OBSTRUCTIVE SLEEP APNEA AND THE BRAIN

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OBSTRUCTIVE SLEEP APNEA AND THE BRAIN

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EDITORIAL
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Editorial: Obstructive Sleep Apnea and the Brain

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Editorial on the Research Topic

Obstructive Sleep Apnea and the Brain

There is accumulating evidence that sleep disturbance, including sleep disorders such as obstructive sleep apnoea, can adversely affect restorative brain processes and function (1–5). In this interdisciplinary Research Topic, the interplay between clinical diseases of the central nervous system (CNS) such as multiple sclerosis Hensen et al. and stroke Stevens et al. and sleep disordered breathing is highlighted. Both of these reviews discuss potential shared mechanisms, consequences, and novel treatment approaches. In addition, a review of the clinical challenges of managing patients with comorbid insomnia and obstructive sleep apnoea and treatment modalities, including the role of cognitive behavioural therapy, is presented Bahr et al.. In the final piece in this series, original research findings provide insight into a novel computerised test battery to examine neurobehavioural function in adults with and without obstructive sleep apnoea D'Rozario et al..

From a mechanistic perspective, the coining of the concept of at least four phenotypic traits that cause sleep disordered breathing has recently emerged (6). Namely, high loop gain, low respiratory arousal threshold, poor pharyngeal muscle responsiveness during sleep, and upper airway anatomic compromise (6–8). This new framework has provided insights into this common condition. Clinical phenotypes to define the different clinical manifestations and consequences of sleep disordered breathing have also recently been described (9). These mechanistic and clinical concepts pave the way for targeted therapy or "precision sleep medicine" to reduce the adverse health, safety, and social impact of untreated sleep disordered breathing (10). Indeed, the framework to provide personalised therapy for sleep disordered breathing in those without major comorbid disease has been set (11). Non-CPAP interventions that show promise in small physiological studies or clinical trials include pharmacologic, surgical, oral appliance, positional, oxygen, myofunctional training, or combinations thereof (11).

In accordance with these concepts, Hensen et al. detailed review highlights the differences in clinical presentation of sleep disordered breathing in people with MS. While the prevalence remains unclear, the available evidence suggests that sleep disordered breathing is likely at least as common in people with MS if not more so. This is despite clear differences in the clinical manifestation of sleep disordered breathing in this patient population that would tend to favour lower risk of sleep apnoea (i.e., predominantly non-obese females). This suggests that the causes, and by extension the ideal therapy or therapies for sleep apnoea, is likely to be quite different in people with MS compared to typical sleep apnoea patient populations. Concepts of bidirectionality between the causes and consequences of sleep disordered breathing and MS (e.g. inflammation, hypoxia, depression, fatigue/sleepiness, and neurocognitive impairment) are also proposed. These new concepts pave the way for an important research agenda that has the potential to lead to

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targeted therapies to reduce the common consequences of both conditions and potentially MS disease progression.

Another example of CNS disruption and high rates of sleep disruption/sleep apnoea is stroke. Neuroimaging studies after acute neurologic impairment (e.g., in the acute phase after stroke) combined with sleep investigations may provide important insight into the central nervous system mechanisms of sleep disordered breathing. In their mini review, Stevens et al. discuss the need for new knowledge into the specific causes of sleep disordered breathing post stroke using mechanistic phenotyping concepts. Similar to MS, the size and location of CNS lesions is likely crucial in determining the type and extent to sleep disordered breathing that occurs post stroke. Despite evidence that functional recovery outcomes post stroke improve after treatment of sleep disordered breathing (12, 13), CPAP therapy is particularly poorly tolerated in this patient population. Thus, there is a need to test and develop new therapeutic approaches for sleep disordered breathing to improve post stroke outcomes Stevens et al.. The same may apply to other disorders that affect central locomotor control such as Parkinson's disease (14–16).

Bahr et al. highlight the treatment challenges when two common unwanted bedfellows co-exist, namely insomnia and sleep apnoea. It is clear that when insomnia, which is characterised by cortical hyperarousal, combines with sleep disordered breathing there are additive or potentially synergistic adverse consequences (17–19). The goal remains to better understand the specific causes of each and different phenotypic presentations so that therapies can be tailored accordingly.

In the final original research contribution in this series, D' Rozario et al. highlight the shortcomings of sleep study parameters using gold standard polysomnography to accurately identify neurobehavioural dysfunction. Indeed, there is currently no standardised neuropsychological test battery to assess daytime dysfunction which can be administered in a timely manner in a sleep laboratory setting. The 30 min computerised test battery that they developed was used to examine neurobehavioural function in over 200 people with untreated sleep apnoea versus a control group of 50 healthy participants. People with OSA had impaired neurobehavioural performance in all domains. Consistent with previous findings, polysomnography disease severity measures were only weakly associated with performance. The authors conclude that the test battery provides a sensitive method of assessing daytime dysfunction in patients with sleep apnoea. Nonetheless, there remains a need to further test and develop instruments to assess cognition, attention, alertness, short-term and long- term memory and executive function in the context of sleep disruption (20–23). There is increasing evidence that a possible gender—specific dimension of sleep disordered breathing should also be taken into account (20, 24–26).

In summary, there may be important bidirectional relationships between sleep disruption/sleep disordered breathing and a range of disorders that adversely affect brain/CNS function. Sophisticated approaches to better understand these links are required along with simple, accurate testing tools that can be used in the clinical setting to inform treatment decision making. This will then facilitate targeted strategies to improve sleep disruption/sleep disordered breathing across a range of CNS/brain disorders. This approach has the potential to also reduce the numerous shared disease consequences which often coexist in people who have sleep disordered breathing and a CNS/brain disorder. Given the increasing rates of sleep apnoea and disorders of the CNS/brain and considerable gaps in knowledge and treatment, these topics remain research priorities.

AUTHOR CONTRIBUTIONS

Both HG and DE drafted and revised the manuscript and gave approval for publication of this manuscript.

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SYSTEMATIC REVIEW
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Current Treatment of Comorbid Insomnia and Obstructive Sleep Apnea With CBTI and PAP-Therapy: A Systematic Review

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Insomnia and obstructive sleep apnea (OSA) are often both present in patients with sleep-disordered-breathing (SDB). The coexistence of the two disorders shows an increase in cumulative morbidity and an overall greater illness severity. There is still considerable controversy regarding management decisions in this group of patients. This systematic review focused on more recent evidence regarding treatment of patients presenting with both clinical entities of comorbid insomnia and OSA (COMISA) in terms of their management, especially using combinations of positive airway pressure [PAP, namely aPAP, cPAP, adaptive servo-ventilation (ASV)] and CBTi as well as each one of these two modalities alone. As a conclusion it is necessary to specifically target distinct combinations of both insomnia (initial, middle, late) and OSA (mild, moderate, severe) phenotypes. The present review gives reason to assume that both CBTi and PAP-therapy are necessary. However, it appears that distinct treatment patterns may suit different COMISA phenotypes.

Keywords: COMISA, sleep apnea, insomnia, PAP-therapy, cognitive behavioral therapy

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INTRODUCTION

Insomnia and obstructive sleep apnea (OSA) are often both present in patients with sleep-disordered-breathing (SDB) (1–3). An association between insomnia and OSA was first described in 1973 (4). Some studies have shown a high prevalence (39 to 55 %) of insomnia symptoms in patients with OSA in the past (1, 5–7). Insomnia and OSA both share a number of negative consequences, which include increased cardiovascular risk and decreased health-related quality of life (QOL) (8–11). The two disorders combined show an increase in cumulative morbidity and an overall greater illness severity (5). It is believed that OSA could either cause insomnia or exacerbate it (12).

Some studies suggest that the presence of insomnia symptoms may reduce the positive airway pressure (PAP)-compliance in OSA patients (13–16). On the other hand, some studies give reason to believe that insomnia refractory to usual cognitive behavioral therapy (CBTI) may be associated with coexistent SDB. It is also suggested that adequate OSA-therapy leads to improvement of insomnia symptoms (13). Nonetheless, there is still considerable controversy regarding management decisions in this group of patients. The correlation between OSA severity and severity

of co-existent insomnia is weak. This fact in combination with a usually indistinguishable clinical presentation of comorbid insomnia and obstructive sleep apnea (COMISA) (17) and insomnia alone raises questions as to whether COMISA is a separate distinct clinical entity at all (18).

To date, the most recent reviews on this topic are from the year 2010 and 2017. In their systematic review from the year 2010, Luyster et al. suggested that the combination of both CBTI and OSA treatment resulted in greater improvements in insomnia than did either CBTI or OSA treatment alone (13). Sweetman et al. reviewed research focusing on prevalence, characteristics and theoretical mechanistic relationships in COMISA patients (17). They emphasize on different insomnia entities, stating that insomnia and its symptoms in COMISA could either be secondary to OSA or an independent entity. Thus, depending on its entity, COMISA needs to be treated differently. However, the differentiation between independent and secondary COMISA is difficult.

We extended the information of these two studies by reviewing literature from 2010 to 2017 focusing on the following aspects:

Our primary research question was to review observational or interventional studies about the association between PAP-therapy and CBTI as exposures and insomnia as the outcome in COMISA patients. A secondary aim was reviewing observational or interventional studies about insomnia as exposure and adherence to PAP-therapy as the outcome. A tertiary aim was reviewing the comparators of PAP-therapy and CBTI on the one hand and adherence to PAP-therapy on the other, in order to make recommendations for future research.

METHODS

Literature Search

Eligible studies included populations with OSA and insomnia. Acceptable definitions of OSA were an apnea-hypopnea-index (AHI) $\geq$5 events/hour or a respiratory-distress-index (RDI) of $\geq$5 events/hour. Acceptable definitions of insomnia were an insomnia severity index (ISI) $\geq$ 14 points, a Regensburg-Insomnia-Score (RIS) $\geq$ 14 points or a Nordic sleep questionnaire $\geq$ 4 points on one of the insomnia questions. Eligible studies included interventions of PAP and/or CBTI starting at study beginning or prior. Pharmacological and surgical interventions were out of the scope of this review. Comparators were presence vs. absence or different levels of OSA or insomnia. Although the focus of this review was the direct association between OSA and insomnia, outcomes such as adherence to the intervention were also eligible, as long as they referred to OSA or insomnia. Outcomes related to other chronic conditions, such as dementia or multiple sclerosis, were an exclusion criterion. Eligible study designs were interventional studies as well as cohort studies, case control studies and case series.

The Medline terms for the identification of literature were [(insomnia asv) OR (insomnia pap) OR (insomnia apap) OR (insomnia cpap) OR (CBTI OSA) OR (cognitive behavioral therapy OSA insomnia) OR (CBTI sleep apnea insomnia) OR (cognitive behavioral therapy sleep apnea insomnia)] AND ("2010/01/01"[PDat]: "2017/10/15"[PDat]). During the selection process, the first and third author classified the search results according to a protocol established by the second author. They performed a title/abstract screening followed by a full text screening and met after each round to solve disagreement regarding eligibility and main reason for exclusion in consensus. The study selection protocol followed the PICOS algorithm (population, interventions, comparators, outcomes, and study designs). The language was restricted to English or German articles. The first and third author screened the selected articles for further eligible studies.

Extraction and Presentation of Data

Following a PICOS-based protocol, the first and second author extracted data about methods and results of the original articles and presented it in two tables. In case of multiple exposures/interventions and outcomes related to OSA or insomnia as well as multiple analyses of one association, they presented the data most related to the primary objective of this systematic review, which was the direct association between OSA and insomnia. Second, they favored exposures/interventions clearly preceding the outcome. Third, they preferred results from thorough analyses with straightforward association measures supported by confidence intervals and *p*-values. Based on quantitative information, the authors made an effort to provide their own interpretation of the results rather than blindly repeating statements from the discussions of the original articles. They solved disagreements between each other in consensus and summarized interpretational deviations from the conclusions of the original articles in the text. They summarized characteristics of the original samples with standard measures. Due to a majority of observational original studies, they followed the MOOSE checklist [(19); **Supplementary Material**] and completed it with the PRISMA checklist (20), if necessary.

RESULTS

Methodological Issues

Of 130 records identified in Medline, 12 studies were eligible (**Figure 1**). Additional handsearch revealed another study eligible to our research question (21). Of these 13 studies, six addressed our primary research question (21–26) and the other seven analyzed the association between insomnia as exposure and adherence to PAP as outcome (12, 27–32). To define OSA, seven studies used the AHI with three different cutoffs, three used the RDI with two cutoffs, one study used both RDI and AHI, and two relied on the international classification of sleep disorders. In order to define insomnia, seven studies used the Insomnia Severity Score (ISS) with three different definitions. Two studies used the Basic Nordic sleep questionnaire, two relied on the international classification of sleep disorders and one study used the RIS. Ten studies had PAP-therapy as the only intervention, two studies investigated CBTI alone, and one study examined both therapies. Four studies differentiated between initial, middle and late insomnia (**Table 1**). Three of the six studies that addressed our primary research question and two of

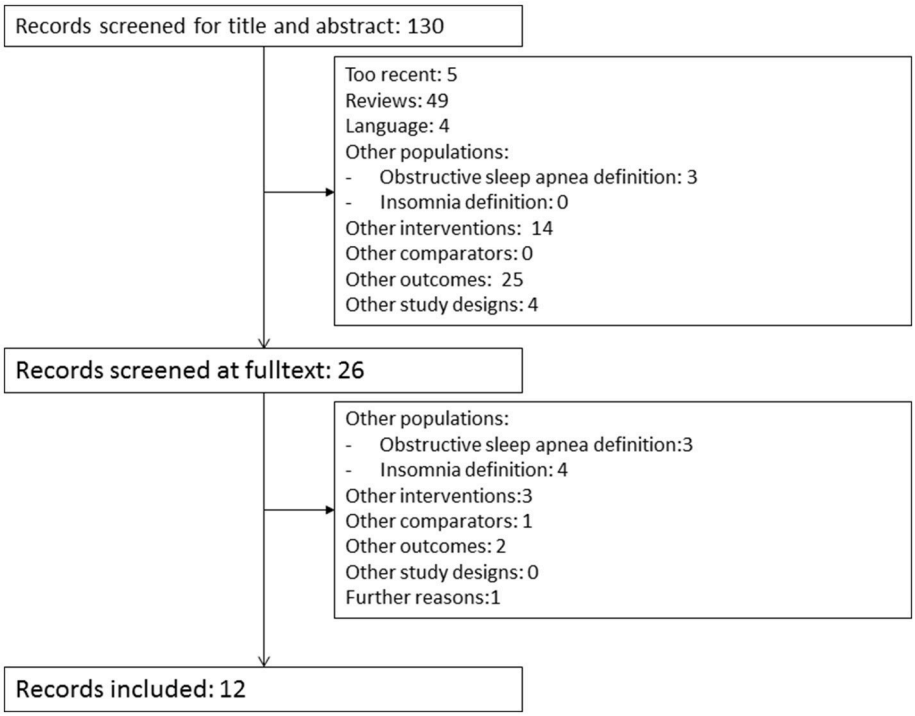

FIGURE 1 | Literature selection process.

the seven studies that analyzed the association between insomnia and adherence to PAP used more eligibility criteria than OSA and insomnia to define their populations. In the former group, one study included only military veterans with a mini mental state ≥24 points and without serious physical or mental health issues (24), one included only patients with psychophysiological risk factors of insomnia such as poor sleep hygiene (25), and one excluded other sleep disorders such as narcolepsy (26). In the latter group, two included only military veterans without previous OSA-surgery or oxygen supplementation (27, 30). Two studies included participants from the icelandic sleep study for different objectives (28, 32). Their data probably overlapped.

Outcomes

Of the six studies addressing our primary research question, four indeed analyzed the effect of PAP, i.e., OSA-therapy, on insomnia (22, 23, 25, 26), while two studies analyzed the direct effect of OSA on insomnia comparing two groups without PAP, and with equal CBTI for both groups (21, 24) . Of the four studies analyzing the effect of PAP on insomnia, three measured the exposure in minutes per night and one used no control. Of the former three studies, two used a cut-off, namely 240 min PAP-use per night and 171 min per night (22, 25), and the third looked at the exposure continuously (23). The second only reported results for participants above the cut-off stating that those below were not statistically significant (26). One defined the outcome as improvement of the ISI of 9 points (22), one defined it as follow-up subscale score of <4 of the ISI (23), and one reported no definition. The last differentiated between initial, middle, and late insomnia (25). The first found that adherence to OSA therapy increased the chance of successful insomnia therapy by 1.1 times (22), the second found that patients with persistent insomnia have 72 min less PAP-use per night (23), and the study omitting the results for the control found improvements of 0.7 standard deviations in initial, 0.9 in middle, and 0.6 in late insomnia (25). The study without control for the exposure found that PAP and/or CBTI decreased insomnia by 0.55 standard deviations and the total wake time by 41 min on the average (26). The findings were statistically significant in the second and the third of these four studies. The studies analyzing the direct effect of OSA on insomnia were the only interventional studies that fitted our eligibility criteria. The first one found that insomnia decreased more in participants randomized to sleep education than those randomized to CBTI (24). Besides, it found that the difference between sleep education and CBTI was 21 min higher in participants with mild OSA than in those without. This interaction was not statistically significant (**Table 2**) (24). The second study dealing with CBTI found that CBTI decreases insomnia by 2 points less and increases sleep efficiency by 1.8% more in patients with OSA compared to those without (21). Generally, the robust clinical improvements with CBTI were comparable between those with insomnia alone and the COMISA patients.

In the six studies addressing our primary research question, the proportion of women ranged between 3.0 and 66.9%, the mean age ranged between 47.5 and 72.2 years, and the AHI/RDI ranged between 9.4 and 45.0 events per hour. In the seven studies addressing the effects of insomnia on adherence to PAP,

TABLE 1 | Methods of the included studies on insomnia, obstructive sleep apnea, and positive airway pressure therapy/cognitive behavioral Therapy.

References	Population (eligibility criteria)				Exposure/ intervene-tion	Comparison/ control	Outcome	Study		
	Obstructive sleep apnea	Insomnia	Positive airway pressure (PAP)	Cognitive behavioral therapy				Type	Design	Measurement time points
Nguyen and Chaskalovic (12)	Respiratory distress index ≥10 events/hour	Insomnia severity index ≥ 14	From study beginning; auto-adjusting	No	Insomnia at baseline	No insomnia at baseline	Continuous therapy adherence in minutes/night in the last 4 weeks	Observation	Cohort study	Baseline, 1 month, 6 months
Wickwire et al. (27)	Diagnosis of obstructive sleep apnea	Insomnia severity subscale score (first 3 questions) ≥ 4	From study beginning; continuous	No	Initial, middle and late insomnia	No initial, middle, late insomnia	≥ 4 h/night in 70% of the nights in the last 4 weeks vs. less therapy adherence	Observation	Cohort study	Baseline, 28 up to 365 days
Björnsdottir et al. (28)	Apnea-hypopnea-index ≥15 events/hour	Basic nordic sleep questionnaire (1 item ≥ 4)	From study beginning; auto-adjusting, continuous, bilevel and adaptive servoventilation	No	Initial, middle and late insomnia	No initial, middle and late insomnia	≥ 4 h/night in 70% of the nights in the last 4 weeks vs. less therapy adherence	Observation	Cohort study	Baseline, 2 years
Nguyen et al. (22)	Apnea-hypopnea-index ≥10 events/hour	Insomnia severity index ≥ 15	From study beginning; auto-adjusting	No	≥ 240 min auto-adjusting positive airway pressure/night	Less hours or discontinuation	Insomnia improvement from baseline to follow-up ≥ 9 points	Observation	Cohort study	Baseline, 24 month
Pieh et al. (29)	International classification of sleep disorders-2	Regensburg Insomnia Scale	From study beginning; continuous	No	Continuous change for one insomnia point at baseline		Continuous therapy adherence in minutes/night (period not specified)	Observation	Cohort study	Baseline, 6 months
Wallace et al. (30)	International classification of sleep disorders-2	Insomnia severity index ≥ 15	512 days ± 484 prior to baseline; continuous	No	Continuous change for one insomnia standard deviation at baseline		Continuous therapy adherence in minutes/night over the entire period	Observation	Cross-sectional study	Baseline
Glidewell et al. (23)	Apnea-hypopnea-index >5 events/hour or respiratory distress index >15 events/hour	Insomnia severity subscale score (first 3 questions) ≥ 4	From study beginning (unspecified devices)	No	Exploration of different predictors, of which minutes auto-adjusting positive airway pressure/night and the respiratory distress index at baseline were the most related to our research objective		Improve-ment vs. persistence of insomnia (< 4 vs. ≥ 4 at follow-up)	Observation	Cohort study	Baseline, 43 ± 7.1 days
Wohlgemuth et al. (31)	Diagnosis of obstructive sleep apnea	Insomnia severity index	Up to 5 years prior to study beginning	No	Exploration of different predictors, of which insomnia and the respiratory distress index at baseline were the most related to our research objective		Non-adherers, attempters and adherers according to a cluster analysis	Observation	Cross-sectional study	Baseline
Eysteinsdottir et al. (32)	Apnea-hypopnea-index >15 events/hour	Basic Nordic sleep questionnaire (1 item ≥ 4)	From study beginning; auto-adjusting and continuous	No	Initial, middle, late insomnia at baseline	No initial, middle, late insomnia at baseline	Quitting the therapy ≤ 1 year vs. quitting later (non-quitters excluded)	Observation	Cohort study	Baseline, 6,7 ± 1.2 years

(Continued)

TABLE 1 | Continued

References	Population (eligibility criteria)				Exposure/ intervene-tion	Comparison/ control	Outcome	Study		
	Obstructive sleep apnea	Insomnia	Positive airway pressure (PAP)	Cognitive behavioral therapy				Type	Design	Measurement time points
Fung et al. (24)	Apnea-hypopnea-index <15 events/hour	International classification of sleep disorders-2	No	From study beginning for 6 weeks	Mild obstructive sleep apnea (apnea-hypopnea-index ≥ 5 events /h)	No obstructive sleep apnea (apnea-hypopnea-index < 5 events /h)	Sleep improvement	Intervention	Randomized Cognitive behavior-ral therapy or sleep education	Baseline, 6 weeks, 6 months, 12 months
Krakow et al. (25)	Apnea-hypopnea-index >5 events/hour or respiratory distress index >15/h	Insomnia severity index ≥ 15	More than 6.9 months prior to study beginning auto-adjusting and adaptive servoventilation	unknown	Full users of therapy (≥ 20 h/week, probably last 4 weeks)	Partial users of therapy	Continuous change of subscale scores for initial, middle and late insomnia between the baseline and the previous visit	Observation	Case series	Baseline
Ong et al. (26)	Apnea-hypopnea-index ≥5 events/hour	International classification of sleep disorders-2	From study beginning	From study beginning	Positive airway pressure therapy or/and cognitive behavioral therapy	None	Insomnia severity index, total wake time in minutes	Observation	Cohort study	Baseline, 90 days
Sweetman et al. (21)	Apnea-hypopnea-index ≥ 11 events/hour or respiratory distress index ≥15/h	Insomnia according to the diagnostic and statistical manual of mental disorders IV and V	No	From study beginning	Obstructive sleep apnea at baseline	No obstructive sleep apnea at baseline	Continuous insomnia change from baseline to 3 months	Observation	Cohort study	Baseline, post-treatment, 3 months

TABLE 2 | Results of the included studies on insomnia, obstructive sleep apnea, and positive airway pressure therapy/cognitive behavioral therapy.

References	Population (characteristics of the sample)					Association between exposure/intervention and outcome				
	Sample size	% of women	Age in years (mean ± standard deviation)	Body mass index in kg/m² (mean ± standard deviation)	Apnea-Hypopnea-Index/Respiratory Distress Index in events/hour (mean ± standard deviation)	Association measure	Strength of the association**	Interpretation	Confidence Interval	*p*-value
Nguyen and Chaskalovic (12)	148	18.2	54.8 ± 11.8	29.1 ± 6.3	39.0 ± 21.3	Unadjusted mean difference at 6 months	24	Insomnia decreases the adherence by 24 min/night	Missing	Not significant (*p*-value missing)
Wickwire et al. (27)	232	43.5	53.6 ± 12.4	43.4 ± 7.7	41.8 ± 27.7	Odds ratios of adherence adjusted for age and gender	Initial: 0.95 Middle: 0.81 Late: 1.07	Initial insomnia decreases the chances of adherence by 1.05, middle insomnia by 1.23; Late insomnia increases the chances by 1.07	Missing	Initial: 0.55 Middle: 0.02 Late: 0.53
Bjornsdottir et al. (28)	705	19.4	54.9 ± 10.2	33.7 ± 5.6	45.5 ± 20.5	Odds ratios of adherence adjusted for sex, age, body mass index, and obstructive sleep apnea severity	Unadjusted: −0.56 for initial for middle 0.53 for late Adjusted: 0.59 for initial 0.98 for middle 0.55 for late insomnia	Initial and late insomnia almost halves the chances of adherence, while middle insomnia has no effect	Adjusted 95 % 0.38–0.91 for initial 0.70–1.37 for middle 0.39–0.79 for late insomnia	Initial: 0.01 Middle:0.89 Late: <0.001
Pieh et al. (29)	73	32.9	55.1 ± 11.5	30.8 ± 5.0	39.2 ± 26.7	Linear regression coefficient adjusted for statistically significant univariate correlations*; Pearson-Correlation between exposure and outcome at 6 months	0.347 h per insomnia point on a standard deviation of 7.5 points; 0.12	Adherence to therapy diminishes by 156 min/night for one standard deviation of insomnia, which explains 12% of its variance	Missing	0.007
Nguyen et al. (22)	80	12.5	54.9 ± 10.6	30.5 ± 6.0	45.0 ±24.6	Odds ratio of response to therapy on adherence to therapy adjusted for age and body mass index, Epworth sleepiness score and respiratory distress index	1.124	Adherence to therapy increased the chance of insomnia responding to therapy by 1.124 times	0.986–1.280	Missing; non-significant according to the 95 % confidence interval
Wallace et al. (30)	248	6.0	59.0 ± 11.0	33.0 ± 5.0	40.0 ± 30.0	Standardized linear regression coefficient in daily hours of positive airway pressure use adjusted for race, OSA severity, CPAP adherence download variables and sleep related questionnaire responses	−0.28	Adherence to therapy diminishes by 17 min/night for one standard deviation of insomnia	Missing	<0,001

(Continued)

TABLE 2 | Continued

References	Population (characteristics of the sample)					Association between exposure/intervention and outcome				
	Sample size	% of women	Age in years (mean ± standard deviation)	Body mass index in kg/m² (mean ± standard deviation)	Apnea-Hypopnea-Index/Respiratory Distress Index in events/hour (mean ± standard deviation)	Association measure	Strength of the association**	Interpretation	Confidence Interval	*p*-value
Glidewell et al. (23)	68	32.4	47.5 ± 12.4	32.2 ± 7.3	34.7 ± 32.2	Differences of means (standard deviations) between both groups adjusted for total number of medications, medical and psychiatric diagnoses	Average PAP use: 71.6 Respiratory distress index: 17.8 (40)	Patients with persistent symptoms have 72 min less PAP-use per night and 0.4 standard deviations less respiratory distress at baseline	Missing	PAP-use: 0.02 Respiratory distress index: 0.01
Wohlgemuth et al. (31)	207	6.3	58.4 ± 11.9	32.4 ± 5.0	40.0 ± 29.4	Odds ratio for attempters and adherers vs. non-adherers adjusted for age and years	Insomnia: 0.956, 0.870 Apnea-hypopnea -0.55-index: 0.977, 1.003	Insomnia decreases the chance of being an attempter by 1.046 and the chance of being an adherer by 1.149	Missing	Insomnia: 0.248, 0.004 Apnea-hypopnea-index: 0.005, 0.722
Eysteinsdottir et al. (32)	796	19.1	54.4 ± 10.6	33.5 ± 5.7	44.9 ± 20.,7	Odds ratio for quitting therapy early adjusted for OSA severity, daytime sleepiness, age and gender	Initial insomnia: 2.03 Middle insomnia: 0.99 Late insomnia: 1.75	While late and middle insomnia has no influence on being an early-quitter, initial insomnia doubles the chances.	Initial: 1.17–3.52 Middle: 0.63–1.56 Late: 1.09–2.82	Missing; initial and late insomnia significant according to the 95% confidence
Fung et al. (24)	134	3.0	72.2 ± 7.7	Missing	9.4 ± 5.3	Unadjusted mean difference of total wake time minutes in post-treatment effect between mild and no obstructive sleep apnea	21.3	The advantage of sleep education over cognitive behavioral therapy increases by 21 min in mild obstructive sleep apnea	−54.3 to +96.8	0.58
Krakow et al. (25)	302	54.4	53.4 ± 14.2	31.6 ± 8.0	32.0 ± 28.2	Cohen's ds of insomnia improvement in full PAP-users (partial users missing because not significant)	Initial: 0.70 Middle: 0.87 Late: 0.65	In full PAP-users initial insomnia improved by 0.7, in middle by 0.87 and in late by 0.65 standard deviations	Missing	<0,01 for ANOVA
Ong et al. (26)	32	61.8	54.1 ± 13.3	37.6 ± 10.9	35.3 ± 31.6	Unadjusted Cohen's ds between baseline and follow-up for insomnia; Mean difference for total wake time	Insomnia severity index: −0.55 Total wake time: −41	The therapy decreases insomnia by 0.55 standard deviations and total wake time by 41 minutes	Missing	Insomnia: 0.002 Total wake time: 0.003

(Continued)

TABLE 2 | Continued

References	Population (characteristics of the sample)					Association between exposure/intervention and outcome				
	Sample size	% of women	Age in years (mean ± standard deviation)	Body mass index in kg/m² (mean ± standard deviation)	Apnea-Hypopnea-Index/Respiratory Distress Index in events/hour (mean ± standard deviation)	Association measure	Strength of the association**	Interpretation	Confidence Interval	*p*-value
Sweetman et al. (21)	455	66.9	51.7 ± 15.7	26.3 ± 4.9	14.3 ± 8.0	Unadjusted differences of means between groups for insomnia and sleep efficiency	Insomnia severity index: 2.4 Sleep efficiency: 1.8%	Therapy decreases insomnia by 2 points less and increases sleep efficiency by 1.8% more in patients with obstructive sleep apnea than in patients without	For the within group estimators: ± 1.8 (exposure), ± 1.1 (control) for insomnia; ± 3.7 (exposure), ±2.4 (control) for sleep efficiency	0.011 unadjusted for insomnia (adjusted not significant), 0.156 unadjusted for sleep efficiency

*Age, sex, educational level, body mass index (BMI), intake of hypnotic medication.
**Whenever applicable, exposure minus or divided by control.

the proportion of women ranged between 6.0 and 43.5%, the mean age ranged between 53.6 and 59.0 years, and the AHI/RDI ranged between 39.0 and 45.5 events per hour. Three of them differentiated between initial, middle and late insomnia (27, 28, 32). Four studies compared presence of insomnia according to criteria summarized above vs. absence of insomnia (12, 27, 28, 32). The other three looked at the exposure as a continuous predictor (29–31). With respect to the outcome, five of seven studies measured PAP-adherence in minutes per night (12, 14, 28–30), one defined non-adherers, attempters, and adherers by cluster analysis (31), and one compared participants quitting the therapy before 1 year after initiation with those quitting later and excluded the continuers (32). Of the first five, three looked at insomnia continuously, where one found that insomnia decreases the adherence by 24 min per night (12), one found that one standard deviation of insomnia diminishes it by 156 min per night (29), and the last one found that the standard deviation decreases it by 17 min per night (30). Two divided insomnia into three phenotypes, where one found that initial insomnia decreases the chances of adherence by 1.05, middle insomnia by 1.23 and that late insomnia increases the chances by 1.07 (27), and one found that initial and late insomnia almost halves the chances of adherence, while middle insomnia has no effect (28). The study that defined adherence by cluster analysis found that insomnia has no effect on being an attempter and decreases the chance of being an adherer by 1.1. The last study found that late and middle insomnia has no influence on being an early-quitter, while initial insomnia doubles the chances (31) (**Table 2**).

DISCUSSION

Two of four studies reporting controlled results are too few to draw well-supported conclusions on the influence of the OSA-therapy on insomnia (22, 23), and two clinical trials reporting an interaction between OSA and the effect of insomnia-therapy on insomnia is little evidence for or against the influence of OSA itself on insomnia (21, 24). While the first of the two controlled observational studies found a very small effect of OSA-therapy on insomnia (OR 1.1, 95%CI: 1.0 to 1.2) (22), the second found that increasing PAP-use by 72 min per night may favor the improvement of insomnia ($p = 0.02$) (23). It remains uncertain, however, how likely this additional PAP-use might improve insomnia. One of the clinical trials found that the presence of OSA increases insomnia by 21 min per night, more precisely, it detected the superiority of sleep education over CBTI that increases so much if the patient has OSA (24). Reporting this interaction, the direct effect of OSA on insomnia was omitted. The 21 min are neither clinically relevant nor statistically significant ($P = 0.58$). Altogether, the small number of studies plus the inconsistency and incompleteness of the results provide little evidence about a potential association between OSA-therapy and insomnia.

With seven controlled observational studies, the effect of insomnia on PAP-adherence is better investigated than the effect of OSA-therapy on insomnia. However, four studies with clinically relevant associations [156 min decrease of adherence

per night, 1.23 lower, and halved chances of being adherent (27–29, 32)] against three studies with negligible associations (24 and 17 min decrease per night, 1.1 lower chances) (12, 30, 31) favor neither one conclusion nor the other. The strongest associations (halved chances of being adherent) favor a decrease of PAP-adherence caused by insomnia. As all studies distinguishing between initial, middle and late insomnia found very different associations regarding these three entities, this distinction seems important (25, 27, 28, 32) . One study found clinical relevance in middle insomnia only, which decreased adherence (OR 1.2) (14), one found high clinical relevance in initial and late insomnia, which decreased adherence (OR 2) (28), and one found high clinical relevance again for initial insomnia, which decreased adherence (OR 2) (32). Taken together, the association with late insomnia seems the strongest. However, the evidence is again too small for conclusions.

At study level, heterogeneous populations, distinct definitions and measurements of exposures/interventions, outcomes and controls, and different analyses might be some reasons for the heterogeneity of the findings. The thirteen studies used seven different definitions of OSA and eight different definitions of insomnia. However, most of these definitions match well, and most studies used PAP-therapy. The most striking heterogeneity in terms of populations is that three studies included only military veterans with a percentage of women ranging between three and six vs. 12 and 62 in the other studies (24, 30, 31). Two of these three populations had a similar age distribution as the other studies, and one was clearly elder (72 years with a standard deviation of eight) (24). The most probable reason for that was the fact that this study sampled insomnia patients and screened them for OSA, while the other studies sampled OSA-patients and screened them for insomnia. In conclusion, the populations were heterogeneous but still comparable. The fact that three studies measuring adherence to PAP-therapy as exposure and the seven measuring adherence to PAP-therapy as outcome used seven very different definitions of adherence to PAP-therapy compromised the comparability more than the different populations. The remaining three used CBTI and a mix of CBTI and OSA.

At review level, two main limitations may contribute to the small number of studies and to the incompleteness of the results. First, we relied on Medline as the only search engine; second, we had no contact with the authors when information was missing or our and their interpretation of the findings differed. However, our structured approach included more than 100 working hours per person in a thorough section of literature and data extraction following the PICOS algorithm. A publication period ranging from the last original article of the updated review by Luyster et al. up to 6 months before identifying the literature reduced the publication bias, because search engines rapidly process publications that are easy to find, but need several months to process publications with lower impact factor. The entire search was double-checked and two investigators discussed and interpreted all findings together without merely relying on statements from the discussions of the original articles. While they did so, they found that the cited research confirmed the completeness of the identified literature. A further strength at review level at the expense of the number of eligible studies was a satisfactory definition of the population as inclusion criterion. It resulted in the exclusion of studies confirming insomnia by superficial questions such as "do you have insomnia." Overall, the ratio between efforts to improve quality on the one hand and availability information on the other was considerable.

The review by Luyster that we updated found two studies with OSA-therapy as exposure and insomnia as outcome, as well as one study with insomnia therapy as intervention and adherence to PAP-therapy as the outcome (13). As it used no defined publication period as inclusion criterion, the period was probably longer than ours. Nevertheless, the previous review found fewer studies fitting our other criteria than we did, which also points out the comprehensiveness of the literature that we identified. Of the first two studies, one was a pilot study attaining a non-clinical level of insomnia in eight of 17 patients with CBTI alone. After adding OSA-therapy, further seven of the remaining nine patients attained a non-clinical level (33). In other words, this before after study, just as two of our four studies, had no control. The other found that the combination of OSA-surgery and CBTI was the best option for COMISA (34). This surgical study was out of the scope of our PAP-review. The third study found regular PAP-use in 26 of 39 patients assigned to a daytime sleep medical procedure compared to 14 of 60 historical controls (35). This very impressive finding corresponds to an OR of six and makes our ORs of two for the effect of initial and late insomnia on adherence and for the effect of initial insomnia on non-adherence looking small. It is surprising, because the treatment of the disease in the best case annuls 100% of the impact of the disease itself. It would have been interesting to know how the daytime sleep medical procedure influenced initial, middle, and late insomnia itself. In other words, we found thin evidence but the evidence of the studies we updated was even thinner. An effect of insomnia on adherence to PAP-therapy is probable, however.

The more recent review by Sweetman et al. found in total 8 studies dealing with either CBTI alone or with combined treatments in COMISA patients including drug studies, case studies and studies dating back up to the year 2001 (17). One study in the review by Sweetman et al matched our well-defined eligibility criteria, namely the study by Lack et al. presented at SLEEP in 2011. They found that independently of OSA the treatment of insomnia decreased the sleep latency by 36 min and increased the total sleep time by 0.7 h and the sleep efficiency by 18% (36).

Given the sparse evidence and the inconsistency of the current evidence, more research is needed in this topic. Nonetheless, the general conclusion from the study by Sweetman et al. is that both groups, namely patients with insomnia only and COMISA, benefited in their sleep and daytime measures from CBTi about equally well (21). Thus having co-morbid OSA did not impair the treatment of the insomnia in the COMISA group.

Several studies investigated whether the presences of comorbid insomnia impaired PAP-adherence but the inconsistent results make it difficult to conclude that comorbid insomnia impairs PAP adherence. To answer this question a randomized controlled trial should be performed in the future

with a group of patients treated with PAP alone and another group treated with a combination of PAP and CBTI, e.g., in the form suggested by Crawford et al. (37).

There is evidence that insomnia can be treated also in COMISA patients with CBTI (21). That, in itself may reduce the disease burden and justify the use of CBTI, even if it does not improve PAP adherence in the OSA treatment. However, two studies are few and more studies are needed. Especially studies pre-treating or concurrently treating the insomnia in COMISA patients deserve to be thoroughly assessed. Even more, the findings of our review are inconsistent with those of Luyster et al., who found one study with a remarkable effect of CBTI in OSA patients, namely an increased PAP-adherence with CBTI in OSA with an OR of 6 (35).

As a few studies suggest that OSA-treatment has an impact on insomnia, an immediate PAP-therapy and reevaluation of insomnia symptoms in the course of it, might lead to insomnia improvement or abandonment of CBTI due to subclinical severity scores.

The revision of studies on PAP-adherence revealed several attempts to build adherence groups, which is an indicator of missing thresholds for PAP-adherence evaluation. We recommend a definition of adherence to PAP-therapy in hours per night or nights of use per months, since it would increase the comparability of the results and might ease the decision whether or not an intervention is reasonable.

The time pattern of insomnia symptoms, namely middle insomnia with awakenings during the nights, initial insomnia with difficulties to fall asleep and late insomnia, which is to say early morning awakenings, seem to be entirely different COMISA entities that react differently to PAP-therapy and might have different effects on PAP-therapy-adherence. Such a phenotypic classification may prove to be quite useful in future studies in order to provide personalized care in this broad group of patients.

Reviewing the literature, it has been interesting to see, that pneumologists and sleep physicians put emphasis on apneic events, whereas neurologists and psychologists focused more on insomnia criteria. Therefore, we suggest an interdisciplinary approach in the treatment of COMISA patients in order to reflect on both entities equally.

Due to the above mentioned inconsistency of study designs and results the temporary evidence level is not yet sufficient for a meta-analysis on COMISA therapy. In order to promote personalized management to COMISA patients and to perform meta-analyses in the future, it might be advisable to use study designs that specify both insomnia in the time domain (initial, middle, late) and that consider CBTI as well as PAP-therapy regimens in distinct combined patient phenotypes.

AUTHOR CONTRIBUTIONS

IT reviewed the part of COMISA and CBTI as well as **Table 2**. RC is responsible for the study design, provided data extraction from the original literature, analysis, presentation, and interpretation of data eligibility criteria and draft the flow chart. HG is responsible for study conception and design, helped on the introduction and the discussion. KB reviewed the part of COMISA and PAP-therapy, created tables, created introduction, conclusion, and parts of the discussion. All authors approved the submitted version of the manuscript and take full responsibility for it.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00804/full#supplementary-material

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Impaired Neurobehavioural Performance in Untreated Obstructive Sleep Apnea Patients Using a Novel Standardised Test Battery

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Objective/Background: Although polysomnography (PSG) is the gold-standard measure for assessing disease severity in obstructive sleep apnea (OSA), it has limited value in identifying individuals experiencing significant neurobehavioural dysfunction. This study used a brief and novel computerised test battery to examine neurobehavioural function in adults with and without OSA.

Patients/Methods: 204 patients with untreated OSA [age 49.3 (12.5) years; body mass index, [BMI] 33.6 (8.0) kg/m^2; Epworth sleepiness scale 12 (4.9)/24; apnea hypopnea index 33.6 (25.8)/h] and 50 non-OSA participants [age 39.2 (14.0) years; BMI 25.8 (4.2) kg/m^2, ESS 3.6 (2.3)/24]. All participants completed a computerised neurobehavioural battery during the daytime in the sleep clinic. The OSA group subsequently underwent an overnight PSG. The 30 min test battery assessed cognitive domains of visual spatial scanning and selective attention (Letter Cancellation Test), executive function (Stroop task) and working memory (2- and 3-Back tasks), and a validated sustained attention task (psychomotor vigilance task, PVT). Group differences in performance were compared. Associations between disease severity and performance were examined in the OSA group.

Results: After controlling for age, gender and education, OSA patients demonstrated impaired performance on the Stroop-Text, 2 and 3-Back tasks, and the PVT compared with the non-OSA group. OSA patients had worse performance on the LCT with fewer average hits albeit with better accuracy. Some OSA polysomnographic disease severity measures were weakly correlated with performance.

Conclusions: This brief test battery may provide a sensitive, standardised method of assessing daytime dysfunction in OSA.

Keywords: polysomnography, sleep-disordered breathing, inter-individual variability, cognitive impairment, vigilance, attention

HIGHLIGHTS

- A brief computerised test battery assessed cognitive function in untreated OSA
- OSA patients demonstrated impaired neurobehavioural performance in all domains
- Polysomnographic disease severity measures were weakly correlated with performance
- The battery provides a sensitive method of assessing daytime dysfunction in OSA

INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent sleep disorder affecting 25–50% of middle-aged adults in the general community (1). It is characterised by repeated episodes of upper airway obstruction, intermittent hypoxemia/hypercapnia and repeated arousals during sleep. Untreated OSA results in a substantial health care burden with varying levels of excessive daytime sleepiness and neurobehavioural dysfunction (2, 3), increased incidence of workplace accidents (4) and more than a 2-fold increased motor vehicle crash risk (5). Neuropsychological tests show deficits in the cognitive domains of vigilance and attention, visuospatial abilities, executive functions and some components of memory in OSA, while data for other domains remain equivocal (6). There is currently no standardised neuropsychological test battery for assessing daytime dysfunction which can be briefly administered in a sleep laboratory setting. Current tests assessing sleepiness such as the multiple sleep latency test (MSLT) or maintenance of wakefulness test (MWT) are time consuming and expensive. These specialised tests are not routinely indicated to evaluate OSA or treatment effectiveness unless associated with a safety issue (7).

Clinicians predominantly rely on both traditional PSG-derived measures to assess OSA disease severity and self-report questionnaires to evaluate daytime dysfunction. However disease severity measures are inconsistently (8) or weakly related to neurocognitive test performance (9). A recent meta-review provided evidence that sleep fragmentation measures were more strongly related to performance on tests of vigilance and attention than hypoxemia measures (6). Although hypoxemia may affect global cognitive functioning, no clear links were found between disease severity and performance assessing executive functions, memory, visuospatial capacity, language ability and psychomotor function (6). Continuous positive airway pressure (CPAP) therapy which is still the "gold-standard" treatment for OSA has limited or partial reversibility of cognitive deficits (10–12). These outcomes emphasise the need for early detection of sleep-disordered breathing and potential cognitive decline in OSA. Targeted treatment particularly in light of recent research identifying untreated sleep apnea as a significant risk factor for developing mild cognitive impairment or dementia is imperative (13).

Current neurobehavioural test batteries attempt to evaluate the impact of sleep breathing disorders on daytime functioning but differences between OSA and non-OSA groups are not clearly delineated (14–16). Differing methodologies, the timing and the type of neuropsychological tests administered, and characteristics of the patient groups studied e.g., age, daytime sleepiness levels and variable treatment histories; as well as different levels of CPAP compliance may account for the varied results in both case-controlled observational studies and in treatment interventions. Simple but sensitive tools which can be administered with ease in a clinical setting are needed to evaluate neurobehavioural dysfunction as well as treatment efficacy in OSA patients. While large (2.5–3 h in duration) test batteries provide comprehensive assessment with the potential for a greater understanding of the patterns of neurobehavioural deficits (17), shorter testing protocols may be more practical and cost-effective in the clinical setting and minimise patient fatigue. Easy access to neurocognitive batteries could potentially enable newly diagnosed patients reticent to undertake treatment to then become aware of their individual cognitive deficits. Detecting early changes in cognition may also be useful for the assessment of future risk of dementia in sleep apnea patients (18).

In this study, we compared the performance of treatment naïve OSA patients with a non-OSA group, using a short (30 min in duration) standardised computerised neurobehavioural test battery which assessed the salient cognitive domains known to be impaired in OSA: attention/vigilance, visuospatial abilities, executive functions and working memory. In a secondary analysis, we examined the association between PSG measures of disease severity and test battery performance.

MATERIALS AND METHODS

Participants

This study is a secondary analyses using baseline performance data collected from OSA patients who participated in a large randomised trial comparing a psychoeducation intervention to improve CPAP adherence (Australia and New Zealand clinical trials registry number 12606000065594) (19). The Sydney South West Area Health Service Human Research Ethics Committee approved the protocol and volunteers provided written informed consent. Individuals were asked to participate in a study that would be valuable in helping them to use CPAP. Participants were recruited following a polysomnography-confirmed diagnosis of OSA (respiratory disturbance index ≥5/h. This index included apneas, hypopneas and respiratory-event related arousals) and sleep physician referral for a CPAP-titration study from three geographically distinct clinics in Sydney, New South Wales (Royal Prince Alfred Hospital, Royal North Shore Hospital and the Woolcock Institute of Medical Research). Recruitment took place between November 2007 and August 2009. Sleep physicians referred patients to the study on the basis of their diagnostic sleep study and the need to improve their current health and sleep. Patient data from n = 204 who met the inclusion criteria of a respiratory disturbance index ≥5/h confirmed by diagnostic PSG and who underwent neurobehavioural testing were included in the present analyses. Exclusion criteria for the OSA patients included any previous or current use of CPAP and non-fluency in both written and spoken English, or use of psychotropic medications. As part of the large randomised trial, participants

were screened for any significant co-morbidity by the sleep physician prior to entry into the study. The physicians used their own judgement and considered any significant health conditions e.g., dementia, major neurological problems (e.g., stroke, epilepsy); severe mental health disorders (e.g., schizophrenia, major depression, bipolar disorder) prior to confirming eligibility to participate in the trial. During the eligibility screening visit, a family history of cardiovascular disease was taken and the presence of hypertension was recorded but hypertension was not an exclusion criteria.

For the non-OSA group, fifty healthy individuals without OSA were recruited from January to December 2009 specifically for this current study by general community advertisement and local newspaper. The University of Sydney Human Research Ethics Committee approved the protocol and all participants provided written informed consent. They were at low-risk of OSA [Multivariable Apnea Prediction Index (MAP index) value <0.5] (20). Exclusion criteria for the non-OSA group were: significant sleepiness (Epworth Sleepiness Scale score (ESS) >10) (21); clinical insomnia (Insomnia Severity Index [ISI] score >15) (22); history of sleep disorders, neurological disorders, major psychiatric disorders, other significant concomitant medical co-morbidities, or head injury; usage of medications affecting sleep or cognitive function; and colour-blindness.

The educational status of each participant was categorised as either: primary, secondary or tertiary level.

Neurobehavioural Test Battery

The test battery comprised two parts: (1) computerised neurobehavioural tasks modelled on conventional neuropsychological tests (23); and, (2) the hand-held 10 min psychomotor vigilance task (PVT) (24). The neurobehavioural tasks selected were based on cognitive domains which previously identified impairment in OSA: attention/vigilance, visuospatial abilities, executive functions and working memory. The computerised battery was developed on a web-based platform, and delivered on a conventional desktop personal computer with a 17-inch colour display, keyboard and mouse. Administration of the full test battery lasted approximately 30 min including the 10 min PVT. All participants first performed a practice session of the test battery in the presence of a researcher. Individual tasks were repeated until the participant felt comfortable with each task. The test battery was undertaken in a private testing room in the sleep clinic. The OSA patients stayed in the sleep clinic and had an in-lab overnight sleep study on the same evening following the performance testing which occurred in the afternoon. The non-OSA group did not undergo PSG. Itemisation of the tests incorporated within the neurobehavioural battery is detailed below (see **Figure 1**).

Letter Cancellation Test (LCT)

The LCT predominantly evaluates attention, concentration and visuospatial scanning ability or visuospatial neglect, as well as measuring accuracy of selective attention (23). A large field of letters is displayed on the computer screen, including a target CAPITAL LETTERS, d o u b l e s p a c e s, or a mixture of both (25). Participants scanned this field and were asked to mark as many capital letters displayed on the computer screen in 60 s using the mouse (this was performed twice – trials 1 and 2); then mark as many double spaces (trials 3 and 4), then as many capital letters and double spaces (trials 5 and 6). On the final screen (trial 7) a combination of the two targets were displayed and participants were asked to complete the test in their own time. Variables evaluated were the mean number (average performance on trials 1–6) of: (a) correctly marked targets ("average hits"); (b) missed targets ("average omissions"); and, (c) non-targets incorrectly marked ("average commissions"). Performance variables assessed during the final trial were final hits, finals omissions, final commissions and final trial duration.

Stroop Text and Stroop Colour

The Stroop test assesses the inhibition of dominant responses, and reflects the "higher-order" executive functions (23). It is a two-part test (Stroop-Text and Stroop-Colour) assessing reaction time to colours and words displayed and gauges cognitive interference which is impacted by the presentation of simultaneous conflicting information. Words (red, green, or blue) and three different coloured squares (red, green, or blue) were displayed on the computer screen. Participants were required to click on the coloured square that matched either the MEANING (Stroop-Text) or the COLOUR (Stroop-Colour) of

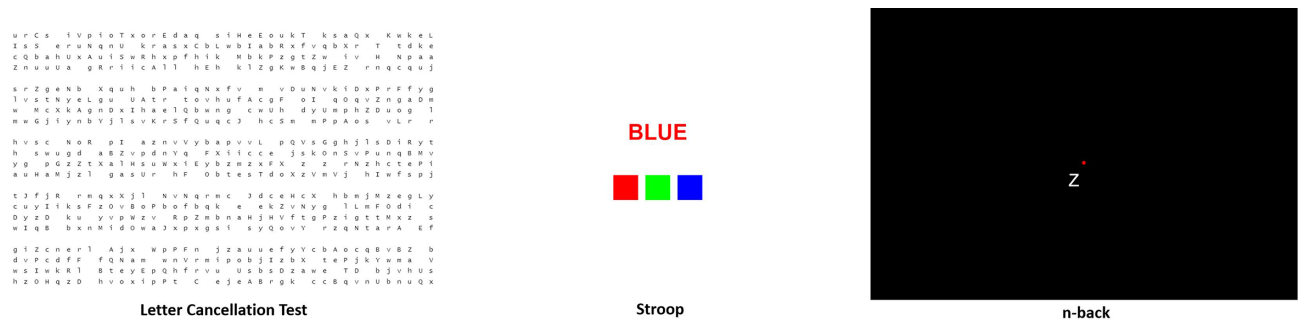

FIGURE 1 | Screen shots of the computerised neurobehavioural tasks included in the test battery. Appropriate permissions for use of screen shots granted.

the word presented. Each part of the test was 45 s in duration and involved multiple trials. Variables evaluated were percentage of correct total responses; and average response latency.

N-Back

The n-Back assesses working memory, encompassing short-term memory storage and information processing (26), and reflects "central executive" processes (27). For this visuospatial test, the 2-Back and 3-Back were used (as 1-Back is thought to assess vigilance only). The participant was asked to compare the position of a letter displayed on the screen to the position of the letter presented 2 or 3 trials previously. For example, for 2-back, the position of the 3rd letter is compared to the position of the 1 st letter and the position of the 4th letter to the 2nd letter, and so on. If the position of the letters matched, the participant pressed "M" on the keyboard for "Match" as quickly as possible. If the position of the letters did not match, the participant pressed "N" for "No Match" as quickly as possible. The first of 50 trials was presented after 1.5 s with subsequent stimulus intervals of 4.5 s. Each n-Back task was 4 mins in duration and the percentage of total accuracy was calculated.

Psychomotor Vigilance Task (PVT)

The PVT is a 10 min reaction-time task of sustained attention sensitive to sleep loss (24) and can identify attentional lapses even in mild OSA (28). The device is a hand-held box with a red light-emitting diode (LED) display of a three-digit millisecond counter (PVT-192, Ambulatory Monitoring, Inc., Ardsley, NY, USA) (29). Participants were instructed to respond as fast as possible when they first saw a visual stimulus appear. The time taken to respond to the stimulus was displayed in milliseconds (ms). During the task visual stimuli appeared at random intervals between 2 to 10 s. Variables analysed were: (a) mean reaction time (RT); (b) mean of the fastest 10% of RTs; (c) mean reciprocal of slowest 10% of RTs; and, (d) number of lapses (response time >500 ms).

Statistical Analysis

Regression using general linear models was used to evaluate differences in neurobehavioural performance outcomes between OSA and non-OSA groups while controlling for age, gender and education. All analyses were two-tailed and used an alpha level of 0.05. Mean and SD for the findings are presented as "mean (SD)", unless otherwise noted. Variables deemed not normally distributed were transformed using appropriate methods as determined by the Box-Cox method using R. Correlations between subjective sleepiness, PSG measures of disease severity and performance were examined using Spearman's non-parametric correlation coefficient. Data was analysed using SAS software v9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Participant characteristics for OSA (n = 204) and non-OSA (n = 50) groups are shown in **Table 1**. During diagnostic polysomnography, the OSA group had on average a sleep efficiency of 76.9% (13.6), an apnea hypopnea index (AHI, number of apneas and hypopneas per hour of sleep) of 33.6/hr (25.8), EEG arousal index of 33.6/hr (22.3), and a 3% oxygen desaturation index (ODI) of 34.9/hr (48.0) and a minimum oxygen saturation of 78.6% (11.7). They reported on average significant levels of daytime sleepiness as measured by the ESS.

TABLE 1 | Demographic and clinical features of non-OSA and OSA Groups.

	Non-OSA n = 50	OSA n = 204
Gender, n (%) male	22 (44.0%)	145 (71.1%)
Age, years [range]	39.2 (14.0) [25 – 69]	49.3 (12.5) [22 – 80]
Body Mass Index, kg/m^2	25.7 (4.3)	33.6 (8.0)
Epworth sleepiness scale	3.6 (2.3)	12.0 (4.9)
Apnea hypopnea index, events/hour	-	33.6 (25.8)
Education Primary, n (%)	0 (0%)	5 (2.5%)
Education Secondary, n (%)	3 (6%)	54 (26.5%)
Education Tertiary, n (%)	47 (94%)	104 (51.0%)
Education Unknown, n (%)	0 (0%)	41 (20.1%)

Data are mean (SD) unless otherwise stated.

The non-OSA group had a higher proportion of females, were younger, and as expected they had a lower body mass index (BMI) and lower ESS score than the OSA group, see **Table 1**. A greater proportion (94%) had completed tertiary education compared with the OSA group (51%). The non-OSA group were considered low risk for the presence of sleep apnea with an average MAP index of 0.19 (0.16), and did not report clinical insomnia with an average ISI score of 3.2 (2.8).

Neurobehavioural Performance – Comparing OSA and Non-OSA Groups

Neurobehavioural performance measures for both OSA and non-OSA groups are reported in **Table 2**. One hundred and sixty three patients of the 204 in the OSA group who had a known education status and all 50 non-OSA participants were included in the between–group comparisons.

After controlling for age, gender and education, the OSA group demonstrated significantly impaired task performance compared with the non-OSA group in executive functions (Stroop-Text), working memory (n-Back) and sustained attention (PVT), see **Table 2**. In the Letter Cancellation Test the OSA patients had worse performance with fewer average hits compared with the non-OSA group. However they showed better accuracy with fewer missed targets.

Correlations Between Subjective Sleepiness, Disease Severity and Neurobehavioural Performance

In a secondary analysis, we assessed associations between subjective sleepiness (ESS), and PSG-derived sleep efficiency (%) and disease severity (AHI, EEG arousal index, 3% ODI, min SaO_2) measures, and neurobehavioural performance in all 204 patients in the OSA group, see Supplementary Table S1 for the full correlation matrix.

TABLE 2 | Comparison of neurobehavioural performance in visual spatial scanning and selective attention, executive functions and sustained attention between OSA and non-OSA groups.

Performance Measure	Non-OSA *n* = 50	OSA *n* = 163	Adjusted p-value
Letter Cancellation Test (Visual spatial scanning and selective attention, LCT)			
LCT Average Hits, n (Higher Better)	61.74 (12.39)	50.26 (13.37)	0.04
LCT Average Omissions, n (Lower Better)	5.27 (7.32)	3.69 (5.27)	0.02
LCT Average Commissions, n (Lower Better)	1.50 (2.71)	1.05 (1.77)	0.11
LCT Hits Final Trial, n (Higher Better)	287.58 (35.06)	281.74 (53.65)	0.64
LCT Omissions Final Trial, n (Lower Better)	22.42 (35.06)	28.26 (53.65)	0.64
LCT Commissions Final Trial, n (Lower Better)	1.08 (2.46)	4.18 (10.17)	0.37
LCT Duration Final Trial*, sec (Lower Better)	287.60 (70.04)	371.08 (171.38)	0.06
Stroop Test (Inhibition of dominant responses)			
Stroop-Text Accuracy*, % (Higher Better)	98.73 (2.61)	93.29 (16.51)	0.02
Stroop-Text Reaction Time, sec (Lower Better)	1.05 (0.29)	1.28 (0.48)	0.20
Stroop-Colour Accuracy, % (Higher Better)	94.43 (14.72)	79.99 (25.67)	0.08
Stroop-Colour Reaction Time, sec (Lower Better)	1.10 (0.60)	1.44 (0.58)	0.34
N-Back (Working memory)			
2-Back Accuracy*, % (Higher Better)	87.24 (12.60)	64.55 (26.42)	<.0001
2-Back Correct Responses, n (Higher Better)	42.22 (9.58)	31.06 (13.51)	<.0001
2-Back Incorrect Responses, n (Lower Better)	6.08 (6.49)	8.18 (7.73)	0.33
2-Back Missed Responses, n (Lower Better)	3.77 (8.48)	11.29 (14.79)	0.02
3-Back Accuracy, % (Higher Better)	80.57 (14.22)	55.69 (24.29)	<.0001
3-Back Correct Responses, n (Higher Better)	38.06 (11.14)	26.69 (12.30)	<.0001
3-Back Incorrect Responses, n(Lower Better)	8.71 (6.73)	11.04 (7.81)	0.17
3-Back Missed Responses, n (Lower Better)	4.29 (10.24)	13.26 (17.80)	0.02
Psychomotor Vigilance Task (Sustained attention, PVT)			
PVT Mean RT*, msec (Lower Better)	272.57 (61.92)	303.01 (76.42)	0.0003
PVT Mean Fastest 10% RT, msec (Lower Better)	195.00 (23.10)	204.30 (25.93)	0.06
PVT Mean Slowest 10% RRT, rate per 1000 msec (Higher Better)	2.57 (0.51)	2.23 (0.64)	<.0001
PVT Lapses*, n (Lower Better)	1.64 (3.12)	4.19 (6.09)	<.0001

*P value determined by linear regression adjusted for age, gender and education. *denotes outcomes that were transformed using a Box-Cox transformation. RT, reaction time; RRT, reciprocal reaction time. For non-OSA group: n = 48 for LCT, n = 50 for Stroop, n = 49 for n-back, and n = 50 for PVT. For OSA group: n = 159 for LCT, n = 159 for Stroop, n = 160 for n-back, and n = 142 for PVT.*

Subjective Sleepiness

Higher ESS was associated with slower reactions times on the PVT sustained attention task (mean reaction time [rho = 0.170, p = 0.022], mean reciprocal of slowest 10% of reaction times [rho = −0.166, p = 0.026] and lapses [rho = 0.168, p = 0.023]), but not any other task.

Sleep Efficiency

Reduced sleep efficiency (%) was significantly associated with fewer correctly marked targets and slower completion time for the final trial on the LCT (average hits [rho = 0.203, p = 0.010], final trial duration [rho = −0.161, p = 0.043]); slower reaction times on the Stroop-Colour test [rho = −0.158, p = 0.047]; worse working memory (accuracy and number of correct responses on 2 and 3 back tasks [rho = 0.176 to 0.196, p = 0.013 to 0.026]).

Disease Severity

The AHI or the EEG arousal index was not significantly correlated with any performance measure ($p > 0.05$) see Supplementary Table S1.

Worse hypoxemia measures were significantly related to poorer performance on tasks of executive function. Those who had the lowest minimum oxygen saturation levels showed lower accuracy on the Stroop-Colour task (rho = 0.169, p = 0.046), while those with a higher ODI had slower reaction times on the Stroop-Text (rho = 0.172, p = 0.038) and Stroop-Colour (rho = 0.179, p = 0.031) tasks.

DISCUSSION

Our brief computerised neurobehavioural test battery identified significant deficits in working memory, selective attention and sustained attention in patients with untreated OSA compared with the non-OSA group. This pattern of impairment parallels previous investigations of neurobehavioural performance in OSA (8, 30–32). Commonly used PSG-derived measures of sleep disordered breathing/hypoxemia or sleep fragmentation were inconsistently or weakly related to performance measures.

We deliberately selected tasks for the test battery based on sensitivity to evaluate cognitive domains negatively affected by OSA, with attention/vigilance and executive functions showing the most consistent impact (8, 30). The simple 10 min PVT (attention/vigilance) was sensitive to the effects of OSA with statistically significant between-group differences in 3 of the 4 PVT outcomes assessed. PVT impairment was associated with greater subjective sleepiness (higher ESS) in the current study, consistent with prior findings (33).

In the Stroop test, performance was significantly impaired on the Stroop-Text but not the Stroop-Colour component in the OSA patients. This may reflect impairment in attentional capacity and processing speed rather than an inhibition of stereotypical responses. However there was a trend for lower accuracy in Stroop-Colour in the OSA group (p = 0.08). Naegele et al. reported significant abnormalities in Stroop-Colour suggesting frontal lobe

deficits in a group of severe OSA patients compared with age-matched controls (34). This discrepancy likely reflects differences in OSA disease severity between the populations studied, and the heterogeneity of performance amongst patients. Both sleep disruption and blood gas abnormalities have been implicated in the dysfunction of the pre-frontal cortex manifesting as "executive dysfunctions" (2). Underlying levels of alertness and attention, considered to be "lower-level cognitive processes" also influence executive functioning and response to treatment (35). Excessive daytime sleepiness is often an important factor underlying attentional deficits and neurobehavioural dysfunction (16, 27, 36), and a significant contributor to the 2-fold increased risk of workplace (4) and motor vehicle accidents (5) in those with OSA. Importantly, the largest improvements in cognitive deficits following CPAP treatment are observed in patients who are excessively sleepy at baseline (12).

To delineate the role of sleep disruption and hypoxemia on neurobehavioural dysfunction we examined the association between nocturnal PSG measures and performance in 204 OSA patients. We found inconsistent findings and weak associations, similar to those reported by others (9, 37–39). Reduced sleep efficiency was significantly but weakly associated with poor performance on the selective attention (LCT), executive function (Stroop-Text and Stroop-Colour) and working memory tasks. A lower minimum oxygen saturation level and ODI were associated with impaired executive functioning with reduced accuracy and slower reaction times on the Stroop task, respectively. The AHI and the EEG arousal index were not significantly related to any performance measure. The length of time individuals have been affected by OSA is often unclear and is a likely factor in the magnitude and reversibility of performance deficits, and may explain, at least in part, the inconsistencies with performance and disease severity.

In the selective attention task (LCT), OSA patients had fewer average hits but were more accurate compared with the non-OSA group. There was also a trend for the OSA patients to take longer to complete the final combined trial ($p = 0.06$), possibly reflecting less impulsivity and "appreciation of the complexity of the task" (2) often associated with increasing age. However it may also highlight the wide variation in deficits and performance more resilient to the effects of untreated OSA. Previous research found increasing age in healthy adults (age range of 18–91 years) resulted in similar LCT deficits in speed but not in spatial distribution of cancellation errors (40). Although group differences could be explained by differences in age (41) and education, we controlled for these variables, suggesting these deficits are more likely to relate to the presence of untreated OSA.

Prior neuroimaging research has provided insight into the OSA-related deficits observed in higher-level cognitive functions such as those targeted by the current battery, and the mechanisms which underlie them. Using functional MRI, altered brain responses have been identified during the completion of response inhibition and working memory tasks in OSA (42–45), including reduced activation in the prefrontal cortex with working memory (45). When OSA patients performed equally well to controls on 2-back, an over-recruitment of brain regions during the task was apparent with increased activation in the frontal cortex and hippocampus (44). This lack of activation of the prefrontal cortex potentially indicates injury to this area with a compensatory over-recruitment of the frontal cortex and hippocampus. Interestingly some OSA patients appear able to reallocate or recruit additional neuronal resources to maintain comparable executive functioning performance to controls (44, 46).

There are a number of study limitations including using a previously-collected data set constructed for a CPAP adherence research outcome. However, the parsimonious use of the 204 prior patients and 50 non-OSA participants is an important ethical use of the data, and is sufficiently large to detect clinically meaningful differences between the OSA patients and non-OSA participants. Our non-OSA healthy comparison group was less sleepy, had a lower BMI, was younger, and had a higher percentage of females and with more tertiary education than in the OSA group. It is difficult to control for potential differences in BMI and sleepiness as these are both contributing factors to the disease in untreated OSA. As this clinical OSA cohort are more likely to have presented to the sleep centre for management of symptoms of OSA, including neurobehavioural impairment some selection bias is possible. However these individuals were primarily recruited to explore the effects of a psychoeducation program to improve CPAP adherence and any self-selection bias to determine any cognitive deficits is likely to be minimal. While the non-OSA group was not individually-matched to the OSA group for gender, age and education, the differences between groups persisted after statistical modelling adjusting for these potential confounders. The non-OSA group did not undergo polysomnography to rule out the presence of sleep apnea, however the screening tools of the MAP index and ESS showed data consistent with that reported from normal controls without OSA (20, 21). There was no single neurobehavioural performance outcome nominated as the pre-specified primary outcome. We specifically chose to evaluate all component outcomes for each task to determine the sensitivity of the test battery to detect differences between OSA and non-OSA groups. As a consequence, multiple comparisons were conducted increasing the likelihood of falsely detecting a between-group difference (type I error). Lastly, we did not assess more complex components of executive functioning such as problem solving and planning in order to maintain the brevity of the test battery.

The currently developed battery is well placed to examine the negative effects of OSA and effectively detect between-group differences in cognitive performance. It has potential, not only in terms of its ease of application without loss of fidelity, but also in the long term, to broaden our knowledge of the variability in the manifestations of the disease between patients, and assess response to treatment. This brief 30 min assessment may provide a sensitive, standardised method of assessing daytime dysfunction in OSA. However, to date it has not yet been subjected to more rigorous psychometric evaluation, and further research is now required to document the reliability and validity of these tools in OSA.

ETHICS STATEMENT

This work was carried out in accordance with the recommendations of the ICH-GCP guidelines and the Australian National Statement on Ethical Conduct in Human Research with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The study protocols were approved by the Human Ethics Review Committees of the Sydney South West Area Health Service and the University of Sydney.

AUTHOR CONTRIBUTIONS

Study design: RG, DB, KW, AD. Data collection: DJB, ALD. Data analysis: CF, CH, KW, GD. Interpretation of results: AD, DB, KW, CF, CH, SN, GD. Drafting of the manuscript: AD, CF, DB, CH, KW, RG, SN and all other authors contributed to the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fsurg.2018.00035/full#supplementary-material

TABLE S1 | Correlations between subjective sleepiness, disease severity and neurobehavioural performance.

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MINI REVIEW
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Post-Stroke Sleep-Disordered Breathing—Pathophysiology and Therapy Options

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Sleep-disordered breathing (SDB), encompassing both obstructive and central sleep apnea, is prevalent in at least 50% of stroke patients. Small studies have shown vast improvements in post-stroke functional recovery outcomes after the treatment of SDB by continuous positive airway pressure. However, compliance to this therapy is very poor in this complex patient group. There are alternative therapy options for SDB that may be more amenable for use in at least some post-stroke patients, including mandibular advancement, supine avoidance, and oxygen therapy. There are few studies, however, that demonstrate efficacy and compliance with these alternative therapies currently. Furthermore, novel SDB-phenotyping approaches may help to provide important clinical information to direct therapy selection in individual patients. Prior to realizing individualized therapy, we need a better understanding of the pathophysiology of SDB in post-stroke patients, including the role of inherent phenotypic traits, as well as the contribution of stroke size and location. This review summarizes the available literature on SDB pathophysiology and treatment in post-stroke patients, identifies gaps in the literature, and sets out areas for further research.

Keywords: stroke, sleep apnea, hypopnea, treatment, phenotyping

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INTRODUCTION

Sleep-disordered breathing (SDB) encompasses a range of respiratory sleep disorders which affects ~20% of the middle-aged population (1, 2). The known risk factors for SDB include obesity, age, and male gender (3). SDB is associated with a range of negative health outcomes including excessive daytime sleepiness leading to neurobehavioral and cognitive dysfunction (4), hypertension (5), and diabetes (6).

Stroke is one of the leading causes of morbidity and mortality. Stroke can occur ischemically, where there is a blockage of a cerebral artery, or hemorrhagically, where the cerebral artery has ruptured. Hemorrhagic strokes only comprise 15–20% of strokes, but account for almost half of stroke deaths. There is a strong link between SDB and stroke risk (7); however, the effectiveness of continuous positive airway pressure (CPAP), the gold-standard treatment of SDB, in reducing stroke risk is not supported. For example, a recent large randomized control trial (RCT) did not support CPAP as a risk reduction strategy for recurrent stroke in patients with moderate to severe OSA, although in highly compliant CPAP users, there may be some protective effect (8). SDB is more

severe during the acute stroke phase; however, despite improvement over time, 53% of stroke patients demonstrate at least moderate–severe OSA after 1 month according to a meta-analysis (9). Post-stroke acute SDB, however, has received less attention in the literature, but there is emerging evidence that post-stroke SDB is very common and is associated with adverse effects, including poorer stroke recovery outcomes (10, 11). Emerging evidence, however, suggests that CPAP treatment in post-stroke patients may lead to faster functional recovery and reduction in the length of hospitalization and frequency of re-hospitalization (12–14).

It is important to improve our understanding of the pathophysiology of post-stroke SDB in order to initiate appropriate rehabilitation therapy to facilitate faster recovery in stroke patients. This review will briefly summarize and highlight the growing literature on post-stroke prevalence and the clinical presentation of SDB. Furthermore, with the increased use of neuroimaging and a greater understanding of SDB pathophysiology, recent studies have begun examining whether stroke lesion location and size are associated with SDB presentation. Lastly, we will review the emerging novel SDB-phenotyping approaches that may be clinically useful to better characterize the nature of SDB in post-stroke patients and help guide targeted post-stroke therapy.

PREVALENCE AND PATHOPHYSIOLOGY OF SDB POST STROKE

The most common form of SDB is obstructive sleep apnea (OSA), which is the reduction (hypopnea) or cessation (apnea) of airflow during sleep as a consequence of upper-airway collapse. Another form of SDB is central sleep apnea (CSA), which is also characterized by cessation of respiration but as a consequence of loss in central respiratory drive and effort, rather than physical upper-airway collapse (**Figure 1**).

The gold-standard diagnosis for SDB is performed by overnight laboratory polysomnography (PSG), comprising electroencephalography (EEG) and respiratory measures (pulse oximetry, nasal pressure, and respiratory effort). PSG, however, can be cumbersome and time-consuming, making it impractical in some clinical settings such as post-stroke (15). As such, the vast majority of studies examining SDB and stroke use respiratory polygraphy, which is a limited channel sleep study measuring respiratory parameters without EEG. There is good agreement between the limited channel studies compared with gold-standard PSG (16, 17) suggesting that the prevalence estimates for SDB post stroke are reasonable.

Prevalence of SDB after Stroke Compared to Prevalence in Non-Stroke Patients

There is cross-sectional evidence suggesting that SDB is more common among stroke patients, compared with the general population, with a recent meta-analysis showing that SDB affects >50% of stroke patients (9). Furthermore, studies have demonstrated that stroke patients experience a higher prevalence of CSA (>5 respiratory events/hour) compared with non-stroke SDB patients (18–20).

An important limiting factor in this area is determining whether there was preexisting SDB prior to the stroke and how this may influence post-stroke acute SDB pathophysiology. Few studies have used questionnaires to quantify snoring prevalence prior to the stroke (21, 22), and there are screening questionnaires for SDB that may provide information on whether SDB was present prior to the stroke. Nevertheless, the use of these questionnaires would be subject to recall bias. Ultimately, unless there has been a prior objective clinical diagnosis of SDB, it is very difficult to determine the relationship between prior and post-stroke SDB.

TREATMENT OF SDB IMPROVES CLINICAL RECOVERY IN STROKE PATIENTS

Untreated SDB in stroke patients leads to numerous adverse outcomes during acute and chronic recovery from stroke including higher long-term mortality (23–25) and reduced functional outcomes (10, 25, 26).

Traditionally, as the majority of SDB events in the general population are obstructive in nature, this was considered to be caused by a collapsible airway (27, 28). CPAP acts as a pneumatic splint *via* the application of pressurized air to prevent airway collapse. There are different types of positive airway pressure (PAP) machines that can operate at a set pressure, or other machines that can automatically detect the pressure needed to maintain airway patency (known as an auto-CPAP, or APAP). CPAP usage of more than 4 h a night, for at least 70% of nights, is considered clinically compliant (29). Adaptive servo-ventilation (ASV) has in the past been used to treat CSA; however, a recent study has questioned the efficacy of this treatment (30). Furthermore, there has been no research examining the effects of ASV in post-stroke SDB patients.

Successful treatment of SDB by both CPAP (13) and APAP (12) in stroke patients has been shown to improve NIH Stroke Scale. In addition, treatment has been shown to reduce the risk of mortality by 32% (14). Yet, despite the well-documented benefits of PAP, compliance to therapy in general populations remains poor, with several studies showing an average nightly usage of less than 4 h a night, and in many cases, less than half the nights of the week. Furthermore, up to 50% of patients abandon CPAP treatment in the long term (8, 31). Many of the reasons for low compliance in the general population include mask discomfort, anxiety, and difficulty using CPAP therapy (32, 33). Compliance with CPAP appears to be even worse in stroke patients with SDB, with uptake in stroke populations regularly below 50% (23, 34). Furthermore, those that do use CPAP often use it for less than 4 h/night (34–36).

Despite the prevalence of CSA in stroke patients, no study has attempted to treat CSA directly in SDB patients. This is further exacerbated by an RCT highlighting that the previous treatment strategy of CSA, ASV, provided no protection against CSA-related death (30). While CSA is not caused by a collapsed airway, CPAP has been shown to have some efficacy in reducing CSA; however, this is due to addressing non-stroke causes in CSA, such as decreased left-ventricular ejection fraction (37, 38). Thus, it is yet unclear whether CPAP would benefit stroke-related CSA.

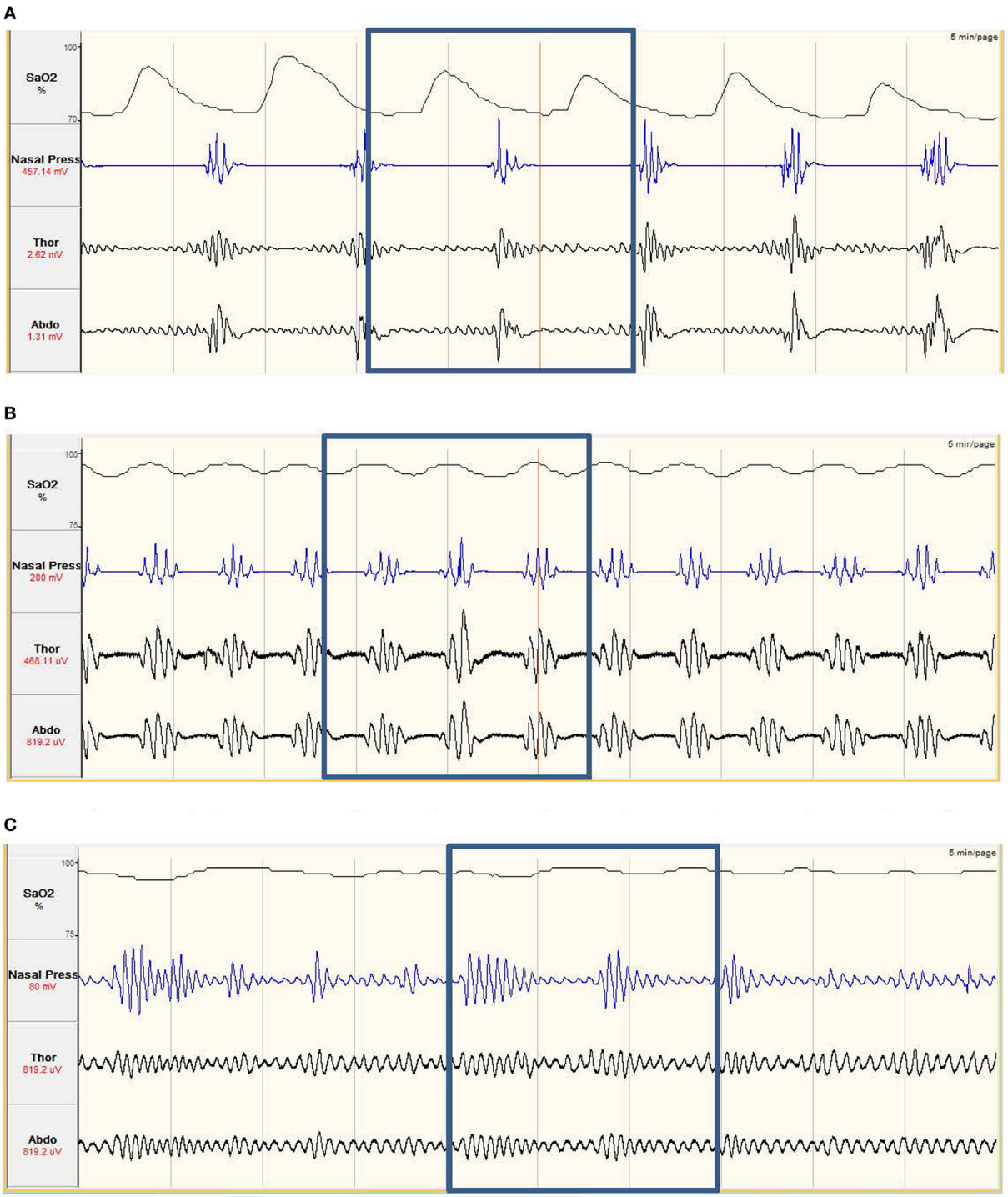

FIGURE 1 | **(A)** Obstructive sleep apnea. The nasal pressure (second tracing from top) goes through periods of 'flattening', where airflow has ceased. The abdominal and thoracic respiratory bands (third and fourth tracing) show continued effort to breath, with effort increasing prior to the recovery of breathing. The continued respiratory effort with no airflow implies the airway has collapsed. The oxygen saturation (SaO2%, top tracing) shows periods of desaturation. The desaturation, and recovery, is delayed compared to the respiratory effort. Obstructive apneas occur multiple times in the example. **(B)** Central sleep apnea. The nasal pressure (second tracing from top) goes through periods of 'flattening', where airflow has ceased. This is combined with the abdominal and thoracic respiratory bands, which are also 'flattening', showing no effort to breathe. This combination of no airflow and no effort to breathe imply the neural drive to breathe is impaired. Central apneas occur multiple times in the example and also result in periods of SaO2% (top tracing) desaturation. **(C)** Hypopnea. The nasal pressure shows periods of increased and decreased breathing, coupled with increased and decreased respiratory effort. As airflow is still maintained but leads to decreases in SaO2% (top tracing) of at least 3%, this is classed as a hypopnea.

Nevertheless, given the documented benefits of the treatment of SDB on the functional recovery of stroke patients, it is imperative to develop strategies and care pathways to motivate and encourage SDB treatment in stroke patients. These may include the use of non-CPAP-related treatments in conjunction with novel respiratory phenotyping techniques, which may be more suitable and acceptable for stroke populations during recovery in both hospital and home environments.

Other Potential Treatments for Post-Stroke SDB

The development of non-CPAP treatments for SDB has been growing. Diet and physical exercise to reduce obesity has shown promise to reduce the severity of SDB in non-stroke populations (39, 40); however, as in general populations, it is difficult to achieve and maintain in non-stroke patients (41, 42). The functional impairment caused by stroke, such as immobility, means weight loss is difficult to implement. Furthermore, during the post-stroke period, stroke patients with variable degrees of hemiparesis often lose muscle mass but increase fat mass (43), leading to obesity, which can worsen SDB.

Obstructive sleep apnea is often more severe in the supine position compared to that in lateral postures (44). Recent technological developments in supine avoidance devices for OSA have shown promising results in terms of efficacy in reducing OSA severity as well as treatment adherence (45, 46). A small RCT involving SDB stroke patients using a supine avoidance pillow showed a significant decrease in apnea/hypopnea index (AHI) while using the pillow; however, larger studies are needed to properly elucidate the effect of supine avoidance on SDB in stroke patients (47). Furthermore, this technique may not be suitable for all stroke patients, particularly those with hemiparesis, as they may not be able to shift their body weight to, or maintain, a lateral position.

Mandibular advancement splints (MAS) move the mandible forward, thereby opening the airway and are effective at reducing OSA in 30–50% of patients (48). This therapy may be beneficial in some stroke patients and may be better suited and tolerated in stroke populations compared to CPAP treatment; however, MAS has not been tested in stroke patients thus far.

Surgical interventions to reduce OSA severity have shown promise in non-stroke populations; however, studies are lacking in this area (49). Furthermore, given the potential complications from stroke, surgery may not be a feasible option.

Oxygen therapy has also been evaluated as a potential treatment option in OSA (50) and would seem to be an appropriate, minimally invasive therapy in post-stroke patients with SDB. The effectiveness of oxygen therapy may be limited, however, with evidence suggesting that it is effective at significantly reducing oxygen desaturation, but may prolong apneic events (50). More recent evidence suggests that only certain OSA patients with particular phenotypic traits respond positively to oxygen therapy (51), highlighting the need for future research on simple phenotyping and therapies in post-stroke patients.

Despite the availability of various treatment options for OSA, there has been very limited research examining the acceptance and efficacy of non-CPAP therapies on improving SDB and functional recovery in stroke patients.

Phenotyping SDB in Stroke Patients to Inform Novel Treatment Strategies

There are several nonanatomical contributors to SDB, being a low-respiratory arousal threshold, abnormal chemoreflex response to differing carbon dioxide (CO_2) levels, and low activation of the main upper-airway dilator muscle, the genioglossus (52). This knowledge has allowed for the development of emerging "tailored" treatments for those that have these nonanatomical contributors to SDB. Low arousal threshold can be treated by the use of sedative (53), abnormal chemoreflex has been treated by supplementary oxygen (54), and low activation of the upper-airway dilator muscles can be improved by targeted oral exercises (55). Importantly, these SDB phenotypes can be identified from diagnostic PSG studies (56, 57); however, the characterization of these phenotypes has not been performed in post-stroke SDB patients.

DOES STROKE LESION SIZE AND LOCATION IMPACT SDB PRESENTATION?

The three nonanatomical contributors to SDB are controlled through the brainstem. Thus, it is biologically plausible that stroke lesions that involve the brainstem may contribute to SDB. This may explain why stroke patients experience higher rates of SDB (58). If stroke lesion location does contribute to SDB, this knowledge, combined with SDB phenotype information, could potentially be used clinically to inform the optimal mode of therapy for a particular patient.

Neural Centers of Respiratory Control

Within the brainstem, the medulla oblongata plays the primary role in respiratory control (59). The medulla oblongata contains central chemoreceptors (with peripheral chemoreceptors located in the carotid bodies). The chemoreflex response controls respiration through a loop-gain feedback system depending on the partial pressure of CO_2 detected ($PaCO_2$). In people with "normal" chemosensitivity, an increase in $PaCO_2$ will increase respiration, while a decrease in $PaCO_2$ will reduce respiration. In those with "abnormal" chemosensitivity, increases in $PaCO_2$ lead to above normal increase in ventilation, which can contribute to CSA (60). Lesions to the respiratory centers within the medulla have shown decreased chemosensitivity during wakefulness, sleep, and even exercise (61).[1]

The medulla also receives input from the respiratory center within the pons to innervate the pharyngeal muscles, which play an important role in maintaining the patency of the upper airway, as well as the regulation of diaphragm activity. The largest pharyngeal muscle, the genioglossus, is innervated by the hypoglossal nerve, which originates from the brainstem (62) and acts to pull the tongue forward. SDB patients experience a reduction in genioglossus activation during sleep, which importantly contributes to upper-airway collapsibility (63, 64). Several studies have shown that brainstem strokes affect pharyngeal muscle activity (65, 66) causing dysphagia and can contribute to higher rates

[1] Patients in this study had focal lesions to the rostrolateral medulla; however, this study did not specify how the lesions occurred.

and severity of SDB observed in stroke patients. This implies that stroke-induced damage to the respiratory brain regions innervating the genioglossus muscle activity may, at least in part, explain the increase in upper-airway collapsibility in stroke patients.

Lesion Location

Severity and Type of SDB

Early studies examining brainstem strokes showed lesions to this region led to the development of Cheyne-Stokes respiration (periodic breathing occuring whilst awake) (67, 68). Lee et al. was the first to show high levels of CSA in patients who had suffered a brainstem lesion (67). Several case–control studies suggest that there is a link between brainstem stroke and SDB severity and in particular increased CSA severity (69, 70). The limited research in this area, however, means larger prospective studies are needed to make strong conclusion regarding this relationship.

The advent of neuroimaging has allowed for a more detailed examination of the potential role that lesion location might have on SDB in stroke patients. These studies have produced conflicting findings on whether stroke in the brainstem contributes to SDB and whether it contributes to specific types of SDB (obstructive vs central). Infratentorial lesions, which encompass both the brainstem and cerebellum, have been shown to generally result in higher AHI (20, 71) when compared to cortical lesions. Likewise, another study (18) has shown that when compared to cortical strokes, brainstem strokes have been associated with three times greater odds of significant SDB, particularly CSA, along with greater nocturnal desaturations (26). No study has yet examined whether brainstem lesions are associated with changes in respiratory arousal threshold. Given that a low arousal threshold contributes to unstable respiratory control and reduces the likelihood of entering slow-wave sleep, while a high arousal threshold may exacerbate arterial hypoxemia, it is important to determine whether stroke in the brainstem changes arousal threshold.

By contrast, other studies have found that non-brainstem regions might be more related to SDB in stroke patients. For example, Siccoli et al. found that patients who experience total anterior circulatory strokes had the highest AHI compared to other brain regions assessed, with CSA making up 40% of the overall AHI (19). Furthermore, the authors showed that the second highest AHI resulted from strokes in the pons, which is part of the midbrain, where CSA made up only 12% of AHI events. Ahn et al. found that bilateral cerebral lesions were associated with significantly higher SDB severity, while stroke in other regions, including the brainstem, was not associated with SDB, and the authors did not report on the type of SDB (72). De Paolis et al. have hypothesized that cerebral infarctions can lead to increased cranial pressure leading to a reduction in cerebral blood volume, which would precipitate hypocapnia, leading to unstable ventilatory control and CSA (73). This hypothesis may partly explain why another study (74) has showed a spontaneous decrease in SDB, in particular CSA after 3 months, despite not showing SDB severity or the type to be associated with lesion location.

Several studies have also shown that there is no association between lesion location and SDB severity and SDB type (74–78); however, the reasons for this are unclear. It is important to note that brainstem-specific strokes contribute to less than 10% of the number of cortical strokes, limiting the power to demonstrate lesion location impact on SDB (18, 77).

In summary, it appears that the literature on lesion location and SDB is mixed and inconclusive. There is large variation in methodology and patient populations, lesion location definitions, and even the timing of the SDB measurement relative to stroke onset, which may contribute to conflicting results.

Brainstem and Pharyngeal Muscles

Despite the importance of the pharyngeal muscles in maintaining upper-airway patency, there has been relatively little research directly examining the potential role of damage to the pharyngeal nerves in post-stroke SDB patients, despite studies showing both brainstem lesions (79) and lesions to the pharyngeal cortex (80), leading to dysphagia. Turkington et al. showed that BMI and neck circumference, but not the presence of dysphagia, contributed to worse SDB severity (81). Brown et al. showed that stroke patients with SDB had a narrower retropalatal distance, which is the size of the opening of the airway, compared to non-SDB. Importantly, dysphagia was not different between SDB and non-SDB stroke patients (82). By contrast, Martinez-Garcia et al. showed that stroke patients with brainstem stroke were 1.73 times more likely to experience dysphagia and a significantly higher number of obstructive apnea events compared to stroke patients without dysphagia during the acute phase (83). Furthermore, stroke patients with dysphagia experienced larger reductions in AHI, particularly obstructive apneas, during recovery.

Lesion Size

Few studies have examined how the size of stroke, regardless of whether the stroke in hemorrhagic or ischemic, effects SDB prevalence and type. Ahn et al. demonstrated that bilateral hemisphere lesions resulted in a significantly higher SDB severity compared to strokes that occurred in a single area (72). By contrast, Brown et al. compared brainstem to cortical strokes and showed that the lesion size was not associated with the severity of SDB (18). Siccoli et al. found that the worst SDB severity occurred with total anterior circulatory stroke, implying that the lesion size was a significant contributor to SDB severity (19). Yet, lesions occurring in the pons, a specific area of the brainstem, resulted in the second largest AHI, questioning whether the size of stroke is a contributing factor.

Differences between Ischemic and Hemorrhagic Strokes on SDB Severity

Only a single study has examined SDB differences between ischemic and hemorrhagic strokes (78). SDB severity immediately post stroke was similar between ischemic and hemorrhagic strokes, but after 3 months, SDB severity remained unchanged in ischemic stroke, but was significantly reduced for those who experienced hemorrhagic stroke. The type of SDB was not recorded; thus, it is difficult to determine whether stroke type leads to differences in SDB type from this study. The authors

suggest that the observed reduction in SDB in the hemorrhagic stroke group after 3 months may have been due to reductions in intracerebral pressure (73). More research is needed on the impact of stroke type on SDB as it appears that this information might be clinically meaningful when evaluating prognosis and therapy options in post-stroke SDB.

DISCUSSION

This review has highlighted that post-stroke SDB is significantly more prevalent compared to non-stroke populations. This is likely driven by lesion damage to respiratory control neurocircuitry in the brainstem and/or the cortex, and due to the complexity of these regions, the causes and the resulting type of SDB differ significantly between individual stroke patients. The literature on lesion location and size is limited and mixed with some studies reporting a link between brainstem stroke and SDB, in particular CSA, while others show cortical strokes to be more important and yet others showing no association between lesion location and SDB. It is too early to make strong conclusions on this, and further research is necessary to determine the link between stroke location/size and SDB.

Although SDB may reduce and resolve in severity in many patients over time, in parallel with functional recovery after stroke, SDB can significantly hinder and delay post-stroke rehabilitation, resulting in increased hospitalization and slower recovery. Importantly, the small number of studies that have examined the therapeutic effect of CPAP on recovery outcomes in stroke patients has reported significantly faster functional recovery, reduced hospitalization time, and frequency of re-hospitalization. This provides good rationale for attempting to treat post-stroke SDB to improve clinical outcomes, but clearly using CPAP in this patient group presents significant challenges due to disabling and varying impact of stroke, leading to limited CPAP adherence and use in hospital environment. There are several alternate options to treat SDB, such as MAS and supine avoidance that may be suitable in some patients to at least reduce SDB severity. New SDB-phenotyping techniques are being developed, which will inform regarding the nature and cause of SDB in individual patients, and as a result, new therapies are being developed to target phenotypic causes of SDB to provide tailored treatment for individual patients. Although at present many of these phenotyping techniques are complex and experimental, making them out of scope for clinical use, there are efforts to utilize simple sleep recordings from oximetry and flow measurements suitable for in-hospital assessment. These new phenotyping and therapy developments together with stroke location and size data could provide important clinical information to help prove SDB therapy in post-stroke and improve clinical outcomes for patients. In conclusion, the relative lack of studies examining SDB in the aftermath of stroke, along with the discrepancies in findings, highlights the need for more research in this area. Specifically, research links lesion location to SDB phenotypes toward informing what drives SDB post stroke in individual patients and guiding the choice of SDB treatment and stroke rehabilitation.

AUTHOR CONTRIBUTIONS

DS: manuscript concept, preparation, write-up, reviewing, and editing; RM: manuscript reviewing and editing; SM: manuscript reviewing and editing; AV: manuscript concept, preparation, write-up, reviewing, and editing.

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Sleep-Disordered Breathing in People with Multiple Sclerosis: Prevalence, Pathophysiological Mechanisms, and Disease Consequences

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Sleep problems are common in people with multiple sclerosis (MS). Reported prevalence rates of sleep-disordered breathing (SDB) vary between 0 and 87%. Differences in recruitment procedures and study designs likely contribute to the wide variance in reported prevalence rates of SBD in MS. This can make attempts to compare SDB rates in people with MS to the general population challenging. Little is known about the pathophysiological mechanisms that contribute to SDB in people with MS or whether MS contributes to SDB disease progression. However, compared to the general obstructive sleep apnea (OSA) population, there are clear differences in the clinical phenotypes of SDB in the MS population. For instance they are typically not obese and rates of SDB are often comparable or higher to the general population, despite the high female predominance of MS. Thus, the risk factors and pathophysiological causes of SDB in people with MS are likely to be different compared to people with OSA who do not have MS. There may be important bidirectional relationships between SDB and MS. Demyelinating lesions of MS in the brain stem and spinal cord could influence breathing control and upper airway muscle activity to cause SDB. Intermittent hypoxia caused by apneas during the night can increase oxidative stress and may worsen neurodegeneration in people with MS. In addition, inflammation and changes in cytokine levels may play a key role in the relationship between SDB and MS and their shared consequences. Indeed, fatigue, neurocognitive dysfunction, and depression may worsen considerably if both disorders coexist. Recent studies indicate that treatment of SDB in people with MS with conventional first-line therapy, continuous positive airway pressure therapy, can reduce fatigue and cognitive impairment. However, if the causes of SDB differ in people with MS, so too may the optimal therapy. Thus, many questions remain concerning the relationship between these two disorders and the underlying mechanisms and shared consequences. Improved understanding of these factors has the potential to unlock new therapeutic targets.

Keywords: sleep disorders, sleep apnea, obstructive, central, pathophysiology, fatigue, multiple sclerosis, cognition

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Abbreviations: BMI, body mass index; EDSS, expanded disability status scale; ESS, Epworth sleepiness scale; FSS, fatigue severity scale; CPAP, continuous positive airway pressure; CSA, central sleep apnea; MFIS, modified fatigue impact scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; OSA, obstructive sleep apnea; PSG, polysomnography; SDB, sleep-disordered breathing.

INTRODUCTION

Understanding the potential link between sleep disruption and multiple sclerosis (MS) due to a sleep disorder or other MS disease-related causes is important. Recent studies have demonstrated that "poor sleep" is more common in people with MS compared to the general population (1, 2). Poor sleep can worsen quality of life and may contribute to the frequently experienced consequences of MS including fatigue and impaired neurocognitive function. Disrupted sleep may also contribute to MS disease progression (3–6). Potential disease-related contributors to sleep disruption in people with MS include symptoms such as pain, spasms, bladder dysfunction, or anxiety. However, sleep disorders such as insomnia, restless legs syndrome, and sleep-disordered breathing (SDB) have also been documented in MS (7, 8). Nonetheless, it remains uncertain if sleep disorders are more common in people with MS compared to the general population (9). This review focuses on SDB in MS. A summary of what is known regarding its prevalence, potential underlying mechanisms and links between the consequences of MS and SBD and how these may further perpetuate disease severity are discussed.

The estimated prevalence of SDB in middle-aged adults in the community ranges between 10 and 50% in men and 3 and 20% in women (10–12). Untreated SDB is associated with multiple adverse consequences including poor sleep quality, excessive daytime sleepiness, cognitive impairment, increased risk of motor vehicle accidents, and adverse cardiovascular outcomes (13–15). Recent data on the prevalence of SDB in MS are conflicting (16–19). Thus, it remains uncertain if SDB is more common in MS than in the general population. However, it is clear that MS and SDB have shared consequences such as fatigue, neurocognitive impairment, and depression which may contribute to increased morbidity. As will be discussed, there are also bidirectional pathophysiological pathways that may contribute to disease progression for both disorders (6, 20, 21).

Sleep-disordered breathing and other sleep disorders are often underdiagnosed in MS (7, 22). This is possibly due to the fact that fatigue is generally accepted as being an "intrinsic" symptom of the disease rather than due to other potentially contributing causes such as sleep disruption (23). Thus, the treating clinician might be less likely to refer a patient with MS for polysomnography (PSG) compared to a person without MS. To what extent SDB contributes to the fatigue, neurocognitive impairment and disease progression in people with MS is not known. However, treating SDB may improve multiple aspects of MS. Recent studies that have included a relatively small number of participants have highlighted the potential beneficial role of treatment of SDB with continuous positive airway pressure (CPAP) to reduce fatigue in people with MS (24, 25).

In this review, current knowledge regarding the following key questions are addressed: In people with MS, how common is SDB? What are the risk factors and the pathophysiological causes? How will treatment influence key outcomes such as fatigue, neurocognitive function, balance, and disease severity/progression?

HOW COMMON IS SDB IN MS?

Sleep studies in people with MS show conflicting results with regard to the prevalence of SDB. Indeed, the reported prevalence varies between 0 and 87% (6, 7, 16–19, 24–35). A summary of the studies is shown in **Tables 1** and **2**. **Table 1** highlights studies with objective sleep data (i.e., PSG or equivalent) and **Table 2** covers studies with subjective data (i.e., questionnaires).

The variability in SDB prevalence between PSG studies in people with MS (0–87%) can be explained by differences in study design, study population and methodology. Most of the studies were not designed to measure the prevalence of SDB *per se*. Some studies are retrospective (35), or included only fatigued patients (16, 19, 30). The study populations vary greatly in characteristics such as age, disability level, body mass index (BMI), and female to male ratio. Regarding methodology the studies used different recording equipment and respiratory event scoring criteria. PSG technology has advanced significantly in recent years leading to increased sensitivity to detect respiratory events. The American Academy of Sleep Medicine scoring criteria have also been modified several times which have influenced respiratory event and SDB thresholds (36, 37).

The estimated prevalence of SDB based on questionnaire studies is more consistent and varies between 36 and 56% (7, 22, 32, 33). However, these data are somewhat difficult to interpret as they represent the proportion of people with a high risk of obstructive sleep apnea (OSA) rather than direct objective assessment. It is also unclear whether current OSA screening tools, such as the STOPBANG (38) and Berlin questionnaires (39), are appropriate in the MS population. Indeed, they were designed and validated to assess OSA risk in the general non-MS population and have not been validated in people with MS. Nonetheless, a positive STOPBANG screening (a score of 3 or more out of a possible 8) has a positive predictive value of between 75 and 85% to detect OSA in the general population (38, 40). If this is similar in the MS population, these studies (7, 22, 32, 33) indicate a high prevalence of OSA. However, these questionnaires may not be accurate in the MS population because tiredness plays a major role in both questionnaires. These questions may confound the ability to detect sleep-specific consequences in the context of MS where disease-related symptoms of fatigue and tiredness are common. Indeed, while fatigue and sleepiness are separate constructs these aspects may be difficult for some people with MS to separate in OSA screening questionnaires. Additionally, these questionnaires are based on well-known risk factors for OSA in the general population. However, it is uncertain whether these risk factors play the same key roles in the development of SDB in people with MS. Accordingly, studies that combine questionnaire with PSG data are needed to define the accuracy of these questionnaires in the MS population. Additional knowledge about MS specific risk factors for SDB is also required as outlined below.

In summary, data from studies conducted over the past 20 years indicate that SDB is common in MS but the varied study designs and populations tested make it challenging to make direct comparisons with population based studies in the general community.

TABLE 1 | Sleep studies in people with multiple sclerosis.

% of SDB	Study	Year	*N* (♀)	Study type	Patient selection	AASM scoring criteria	EDSS [mean ± SD or (range)]	Age (years) (mean ± SD)	BMI (kg/m²) (mean ± SD)	SDB (%)	OSA/SDB[a] (%)	CSA/SDB[a] (%)	Disease-modifying therapy (%)
<20	Ferini-Strambi et al. (26)	1994	25 (12)	PSG-L	N	–	3.5 (1–5.5)	39.9	–	12	33	66	0
	Tachibana et al. (28)	1994	28 (16)	OXI and PSG-L	N	–	6.4 ± 2.0	42.3 ± 11	23 ± 3.8	7	50	50	–
	Kaynak et al. (27)	2006	37 (21)	PSG-U	N	1999	2.4 ± 1.4	37.4 ± 8.7	–	0	0	0	–
	Vetrugno et al. (29)	2007	6 (2)	PSG-L	Fatigued	–	2.4 ± 1	36.6 ± 11.2	26 ± 1.7	0	0	0	None
	Veauthier et al. (25)	2011	66 (45)	PSG-H	N	–	2 ± 1.8	43.2 ± 10	25♀ 26♂	12	75	12.5	–
	Neau et al. (16)	2012	25 (15)	PSG-L	Fatigued	–	2.2 ± 1.7–4.1 ± 2.5[b]	39.7 ± 9.3–40.1 ± 11.2[b]	24.8 ± 4.6	0	0	0	48
	Chen et al. (18)	2014	21 (15)	RESP and PSG-L	N	2007	4.0 ± 2	29 ± 8.5	23.9 ± 1.0 (NF) 25.3 ± 3.1 (F)	0	0	0	–
	Lin et al. (34)	2016	19 (14)	RESP	EDSS (2–6)	2007	3.3 ± 1.2	56 ± 10	28 ± 8	16	0	100	84
>20	Kallweit et al. (30)	2013	69 (48)	RESP	Severely fatigued	2007	5.8 ± 1.4	49.8 ± 9.2	26 ± 4.9	41	94	6	–
	Kaminska et al. (17)	2012	62 (45)	PSG-L	N	1999	3.6 ± 1.8	47.3 ± 10.4	26 ± 5.1	58	100	0	69
	Braley et al. (35)	2012	48 (32)	PSG-L	PSG referred	2007	–	47.6 ± 10.8	32 ± 5.2	67	84	6	69
	Carnicka et al. (31)	2015	50 (35)	PSG-L	N	2007	2.5 (0–6.5)	40.3 ± 10.7	N/R	28	79	21	–
	Sater et al. (19)	2015	32 (24)	PSG-L	Fatigued/sleepy	2007	2.7 ± 1.8	45.7 ± 9.2	28.9 ± 6.4	38	92	8	None
	Braley et al. (6)	2016	38 (21)	PSG-L	Sleepy/CD	2007	3.4 ± 1.6	48.3 ± 10.1	N/R	87	100	0	50

[a]*Remaining percentages not mentioned here are made up by people with mixed sleep apnea.*

[b]*In patients with Epworth sleepiness scale score > 10, the mean EDSS was 4.1 ± 2.5 and age 39.7 ± 9.3; and in patients with Epworth sleepiness score < 10, EDSS score was 2.2 ± 1.7 and age 40.1 ± 11.2.*

Sleep study type: PSG, polysomnography; PSG-L, in lab PSG; PSG-H, home-based PSG; PSG-U, unknown home or in lab PSG; OXI, oximetry; RESP, respirography. Patient selection: N, no specific selection except MS diagnosis; CD, cognitive dysfunction. Study design: all studies were prospective except Braley et al. (35) was retrospective. AASM, American Academy of Sleep Medicine; EDSS, expended disability status scale; BMI, body mass index; NF, non-fatigued; F, fatigued; SDB, sleep-disordered breathing; OSA, obstructive sleep apnea; CSA, central sleep apnea.

WHAT ARE POSSIBLE RISK FACTORS FOR SDB IN MS?

In order to determine possible risk factors for SBD in MS, we have separated PSG studies into two groups: (1) studies with a lower than 20% prevalence of SDB and (2) studies with a higher than 20% prevalence of SDB (**Table 1**). In the subsequent section, we compare these groups and individual studies by known risk factors for SDB including: age, BMI, sex, and the MS-specific expanded disability status scale (EDSS) score.

Age

The mean age of the participants in the studies that detected a high prevalence of SDB is typically 45 years or above with the exception of the Carnicka et al. (31) study in which the mean age was 40 years (**Figure 1**). Conversely, in the lower prevalence studies the mean age was below 43 years in all cases with the exception of our recent pilot study in which the mean age was 50 years (34). Thus, similar to the general population (11, 41), increasing age appears to be risk factor for SDB in the MS population.

However, based on the available knowledge, it is not possible to distinguish if the increasing age causes SDB *via* the same mechanisms in the general versus MS population or whether MS specific disease duration factors are involved.

Body Habitus

While not all SDB studies in MS provide BMI data, in general, group mean BMI is less (BMI 23–28 kg/m^2) in studies with a low prevalence compared to those with a higher prevalence of SDB (BMI 26–32 kg/m^2) (**Figure 2**). Thus, similar to the general population (42), elevated BMI appears to be a risk factor in the MS population. However, with the exception of the Braley et al. study (35), the mean BMI for all of the MS studies is under 30 kg/m^2. Indeed, in the studies of Kallweit et al. and Kaminska et al., the average BMI is 26 kg/m^2, but the prevalence of SDB is 62 and 69%, respectively (17, 30). This is clearly very high for a non-obese population. Thus, while BMI still appears to be a risk factor for SDB in the MS population, many people with MS who have SDB have much lower BMI's than the typical OSA patient population. Thus, the pathophysiological causes of OSA are likely to be quite different as outlined below.

Sex Differences

In the general population, SDB is two to three times more common in men compared to women (43). MS on the other hand is more common in women (3:1). Thus, almost all of the populations in which polysomnographs have been performed involve more women than men. Thus, it is important to consider the female to male ratios when interpreting the prevalence of SDB in MS. Unfortunately, most studies do not specify the prevalence of SDB by gender. However, in the two studies that do (25, 30), the prevalence of SDB is higher in men compared to women. In the Kallweit et al. study, the prevalence was 33% in women and 60% in men (41% overall); and in the Veauthier et al. study, 11% of women and 14.2% of men (12% overall) had SDB. Thus, while the number of studies is small, similar to the general population, male gender is a risk factor for SDB in the MS population.

TABLE 2 | Screening questionnaires for OSA in people with multiple sclerosis.

Study	*N* (♀)	Patients selection	Disease duration (years) (mean ± SD)	Age (years) (mean ± SD)	BMI (kg/m²) (mean ± SD)	Questionnaire	High risk of OSA (%)	Official SDB diagnosis (%)
Dias et al. (32)	103 (74)	OPC	11.7 ± 8.9	45.8 ± 11.0	28 ± 6.5	STOPBANG	42 (28♀, 76 ♂)	2
Brass et al. (7)	2,375 (1,917)	Membership list MS society	16.3 ± 10.8	54.7 ± 12.4	>25 in 61%[a]	STOPBANG and Berlin	STOPBANG: 37 Berlin: 37	4
Braley et al. (22)	195 (128)	OPC	10.2 ± 8.2	47.1 ± 12.1	29.6 ± 7.4	STOPBANG	56	21
Ma et al. (33)	231 (135)	OPC	4.9 ± 2.2	40.2 ± 7.8	24.8 ± 4.6	STOPBANG	36	–

[a]*Mean BMI not provided, only percentage of people with BMI above 25 kg/m² is available.*

Patient selection: OPC, outside patient clinic; BMI, body mass index; SDB, sleep-disordered breathing; OSA, obstructive sleep apnea; high risk of OSA, >3 points on STOPBANG questionnaire or 2 positive categories on Berlin questionnaire.

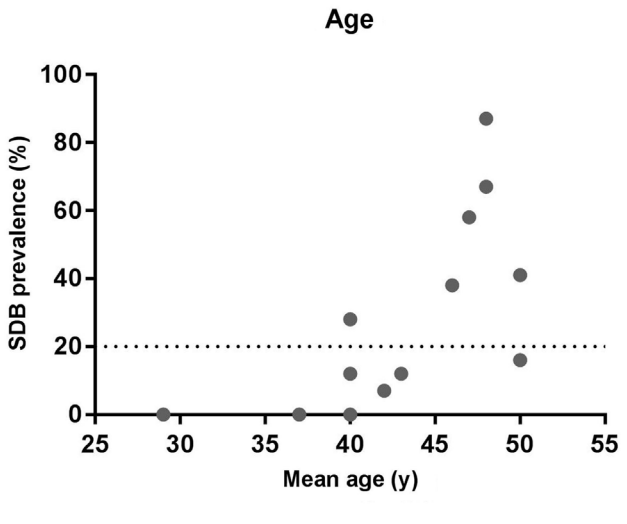

FIGURE 1 | Relationship between sleep-disordered breathing (SDB) prevalence and age. The data show the prevalence of SDB and the mean age from the studies listed in **Table 1**.

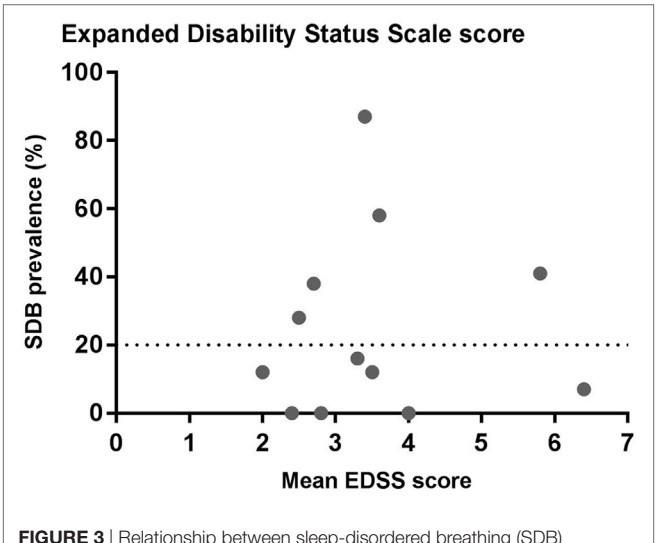

FIGURE 3 | Relationship between sleep-disordered breathing (SDB) prevalence and expanded disability status scale score (EDSS). The data show the prevalence of SDB and the mean EDSS scores from the studies listed in **Table 1**.

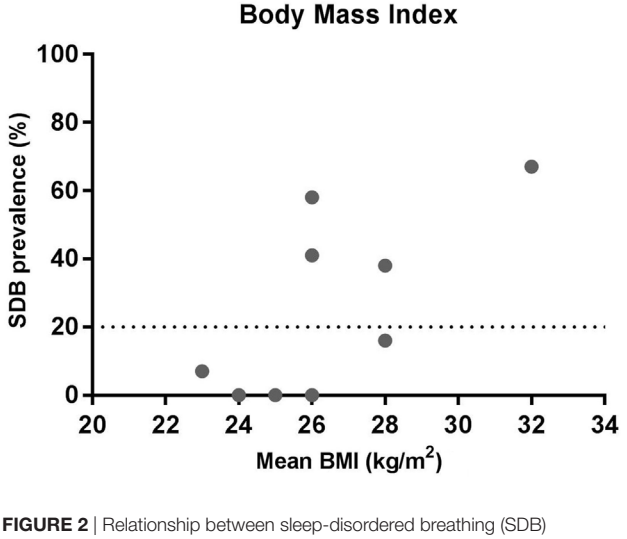

FIGURE 2 | Relationship between sleep-disordered breathing (SDB) prevalence and mean body mass index (BMI). The data show the prevalence of SDB and mean BMI from the studies listed in **Table 1** where BMI was reported.

Nevertheless, it is noteworthy that some studies show such high rates of SDB even though the majority of the study populations are pre-menopausal women.

MS Disability

Multiple sclerosis disability is most commonly measured using the well-established EDSS score. EDSS varies from 0 (normal neurological examination) to 10 (death due to MS) (44) (**Figure 3**). There is substantial variation in mean EDSS scores in the studies that have investigated SBD in MS. There is no clear relationship between the prevalence of SDB and mean EDSS score based on the existing studies (**Figure 3**). However, this does not necessarily mean that MS severity does not influence SDB. The EDSS score is a good measure of clinical and functional disability, but it is heavily weighted toward motor and ambulatory deficits. Its correlation with lesion load and brain atrophy on magnetic resonance imaging (MRI) varies (45, 46). Thus, the extent to which other disease severity measures (e.g., lesion load and brain atrophy on MRI) influences the prevalence of SDB in people with MS is a valuable objective to assess in future studies.

In summary, standard SDB risk factors (e.g., age and BMI) also appear to play a contributing role in people with MS. However, in general, people with MS and SDB tend not to be obese. The extent to which MS specific factors like disability and severity influence the prevalence of SDB is unclear.

PATHOPHYSIOLOGICAL MECHANISMS OF SDB IN MS AND POTENTIAL BIDIRECTIONAL LINKS

In this section, we attempt to address the following key questions: What are the causal pathways of SDB in people with MS? Are they the same as in the general population? How do SDB and MS influence each other?

To further explore these questions, a brief overview of the current understanding of the pathophysiology of SDB (OSA and central sleep apnea [CSA]) in the general population is highlighted below.

Obstructive Sleep Apnea

In OSA, there is an absence of airflow due to collapse of the upper airway, despite ongoing respiratory effort. Apneas and hypopneas are often associated with cortical arousals. The pathophysiological causes of OSA vary markedly between individuals. There are anatomical and non-anatomical contributors. The key pathophysiologic causes are: (1) an anatomically narrow or collapsible upper airway, (2) insufficient upper airway dilator muscle responsiveness during sleep, (3) a low respiratory arousal threshold, and (4) having an oversensitive ventilatory response system (high loop gain) (47–49). Inflammation state can also influence OSA (50, 51).

Major risk factors for OSA are aging, male sex, and obesity. The underlying mechanisms remain largely unclear, although other mediating mechanisms likely contribute *via* the pathophysiological causes highlighted above.

Central Sleep Apnea

In CSA, there is an absence of airflow, without respiratory effort. Thus, in CSA there is a fundamental issue with respiratory control during sleep. Briefly, the primary centers for central respiratory control are based in the pons and the medulla. These centers receive input from a variety of sources within the body including: the cortex (voluntary control), the limbic system (emotional stimuli), stretch receptors in the lungs, receptors for touch temperature and pain, receptors in muscles and joints, peripheral O_2, CO_2, and H^+ chemoreceptors located at the bifurcation of the carotid arteries, and central CO_2 and H^+ chemoreceptors located at ventral surface of the medulla. Most of these inputs are capable to influence breathing during wakefulness, but are absent or decreased during sleep. Chemical control *via* the chemoreceptors is also decreased in sleep. However, it is the key regulator of breathing during sleep (52). There are several manifestations of CSA and the precise pathophysiological mechanisms vary, but in all instances unstable ventilatory drive is the principal underlying mechanism. There are three levels in the control of breathing during sleep where impairment could lead to CSA. There is (1) primary impaired central drive, for example caused by a lesion in the brain stem affecting the respiratory control center, (2) impaired output of central drive due to abnormalities located anywhere from upper motor neurons down to the respiratory muscles, for example caused by neuromuscular dysfunction, or (3) the central drive feedback loop is impaired, for example caused by prolonged blood circulation time in people with heart failure, resulting in a mismatch between arterial blood gas concentrations and respiratory controllers (53). Thus, impairment in one or more of these levels of the control of breathing can lead to CSA.

Bidirectional Relationships

To date, no studies have been conducted to characterize the phenotypic causes of SDB in people with MS. There are several possibilities and potential bidirectional relations that may create a vicious cycle between both disorders as highlighted in **Figure 4**.

MS As a Contributor to SDB

Demyelinating lesions of MS in the brain stem and spinal cord could influence or evoke CSA *via* impairment of ventilatory drive. Lesions in the brain stem may influence primary central ventilatory drive centers directly or key components of the central breathing control feedback loop. Lesions in the spinal cord could also cause impairment of motor neurons that control the respiratory muscles to reduce ventilatory drive output. In accordance with this theory, Braley et al. have shown that the mean apnea hypopnea index and central apnea index of people with brain stem lesions in MS was significantly higher than controls or people with MS without known brain stem lesions (35). Furthermore, in the MS population studied by Lin et al., the only SDB that was detected was CSA and not OSA which is very rare in the non-MS population in the absence of key comorbidities such as heart failure. Other neurological disorders that affect brain stem function such as tumors (54, 55), hemorrhages, ischemia (56, 57), and Arnold-Chiari malformation (58), can also influence or cause SDB. However, in the studies listed in **Table 1**, the majority of people had OSA not CSA. This could be explained, because demyelinating lesions in the brain stem and spinal cord could also result in impaired upper airway muscle responsiveness and an unstable ventilatory response system, both of which contribute to OSA. Thus, demyelinating lesions in the brain stem and spinal cord are potentially important contributors to SDB in MS.

Second, inflammation in MS may also play a role in the occurrence of SDB. MS is an autoimmune disorder associated with changes in cytokine levels (59). How proinflammatory cytokines influence SDB is not known. However, systemic cytokine levels of TNF-a, IL-6, C-reactive protein, IL-1b, reactive oxygen species, and adhesion molecules are increased in people with OSA (50, 60). In MS, levels of TNF-α, IL-6, and IL-1b amongst others are also elevated. Anti-inflammatory therapy with entracept (a TNF α antagonist) can improve OSA severity in the general population (51). This suggests that disease-modifying therapy with anti-inflammatory agents used in MS may also have a beneficial effect on OSA. However, to our knowledge there have been no studies conducted to investigate the potential relationship between inflammation in SDB and MS.

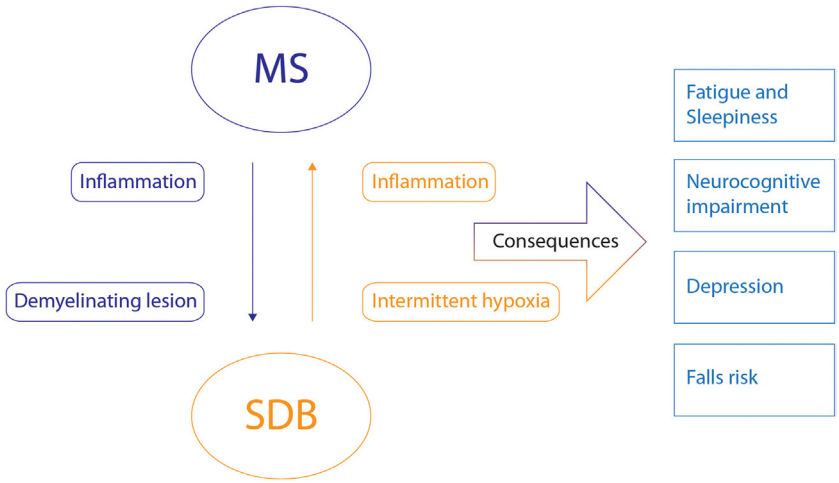

FIGURE 4 | Potential bidirectional relationships between multiple sclerosis (MS) and sleep-disordered breathing (SDB) and their shared consequences. The potential bidirectional pathophysiological relationship between MS and SDB is indicated by the arrows with the corresponding mechanisms. Inflammatory state and demyelinating lesions of MS may induce or influence SDB. Intermitted hypoxia and inflammation caused by SDB may also influence MS. The consequences that these disorders share are indicated on the right. The combination of these disorders will likely negatively influence these consequences.

SDB As a Contributor to MS

As highlighted, chronic inflammation is a feature of both SDB and MS. Thus, the proinflammatory state caused by SDB may interact with the inflammatory process taking place in MS and contribute to disease progression or relapse frequency. However, this theory has not been formally investigated.

The second factor that can play an important role in the progression of MS due to SDB is intermittent hypoxia. One of the potential factors attributed to lesion progression in MS is "virtual hypoxia," which is a state of reduced oxygen consumption and energy failure in conditions of normal blood and oxygen supply leading to cell death. "Virtual hypoxia" is caused by damaged mitochondria, likely attributed to chronic oxidative injury. Inflammation of the brain tissue drives microglia and macrophage activation, resulting in oxidative stress, causing mitochondrial injury, making it a vicious cycle of tissue destruction and energy failure (61, 62). When brain tissue is affected by "virtual hypoxia," additional intermittent hypoxia due to SDB may amplify neurodegeneration. Indeed, studies have shown that there are increased MS lesion loads in the "watershed" areas of the brain and spinal cord, which are areas that are on the boundaries between the blood supply of the cerebral arteries and therefore less well perfused and most vulnerable to reduced blood flow or reduced oxygen. This suggests that hypoxia may play an important role in lesion pathology (63). In addition, animal studies indicate that demyelination can be reduced or eliminated by increasing inspired oxygen to alleviate transient hypoxia (64). This progression of disease due to mitochondrial injury and energy failure is thought to play an especially important role in the progressive phase of the disease. Progressive MS is divided in primary progressive (being progressive from the moment of diagnosis) and secondary progressive (being progressive after the initial relapsing remitting phase). Progressive MS commonly affects the middle aged population (65). This is important since middle aged adults are at high risk of SDB. There are only few treatments available for the progressive phase of the disease and anti-inflammatory drugs yield little improvement (61). Thus, diagnosing SDB and effectively treating SDB to restore oxygenation in the brain may play a pivotal role in slowing progression in this phase of the disease. This is a priority for future research.

SHARED CONSEQUENCES OF SDB AND MS

Sleep-disordered breathing and MS have shared consequences, as shown in **Figure 4**. These consequences may be synergistic if both disorders are present. Important shared consequences include: fatigue/sleepiness, neurocognitive dysfunction, depression, and falls risk. Although not covered in this review, there may also be other shared links between cardiovascular risk, inflammation, SDB, and MS (66–68). Diagnosis and treatment of SDB in afflicted people with MS may help alleviate these common consequences as discussed below.

Fatigue and Sleepiness

Fatigue is a common symptom in MS. Indeed, fatigue is often the most debilitating symptom of MS and has a major impact on quality of life (20, 21, 23, 69). There have been multiple studies on fatigue in MS including various strategies on quantification, its potential origin and treatment. However, the pathophysiology still remains to a large extend unknown. Kos et al. (70) divided fatigue in MS into primary fatigue and secondary fatigue. Primary fatigue may be due to centrally mediated processes, like demyelination in the central nervous system and immune activity. Factors that may influence secondary fatigue are sleeping problems, pain, depression, reduced activity, psychological functioning, and medication use.

It is important to note that fatigue and sleepiness are two distinct but potentially interrelated symptoms that often coexist. Chervin et al. have shown that patients with moderate to severe OSA report problems with fatigue, tiredness, and lack of energy more frequently than sleepiness (57, 61, 62, and 47%) (71). Hossain et al. assessed 283 patients with sleep disorders and in this cohort 64% reported pathological fatigue without overlap of sleepiness and only 4% reported sleepiness without overlap fatigue. This suggests that fatigue and sleepiness can be independent manifestations of sleep disorders (72). The extent to which SDB plays a role in fatigue in MS has been assessed in several studies. Veauthier et al. studied 66 MS patients who underwent PSG and completed the modified fatigue impact scale (MFIS) to quantify fatigue severity. There were eight patients with SDB, of which seven were fatigued, defined as a score > 45 on the MFIS. The people with SDB also had higher scores on the MFIS compared to fatigued people without SDB (25). Kaminska et al. found a relationship between severe OSA (apnea hypopnea index > 30 events/h sleep) and severe fatigue in people with MS. The mean fatigue severity scale (FSS) scores were also significantly higher in people with MS and severe OSA compared to those without severe OSA (17).

In addition, some studies have assessed the risk of OSA, using the STOPBANG questionnaire, and its relationship with fatigue. Dias et al. found a significant correlation in STOPBANG scores and FSS scores in males but not in females (32). Braley et al. demonstrated that OSA is a significant predictor of fatigue when adjusted for other clinical- and sleep-related factors for fatigue (22). Brass et al. demonstrated an odds ratio of a STOP BANG > 3 to having a FSS > 36 is 1.85, consistent with an association between OSA and fatigue (7). Thus, it appears that SDB has a negative effect on fatigue in people with MS.

Fatigue is a very difficult symptom of MS to treat. All current therapies are either ineffective or only partially effective (73). To date, there have only been a few studies to examine whether treatment of SDB improves fatigue in MS. Kallweit et al. treated 6 MS patients with OSA with CPAP therapy for 6 months with a daily average adherence of >5h per night. Measures of sleepiness with the Epworth sleepiness scale (ESS) and fatigue with the FSS were assed at baseline and after 6 months. The apnea hypopnea index decreased from 39 to 5 events/h sleep. ESS scores did not show any significant change (9.8–9.5), but there was a significant decrease in FSS scores from 5.8 to 4.8. However, the FSS score remained pathologic (>4) in all patients (30). Cote et al. also treated MS patients with OSA with CPAP and compared ESS and FSS scores before and after 3 months of therapy. ESS scores decreased significantly with treatment from 8.9 to 5.4 and FSS scores decreased from 5.0 to 4.3. However, this change was not statistically significant (24). Larger studies are needed in people with MS and SDB to quantify the effects of treatment on fatigue in people with MS.

Neurocognitive Dysfunction

In the general population, SDB can result in neuropsychological impairment (15, 74). Changes in brain structure have also been demonstrated in people with OSA and impaired cognitive function using imaging techniques (75, 76). Neuropsychological domains influenced by OSA include: attention/vigilance, executive function, and memory. The ethology of cognitive dysfunction in OSA is believed to be multifactorial with sleep fragmentation and hypoxemia as key contributors. These factors may have similar or greater effects in people with MS. Nocturnal hypoxia in OSA can cause neuroimaging and neuropathological abnormalities in regions of the cortex and axons that are similar to cognitive domains affected in MS (77). There has been only one study conducted to investigate the relationship between cognitive function and OSA in people with MS. Braley et al. assessed 38 MS patients from an outside patient clinic that asked about sleep or cognition during routine visits. Participants were evaluated by a neurologist, neuropsychologist and an overnight PSG was conducted. Cognitive function testing was performed using the validated 90-min battery, minimal assessment of cognitive function in MS. Regression models demonstrated an association between several components of neuropsychological function (attention and working memory) and oxygen desaturation index, minimum oxygen saturation, and respiratory disturbance index. An association between verbal memory and response inhibition and sleep quality parameters was also shown (6). Similar findings have been demonstrated in the general population (78, 79).

Cognitive function in people with MS and OSA could potentially be improved with CPAP therapy. Beneficial effects of CPAP on cognitive performance have been shown in the non-MS OSA population in some (75, 76) but not all studies (74). Given that oxygen levels may play a key role in the decrease in cognitive function, oxygen therapy may also be beneficial, either indirectly *via* reductions in SDB or directly *via* restoration of oxygenation (80). Braley et al. have a randomized controlled trial on the effects of CPAP on cognitive function in MS patients with OSA that is currently underway (NCT02544373). The results will be of great importance to evaluate the potential need for early diagnosis of SDB and the influence of treatment on cognitive function. There are currently few options to improve cognitive function in MS. However, immunomodulatory therapy may slow and reverse MS-related cognitive dysfunction and have a positive effect on OSA severity in MS (81, 82).

Depression

Depression is common in people with MS, with an estimated annual prevalence of 20% and lifetime prevalence as high as 50% (83). Depression is more common in people with SDB compared to the general population. The estimated prevalence of depression in people from the general community who have OSA is between 17 and 22% and in clinical population studies ranges between 21 and 41% (84). For both disorders it is to a large extent unknown what their role is in the causation of depression. However, given the bidirectional relationship between sleep and the brain, it is likely that people with MS who experience sleep disruption due to SDB will be at higher risk of depression.

Falls Risk

Falls frequently occur in people with MS. Several studies have shown that 50–60% of people with MS report falling at least once in a 2- to 6-month period (85–87). Medical care is often required. Important factors that increase the risk of falling in people with

MS are loss of balance, impaired gait, use of a walking aid, leg weakness, visual impairment, reduced cognitive function, and fatigue (88).

There is growing evidence that poor sleep and sleep disorders can increase falls risk in the elderly independent of other factors (89–91). Since factors that increase the risk of falling in elderly are to a large extend similar to the ones in MS (like reduced balance, visual impairment, cognitive decline, and the use of a walking aid), poor sleep might have an equivalent impact on people with MS. In young adults postural sway, a measure of balance, significantly increases after sleep deprivation (92, 93). Excessive daytime sleepiness defined as a score > 10 on the ESS is also an independent risk factor for falls (94). Given that sleepiness is common in people with moderate to severe SDB, sleepiness due to SDB in people with MS may increase falls risk. There have only been a few studies that have examined the relationship between SDB and balance control. A recent study by Degache et al. noted an association between overnight hypoxia and postural instability (95). Two additional studies also showed an altered gait pattern in people with OSA compared to healthy controls (96, 97). The precise mechanism as to how falls risk increases due to poor sleep is unknown, but the combination of MS and SDB may have an additive effect in increasing the risk of falls. Therefore, given that SDB is a modifiable factor, treatment of SDB may reduce the risk of falling in people with MS.

SUMMARY AND FUTURE RESEARCH DIRECTIONS

It remains uncertain how common SDB is in people with MS. However, many of the existing studies indicate that it is quite common despite the female predominance and typical lack of obesity in the MS population. Understanding the mechanisms of SBD in people with MS for which there are multiple plausible possibilities, may provide novel targets for therapy. Given the shared links between the two disorders and supported by several initial studies, improvements in sleep by treating SDB has the potential to reduce the burden of several of the key shared consequences and may also reduce MS disease progression. These are all important topics for future research.

AUTHOR CONTRIBUTIONS

HH drafted the manuscript, and all authors provided important intellectual input and contributed to the final version.

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