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Anxiety, Respiration and Cerebral Blood Flow: Implications for Functional Brain Imaging

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Abstract

Brain functional imaging methods, such as fMRI, are sensitive to changes in cerebral blood flow (CBF) that are normally associated with changes in regional neural activation. However, other endogenous and exogenous factors can alter CBF independently of brain neural activity, thus complicating the interpretation of functional imaging data. The presence of an anxiety disorder, as well as change in state anxiety, is often accompanied by respiratory alterations that affect arterial CO₂ tensions and produce significant changes in CBF that are independent of task-related neural activation. Therefore, the effects of trait and state anxiety need to be given close consideration in interpreting functional imaging findings. In this paper, we review the dependence of most brain functional imaging methods on localized changes in CBF and the potentially confounding effects of anxiety-related alterations of respiration on interpreting patterns of functional activation. Approaches for addressing for these effects are discussed.

Keywords

Anxiety; Respiration; Hyperventilation; Cerebral Blood Flow; Imaging; fMRI

Introduction

Methods for imaging brain function are increasingly being used to investigate brain functional pathways, regulatory mechanisms, and changes associated with treatment in psychiatric disorders. This research has produced valuable insights regarding the pathophysiology of psychiatric disorders. Earlier functional imaging modalities, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), have been supplemented by functional magnetic resonance techniques (1), most commonly blood oxygen level-dependent (BOLD) fMRI. BOLD fMRI derives contrast from deviations in blood oxygenation that accompanies neural activity (2). During activation, the general increase in local blood flow results in an increased ratio of oxygenated to deoxygenated hemoglobin in that region. Oxyhemoglobin and deoxyhemoglobin have different magnetic properties that influence the magnetic susceptibility of surrounding tissues. In a typical experimental design, the so-called “boxcar design,” a rest and experimental state are alternated for a number of trials. The resultant data analyses average these relative signal differences (e.g., percent change) across periods to yield an activation map. This map shows areas with large changes (statistically

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inferred) in activity. By contrast, measuring resting state fluctuations in signal intensity (3) reveals what event-related BOLD analyses remove, constant activations readying the system for efficient processing.

BOLD fMRI is powerful investigational tool, and provides a number of advantages over other functional imaging methods. For example, compared to PET, BOLD fMRI provides greater sensitivity and spatial and temporal resolution, allowing the acquisition of more reliable event-related measurements in single subjects. However, a number of limitations are recognized for the method, as well. First, BOLD fMRI does not deliver quantitative measures. This makes changes in signal response sensitive to within- and between-group differences in baseline activity and reactivity (4). More recent developments have sought to quantify fMRI acquisition, but these methods are not widely used (5–7). Some newer approaches, which calibrate the BOLD signal using breath-hold techniques, hold promise for standardizing functional measurements across experiments and scanner field strengths (8). Second, the physiological interaction between neurons and glia during neuronal firing is elegantly complicated (9), with BOLD fMRI changes measuring only a single component of the interaction. The precise relationship between BOLD signal intensity changes, blood flow, oxygenation, baseline metabolic rates and neurotransmitter shuttling are very difficult to investigate (10). However, some recent studies utilizing new or combined techniques have begun to make substantial inroads and largely support assumptions of a qualitative relationship between changes in brain activation and blood flow (11) (fMRI based on changes in vascular space occupancy (12), for example). Third, BOLD signal intensity changes may not be precisely co-localized with neural activity. For example, differences in the magnetic resonance properties of blood and tissue can lead to detection of activity-related signal changes in draining veins at a distance from the site of brain activity (13). Other sources of spatial distortion may include incidental neural activation or blood flow increases extending beyond the area of target activation (14). Recent data suggest also that there may be only a small window of time (e.g., 2–3 sec) following neuronal activation during which spatially specific functional images may be acquired (15).

Since the blood oxygen changes on which BOLD signal responses rely are mediated by changes in CBF, factors affecting CBF that are independent of local brain activity need to be considered. A number of studies have shown that factors such as age (16), gender (17), hematocrit level (18), menstrual cycle (19,20), caffeine (21,22) and nicotine (23) use and withdrawal, can all have significant impacts on the relationship between brain metabolic activity, CBF and BOLD fMRI signal response. One factor that can have an even greater effect on this interrelationship, but has not been widely accounted for, is the change in respiration associated with acute and chronic anxiety. Respiratory change is a sensitive index of both trait and state-anxiety and even small changes in respiration can significantly alter arterial carbon dioxide tension (P_{CO_2}) which, in turn, has a large effect on CBF. P_{CO_2} has a large regulating influence on CBF, even greater than other intrinsic physiological factors, such as cerebral metabolism, cerebral perfusion pressure, or cardiac output. Global CBF is positively correlated to PCO_2 , with an approximately linear relationship between 20–60 mmHg PCO_2 . Thus, for each 1 mmHg increase or decrease in PCO_2 over the range of 20–60 mmHg, there is a corresponding CBF change in the same direction of approximately 1–2 ml/100g/min, or 2–5% (24,25). So, even small alterations in respiration can produce significant changes in global CBF. This may be particularly true in certain groups, such as those with panic disorder, who may experience greater changes in CBF during periods of hypoxia (26).

Neuroimaging Studies of Anxiety

A comprehensive review of neuroimaging findings in anxiety states and disorders is beyond the scope of this paper. A number of recent reviews on the topic have been published (27–31). To summarize, consistent with many neurobiologic theories of pathological fear and

anxiety (32), most functional neuroimaging studies have found evidence of abnormal activity in frontal and limbic-paralimbic cortical areas in patients with a variety of anxiety disorders. In panic disorder, for example, abnormal hippocampal activity at baseline (33), and higher insular activation and decreased prefrontal activation during symptomatic periods, have been shown (34,35). Generally, patients with post traumatic stress disorder (PTSD) exhibit lower basal activation of the anterior cingulate and increased activation of paralimbic regions and the amygdalae, as well as greater decreases in frontal cortical regions during stressful tasks, such as trauma cues (36–40).

Anxiety, Respiration and CBF

Respiratory dysregulation is characteristic of anxiety and related symptoms are a diagnostic feature of several anxiety disorders. Patients with panic disorder, for example, typically exhibit chronic hyperventilation (41), breath-to-breath respiratory instability and frequent sighing (42,43), even during panic-free periods (44). Sustained hyperventilation causes large reductions in global CBF, but even a single sigh can produce a 1–3 mmHg decrease in PCO₂, enough to decrease CBF. Respiratory pattern differences are similarly present, albeit less consistently, in other anxiety disorders (e.g., generalized anxiety disorder) (44). Even for subjects without an anxiety disorder, increases in state-anxiety can be accompanied by acute increases in respiration rate and a corresponding hypocapnia (45–47). Individuals with high trait-anxiety may be more likely to respond to psychological stress with exaggerated respiratory increases (48). Since even mild hyperventilation produces significant decreases in CBF that are unrelated to task-evoked activation, the effects of both trait and state anxiety need to be carefully considered when interpreting functional imaging studies based on localized changes in CBF. While it is more common for patients with anxiety disorders to increase ventilation (hypocapnia), the effects of breath holding are equally important to consider in the context of induced signal changes. A number of recent studies have focused on breath holding and BOLD signal changes as a metric to evaluate vascular tone, demonstrated to differ between children, adults (49) and aged samples (50). While vascular tone is an interesting concept to consider separately when evaluating BOLD signal changes, the impact of even short breath-holds (e.g., 3 seconds) at the start of an activation block (as may occur with increasing task demand) may confound fMRI results (51).

The MRI scanning process itself has been shown to increase anxiety and reduce CBF in a substantial portion of healthy subjects (52,53). More than one-third of non-psychiatric general clinical patients report moderate to severe levels of anxiety when undergoing a clinical MRI procedure, with some experiencing severe anxiety or new onset of panic attacks (54–58). One recent study reported that almost half of patients experienced distress related to the noise and confinement during MRI scanning (59). It was also found that subjects differ significantly in how they cope to the stress of the MR environment (60). Marked changes in CBF associated with procedural distress appear to habituate after the first session in most healthy subjects undergoing multiple sessions (61).

However, patients with anxiety disorders habituate physiologically more slowly to stressful experimental stimuli, and so might be expected to show less habituation to the scanning process, as well (62). There is also some evidence to suggest that CBF effects due to anxiety follow a Yerkes-Dodson-type curve (52), with low anxiety subjects demonstrating an increase in CBF with anxiety, whereas highly anxious subjects show linear decrease in CBF with increasing anxiety (52). This may be due to an intrinsic tendency for greater respiratory reaction in anxiety patients, since state-related mood effects on respiratory responses are proportional to trait anxiety levels (63). These data also suggest that greater anxiety-related CBF responses can be expected in other psychiatric populations with overlapping features, such as major depressive disorder. These respiratory changes may have both long and short time components,

for example, the initiation of a mild hyperventilation state which persists for minutes, interspersed with individual breath-holds or sighing during task initiation.

The confounding effects of arousal and state anxiety on functional contrast have been shown in several functional neuroimaging studies (64). However, in the published functional neuroimaging studies investigating situational anxiety or pathological anxiety states, there have been inconsistent efforts to control or account for the effects of respiration on imaging data. From efforts to account for respiratory influences, respiratory differences between anxious and non-anxious subjects have been found to exert such a large effect that, when CBF values are adjusted to PCO₂ levels, any functional activation became non-significant (65). Others have found that CBF changes associated with anxiety are not wholly explained by changes in PCO₂ (66,67). Factors associated with anxiety states, such as systemic sympathetic activation also have a small direct effect on cerebral vasoconstriction (68) and can modulate CO₂-mediated CBF reactivity (69) and additionally contribute to CBF changes associated with anxiety. Thus, differences in respiratory patterns or PCO₂ cannot entirely account for CBF changes associated with anxiety, but the importance of PCO₂ effects on CBF remains critical for interpreting functional imaging data.

Mechanisms of effect

The pathway through which PCO₂ changes produce alterations in CBF is well delineated. PCO₂ affects extracellular and perivascular pH, which alters the properties of vascular smooth muscle (70,71). In the presence of carbonic anhydrase, CO₂ is quickly hydrated to form carbonic acid and its dissociation products, bicarbonate and hydrogen ions. The resultant acidic extracellular environment enhances the vasodilatory effect of adenosine (72) and increases potassium ion conductance across vascular smooth muscle (73), resulting in blood vessel dilation and thus increased flow (74). The effect of pH on cerebral vascular tone may be mediated by a variety of factors, including nitric oxide (NO) (75), lactate (76), prostanoids (77), cyclic nucleotides (78), potassium channels (79) and intracellular calcium (80). Further, the degree to which CBF is altered by changes in PCO₂ is also influenced by various intrinsic factors in addition to anxiety state, such as baseline CBF, age, cardiopulmonary status and the presence of cerebrovascular pathology. For example, CBF responsivity to changes in PCO₂ progressively decreases with age and during periods of hypotension (81–83). Regional cerebral ischemia also can affect CBF responses to PCO₂, with graded reductions in reactivity occurring as a function of proximity to the site of occlusion and related to CBF reduction in the area (84). In contrast, chronic hypertension does not appear to alter PCO₂ reactivity when subjects with hypertension are compared to normotensive subjects (85).

Cerebrovascular reactivity to changes in PCO₂ also varies by brain region. For example, greater decreases in CBF occur in grey matter than in white matter during hypocapnia (86). Significant regional heterogeneity of cerebral vascular response to changes in PCO₂ has also been reported. Using PET, Ito and colleagues (87) observed large relative increases in CBF (i.e., >10% per mmHg increase in PCO₂) in the pons, cerebellum, thalamus and putamen during 5 minutes of hypercapnia induced by inhalation of 7% CO₂ gas which were significantly greater than that measured for the brain as a whole. In contrast, smaller than average relative CBF increases were measured in temporal, temporo-occipital, and occipital cortical regions. During hyperventilation-induced hypocapnia, greater than average CBF decreases were measured in the pons, putamen temporal, temporo-occipital and occipital cortical regions relative to the brain as a whole. In contrast, smaller than average CBF reductions in the precentral gyrus, prefrontal cortex and cerebellum were observed during hypocapnia. However, variable regional decreases in response to hypocapnia were less pronounced (i.e., 3% per mmHg change in PCO₂) than the variation in regional increases observed during hypercapnia. Similarly, evaluation of the regional distribution of BOLD fMRI signal decreases to lower PCO₂ during

sustained hyperventilation has observed greater reductions in the insular cortex, thalamus, striatum and cerebellum than in the frontal, parietal and occipital areas (88). In total, these observations suggest that cerebrovascular responsivity to PCO₂ varies significantly by region, an additional factor to be taken into account when assessing the impact of respiration on functional imaging results.

Global versus regional effects

A related factor in considering the effects of anxiety on functional imaging contrast is how global alterations in CBF can influence localized changes in cerebrovascular reactivity related to neural activity. For example, Posse and colleagues (89) found that graded hypo- and hypercapnia produced significant changes in task-related localized fMRI signal contrast that was inversely proportional to PCO₂. An unresolved controversy is the question of whether changes in global CBF affect local fMRI response patterns in simple (i.e., additive) or more complex ways. The resolution of this question has important implications for the analysis of neuroimaging data to account for the confounding effects of global CBF changes (as well as other factors that affect global signal intensity). Different approaches for analyzing fMRI BOLD responses have either assumed that regional signals are directly proportional to global signal intensity (90), or, conversely, that the effects are independent and additive (91).

In most of the studies that have sought to address this question, alterations in global CBF have been produced by manipulating PCO₂ via CO₂ inhalation, breath holding, or overbreathing. For example, Ramsey et al (92) used PET to measure CBF responses in the insular cortex, centrum semiovale and visual cortex to visual stimulation under conditions of hypocapnia, normocapnia and hypercapnia. They found greater increases in CBF in the insular cortex (grey matter) than in the centrum semiovale (white matter) associated with rising PCO₂ from CO₂ inhalation. In contrast, no significant differences in the magnitude of visual stimulus responses were observed between the three breathing conditions. Thus, it appeared that the increase in signal associated with stimulus-induced regional activation was independent of that associated with CO₂ inhalation-induced increases in CBF. Li et al.(93) used fMRI to study BOLD response to photic stimulation under normo- and hypercapnic (using breath holding) conditions. They similarly found signal increases in visual cortex during breath holding, but BOLD response to visual stimulation did not differ from normocapnic response conditions. Also, Corfield et al.(94) reported no significant interaction between the effects of visual stimulation and PCO₂ level on the intensity of BOLD signal response in occipital cortex.

In contrast to the above noted findings, Shimosegawa et al. (95) reported that absolute increases in PET signal in visual cortex during photic stimulation were significantly lower during hypocapnia than under normocapnic conditions. However, fractional increases (i.e., percent of change relative to baseline) produced by visual stimulation did not differ between hypocapnic, normocapnic and hypercapnic conditions. Bandettini and Wong (96), found that hypercapnia (from breathing 5% CO₂) reduced activation-induced fMRI signal changes in motor cortex relative to normocapnic conditions. Weckesser and colleagues (97) observed that hypocapnia induced by voluntary hyperventilation significantly reduced BOLD fMRI signal response in visual cortex such that, in 3 out of 6 subjects in their study, signal changes were not different from those in unactivated areas (Figure 1). Additionally, Posse et al. (89) found that fMRI contrast changes due to visual stimulation more than doubled when PCO₂ was increased from 20 mmHg to 50 mmHg, whereas, at a PCO₂ of 70 mmHg, functional contrast was virtually abolished (Figure 2).

Other aspects of the event-related BOLD response appear also to be significantly affected by changes in arterial gases. Kemna and Posse (98) reported that the temporal dynamics of the event-related fMRI signal changed in accordance with PCO₂ changes. For example, response

curve full-width-at-half-maximum values increases with increasing PCO₂ during visual stimulation. Likewise Cohen et al. (99) reported that under conditions of hypocapnia, normocapnia or hypercapnia, the magnitude of BOLD response to visual stimulation, as well as the temporal dynamics of those responses (e.g., onset time, time-to-peak), was inversely related to PCO₂ levels. Kashikura and colleagues (100) also examined the effect of hyperoxia on visual event-related BOLD fMRI signals with findings that, in comparison with normoxic conditions, hyperoxia is associated with larger peak height and shorter peak time of BOLD response curves measured in V1 (101). However, those findings are in contrast to those of Lindauer et al. (102), who found a decreased stimulus-induced response during hyperoxia.

Thus far, we have discussed the influence of arterial gas tensions on CBF and, so, BOLD signal response. However, it may also be the case that changes in gas tensions affect neural activity itself. For example, increased extracellular pH has been associated with increased neural excitability. And, conversely, extracellular acidosis is accompanied by decreased neural activity (103,104). Thus, Huttunen et al. (105) found that certain EEG auditory evoked potentials are reduced during hypocapnia. They postulated that a rise in pH in neuronal tissues increases neural excitability and leads to greater spontaneous, asynchronous cortical neuron activity, thus, decreasing stimulus-locked neural responses. Recently, Friedman et al. (106) observed that patients with panic disorder exhibited a blunted brain pH response to hypocapnia during carefully regulated hyperventilation. This finding is consistent with prior reports of excessive brain lactate production in the disorder (107–109), and might imply different neuronal activation response to PCO₂ changes (from differential pH response) in this population. Though speculative, these results suggest that PCO₂ changes can impact BOLD signal change by modulating both CBF and, potentially, neuronal activity, as well.

PCO₂ and CBF oscillations

Periodic oscillations are another factor impacting signal measurement. Spontaneous periodic oscillations in cerebrovascular and metabolic resting states that are not directly related to brain-activity can be a significant source of noise in neuroimaging studies (assuming the oscillations are not themselves the subject of study, e.g. (3,110)) as they can reach similar magnitudes as stimulus-induced changes (111). Periodic oscillations observed in CBF appear to be similar to flow changes seen in the peripheral arteries and occur in a least four distinct frequency ranges: heart rate, respiration rate, low frequency (~ 0.1 Hz) and very low frequency (~0.01–0.05 Hz) (112). Oscillations at these same frequencies have been observed in oxy- and deoxyhemoglobin and cytochrome-oxidase levels (111). Low and very low frequency range oscillations are also observed for PETCO₂ (113). It has been posited that CBF oscillations facilitate cerebral autoregulation (114) in much the same way that peripheral vasculature regulatory control may be facilitated by periodic oscillatory behavior (115,116), as has been described in more general terms of dynamic autoregulation (117–119). However, because spontaneous periodic oscillations in cerebrovascular and metabolic elements are not random, signal variability due to these activities is not significantly reduced by time averaging of data sets. In this context, oscillations in CBF can be significantly influenced by varying PCO₂ levels with periods of hypercapnia suspending periodic fluctuations in CBF that, conversely, are augmented during hypocapnia (120). Therefore, some have sought to improve functional signal-to-noise ratios by filtering spontaneous physiological oscillations of known frequencies (e.g., heart rate, respiration rate) out of imaging signals (121). More recently, it was demonstrated that regressing out BOLD signal changes linked to periodic variability in respiratory tidal volume (or pacing subjects' respiratory rate and depth) significantly improved detection of task-related activation and deactivation (122).

Approaches to accounting for PCO₂ effects on BOLD fMRI response

There are several approaches for managing the effects of anxiety and PCO₂ changes on functional neuroimaging studies. All require that investigators obtain continuous measurements of PCO₂, or end-tidal CO₂, which has been shown to be a reliable and accurate estimate of PCO₂(123), even during hyperventilation (124). One approach has been to acquire imaging data only during periods when PCO₂ and CBF have reached steady state levels, both at baseline and during challenges (86). This may be especially important for provocation studies, such as those that employ hyperventilation or breathing CO₂-enriched air to induce anxiety or panic. However, steady states might not be achievable with some study designs or for highly anxious subjects. During hyperventilation, CBF begins to decrease rapidly within 20 seconds of onset of the drop in PCO₂ (125), and then begins to level off within 1–2 minutes. With sustained hypocapnia, CBF values then gradually rise back toward baseline values. Similarly, during CO₂ inhalation, CBF rapidly increases with increasing PCO₂ and then slowly declines toward baseline levels during sustained hypercapnia. Thus, both under conditions of hypercapnia and hypocapnia it is unclear whether a true steady-state period in CBF can be attained. However, available data suggest relatively stable CBF for at least 2 minutes (88, 126), and possibly as long as 10 minutes (127), following the initial change in PCO₂. Within 1–2 minutes of the termination of short periods of hyperventilation or CO₂ inhalation, CBF appears to return to baseline levels, although a brief “overshoot” past baseline values may also occur (128). It should be emphasized, though, that characterizations of the CBF time course during experimental hypo- and hypercapnia have come from studies of healthy subjects and changes in CBF were estimated from measures of blood velocity changes in the middle cerebral artery. Therefore, it is unclear whether these time course data can be generalized to specific patient groups and to all brain regions. For example, this time course probably differs for patients with panic disorder, who exhibit slower recovery from hyperventilation episodes (129) (Figure 3).

A second approach has been to adjust for the effect of PCO₂ on global CBF (74,130). General bivariate adjustment formulas based on previously published findings can be utilized. However, large individual variability exists in the quantitative relationship between PCO₂ and CBF. Therefore it is likely that this approach introduces new sources of error. An alternative approach to accounting for the effects of PCO₂ on BOLD fMRI signal response is to calibrate the two variables within each subject by using transfer function analysis as the basis for regressing out changes in CBF due to PCO₂ changes. For example, during a pre-experiment calibration session, images are acquired during each of three breathing conditions: resting PCO₂ and then at sustained breathing levels adequate to maintain PCO₂ above (e.g., 45 mmHg) and below (e.g., 35 mmHg) a subject’s resting level. A regression line of MR signal on PCO₂ can then be computed as a with-in subject estimate of the respiratory influence on BOLD signal intensity by region that is then used as a scaling factor in interpreting subsequent experimental data for that subject.

Summary

Changes in respiration associated with anxiety and anxiety disorders can produce local and global changes in cerebral blood flow that is unrelated to regional neuronal activation. These changes confound the interpretation of neuroimaging study results and increase the risk of either identifying spurious results or masking potentially real findings. By integrating measurement of real-time PCO₂ and fMRI indices, this important factor can be minimized, thereby ensuring that specific targeted experimental features are more clearly identified.

References

1. Posse S, Muller-Gartner HW, Dager SR. Functional Magnetic Resonance Studies of Brain Activation. *Semin Clin Neuropsychiatry* 1996;1(1):76–88. [PubMed: 10229785]
2. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A* 1990 Dec;87(24):9868–72. [PubMed: 2124706]
3. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A* 2005 Jul 5;102(27):9673–8. [PubMed: 15976020]
4. Stark CE, Squire LR. When zero is not zero: the problem of ambiguous baseline conditions in fMRI. *Proc Natl Acad Sci U S A* 2001;98(22):12760–6. [PubMed: 11592989]
5. Posse S, Binkofski F, Schneider F, Gembris D, Frings W, Habel U, et al. A new approach to measure single-event related brain activity using real-time fMRI: feasibility of sensory, motor, and higher cognitive tasks. *Hum Brain Mapp* 2001;12(1):25–41. [PubMed: 11198103]
6. Fujita N, Shinohara M, Tanaka H, Yutani K, Nakamura H, Murase K. Quantitative mapping of cerebral deoxyhemoglobin content using MR imaging. *Neuroimage* 2003;20(4):2071–83. [PubMed: 14683711]
7. Posse S, Wiese S, Gembris D, Mathiak K, Kessler C, Grosse-Ruyken ML, et al. Enhancement of BOLD-contrast sensitivity by single-shot multi-echo functional MR imaging. *Magn Reson Med* 1999;42(1):87–97. [PubMed: 10398954]
8. Cohen ER, Rostrup E, Sidaros K, Lund TE, Paulson OB, Ugurbil K, et al. Hypercapnic normalization of BOLD fMRI: comparison across field strengths and pulse sequences. *Neuroimage* 2004;23(2):613–24. [PubMed: 15488411]
9. Bonvento G, Herard AS, Voutsinos-Porche B. The astrocyte-neuron lactate shuttle: a debated but still valuable hypothesis for brain imaging. *J Cereb Blood Flow Metab*. 2005in press
10. Logothetis NK, Wandell BA. Interpreting the BOLD signal. *Annu Rev Physiol* 2004;66:735–69. [PubMed: 14977420]
11. Hoge RD, Franceschini MA, Covolan RJ, Huppert T, Mandeville JB, Boas DA. Simultaneous recording of task-induced changes in blood oxygenation, volume, and flow using diffuse optical imaging and arterial spin-labeling MRI. *Neuroimage* 2005 Apr 15;25(3):701–7. [PubMed: 15808971]
12. Lu H, van Zijl PC. Experimental measurement of extravascular parenchymal BOLD effects and tissue oxygen extraction fractions using multi-echo VASO fMRI at 1.5 and 3.0 T. *Magn Reson Med* 2005;53(4):808–16. [PubMed: 15799063]
13. Lai S, Hopkins AL, Haacke EM, Li D, Wasserman BA, Buckley P, et al. Identification of vascular structures as a major source of signal contrast in high resolution 2D and 3D functional activation imaging of the motor cortex at 1.5T: preliminary results. *Magn Reson Med* 1993;30(3):387–92. [PubMed: 8412613]
14. Saad ZS, Ropella KM, DeYoe EA, Bandettini PA. The spatial extent of the BOLD response. *Neuroimage* 2003 May;19(1):132–44. [PubMed: 12781733]
15. Sheth SA, Nemoto M, Guiou MW, Walker MA, Toga AW. Spatiotemporal evolution of functional hemodynamic changes and their relationship to neuronal activity. *J Cereb Blood Flow Metab* 2005 Jul;25(7):830–41. [PubMed: 15744249]
16. Ross MH, Yurgelun-Todd DA, Renshaw PF, Maas LC, Mendelson JH, Mello NK, et al. Age-related reduction in functional MRI response to photic stimulation. *Neurology* 1997;48(1):173–6. [PubMed: 9008514]
17. Levin JM, Ross MH, Mendelson JH, Mello NK, Cohen BM, Renshaw PF. Sex differences in blood-oxygenation-level-dependent functional MRI with primary visual stimulation. *Am J Psychiatry* 1998;155(3):434–6. [PubMed: 9501761]
18. Levin JM, Frederick Bde B, Ross MH, Fox JF, von Rosenberg HL, Kaufman MJ, et al. Influence of baseline hematocrit and hemodilution on BOLD fMRI activation. *Magn Reson Imaging* 2001;19(8):1055–62. [PubMed: 11711229]

19. Rasgon NL, Thomas MA, Guze BH, Fairbanks LA, Yue K, Curran JG, et al. Menstrual cycle-related brain metabolite changes using 1H magnetic resonance spectroscopy in premenopausal women: a pilot study. *Psychiatry Res* 2001;106(1):47–57. [PubMed: 11231099]
20. Epperson CN, Haga K, Mason GF, Sellers E, Gueorguieva R, Zhang W, et al. Cortical gamma-aminobutyric acid levels across the menstrual cycle in healthy women and those with premenstrual dysphoric disorder: a proton magnetic resonance spectroscopy study. *Arch Gen Psychiatry* 2002;59(9):851–8. [PubMed: 12215085]
21. Dager SR, Layton ME, Strauss W, Richards TL, Heide A, Friedman SD, et al. Human brain metabolic response to caffeine and the effects of tolerance. *Am J Psychiatry* 1999;156(2):229–37. [PubMed: 9989559]
22. Laurienti PJ, Field AS, Burdette JH, Maldjian JA, Yen YF, Moody DM. Dietary caffeine consumption modulates fMRI measures. *Neuroimage* 2002;17(2):751–7. [PubMed: 12377150]
23. Stein EA, Pankiewicz J, Harsch HH, Cho JK, Fuller SA, Hoffmann RG, et al. Nicotine-induced limbic cortical activation in the human brain: a functional MRI study. *Am J Psychiatry* 1998;155(8):1009–15. [PubMed: 9699686]
24. Poulin MJ, Liang PJ, Robbins PA. Dynamics of the cerebral blood flow response to step changes in end-tidal PCO₂ and PO₂ in humans. *J Appl Physiol* 1996;81(3):1084–95. [PubMed: 8889738]
25. Ide K, Eliasziw M, Poulin MJ. The relationship between middle cerebral artery blood velocity and end-tidal PCO₂ in the hypocapnic-hypercapnic range in humans. *J Appl Physiol* 2003;95:129–37.
26. Ball S, Shekhar A. Basilar artery response to hyperventilation in panic disorder. *Am J Psychiatry* 1997;154(11):1603–4. [PubMed: 9356573]
27. Deckersbach T, Dougherty DD, Rauch SL. Functional imaging of mood and anxiety disorders. *J Neuroimaging* 2006 Jan;16(1):1–10. [PubMed: 16483270]
28. Bremner JD. Brain imaging in anxiety disorders. *Expert Rev Neurother* 2004 Mar;4(2):275–84. [PubMed: 15853569]
29. Liberzon I, Phan L. Brain-imaging studies of posttraumatic stress disorder. *CNS Spectrums* 2003;8:614–50.
30. Phan KL, Wager TD, Taylor SF, Liberzon I. Functional neuroimaging studies of human emotions. *CNS Spectr* 2004 Apr;9(4):258–66. [PubMed: 15048050]
31. Rauch SL, Shin LM, Wright CI. Neuroimaging studies of amygdala function in anxiety disorders. *Ann N Y Acad Sci* 2003 Apr;985:389–410. [PubMed: 12724173]
32. Gorman JM, Kent JM, Sullivan GM, Coplan JD. Neuroanatomical hypothesis of panic disorder, revised. *Am J Psychiatry* 2000 Apr;157(4):493–505. [PubMed: 10739407]
33. De Cristofaro MT, Sessarego A, Pupi A, Biondi F, Faravelli C. Brain perfusion abnormalities in drug-naïve, lactate-sensitive panic patients: a SPECT study. *Biol Psychiatry* 1993 Apr 1;33(7):505–12. [PubMed: 8513034]
34. Woods SW, Koster K, Krystal JK, Smith EO, Zupal IG, Hoffer PB, et al. Yohimbine alters regional cerebral blood flow in panic disorder. *Lancet* 1988 Sep 17;2(8612):678. [PubMed: 2901529]
35. Bystritsky A, Pontillo D, Powers M, Sabb FW, Craske MG, Bookheimer SY. Functional MRI changes during panic anticipation and imagery exposure. *Neuroreport* 2001 Dec 21;12(18):3953–7. [PubMed: 11742218]
36. Shin LM, Orr SP, Carson MA, Rauch SL, Macklin ML, Lasko NB, et al. Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Arch Gen Psychiatry* 2004 Feb;61(2):168–76. [PubMed: 14757593]
37. Shin LM, Whalen PJ, Pitman RK, Bush G, Macklin ML, Lasko NB, et al. An fMRI study of anterior cingulate function in posttraumatic stress disorder. *Biol Psychiatry* 2001 Dec 15;50(12):932–42. [PubMed: 11750889]
38. Liberzon I, Taylor SF, Andur R, Jung TD, Chamberlain KR. Brain activation in PTSD in response to trauma-related stimuli. *Biol Psychiatry* 1999;45:817–26.
39. Bremner JD, Staib LH, Kaloupek D, Southwick SM, Soufer R, Charney DS. Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. *Biol Psychiatry* 1999 Apr 1;45(7):806–16. [PubMed: 10202567]

40. Rauch S, Wahalen PJ, Shin LM, McInerney SC, Macklin ML. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biol Psychiatry* 2000;47:769–76.
41. Papp LA, Martinez JM, Klein DF, Coplan JD, Norman RG, Cole R, et al. Respiratory psychophysiology of panic disorder: three respiratory challenges in 98 subjects. *Am J Psychiatry* 1997;154(11):1557–65. [PubMed: 9356564]
42. Abelson JL, Weg JG, Nesse RM, Curtis GC. Persistent respiratory irregularity in patients with panic disorder. *Biol Psychiatry* 2001;49(7):588–95. [PubMed: 11297716]
43. Schwartz GE, Goetz RR, Klein DF, Endicott J, Gorman JM. Tidal volume of respiration and "sighing" as indicators of breathing irregularities in panic disorder patients. *Anxiety* 1996;2(3):145–8. [PubMed: 9160616]
44. Wilhelm FH, Trabert W, Roth WT. Physiologic instability in panic disorder and generalized anxiety disorder. *Biol Psychiatry* 2001;49(7):596–605. [PubMed: 11297717]
45. Gomez P, Stahel WA, Danuser B. Respiratory responses during affective picture viewing. *Biol Psychol* 2004;67(3):359–73. [PubMed: 15294392]
46. Boiten FA. The effects of emotional behaviour on components of the respiratory cycle. *Biol Psychol* 1998;49(1–2):29–51. [PubMed: 9792483]
47. Van Diest I, Winters W, Devriese S, Vercamst E, Han JN, Van de Woestijne KP, et al. Hyperventilation beyond fight/flight: respiratory responses during emotional imagery. *Psychophysiology* 2001;38(6):961–8. [PubMed: 12240672]
48. Horvath S, Fenz WD. Specificity in somatic indicants of anxiety in psychoneurotic patients. *Percept Mot Skills* 1971;33(1):147–62. [PubMed: 5095781]
49. Thomason ME, Burrows BE, Gabrieli JD, Glover GH. Breath holding reveals differences in fMRI BOLD signal in children and adults. *Neuroimage* 2005;25(3):824–37. [PubMed: 15808983]
50. Riecker A, Grodd W, Klose U, Schulz JB, Groschel K, Erb M, et al. Relation between regional functional MRI activation and vascular reactivity to carbon dioxide during normal aging. *J Cereb Blood Flow Metab* 2003;23(5):565–73. [PubMed: 12771571]
51. Abbott DF, Opdam HI, Briellmann RS, Jackson GD. Brief breath holding may confound functional magnetic resonance imaging studies. *Hum Brain Mapp* 2005;24(4):284–90. [PubMed: 15678482]
52. Gur RC, Gur RE, Resnick SM, Skolnick BE, Alavi A, Reivich M. The effect of anxiety on cortical cerebral blood flow and metabolism. *J Cereb Blood Flow Metab* 1987;7(2):173–7. [PubMed: 3494027]
53. Giordani B, Boivin M, Berent S, Koeppe B, Rothley J, Modell JG, et al. Anxiety and cerebral cortical metabolism in normal persons. *Psychiatry Res Neuroimagin* 1990;35:49–60.
54. MacKenzie R, Sims C, Owens RG, Dixon AK. Patients' perceptions of magnetic resonance imaging. *Clin Radiol* 1995;50(3):137–43. [PubMed: 7889700]
55. Katz RC, Wilson L, Frazer N. Anxiety and its determinants in patients undergoing magnetic resonance imaging. *J Behav Ther Exp Psychiatry* 1994;25(2):131–4. [PubMed: 7983222]
56. Brennan SC, Redd WH, Jacobsen PB, Schorr O, Heelan RT, Sze GK, et al. Anxiety and panic during magnetic resonance scans. *Lancet* 1988;2(8609):512. [PubMed: 2900435]
57. Quirk ME, Letendre AJ, Ciottone RA, Lingley JF. Anxiety in patients undergoing MR imaging. *Radiology* 1989;170(2):463–6. [PubMed: 2911670]
58. Melendez JC, McCrank E. Anxiety-related reactions associated with magnetic resonance imaging examinations. *JAMA* 1993;270(6):745–7. [PubMed: 8336378]
59. Harris LM, Cumming SR, Menzies RG. Predicting anxiety in magnetic resonance imaging scans. *Int J Behav Med* 2004;11(1):1–7. [PubMed: 15194514]
60. Nazemi H, Dager SR. Coping strategies of panic and control subjects undergoing lactate infusion during magnetic resonance imaging confinement. *Compr Psychiatry* 2003;44(3):190–7. [PubMed: 12764706]
61. Warach S, Gur RC, Gur RE, Skolnick BE, Obrist WD, Reivich M. The reproducibility of the ¹³³Xe inhalation technique in resting studies: task order and sex related effects in healthy young adults. *J Cereb Blood Flow Metab* 1987;7(6):702–8. [PubMed: 3693427]

62. Roth WT, Ehlers A, Taylor CB, Margraf J, Agras WS. Skin conductance habituation in panic disorder patients. *Biol Psychiatry* 1990;27(11):1231–43. [PubMed: 2191728]
63. Masaoka Y, Homma I. The effect of anticipatory anxiety on breathing and metabolism in humans. *Respir Physiol* 2001;128(2):171–7. [PubMed: 11812381]
64. Dager SR, Layton M, Richards T. Neuroimaging Findings in Anxiety Disorders. *Semin Clin Neuropsychiatry* 1996;1(1):48–60. [PubMed: 10229783]
65. Mountz JM, Modell JG, Wilson MW, Curtis GC, Lee MA, Schmaltz S, et al. Positron emission tomographic evaluation of cerebral blood flow during state anxiety in simple phobia. *Arch Gen Psychiatry* 1989;46(6):501–4. [PubMed: 2499295]
66. Mathew RJ, Wilson WH. Hematocrit and anxiety. *J Psychosom Res* 1986;30(3):307–11. [PubMed: 3735174]
67. Mathew RJ, Wilson WH. Behavioral and cerebrovascular effects of caffeine in patients with anxiety disorders. *Acta Psychiatr Scand* 1990;82(1):17–22. [PubMed: 2399815]
68. Edvinsson L, Owman C, Siesjö B. Physiological role of cerebrovascular sympathetic nerves in the autoregulation of cerebral blood flow. *Brain Res* 1976;117(3):519–23. [PubMed: 990942]
69. Sercombe R, Aubineau P, Edvinsson L, Mamo H, Owman CH, Pinard E, et al. Neurogenic influence on local cerebral blood flow. Effect of catecholamines or sympathetic stimulation as correlated with the sympathetic innervation. *Neurology* 1975;25(10):954–63. [PubMed: 1237106]
70. Gotoh F, Tazaki Y, Meyer JS. Transport of gases through brain and their extravascular vasomotor action. *Exp Neurol* 1961;4:48–58. [PubMed: 13707422]
71. Kontos HA, Wei EP, Raper AJ, Patterson JL Jr. Local mechanism of CO₂ action of cat pial arterioles. *Stroke* 1977;8(2):226–9. [PubMed: 15334]
72. Fenton RA, Rubio R, Berne RM. Adenosine and the acid-base state of vascular smooth muscle. *J Appl Physiol* 1981;51(1):179–84. [PubMed: 6790498]
73. Karaki H, Weiss GB. Effect of transmembrane pH gradient changes on potassium-induced relaxation in vascular smooth muscle. *Blood Vessels* 1981;18(1–2):36–44. [PubMed: 7470635]
74. Grubb RL Jr, Raichle ME, Eichling JO, Ter-Pogossian MM. The effects of changes in PaCO₂ on cerebral blood volume, blood flow, and vascular mean transit time. *Stroke* 1974;5(5):630–9. [PubMed: 4472361]
75. Iadecola C, Pelligrino DA, Moskowitz MA, Lassen NA. Nitric oxide synthase inhibition and cerebrovascular regulation. *J Cereb Blood Flow Metab* 1994;14(2):175–92. [PubMed: 7509338]
76. Ido Y, Chang K, Woolsey TA, Williamson JR. NADH: sensor of blood flow need in brain, muscle, and other tissues. *FASEB J* 2001;15(8):1419–21. [PubMed: 11387243]
77. Leffler CW, Parfenova H. Cerebral arteriolar dilation to hypoxia: role of prostanoids. *Am J Physiol* 1997;272(1):H418–24. [PubMed: 9038964]Pt 2
78. Pelligrino DA, Wang Q. Cyclic nucleotide crosstalk and the regulation of cerebral vasodilation. *Prog Neurobiol* 1998;56(1):1–18. [PubMed: 9723128]
79. Faraci FM, Sobey CG. Role of potassium channels in regulation of cerebral vascular tone. *J Cereb Blood Flow Metab* 1998;18(10):1047–63. [PubMed: 9778181]
80. Long W, Zhao Y, Zhang L, Longo LD. Role of Ca(2+) channels in NE-induced increase in fetal and adult cerebral arteries. *Am J Physiol* 1999;277(1):R286–94. [PubMed: 10409284]Pt 2
81. Artru AA, Colley PS. Cerebral blood flow responses to hypocapnia during hypotension. *Stroke* 1984;15(5):878–83. [PubMed: 6433518]
82. Harper AM, Glass HI. Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial blood pressures. *J Neurol Neurosurg Psychiatry* 1965;28(5):449–52. [PubMed: 5838479]
83. Gregory P, Ishikawa T, McDowall DG. CO₂ responses of the cerebral circulation during drug-induced hypotension in the cat. *J Cereb Blood Flow Metab* 1981;1(2):195–201. [PubMed: 6799528]
84. Jones SC, Bose B, Furlan AJ, Friel HT, Easley KA, Meredith MP, et al. CO₂ reactivity and heterogeneity of cerebral blood flow in ischemic, border zone, and normal cortex. *Am J Physiol* 1989;257(2):H473–82. [PubMed: 2504058]Pt 2
85. Tominaga S, Strandgaard S, Uemura K, Ito K, Kutsuzawa T. Cerebrovascular CO₂ reactivity in normotensive and hypertensive man. *Stroke* 1976;7(5):507–10. [PubMed: 960176]

86. Rostrup E, Knudsen GM, Law I, Holm S, Larsson HB, Paulson OB. The relationship between cerebral blood flow and volume in humans. *Neuroimage* 2005;24(1):1–11. [PubMed: 15588591]
87. Ito H, Yokoyama I, Iida H, Kinoshita T, Hatazawa J, Shimosegawa E, et al. Regional differences in cerebral vascular response to PaCO₂ changes in humans measured by positron emission tomography. *J Cereb Blood Flow Metab* 2000;20(8):1264–70. [PubMed: 10950385]
88. Posse S, Olthoff U, Weckesser M, Jancke L, Muller-Gartner HW, Dager SR. Regional dynamic signal changes during controlled hyperventilation assessed with blood oxygen level-dependent functional MR imaging. *AJNR Am J Neuroradiol* 1997;18(9):1763–70. [PubMed: 9367329]
89. Posse S, Kemna LJ, Elghahwagi B, Wiese S, Kiselev VG. Effect of graded hypo- and hypercapnia on fMRI contrast in visual cortex: quantification of T^{*}(2) changes by multiecho EPI. *Magn Reson Med* 2001;46(2):264–71. [PubMed: 11477629]
90. Fox PT, Mintun MA, Reiman EM, Raichle ME. Enhanced detection of focal brain responses using intersubject averaging and change-distribution analysis of subtracted PET images. *J Cereb Blood Flow Metab* 1988;8(5):642–53. [PubMed: 3262113]
91. Friston KJ, Frith CD, Liddle PF, Dolan RJ, Lammertsma AA, Frackowiak RS. The relationship between global and local changes in PET scans. *J Cereb Blood Flow Metab* 1990;10(4):458–66. [PubMed: 2347879]
92. Ramsay SC, Murphy K, Shea SA, Friston KJ, Lammertsma AA, Clark JC, et al. Changes in global cerebral blood flow in humans: effect on regional cerebral blood flow during a neural activation task. *J Physiol* 1993;471:521–34. [PubMed: 8120819]
93. Li TQ, Kastrup A, Moseley ME, Glover GH. Changes in baseline cerebral blood flow in humans do not influence regional cerebral blood flow response to photic stimulation. *J Magn Reson Imaging* 2000;12(5):757–62. [PubMed: 11050647]
94. Corfield DR, Murphy K, Josephs O, Adams L, Turner R. Does hypercapnia-induced cerebral vasodilation modulate the hemodynamic response to neural activation? *Neuroimage* 2001;13(6):1207–11. [PubMed: 11352626]Pt 1
95. Shimosegawa E, Kanno I, Hatazawa J, Fujita H, Iida H, Miura S, et al. Photic stimulation study of changing the arterial partial pressure level of carbon dioxide. *J Cereb Blood Flow Metab* 1995;15(1):111–4. [PubMed: 7798327]
96. Bandettini PA, Wong EC. A hypercapnia-based normalization method for improved spatial localization of human brain activation with fMRI. *NMR Biomed* 1997;10(4–5):197–203. [PubMed: 9430348]
97. Weckesser M, Posse S, Olthoff U, Kemna L, Dager S, Muller-Gartner HW. Functional imaging of the visual cortex with bold-contrast MRI: hyperventilation decreases signal response. *Magn Reson Med* 1999;41(1):213–6. [PubMed: 10025633]
98. Kemna LJ, Posse S. Effect of respiratory CO₂ changes on the temporal dynamics of the hemodynamic response in functional MR imaging. *Neuroimage* 2001;14(3):642–9. [PubMed: 11506537]
99. Cohen ER, Ugurbil K, Kim SG. Effect of basal conditions on the magnitude and dynamics of the blood oxygenation level-dependent fMRI response. *J Cereb Blood Flow Metab* 2002;22(9):1042–53. [PubMed: 12218410]
100. Kashikura K, Kershaw J, Kashikura A, Zhang X, Matsuura T, Kanno I. Hyperoxia modified activation-induced blood oxygenation level-dependent response of human visual cortex (V1): an event-related functional magnetic resonance imaging study. *Neurosci Lett* 2001;299(1–2):53–6. [PubMed: 11166936]
101. Kashikura K, Kershaw J, Kashikura A, Matsuura T, Kanno I. Hyperoxia-enhanced activation-induced hemodynamic response in human VI: an fMRI study. *Neuroreport* 2000;11(5):903–6. [PubMed: 10790852]
102. Lindauer U, Gethmann J, Kuhl M, Kohl-Bareis M, Dirnagl U. Neuronal activity-induced changes of local cerebral microvascular blood oxygenation in the rat: effect of systemic hyperoxia or hypoxia. *Brain Res* 2003;975(1–2):135–40. [PubMed: 12763601]
103. Balestrino M, Somjen GG. Concentration of carbon dioxide, interstitial pH and synaptic transmission in hippocampal formation of the rat. *J Physiol* 1988;396:247–66. [PubMed: 2842490]

104. Lee J, Taira T, Pihlaja P, Ransom BR, Kaila K. Effects of CO₂ on excitatory transmission apparently caused by changes in intracellular pH in the rat hippocampal slice. *Brain Res* 1996;706(2):210–6. [PubMed: 8822358]
105. Huttunen J, Tolvanen H, Heinonen E, Voipio J, Wikstrom H, Ilmoniemi RJ, et al. Effects of voluntary hyperventilation on cortical sensory responses. Electroencephalographic and magnetoencephalographic studies. *Exp Brain Res* 1999;125(3):248–54. [PubMed: 10229015]
106. Friedman SD, Mathis CM, Hayes C, Renshaw PF, Dager SR. Brain pH Response to hyperventilation in panic disorder: Preliminary evidence for metabolic dysregulation. *Am J Psychiatry*.
107. Dager SR, Friedman SD, Heide A, Layton ME, Richards T, Artru A, et al. Two-dimensional proton echo-planar spectroscopic imaging of brain metabolic changes during lactate-induced panic. *Arch Gen Psychiatry* 1999;56(1):70–7. [PubMed: 9892258]
108. Dager SR, Strauss WL, Marro KI, Richards TL, Metzger GD, Artru AA. Proton magnetic resonance spectroscopy investigation of hyperventilation in subjects with panic disorder and comparison subjects. *Am J Psychiatry* 1995;152(5):666–72. [PubMed: 7726305]
109. Dager SR, Marro KI, Richards TL, Metzger GD. Preliminary application of magnetic resonance spectroscopy to investigate lactate-induced panic. *Am J Psychiatry* 1994;151(1):57–63. [PubMed: 8267135]
110. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 1995 Oct;34(4):537–41. [PubMed: 8524021]
111. Obrig H, Neufang M, Wenzel R, Kohl M, Steinbrink J, Einhaupl K, et al. Spontaneous low frequency oscillations of cerebral hemodynamics and metabolism in human adults. *Neuroimage* 2000;12(6): 623–39. [PubMed: 11112395]
112. Kuo TB, Chern CM, Sheng WY, Wong WJ, Hu HH. Frequency domain analysis of cerebral blood flow velocity and its correlation with arterial blood pressure. *J Cereb Blood Flow Metab* 1998;18 (3):311–8. [PubMed: 9498848]
113. Wise RG, Ide K, Poulin MJ, Tracey I. Resting fluctuations in arterial carbon dioxide induce significant low frequency variations in BOLD signal. *Neuroimage* 2004;21(4):1652–64. [PubMed: 15050588]
114. Diehl RR, Linden D, Lucke D, Berlitz P. Spontaneous blood pressure oscillations and cerebral autoregulation. *Clin Auton Res* 1998;8(1):7–12. [PubMed: 9532415]
115. Appel ML, Berger RD, Saul JP, Smith JM, Cohen RJ. Beat to beat variability in cardiovascular variables: noise or music? *J Am Coll Cardiol* 1989;14(5):1139–48. [PubMed: 2681319]
116. Hyndman BW. The role of rhythms in homeostasis. *Kybernetik* 1974;15(4):227–36. [PubMed: 4845823]
117. Yates FE. The 10th J. A. F. Stevenson memorial lecture. Outline of a physical theory of physiological systems. *Can J Physiol Pharmacol* 1982;60(3):217–48. [PubMed: 7074418]
118. Rapp PE. Why are so many biological systems periodic? *Prog Neurobiol* 1987;29(3):261–73. [PubMed: 3299493]
119. Giardino, ND.; Lehrer, PM.; Feldman, JM. The role of oscillations in self-regulation: A revision of the classical model of homeostasis. In: Kenney, D.; Carlson, JG.; McGuigan, FJ.; Sheppard, JL., editors. *Stress and health: Research and clinical applications*. Chur, Switzerland: Harwood Academic Publishers; 1999. p. 27-51.
120. Biswal B, Hudetz AG, Yetkin FZ, Haughton VM, Hyde JS. Hypercapnia reversibly suppresses low-frequency fluctuations in the human motor cortex during rest using echo-planar MRI. *J Cereb Blood Flow Metab* 1997;17(3):301–8. [PubMed: 9119903]
121. Biswal B, DeYoe AE, Hyde JS. Reduction of physiological fluctuations in fMRI using digital filters. *Magn Reson Med* 1996;35(1):107–13. [PubMed: 8771028]
122. Birn RM, Diamond JB, Smith MA, Bandettini PA. Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. *Neuroimage*. 2006 Apr 21;
123. Nunn JF, Hill DW. Respiratory dead space and arterial to end-tidal carbon dioxide tension difference in anesthetized man. *J Appl Physiol* 1960;15:383–9. [PubMed: 14427915]
124. Dubois AB, Britt AG, Fenn WO. Alveolar CO₂ during the respiratory cycle. *J Appl Physiol* 1952;4 (7):535–48. [PubMed: 14907569]

125. Severinghaus JW, Lassen N. Step hypocapnia to separate arterial from tissue PCO₂ in the regulation of cerebral blood flow. *Circ Res* 1967;20(2):272–8. [PubMed: 6016780]
126. Hauge A, Thoresen M, Walloe L. Changes in cerebral blood flow during hyperventilation and CO₂-breathing measured transcutaneously in humans by a bidirectional, pulsed, ultrasound Doppler blood velocitymeter. *Acta Physiol Scand* 1980;110(2):167–73. [PubMed: 6782831]
127. Ellingsen I, Hauge A, Nicolaysen G, Thoresen M, Walloe L. Changes in human cerebral blood flow due to step changes in PAO₂ and PACO₂. *Acta Physiol Scand* 1987;129(2):157–63. [PubMed: 3554898]
128. Albrecht RF, Miletich DJ, Ruttle M. Cerebral effects of extended hyperventilation in unanesthetized goats. *Stroke* 1987;18(3):649–55. [PubMed: 3109079]
129. Wilhelm FH, Gerlach AL, Roth WT. Slow recovery from voluntary hyperventilation in panic disorder. *Psychosom Med* 2001;63(4):638–49. [PubMed: 11485118]
130. Reiman EM, Raichle ME, Robins E, Butler FK, Herscovitch P, Fox P, et al. The application of positron emission tomography to the study of panic disorder. *Am J Psychiatry* 1986;143(4):469–77. [PubMed: 3485385]

Figure 1.

(a) Results of the pixel-based analysis of the effect of visual stimulation during normocapnia (left) and hypocapnia (right). All pixels shown in white exhibit a positive correlation to the reference function (correlation coefficient .0.6). Four adjacent axial echoplanar images through the occipital cortex are shown for each condition. An extensive activation of primary and secondary visual areas is evident in normocapnia; no significant activation remains during hypocapnia. (b) Time course of signal intensity in the experiment with a long repetition time (3 sec), displaying visual activation during normocapnia and the effect of hyperventilation and visual activation during hypocapnia [visual stimulation indicated by the gray background;

hyperventilation (HV) indicated by the fat horizontal line]. (Reproduced from(97), with permission).

Figure 2.

(top) Averaged time course of fMRI signal before, during and after a 3-second light flicker stimulus at different PETCO₂. The prestimulus signal has been set to 100%. Time in seconds after the start of 8 Hz flicker light indicated by the gray bar. (bottom) Averaged time course for 20, 40, and 60 mmHg, normalized to the individual and global maximal amplitude, including standard deviation. (Reproduced from (98), with permission).

Figure 3.

Means and standard errors of self-reported anxiety and minute-by-minute mean end-tidal pCO₂ for the three groups over the course of the experiment. BASE is the baseline. 6 x FB/ REC refers to 6 1-min fast breathing periods and 1-min recovery periods, the following FB refers to a 3-min fast breathing period, and REC refers to a 10-min final recovery period. Anxiety ratings were not evaluated during the initial 6 recovery periods. (Modified from (129), with permission.)