Sleep-disordered breathing in major depressive disorder

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SUMMARY

Individuals with major depressive disorder often experience obstructive sleep apnea. However, the relationship between depression and less severe sleep-disordered breathing is unclear. This study examined the rate of sleep-disordered breathing in depression after excluding those who had clinically significant sleep apnea (>5 apneas·h^{-1}). Archival data collected between 1991 and 2005 were used to assess the prevalence of sleep-disordered breathing events in 60 (31 depressed; 29 healthy controls) unmedicated participants. Respiratory events were automatically detected using a program developed in-house measuring thermal nasal air-flow and chest pressure. Results show that even after excluding participants with clinically significant sleep-disordered breathing, individuals with depression continue to exhibit higher rates of sleep-disordered breathing compared with healthy controls (depressed group: apnea–hypopnea index mean = 0.524, SE = 0.105; healthy group: apnea–hypopnea index mean = 0.179, SE = 0.108). Exploratory analyses were also conducted to assess for rates of exclusion in depression studies due to sleep-disordered breathing. Study exclusion of sleep-disordered breathing was quantified based on self-report during telephone screening, and via first night polysomnography. Results from phone screening data reveal that individuals reporting depression were 5.86 times more likely to report a diagnosis of obstructive sleep apnea than presumptive control participants. Furthermore, all of the participants excluded for severe sleep-disordered breathing detected on the first night were participants with depression. These findings illustrate the importance of understanding the relationship between sleep-disordered breathing and depression, and suggest that screening and quantification of sleep-disordered breathing should be considered in depression research.

INTRODUCTION

Over two decades of research and clinical data have linked symptoms of depression to sleep-disordered breathing (SDB; for review, see Harris *et al.*, 2009). For example, there is convincing evidence that individuals diagnosed with obstructive sleep apnea (OSA) experience more symptoms of depression than individuals without OSA (Ong *et al.*, 2009; Schroder and O'Hara, 2005). Furthermore, epidemiological data indicate that 18% of individuals with major depressive disorder (MDD) endorse symptoms consistent with breathing-related sleep disorders (Ohayon, 2003).

While these studies indicate a higher prevalence of clinically significant SDB in individuals with MDD compared with healthy controls (HC), sub-clinical SDB may also play an important role in the onset and maintenance of MDD. A previous study by Deldin *et al.* (2006) indicated more SDB events in depressed compared with non-depressed participants, and predicted accurate diagnostic grouping (depressed, non-depressed) in 81% of participants using SDB variables. These findings may have important implications in treatment for depression. For example, non-response to antidepressants may be explained by occult SDB. Additionally, psychotropic medications such as benzodiazepines may be contraindicated in individuals with co-occurring SDB. While screening for SDB (such as OSA) is common practice in most sleep laboratories, non-sleep-related depression studies do not commonly screen for SDB. These differences

in protocol may result in different samples of depressed subjects, thereby decreasing the generalizability of results, and may adversely affect the validity of such research. A more defined understanding of the relationship between SDB and depression may motivate standard inclusion of SDB screening in all depression studies and consideration of treatment for less severe SDB in those with MDD. Studies support improvement in mood and depressive symptoms after continuous positive airways pressure (CPAP) treatment of SDB (Habukawa *et al*., 2010; Harris *et al*., 2009). To date, however, there are only limited data on the impact of SDB on depression outcomes in those who meet diagnostic criteria for MDD. The data presented by Deldin *et al*. (2006) highlight the importance of SDB in MDD, but the study is limited by the absence of controlled screening for SDB. Furthermore, SDB was assessed at home via a portable monitoring device rather than in-laboratory polysomnography (PSG). The present study seeks to address these limitations by assessing the prevalence of SDB events using in-lab PSG in unmedicated individuals diagnosed with MDD, and HC. Based on previous research, it was predicted that those with MDD would show higher rates of SDB, even after excluding individuals with clinically significant SDB.

MATERIALS AND METHODS

Assessment of SDB was based on archival data collected by the fourth and fifth authors (R.H. and R.A.) at the University of Texas Southwestern Medical Center at Dallas (UTSW) and the University of Michigan (UM) between 1991 and 2005. All participants completed an initial telephone interview that included screening questions for depression, which was followed by a clinical interview if no exclusion criteria were reported. Individuals were excluded for current shift-work or current sleep disorders (e.g. OSA, narcolepsy, bruxism).

Individuals enrolled based on phone screening underwent a Structured Clinical Interview for DSM-IV Axis I Disorders (Spitzer *et al*., 1990). The 17-item Hamilton Rating Scale for Depression quantified depressive symptom severity (HRSD; Hamilton, 1960). Participants were included in the HC group if they reported no personal or family history of psychopathology, and participants were included in the MDD group if they met criteria for MDD, were in a current depressive episode and had an HRSD score of at least 17. Exclusionary criteria included lifetime histories of substance dependence, bipolar disorder, psychosis, and anorexia or bulimia. All participants were medication-free for a minimum of 2 weeks. Participants maintained regular sleep schedules and completed sleep diaries for 5 days prior to overnight PSG.

All first-night PSG recordings were reviewed for clinically significant SDB in individuals who did not endorse symptoms of OSA during phone screening. PSG was visually screened for SDB events by a doctoral-level clinical psychologist with substantial clinical experience in assessment of SDB. Individuals for whom SDB events were severe enough to obscure electroencephalogram recording were screened out. Additional details regarding PSG recording and data processing can be found in previous manuscripts (e.g. Armitage *et al*., 1994). All study procedures were approved by the Institutional Review Boards of UTSW and UM, and all participants provided informed consent prior to study participation.

Exploratory analyses assessing rates of exclusion due to SDB were conducted in two samples. The first analysis assessed exclusion of subjects due to expressed knowledge of SDB during telephone screens of 4 663 adults. The second analysis quantified the exclusion of participants on the basis of PSG-defined clinically significant SDB recorded on the first night in 631 adults who participated in laboratory sleep and depression studies.

A final analysis was conducted to further quantify and compare the incidence of occult SDB (i.e. that below clinical threshold) in MDD and HC participants after excluding individuals with clinically significant SDB (>5 apneas·h^{-1}) based on PSG recordings. A random sample of participants was selected from the archival database. Files noted for significant SDB or poor signal quality were excluded, resulting in a total of 31 MDD and 29 HC participants in the analysis. Groups did not differ by age or sex (Table 1). Respiratory events were quantified using a program developed in-house to measure the reduction in amplitude of thermal nasal air-flow (N/O) and chest pressure signals compared with baseline stable-breathing epochs established for each individual.

A distinction between standard and sub-clinical hypopnea events was made in order to capture a range of occult SDB. Events were classified as hypopneas (Hp) when a decrease of 50% or more in N/O and chest signal was detected (Iber *et al.* 2007). Events with a 10–50% amplitude reduction in N/O and chest signals were marked as occult-hypopnea events (oHp) to represent a sub-clinical range of SDB. All events lasted for 10 s or longer. Respiratory events were also coded as either arousals (Ar) or non-arousals (Na) depending on coincidental increase of alpha waves and body movement, reflecting increased sleep disruption. Epochs containing artifacts were excluded from analysis. The apnea–hypopnea Index (AHI; number of events per hour) for all SDB events was calculated, and subsequently entered as the dependent variable into a three-way Type (Hp, oHp)×Arousal (Ar, Na) ×Group (MDD, HC) repeated-measures ANOVA.

Table 1 Demographic information by group

	MDD	*HC*	P
Sex (M:F)	16 : 15	15 : 14	ns
Age (years)	33.32	32.17	ns

F, female; HC, healthy control; M, male; MDD, major depressive disorder;
ns, not significant ($P > 0.05$).

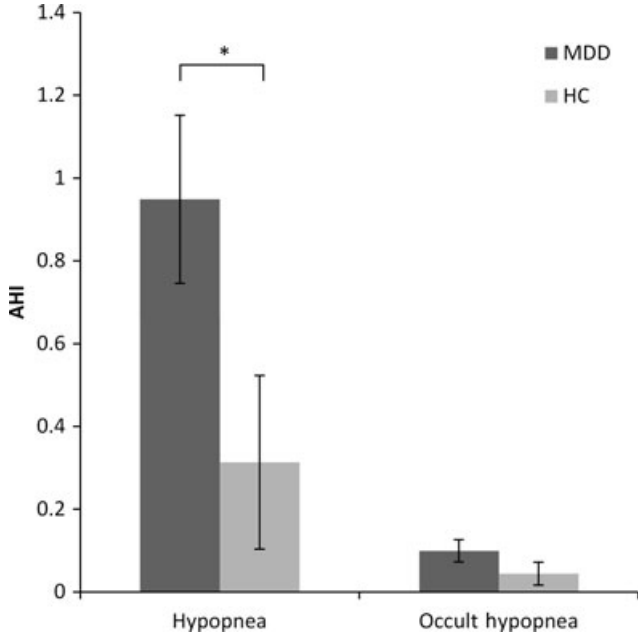

Figure 1. Individuals with major depressive disorder (MDD) exhibit more breathing events per hour compared with healthy controls (HC). The difference is most pronounced for hypopnea events. Error bars represent one standard error. AHI, apnea–hypopnea index.

RESULTS

Results from the repeated-measures ANOVA revealed higher rates of disordered breathing events per hour in the MDD group (AHI mean = 0.524, SE = 0.105) compared with the HC group (AHI mean = 0.179, SE = 0.108; Group, $F_{1,58} = 5.270$, $P < 0.05$). Furthermore, results indicated group differences by type of breathing event ($F_{1,58} = 4.072$, $P < 0.05$). *Post hoc* analyses revealed a higher AHI for hypopneas in MDDs compared with HCs (Type×Group, $F_{1,58} = 4.744$, $P < 0.05$; Fig. 1). No significant effects were found for arousal.

Additionally, exploratory descriptive analyses examined reported OSA at phone screening. Results indicated that of 1625 subjects who reported signs of depression, 64 disclosed a diagnosis of OSA. Chi-square analysis suggested that although the majority of participants did not report OSA during phone screening, those with depression were much more likely to have received a diagnosis of OSA than presumptive control subjects [five of 713; χ^2 (1, $N = 2338$) = 18.132, $P < 0.001$]. Specifically, participants who screened positive for depression were 5.86 times more likely to report a diagnosis of OSA than controls. Furthermore, all of the participants (14 out of 631 total participants) who were excluded from sleep studies between 1991 and 2005 due to severe SDB detected on the first night of PSG had been diagnosed with MDD.

DISCUSSION

The primary aim of this study was to delineate the relationship between SDB and depression using laboratory PSG. Even after excluding individuals with clinically significant SDB through self-report (phone screening) and first-night PSG, those with MDD still exhibited more flow-limitation events than HCs, suggesting a relationship between SDB and depression. Group differences were more notable in hypopneas than in occult-hypopneas, suggesting that the relationship between disordered breathing and depression is possibly related to the degree of hypoxia. Results also suggest that future research should examine the efficacy of CPAP or other treatments for sub-clinical SDB in MDD.

These findings have implications for current standards of depression research, especially because this sample was derived within a research context. While sleep research on depression routinely excludes for diagnosable OSA, most if not all do not account for sub-clinical levels of SDB. Results showing group differences based on the decrease of airflow, rather than subsequent arousals, further support hypoxia as an important variable in the relationship between SDB and depression. Adopting a dimensional approach to SDB may be a better way of characterizing the relationship between MDD and SDB.

LIMITATIONS

Limitations of the current study include the use of archival data from studies that were not originally designed to assess SDB. Other limitations include the small sample size and a lack of pressure transducer data to confirm the nature of the disordered breathing events.

CONCLUSIONS

This study revealed higher levels of SDB in MDD, even after excluding individuals with clinically significant SDB. This result suggests that screening and quantification of SDB should be standard practice in depression research and clinical care.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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