Using Polysomnographic Data to Investigate Symptom Clusters Associated with Cognitive Decline in Patients with Obstructive Sleep Apnea

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***Abstract*—Cognitive decline (CD) is common in Obstructive Sleep Apnea (OSA) cohorts. Once CD has occurred it may be permanent. If patients at risk for developing CD are detected prior to the onset of symptoms, positive interventions can modify risk factors for CD to prevent or delay its onset. We propose a symptom clustering approach to identify an "At Risk Group" (ARG) with modifiable risk factors for CD. We hypothesized that the levels of individual risk factors in the ARG would indicate increased risk for CD. We used the Psychomotor Vigilance task (PVT) as a measure of established CD and in particular the 10% Slowest Reaction Time (10% SRT). We gathered information from 89 patients having Type 1 diagnostic polysomnography in a hospital sleep laboratory. We defined clusters of ascending severity for excessive daytime sleepiness (EDS), overnight (evening to morning) change of systolic blood pressure (CSBP) and sleep fragmentation (SF), and combined the most severe cluster from each symptom to form an ARG. We obtained PVT parameters from 42 subjects with good and poor results. We compared the levels of EDS, CSBP and SF in the ARG, the best and worst 10% SRT groups and the poor PVT group. The ARG had a CSBP of 9.9±14.8 mmHg and EDS of 12.5±6.4 on the Epworth Sleepiness Scale, in line with reported levels for risk for CD. The severe EDS and the combined severe EDS+CSBP clusters were present at statistically significant levels in the severe 10% SRT group. The ARG may be a viable screening method for patients with OSA at risk for CD.**

Keywords—cognitive decline, sleepiness, systolic blood pressure, obstructive sleep apnea, sleep fragmentation

I. Introduction

Cardiovascular disorders (CVD) [1], Excessive Daytime Sleepiness (EDS) [2], sleep fragmentation (SF) [3] and Obstructive Sleep Apnea (OSA) [4] are often comorbid and are associated with the onset of Cognitive Decline (CD). There are many tests for assessing CD, including the Psychomotor Vigilance Task (PVT) which measures established CD by measuring the ability to maintain attention using the reaction time (RT) to a visual stimulus [5]. The PVT metrics which relate to the speed of the RT have been found to best distinguish between alert and non-alert patients [5]. Once established, CD may be associated with permanent structural changes to brain white matter [6]. Compliant use of Continuous Positive Airway Pressure (CPAP) may delay the onset of CD [4], but it does not always reduce established objectively measured CD in all domains including PVT [7]. Another strategy is to identify individuals with severe levels of risk factors that can be modified to prevent the onset of irreversible changes and may be more sensitive to acute changes in risk factors than PVT. Patients undergoing polysomnography for OSA diagnosis are ideal candidates for such a screening tool due to the high prevalence of risk factors such as hypertension, SF, and EDS.

Diagnostic Polysomnography collects information about risk factors for CD such as cardiovascular disorders [1], EDS [2] and SF [3]. An evening to morning increase of 20 mmHg in systolic blood pressure (SBP) has been associated with left ventricular hypertrophy [8], and an overnight average SBP≥10 mmHg predicts future cardiovascular events [9]. An ESS≥10 is associated with incident CD [10], and cardiovascular events [2]. A SF severity in the 90th percentile may increase the rate of CD [3]. All of these factors are linked to OSA (Fig. 1). A proposed mechanism for the OSA link with CD is the formation of white matter lesions via blood pressure related damage to endothelial and smooth muscle cells, leading to cerebral hypoperfusion and white matter lesions [11]. White matter lesions correlate to PVT results, residual sleepiness [6] and SF related increases in the incidence of CD [3]. Diagnostic polysomnographic data may be useful in identifying and quantifying the risk of CD in patients with suspected OSA. In this paper, we examine the relationships between severe symptoms and combinations of severe symptoms, in two PVT groups with

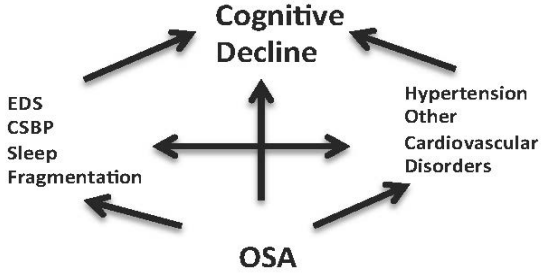

Fig. 1. Interactions between CD, OSA and Excessive Daytime Sleepiness (EDS), CSBP, SF, Hypertension and Cardiovascular Disorders.

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normal and poor outcomes, and the best and worst groups from the slowest 10% RT component of the PVT. If the severity of symptoms in the ARG is consistent with an increased risk for CD as identified in the literature (CSBP$\geqslant$ 10 mmHg, ESS > 10, and severe SF (SSF)) and if there is an overlap between severe symptoms and the groups with established CD we will have identified a group which may be a viable target for proactive treatment of the modifiable risk factors that predispose to CD.

II. Material and Method

A. Study Population and Data Gathering

The study population was a database of patients having Type 1 Polysomnography (Siesta Compumedics®, Sydney, Australia) at the Princess Alexandra Hospital's Sleep Disorders Centre in Brisbane for suspected OSA. This study has approval from the Human Research Ethics Committees of the Metro South Hospital and Health Services and The University of Queensland. Scoring was according to the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events, Alternate Criteria 2007 [12]. Data was collected for electroencephalography, left and right eye movements, bilateral anterior tibialis and submental electromyography, nasal air pressure and oro-nasal airflow, respiratory effort (abdominal and thoracic bands), peripheral capillary oxygen saturation (SpO2), body position, electrocardiography, digital video and sound. The Epworth Sleepiness Scale (ESS) was used to measure EDS [13]. Subjects with complete data were included in the analysis.

B. Electroencephalography

Electroencephalography was recorded from electrodes placed at C3, C4, M1, M2, F3, F4, O1 and O2 according to the International 10-20 electrode placement system. In addition, the inter-hemispheric asynchrony ($\psi_{a\to b}$) [14] was analysed as the correlation of data across electrodes C4-A2 and C3-A1 so that:

$$\psi_{a\to b} = \frac{\bar{r}_a - \overline{r_b}}{\overline{r_b}} \times 100. \quad (1)$$

The electroencephalographic data was segmented into standard 30 second epochs, categorized as REM or NREM related EEG and filtered into the following bands: δ (0.1-4Hz), θ (4.1-8Hz), α (8.1-12Hz), β (12.1-16Hz), high β (16.1-25Hz) and γ (25.1-35Hz). The mean (*m*), standard deviation (*sd*), variance (*v*) skewness (*sk*) and kurtosis (*k*) were calculated for each band. In addition, the product of the *m*, *sd*, *v*, *sk* and *k* of each EEG band was formed with the values for each EEG band in NREM, REM and all Sleep with the Time in NREM Stage 1, Time in NREM Stage 2, Time in NREM Stage 3, Time in REM, REM Latency, and the Arousal Index.

C. Sleep Fragmentation

Sleep fragmentation data was computed according to the Weighted Transition Sleep Fragmentation Index (WTSFI) protocol [15]. The WTSFI is given as:

$$\chi = \frac{R}{M} \quad (2)$$

where:

$$R = \frac{\sum_i^{N-1} w_i}{TST}, \forall_{w_i} > 0 \quad (3)$$

$$w_i = \mathrm{HTS(i)} - HTS(i+1) \quad (4)$$

where i = 1, 2, …, N-1. N is the number of epochs, HTS is the Hypnogram Time Series, TST is the total sleep time in hours. M is a quality of sleep indicator: the median of the HTS, and w_i is the transition weight between the sleep epochs i and i+1. We also computed the mean (*m*), standard deviation (*sd*), variance (*v*), skewness (*sk*), and kurtosis (*k*) of the WTSFI.

D. Change of Systolic Blood Pressure

Seated systolic and diastolic blood pressure were collected in the evening and in the morning after 5 minutes of quiet rest, using a mercury column sphygmomanometer and an appropriate size cuff. The change in systolic blood pressure (CSBP) was calculated by subtracting the morning SBP from the evening SBP.

E. At Risk Group Formation

In order to grade the severity of EDS, the overnight CSBP and SF (*m*WTSFI) within our cohort, we first standardized the data for CSBP, ESS and the mean of the WTSFI (*mWTSFI*). The *Z*-score was calculated so that:

$$Z(\propto) = \frac{\propto - u_\propto}{\sigma_\propto} \quad (5)$$

where $\propto$ can represent 'CSBP', 'ESS' or 'mWTSFI', and $u_\propto$ and $\sigma_\propto$ respectively represent the population mean and standard deviation of CSBP, ESS or mWTSFI.

Each symptom was divided into four groups: Group 1: $Z_{(\propto)} < \mu_\propto - \sigma_\propto$, Group 2: $\mu_\propto \geq z_{(\propto)} \geq \mu_\propto - \sigma_\propto$, Group 3: $> \mu_\propto \leq Z_{(\propto)} \leq \mu_\propto + \sigma_\propto$ and Group 4: $Z_{(\propto)} > \mu_\propto + \sigma_\propto$.

Unsupervised cluster analysis was performed using the four symptom groups (Fig. 2) in the Two Step Cluster Analysis [16] (SPSS version 25, SPSS Inc., Chicago, IL, USA) for ESS, CSBP and WTSFI. Group 4 from each cluster ($> \mu_i + \sigma_i$) for ESS, CSBP, and SF were combined to form an at risk group (ARG). A Kruskal Wallis Anova [17] was performed to discover if there were significant between group differences in medians of data collected during routine PSG for the ARG.

TABLE I. STUDY ACRONYMS

CD	Cognitive Decline
ARG	At Risk Group
PVT	Psychomotor Vigilance Task
ESS	Epworth Sleepiness Scale
CSBP	Evening to Morning Change in Systolic Blood pressure
WTSFI	Weighted Transition Sleep Fragmentation Index
SF	Sleep Fragmentation
SRT	Slowest 10% Reaction Time
EDS	Excessive Daytime Sleepiness

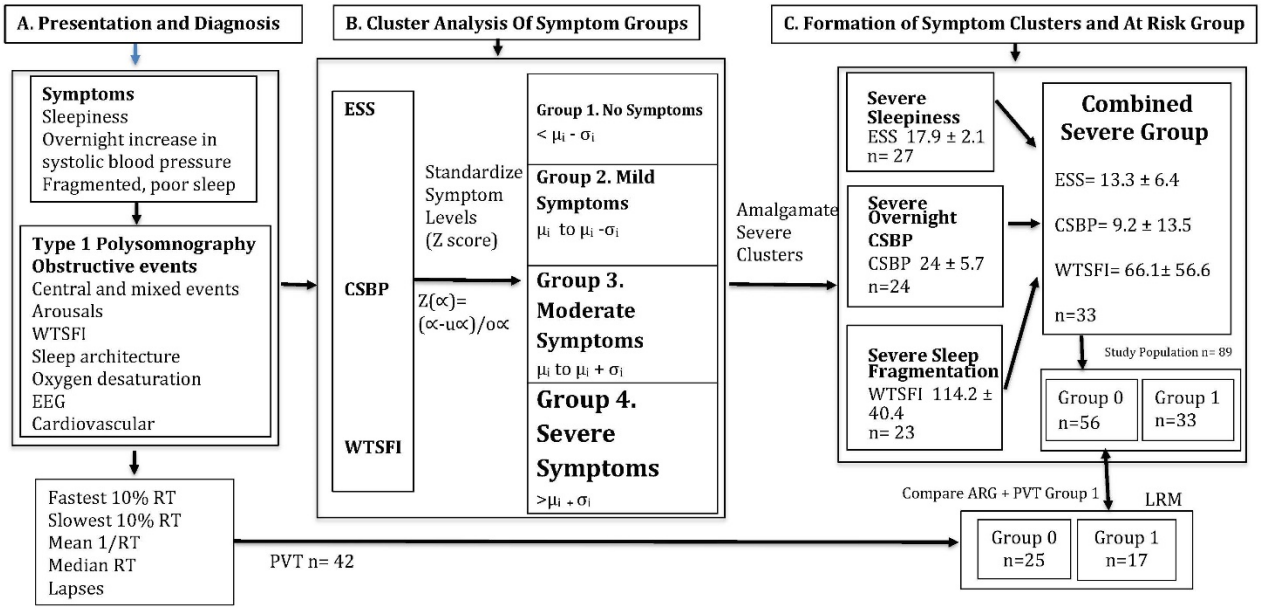

Fig 2. Study Method: Polysomnography, Four Groups for ESS, CSBP, and Weighted Transition Sleep Fragmentation (WTSFI), Psychomotor Vigilance Task (PVT). Clustering and comparison with the Slowest 10% Reaction Time Group using Logistic Regression Model (LRM).

F. Psychomotor Vigilance Testing

In a companion study [18], a subgroup of 47 patients underwent PVT to measure their level of sustained attention. They were required to press a button after the appearance of a red dot, and performance was measured by the reaction time (RT) and recorded as i) Mean 1/RT, ii) Median RT, iii) Fastest 10% RT, iv) Slowest 10% RT, and v) Number of lapses (RT $\geqslant$ 500ms). The results were combined and clustered in an unsupervised method using the k-means clustering algorithm. Two clusters were formed, PVT Group 0 with stronger RT results, and PVT Group 1 with poor RT results. We formed groups of four severity levels of the slowest 10% RT (SRT), as in section II-E, and compared the most severe group $> \mu_\propto + \sigma_\propto$ with the least severe group $< \mu_\propto - \sigma_\propto$. We hypothesized that if severe EDS (SEDS), SSF and severe CSBP (SCSBP) were risk factors for CD, they would occur more frequently in the most severe 10% SRT group than in the least severe 10% SRT group.

III. RESULTS

A. Cluster and Group Characteristics

There were 89 subjects with complete data (Fig. 1). The ARG had 33 members. The clusters contributing to the ARG had an ESS of 18, CSBP 23.5 mmHg and *m*WTSFI of 116. These scores place the individuals from each severe cluster into the 90th percentile of the total population values for each symptom (90th percentile for ESS = 17, CSBP = 22 mmHg, mWTSFI = 95).

Compared to the non-ARG group (Table II), the ARG Group 1) had significantly higher scores for ESS (12.5:7.2) and CSBP (9.9:-4.6mmHg), and a lower kurtosis of WTSFI (3:6.1). The *m*WTSFI was higher in both the ARG and the PVT group 1, but this did not reach statistical significance.

The group means for ESS (12.5), CSBP (9.9 mmHg), and mWTSFI (58.8) within the ARG are above the population 70th percentile for ESS and CSBP (12 and 9), and above the 75th percentile for mWTSFI (45.3). There were 6 subjects in the ARG who had both SESS + SCSBP, 2 had both SESS + SSF, and 3 had SCSBP + SSF.

The PVT group with the worst performance (Group 1), had 17 members, 47% of PVT Group 1, and 30% of PVT Group 0 were members of ARG Group 1. There were 6 subjects in PVT Group 1 and 1 in PVT Group 0 with SSF, which places them above the 90th percentile for population levels of SF (p=0.01). The levels of other severe symptoms were not statistically different between the two PVT groups, although the level of overnight CSBP was 5.8 mmHg for PVT Group 1 and 3 mmHg for PVT Group 2.

The SESS and SESS+SCSBP combinations reached statistically significant levels in the severe 10 %SRT groups at p<0.1 and p<0.05 (Table III). This means that the subjects with the SESS in the worst slowest 10% SRT group had a mean ESS of 17.9 and those with SESS+SCSBP had both a mean ESS of 17.9 and CSBP of 24 mmHg, both above the population 90th percentile. There were no statistically significant relationships between any of the severe symptom clusters and the best 10% SRT group (Table III). All of the patients in the severe 10% SRT group had measureable CD and were in PVT group 1.

TABLE II. SYMPTOM CHARACTERISTICS FOR THE ARG AND PVT GROUPS AT P<0.05

	At Risk Group (mean)			PVT Group (mean)		
	0 (n=56)	1 (n=33)	p	0 (n=25)	1 (n=17)	p
ESS	7.2	12.5	0.039	9.8	9.1	0.99
CSBP	-4.6	9.9	0.039	3	5.8	0.21
mSF	34.8	58.8	0.94	30.7	55.8	0.53
kSF	6.1	3	0.035	3.1	6.6	0.53

TABLE III. DISTRIBUTION OF SEVERE EDS (SEDS), SEVERE CSBP (SCSBP), SEVERE SF (SSF) AND THE WORST AND BEST SRT IN THE ARG AND PVT GROUPS.

	SEDS	SCSBP	SSF	SEDS+ SCSBP	SEDS +SSF	SCSBP +SSF
Worst SRT	3^{b}	2	1	2^{a}	0	0
Best SRT	7	7	4	3	2	1
ARG 1	17^{a}	15^{a}	10^{a}	6^{a}	2	3^{a}
ARG 0	0^{a}	0^{a}	2^{a}	0^{a}	0	0^{a}
PVT 1	4	4	6^{a}	3	1	1
PVT 0	5	6	1^{a}	2	1	0

$^{a}p<0.05$, $^{b}p<0.1$

IV. Discussion and Conclusions

We have identified a group containing patients with untreated OSA and a high severity of symptoms associated with significant health outcomes related to CD. This group, especially the individuals with combinations of severe symptoms, has levels of symptoms generally above the 90th percentile found in a population with suspected OSA, and should be prioritized for therapeutic interventions both for general health and prevention of CD.

There was a statistically significant association between SEDS and SEDS + SCSBP in the group with severe levels of the 10% SRT which did not appear in the combined PVT groups. The components of the PVT describe different aspects of cognition and have different levels of sensitivity for the detection of alertness. Shorter versions of the protocol using the components relating to the speed of the reaction may be as effective as the current 10 minute version and may be more clinically applicable [5]. Combining speed based components of the PVT with measurements of mean and median response values may decrease the sensitivity of the test to decrements in vigilance. In particular a symptom clustering approach may detect changes in risk of CD that may only be detected using PVT over longer time scales and after permanent cognitive change.

We found a significant difference in the levels of SSF between the good and poor PVT groups. Levels of SF have been associated with CD and poorer learning, but not always with vigilance outcomes [19]. One difficulty is that there is no accepted metric for SF. We have used an experimental index, the Weighted Transition Sleep Fragmentation Index [14], which allots different levels of importance to particular sleep stage transitions such as from REM or Stage 3 NREM. It needs to be validated in future clinical trials, but appears to have potential clinical efficacy as an index of sleep fragmentation.

The current study has been conducted on a small database. There is a need for replication of this work with larger numbers in independent databases. Prospective studies are required to determine the rate at which patients from ARG Group 1 eventually suffer cognitive decline.

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