24) | AHI | Average $SpO_2$ (Maximum 100) |
|---|---|---|---|---|---|---|---|---|---|
| Sleep clinic sample | | | | | | | | | |
| Strong thinkers (n = 46) | 33.91 (7.63) | 54.78 (11.38) | 37.5 | 4.68 (4.25) | 3.56 (2.76) | 5.81 (4.35) | 10.20 (4.67) | 40.38 (26.23) | 92.24 (2.68) |
| Inattentive fast thinkers (n = 54) | 34.00 (7.07) | 54.62 (12.91) | 51.2 | 6.68 (5.57) | 4.47 (3.60) | 6.80 (4.91) | 10.38 (4.61) | 42.93 (25.05) | 92.59 (2.81) |
| Accurate slow thinkers (n = 21) | 34.04 (9.12) | 50.36 (12.40) | 58.6 | 4.39 (4.11) | 4.58 (3.06) | 5.97 (4.86) | 8.40 (5.28) | 45.62 (25.99) | 91.14 (4.77) |
| Community sample | | | | | | | | | |
| Strong thinkers (n = 267) | 30.52 (5.08) | 59.84 (5.38) | 49.0 | 3.70 (5.47) | 2.64 (4.03) | 6.32 (6.68) | 6.32 (3.76) | 23.96 (11.11) | 93.35 (2.75) |
| Inattentive fast thinkers (n = 97) | 30.64 (5.55) | 61.24 (6.03) | 55.3 | 4.27 (6.04) | 2.66 (3.63) | 6.49 (7.06) | 6.87 (4.20) | 26.16 (13.38) | 93.74 (3.25) |
| Accurate slow thinkers (n = 34) | 30.43 (7.67) | 57.74 (4.38) | 48.3 | 5.18 (5.79) | 3.00 (4.13) | 7.94 (7.49) | 6.85 (4.05) | 26.91 (12.33) | 93.39 (3.36) |

None of these demographic and sleep variables were different between the 3 samples, and only $SaO_2$ moderated by premorbid IQ for the clinic and no. of comorbidities for the community sample explained group membership. Depression, anxiety, and stress were measured on the Depression Anxiety, and Stress Scale-21. All scores on these subscales fell in the normal range of symptomatology. Only individuals in the strong and inattentive fast thinkers of the sleep clinic population fell over the normal range with scores ≥ 10. AHI = apnea-hypopnea index, BMI = body mass index, ESS = Epworth Sleepiness Scale, $SpO_2$ = saturation over sleep study period.

cognition more generally. This, at first glance, is surprising because these are some of the factors posited to be associated with cognitive dysfunction in the primary model of cognitive dysfunction in OSA.[15] Clearly, the relationship between these facets is complex, with previous analyses also failing to identify consistent relationships between the cognitive effects of OSA and body mass index,[21] mood,[5] sleepiness,[40,43] or overall disease severity as indexed by the AHI.[44]

Indeed, some authors propose more complex interactions between factors that cause harm as proposed in the dominant theoretical models of cognitive dysfunction in OSA.[45–47] For example, Lim and Pack[47] propose that hypoxia and hypercarbia do not cause harm, *per se*, but rather cause changes in nutrient demand which, in turn, alter the functioning and permeability of the blood–brain barrier to meet these challenges. Although adaptive, initially, these changes ultimately disrupt the brain's microenvironment and cause damage and cognitive change. In support of this hypothesis, there is preliminary work examining the glymphatic system that suggests that individual differences in permeability alter waste clearance from the brain,[48,49] which may impact cognitive function, albeit most of this work has been completed in animal models and little completed in humans with OSA.[50] Examination of glymphatic function in those with OSA may demonstrate group differences associated with cognitive profile, for example, genetic differences in type or number of aquaporins.

## Differences between the clinic and community samples

As discussed previously, the clinic and community samples differed with regard to the diurnal, nocturnal, risk, and resilience factors that predicted cognitive profile membership. For certain factors, this may be an artifact of the different sleep measurements used in each sample; for example, the full PSG completed in the clinic sample may have provided a more sensitive and accurate measure of sleep-related $SaO_2$, given constant monitoring by sleep technologists who are trained to monitor signals for integrity and relate them to sleep state. On the other hand, premorbid IQ and other cognitive tasks were measured the same way in both samples and, as such, that the clinic sample demonstrated a relationship between cognition and cognitive reserve whereas the community sample did not is unlikely caused by measurement differences. This clinic-to-community sample difference may represent a bias of those who seek help for their sleep difficulty.

Although ApneaLink automatic scoring is equivalent to manual scoring where AHI > 20 events/h (the individuals in the present study had an AHI ≥ 15 events/h), manual scoring demonstrates higher specificity in all OSA (AHI > 5 events/h) and therefore should be considered the gold standard.[51] Given this, our use of the automatic analysis feature of the ApneaLink software to analyze sleep data from the community sample is a limitation of the study.

A further limitation was that the proportion of individuals in each profile was different between the clinic and community samples. Although strong thinkers represented the largest proportion in both the clinic and community samples, there was

a much more even spread of participants across profiles in the clinic sample. Perhaps this represents a movement of individuals from the strong thinker to the inattentive fast or accurate slow thinker profiles over time and disease progression. However, that cognitive reserve was a predictor of group membership makes this suggestion seem unlikely because cognitive reserve should not change over time[52] and, rather, could indicate that those with the highest levels of cognitive reserve (strong thinkers) are less likely to visit a clinic because they are better able to compensate for the cognitive impairment of OSA. However, because comorbidity and mean nocturnal $SaO_2$ were also predictors of cognitive profile, it is possible that, as an individual acquires a greater disease load, their cognition could be further impeded, and they move across OSA profiles. Longitudinal data that investigate factors impacting cognition (eg, exercise) would be required to investigate these hypotheses.

### Future directions

Although data were not available on CPAP use, other research has shown a relationship between CPAP uptake and physiologic phenotypes.[53] This may be true for cognitive profiles as well. Indeed, treatment uptake is poor in individuals with OSA, and poor cognitive function is suggested to be a factor that reduces uptake.[54] This may make identification of cognitive profiles useful in planning intervention with more in-clinic cognitive support for slow thinkers and community activities to raise awareness of OSA and its associated health consequences for strong thinkers, where less impairment in their thinking skills could translate into lower motivation to engage with therapy.[54]

Furthermore, it may also be that certain cognitive characteristics impart a different recovery trajectory when established on CPAP, depending on the type of damage (speed or accuracy), the nocturnal profile (mean $SaO_2$), and the risk (comorbidity) and resilience (cognitive reserve) factors at play. It is certainly true that recovery of cognitive functions in response to CPAP treatment is mixed. A review of studies comparing CPAP with placebo revealed that, with regard to cognition, CPAP was rarely superior to sham[55]; however, paradoxically meta-analytic evidence of cognitive function before and after CPAP shows gains in cognitive function.[8,10] These inconsistent findings may be clarified if we were to account for cognitive profiles. Longitudinal data are needed to explore how different cognitive profiles affect engagement with treatment, the effect of treatment, and/or the course of disease severity.

Individuals with OSA show neuro-anatomical and functional changes.[56,57] It is entirely possible that accurate slow thinkers will demonstrate more white matter damage than other profiles, whereas inattentive fast thinkers, with attention deficits, might be expected to have frontal lobe or parietal changes. Future research may examine whether neuro-anatomical or neuro-functional changes predict cognitive profile.

Finally, in this study, cognitive assessments captured aspects of attention, memory, and working memory; however, reviews of the literature show that OSA impacts a wider array of cognitive functions. These include aspects of executive function, psychomotor speed, language abilities, and visuospatial function.[6,7] A full examination of cognition may extend the work undertaken in this paper.

## CONCLUSIONS

There is very strong evidence that individuals with OSA have poorer cognition than individuals with healthy sleep. However, individual studies show a variety of outcomes, with some reporting no effect of OSA on cognition, whereas others find an effect, the size of which may vary markedly between studies. This study offers some explanation as to why these different results might occur. It demonstrates that different cognitive reserve, nocturnal blood oxygen saturation, presence of CVD and/or diabetes affect how cognitive problems are expressed in those with OSA. This suggests that, if studies systematically recruit people with greater cognitive reserve (eg, university samples), low $SaO_2$ (eg, clinic samples), and greater comorbidity (eg, older samples), then sample bias will be introduced, resulting in systematic differences in cognition in those with OSA. These factors need to be accounted for when recruiting for studies examining cognition in OSA and in their statistical analyses. They also need to be accounted for in clinical assessment of individuals with OSA, because cognitive profile can influence symptom presentation and burden, and possibly treatment uptake.

## ABBREVIATIONS

AHI, apnea-hypopnea index
CPAP, continuous positive airway pressure
CVD, cardiovascular disease
LPA, latent profile analysis
OSA, obstructive sleep apnea
PSG, polysomnography
$SaO_2$, nocturnal arterial oxygen saturation

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## DISCLOSURE STATEMENT

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