ELSEVIER

Sleep Medicine 7 (2006) 131–139

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Original article

# A preliminary study of sleep-disordered breathing in major depressive disorder

Patricia J. Deldin[a,1], Laura K. Phillips[b,*], Robert J. Thomas[c]

[a]*Department of Psychology, University of Michigan, Ann Arbor, 525 E. University, 2252 East Hall, Ann Arbor, MI, 48109, USA*
[b]*Department of Psychology, Harvard University, 33 Kirkland St. Rm. 1205 William James Hall, Cambridge, MA, 02138, USA*
[c]*Division of Pulmonary Critical Care and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Boston*

Received 15 March 2005; received in revised form 26 May 2005; accepted 27 June 2005
Available online 2 November 2005

**Abstract**

*Background and purpose*: Individuals with obstructive sleep-disordered breathing (OSDB) commonly report symptoms of depression; however, the percentage of individuals with major depressive disorder (MDD) who experience OSDB is less clear. This study aimed to examine OSDB in a sample of individuals with MDD, unselected for sleep-related complaints, along a continuum of ventilatory and hypoxic abnormalities.

*Patients and methods*: The overnight sleep-related breathing of 19 individuals with MDD and 15 non-depressed controls was recorded using an unattended nasal pressure-based home sleep monitoring device. The device recorded nasal airflow, breathing effort, heart rate, oxygen saturation, and body position.

*Results*: The two groups varied significantly on three sleep-related breathing variables: major flow-limitation events, major flow-limitation events accompanied by a desaturation, and average saturation throughout the evening; and these groups approached significance on minor flow-limitation events accompanied by a desaturation and average number of desaturations throughout the evening. Sleep-related breathing variables predicted accurate grouping in 81.3% of those with MDD and 80.6% of the non-depressed participants.

*Conclusions*: These results suggest that OSDB may play a more important role in MDD than previously recognized. OSDB may contribute to or exacerbate the condition of someone predisposed to MDD, and the treatment of OSDB may ameliorate or possibly prevent depressive symptoms.



*Keywords:* Sleep apnea; Depression

## 1. Introduction

Numerous studies demonstrate a high rate of depressive symptoms in individuals with obstructive sleep-disordered breathing (OSDB) [1]. The interaction of OSDB and mood is reciprocal and complex [2–3]. In randomized controlled trials of positive airway pressure, pre-treatment depressed mood reportedly improved [4]. A population study using the Sleep-EVAL expert system questionnaire reported that after controlling for obesity and hypertension, the odds of having a Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) breathing-related sleep disorder diagnosis was 5.6 for individuals with a major depressive disorder [5]. Two decades ago, a report [6] found a 15.1% prevalence rate of at least 'some degree of sleep apnea' (p. 566) within a depressed group of 86 inpatients. The authors concluded that the percentage is neither clinically significant nor an indication for routine OSDB screening. This conclusion may be premature given the following: (1) OSDB was described as present or absent, rather than studied along a continuum of disordered breathing events, (2) groups included a heterogeneous in-patient population that included individuals with unipolar major depression, bipolar, and schizoaffective disorder, (3) the study lacked a non-depressed control group, (4) the study employed thermistors to monitor airflow, an inaccurate method for

* Corresponding author. Tel.: +781 718 7921; fax: +617 495 3728.
*E-mail address:* phillips@wjh.harvard.edu (L.K. Phillips).

[1] Order of authors of authors is alphabetical as all authors contributed equally to this work.

1389-9457/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.sleep.2005.06.005

detecting partial airflow obstructions (hypopneas) [7], and (5) only apneas were scored.

### *1.1. Symptom profile commonalities between OSDB and major depressive disorder (MDD)*

Patients with OSDB experience repetitive episodes of complete or partial airway obstruction, coupled with variable degrees of intermittent oxygen desaturation. The consequent sleep fragmentation may result in excessive daytime sleepiness, executive dysfunction and mood impairment [8]. Other symptoms include restless sleep, snoring, morning headaches, sexual dysfunction, irritability, impatience, and anxiety [9–11]. With the exception of snoring, all of the above symptoms have also been associated with MDD [12–14]

### *1.2. Neurological and pharmacological similarities between OSDB and MDD*

Deficits in concentration, working memory, and executive cognitive functioning are common to OSDB [15–16] and MDD [17–19]. Auditory tone-induced sleep fragmentation causes changes in memory, attention and mood [20]. Beebe and Gozal (2002) theorize that sleep fragmentation and hypoxia during sleep lead to a disruption of sleep-related restorative effects on the prefrontal cortex. In turn, this may result in 'executive dysfunction,' which refers to the capacities crucial for organization, planning, and adaptation [21]. In addition, functional magnetic resonance imaging (fMRI) results suggest that OSDB is associated with reduced lateral prefrontal activation during working memory tasks [22]. Functional neuroimaging abnormalities within the prefrontal cortex have also been associated with MDD [24–25].

Symptoms of depression in patients with OSDB may improve following treatment with continuous positive airway pressure [26–27], though this has not always been observed [28]. The use of the wake-promoting drug Modafinil improves a range of cognitive symptoms and sleepiness in sleep apnea [29] and preserves prefrontal activation on working memory tasks following overnight sleep deprivation [30]. This drug is also effective as an augmenting agent in depression [31]. In summary, several clinical, neuropsychological, and functional neurobiological phenomena are common to OSDB and MDD, and treatment of sleep-disordered breathing has lead to a reduction in both depressive symptoms and neuropsychological impairment.

The purpose of the present study was to explore whether there was abnormal respiration and nocturnal oxygen desaturation within a group of individuals diagnosed with MDD. Unlike prior work on the relationship between MDD and OSDB, which has involved examining the number of individuals with MDD who meet certain limited criteria, the current study measures the relationship between MDD and OSDB along a continuum of ventilatory and hypoxic disturbances. A study with this methodology allows for an exploration of smaller, yet potentially significant, sleep-related breathing and desaturation phenomena. Our sample was comprised entirely of outpatient, unipolar-depressed individuals. In addition, a control group was included, providing critical normative data for the technique used to monitor airflow, a nasal cannula-pressure transducer technique; this method has been found to be a more accurate measure of abnormal sleep-related respiration than thermistors [7], including when it is used without sleep monitoring [32].

## 2. Materials and methods

### *2.1. Participants*

Participants were recruited through newspaper advertisements and flyers, announcing a study on thoughts and emotions, intended to recruit participants for a larger study on depression and memory. No reference to sleep or the examination of sleep was mentioned. A phone screen served as a preliminary test for study eligibility.

One hundred and sixty-eight individuals were interviewed using the Structured Clinical Interview for the DSM-IV Axis I Disorders Patient Edition (SCID-I/P: [33]), by a doctoral-level clinical psychologist (PJD) or clinical psychology graduate students trained in SCID administration. All interviews were audiotaped for reliability purposes. Sixty-five percent of the tapes of the individuals in the major depression group and 93% of the tapes of the individuals in the control group were reviewed to ensure diagnosis. The inter-rater reliability was 100%.

Fifteen non-depressed controls were found to have no current or past Axis I psychiatric diagnosis and no current or past diagnosis of OSDB, and none had a history of taking psychotropic medication. Nineteen individuals met DSM-IV criteria for a current major depressive episode (MDE). The average age of onset of the current major depressive episode was 30.79 (SD = 12.09) with a mean duration of 17.61 months (SD = 29.83). Eighty-four percent ($n = 16$) had experienced at least one previous MDE. Twenty-one percent ($n = 4$) had a history of hospitalization. Forty-seven percent had sought treatment in the past for a MDE ($n = 9$), and 37% ($n = 7$) were currently taking antidepressants. Sixteen percent ($n = 3$) were taking sedative-hypnotics.

The demographic variables collected include gender, ethnicity, age, education level (in years completed), and body mass index (BMI). The major depression group consisted of 15 women and 4 men, 13 of whom were Caucasian, 5 African-American, and 1 Portuguese-American, with a mean age of 34.37 years (SD = 11.52), education of 14.71 years (SD = 2.47), and body mass index (BMI) of 26.13 (SD = 7.40). The control group was made up of 10 women and 5 men, 13 of whom were Caucasian, 1 African-American, and 1 Asian-American,

Table 1
Participant characteristics

| Characteristic | Mean (SD) | | df | T | p |
|---|---|---|---|---|---|
| | Control group | MDD group | | | |
| Gender | 10F;5M | 15F;4M | 1 | $X^2=0.292$ | ns |
| Education | 14.71 (2.47) | 16.13 (2.13) | 32 | 1.738 | ns |
| Age | 34.27 (13.33) | 34.37 (11.52) | 32 | .024 | ns |
| Ethnicity[a] | 13C;1AA;1A | 13C;5AA;1P | 3 | $X^2=4.073$ | ns |
| BMI | 24.53 (5.10) | 26.13 (7.40) | 29 | 0.500 | ns |
| BDI | 1.64 (2.02) | 25.84 (8.24) | 31 | 10.710 | <0.01 |
| STAI-T | 31.54 (8.79) | 57.50 (11.51) | 29 | 6.812 | <0.01 |
| *Self-report sleep indices* | | | | | |
| PSQI | 4.00 (2.20) | 7.87 (3.11) | 29 | 3.64 | 0.001 |
| ESS | 5.54 (3.48) | 6.93 (4.93) | 29 | 0.742 | ns |
| HO | 51.38 (12.33) | 46.87 (12.86) | 28 | 1.033 | ns |
| SE | 91.38 (8.50) | 77.67 (15.18) | 28 | 2.798 | 0.010 |
| SL | 18.85 (12.10) | 31.80 (25.40) | 28 | 1.655 | ns |

[a] C, Caucasian; AA, African American; P, Portuguese; A, Asian.

with a mean age of 34.27 years (SD = 13.33), education of 15.85 years (SD = 2.15), and BMI of 24.53 (SD = 5.10) (Table 1).

Exclusionary criteria for both the depressed and non-depressed groups eliminated those who reported or diagnosed via interview: current or past mania, cognitive impairments (learning disabilities), head injuries resulting in loss of consciousness for more than 10 min, anorexia nervosa, or seizure disorders. Since this study was performed in the context of a larger study employing psychophysiology, exclusion criteria were identical to those of the larger study.

All study procedures were approved by the Harvard Institutional Review Board. The details of the study were explained to all participants, and after all questions were addressed, written informed consent was obtained. Participants were compensated $10 for each hour of the SCID interview and $50 for the overnight sleep monitoring.

### 2.2. Measures

Participants completed a battery of questionnaires to assess current depressive and anxiety symptom severity and current sleep patterns. The Beck Depression Inventory (BDI) was used to evaluate each participant's self-rated current level of depression [34]. The Spielberger Trait Anxiety Inventory (STAI-T: [35]) provided indices of general patterns of anxiety. Participants also completed three questionnaires to assess the following: (1) sleep difficulties (Pittsburg Sleep Quality Index, PSQI) [36], (2) the degree to which one is a 'morning person' versus a 'night person' (Horne and Ostberg, MEQ) [37], and 3) the severity of daytime sleepiness during certain activities (Epworth Sleepiness Scale (ESS) [38]). Additional items were selected from the PSQI to be analyzed separately. These included self-reported sleep latency (SL = amount of time on average it takes one to fall asleep at night) and sleep efficiency (SE = reported total time in bed/reported time asleep). In addition, we took special note of the responses to the SCID A module. The specific module A items noted include depressed mood, anhedonia, appetite, sleep, psychomotor change, energy, worthlessness, concentration, and suicidality.

### 2.3. Sleep-related breathing recordings

The Stardust™ (Respironics Inc, Murrayville, USA) system, an empirically validated portable device for the diagnosis of obstructive sleep apnea [39], consists of a recording device and host software. The device is a portable, computerized polysomnographic system that allows for the recording of physiologic inputs within the participant's natural sleep environment. The participants were asked to take the device home with them and to return the machine the following day; thus, the sleep studies took place at the homes of the participants. The signals recorded were body position (measured by the position of the recorder itself), nasal airflow and respiratory rate (through a nasal cannula-pressure transducer system), oximetry and heart rate (through a finger pulse oximeter), and respiratory effort (through a respiratory effort belt). Sampling rates and filter settings were as follows: airflow bandwith = 0.05 to 2 Hz, sample rate = 200 samples per second, and storage rate = 10 per second; effort bandwith = 0.03 to 3.2 Hz, sample rate = 200 samples per second, storage rate = 10 per second; $Sp0_2$ = 8 s weighted average, and heart rate = 8 s weighted average; body position bandwith = 1 Hz; and patient event marker bandwith = 1 Hz.

The recorder digitized and stored physiologic inputs from the sensors. Data were later downloaded by serial connection to a computer with loaded Stardust Host software, designed to download, scan, display, and sort the data. Participants used an event button to record lights-off and lights-on, which was used to estimate recorded time

as a surrogate of total sleep time, as well as other events that signified wake (e.g. using the bathroom).

### 2.4. Scoring of respiratory events

The Stardust host software scanned, according to predetermined parameters located in a series of configuration files for pathological events, distinguished by their length, associated pulse rate and/or saturation decrease. The system continually modified a model, which at any point was based on the last 16 breaths, of the participant's breathing and saturation. After the system scanned for major abnormalities, detailed event-by-event manual scoring was performed and abnormalities categorized as 'major' or 'minor' respiratory events rather than apneas and hypopneas (Fig. 1), as oral airflow was not recorded and the untransformed nasal pressure signal is not linearly related to flow. A major respiratory event consisted of a flat nasal flow signal for $\geq 10$ s that was terminated by an abrupt recovery of sinusoidal flow or a large recovery breath. A minor flow-limitation event was scored when there was clear evidence of inspiratory flow-limitation for a similar duration or a clearly visible (cut-off of 20%) reduction in amplitude of the nasal flow signal that terminated in an abrupt return to sinusoidal flow or a large recovery breath (see Fig. 1). Major and minor events were scored without regard to the occurrence of oxygen desaturation. An $O_2$ saturation drop % parameter, set at 3%, specified the percent $SaO_2$ drop required to annotate a major or minor event as 'with $SaO_2$ drop'; the system also calculated the total number of drops in $SaO_2$ throughout the night's sleep, irrespective of the association of a respiratory event. A board certified sleep specialist (RT), blind to diagnosis, validated each individual respiratory event and manually made required changes. The Stardust software computed relevant summary statistics.

### 2.5. Data analyses

Variables analyzed were total scores from the BDI, STAI-T, and the three self-report sleep questionnaires (PSQI, H-O, ESS); sleep latency (SL) and sleep efficiency (SE); and each scored module A SCID item. The Stardust system events analyzed included total number of major and minor events (i.e. the respiratory disturbance index (RDI), regardless of change in oxygen saturation), number of major flow-limitation events per hour (MJ), percentage of major events accompanied by at least a 3% drop in $SaO_2$ (%MJ), number of minor flow-limitation events per hour (MN), percentage of minor events accompanied by at least a 3% drop in $SaO_2$ (%MN), mean $SaO_2$ throughout the evening (%AVG), and number of drops in $SaO_2$ per hour (DST). In addition, to obtain a measure of sleep apnea according to the conventional style, we calculated the total number of major events plus the number of minor events accompanied by a desaturation of 3% or more, per hour of sleep. Those individuals who experienced greater than five events per hour were classified as having sleep apnea. The majority of the participants slept with the machine for a single night.

A binary hierarchical logistic regression analysis was performed to determine if respiratory variables could correctly classify those with MDD verses the non-depressed controls. The logistic regression was followed up with two multivariate analyses of covariance (MANCOVAS) and a *t*-test to evaluate specific differences between groups on each of the self-rated mood and sleep scales, SL, SE, and each of

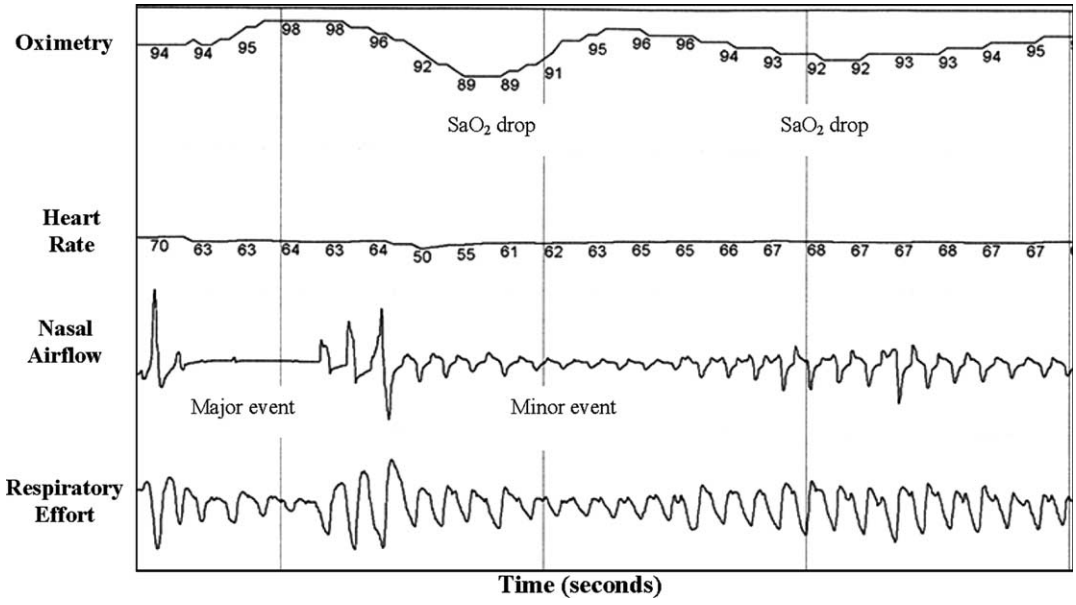


Fig. 1. Scoring of Respiratory Variables. Samples of scored respiratory events. A 'major' event is associated with a 'flat line' in the nasal pressure trace, while a 'minor' event shows flow limitation but evidence of individual breaths.

the Stardust system recorded events. Because BMI is often correlated with OSDB, BMI was covaried within the analyses. Correlations were performed among all of the variables between and within each group to examine, in particular, whether there were any relationships between respiratory variables and (1) severity of depressed mood, using the BDI, (2) module A SCID items, (3) current or past history of medications, and (4) number of previous episodes.

## 3. Results

No significant differences in any of the breathing variables or the sleep scales were found between those who were and were not taking antidepressant or sedative hypnotic medications. The sleep-related breathing of individuals with and without MDD was recorded for a mean duration of 6.09 h (SD = 2.30 h.) and 6.58 h (SD = 1.84 h), respectively. No significant differences were found between the two groups in the amount of time spent in the supine position versus non-supine position (for MDD group, mean percentage of time in the supine position = 46.08 (30.09); for the non-depressed control group, mean percentage of time in supine = 42.07 (30.19)). Finally, no significant between-group differences were found on any of the demographic variables.

### 3.1. Self-rated questionnaires

As expected, significant differences were found on the BDI between groups, with a mean BDI score of 25.84 (SD = 8.24) for the MDD group and a mean BDI score of 1.64 (SD = 2.02) for the control group. Trait anxiety scores also varied between groups with a mean Trait score of 57.50 (SD = 11.51) for the MDD group and a mean Trait score of 31.54 (SD = 8.79) for the control group. A MANCOVA ($F = 2.906$, $P = .038$, $\text{eta}^2 = .410$) revealed significant differences between the groups on the PSQI ($P = .001$) and on Sleep Efficiency ($P = .01$). The Epworth sleepiness scores were not significantly different, and there were no significant morningness-eveningness group differences.

### 3.2. Sleep-disordered breathing

All of the sleep-related breathing indices (MN, %MN, MJ, %MJ, AVG%, and DST) were included in the hierarchical logistic regression analysis. The RDI was not included in the logistic regression analysis because the RDI is equal to the combination of the number of MN and MJ, and would thus be a redundant factor. Because of the relationship between BMI and OSDB, body mass was entered first. Next, the sleep-related breathing variables were entered together. A Hosmer-Lemeshow statistic [40] was employed to ensure the use of a good model ($x^2 = 9.403$, $P = .309$). The regression was performed to determine whether respiratory variables could correctly predict group membership. Indeed, 81.3% of those with MDD and 80.0% of the non-depressed group were correctly classified. Overall correct classification was 80.6% ($x^2 = 17.88$, $P = .013$).

MANCOVA revealed significant differences between those with MDD and non-depressed controls ($F = 2.880$, $P = .033$, partial $\text{eta}^2 = .451$) on the following respiratory variables: major events, percentage of major and minor events accompanied by at least a 3% desaturation, and average $SaO_2$ throughout the night (Table 2). Five out of 19 (25%) individuals with MDD experienced greater than five major events per hour. The mean number of major events per hour of sleep in the controls was 0.42, while the MDD group average was 4.19. The severity of the events in the MDD group was higher, evidenced by the higher percentage of events accompanied by an oxygen desaturation (46.98% vs. 15.32%). The minor events associated with desaturation showed a similar relationship for the MDD versus the non-depressed participants (28.09% vs. 16.54%). The difference in average nocturnal saturation was small (98.86% in non-depressed controls vs. 97.40% in the MDD group) and, although statistically significant, was well within the normal range [41]. Ten of the individuals with MDD and five of the healthy controls evidenced more than a total of five major events plus minor events per hour accompanied by a desaturation. There was no significant difference between the two groups on this measure ($x^2 = 1.630$, $P = .202$).

Table 2
Mean number of respiratory events per hour by group

| Sleep variable | Mean (SD) | | df | F | p |
|---|---|---|---|---|---|
| | Control group | MDD group | | | |
| MN | 33.48(19.37) | 34.18(24.60) | 30 | 0.012 | 0.92 |
| MN% | 16.54(13.69) | 29.46(20.20) | 30 | 3.287 | 0.08 |
| MJ | 0.42(.51) | 4.65(5.95) | 30 | 5.996 | 0.02 |
| MJ% | 15.32(30.48) | 48.87(33.85) | 30 | 7.045 | 0.01 |
| RDI | 33.90(19.57) | 38.82(29.66) | 30 | $t = 0.751$ | 0.27 |
| AVG | 98.86(1.17) | 97.06(2.24) | 30 | 6.259 | 0.02 |
| DST | 6.07(5.63) | 13.72(13.05) | 30 | 3.305 | 0.08 |

MN, Number of minor events; MN%, Percentage of minor events accompanied by a desaturation of at least 3%; MJ, Number of major events; MJ%, Percentage of major events accompanied by a desaturation of at least 3%; RDI, Respiratory disturbance index; AVG, Average oxygen saturation; DST, Number of desaturations by at least 3%.

Significance might have been reached with greater power; however, this analysis reveals that traditional methods of categorization may be insufficient in capturing group differences that, according to our findings, occur along a continuum of breathing and $O_2$ saturation abnormality.

To examine whether medication might account for the sleep-related breathing differences between the two groups, we reanalyzed the data without those individuals currently taking antidepressants ($n=7$) and/or sedative hypnotics ($n=3$, one of whom was not also taking an antidepressant). The binary logistic regression remains significant ($x^2=28.841$, $P<.001$) and prediction of classification increases to 100%. Furthermore, overall differences between the two groups on the six sleep-related breathing variables remains significant (MANCOVA: $F=3.330$, $P=.030$, partial eta$^2=.588$). There were no differences between those taking medications and those not taking medications on any of the demographic, sleep self-report, or sleep-related breathing variables.

Within the depressive group, correlations were found between psychomotor agitation and the following respiratory events: RDI ($r=.537$, $P=.02$), MN ($r=.515$, $P=.03$), MJ ($r=.514$, $P=.03$) MJ% ($r=.500$, $P=.041$), and DST ($r=.592$, $P=.01$). Within the non-depressed control group, there was a significant relationship between being male and MN% ($t=3.141$, $P=.008$), MJ% ($t=2.457$, $P=.029$), and DST ($t=4.976$, $P=.000$).

## 4. Discussion

The purpose of this study was to investigate the relationship between sleep-related breathing abnormalities and depression; specifically, we compared sleep-related respiration in a group of individuals with MDD diagnosed by DSM-IV, unselected for sleep abnormalities, in comparison to that of a healthy control group. Sleep-related breathing indices were measured along a continuous spectrum of abnormality in addition to a present/absent dichotomy. A nasal cannula-pressure transducer system detected a spectrum of respiratory events. Individuals with MDD experienced a greater number of self-reported sleep abnormalities, major flow-limitation events per hour, percentage of major flow-limitation events accompanied by a desaturation, and average nocturnal saturation. In addition, those with MDD showed a trend toward a higher percentage of minor flow-limitation events accompanied by a desaturation and average number of desaturations (3%) per hour. The decreased mean saturation in the MDD group, although not clinically significant with respect to absolute levels, may suggest an increased burden of abnormal respiration. Finally, the high rate of accuracy in discrimination of group by respiratory events (80.6%) suggests that OSDB is likely an important factor in MDD. The fact that removing those individuals who were taking antidepressants at the time of the study improved prediction of group membership (MDD versus control) raises the possibility that antidepressant medications may improve the sleep-related breathing in individuals who are clinically depressed. However, this study is not powered to address this hypothesis.

While there was a difference between groups on the PSQI, there was no significant difference in subjective sleepiness as measured by the ESS, even though MDD patients had greater degrees of sleep-disordered breathing. Patients with MDD often present with insomnia and hyperarousal (a minority do indeed present with hypersomnia), and this may continue into the daytime and inhibit overt sleepiness behavior (similar to the difficulty patients with psychophysiological insomnia experience trying to nap in the daytime). Several antidepressants, such as fluoxetine and buproprion, have stimulating properties and may reduce sedation. It is possible that as a group the severity did not reach the threshold to induce subjective sleepiness, and individual differences to the effect of sleep fragmentation may have a role. In large samples such as in the Sleep Heart Health Study, a significant proportion of those with moderate or greater degrees of sleep apnea had minimal daytime sleepiness, confirming that the correlation between ESS and RDI is low [42]. It is possible that the individual response to chronic sleep fragmentation will be determined by trait and state factors, and the outcome could be dominated by subjective sleepiness, depression, an attention deficit phenotype, or fatigue. The results do suggest that subjective sleepiness alone would not adequately discriminate between individuals with MDD who have a secondary cause of sleep fragmentation.

### 4.1. Assessment of sleep-related breathing

The gold standard for the diagnosis of sleep-disordered breathing (SDB) is attended polysomnography. This allows accurate discrimination between sleep versus wake, as well as the effect of sleep stages on respiration. The gold standard for measuring airflow is the pneumotachograph; however, current evidence strongly suggests that the signal obtained using a nasal cannula-pressure transducer system provides comparative or even superior information [42]. If quantitative (% reduction in flow signal) and qualitative (flow-limitation terminating with abrupt reversals) are both incorporated into a scoring rule, as in this study, the entire spectrum of respiratory abnormality is captured. To our knowledge, this is the first use of this technique in a sample of individuals with major depression, and it is possible that previously published literature report an underestimation of the true prevalence and severity of respiratory abnormality in this population.

### 4.2. SDB and mood disorders

As stated above, depression and SDB can interact in multiple ways. Abnormalities in sleep architecture common

to depression and SDB at a macroscopic level are well documented, and the most typical features include increased wake time after sleep onset, reduced REM sleep latency and slow-wave sleep, increased awakenings, and reduced total sleep time [43]. At the microscopic level, the percentage of non-rapid eye movement (NREM) sleep with the cyclic alternating pattern morphology (a marker of sleep state instability) is increased in depression [44]. In addition, sleep fragmentation by auditory stimuli, which shares characteristics with the sleep fragmentation associated with SDB, impairs mood [20].

Functional magnetic resonance imaging reveals hypofrontality in patients with OSDB [22–23] and in those with MDD [24–25]. Specifically, OSDB patients with and without hypoxia show impairments of lateral prefrontal activation on a working memory task [22]. Similarly, a single night of auditory sleep fragmentation induces hypofrontality on working memory and Stroop-type tasks (Thomas, unpublished data). Further, when scanned early in circadian time, reduced activation following sleep deprivation is the dominant effect demonstrated [45–48]. Lastly, subjects with narcolepsy may exhibit hypofrontality when performing under fatiguing conditions. As mentioned above, depression is associated with impaired prefrontal metabolism and function [24–25], suggesting a common neurobiological substrate for sleep fragmentation and impaired mood. Sleepiness and fatigue associated with depression may explain some of the hypofrontality associated with depression. OSDB may contribute to or exacerbate the condition of someone who is predisposed to MDD, and the treatment of OSDB may ameliorate or prevent depressive symptoms.

### *4.3. Relevant participant characteristics*

We found that variables of sleep-related breathing correlated with increased daytime psychomotor agitation. Specifically, individuals who through self-report described feeling fidgety and restless showed increased abnormalities in sleep-related breathing. In addition, gender of participant appeared to play a role among the non-depressed controls, as males experienced a greater percentage of minor flow-limitation events accompanied by a desaturation, percentage of major events accompanied by a desaturation, and total number of desaturations per hour, than female non-depressed participants. This supports previous findings in the literature concerning an increase of sleep-related respiratory events in males [8].

### *4.4. Limitations*

Limitations of the current study include the constraints of the take-home sleep monitoring device and the relatively small sample sizes. The Stardust system involves an unattended recording of sleep events; therefore, sensor stability during the recording can vary. In addition, sleep architecture of the participants was not measured; therefore, the difference between the groups in the amount of time spent in rapid eye movement (REM) sleep is unknown. Further, the number of arousals and the time spent in stage 1 sleep is unknown. A follow-up study that would include sleep architecture would clarify the impact of these factors on group differences. There are several possible explanations for the high number of 'minor' events in controls other than by chance (i.e. that an unusual number of selected healthy subjects had sub-clinical sleep-disordered breathing): (1) the technique usually detects more events than possible with the thermistor; (2) respiratory events while awake and normal sleep-onset respiratory instability may be erroneously scored; (3) oral breathing was not monitored; and (4) events in REM sleep may be over-scored, as the sensitivity of the nasal pressure technique allows identification of respiratory changes that are normal components of this stage, but cannot be confidently categorized as such without sleep staging. However, respiratory events, such as those illustrated in the Fig. 1, generally do not occur during periods of wake in otherwise healthy individuals. As we carefully evaluated the flow-morphology of each event (also see Fig. 1), we are confident that the vast majority of respiratory abnormality scored did occur during sleep.

## 5. Conclusion

Considering the overlap with respect to symptom presentation, neuropsychological impairment, and prefrontal-based dysfunction, the relationship between OSDB and MDD appears important enough to consider a more definitive study: a randomized placebo-controlled trial of positive airway pressure in individuals with MDD versus healthy controls. Additionally, accurate assessments of sleep-related breathing may usefully contribute to the management of MDD patients. Respiratory-related sleep fragmentation or hypoxia-induced prefrontal dysfunction is a biologically plausible link between depressed mood and sleep-disordered breathing. Routine assessment of sleep-related respiration in those diagnosed with MDD may be indicated, particularly in those who report sleep abnormalities or psychomotor agitation or who are of male gender. Continued exploration of the extent of this overlap through additional measures, such as those aimed at examining sleep architecture, functional neuroanatomical substrates, and receptor biology, will add further insight into the underlying mechanisms of OSDB and MDD and their potential mutual roles as risk, exacerbation, or treatment response-modifying factors.

## Acknowledgements

The authors wish to thank Brooks Casas, Pearl Chiu, and Avgusta Shestyuk for their help with administration of

SCIDS, in addition to Christen Deveney and Ben Worthen for reading early drafts of the paper.

## References


[1] Al-Barrak M, Shepertycky MR, Kryger MH. Morbidity and mortality in obstructive sleep apnea syndrome 2: effect of treatment on neuropsychiatric morbidity and quality of life. Sleep Biol Rhythms 2003;1:65–74.

[2] Baran AS, Richert AC. Obstructive sleep apnea and depression. CNS Spectrum 2003;8:120–34.

[3] Bardwell WA, Moore P, Ancoli-Israel S, Dimsdale JE. Fatigue in obstructive sleep apnea: driven by depressive symptoms instead of apnea severity? Am J Psychiatry 2003;160:350–5.

[4] McMahon JP, Foresman BH, Chisholm RC. The influence of CPAP on the neurobehavioral performance of patients with obstructive sleep apnea hypopnea syndrome: a systematic review. West Med J 2003; 102:36–43.

[5] Ohayon MM. The effects of breathing-related sleep disorders on mood disturbances in the general population. J Clin Psychiatry 2003;64: 1195–200.

[6] Reynolds CF, Coble P, Spiker DG, Neil JF, Holzer BC, Kupfer DJ. Prevalence of sleep apnea and nocturnal myoclonus in major affective disorders: clinical and polysomnographic findings. J Nerv Ment Dis 1982;170:565–7.

[7] Ayappa I, Norman RG, Krieger AC, Rosen A, O'Malley RL, Rapoport. Non-invasive detection of respiratory effort-related arousals (RERA's) by a nasal cannula/pressure transducer system. Sleep 2002;23:763–71.

[8] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–5.

[9] Mendelson WB. Human sleep: research and clinical care. New York, NY: Plenum; 1987.

[10] Neau JP, Paquereau J, Bailbe M, et al. Relationship between sleep apnoae syndrome, snoring and headaches. Cephalalgia: An International Journal of Headache 2002;22:333–9.

[11] Flemons WW, Tsai W. Quality of life consequences of sleep-disordered breathing. J Allergy Clin Immunol 1997;99:S750–S6.

[12] Beckham EE, Leber WR, Youll LK. In: Beckham, Leber, editors. Handbook of depression. 2nd ed. New York, NY: The Guilford Press; 1995.

[13] Wu LR, Parkerson Jr GR, Doraiswamy PM. Health perception, pain, and disability as correlates of anxiety and depression symptoms in primary care patients. J Am Board Fam Pract 2002;15:183–90.

[14] Shabsigh R, Zakaria L, Anastasiadis AG, Seidman AS. Sexual dysfunction and depression: etiology, prevalence, and treatment. Curr Urol Rep 2001;2:463–7.

[15] Fuerstein C, Naegele B, Pepin JL, Levy P. Frontal lobe-related cognitive functions in patients with Sleep Apnea Syndrome before and after treatment. Acta Neurol Belg 1997;97:96–107.

[16] Kim H, Young T, Matthews CG, Weber SM, Woodward AR, Palta M. Sleep-disordered breathing and neuropsychological deficits. Am J Respir Crit Care Med 1997;156:1813–9.

[17] Landrø NI, Stiles TC, Sletvold H. Neuropsychological function in nonpsychotic unipolar major depression. Neuropsychiatry Neuropsychol Behav Neurol 2001;14:233–40.

[18] Jones BP, Henderson M, Welch CA. Executive functions in unipolar depression before and after electroconvulsive therapy. Int J Neurosci 1988;38:287–97.

[19] Veiel HO. A preliminary profile of neuropsychological deficits associated with major depression. J Clin Exp Neuropsychol 1997; 19:587–603.

[20] Martin SE, Wraith PK, Deary IJ, Douglas NJ. The effect of nonvisible sleep fragmentation on daytime function. Am J Respir Crit Care Med 1997;155:1596–601.

[21] Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res 2002;11:1–16.

[22] Thomas RJ, Rosen BR, Stern CE, Weiss JW, Kwong KK. Functional imaging of working memory in obstructive sleep-disordered breathing. J Appl Physiol 2005;98:2226–34.

[23] Chee MW, Choo WC. Functional imaging of working memory after 24 h of total sleep deprivation. J Neurosci 2004;12(24):4560–7.

[24] Videbech P. PET measurements of brain glucose metabolism and blood flow in major depressive disorder: a critical review. Acta Psychiatr Scand 2000;101:11–20.

[25] Drevets WC. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. Prog Brain Res 2000;126:413–31.

[26] Millman RP, Fogel BS, McNamara ME, Carlisle CC. Depression as a manifestation of obstructive sleep apnea: reversal with nasal continuous positive airway pressure. J Clin Psychiatry 1989;50: 348–51.

[27] Platon MJR, Sierra JE, Javier E. Changes in psychopathological symptoms in sleep apnea patients after treatment with nasal continuous positive airway pressure. Int J Neurosci 1992;62: 173–95.

[28] Bum-Hee Y, Ancoli-Israel S, Dimsdale JE. Effect of CPAP treatment on mood states in patients with sleep apnea. J Psychiatr Res 1999;33: 427–32.

[29] Pack AI, Black JE, Schwartz JR, Matheson JK. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. Am J Respir Cell Mol Biol 2001;164:1675–81.

[30] Thomas RJ, Kwong KK, Scammell TE. Effect of Modafinil on working memory after sleep-a functional magnetic resonance imaging study. Sleep 2002;25:452.I.

[31] DeBattista C, Doghramji K, Menza MA, et al. Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. J Clin Psychiatry 2003;64:1057–64.

[32] Ayappa I, Norman R, Suryadevara M, Rapoport D. Comparison of limited monitoring of a nasal cannula flow signal to full polysomnography in sleep disordered breathing. Sleep 2004;27:1171–9.

[33] First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for the DSM-IV axis I disorders—patient edition (SCID I-P, Version 2.0). Washington, DC: American Psychiatric Press; 1995.

[34] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring.depression. Arch Gen Psychiatry 1961;4:561–71.

[35] Spielberger CD, Gorsuch RL, Lushene RE. Manual for the state-trait anxiety inventory. Palo Alto, CA: Consulting Psychologists Press; 1970.

[36] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.

[37] Horne JA, Osteberg O. A self-assessment questionnaire to determine morningness–eveningness in human circadian rhythms. Int J Chronobiol 1976;4:97–110.

[38] Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14:540–5.

[39] Ferguson KA, Heighway K, George CFP. Home Studies Versus Polysomnography in the diagnosis of suspected obstructive sleep apnea (OSA). Presented at the American Thoracic Society Meeting; 2002.

[40] Tabachnick BG, Fidell LS. In: Tabachnick BG, Fidell LS, editors. Using multivariate statistics. 4th ed. Needham Heights, MA: A Pearson Education Company; 2001. p. 539.

[41] Yamashiro Y, Kryger MH. Nocturnal oximetry: is it a screening tool for sleep disorders? Sleep 1995;18:167–71.

[42] Kapur VK, Baldwin CM, Resnick HE, et al. Sleepiness in patients with moderate to severe sleep-disordered breathing. Sleep 2005;28:472–7.
[43] Johnson PL, Edwards N, Burgess KR, Sullivan CE. Detection of increased upper airway resistance during overnight polysomnography. Sleep 2005;28:85–90.
[44] Reynolds CF. Sleep and affective disorders, A minireview. Psychiatr Clin N Am 1987;10:583–91.
[45] Mu Q, Nahas Z, Johnson KA, et al. Decreased cortical response to verbal working memory following sleep deprivation. Sleep 2005;28:55–67.
[46] Drummond SP, Brown GG, Salamat JS, Gillin JC. Increasing task difficulty facilitates the cerebral compensatory response to total sleep deprivation. Sleep 2004;1(27):445–51.
[47] Chee MW, Choo WC. Functional imaging of working memory after 24–h of total sleep deprivation. J Neurosci 2004;12(24): 4560–7.
[48] Habeck C, Rakitin B, Moeller JR, et al. An event-related fMRI study of the neurobehavioral impact of sleep deprivation on performance of a delayed-match-to-sample task. Cogn Brain Res 2004;18:306-21.