Physiology & Behavior, Vol. 67, No. 5, pp. 783–789, 1999

0031-9384/99/$–see front matter

ELSEVIER

PII S0031-9384(99)00183-3

Cognitive Performance, Hyperoxia, and Heart Rate Following Oxygen Administration in Healthy Young Adults

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Received 8 June 1998; Revised 17 June 1999; Accepted 29 June 1999

SCHOLEY, A. B., M. C. MOSS, N. NEAVE AND K. WESNES. *Cognitive performance, hyperoxia, and heart rate following oxygen administration in healthy young adults.* PHYSIOL BEHAV **67**(5) 783–789, 1999.—It was recently established that supplemental oxygen administration significantly enhances memory formation in healthy young adults. In the present study, a double-blind, placebo-controled design was employed to assess the cognitive and physiological effects of subjects' inspiration of oxygen or air (control) prior to undergoing simple memory and reaction-time tasks. Arterial blood oxygen saturation and heart rate were monitored during each of six phases of the experiment, corresponding to baseline, gas inhalation, word presentation, reaction time, distractor and word recall, respectively. The results confirm that oxygen administration significantly enhances cognitive performance above that seen in the air inhalation condition. Subjects who received oxygen recalled more words and had faster reaction times. Moreover, compared to participants who inhaled air, they exhibited significant hyperoxia during gas administration, word presentation, and the reaction-time task, but not at other phases of the experiment. Compared to baseline, heart rate was significantly elevated during the word presentation, reaction-time, and distractor tasks in both the air and oxygen groups. In the oxygen group, significant correlations were found between changes in oxygen saturation and cognitive performance. In the air group, greater changes in heart rate were associated with more improved cognitive performance. These results are discussed in the context of cognitive demand and metabolic supply. It is suggested that under periods of cognitive demand a number of physiological responses are brought into play that serve to increase the delivery of metabolic substrates to active neural tissue. These mechanisms can be supplemented by increased availability of circulating blood oxygen, resulting in an augmentation of cognitive performance. Heart rate reactivity and the capacity for increased blood oxygen appear to be important physiological individual differences mediating these phenomena. © 1999 Elsevier Science Inc.

Oxygen Hyperoxia Cognition Demand Heart rate Metabolism

THE brain is the most metabolically active organ in the body (39). This metabolism consists almost exclusively of the oxygen-dependent breakdown of glucose. Indeed, a number of brain imaging techniques exploit the fact that there is enhanced uptake of glucose and oxygen into brain areas that are differentially active, depending on the cognitive task involved (18,33,35).

The availability of glucose and oxygen can affect cognitive functioning. Reversible cognitive impairments are evident during hypoglycaemia (16,17,41,46) and hypoxia (8,14,31). Similarly, aging-related cognitive decline has been attributed to the compromised delivery of oxygen and glucose through the cerebral vasculature (11,14,40). It has also been demonstrated that memory performance can be enhanced through the administration of a glucose drink. The phenomenon is more pronounced in the elderly (7,15), but has also been observed in younger individuals (4,5,12). Elevated blood glucose is also associated with improvement on a number of nonmnemonic cognitive tasks particularly when such tasks require "effortful" mental processing (10). Some of these studies suggest that the magnitude of response to a glucose load in terms of rising (4,7) or falling (5,32) blood glucose predicts the level

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of cognitive performance [see Foster et al (12) for a recent critique of the area].

Previous work in our laboratory has established that, like glucose, oxygen administration is capable of enhancing aspects of cognitive performance. Oxygen inspiration for 1 min prior to presentation of a word list resulted in a significant increase in number of words recalled 10 min or 24 h later (28). Administration of oxygen immediately preceding recall did not increase the number of items recalled, suggesting that supplemental oxygen can affect memory formation but not retrieval. This interpretation was supported in a related study where blood oxygen saturation was monitored constantly, and oxygen administered at different time points relative to a simple word recall task (38). Word recall (tested 12 min following presentation) was enhanced only when transient (2-min) oxygen delivery, and consequent hyperoxia, occurred immediately before, immediately following, or 5–3 min prior to word presentation. No effect was evidence when oxygen administration occurred 10 min prior to, nor 5 min following, word presentation nor immediately prior to word recall. We have also assessed oxygen's impact on performance of other cognitive tasks (29). The overall finding was that cognitive performance on computerized tests of various aspects of information processing, including attention and verbal memory, were selectively enhanced through supplemental oxygen administration in a dose-dependent manner. Individual tasks were differentially enhanced by various durations of the gas. Elsewhere, oxygen (but not glucose) administration was found to improve aspects of "everyday" memory, including shopping list items and matching names to faces (48). It should also be noted that not all cognitive measures are improved by oxygen. Computerized tests of working memory were unaffected by oxygen administration, although methodological factors may account for this finding (29,38). Similarly, induced hyperoxia improved neither forward nor backward digit span performance (38), a result that is consistent with those reported for glucose (13). Clearly, further research is required in which direct comparisons are made between the cognitive effects of glucose, oxygen, and their combination.

What of the relationship between glucose, oxygen, and cognitive processing in the absence of a glucose or oxygen load? The brain's metabolism is altered in response to cognitive demand (19), an effect mediated by a number of physiological changes that may serve to increase the levels of glucose and oxygen in the blood, and their delivery to task-sensitive neural mechanisms. In a series of studies in the 1970s the Laceys demonstrated that tasks requiring cognitive processing are associated with heart rate acceleration (21,22). In a more recent example of the phenomenon, memory improvements during muscle tension-induced arousal were accompanied by accelerated heart rate (30). Similarly, both heart rate and oxygen consumption were increased in subjects who played a video game or performed complex mental arithmetic (42), and effortful information processing was shown to be associated with faster and more shallow respiration (1,47). In a related study, increased memory load (number of items) was accompanied by accelerated heart rate, faster respiration rate, and greater volume of exhaled carbon dioxide, a direct indicator of oxygen uptake (2). With respect to physical exercise, induced hyperoxia has been shown to increase subjects' endurance time to exhaustion by some 41% (34), an effect that was accompanied by increased heart rate and oxygen uptake.

In resting subjects, the usual responses to induced hyperoxia include heart rate deceleration (6,9,23). This finding, and the possibility that increased heart rate may serve to deliver higher levels of metabolic substrates to active neural mechanisms, suggests that increased heart rate associated with cognitive processing may be of a lesser magnitude in hyperoxic individuals. We are not aware of any study in which the interaction between induced hyperoxia, cognitive processing, and heart rate has been studied.

The aims of this study were twofold. First, we wished to further examine whether, following oxygen administration, blood oxygen levels are indeed higher during memory formation and a reaction time task—two measures that are known to be sensitive to oxygen-associated improvements (29). Second, we were particularly interested in exploring the relationship between blood oxygen levels and heart rate during information processing. These issues were addressed by monitoring subjects' arterial hemoglobin oxygen saturation and heart rate during a word memory and a simple reaction-time task following inspiration of oxygen or air.

METHOD

Subjects

Twenty-one female and 11 male volunteers (mean age 21.06 years) took part in the study. This sample size was selected on the basis of previous results (28,29,38), and allowed a between-subjects design to be utilized. Prior to their participation in the experiment each subject signed an informed consent form that had been approved by the Divisional Ethics Board.

Cognitive Measures

Word recall and Simple Reaction-Time tasks, drawn from the Cognitive Drug Research Ltd computerized assessment battery (44,45), were run on an Elonex 386 personal computer. Word presentation consisted of 15 two-syllable words being presented sequentially on the screen for 1 s each, with an interstimulus interval of 1 s. In the recall phase, subjects were instructed to write down as many of the words as possible. In the Simple Reaction-Time task subjects were required to press a response button as quickly as possible following each (random interval) presentation of the word "YES" on the computer screen.

Physiological Measures

Arterial hemoglobin oxygen saturation (%) and heart rate (beats per minute) data were sampled automatically at 30-s intervals using a N100-P hand-held pulse oximeter (Nellcor Puritan Bennet, Coventry, UK) according to the manufacturer's instructions. These data were collected throughout the experiment, with each reading representing a "snapshot" of the two measures at that time point.

Gas Administration

Gas delivery was achieved using the following assembly, arranged so that neither experimenter nor subject were aware of whether oxygen or air was being administered. Cylinders containing medical quality compressed air and oxygen, respectively, were purchased from British Oxygen Company, Guilford, UK. Attached to each cylinder was a full-nose regulator and an air flow meter; these were both set to simultaneously deliver the gases at a rate of 8 liters per min. Each subject inspired one of the gases (depending on their experimental condition) for 70 s via a hand-held face mask. This was attached by tubing to one arm of a three-way "Y"-junction, the other two branches of which were connected by tubes to the oxygen and air sources, respectively. The assembly was arranged such that the gas source for each gas delivery session was hidden from both subject and experimenter. Situated on these tubes, adjacent to the Y-junction, were valves that were closed off, thus preventing the gases from entering the piping to which the face mask was attached. Following allocation to experimental condition, one of the valves (which were labeled by code) was opened, causing oxygen or air to be fed into the face mask for inspiration.

Procedure

Subjects were tested individually following a placebo-controlled double-blind design. Upon entering the laboratory, each subject was randomly assigned to one of the two coded conditions representing oxygen and air. They were familiarized with the use of the face mask, and the oximeter probe was placed on the index finger of their nondominant hand. The start of each subjects' data collection (time zero) was synchronized with switching on the pulse oximeter. Four readings were taken to establish baseline levels of oxygen saturation and heart rate. Oxygen/air delivery began 2 min 20 s following the start of the experiment, and ended immediately following the oximeter data output at 3 min 30 s. Word presentation began at 3 min 55 s, encompassing two oximeter readings, and was followed at 4 min 55 s by the Simple Reaction-Time task, that terminating at 7 min 15 s (during which time five oximetry readings were collected). Between 7 min 25 s and 9 min 15 s subjects underwent a distractor task in which they were instructed to count out loud backwards in threes from one thousand (this phase encompassed five oximetry readings). At 9 min 25 s subjects were instructed to write down as many of the words as they could remember (five oximetry readings were collected during this phase). The experimental session terminated with the final pulse oximeter output at 11 min and 30 s. Prior to debriefing, subjects were asked to indicate which gas they thought they had received by responding "oxygen," "air," or "don't know."

Statistics

Word recall and Simple Reaction-Time data were analyzed by independent sample *t*-test. Oxygen saturation and heart rate data were investigated statistically by analyses of variance (ANOVA).

Any relationship between physiological measures and cognitive performance were further explored using Pearson moment-product correlations. Mean baseline hemoglobin saturation and mean baseline heart rate were each compared to reaction time scores and word recall scores, separately for the air group and the oxygen group. The change in each of the two physiological measures during the experiment were also compared to cognitive scores: mean baseline oxygen level and mean baseline heart rate were subtracted from the mean oxygen level and mean heart rate, respectively, for each of the three experimental phases involving cognitive processing (i.e., word presentation, reaction time, and word recall). Each of the resulting six measures were compared to both number of words recalled and reaction time, separately for the air group and the oxygen group, again using Pearson moment-product correlations.

The responses as to which condition subjects believed they had been in were subjected to a χ^2 contingency test.

RESULTS

Cognitive Measures

There was a significant effect of experimental condition on both word recall, $t(30) = 2.127$, $p < 0.05$, and reaction time, $t(30) = 1.975$, $p < 0.05$ (see Fig. 1). Subjects who received oxygen recalled more words than those who received air (means = 6.219 and 4.688, respectively). Simple Reaction Time was faster in the oxygen condition than the air condition (means = 237.461 and 256.050 ms, respectively).

Physiological Measures

Mean levels of arterial oxygen saturation and heart rate over the duration of the experiment are plotted in Fig. 2a and b, respectively. For the purpose of statistical analyses data were collapsed into six categories representing the mean heart rate or oxygen saturation for each phase of the experiment; baseline, gas administration, word presentation, reaction time, distractor, and recall.

There was a significant condition × phase of experiment interaction, $F(1, 5) = 17.356$, $p < 0.0001$, with simple main effects analysis revealing a significant elevation of blood oxygen saturation in the oxygen compared to the air condition, during gas administration, $F(1, 45) = 12.901$, $p < 0.005$, and word presentation, $F(1, 45) = 21.228$, $p < 0.0001$. There was also a significant main effect of phase of experiment on blood oxygen saturation, $F(1, 5) = 34.083$, $p < 0.0001$. With the excep-

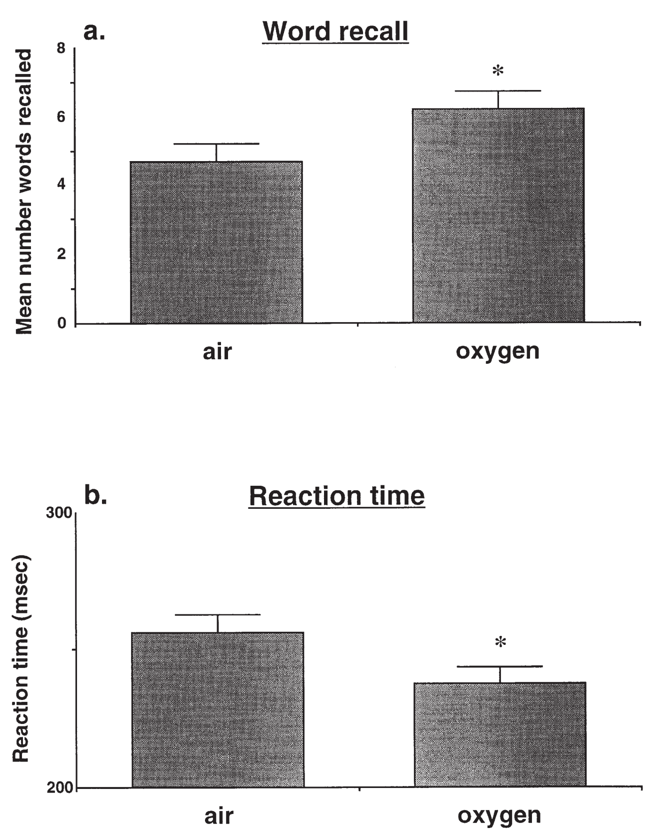

FIG. 1. The effect of oxygen administration on (a) word recall, and (b) simple reaction time. Error bars depict standard errors (*$p < 0.05$; compared to air condition).

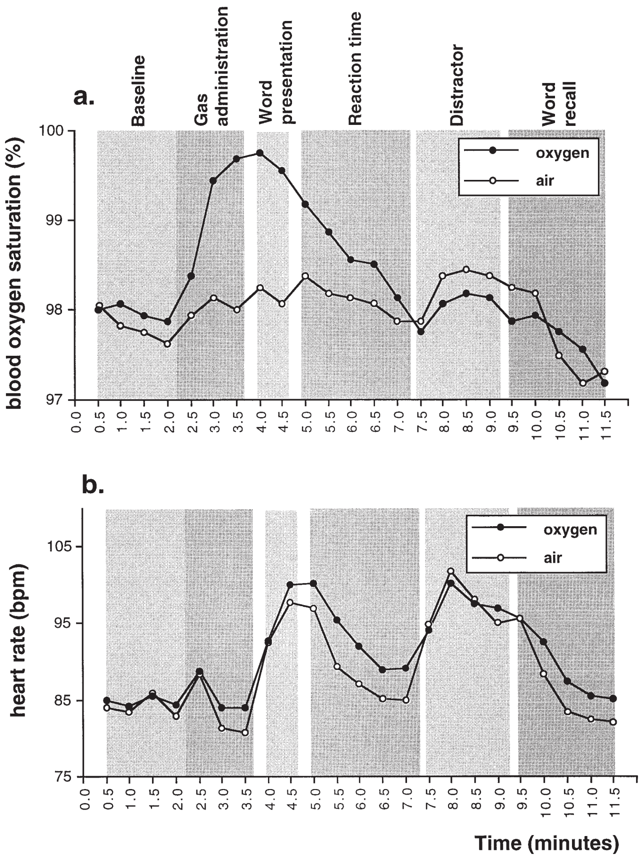

FIG. 2. (a) Blood hemoglobin oxygen saturation (%), and (b) heart rate (beats per minute) during experimental phases. Shaded bars indicate the various phases of the experiment (see text for details).

tion of the difference between mean values obtained during the baseline and the distractor phase (which was not significant), oxygen saturation in each phase was significantly different to that in every other phase.

Comparisons of overall mean oxygen saturation did not show a significant difference between groups during the Simple Reaction Time task. However, an ANOVA performed on the five individual oximeter readings during the reaction time task revealed that there was a significant condition × time interaction, $F(1, 4) = 3.676$, $p < 0.01$, and a significant main effect of time point, $F(1, 4) = 12.162$, $p < 0.0001$. Subjects who received oxygen had significantly higher blood oxygen saturation. Examination of the data suggests that this effect was masked in the overall means analysis due to decaying oxygen levels during the Simple Reaction Time task (see Fig. 2a).

With respect to heart rate, there was a significant main effect of phase of experiment, $F(1, 5) = 17.392$, $p < 0.0001$, but no significant main effect of condition, or phase × condition interaction. In fact, the two experimental groups' heart rates were very similar in response to each experimental phase (see Fig. 2b). ANOVAs performed on heart rate using the experimental phase as a repeated-measures variable revealed that this difference was due to increased heart rate, compared to baseline, during word presentation, the reaction-time task, and the distractor task ($p < 0.01$ in each case). These significant differences were maintained when the oxygen and air groups' data were analyzed separately.

Effect of Oxygen Saturation Changes and Heart Rate Changes on Cognitive Measures

There were a number of significant correlations between physiological measures and cognitive performance.

For the oxygen group, there was a significant negative correlation between baseline blood oxygen saturation and number of words recalled, $r(14) = -0.653$, $p < 0.01$. Subjects with lower baseline oxygen levels recalled more words. There were several significant correlations between cognitive performance and changes in physiological responses relative to baseline. For the oxygen-breathing group, there was a significant correlation between the change in oxygen level from baseline to word presentation phase and the number of words recalled, $r(14) = -0.631$, $p < 0.01$. Greater magnitude of change in oxygen levels was associated with higher word recall. For the oxygen group, there was also a significant correlation between the change in oxygen level from baseline to reaction time phase and reaction time, $r(14) = 0.684$, $p < 0.01$, suggesting that lower differences in oxygen levels were related to faster reaction times.

For the air-breathing group there was a significant positive correlation between change in heart rate from baseline to word presentation phase and recall score, $r(14) = 0.550$, $p < 0.05$, subjects whose heart rate increased more during word presentation had a higher recall score. There was also a significant negative correlation between change in heart rate from baseline to word recall phase and reaction time score, $r(14) = -0.551$, $p < 0.05$.

Subjective Condition Responses

There were no significant differences between subjects' responses as to which gas condition they thought they had been in and those expected by chance, $\chi^2(2) = 3.436$, $p = 0.179$ (see Table 1). This suggests that the cognitive enhancing effects of oxygen cannot be attributed to subjective expectancy based on some nonspecific oxygen-induced state.

DISCUSSION

The results of this study confirm that oxygen administration results in improved cognitive performance, including memory formation and reaction time (28,29,38). Moreover, the oxygen-induced hyperoxia measured during word presentation and the reaction time task supports the hypothesis that elevated circulating blood oxygen may be utilized by task-sensitive neural substrates during periods of cognitive processing. There were significant correlations between cognitive performance and changes in individuals' oxyhemoglobin levels for the oxygen group, and between cognitive performance and heart rate changes in the air group. These latter findings suggest that the capacity to carry further oxygen and heart rate

TABLE 1

NUMBER OF SUBJECTS IN EACH EXPERIMENTAL CONDITION INDICATING WHICH GAS THEY BELIEVED THEY HAD INSPIRED

	Condition Indicated by Subject		
Experimental Condition	Air	Oxygen	Don't Know
Air (n = 16)	8	7	1
Oxygen (n = 16)	5	6	5

reactivity are both important physiological individual differences mediating cognitive performance. Subjects' responses as to which gas they believed they had inhaled were not significantly different to chance levels. This suggests that the cognitive enhancement observed following oxygen administration cannot be attributed to some subjective state following hyperoxia (an issue that could be further explored by obtaining subjects' confidence ratings for their perceived condition and examining the relationship between this, their actual condition, and their cognitive performance). This latter results also supports previous findings where mood was unaffected by oxygen administration (28).

Differences in blood oxygen saturation between experimental groups were found only in the gas administration, word presentation, and Simple Reaction-Time phases of the experiment. In the case of the recall task, this result is consistent with earlier findings from our laboratory, and suggests that hyperoxia improves memory consolidation but not retrieval (28,38). We would tentatively suggest that such data support the idea that target material is encoded more deeply under conditions of hyperoxia. In the present study, and previously (38), there were differences in the hyperoxic state of subjects between encoding and retrieval of target material. This begs the question as to whether the possibility of "state dependency"—a phenomenon whereby learned material is more readily assessed at retrieval when the subjective state at encoding is reinstated during retrieval—may further increase hyperoxia-associated mnemonic improvement. Our laboratory is presently investigating this possibility.

There were a number of significant correlations that were specific to the air-breathing group and the oxygen group, respectively. Although caution should be taken in interpreting these data—corrections for multiple comparisons were not considered to be appropriate in such exploratory analyses—it is interesting to speculate on their possible relationship to cognitive performance. Comparisons between individual mean blood oxygen saturation and cognitive performance revealed a significant negative correlation between baseline blood oxygen saturation and word recall scores. This may reflect the fact that oxygen's cognitively enhancing effect may be relatively more pronounced where there is greater potential for increasing blood oxygen saturation. There was no such correlation for the air-breathing group; therefore, the effect is not due to lower baseline levels per se. The interpretation is supported by the positive correlation, in the oxygen group only, between the relative changes in blood oxygen saturation during the word presentation phase and the number of words recalled, a result that is consistent with reports of a positive relationship between rising blood glucose levels and cognitive performance (4,7). Again, this suggests that a higher capacity for increasing blood oxygen levels is associated with a greater amount of cognitive enhancement. Less clear is the meaning of the significant positive correlation, in the oxygen group, between the change from baseline to reaction-time oxygen saturation and reaction-time scores. A similar relationship has been reported for falling glucose levels and reaction times (5), although the same study found that falling blood glucose was associated with improved word recall. The reason that increased oxygen levels are associated with better encoding but slower reaction times may be due to the relationship between task order, and oxygen delivery and uptake. Increased levels of circulating blood oxygen may be available to neural processes involved in encoding target material. In the case of reaction times, hyperoxia is already decaying at this phase of the experiment (see Fig. 2a), and increased uptake of oxygen, reflected by an accelerated decay in the blood, may be associated with improved reaction time. This possibility could be tested through reversing the task order to determine whether the pattern of the relationships between rising and falling oxygen levels and individual task performance were reversed (indeed, given the transient nature of hyperoxia, future studies may usefully be directed at examining these effects using different task orders in relation to oxygen delivery). The fall in blood oxygen to below baseline levels for both groups during word recall may also be related to this phenomenon. It is interesting to note the apparent rise in heart rate during the distractor task followed by a fall during word recall (Fig. 2b). It is possible that, in the absence of an increased heart rate during word recall, there is an uptake of oxygen over and above that maintained by baseline heart rate. Clearly, the relationship between rising and falling blood oxygen (and glucose) levels in response to cognitive processing requires further exploration. In particular, the relationship between hyperoxia and glucose levels has received scant attention, comeasurement of the two indices during cognitive processing would provide useful information about this issue.

Significant heart rate acceleration occurred during word presentation and the reaction-time phases of the experiment in both the air- and oxygen-breathing groups. Accelerated heart rate was also observed during the distractor, a mathematical task where subjects may have felt that their performance was being monitored (because no performance measures were actually taken here, we cannot rule out the possibility that some subjects surreptitiously rehearsed the words during this phase of the experiment). These findings support the hypothesis that effortful information processing is accompanied by an increase in autonomic activity. Our laboratory is currently investigating the extent to which the level of effort involved in task performance interacts with changes in heart rate, glucose levels, and oxygen levels (both in the presence and absence of a glucose/oxygen load).

Despite no significant differences in heart rate between the air- and oxygen-breathing groups, there were significant correlations between heart rate changes and cognitive performance when individual mean heart rates were analyzed for the air-breathing group. There was a significant positive correlation between the relative change in heart rate during word presentation and the number of words recalled. We would tentatively suggest that this is part of a physiological response to increased neural activity that results in the increased delivery of oxygen for energetic processes. The same relationship was not observed in the oxygen group where the demand for increased oxygen may have been reduced due to increased availability of circulating oxygen following gas inspiration. Finally, in the air-breathing group only, there was a significant negative correlation between the change in heart rate relative to baseline in the recall phase and reaction-time scores. The reason for this relationship is unclear, although there was a similar (not significant) trend with respect to change in heart rate from baseline to word presentation phase and reaction times ($r = -457$, $0.1 > p > 0.05$). It is possible that subjects whose heart rate is more responsive to cognitive processing may perform better.

We would suggest that the increased heart rate during cognitive processing facilitates the delivery of metabolic substrates to the brain; these are then utilized by neural mechanisms underpinning cognitive performance. The results of this study suggest that mental effort results in increased metabolic activity (heart rate). For example, it is evident that heart rates during the reaction time task are raised less than during either word presentation or word recall (Fig. 2b). It seems likely that a cognitive load of a simple reaction time task is less than that of a memory task. It would appear that the effectiveness of this process on information processing may be related to individual physiological sensitivity to cognitive demand. Induced hyperoxia seems to supplement this process, thereby improving cognitive performance. This (unknown) demand-related mechanism may also override the decreased heart rate, which is among the usual physiological responses to hyperoxia, although recent evidence suggests that this slowing stabilizes to a steady state only after some 5 min of continuous hyperoxia (23). Clearly, this issue requires further investigation.

The mechanism by which oxygen improves cognitive performance remains unknown. In the case of cognitive-enhancing agents (so-called "smart drugs"), a number of authors have suggested that improved cognitive performance is mediated via liberation of glucose stores and the increased synthesis of acetylcholine [e.g. (43)]. Although the same model would account for oxygen's effects on some measures of cognitive function, it is unlikely that the cholinergic system fulfills the role of being the necessary, sufficient, and exclusive mediator of such phenomena. Although turnover of both oxygen and glucose would lead to increased synthesis of acetylcholine via a side branch of the glycolytic pathway, it seems equally probable that the increased availability of metabolic substrates, possibly leading to increased synthesis of adenosine triphosphate (the universal cellular "energy currency"), per se may account for their performance-enhancing properties (28). It should also be noted that the temporal relationship between oxygen (or glucose) administration and improved cognitive performance are not similar to those observed for cholinergic drugs (12,36,38). Additionally, we have some preliminary evidence that certain aspects of cognitive performance are very differently effected by oxygen when compared with the cholinergic agonist nicotine (37). It may also be relevant that a number of putative cognitive enhancers are reported to have their effects through mechanisms including increased blood flow, glucose metabolism, and cerebral blood oxygenation (26,27). Future research should also be directed at delineating the brain areas mediating hyperoxia-associated cognitive enhancement.

There has been debate over the past decade as to the whether increased neural activity relies on oxidative metabolism (3). Early studies, using simultaneous oxygenation measurement with positron emission tomography, found an insignificant rise in oxygen uptake in active brain areas (13). However, the development of functional magnetic resonance imaging, and more sophisticated techniques for monitoring blood oxygen fractions, has generated results that are consistent with the proposal that there is a substantial increase in oxygen utilization in active neural tissue (25). The evidence presented here provides behavioral support for the latter model.

The results of the present study mirror those from studies of low oxygen levels where hypoxic individuals show deficits in reaction time (24,31) and free recall (8). It is possible that cognitive performance is related to a continuum of blood oxygenation ranging from hypoxia, through normoxia, to hyperoxia. It is commonly accepted that the brain has evolved to function optimally. However, results from our laboratory and studies elsewhere of hyperglycaemia-associated cognitive improvement lead to the somewhat paradoxical conclusion that cognitive performance may be physiologically resource limited. This concept has previously been described in terms of information-processing resources, where "mental effort" describes the level of such resources required to maintain task performance (20). There is now ample evidence to suggest that such mental effort is also a reflection of the availability of metabolic resources drawn upon during task performance, an effect supported by brain imaging studies during differing mental loads (19). Such an intuitively pleasing model makes a number of specific predictions about the relationship between cognitive demand, availability of oxygen and glucose, and task performance; for example, that tasks requiring higher mental effort should be more susceptible to the enhancing effects of oxygen administration. Our laboratory is currently investigating these matters.

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