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Oxygen administration selectively enhances cognitive performance in healthy young adults: a placebo-controlled double-blind crossover study

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Abstract It was recently demonstrated that oxygen administration can improve performance on a simple word recall task in healthy young adults. This study was aimed at determining the impact of various durations of oxygen administration on a wider range of cognitive measures. This was achieved using the Cognitive Drug Research computerised test battery, and employing a double-blind, placebo-controlled crossover design. Over a period of 7 weeks, 20 participants were trained and subsequently assessed on the test battery under several durations of oxygen inhalation; air administered in an identical fashion served as a control. The results provided support for our earlier work in that increases were found in both immediate and delayed word recall. In addition, oxygen administration significantly improved performance on several measures of attention and vigilance. Simple reaction time, choice reaction time, digit vigilance reaction time and picture recognition reaction time were improved in a manner which depended on the duration of oxygen inspired. With the exception of word recall, no significant improvements were found for any measure of accuracy, nor were word recognition, digit memory scanning, or spatial memory improved. These results are discussed in the context of stages of information processing and are consistent with the hypothesis that cognitive performance is "fuel-limited" and can be differentially augmented by increasing the availability of the brain's metabolic resources.

Key words Oxygen · Metabolism · Memory · Attention · Energy · Cognition

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Introduction

The brain is the most metabolically active organ in the body, and accounts for up to 30% of basal energy production, all of which is essentially dependent on the oxidative breakdown of glucose (Roland 1993). This energy is consumed to drive neural activity which is differentially distributed in response to the cognitive demands of the task in question (Frackowiak et al. 1981; Reivich and Alavi 1983). The requirements for metabolism are blood-borne and are actively transported or diffuse across the blood-brain barrier. Any changes in the availability of glucose and oxygen may influence brain metabolism and, consequently, cognitive function (Lund-Andersen 1972; Sage et al. 1981).

Importantly, supplemental glucose administration has been shown to produce cognitive enhancement in animals (Oomura et al. 1993; Kopf and Baratti 1994; Ragozzino et al. 1994). Similar results have been found in humans where consumption of a glucose drink is particularly effective in enhancing performance on tests of declarative memory in aged subjects (Manning et al. 1990; Craft et al. 1992) and younger individuals (Benton and Owens 1993; Owens and Benton 1993; Craft et al. 1994). There is now increasing evidence that glucose may also improve performance on tests of non-mnemonic cognitive function, including reaction time (Owens and Benton 1994). In later stages of information processing, glucose is particularly effective when the task requires "effortful" information processing (e.g. Benton et al. 1994; Donohoe 1997).

The level of transport of glucose across the blood-brain barrier, and thus the rate of cerebral glucose metabolism, is intrinsically linked to oxygen availability (Pardridge 1983). Certainly, anoxia and ischemia are well documented as causing a depression in blood brain barrier transport, which is reflected in a decrease in oxidative glucose metabolism (Betz et al. 1974; Kintner et al. 1980) and an associated cognitive decline (Tune 1964; Crow et al. 1973). We propose that elevated cerebral blood oxygen levels may enhance glucose transport and metabolism, and as a result improve cognitive performance. Recent work in our laboratory demonstrated that a significant increase in word recall resulted from the inhalation of oxygen for 1 min prior to hearing a word list (Moss and Scholey 1996). This effect was not observed in a group who received placebo (compressed air inhaled in the same manner). Oxygen-dependent enhancement was evident when the learning-test interval was 10 min or 24 h and was not seen when oxygen was administered immediately prior to recall. We previously speculated that oxygen was affecting an energy-dependent consolidation process and, given that glucose administration improves performance on a number of non-memory tasks, we postulated that the cognitive-enhancement following oxygen inspiration may not be restricted to verbal declarative memory.

The present study was formulated to test the effect of various durations of oxygen on a range of cognitive measures using an established psychopharmacological assessment instrument (including tests of attention, working memory and long term memory). It was postulated that oxygen administration may differentially improve cognitive performance and was aimed at determining the optimal "dose" (i.e. duration of oxygen inspiration) for any such enhancement. This was achieved by using the Cognitive Drug Research computerised assessment battery to test subjects who inhaled oxygen for various durations using a placebo-controlled, double-blind crossover design.

Materials and methods

Participants

Twenty healthy adults (14 males, six females), aged 21–48 years (mean = 24.5), were each paid 20 sterling for participation in the study. Twelve of the participants were regular smokers. On recruitment, each subject was briefed as to the nature of the experiment and signed a consent form which had been approved by the Divisional Ethics Board.

Cognitive tests

A tailored version of the Cognitive Drug Research (CDR) computerised assessment system (installed on an Elonex pc386sxm/16 computer) was used to evaluate cognitive performance. The CDR system includes a number of measures which are specific to particular aspects of attention, working memory and long term memory. Stimuli are presented on a colour monitor and responses are made using a simple response module containing two buttons labelled "yes" and "no", respectively. A suite of programmes controls all aspects of testing, including selection of appropriate sets of stimuli for presentation and recording all responses.

The tests employed in this study were always presented in the following order:

Word presentation. A series of 15 words is presented, one every 2 s. The words are a mix of one two and three syllables, and are matched for frequency, concreteness and imagery between sessions.

Immediate word recall. The computer counts down 60 s, during which time participants free recall as many of the words from the list as possible. Recall is scored for number of correct words; number of intrusions (words from previous lists) and errors (words not presented in the current or previous lists).

Picture presentation. Twenty pictures are presented, one every 3 s. The pictures are matched for subject matter between sessions.

Simple reaction time. The word Yes is presented in the centre of the screen. The participant has to press the Yes button as quickly as possible. There are 50 trials and the intertrial interval varies randomly between 1 and 2.5 s. The reaction time is recorded in ms.

Digit vigilance. A number is displayed constantly to the right of the screen. A series of 240 digits is presented one at a time in the centre at a rate of 80 per minute; 45 match the constantly displayed digit. The participant has to press the Yes button as quickly as possible every time the digit in the centre matches the one constantly displayed. Accuracy of response (%), reaction time (ms), and number of false alarms are recorded.

Choice reaction time. Either the word Yes or the word No is presented in the centre of the screen. The participant has to press the Yes or No button as appropriate and as quickly as possible. There are 50 trials (25 "Yes" and 25 "No") and the intertrial interval varies randomly between 1 and 2.5 s. Accuracy and reaction time are recorded.

Spatial working memory. A picture of a house is presented for 5 s. The house has nine windows, four of which are lit. A series of 36 presentations of the same house in which just one window is lit follow, and the participant has to respond Yes if the window was one of the four lit in the original presentation, or No if it was not. Sixteen of the stimuli require a Yes response and 20 a No response. Reaction time and a sensitivity index are recorded.

Memory scanning. Five digits are presented singly at the rate of one every second for the participant to remember. A series of 30 digits is then presented. For each, the participant must press Yes or No, according to whether the digit is thought to be one of the three presented initially. Fifteen stimuli require a Yes response and 15 a No response.This is repeated three times. Reaction time and a sensitivity index are recorded.

Delayed word recall. The computer counts down 60 s, during which time participants free recall as many of the words from the list as possible. Recall is scored for number of correct words; number of intrusions (words from previous lists) and errors (words not presented in the current or previous lists).

Word recognition. The 15 words presented for the word recall are presented again in random order interspersed with 15 new words. The participant presses Yes or No each time to signal whether or not the word was from the original list. Reaction time and a sensitivity index are recorded.

Picture recognition. The 20 pictures presented earlier are shown again in random order interspersed with 20 similar new ones. The participant signals recognition by pressing the Yes or No button as appropriate. Reaction time and a sensitivity index are recorded.

"Pencil and paper" visual analogue scales. assessing subjective levels of alertness, calmness and contentedness, were presented following the computerised tests. Participants are required to indicate their current state by marking a line drawn between two bipolar adjectives. The entire battery took approximately 25 min to administer.

Gas administration

Medical grade oxygen and compressed air cylinders (supplied by British Oxygen Company, Guildford, UK) were connected through quick release valves and a three-way tap system to a face mask. The apparatus was assembled to allow double-blind administration of the gases. Supply was maintained at 8 l/min for both gases during the experimental testing procedures.

Procedure

A double-blind, placebo-controlled, balanced, crossover design was employed in this study. Each participant visited the laboratory on seven occasions. Each visit was at the same time of day and, as far as was practicable, on the same day each week. All participants were asked to refrain from smoking and from drinking caffeinated drinks for 1 and 2 h, respectively prior to presentation for testing. Each visit consisted of two sessions. The first two visits (i.e. a total of four test sessions) were dedicated to training participants on the system and to ensure that baseline performance did not fall outside established population mean parameters for each task. On each of the five subsequent visits, the participants once again performed a baseline session which was immediately followed by an experimental test session under one of the five intervention protocols. These consisted of compressed air inspiration throughout the experimental test session (control), 30 s of oxygen prior to each task in the battery, 1 min of oxygen prior to the start of the experimental test session, 3 min oxygen prior to the start of the session, and constant oxygen administration throughout the session. The order in which each participant received the different conditions was pseudo-random following a Latin Squares design, allowing each participants to be tested under all conditions.

Other than word recall and visual analogue scale results, which were recorded manually at each test session, data were downloaded onto floppy disks. Analysis was performed blind with respect to condition and results were not available to the experimenters until completion of the study.

Statistics

The statistical package SAS was used to analyse the data. Differences between performance pre- and post- gas administration were calculated for each task in each condition, and these differences form the data for the analysis. Comparisons between groups were made using the general linear models procedure (PROC GLM), and planned comparisons between the four oxygen conditions and the control (air) condition. To ensure the overall protection level, only probabilities associated with pre-planned comparisons were used.

Results

As is conventional with such studies, the variables tested in this study were grouped into three main categories: attention, long term memory and working memory. Any effect of condition on reaction times was assessed by calculating the difference in scores between baseline and test on each visit. Thus a result of less than zero indicates that reaction time is speeded above that seen at baseline, whereas a reaction time which is faster than control (air) but above zero represents a speeding of the slower reaction times usually observed subsequent to baseline measurement. Word recognition, picture recognition and spatial working memory were tested by the randomised sequential presentation of appropriate stimuli from the presentation phase and an equal number of distractor items (similar stimuli not seen at presentation). This allows the calculation of both accuracy scores and reaction times for these tasks. The sensitivity indices are calculated using the non-parametric signal theory index (SI) presented by Frey and Colliver (1973). The calculation of the index combines the probability of correctly identifying previously presented items, with the probability of accepting novel items as being previously presented. The index ranges from 1 (all items correctly classified) through 0 (chance performance) to -1 (every item incorrectly classified).

Attention

Oxygen administration had a significant effect on a number of performance measures pertaining to attentional processes (Table 1).

Simple reaction time

Significant differences were found between the oxygen conditions and the air condition for simple reaction time. Improvements, were found in the 30 s [$t(76) = 3.75$; $P < 0.0005$], 1-min [$t(76) = 4.03$; $P < 0.0001$] and 3-min $t(76) = 3.03$; $P < 0.005$ oxygen conditions. Constant oxygen administration also improved performance, but this difference did not approach statistical significance.

Choice reaction time

There was a significant effect of oxygen inhalation on choice reaction time. Subjects who inhaled oxygen for 30 s [$t(76) = 2.11$; $P < 0.05$] and 1 min [$t(76) = 2.68$; $P < 0.01$] performed significantly better than those who inhaled air. Individuals in both the 3 min and the constant oxygen conditions displayed improved performance, but these differences were not statistically significant.

Number vigilance

A significant improvement in number vigilance reaction time was found for the 30 s oxygen condition [$t(76) = 2.33$; $P < 0.05$] versus the air condition. A trend for better performance was observed in the 1-min oxygen condition [$t(76) = 1.78$; $P = 0.078$]. Again, subjects in the 3-min and constant oxygen conditions performed better than those in the air condition, but these differences did not approach statistical significance. No significant differences were found for the sensitivity index, or for the number of false alarms recorded.

Long term memory

Scores on the tests of long term memory are presented in Table 2.

Table 1 Results of the tests of attention for all conditions (see text for details). The results are shown as mean ± SE and the units are milliseconds for the reaction times and percentages for the accuracies. The tasks are: *SRT*, simple reaction time; *CRT*, choice reaction time; *CRTACC*, choice reaction time accuracy; *VIGACC*, digit vigilance accuracy; *VIGRT*, digit vigilance reaction time; and *VIGFA*, digit vigilance false alarms, $*P < 0.05$; $**P < 0.01$; $***P < 0.005$; $****P < 0.001$; $*****P < 0.0005$; $******P < 0.0001$. *NS*, not significant

	1 min oxygen	3 min oxygen	30 s oxygen	Constant oxygen	Air	*P* values for pre-planned comparisons
Group	1	2	3	4	5	
n	20	20	20	20	20	
SRT pre	241 ± 7	239 ± 5	242 ± 7	238 ± 4	229 ± 4	
SRT post	237 ± 5	243 ± 7	240 ± 7	257 ± 6	257 ± 7	
Post-pre	−4	4	−2	19	28	1 vs. 5******, 3 vs. 5*****, 2 vs. 5***
CRT pre	398 ± 10	390 ± 10	395 ± 11	391 ± 9	388 ± 10	
CRT post	389 ± 9	399 ± 13	391 ± 11	397 ± 11	409 ± 11	
Post-pre	1	9	−4	6	21	1 vs. 5**, 3 vs. 5*
CRTACC pre	95 ± 0.8	96 ± 0.8	95 ± 0.8	95 ± 0.8	94 ± 1.0	
CRTACC post	95 ± 0.8	96 ± 0.6	97 ± 0.6	96 ± 0.7	95 ± 0.8	
Post-pre	0	0	2	1	1	NS
VIGACC pre	98 ± 0.5	97 ± 1.1	98 ± 1.0	99 ± 0.3	97 ± 0.9	
VIGACC post	98 ± 0.6	97 ± 0.8	98 ± 0.6	98 ± 0.6	98 ± 0.7	
Post-pre	0	0	0	−1	1	NS
VIGRT pre	393 ± 7	382 ± 6	390 ± 8	384 ± 5	381 ± 5	
VIGRT post	395 ± 10	395 ± 8	387 ± 9	388 ± 8	397 ±6	
Post-pre	2	13	−3	4	16	3 vs. 5*
VIGFA pre	0.75 ± 0.3	1.00 ± 0.3	0.85 ± 0.3	1.20 ± 0.4	0.90 ± 0.3	
VIGFA post	0.65 ± 0.2	0.60 ± 0.3	0.55 ± 0.1	0.20 ± 0.1	0.60 ± 0.2	
Post-pre	−0.1	−0.4	−0.3	−1	−0.3	NS

Table 2 Results of the tests of long term memory for all conditions (see text for details). The results are shown as mean ± SE and the units are number of correctly recalled items for the word recall tasks, milliseconds for the reaction times. The tasks are: *IMREC*, immediate word recall; *DELREC*, delayed word recall; *DRECSI*, word recognition sensitivity index; *DRECRT*, word recognition reaction time; *DPICSI*, picture recognition sensitivity index; *DPICRT*, picture recognition reaction time. $*P < 0.05$; $**P < 0.01$; *NS*, not significant

	1 min oxygen	3 min oxygen	30 s oxygen	Constant oxygen	Air	*P* values for pre-planned comparisons
Group	1	2	3	4	5	
n	20	20	20	20	20	
IMREC pre	6.7	7.3	7.4	6.9	6.7	
IMREC post	7.7	7.6	6.8	7	5.5	
Post-pre	1	0.3	−0.6	0.1	−1.1	1 vs. 5**, 2 vs. 5**, 4 vs. 5*
DELREC pre	4.1	4.4	4	5	4.6	
DELREC post	3.8	4.1	3	3.6	2.4	
Post-pre	−0.3	−0.3	−1	−1.4	−2.2	1 vs. 5*, 2 vs. 5*
DRECSI pre	0.60 ± 0.04	0.65 ± 0.03	0.63 ± 0.04	0.65 ± 0.03	0.65 ± 0.04	
DRECSI post	0.61 ± 0.04	0.64 ± 0.03	0.67 ± 0.03	0.61 ± 0.05	0.59 ± 0.04	
Post-pre	0.01	−0.01	0.04	−0.04	−0.06	NS
DRECRT pre	673 ± 24	678 ± 24	682 ± 25	675 ± 27	690 ± 29	
DRECRT post	663 ± 27	677 ± 27	692 ± 29	690 ± 23	705 ± 33	
Post-pre	−10	−1	10	15	15	NS
DPICSI pre	0.77 ± 0.05	0.87 ± 0.04	0.78 ± 0.05	0.81 ± 0.03	0.82 ± 0.05	
DPICSI post	0.76 ± 0.05	0.78 ± 0.04	0.75 ± 0.04	0.77 ± 0.05	0.73 ± 0.04	
Post-pre	−0.01	−0.09	−0.03	−0.04	−0.09	NS
DPICRT pre	750 ± 33	709 ± 25	753 ± 34	751 ± 33	728 ± 31	
DPICRT post	729 ± 29	730 ± 28	721 ± 28	753 ± 34	789 ± 46	
Post-pre	−21	21	−32	2	59	2 vs. 5**, 1 vs.5*

Immediate word recall

Three of the oxygen conditions produced a significant improvement in word recall (post - pre administration) compared to the compressed air condition. Compared with the air condition (mean = −1.125), recall was enhanced by 1 min of oxygen [mean = 0.975; $t(76) = 2.69$, $P < 0.01$], 3 min of oxygen [mean = 0.15; $t(76) = 2.1$, $P < 0.05$], and constant oxygen [mean = 0.325; $t(76) = 2.21$, $P < 0.05$.

No significant differences were found between any of the conditions for intrusion (words recalled from previously learnt lists) and error (words given as recalled but not present in any of the learnt lists) scores.

Delayed word recall

Planned comparisons of the mean differences indicated that, compared to the air condition (mean = −2.1), delayed recall scores were significantly improved in subjects who inspired oxygen for 1 min [mean = 0.35; $t(76) = 2.19$, $P < 0.05$] and 3 min (mean = 0.3; $t(76) = 2.14$, $P < 0.05$].

Word recognition

No significant differences were found between the conditions for either accuracy of recognition or reaction time to correct detection of positive and negative items.

Picture recognition

There was a significant effect of oxygen breathing on picture recognition reaction time. Compared to subjects who inspired air, there was a significant improvement in reaction time for subjects who received oxygen for 30 s [$t(76) = 2.72$, $P < 0.01$; and 1 min [$t(76) = 2.40$, $P < 0.05$. No significant differences were found between the conditions for the accuracy variable.

Working memory

Scores on the tests of working memory memory are presented in Table 3.

Memory scanning

No significant differences were found for the sensitivity index, or for reaction times.

Spatial memory

No significant differences were found for accuracy or reaction times.

Visual analogue scales

The scales were completed by all participants at the end of each test session to determine if any subjective ratings of arousal or similar variables were affected by the administration of oxygen. No significant differences were found between the conditions on the scales of alertness, calmness and contentedness.

Table 3 Results of the tests of working memory for all conditions (see text for details). The results are shown as mean ± SE, the units are milliseconds for the reaction times. The tasks are: *SPMSI*, spatial memory sensitivity index; *SPMRT*, spatial memory reaction time; *MSSI*, memory scanning sensitivity index; *MSRT*, memory scanning reaction time. *$P < 0.05$; **$P < 0.01$; *NS*, not significant

	1 min oxygen	3 min oxygen	30 s oxygen	Constant oxygen	Air	P values for pre-planned comparisons
Group	1	2	3	4	5	
n	20	20	20	20	20	
SPMSI pre	0.92 ± 0.02	0.95 ± 0.01	0.94 ± 0.01	0.95 ± 0.01	0.93 ± 0.02	
SPMSI post	0.90 ± 0.03	0.91 ± 0.02	0.94 ± 0.02	0.93 ± 0.01	0.92 ± 0.02	
Post-pre	−0.02	−0.04	0	−0.02	−0.01	NS
SPMRT pre	623 ± 68	588 ± 31	571 ± 29	569 ± 32	594 ± 44	
SPMRT post	591 ± 45	548 ± 25	550 ± 45	560 ± 34	577 ± 55	
Post-pre	−32	−40	−21	−9	−17	NS
MSSI pre	0.93 ± 0.01	0.92 ± 0.01	0.89 ± 0.02	0.92 ± 0.01	0.90 ± 0.01	
MSSI post	0.90 ± 0.02	0.90 ± 0.03	0.88 ± 0.02	0.90 ± 0.02	0.90 ± 0.02	
Post-pre	−0.03	−0.02	−0.01	−0.02	0	NS
MSRT pre	575 ± 32	555 ± 20	579 ± 28	565 ± 23	571 ± 28	
MSRT post	544 ± 29	549 ± 29	539 ± 24	553 ± 27	560 ± 25	
Post-pre	−31	−6	−40	−12	−11	NS

Discussion

The results of this study clearly demonstrate that the transient administration of pure oxygen to healthy young adults significantly improves performance on a number of cognitive tasks. Furthermore, cognitive enhancement appears to be differential with respect to the type of task, the duration of oxygen inspired and the temporal position of the individual task relative to gas administration. The strongest effects were observed in measures of attention and vigilance, and on long term memory, with no improvement apparent on tests of working memory. However, methodological factors (discussed below) may account for this latter finding.

The influence of oxygen administration appears to obey the inverted U-shaped function as first described by the Yerkes-Dodson law with respect to arousal (Yerkes and Dodson 1908). The most effective doses were 1 and 3 min for both immediate and delayed word recall, and 30 s for tests of attention. Constant oxygen inspiration had a less dramatic influence on performance, at least for tasks which appeared at late stages in the battery.

The degree of oxygen's influence was also apparently dependent on the task in question, and the position of the task within the battery. Those which involved long term memory had encoding stages at the beginning of the battery, and longer durations of oxygen inspiration resulted in more enhancement of these measures. It is possible that consolidation of test material is highly effortful and the greater levels of circulating oxygen are quickly sequestered during this processing. A relatively brief dose (30 s) may not provide sufficient supplemental blood oxygen to raise performance on such tasks. We are currently conducting experiments to test this possibility.

Interestingly, our results support to some degree the possibility of a dissociation between recognition and recall memory. Under conditions of oxygen inspiration, scores were higher for both immediate and delayed word recall. However, no effect was observed for the number of items recognised, nor for reaction time to identify whether words had been encountered previously. There is increasing evidence that recognition and recall are subserved by different neural mechanisms (Aggleton and Shaw 1996). Conversely, however, picture recognition reaction times were faster in subjects who inspired oxygen, but no differences were found in terms of accuracy (sensitivity index).

Tests of attention and vigilance that appeared later in the battery were most effectively enhanced by 30 s oxygen administration immediately prior to the test. Longer administrations also had positive but non-significant effects upon these tests. It is possible that in these attentional tests less cognitive effort is involved and that the shorter duration of oxygen breathing provides a sufficient global upgrade in metabolites to effect the observed enhancement. The reason for longer durations of oxygen inspiration having relatively little effect on these tasks remains unclear. It is plausible that the phenomenon represents a "signal to noise" effect with a background of increased metabolic activity obscuring the specific neural processes required for effective task execution. The general finding that constant oxygen inspiration is not the most effective dose for performance enhancement may also indicate that there is a level beyond which an enhancing factor may become inhibiting. It has been suggested that prolonged normobaric hyperoxia may affect mitochondrial function and the permeability of the blood-brain barrier (Manthos et al. 1991), leading to a downgrade in functional efficiency, an explanation which would account for these data.

The tests of working memory did not exhibit any enhancement in performance in response to oxygen administration. It may be the case that such processes are not amenable to oxygen-induced enhancement. However, it may simply be that the position of these tasks in the test battery meant that by the time they were encountered, the increase in available blood oxygen caused by the longer durations of oxygen breathing had decayed to normal levels. In the case of the shorter durations, these may not have been sufficient to provide the necessary increase in oxygen delivery required to produce a significant effect. An isolated administration and test session for these measures would clarify the issue. The temporal kinetics of oxygen's influence cannot be delineated from the results of this study, but in our hands brief administration of oxygen increases blood oxygen levels for a matter of only 4–5 min.

In conclusion, our results demonstrate that oxygen administration prior to task performance leads to enhancement in a manner dependent on dose duration. Measures of attention, vigilance and long term memory are positively affected. Tests of working memory do not show enhancement, although methodological considerations may account for this finding. The oxygen-induced enhancement follows an inverted U function such that transient oxygen inspiration is more effective than constant administration. Current work in our laboratory is aimed at extending our understanding of the relationship between cognitive performance and blood oxygen levels and the possible applications of this phenomenon.

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