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One Week of Exposure to Intermittent Hypoxia Impairs Attentional Set-shifting in Rats

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Abstract

Intermittent hypoxia (IH), a characteristic of sleep apnea, was modeled in Fischer Brown Norway rats (10 h/day for 7 days) followed by cognitive testing in an attentional set-shifting task. The ability to shift attention from one sensory modality (e.g., odor) to another (e.g., digging medium) was impaired, a finding that could not be attributed to deficits in attention, discrimination, learning, or motor performance. Instead, the deficit is likely to reflect impaired allocation of attentional resources of the working memory system.

Keywords

attention; hypoxia; sleep apnea syndromes; discrimination learning; animal models

Intermittent hypoxia (IH) and sleep fragmentation are primary characteristics of the sleep apnea syndromes. Adult patients with sleep apnea typically exhibit excessive daytime sleepiness, mood disturbances, and impaired cognition (Roehrs et al., 1995). Evidence suggests that both IH (Row, 2007) and sleep fragmentation (Thomas et al., 2005) may contribute significantly to the observed cognitive deficits. Impaired memory has been observed in humans diagnosed with sleep apnea (Bedard et al., 1991), as well as in laboratory rats exposed to IH to model sleep apnea (Gozal, Daniel, and Dohanich, 2001). While spatial memory deficits in rodents have been repeatedly observed following IH (See Row, 2007 for a review), fewer attempts have been made to model the deficits in executive functioning commonly seen in apneic patients.

In the present study, laboratory rats were tested in an attentional set-shifting task following one week (10 h/day for 7 days) of exposure to IH. The task used here was developed by Birrell

and Brown (2000) to provide a rodent-appropriate version of the human intradimensional/extradimensional (ID/ED) shifting task (Owen et al., 1991), a test similar in method and purpose to the more familiar Wisconsin Card Sorting Test (WCST) for humans. The rationale for employing the attentional set-shifting task is based on evidence of dysregulation of inputs to the prefrontal cortex (PFC) in humans diagnosed with sleep apnea (Thomas et al., 2005; Yaouhi et al., 2009; Macey et al., 2008).

The PFC is well known to play a central role in “executive functioning,” a term which refers here to the parceling out of attentional resources in response to changing environmental demands by components of the working memory system, which holds information on-line for immediate use (Baddeley, 1992). Studies employing positron emission tomography (PET) have shown that extradimensional shifting activates the dorsolateral PFC in humans (Rogers et al., 2000). Furthermore, humans who have sustained damage to the PFC exhibit impaired performance on problem solving tasks that require the subject to shift attention from one rule to another (Owen et al., 1991). In rats, lesion studies have demonstrated a key role for the medial PFC in attentional set-shifting (Birrell and Brown, 2000). The present study evaluated the performance of rats on the ID/ED attentional set-shifting task following exposure to one week of IH (10 h/day for 7 consecutive days).

Fourteen adult male Fischer Brown Norway F1 rats (252–274 g; Harlan Laboratories, Ltd.) were first habituated to the custom designed cages ($l \times w \times h = 35.5 \text{ cm} \times 22.8 \text{ cm} \times 20.3 \text{ cm}$) with room air being infused into the chamber through two alternating air sources in order to mimic the experimental conditions of alternating flow rates of N₂ and normal air described below. The habituation period to room air lasted for 48 h prior to the IH exposure. Rats were exposed to the IH protocol for 10h/day (from 2pm to midnight) for 7 consecutive days (lights on at 8 AM, off at 8 PM). With this IH exposure schedule, the morning hours were available to habituate the rats to the ID/ED task apparatus (days 1 & 2) and to shape the rats to find food pellets buried in terra cotta pots (3 to 5 shaping sessions occurred on days 1 to 6; see McCoy et al. 2007 for details). On the morning of day 7, the rats experienced exemplar training to acquaint the animals with the possible reward-response contingencies of the task (McCoy et al. 2007), and then were returned to the IH cages for the final 10 hours of IH exposure. The formal ID/ED task occurred on the morning of day 8.

The IH regimen is a modified version of the protocol originally developed (Gozal et al., 2001) and previously described by us (Ward et al., 2009). The custom designed cages restricted airflow and were designed to allow the cage O₂ levels to be systematically varied. Infused gas cycled inside the cage from room air (21% O₂ at 11 L/min for 60s) to nitrogen rich air (6% O₂ at 8L/min for 60 s). Cage O₂ levels were measured via an oximeter. Thus, rats were exposed to environmental oxygen on a schedule that produced hypoxia with a similar frequency observed in typical human with sleep apnea (30 hypoxic episodes/h); in rats this IH regimen does not significantly alter sleep after the first 24h of exposure (Gozal et al., 2001). The resultant hypoxemia that mimicked the blood O₂ de-saturation typical of sleep apnea (70 to 75% O₂ de-saturation relative to normal blood O₂ using methods previously described by McGuire et al. (2002). This exposure produced at least 20 s of inspired air levels below 10%, followed by 60 s of normal air, which produced at least 20 s of inspired air levels above 18% O₂. Rats had free access to water in the cages. Air control rats lived in a similar cage with identical flow rates of room air infusion (11 L/min for 60 s and 8L/min for 60 s).

The attentional set-shifting task and food restriction procedure for rats has been described in detail previously (McCoy et al., 2007; Birrell and Brown, 2000). Rats were ordered weighing 220 g, allowed food *ad libitum* until they reached at least 250 g. Each rat had an initial body weight between 250 and 275 g at the start of the food restriction protocol. Rats were then given 12 g of dry food pellets per day until they reached 90% of their initial body weight (typically

9 to 14 days of food restriction). Rats were weighed daily and rats that went below their 90% threshold were given additional daily food. Food restriction continued during the 7 days of IH and rats were fed 12 g food per day prior to the daily IH exposure (~1:00p.m.). Rats obtained additional food in the habituation, shaping, and ID/ED experimental procedures. Body weight relative to each rat's initial body weight on the last day of the study ranged from 89.5 to 93% (mean = 90.6%). Rats appeared healthy and groomed normally throughout the course of this experiment suggesting that stress or other non-specific effects of combining IH exposure and moderate food restriction were unlikely to produce the specific behavioral impairments observed.

Rats were trained to discriminate between two terra cotta pots to obtain a small food reward (~0.05–0.15 g bit of rat chow) for each correct response. The pots were placed within the goal box portion of the test apparatus, a large, clear plastic box (16 cm tall, 90 cm long, and 44 cm wide). An opaque, removable divider separated the goal box from the remainder of the apparatus, which functioned as the starting point for each rat. Testing in the set-shift apparatus was conducted during the lights on phase. The task involved 2 pairs of stimuli to be discriminated. Each discrimination was represented by the pair of pots (Table 1). One pot was deemed the “correct” choice, based on either digging medium (e.g., different color paper, beads, etc. that filled the pots) or odor (i.e., scented oils applied to the rim of the pots). See McCoy et al. (2007) for a list of the specific digging media and odors that were used. To prevent rats from using olfactory cues to signal the correct pot, a small amount of powdered food was placed in the incorrect pot.

Following habituation and shaping (see McCoy et al., 2007 for details), animals were tested in the following series of discrimination tests: simple discrimination, compound discrimination, reversal 1, intradimensional shift, reversal 2, extra-dimensional shift, reversal 3. For each discrimination test, animals were required to reach a criterion of 6 consecutive correct responses (referred to as “trials-to-criterion”) before moving on to the next discrimination. A correct response was determined by direct observation of digging in the pot containing the reinforcement. Prior digging in the unrewarded pot constituted an incorrect response and ended the trial. In the simple discrimination, one of the two dimensions (e.g., odor in Table 1) were held constant while the other was varied (i.e., brown versus white paper) with one of the two (e.g., brown) being reinforced. In the complex discrimination, both dimensions were varied, but only one dimension was relevant and reinforced. Thus, rats learned to discriminate between stimuli within the relevant dimension (e.g., digging medium) while disregarding the other dimension (e.g., odor). For reversals, the previously unattended stimulus was now reinforced (e.g., white paper). For the intradimensional shift, animals were required to apply the previously learned rule regarding which stimulus dimension predicts reward to two novel stimuli (see Table 1). For the extradimensional shift, animals were required to shift their attention away from the previously reinforced stimulus dimension (i.e., digging medium) to the previously irrelevant dimension (i.e., a specific odor is now reinforced). The literature indicates that the extradimensional shift is the component that is most susceptible to disruption, with deficits on the ED shift observed following numerous manipulations, including brain lesions, sleep manipulations, pharmacological treatments, etc. (see Danet et al. 2008 for review).

Behavioural performance on the ID/ED task was analyzed using one-way analyses of variance (ANOVA) for independent groups (i.e., IH-exposed and room air controls). A separate one-way ANOVA was conducted for each of the 7 discrimination tests of the attentional set-shifting task. All analyses were performed using SPSS (Version 12) for Windows.

Following 7 consecutive days (10 h/day) of IH, a selective impairment was found in the extradimensional shift component of the ID/ED attentional set-shifting task ($F_{(1,12)}=19.15$,

$P=0.001$). IH-exposed animals required an average of $17.9 (\pm 1.3)$ trials to reach criterion, while room air controls reached criterion in only $10.3 (\pm 0.9)$ trials. This equates to nearly a 58% increase in trials required to reach criterion when making an extra-dimensional shift (see Figure 1). There were no impairments on any of the other phases of the ID/ED task.

The intermittent hypoxia (IH) paradigm employed in the present study was adapted from the protocol used by Gozal and associates (2001) to model the episodic occurrence of hypoxia which characterizes the sleep apnea syndromes. We have previously reported that 3 d of IH (10 h/day) impaired spatial learning of rats in the Morris water maze (Ward et al., 2009). We now report additional impairments in attentional set-shifting following a longer duration of IH (7 days for 10h/day). Since significant differences were not found on the intradimensional shift component, the observed impairment cannot be interpreted as a general deficit in the ability to solve new discrimination problems. A general deficit in attention, cognition or motor performance is also unlikely, as general deficits would have affected multiple components of the ID/ED task. The lack of an effect on reversal learning rules out the possibility that animals exposed to IH might merely be perseverating. Rather, one week of exposure to IH specifically impaired the ability of rats to shift attentional set from one sensory modality (e.g., odor) to another (e.g., digging medium). This selective finding suggests that IH impairs the allocation of attentional resources of the working memory system that are associated with the concept of executive function and the pre-frontal cortex.

It is of interest that both 24 h of sleep fragmentation (McCoy et al., 2007) and the 7 days of IH exposure used herein produce very similar and specific deficits on the ED shift component of the ID/ED task. The severity of the impairment was similar in both groups of experimental animals with rats exposed acute (i.e., 24 h) sleep fragmentation requiring nearly as many trials to reach criterion (15.4 trials) as the rats exposed to one week of IH in the present study (17.9 trials). We hypothesize that this is because both acute sleep disruption and sub-chronic IH exposure interfere with the function of forebrain structures that are involved in the allocation of the working memory resources needed to perform the ED shift in the ID/ED attentional set shifting task.

While the only significant IH-induced impairment occurred on the extradimensional shift in the present study, an overall trend toward diminished performance (i.e., more trials to reach criterion in IH-exposed animals) is noticeable across almost all components of the ID/ED task. Our preferred explanation for this trend is that IH-exposed animals were noticeably hyperactive during the test session, making it more difficult to focus attention on the task at hand. For example, IH animals often attempted to jump out of the test apparatus, whereas control animals exhibited no such behaviour. Our observations are consistent with reports of enhanced locomotor activity (Decker et al., 2003,2005;Row et al., 2002) and executive dysfunction (Decker et al., 2003) in rats following IH exposure. In these studies, rats were exposed to IH during critical early developmental periods in order to model hyperactivity and attentional deficits noted in children with obstructive sleep apnea, or other forms of sleep disordered breathing (Hallbower and Mahone, 2006). We now report executive dysfunction and hyperactivity (although this was not quantified herein) in rats exposed to IH at a mature age (approximately 100–150 days).

The capacity to disregard the originally relevant dimension, and attend to a new (formerly irrelevant) dimension is considered an executive function of the nervous system. Converging evidence strongly suggests that the PFC plays an important role in executive processes not only in human (Owen et al., 1991) and nonhuman (Dias et al., 1997) primates, but also in laboratory rats; thus, lesions to the medial PFC in rats have been shown to impair extradimensional shifting on the ID/ED task (Birrell and Brown, 2000). Changes in frontal lobe perfusion (Alchanatis et al., 2004) as well as deficits in executive functioning (Fulda and

Schultz, 2003) have been documented in humans diagnosed with obstructive sleep apnea including attentional set-shifting (Wong et al., 2006) and working memory (Thomas et al., 2005). These deficits are associated with a disproportionate impairment of function in the dorsolateral prefrontal cortex (Thomas et al., 2005). Specifically, a meta-analysis revealed the most profound cognitive impairments in sleep-disordered patients to be those that involve functions of the PFC. These functions include sustained attention and working memory tasks that require mental flexibility, such as the WCST (Fulda and Schultz, 2003). Thus, dysregulation of the PFC in humans diagnosed with sleep apnea is thought to underlie, at least in part, the impaired cognitive and executive functioning observed in these patients. However, contrary to these reports of deficits, a recent report on healthy adult humans exposed experimentally to four weeks of IH revealed no significant effects on alertness, vigilance, or working memory (Weiss et al., 2009).

The mechanism(s) underlying the IH-induced attentional deficit is presently unknown. Chronic intermittent hypoxia has been shown to induce oxidative stress and neuronal apoptosis (Xu et al. 2004). Certain brain regions, such as the hippocampus and cerebellum, are known to be more sensitive to (the after-effects of) hypoxia than others (Cervos-Navarro and Diemer, 1991). Task-related activations might also render additional brain regions sensitive to such effects. Another possibility involves basal forebrain cholinergic projections to the PFC. Fourteen days of IH in rats resulted in working memory impairments, along with reductions in choline acetyltransferase in the medial septum and the substantia innominata, as well as increases in nicotinic cholinergic binding sites in the PFC (Row et al., 2007). Whether the attentional effects of IH might also be mediated by cholinergic mechanisms remains an open question.

There is some possibility that the effects observed herein are the result of disruptions in sleep, which have been documented following chronic IH in mice (Veasey et al., 2004; Plotsky et al., 2006). Although sleep disruption has also been demonstrated in rats during the first day of IH, sleep has been found to be normalized after the first day of exposure in rats (Gozal et al., 2001, and our unpublished observations). More importantly, in the present study, rats were only exposed to 10h/day of IH, followed by 12 to 14 hours of normoxia allowing sleep without the potential disruptions caused by the IH procedure (air flow noise; changes in oxygen level); this daily period of normoxia always immediately preceded any training or testing in the ID/ED task. Therefore, it is unlikely that the behavioral impairments observed herein are due to sleep disruption. However, sleep recordings, suggested as a future direction, are needed to be 100% certain that the IH regimen used herein does not disrupt sleep.

The deficit reported in rats in the present study should also be viewed with some caution as deficits in the ED shift component of the ID/ED task have been reported following a variety of manipulations (e.g., sleep fragmentation, brain lesions, pharmacological manipulations). Thus, a lack of behavioral specificity for each component of the ID/ED task is a potential concern. However, selective deficits on specific ID/ED task components have been reported by others (McAlonan and Brown, 2003; including an elegant series of experiments by Morilak and colleagues demonstrating bidirectional control of different elements of the ID/ED task by using medial prefrontal cortex microinjections of noradrenergic agonists and antagonists (Lapiz et al., 2006). To address this issue the findings of the present study need to be investigated using neurobiological methods, such as lesions or injections of drugs in specific brain regions.

In summary, exposure to IH (10 h/day for 7 consecutive days) impaired attentional set-shifting in young adult male rats. Additionally, a trend towards diminished performance was noted on the ID/ED task, presumably due to hyperactivity observed in IH animals only. The IH protocol used here produced behavioural effects similar to those which characterize sleep apnea in

humans. Finally, the ID/ED attentional set-shifting task provides a useful method to assess central executive function, and its underlying neural mechanisms, in rodents.

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Figure 1.

Exposure of rats to intermittent hypoxia 10 h per day for 7 consecutive days selectively impairs performance on the extradimensional shift (ES) discrimination of the ID/ED attentional set-shifting task. Data are expressed as the mean ($\pm$ SEM) trials-to-criterion (Y axis) which represents the number of trials required to meet the criterion of 6 consecutive correct responses on each of the 7 discriminations labeled on the X axis, for animals assigned to one of two conditions: room air control (RA; N=6) and intermittent hypoxia (IH; N=8). Discrimination problems (see text for brief description; McCoy et al., 2007 for detailed description) include simple discrimination (SD), compound discrimination (CD), reversal 1 (REV1), intradimensional shift (IDS), reversal 2 (REV2), extradimensional shift (EDS) and reversal 3 (REV3). * $P = 0.001$; one-way ANOVA.

Table 1

Typical example of trial pairings for rat during attentional set-shifting task

Task	Dimensions		Examples of combined exemplars	
	Relevant	Irrelevant	S+	S–
SD	Medium	–	Brown paper *	White paper
CD	Medium	Odor	Brown paper * + jasmine Brown paper * + vanilla	White paper + vanilla White paper + jasmine
REV1	Medium	Odor	White paper * + vanilla White paper * + jasmine	Brown paper + jasmine Brown paper + vanilla
IS	Medium	Odor	Multi-color beads * + clove Multi-color beads * + nutmeg	Clear beads + nutmeg Clear beads + clove
REV2	Medium	Odor	Clear beads * + clove Clear beads * + nutmeg	Multi-color beads + nutmeg Multi-color beads + clove
ES	Odor	Medium	Dark foam + cinnamon * Light foam + cinnamon *	Light foam + patchouli Dark foam + patchouli
REV3	Odor	Medium	Dark foam + patchouli * Light foam + patchouli *	Light foam + cinnamon Dark foam + cinnamon

The animal must choose one of two pots. The correct pot is signified by S+. In contrast, an asterisk (*) denotes the correct dimension to which the animal must attend. For each discrimination problem, the correct choice can be paired with either exemplar from the irrelevant dimension across trials. Each rat performed a series of 7 discriminations: simple discrimination (SD), compound discrimination (CD), reversal 1 (REV1), intra-dimensional shift (IS), reversal 2 (REV2), extra-dimensional shift (ES), and finally reversal 3 (REV3). Twelve such schedules were randomly assigned to individual rats.