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Comparing the effect of hypercapnia and hypoxia on the electroencephalogram during wakefulness

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HIGHLIGHTS

- Hypoxia has been considered as the key mechanism in daytime drowsiness and neurocognitive impairment in sleep-disordered breathing.
- We compared the effect of hypoxia and hypercapnia on EEG spectra during wakefulness using a rigorously controlled experimental method, and found that hypercapnia, but not hypoxia caused EEG slowing.
- These data imply that hypercapnia may be more mechanistically important in neurobiological impairments in sleep-disordered breathing patients.

ABSTRACT

Objective: Hypoxia has been postulated as a key mechanism for neurocognitive impairment in sleep-disordered breathing. However, the effect of hypoxia on the electroencephalogram (EEG) is not clear.
Methods: We examined quantitative EEG recordings from 20 normal volunteers under three 5-min ventilatory control protocols: progressive hypercapnia with iso-hyperoxia (pO_2 = 150 mmHg) (Protocol 1), progressive hypercapnia with iso-hypoxia (pO_2 = 50 mmHg) (Protocol 2), and progressive hypoxia with a CO_2 scrubber in the circuit (Protocol 3). Each protocol started with a 5-min session of breathing room air as baseline.
Results: In Protocol 1, compared to its baseline, iso-hyperoxia hypercapnia led to a lower Alpha% and higher Delta/Alpha (D/A) ratio. Similarly, in Protocol 2, the iso-hypoxia hypercapnia induced a higher Delta%, a lower Alpha% and higher D/A ratio. No difference was found in any EEG spectral band including the D/A ratio when Protocols 1 & 2 were compared. In Protocol 3, the Delta%, Alpha% and D/A ratio recorded during hypoxia were not significantly different from baseline.
Conclusions: We found that hypercapnia, but not hypoxia, may play a key role in slowing of the EEG in healthy humans.
Significance: Hypercapnia may be a greater influence than hypoxia on brain neuroelectrical activities.

1. Introduction

Sleep-disordered breathing (SDB) is a common cause of increased daytime sleepiness and neurocognitive impairment

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which may lead to a 2–3 times increased risk of motor vehicle and occupational accidents (Teran-Santos et al., 1999; Lindberg et al., 2001; Malhotra and White, 2002). Patients with SDB usually have a slower waking electroencephalogram (EEG) which correlates with increased daytime sleepiness and may be corrected by continuous positive airway pressure (CPAP) therapy (Morisson et al., 1998, 2001; D'Rozario et al., 2013). The underlying mechanism of SDB-related daytime drowsiness is unclear. It has been postulated that neurobiological impairments in obstructive sleep apnea (OSA) are a result of a combination of sleep fragmentation and hypoxia. However, the correlation between sleep disruptions measured by apnea and arousal frequency and daytime sleepiness is not robust (Cheshire et al., 1992; Kingshott et al., 1998). SDB is actually characterized by recurrent episodes of both hypoxia and hypercapnia (Dempsey et al., 2010). It has been claimed that it is the intermittent hypoxia that causes daytime sleepiness (Mediano et al., 2007; Dempsey et al., 2010; Canessa et al., 2011; Quan et al., 2011). However, supplemental O_2 therapy does not improve hypersomnolence in OSA patients despite improving oxygenation (Gold et al., 1986; Phillips et al., 1990; Lim et al., 2007). Similarly, there has been a lack of convincing evidence demonstrating that hypoxia alone significantly affects EEG leading to neurocognitive impairment (Kraaier et al., 1988; Van der Worp et al., 1991; Jernajczyk et al., 2006). Hypoxia protocols in previous studies usually lead to concomitant hyperventilation and hypocapnia which can independently affect EEG activity (Burykh, 2008). The potential importance of hypercapnia in sleep-disordered breathing has been neglected partially due to the lack of clinical equipment to reliably measure continuous changes in the arterial CO_2 pressure (pCO_2) during overnight sleep study.

We recently reported increased Slow Wave Sleep (SWS) in 97 patients with respiratory failure with associated high awake arterial CO_2 measurements. Awake pCO_2 measured from arterial blood gas (ABG) sampling in those patients was the best predictor for the increased SWS, while hypoxia related parameters were not related (Wang et al., 2011). Some uncontrolled studies suggest that hypercapnia may cause slowing of the EEG in a dose-dependent manner (Woodbury and Karler, 1960; Matakas et al., 1978; Forslid et al., 1986; Kalkman et al., 1991; Bloch-Salisbury et al., 2000; Halpern et al., 2003; Thesen et al., 2012) and impaired mental and psychomotor function (Hesser et al., 1978; Sayers et al., 1987; Henning et al., 1990; Fothergill et al., 1991). Our recent intervention study demonstrated a significant cross-correlation between a reduced wake pCO_2, a faster sleep EEG (reduced Delta/Alpha ratio) and reduced daytime sleepiness during positive airway pressure treatment in hypercapnic SDB patients (Wang et al., in press). Multiple regression analyses showed that the degree of change in hypercapnia but not hypoxia was the only significant predictor of both the Delta/Alpha ratio and daytime sleepiness (Wang et al., in press). In order to directly compare the generic effect of hypoxia and hypercapnia on EEG, the present study used an experimental design that carefully controlled for the mix of inspired oxygen and carbon dioxide while monitoring EEG activity during wakefulness. Delta/Alpha ratio was the primary outcome of interest.

2. Methods

This experiment was conducted at the clinical sleep laboratory of the Royal Prince Alfred Hospital (RPAH), a major teaching hospital of the University of Sydney. The study protocol was approved by Sydney South West Area Health Service (SSWAHS) Ethics Review Committee (Protocol Number: X11-0325). All participants provided written informed consent. The Australian & New Zealand Clinical Trial Registry number is ACTRN12612000454875.

2.1. Subjects and procedure

The twenty normal volunteers were medical students and staff members from Sydney Medical School/RPAH. They did not have sleep apnea or other medical complaints. All subjects fasted for 3 h prior to the tests. While connected to a two-channel EEG system (C3–A2, C4–A1; Alice 5 diagnostic sleep system, Respironics, USA), they were tested for their ventilatory response to hypercapnia and hypoxia under three standard protocols using a fully computerized testing system (Rebuck and Campbell, 1974; Duffin, 2011). The three rebreathing protocols included testing the EEG responses to (1) hypercapnia plus sustained hyperoxia (Protocol 1) (Duffin, 2011), (2) the combined effect of hypercapnia plus sustained hypoxia (Protocol 2) (Duffin, 2011), and (3) hypoxia with mild hypocapnia induced via a CO_2 scrubber (Protocol 3) (Rebuck and Campbell, 1974). Each of the three protocols started with a 5-min session of breathing room air through a mouth piece connected to the full apparatus. Protocol 1 consisted of a 5-min rebreathing session, measuring the EEG response to hypercapnia with pO_2 held constant at 150 mmHg (hyperoxia). Protocol 2 also included a 5-min rebreathing session, measuring the EEG response to hypercapnia and hypoxia with pO_2 held constant at 50 mmHg (hypoxia). To achieve a stable control of pO_2 for these two protocols, our computer system continuously analyzed O_2 consumption over the previous 3 breaths during the test and used a prediction model to determine how much O_2 to supply to the circuit. Protocol 3 also involved with ~5-min session of rebreathing but with a CO_2 scrubber in the circuit. A 30 min resting break was taken between each protocol. The EEG data were later synchronized with data from the ventilatory response computer. An oximeter was connected to both the ventilatory response computer and the polysomnography (PSG) computer and the oximeter output was recorded simultaneously during each testing session. This channel was also used as a marker for synchronization of the two computers.

2.2. EEG spectral analyses

All EEG recordings were converted to European Data Format (EDF) for the spectral analyses. We analyzed each EEG segment corresponding to each breath cycle because we measured end-tidal pCO_2 breath by breath. To minimize blinking artifact in the EEG we encouraged all subjects to keep their eyes open and stare at a relaxing picture on the wall during each testing session. In addition, we minimized behavioral variability by using subjects as their own control (comparing between sessions). All EEG sampling rates were >200 Hz. The bandpass was between 0.3 and 93 Hz. A standard Fast Fourier Transform (FFT) with a rectangular weighting window was performed twice: first, to the largest power of 2 data points smaller than the total number of data points, selected from the beginning of the segment, and second, to the same number of data points selected from the end. This double FFT method weights middle data points. Delta, theta, alpha and beta bands were defined as the frequency ranges 0.5–4.5 (delta), 4.5–8 (theta), 8–12 (alpha), 12–32 (beta) Hz, respectively. The EEGs were then further examined by an automatic algorithm which excluded EEG segments showing excessive delta power using a standard two sigma rule (i.e., median + 2 standard deviations). For our statistical analyses, we focused primarily on the EEG recorded at C3/A2. However, when the C3/A2 channel was contaminated with many artifacts, we used C4/A1 as an alternative channel. Individual spectral band power and total summed power between 0.5 and 32 Hz were calculated. Spectral band% was calculated as individual band power/total summed power between 0.5 and 32 Hz × 100. Delta/Alpha (D/A) ratio was calculated as delta power/alpha power.

2.3. Statistical analyses

Descriptive data are expressed as mean ± SD, unless otherwise stated. Pair-wise comparisons were tested by paired *t*-test or Wilcoxon signed-rank test depending on whether the data were distributed normally or not. Pearson's correlation coefficient (*r*) was used to test potential correlations. Among the EEG spectral measures, Delta/Alpha ratio was the primary outcome of interest. A *p*-value of less than 0.05 was considered as significant. Analyses were performed using SPSS 17 (SPSS, Chicago, USA).

3. Results

From the 20 healthy volunteers tested, we obtained technically satisfactory data in 19 (9M, 10F) with an average age of 29.7 ± 9.8 years and BMI of 23.2 ± 4.3 kg/m^2.

In Protocol 1, compared to the baseline values, the hypercapnia produced by rebreathing during iso-hyperoxia (150 mmHg) led to a lower Alpha% and higher D/A ratio in the EEG spectra (Table 1). Similarly, in Protocol 2, the hypercapnia produced by rebreathing during iso-hypoxia (50 mmHg) induced a higher Delta%, a lower Alpha% and higher D/A ratio compared to the control session. The only difference between Protocol 1 and 2 was the oxygen level, and no differences were found for any of the EEG spectral bands between these two protocols (Table 1). The Delta%, Alpha% and D/A ratio values recorded during the hypoxia produced during Protocol 3 were not significantly different from the values recorded during the control session. However, there was a higher total summed EEG power and Theta%, and a lower Beta% in Protocol 3 compared to its control session. Those differences were not seen comparing these values between Protocol 1 and 2.

Since the D/A ratio was the primary outcome of interest showing the slowing of EEG, we show the effect of hypercapnia and hypoxia on D/A ratio in Figs. 1 and 2. In Fig. 1, hypercapnia clearly increased the D/A ratio in both Protocols 1 and 2. By contrast, we did not find an effect of hypoxia on D/A ratio (Protocol 3, and the comparison between Protocol 1 and 2). In Fig. 2, there was a linear increase in D/A ratio with time under rebreathing hypercapnia in both Protocol 1 and 2 (both $p < 0.001$). In Protocol 3, D/A ratio did not change with either time ($p = 0.88$), or decreased SpO_2 ($p = 0.91$) under rebreathing hypoxia. A raw EEG example under the 3 protocols was demonstrated in Fig. 3.

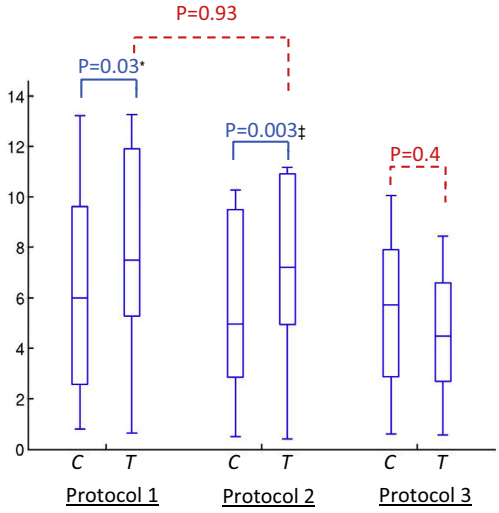

Fig. 1. Box and Whisker Plot of hypercapnia and hypoxia effects on Delta/Alpha ratio of EEG. *C* = Control sessions by breathing room air, *T* = Testing sessions. Protocol 1 Test: response to hypercapnia with pO_2 held constant at 150 mmHg (hyperoxia). Protocol 2 Test: response to hypercapnia with pO_2 held constant at 50 mmHg (hypoxia). Protocol 3 Test: response to hypoxia with CO_2 controlled by a scrubber. Two dashed bars (– – –): compare the effect of hypoxia on D/A ratio, no significant difference was found. Two solid bars (——): compare the effect of hypercapnia on D/A ratio, both showing significant effect. The bottom and top of the box indicates the upper and lower quartile range (IQR) and the middle bar indicates the median value. The whiskers indicate the highest and lowest value after excluding the outliers (>1.5 IQR of the upper and lower quartile). $^*p < 0.05$; $^‡p < 0.005$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

Our controlled experimental data demonstrate that hypercapnia but not hypoxia causes EEG slowing (increased Delta/Alpha

Table 1
Comparisons of EEG spectral under three hypercapnia and hypoxia protocols.

	Protocol 1		Protocol 2		Protocol 3	
	Control	Hypercapnia Iso-hyperoxia	Control	Hypercapnia Iso-hypoxia	Control	Hypoxia
Total-power, μV^2	41.4±13.7	42.2±17.3	45.2±14.2	45.8±16.4	42.6±14.7	55.8±23.4§
Delta%	58.7±12.8	60.5±14.9	54.7±14.2	59.2±15.6*	54.5±13.6	55.0±13.4
Theta%	9.1±2.3	8.8±1.9	9.8±3.1	9.3±2.5	9.8±3.0	11.6±5.3*
Alpha%	12.2±7.3	9.8±5.6†	14.4±8.9	10.8±7.5**	13.9±7.8	14.3±6.3
Beta%	20.0±8.8	21.0±12.4	21.1±10.2	20.7±11.1	21.8±9.5	19.1±7.9*
D/A ratio	7.9±4.1	9.2±4.5*	6.9±3.7	9.2±5.2‡	6.6±3.9	6.0±3.5
pCO_2, mmHg	36.4±4.5	46.1±3.4	36.7±5.0	47.3±4.0	37.0±4.3	34.5±4.0
pO_2, mmHg	114.2±7.8	150.2±2.9	114.3±8.0	55.9±2.3	112.6±6.6	46.9±2.3

Figures in the table are means and SDs. Cells with shadow indicate significant *p* values compared to each control session at $^*p < 0.05$; $^†p < 0.01$; $^‡p < 0.005$; $^§p < 0.001$; $^{**}p < 0.0001$. D/A ratio is the primary outcome of interest. Spectral band% was calculated as individual band power/total summed power between 0.5 and 32 Hz × 100. No significance at $p < 0.05$ was found for any spectral band comparison between the Protocol 1 and 2 intervention sessions. No statistical difference was found between the three control sessions in any spectral parameter.

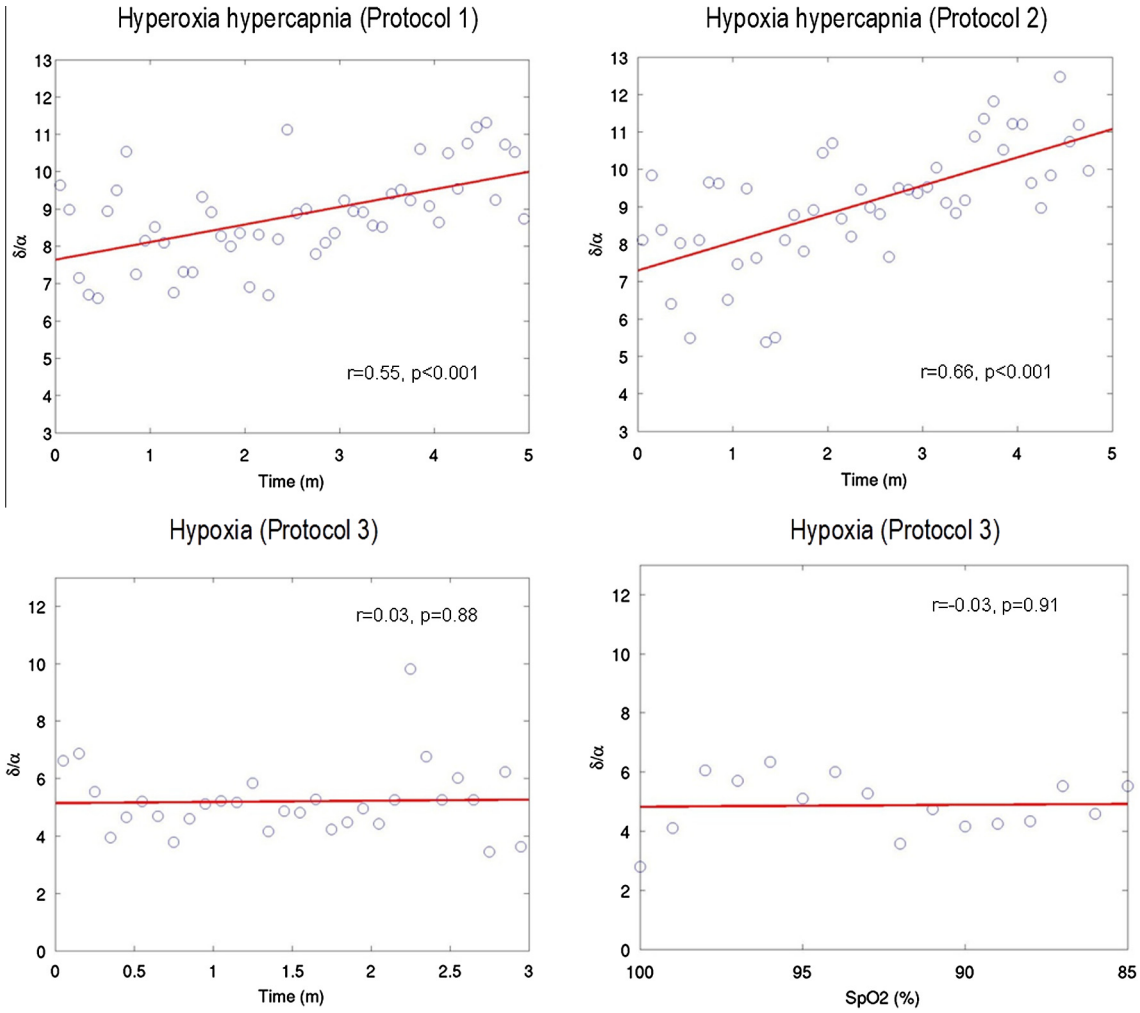

Fig. 2. Average Delta/Alpha ratio change with time under Protocol 1, 2 and 3 in 19 subjects. Pearson's correlation coefficient (r) was used to test the relationships. In the bottom right panel (Protocol 3), each dot represents 1% drop in SpO_2.

ratio). This findings support our latest clinical data showing that hypercapnia might be a key mechanism for EEG slowing and subsequent impairments in waking function, such as daytime sleepiness, in patients with SDB (Wang et al., in press). Certainly our experimental data question the view that hypoxia is the dominant mechanism causing EEG slowing in SDB (Mediano et al., 2007; Dempsey et al., 2010; Canessa et al., 2011; Quan et al., 2011).

Compared to the control sessions, hypercapnia in both Protocols 1 and 2 caused an overall slowing of the EEG (Figs. 1 and 2). We observed that hypercapnia caused increased Delta activity, decreased Alpha activity and increased D/A ratio (Table 1, Figs. 1 and 2). In contrast, hypoxia had no effect on the D/A ratio within Protocol 3 or in the comparison between Protocols 1 and 2 (Table 1, Figs. 1 and 2). The within Protocol 3 comparison suggested that the total summed spectral power and Theta% were increased and Beta% was decreased by hypoxia compared to the control session (Table 1). However, those differences were not observed when comparing Protocol 1 and 2. Protocol 1 and 2 were tested under identical experimental conditions except for the difference in the sustained oxygen level; a more controlled model compared to the comparison within Protocol 3. In Protocol 3, we used a CO_2 scrubber in the closed circuit to keep CO_2 constant while testing the effect of hypoxia. The average pCO_2 during the hypoxia test is ~3 mmHg lower than during the control session (Table 1). The mild hypocapnia itself may cause slowing in EEG which may confound the interpretation of our results (Van der Worp et al., 1991; Halpern et al., 2003). Interestingly, the EEG pattern seen in Protocol 3 is very similar to that of neurogenic pain patients – usually with increased total EEG spectral power and the dominant peak shifted towards lower frequencies (Theta range), which often indicates low-threshold calcium spike bursts in the somatosensory thalamus (Lenz et al., 1989; Sarnthein et al., 2006). We therefore suspect that the differences observed within Protocol 3 may be mostly due to the progressive hypoxia related mental stress/fear of pain/panic and/or mild hypocapnia (Table 1).

In the present study, we used the Delta/Alpha ratio as an objective marker of EEG slowing, which we found to be correlated to the change of daytime sleepiness in our latest clinical study (Wang et al., in press). Indeed, the Delta and Alpha bands were the two major bands affected by the hypercapnia in this study (Table 1). We used the D/A ratio to avoid the misinterpretation of an increased Delta power purely caused by a global, frequency independent, increase in EEG power. Ratios of slow and fast EEG frequency bands are commonly used in neurological studies to indicate changes in activation/deactivation of the EEG (Morisson et al., 2001; Moraes Wdos et al., 2006; Finnigan et al., 2007; Susmakova and Krakovska, 2007). D/A ratio has been previously identified as the best discriminator between wake, and Stage 1, 2 and SWS sleep (Susmakova and Krakovska, 2007), and the best brain bio-marker correlating to the clinical outcomes of sub-acute ischemic stroke (Claassen et al., 2004; Finnigan et al., 2007; Finnigan and van Putten, 2013).

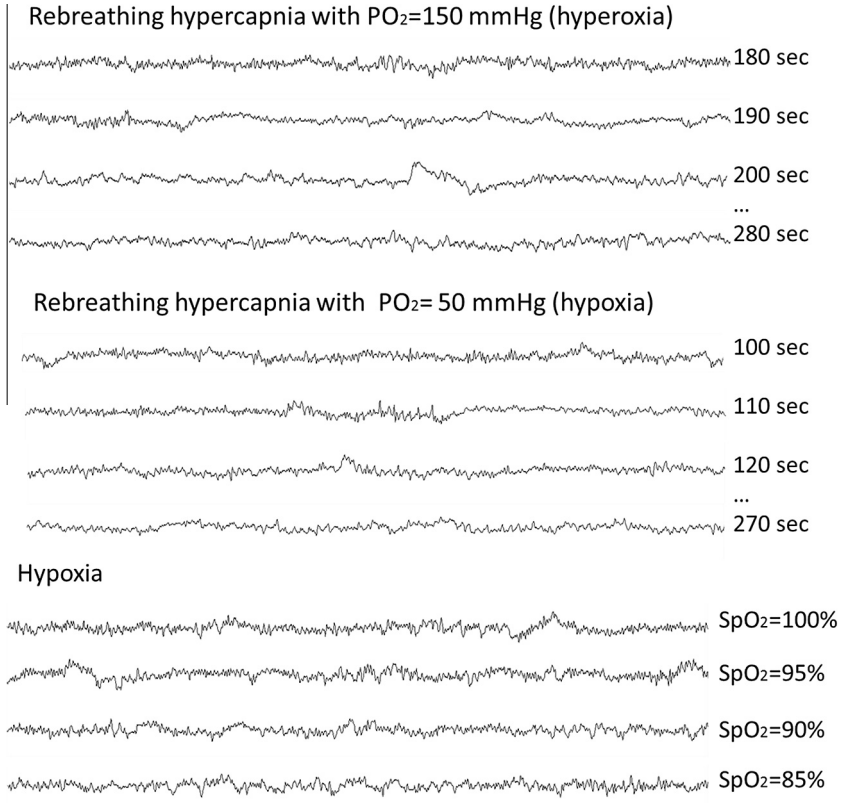

Fig. 3. An example of EEG traces (C3/A2, 10 s/epoch) under Protocol 1, 2 and 3. The bandpass for this example was between 0.3–35 Hz.

Although hypoxia has been considered as a key determinant in causing the neurocognitive symptoms of SDB (Mediano et al., 2007; Dempsey et al., 2010; Canessa et al., 2011; Quan et al., 2011), there has been a lack of well-controlled experimental evidence directly demonstrating EEG changes with hypoxia (Kraaier et al., 1988; Van der Worp et al., 1991; Jernajczyk et al., 2006). Since the 1930s, there have been several animal and human studies investigating the effect of hypoxia on EEG which have produced conflicting findings such as slowing of EEG, no effect on EEG or enhancement of beta activity (Davis et al., 1938; Kraaier et al., 1988; Van der Worp et al., 1991; Jernajczyk et al., 2006; Burykh, 2007). Major problems with extant studies are that CO_2 and stress were not controlled. Hypoxia protocol-related hyperventilation usually leads to hypocapnia, and hypocapnia itself can lead to vasoconstriction and slowing of the EEG (Burykh, 2008). A typical example of studies reporting EEG slowing was a study that investigated EEG during the conditions of hypobaric normoxia and hypoxia (Kraaier et al., 1988). They found that hypobaric normoxia did not change EEG spectra, while hypobaric hypoxia led to a significant increase in slow activity and decrease in alpha activity. However, the pCO_2 also dropped from ~43 to ~36 kPa during the hypoxia session which may have explained their findings (Kraaier et al., 1988). Subsequently, the same research group compared the effect of hyperventilatory hypocapnia and progressive hypoxia on EEG power spectra. They found that hyperventilatory hypocapnia caused an exponential increase in slow wave activity and a decrease in alpha power. In contrast, hypoxia with SpO_2 as low as 60% led to a much less pronounced increase in slow wave activity, and lesser degrees of hypoxia had minimal effect on EEG spectra (Van der Worp et al., 1991). Similarly, Jernajczyk et al. did not find any major change in EEG spectra with hypoxia up to 75% in SpO_2, but found that anxiety substantially altered EEG with a novel EEG complexity measurement (Jernajczyk et al., 2006). The present study compared the effect of hypoxia by comparing Protocol 1 and 2, which have rigorously controlled the potential confounding effects of CO_2 (only ~1 mmHg difference between the two protocols, Table 1) and anxiety (identical procedures between the two protocols).

Our hypothesis that hypercapnia affects cerebral neuro-electrical activity is supported by additional experimental animal and human studies. Acute or chronic hypercapnia leads to the slowing of EEG in eels (Barthelemy et al., 1977), rats (Forslid et al., 1986), rabbits (Matakas et al., 1978), dogs (Smith et al., 1994) and monkeys (Zappe et al., 2008). After 30 s of 80% CO_2, EEG traces in rats were dominated by slow waves (Forslid et al., 1986). Similarly, a strong tendency toward a reduction of neuronal activity was found with CO_2 inhalation of only 3% (pCO_2 = 45 mmHg) in 3 monkeys (Zappe et al., 2008). In a chronic hypercapnia model of 13 rabbits over an eight-week period, arterial CO_2 increased to 60 mmHg and mean EEG frequency decreased by 10 Hz (Matakas et al., 1978). The authors proposed that the slowing of EEG and the accompanying behavioral change may signal a depression in vital activities caused by chronic hypercapnia (Matakas et al., 1978). Some uncontrolled human studies have also suggested that hypercapnia may lead to slower EEG activity with decreased alpha and beta activity (Woodbury and Karler, 1960; Kalkman et al., 1991; Bloch-Salisbury et al., 2000; Halpern et al., 2003; Thesen et al., 2012) and increased delta activity (Halpern et al., 2003). A recent study tested the effects of mild hypercapnia (5% CO_2) on magnetoencephalogram (MEG), event-related potentials (ERP), auditory pattern recognition, and visual semantic tasks in 7 healthy volunteers (Thesen et al., 2012). Hypercapnia attenuated evoked and spontaneous MEG spectral activity. In addition, comparable decreases were observed in early sensory components in both auditory and visual modalities as well as cognitive components related to memory and language, and the depressant effects were

distributed across all cortical regions (Thesen et al., 2012). Similarly, a few experimental studies reported dose–response relationships between higher CO_2 tensions and impaired cognitive and psychomotor performance (Hesser et al., 1978; Henning et al., 1990; Fothergill et al., 1991). In addition, breathing of CO_2 was reported to attenuate sensory and affective components of experimental ischemic pain and produced a dose-dependent elevation of heat pain threshold (Gronroos and Pertovaara, 1994). As an anesthetic agent 80% CO_2 is commonly used as a porcine stunning method to produce unconsciousness before slaughtering; hypoxia does not produce a similar anesthetic effect (Erhardt et al., 1989; Hartung et al., 2002).

Given these data and our study, exposure to sustained hypercapnia or possibly even brief bursts of intermittent hypercapnia in sleep-disordered breathing may produce drowsiness/neurocognitive impairment secondary to reduced brain neuro-electrical activation and overall depression of cortical activity. The cortical depression from hypercapnia has been suggested to reflect a homeostatic mechanism by which neuronal activity is adjusted to a level that can be sustained by available blood flow (Thesen et al., 2012). Animal evidence suggests that the depressive effects may be mediated by pH modulating presynaptic adenosine receptors (Dulla et al., 2005), or via lower local brain temperature caused by higher cerebral blood flow (CBF) rates transferring away heat (Moore and Cao, 2008). However, an interesting paradox is that while both hypercapnia and hypocapnia can slow down EEG activity, they have potent yet opposite effects on cerebral vascular dilation and blood flow. It is therefore unlikely that CBF plays a major role in the effect of CO_2 on the EEG (Halpern et al., 2003; Xu et al., 2011). The effect of hypercapnia on EEG is more likely due to a change in brain metabolism or a direct "anesthesia" like brain neuroelectrical effect (Halpern et al., 2003; Fukuda et al., 2006; Xu et al., 2011). A typical example is that inhalation of 5% CO_2 increased CBF, while suppressed cerebral metabolic rate, decreased neural activity measured by functional magnetic resonance imaging (fMRI), and slowed down EEG activities (Xu et al., 2011). Increased CO_2 levels may cause the brain to reduce metabolism and spontaneous neuroactivity, and enter a lower arousal state (Xu et al., 2011).

Our study has some limitations. First, the hypoxia effect within Protocol 3 needs to be interpreted carefully. The concomitant mild hypocapnia in the hypoxia protocol may also affect EEG activity. Second, we mainly used EEG channels of C3/A2 and C4/A1 for spectral analyses as a standard setting in a clinical sleep laboratory. However, hypoxia may be associated with EEG spectral differences in different areas of the cortex because of differences in sensitivity to oxygen insufficiency (Burykh, 2007). Further studies with comprehensive EEG placement are needed to fully describe the effects of hypoxia and hypercapnia. Third, the levels of hypercapnia and hypoxia in the present study were not profound because we aimed to simulate typical SDB severity. Given the above limitations, we do not want to exclude the possibility that severe hypoxia outside the range we tested might alter EEG activity. Forth, although we consider "D/A ratio" as the primary outcome of interest, we did perform multiple comparisons for individual spectral band in Table 1 which may increase the chance of Type 1 error. This factor needs to be considered when interpreting our results. Fifth, although we conducted this experiment to support our recent clinical findings, the results from acute effects on healthy subjects during awake may not be simply extrapolated to chronic SDB patients during sleep and subsequent waking. The potential "generic" effects have to be interpreted carefully. Further studies using neuro-metabolic imaging and neuro-cognitive performance assessments during hypercapnia/hypoxia are needed to clarify the relationship between hypercapnia/hypoxia, EEG spectral profile and neuro-cognitive impairment.

In conclusion, we found that hypercapnia but not hypoxia caused EEG slowing which may signal a depression of cortical neuroelectrical activity. This implies that hypercapnia might be more relevant than hypoxia in the neurocognitive impairments in sleep-disordered breathing patients.

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