Pflügers Archiv - European Journal of Physiology
https://doi.org/10.1007/s00424-022-02721-8

INVITED REVIEW

Could respiration-driven blood oxygen changes modulate neural activity?

Qingguang Zhang[1] · William D. Haselden[2] · Serge Charpak[3,4] · Patrick J. Drew[1,4,5]

Received: 21 January 2022 / Revised: 26 May 2022 / Accepted: 16 June 2022

Abstract

Oxygen is critical for neural metabolism, but under most physiological conditions, oxygen levels in the brain are far more than are required. Oxygen levels can be dynamically increased by increases in respiration rate that are tied to the arousal state of the brain and cognition, and not necessarily linked to exertion by the body. Why these changes in respiration occur when oxygen is already adequate has been a long-standing puzzle. In humans, performance on cognitive tasks can be affected by very high or very low oxygen levels, but whether the physiological changes in blood oxygenation produced by respiration have an appreciable effect is an open question. Oxygen has direct effects on potassium channels, increases the degradation rate of nitric oxide, and is rate limiting for the synthesis of some neuromodulators. We discuss whether oxygenation changes due to respiration contribute to neural dynamics associated with attention and arousal.

Keywords Oxygen · Respiration · Neural excitability · Cognition · Nitric oxide

Introduction

Our state of mind is reflected in our breathing patterns. We breath rapidly when excited or scared, slowly when calm, and a surprise can make us gasp. Why we change our breathing patterns so drastically cannot be explained by metabolic concerns alone, and has been a long-standing mystery. There is a growing body of work showing that these changes in breathing can dynamically modulate blood oxygenation [22, 79], and by consequence the oxygenation in the brain [123]. Given that the baseline supply of oxygen to the brain has a large safety margin that can easily accommodate the metabolic demands of increases in neural activity, the reason for these changes in respiration (as well as increases in the local flow of oxygenated blood due to changes in neural activity in the brain via neurovascular coupling) remains unexplained.

Here we review the speculative hypothesis that changes in local tissue oxygenation linked to normal respiratory fluctuations modulate neural activity in the brain. Experiments in humans have shown that un-physiologically high levels of blood oxygenation can improve cognitive performance [13] and low levels of oxygenation (like those that occur at high altitude) can impair performance [28, 60], but whether the smaller changes in tissue oxygenation induced by changes in respiration (on a breath-by-breath basis and those caused by a change in respiratory rate) can have a meaningful effect is not known. In this hypothesis, oxygen functions like a neuromodulator, and respiration-driven changes in the level of oxygen [123] can affect the excitability of neurons, via direct actions on ion channels and by increasing the synthesis rate of many different neuromodulators. Like other canonical neuromodulators, oxygen levels are largely controlled by the activity of a small group of neurons that have reciprocal connections with other neuromodulatory nuclei [21, 116, 118, 119]. The physiological processes that modulate

This article is part of the special issue on Embodied Brain in Pflügers Archiv—European Journal of Physiology

✉ Patrick J. Drew
pjd17@psu.edu

1 Center for Neural Engineering, Department of Engineering Science and Mechanics, The Pennsylvania State University, University Park, PA 16802, USA

2 Medical Scientist Training Program, College of Medicine, The Pennsylvania State University, Hershey, PA 17033, USA

3 Institut de La Vision, INSERM, CNRS, Sorbonne Université, Paris, France

4 Department of Biomedical Engineering, The Pennsylvania State University, University Park, PA 16802, USA

5 Department of Neurosurgery, The Pennsylvania State University, University Park, PA 16802, USA

Published online: 28 June 2022

brain oxygenation are modulated by sensory stimuli, arousal levels, and cognitive demands [92], just like other neuromodulatory signals. Un-physiologically large increases or decreases in oxygen can drive changes in cognition [60], as is seen when levels of neuromodulators are changed pharmacologically. We note that these effects of respiration on neural activity via oxygen could co-exist both with direct neural drive in respiratory and olfactory areas to other brain regions [104, 121] and local oxygenation changes driven by neurovascular coupling and functional hyperemia [19, 63]. However, the effects we propose here would be distinct from directly mediated synaptic signaling (as inhalation cycle-linked oscillations [104]) and could be independent of changes in local blood flow (as in the hemo-neuro hypotheses [63]). The effects of oxygen on the brain that we discuss will depend on tissue oxygenation, which will be related to (but not the same as) hemoglobin saturation. The effects we discuss here could also act in parallel to (but distinct from) any changes in neural excitability caused by pH shifts secondary to changes in carbon dioxide levels which could impact neural excitability [5, 50]. The amplitude and frequency of breath-related oxygen fluctuations will vary with species- and individual-specific breathing differences, and will also be impacted by the physiological state of the lung (dead space, etc.). Below we discuss the possibility that oxygen can function in a modulatory fashion in the brain.

Baseline oxygen levels can supply all the metabolic needs of neurons

In many brain regions (but not all—[40, 91, 123]), sensory stimulation drives an increase in neural activity followed by local vasodilation (as known as functional hyperemia) mediated by many signaling mechanisms from neurons and other cells in the brain [89]. While this increase in flow is often attributed to the need to supply oxygen to active neurons, the increased oxygen is not necessary and usually greatly exceeds neuronal demands [53, 58, 62]. This clear oversupply of oxygen can be revealed with the application of vasoconstrictors like indomethacin [96] and caffeine [115], which can decrease cerebral blood flow by 30% without changing metabolism or any adverse cognitive consequences, consistent with a large safety margin in oxygen delivery. In anesthetized preparations, some brain areas even show inverted neurovascular coupling, with increases in activity driving vasoconstriction and oxygen decreases [16, 86, 94, 95]. Anticipation of a stimulus can also drive increase in blood flow without increases in local neural activity [97], suggesting the existence of other preparatory mechanism in the brain that brings arterial blood to the cortex, other than to meet the metabolic demand generated by local neural activity. Vasodilation/blood flow increases can be elicited by the activation of a small set of neurons that express nitric oxide synthase without activation of other neurons in the cortical network [20, 49, 52], showing that the overall metabolic demands are disconnected from the neural control of the vascular system. The lack of tight coupling of the local regulation of blood flow to metabolism in so many instances suggests that the flow increases might serve other purposes than to supply a pressing metabolic need, an idea that has been noted previously [37, 53]. It has been proposed that increase in flow with neurovascular coupling is not to service the bulk of the tissue, but regions where flow is limited [17, 53]. However, simulations have suggested that increasing blood flow does not actually remove low flow regions, but rather relocates them, suggesting that functional hyperemia may not even remove these regions of lower oxygenation, but only shift them [80]. This unintuitive change of perfusion further suggests that increases in oxygenation are not specifically to meet metabolic demands.

Whether increasing oxygenation in the brain affects metabolic activity depends on whether the production of ATP is limited by the concentration of oxygen. It is largely assumed that under physiological conditions, oxygen levels are far from rate limiting for neural metabolism, and increasing oxygen does not result in the increased production of ATP, as mitochondrial oxidative phosphorylation is saturated by oxygen concentrations well below 1 mmHg [29, 54, 108]. The oxygen dependence of mitochondrial oxidative phosphorylation depends on intracellular pH, and oxygen dependence becomes noticeable with alkaline pH [112]. However, the intracellular pH in the brain is near 7 [12, 67]. In the physiological pH range, the oxygen becomes limiting below a few mmHg (~3 mmHg), still well below the state in most of the tissue. Supporting the idea that mitochondrial oxidative phosphorylation in the brain is not limited by oxygen levels, hyperoxia does not increase brain metabolic rate [114] (though these are bulk measures that may not detect elevations of metabolism in small, poorly oxygenated regions). Systemic arterial oxygen levels of less than 20 mmHg (well below normal levels of ~90 mmHg [56]) are required to detectably decrease ATP levels in the brain [28]. Furthermore, measurements of mean cortical oxygen levels in the blood plasma (which will be higher than that in the tissue) in the cortex typically find oxygen concentrations in the range of 20–50 mmHg [11, 56, 85, 123]. In the extracellular space of the cortex, tissue oxygen levels are in the range of 10 to 40 mmHg, though the levels can be much higher immediately adjacent to arteries [17, 87], and veins passing near arteries can become oxygenated through diffusional shunting of oxygen [51]. While a small fraction of tissue may show oxygen levels below ~5 mmHg [56, 123], this is still far above the levels at which oxygen is limiting for ATP production.

Oxygen levels impact neuronal excitability via effects on ion channels

Neuromodulators typically function to make distinct cell types more or less excitable, altering their responses to stimuli and changing network output [18, 34]. While the oxygen sensitivity of neurons is often explored in the context of hypoxia, oxygen levels in neural tissue can fluctuate within the physiological range [56, 123], often following changes in neural activity (functional hyperemia), during exercise, or in phase with breathing [122, 123]. One tempting hypothesis is that the fluctuations in blood oxygenation due to alternating inspiration and expiration, as well as elevations and depression of respiration cycle-averaged blood oxygen over longer time scales, could modulate neuronal excitability and activity patterns. As most of the work we discuss here have been done in slices, one should bear in mind that the normal oxygen tension in slice experiments (where ionic mechanisms are probed) can be much higher than measured in vivo [43, 41]. With in vitro experiments, the oxygen gradient as a function of depth in the slice can be very large (~ 100 mmHg per 100 µm tissue) [8, 33, 43], leading to great heterogeneity of the measure due to effects of changing oxygen levels. As a result, in vitro conditions described as "normal or hypoxic" may range from hyperoxia to anoxia.

Several ion channels expressed widely in the brain are known to be sensitive to oxygen levels via a variety of mechanisms (Fig. 1). TASK-1 and 3 channels (both hetero- and homodimers) are inhibited by hypoxia [9, 105]. The channels are found in the carotid bodies and their activity contributes to (but is not necessary for) oxygen sensing [73]. A decrease in oxygen inhibits mitochondrial electron transport and subsequently leads to TASK channel inhibition. TASK-1 and 3 are also found in neurons in the basal forebrain [101, 109], and single cell RNA sequencing has shown these channels are expressed by thalamic interneurons, cholinergic

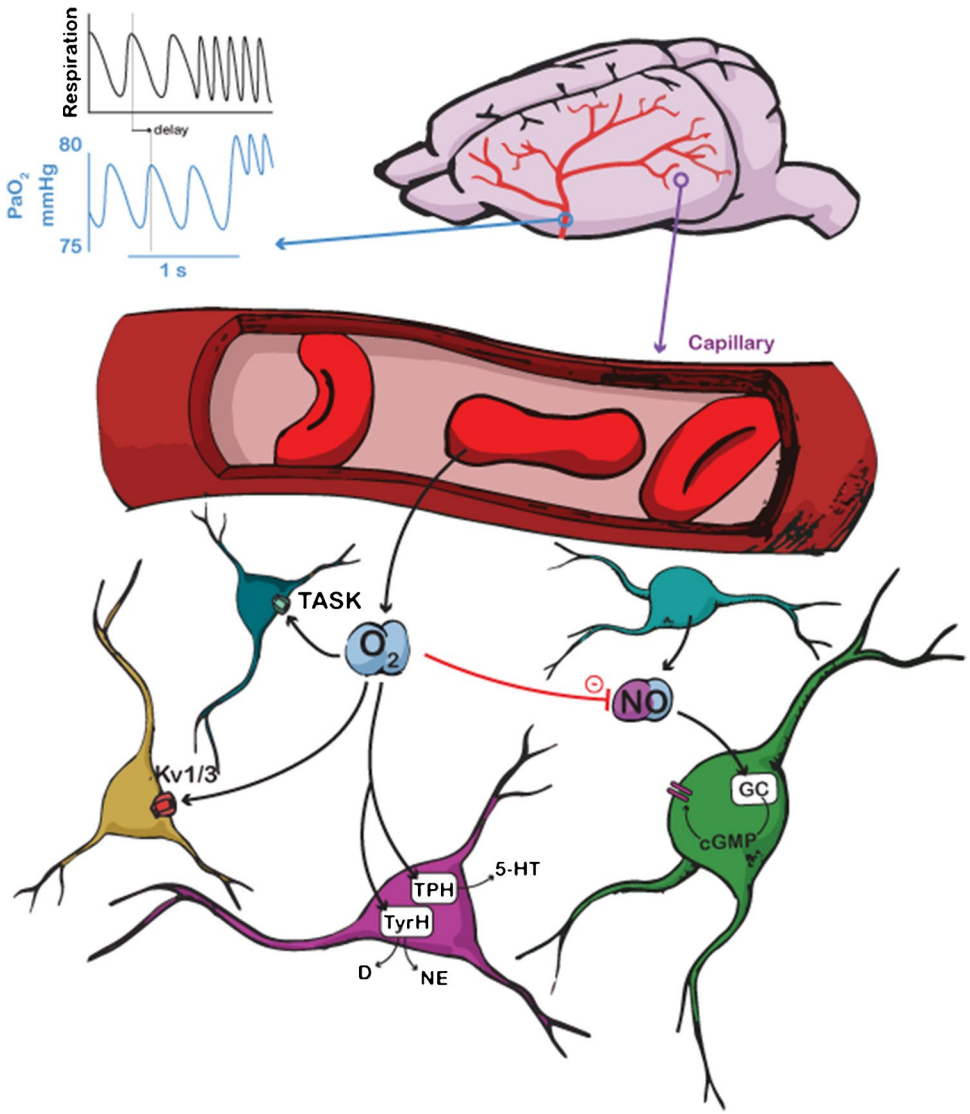


Fig. 1 Schematic showing different pathways by which oxygen can modulate neural excitability. Top, oxygen levels in major supply arteries oscillate on a breath-by-breath basis, as well as showing an overall increase with respiration rate. Scale is for expected values in a mouse. Respiration shows idealized measurement from a thermocouple, with upswings representing exhalation. Bottom left, oxygen modulates K + channels and TASK activity in neurons. Bottom middle, oxygen modulates tryptophan hydroxylase (TPH) synthesis of serotonin (5-HT) and tyrosine hydroxylase (TyrH) synthesis of dopamine (D) and norepinephrine (NE). Coloration of neurons is aesthetic. Bottom right, oxygen decreases nitric oxide (NO) concentrations which modulates neural activity

interneurons, and serotonergic neurons [120] (Fig. 1). Kv3 channels are also sensitive to oxygen levels [74] and are expressed by cortical and hippocampal excitatory and inhibitory neurons [45] (Fig. 1). A depression of oxygen levels will cause K^+ channel inhibition. In addition to potassium channels, L-type calcium channels are also thought to contribute to oxygen sensitivity in peripheral tissue [111]. Cells in the vasculature (smooth muscle, endothelial cells, and red blood cells) are also thought to be sensitive to oxygen, though the mechanisms are not clearly understood (see [42] for review). Changes in vessel tone require changes in the membrane potential [36], implying the activation of ion channels. While the molecular mechanisms linking oxygen levels to ion channel opening and closing are not well understood, several pathways have been implicated, including both NADPH oxidase-dependent mitochondrial superoxide anion generation and changes in the ratio of reduced to oxidized glutathione [55]. Other possible mechanism includes changes in prostaglandin levels and nitric oxide (discussed below). The net effect of oxygen levels would depend on the relative distributions of oxygen-sensitive ion channels in excitatory and inhibitory neurons, as is the case with many neuromodulators.

At the cellular level, neurons and glial cells, located in the medulla oblongata and hypothalamus, are able to sense oxygen levels and modulate respiratory rhythm accordingly [3, 69]. Though the mechanisms underlying these oxygen-induced changes are not completely understood, this demonstrates that some cells of the brain are able to change their activity in response to oxygen levels. Recent studies have shown that astrocytes (including astrocytes in the cortex, which are not traditionally thought of as oxygen-sensing cells) respond to oxygen changes with altering calcium signals [3, 106] and modulating the respiratory network activity [3, 4, 30, 31]. Given that astrocytes display regional diversity at the molecular and functional levels in the brain [7], astrocytes could vary in oxygen sensitivity according to their cellular function and metabolism.

Oxygen levels impact the level of the neuromodulator nitric oxide

In addition to any direct actions oxygen has on neuron excitability, oxygen has an antagonistic relationship with nitric oxide (NO). While increases in NO will increase oxygenation (via its vasodilatory actions), increased tissue oxygen facilitates the removal of NO that is linearly dependent on the oxygen concentration [103] (Fig. 1), creating a negative feedback loop important for equilibrium. Although the presence of central oxygen sensors in the CNS is a topic of debate, hypoxia will dilate and hyperoxia will constrict cerebral arterioles via modulation of NO levels [1, 38, 82, 84]. These blood flow effects occur even under isocapnic conditions [66, 107] and constant pH [83], which demonstrates that the traditional indirect sensing mechanisms of hypoxia via pH and CO_2 are not required for hypoxia-induced vasodilation. The oxygen-dependent rate of NO removal in the tissue may be an additional mechanism of maintaining oxygenation under hypoxic conditions [35].

In addition to its cerebrovascular effects [39], NO can greatly affect neural excitability and has been shown to increase the activity of neurons in the cortex [46], cerebellum [99], and other brain areas [24, 86]. Nitric oxide synthases, which produces NO, are found in the vascular endothelium (eNOS) and in neurons (nNOS). NO can also be produced in response to injury (iNOS). nNOS can exist in the cytoplasm of neurons or attached to the NMDA receptor where it can produce NO in response to glutamate and promote AMPA receptor trafficking to the synapse [81]. Regardless of the source of NO, NO-induced increases in neural excitability can be generated with exogenous application of NO donors or precursors [46] and occur through the GC/cGMP/PKG pathway [99]. In vivo electrophysiological recordings in the visual cortex show that L-arginine, an NO precursor, or DEA-NO, a NO donor, can increase neural excitability during visual stimulation, while inhibition of endogenous NO by a NOS inhibitor, L-MMA, decreases spiking [46]. In addition to modulating stimuli evoked firing rates, spontaneous firing of Purkinje neurons in cerebellar slices could also be increased by a NO donor via cGMP signaling [99]. Oxygen's ability to directly control the rate of NO consumption also provides another avenue by which tissue oxygenation could potentially influence neural activity. Simulations of oxygen-NO diffusion/degradation dynamics in the brain have shown that increasing levels of oxygen in the blood stream led to decreases in NO levels in the tissue [35]. In these simulations, the decreases in NO were enough to drive vascular changes (vasoconstriction). These changes in blood oxygenation would drive changes in NO in the tissue that could impact neural excitability. However, oxygen's interactions with NO degradation mean that cerebral blood flow will undergo compensatory changes that will tend to counter any changes in blood oxygenation on the time scale of seconds that it takes for a vascular response.

Oxygen levels impact the synthesis of many neuroactive substances

While mitochondrial respiration is not oxygen limited, the synthesis of many signaling molecules can be. For example, many of the enzymes involved in neuromodulator synthesis are rate limited by oxygen at physiological concentrations [108]. Acetylcholine synthesis is oxygen limited and is impaired in low oxygen conditions [26]. Tyrosine hydroxylase (involved in the synthesis of dopamine and norepinephrine) has a Km for oxygen in the range of ~ 45 mmHg, and tryptophan hydroxylase (involved in the synthesis of serotonin) has a Km in the range of ~ 20 mmHg

[108]. These Kms are high enough that physiological fluctuations in the level of oxygen in the brain [56, 122,123] could affect local synthesis of these neuromodulators (Fig. 1). Both chemically induced and hypoxemic-induced hypoxia decrease the synthesis of acetylcholine and amino acid-based neurotransmitters [27]. Hypobaric hypoxia lowers the concentration of norepinephrine and dopamine in the brain [77], though sustained hypoxia can drive compensation in these systems [14]. Interestingly, there is evidence that altered serotonin metabolism may contribute to the increased incidence of mental illness in residents at increased altitude [47]. In contrast, increased respiration rate will increase tissue oxygenation [123] and could lead to greater availability of neuromodulators via increased synthesis.

Oxygenation as a link between the peripheral state and the "central governor"

Sustained physical exertion over the time scale of minutes drives many cardiovascular changes [44]: cardiac output and respiration rate increase, while systemic blood carbon dioxide and oxygen levels fall. When we physically exert ourselves voluntarily, we stop when we become fatigued. Traditionally, this fatigue has been attributed to the buildup of lactate in the muscles. However, there is some evidence that this fatigue is detected in the brain, and that the feeling of fatigue is centrally generated [72]. This idea is known as the "central governor" hypothesis [71]. A variety of feedback signals, both via accumulating chemical signals and afferent neural feedback, have been proposed. As oxygen levels fall in the blood during sustained exercise, it is a plausible candidate as a signal from the periphery to the brain, and experiments manipulating inhaled oxygen in exercising humans have shown effects on performance that cannot be entirely ascribed to peripheral effects [72]. Hyperoxymia during all-out exercise increases work output and increases brain (but not muscle) oxygenation, suggesting that cerebral oxygenation could act as a sensor of total cardiovascular state [70]. In humans, increasing or decreasing inhaled oxygen respectively increases or decreases motor output, but has no effect on peripheral fatigue (as measured with electrical stimulation of muscles), suggesting that oxygen's role in preventing fatigue acts via its action on neurons in the brain [2].

Impact of oxygenation on cognitive performance and its relation to respiration

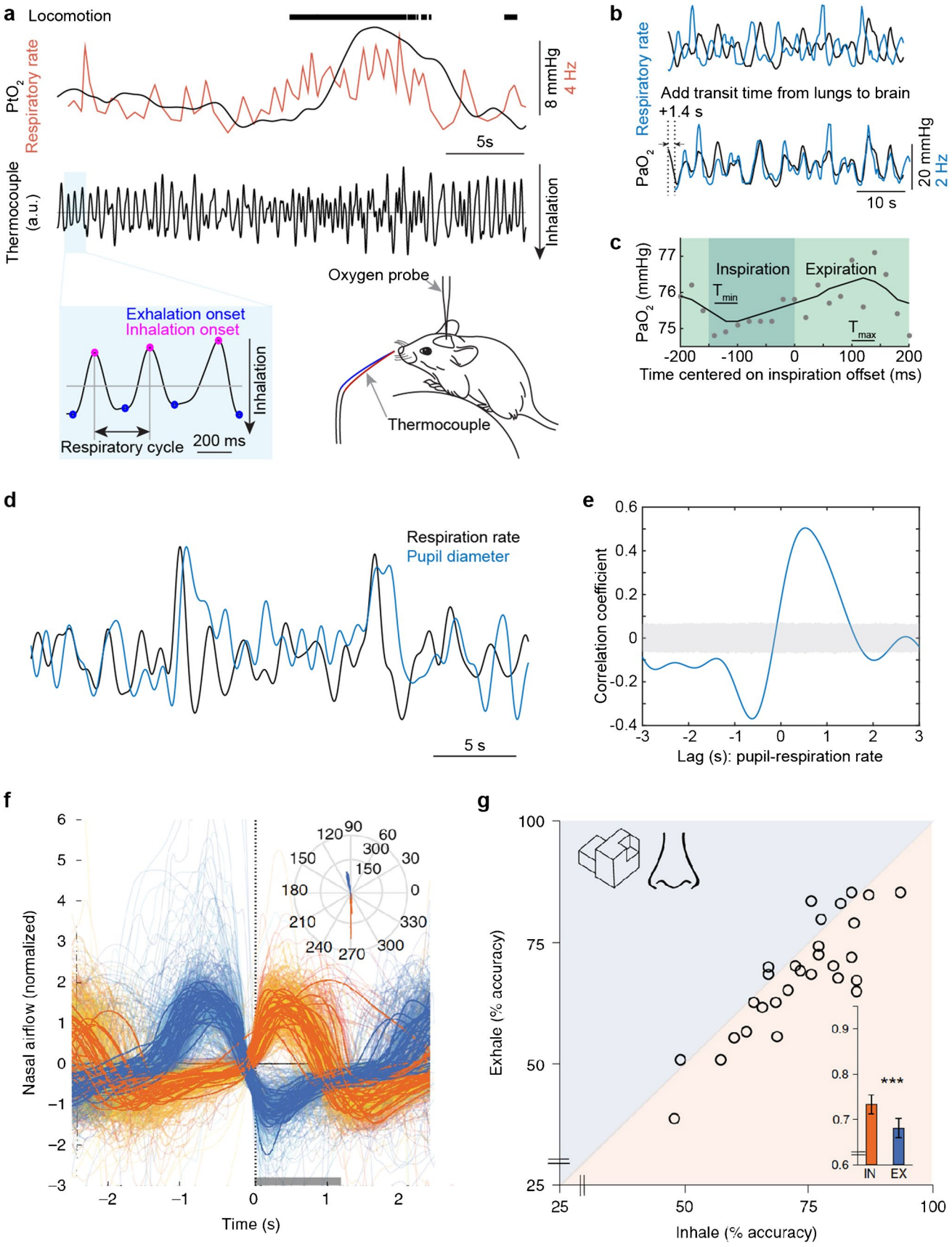
Anyone who has been at very high altitude knows how deleterious a reduction in oxygen can be for the performance of even the simplest of mental tasks. Hypoxia [28, 60] and high altitude causes many cognitive impairments that increase with severity of oxygen deficit [68, 117]. Many studies have shown that lower levels of brain oxygenation cause poorer performance in a wide range of cognitive tasks [60]. There are also numerous studies showing that respiratory entrainment of neural activity has important impacts on mood and cognition [57]. Oxygen levels in the blood decline with age [100], and these declines could contribute to the cognitive decline accompanying aging.

If oxygen serves a modulatory role in the brain, we would expect it to vary with behavioral state in a way that is not just due to increased exertion. In rodents, respiration locks with whisking [64]. In humans, respiration rate changes dynamically in response to stimuli and behavioral state [92]. Merely opening the eyes, reading, or listening to words causes a measurable increase in respiration that is hard to explain with metabolic factors alone [93]. Respiration locks to the onset of cognitive task, even ones that are not olfactory in nature and do not require a verbal answer [75]. Performance in the visuospatial task was significantly better during inhalation vs exhalation, potentially due to augmented brain oxygenation during inhalation [123]. As all these changes in respiration occur with minimal increases in exertion, their existence makes little sense unless oxygen serves some cognitive role.

For changes in respiration to modulate neural activity via changes in oxygen levels, changes in respiration rate and depth need to play an important role in setting arterial oxygenation (Fig. 2). Arterial oxygenation varies over the inhalation-expiration cycle, though the amplitude of the variations is inversely related to the breathing rate of the animal [22, 78, 79, 123]. Increases in respiration globally increase cerebral oxygenation, even in areas with no change or decrease in blood flow [123]. Although the average levels of oxygen and their respiration-linked changes are similar in both frontal and sensory cortices [123], there are wide variations in vascular density across the brain that could potentially make the oxygen fluctuations larger or smaller in different brain regions [48, 113], analogous to greater levels of modulation in certain brain regions.

Reciprocal interactions between respiratory related brain regions and modulatory regions

Neuromodulatory structures make brain-wide projections and also form reciprocal connections with other neuromodulatory nuclei [110, 88]. If oxygen acts like a neuromodulator, we would expect there to be connections between the pre-Bötzinger complex and other respiratory-control nuclei and canonical neuromodulatory regions. Supporting this idea, a genetically defined subset of neurons in the pre-Bötzinger complex has been found to send excitatory projections to the locus coeruleus (LC), and their activation affects LC activity enough to cause increases in arousal [116]. This


a
Locomotion
PtO2
Respiratory rate
8 mmHg
4 Hz
5s
Thermocouple (a.u.)
Inhalation
Exhalation onset
Inhalation onset
Inhalation
Respiratory cycle
200 ms
Oxygen probe
Thermocouple
b
Respiratory rate
Add transit time from lungs to brain
+1.4 s
PaO2
20 mmHg
2 Hz
10 s
c
PaO2 (mmHg)
77
76
75
Inspiration
Expiration
Tmin
Tmax
-200
-100
0
100
200
Time centered on inspiration offset (ms)
d
Respiration rate
Pupil diameter
5 s
e
Correlation coefficient
0.6
0.4
0.2
0
-0.2
-0.4
-3
-2
-1
0
1
2
3
Lag (s): pupil-respiration rate
f
Nasal airflow (normalized)
6
5
4
3
2
1
0
−1
−2
−3
−2
−1
0
1
2
Time (s)
90
120
60
150
30
300
150
180
0
210
330
240
270
300
g
Exhale (% accuracy)
100
75
50
25
25
50
75
100
Inhale (% accuracy)
0.9
0.8
0.7
0.6
***
IN
EX

◂**Fig. 2** **a**–**b** Respiration drives changes in cerebral and blood oxygenation. **a** Measuring respiration using a thermocouple. Top, example data showing tissue oxygenation in the somatosensory cortex of an awake, headfixed mouse measured using an oxygen sensitive microelectrode (black trace) and respiratory rate (orange trace), during locomotion. Middle, signal from a thermocouple placed near the nostril of the mouse. The thermocouple voltage tracks inhalation and exhalation due to the higher temperature of exhaled air, which causes increase in the thermocouple signal. Bottom left, expanded thermocouple signal showing of the detection of the onset of inspiratory (magenta dot) and expiratory phase (blue dot). Bottom right, schematic showing respiration measurement using a thermocouple. **b** Example data showing the temporal relation between respiratory rate (black) and oxygen tension (PaO_2, blue) in the center of one artery in somatosensory cortex of a mouse during periods of rest. The phase shift is caused by transit time from lungs to brain. **c** PaO_2 fluctuates within the respiratory cycle. The PaO_2 change in one artery of a headfixed, un-anesthetized mouse during the respiratory cycle at rest was measured using an intravascularly injected phosphorescent oxygen dye using a two-photon microscope. This technique allows measurement of the concentration of oxygen in the blood plasma from a single location in the vasculature. PaO_2 data (15 recordings with each of 50 s in duration) were aligned to the offset of inspiration. Each circle denotes averaged PaO_2 over a short window (20 ms) and over the 15 recordings. The solid curve denotes filtering of data (first order binomial filter, 5 repetitions). T_{min} denotes the time period (40 ms) PaO_2 reaches minimum. T_{max} denotes the time period (40 ms) PaO_2 reaches maximum. **d** Example data showing the temporal relation between respiratory rate (black) and pupil diameter (blue, an indicator of noradrenergic activity) during periods of rest in an awake, headfixed mouse. **e** Cross-correlation between respiratory rate and pupil diameter during periods of rest. Gray shaded area indicates 95% confidence interval. **f**–**g** Nasal inhalation at visuospatial task onset is associated with improved performance in humans. **f** Mean event-related nasal respiratory signal used to trigger trial-onset time-locked to inhalation (orange) or exhalation (blue). Time 0 denotes task initiation. The gray rectangle along the x axis represents the stimulus (1,200 ms). Inset: a polar plot of the respiratory phase (in degrees) at trial onset is shown. The orange and blue bins are trials triggered by inhalation and exhalation, respectively ($n=28$). **g** Scatter plot of performance in the EEG visuospatial task in inhalation and exhalation. Each point is a participant ($n=28$). The diagonal line is the unit slope line ($x=y$). Thus, if points accumulate below the line, this means performance was better during inhalation. In the inlay, the mean group performance is shown. Error bars are SEM. **a**–**c** adapted from [123], **f**–**g** adapted from [75]

coupling of oxygenation and modulation might take place on a breath-to-breath basis. As neurons from pre-Bötzinger complex neurons are linked with inspiratory phase of respiration [98], one would expect that there will be a direct relationship between the inspiratory phase of respiration and LC activity, if there is indeed a link between respiration and LC activity. Consistent with this idea, pupil diameter, an index of LC activity [102], rises in phase with the pre-inspiratory/inspiratory phase of respiration, and falls during the expiratory phase of respiration [61] (Fig. 2), consistent with a direct role in activation of LC from pre-Bötzinger complex. Different pools of neurons in the pre-Bötzinger complex also project to many nuclei across the brain, including the dorsomedial hypothalamus and lateral preoptic area [118]. The dorsomedial hypothalamus sends orexinergic projections (which play a key role in maintaining wakefulness [76]) to many brain regions. The dorsomedial hypothalamus also sends projections back to the pre-Bötzinger complex [23]. The lateral preoptic area sends projections to the ventral tegmental area (VTA) [25], which sends dopaminergic projections to many brain regions. The retrotrapezoid nucleus (RTN) receives serotonergic input, which can then influence breathing rate independent of pH [15, 65]. Thus the nuclei that control oxygen levels in the brain (via respiration) have connections with other modulatory nuclei.

Relationship to the hemo-neural hypotheses

Our hypothesis that oxygen modulates neural function partially overlaps with the hemo-neural hypothesis [10, 63]. In the hemo-neural hypothesis, increases in blood flow accompanying functional hyperemia send mechanical and/or chemical signals to neurons to enhance information processing [63]. As both respiration (a global factor) and vasodilation (with accompanying increase in blood flow, a local factor) contribute to modulating brain oxygenation [123], we hypothesize that global cerebral oxygen changes, caused by changes in respiration and/or increased consumption by other organs, modulate neural activity. Local oxygen changes due to functional hyperemia could potentially provide a more spatially restricted control of activity.

Issues with testing the modulatory oxygen hypothesis

Foremost, although extreme elevation and depression of blood oxygen (in the tens to hundreds of mmHg over minutes or longer) have been shown to have cognitive (and presumably neural) effects, it has not been determined if the much smaller and briefer changes that occur with respiration (in the range of few mmHg for a few seconds) can change neural activity. Testing this hypothesis is not an easy task. Experiments looking at the impact of respiration phase on cognitive tasks have the confound that in these experiments, other signals are present besides oxygen changes [75]. Oxygen's effects on NO degradation will tend to function as a homeostatic regulator of oxygen levels in the brain, so any change in respiration will tend to drive a compensatory change in cerebral blood flow, reducing the size and duration of respiration-induced oxygenation changes. The flow of red blood cells is stochastic and results in a highly variable delivery of oxygen, and the fluctuations in the oxygen levels that neurons experience [122] will tend to obscure any respiration-related changes. Finally, any experimental test will have to tease out any direct effects of oxygenation

from changes mediated by other neural signals accompanying respiration [104].

There are also several non-neuronal factors that will contribute to the individual details of the oxygen fluctuations in the tissue and thus any potentially modulatory effects of oxygen. The oxygen-affinity curve for hemoglobin shift rightward with increasing animal size [90], and the tidal volume and respiration rate will vary with size as well [32], so the amplitude and frequency of a breath-by-breath oxygen changes in brain tissue will differ by species. The oxygen levels will also be affected by lung physiology and health. Thus, some of the effects may be more or less salient under different physiological or task conditions or in certain animal species.

Summary

The brain receives more oxygen than it needs to power the synthesis of ATP, yet oxygen levels are dynamically regulated by changes in local vessel dilation and by changes in respiration (both breath-by-breath cyclic changes and changes due to overall respiratory rate change). Cognitive tasks increase respiration [75], and large changes in oxygen levels bi-directionally affect mental tasks and reaction times. These puzzling facts suggest that in the brain, oxygen has some other dynamic function above and beyond its direct metabolic role. We discussed the possibility that oxygen serves a neuromodulator-like function in dynamically tuning the responsiveness of neurons. One direct evidence is that oxygen levels modulate neuron excitability, just like canonical neuromodulators. Low oxygen levels can inhibit some ion channels to increase the excitability of neurons. Besides the direct neural excitatory effects, oxygen levels affect the level of neuromodulator nitric oxide via a closed-loop feedback mechanism, i.e., the breakdown rate of nitric oxide will increase with increased oxygen concentration. This provides another pathway by which oxygen can impact neural excitability, as nitric oxide has many effects on neurons via second messengers. In addition, low oxygen levels will reduce the synthesis of many neuromodulators, such as acetylcholine and norepinephrine. The broad link between oxygenation and numerous modulatory pathways at different levels explains the relation between respiration and physical/cognitive performances. It explains how peripheral fatigue (due to sustained exercise) can provide brain-wide signals via changes in oxygen levels in the blood. It also suggests that the increase in oxygenation in the brain caused by increased respiration upon presentation of an unexpected stimulus may serve a similar purpose as the release of a burst of norepinephrine or acetylcholine, which may explain why cognition is locked with respiration and why we have better cognitive performance in high oxygen level environments. While testing this hypothesis will be challenging, it may give us insight into the purpose of our dynamic respiratory patterns.

Funding QZ is supported by a Career Development Award from the American Heart Association (935961). PJD is supported by R01NS078168 and R01NS079737 from the National Institutes of Health. SC is supported by the FRM (EQU201903007811), the ANR (NR-16-RHUS-0004 [RHU TRT_cSVD]; IHU FOReSIGHT [ANR-18-IAHU-0001]), and the Fondation Leducq Transatlantic Networks of Excellence program (16CVD05).

Declarations

Research involving human participants and/or animals This is a review of the published literature, and ethical approvals can be found within the cited references.

Competing interests The authors declare no competing interests.

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