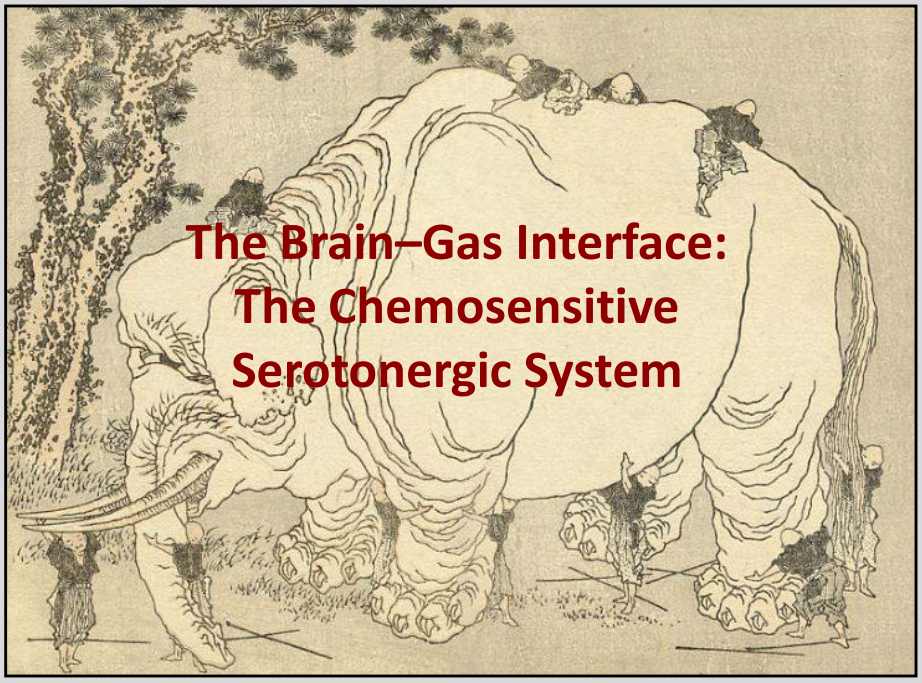
TEREKHIN P. Dr.

m&i-Fachklinik Enzensberg, Hopfen am See/Füssen, Germany

11th European Hypoxia Symposium 2025



The Brain–Gas Interface: The Chemosensitive Serotonergic System

Part One

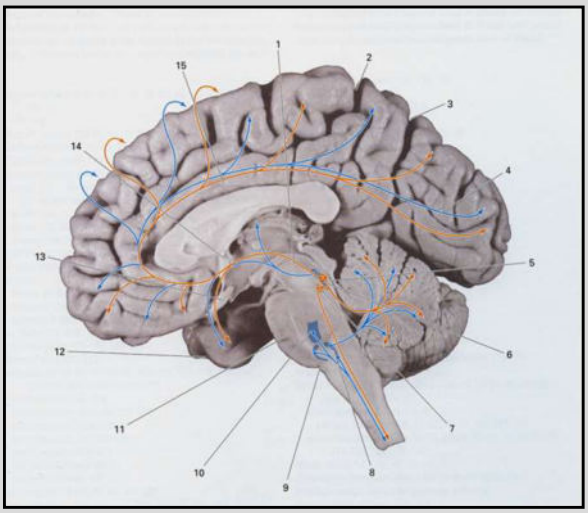
- The serotonergic system is a neural network that uses the neurotransmitter serotonin (5-HT) to regulate a wide array of functions, including mood, sleep, appetite, pain, and motor control, and plays a crucial role in neurodevelopment

Function of the Brain Serotonin System

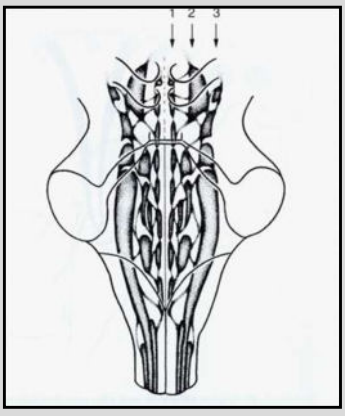
- Cardiovascular regulation
- Respiration
- Gastrointestinal system
- Pain sensitivity
- Thermoregulation
- Maintenance of circadian rhythm
- Developmental and Synaptic Plasticity
- Sensorimotor activity
- Appetite control
- Sexual behavior
- Mood
- Anxiety
- Cognition, learning, attention and other cognitive processes
- Memory
- Aggression
- Psychopathic and sociopathic behavior

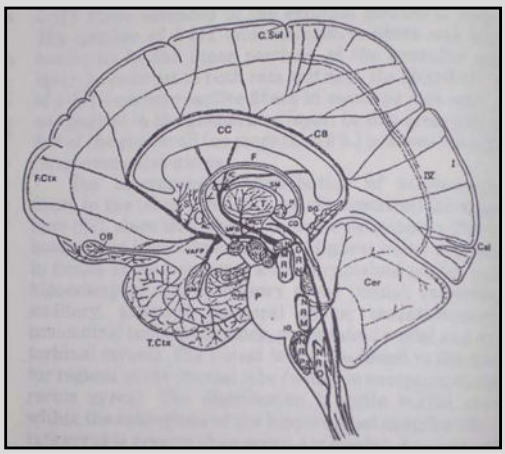
- **MIGRAINE**
- **EPILEPSY**
- **STROKE**
- **ANXIETY and PANIC DISORDERS**
- **FEBRILE CONVULTIONS**
- **ALTERED STATES OF CONSCIOUSSNESS**
- **SLEEP DISORDERS**

Anatomy of the Brain Serotonin System



Anatomy of the Brain Serotonin System





Receptor family	Distribution in the brain
5-HT_1	Pituitary gland, rostral raphe nuclei, hippocampus, prefrontal cortex cerebellum, basal ganglia, amygdala, globus pallidus, putamen, caudate nucleus
5-HT_2	Cerebral cortex, basal ganglia, amygdala, choroid plexus, hypothalamus, hippocampus, caudate nucleus, putamen, globus pallidus, substantia nigra
5-HT_3	Area postrema, tractus solitarius, limbic system, hippocampus, cerebral cortex
5-HT_4	Prefrontal cortex, caudate nucleus, putamen, globus pallidus, hippocampus, substantia nigra
5-HT_5	Cerebral cortex, amygdala, cerebellum, hypothalamus, hippocampus
5-HT_6	Dentate gyrus, hippocampus, olfactory tubercle, nucleus accumbens, amygdala, cerebellum
5-HT_7	Thalamus

The Serotonin Receptors

5-HT_1	5-HT_{1A} 5-HT_{1B} 5-HT_{1D} 5-HT_{1E} 5-HT_{1F}
5-HT_2	5-HT_{2A} 5-HT_{2B} 5-HT_{2C}
5-HT_3	
5-HT_4	
5-HT_5	5-HT_{5A} 5-HT_{5B}
5-HT_6	
5-HT_7	

Serotonin or 5-HT is a biogenic amine which acts as a neurotransmitter. Most of serotonergic neurons are located within the midline raphe nuclei (RN) which can be divided into two groups.

The **caudal group** of the medulla has descending projections and influences breathing, cardiovascular control, autonomic output, and pain processing.

The **rostral group** of the pons and midbrain projects throughout the forebrain, and is associated with arousal, anxiety, and control of cerebral blood flow.

It has been shown, that many of 5-HT neurons are chemosensitive (>75% cell subset). They have widespread connections and might mediate also nonrespiratory responses induced by changes in pH.

Part Two

Hyperventilation (HV), or hyperventilation syndrome (HVS)

The main function of external breathing is the maintaining of the optimum (virtually invariable under ordinary conditions) gas composition in the arterial blood (partial pressure of O_2 and CO_2, as well as pH). The pulmonary ventilation is controlled predominantly by the CO_2 amount produced in the body; i.e., the CO_2 -related homeostasis rather than the O_2 -related homeostasis is maintained.

In the dominant regulatory role, the hypoxic stimulus was replaced by the hypercapnic stimulus and the control over the respiratory center was transferred from the peripheral chemoreceptors to the central (medullar, bulbar) chemosensitive structures reacting to the changes in the extracellular pH and CO_2 pressure in the brain.

The excessive elimination of CO_2 distinguishes the HV from other conditions with intensified breathing, such as hyperpnea or tachypnea, i.e., from the metabolically determined respiratory conditions.

HVS is defined as the pathological condition that manifests itself through the multisystem mental, autonomic, algesic, and musculo-tonic disturbances, as well as through abnormalities of consciousness; the condition associated with the primary dysfunction of the nervous system of a psychogenic or organic nature, leading to the persistently pathological pattern of breathing with **the pulmonary ventilation increased inadequately to the level of the gas exchange in the body**

$EtCO_2$ or end-tidal carbon dioxide

the pressure of CO_2 in the alveolar gas (PA CO_2), as well as the corresponding pressure of CO_2 in the arterial blood ($PaCO_2$), one of the most important parameters of the homeostasis; in humans, it is 35–42 mm Hg), became constant.

The values of $PaCO_2$ are directly related to another parameter, pH of the blood, maintained within the narrow range necessary for the proper metabolic turnover in the cells, because the catalytic activity of enzymes is pH-dependent. The amount of CO_2 released is determined by its concentration in the alveolar gas and by the volume of the alveolar ventilation.

The following grades of hypocapnia can be distinguished:

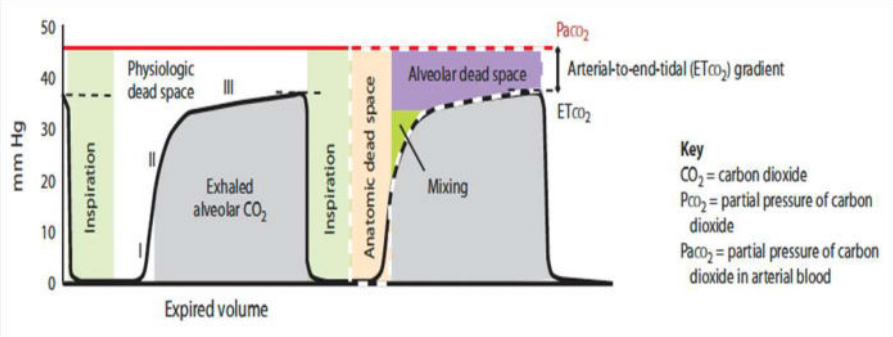
I **Mild hypocapnia ($PACO_2$ over 25–30 mm Hg)**

II **Moderate hypocapnia ($PACO_2$ = 20–25 mm Hg)**

III **Severe hypocapnia ($PACO_2$ under 20 mm Hg)**

$EtCO_2$ or end-tidal carbon dioxide

- $EtCO_2$, or end-tidal carbon dioxide, is the measurement of the concentration of carbon dioxide (CO_2) at the very end of an exhaled breath, providing a non-invasive, breath-by-breath assessment of a patient's ventilation. Measured using capnography, which displays the CO_2 level as both a number and a waveform, $EtCO_2$ monitoring indicates the effectiveness of ventilation, cardiac output, and metabolic activity. Normal $EtCO_2$ values typically range from 35 to 45 mmHg



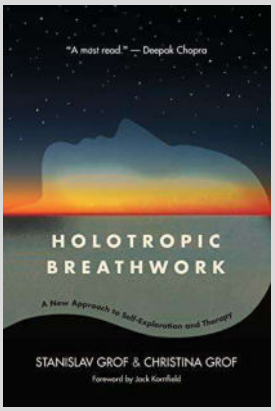
The science behind the technique Capnography

- CO_2 is a byproduct of cellular metabolism. Cells take in oxygen and glucose and release water, carbon dioxide, and energy. CO_2 plays an important role in acid–base buffering. Depending on blood pH at any given time, CO_2 converts either to carbonic acid (H_2CO_3, an acid) or to bicarbonate (HCO_3-, a base).
- CO_2 exists in three primary states in the blood: as HCO_3– (70%), bound to hemoglobin (20%), and dissolved in the plasma (10%). As HCO_3-, CO_2 influences blood pH; direct CO_2 measurement indicates ventilatory effectiveness. Both pH and CO_2 are measured from arterial blood gas (ABG) samples. While $EtCO_2$ monitoring doesn't directly indicate acid-base balance, it can shed light on ventilation efficacy.
- CO_2 combines with water to create H_2CO_3, which can degrade to bicarbonate, water, and CO_2. This process occurs in red blood cells, where HCO_3– is released back into the plasma ready to accept another hydrogen ion (H+), while CO_2 and H_2O are carried to the arterial-alveolar junction for release into the atmosphere. The lungs serve as a pump to promote the activity of ventilation

The altered states of the consciousness (ASC)

An additional aspect in the studies of the HV is the influence exerted by the breathing upon the CNS. The most important manifestation of human mental activity is consciousness; it integrates various mental functions that determine the adequate perception of the environment.

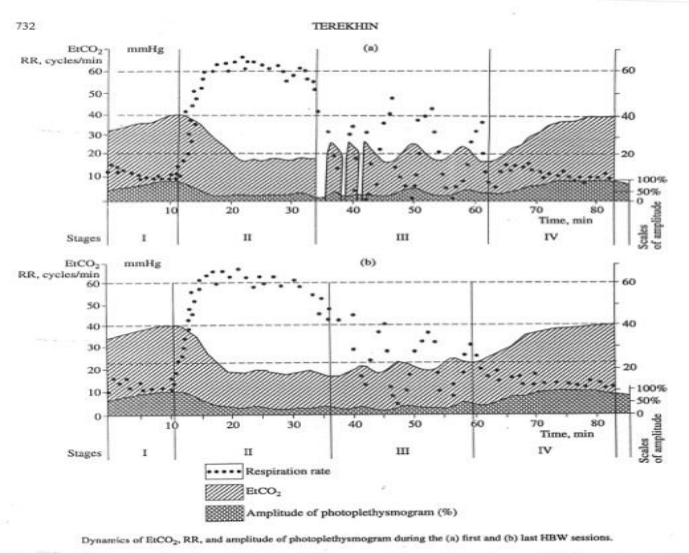
Psychotherapeutic methods based on the ASC induction by the voluntarily controlled breathing (e.g., the **Holotropic Breathwork (HB)** according to S. Grof) are becoming popular.



Different dimensions of Altered States of Consciousness (ASC)

Ludwig's General Characteristics	Tart's Experiential Criteria for Detecting ASC	Farthing's Dimensions of Consciousness	Pekala's 26 Dimensions of Consciousness	Vaitl's Dimensions of Consciousness

• Alterations in thinking
• Disturbed time sense
• Loss of control
• Change in emotional expression
• Body image change
• Perceptual distortions
• Change in meaning or significance
• Sense of the innefable
• Feelings of rejuvenation
• Hypersuggestbility
	• Exteroception
	• Interoception
	• Input-processing
	• Emotions
	• Memory
	• Time sense
	• Sense of identity
	• Evaluation and cognitive processing
	• Motor output
	• Interaction with the environment
		• Attention
		• Perception
		• Imagery
		• Inner speech
		• Memory
		• Decision making
		• Problem solving
		• Emotions
		• Arousal
		• Self-Control
		• Suggestibility
		• Body image
		• Personal identity
		• Experience of time
		• Meaning
			• Altered state of awareness
			• Altered experience
			  • Body image
			  • Time sense
			  • Perception
			  • Unusual meaning
			• Volitional control
			• Self-awareness
			• Rationality
			• Internal dialogue
			• Positive affect
			  • Joy
			  • Sexual excitement
			  • Love
			• Negative affect
			  • Anger
			  • Sadness
			  • Fear
			• Imagery
			  • Amount
			  • Vividness
			• Attention
			  • Direction
			  • Absorption
			• Memory
			• Arousal
				• Activation
				• Awareness span
				• Self-awareness
				• Sensory dynamics



Dynamics of $EtCO_2$, RR, and amplitude of photoplethysmogram during the (a) first and (b) last HBW sessions.

Our study of the external respiratory function during the HB sessions revealed a clearly periodic character of the developing respiratory phenomena (e.g., a periodic breathing), as well as stable hypocapnia that persisted during the entire HB session, which was sufficient for the ASC induction.

Part Three

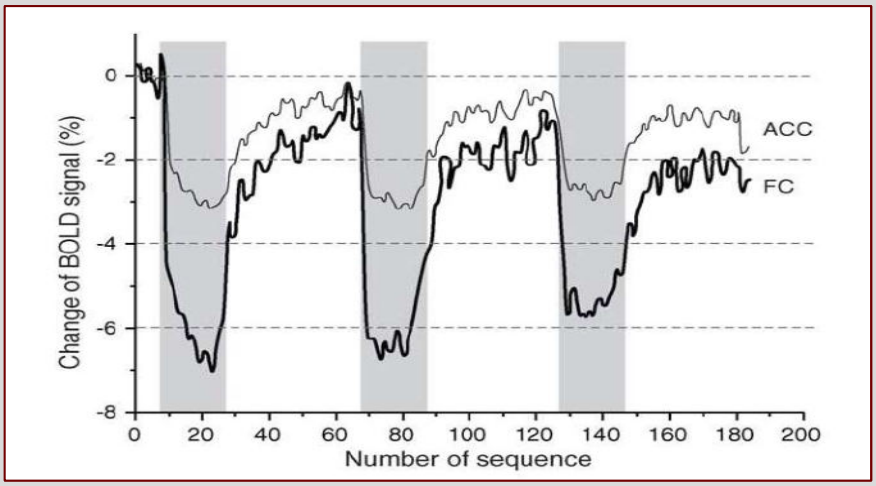
Application of voluntary performed respiratory maneuvers for study cerebrovascular reactivity (CVR) and sensivity to carbon dioxide.

An fMRI Study.

- **BOLD fMRI (Blood-Oxygen-Level-Dependent functional magnetic resonance imaging)** is the standard technique used in fMRI to detect and map brain activity by measuring the magnetic properties of blood, specifically the concentration of deoxygenated hemoglobin
- Neural Activity and Blood Flow: When neurons in a specific brain area become active, they require more oxygen, which triggers a local increase in cerebral blood flow.
- Blood Composition Change: This increased blood flow delivers more oxygenated blood than is consumed by the neurons, leading to a temporary rise in the concentration of oxygenated hemoglobin (oxyHb) and a drop in deoxygenated hemoglobin (deoxyHb)
- The key is the difference in magnetic properties between oxyHb and deoxyHb. DeoxyHb is paramagnetic, meaning it disrupts the magnetic field, while oxyHb is not

The time course of the BOLD signal in frontal cortex and ACC during voluntary hyperventilation.

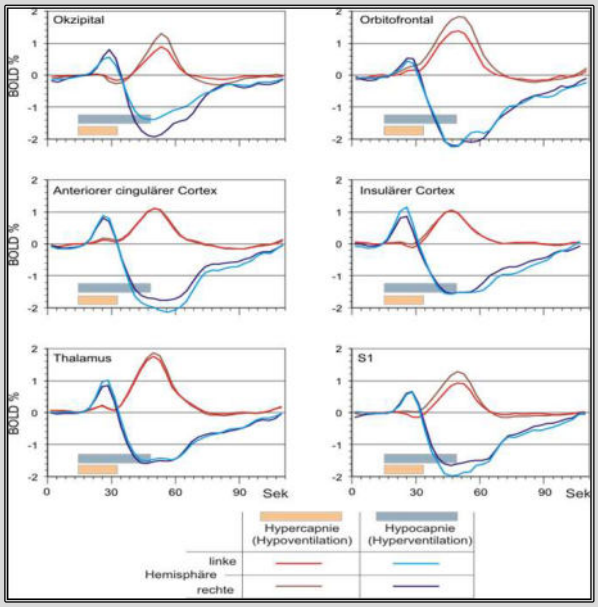
The gray bars mark the periods of voluntary hyperventilation which of each lasted 3 min. The resolution in time is one sequence every 10 s.



Terekhin, Forster 2006

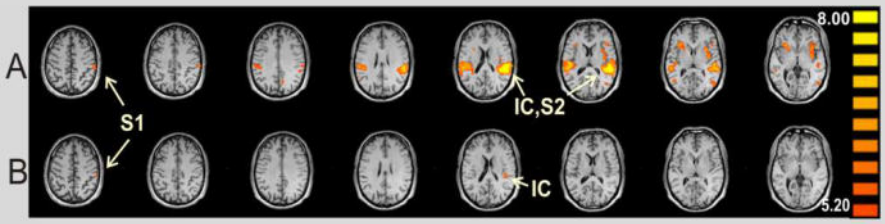
The time courses of the BOLD signal in different cortex areas and thalamus during breath hold and hyperventilation

It depicts the average signal of 12 subjects during BH (20 sec) and 10 subjects during HV (30 sec).

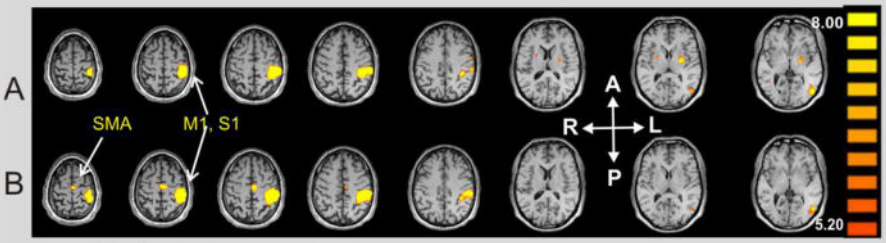


- Cerebral vasodilatation due to hypercapnia and vasoconstriction due to hypocapnia are universal findings in these studies.
- The relative change in cerebral blood flow (CBF) during variations of $PaCO_2$ depends on several factors, including baseline CBF and cerebral perfusion pressure.
- Reducing $PaCO_2$ to 20–25mmHg decreases the global CBF by 40–50%, while further reductions in $PaCO_2$ do not reduce the CBF any further.
- Several mechanisms, like prostanoids, cyclic nucleotides, potassium channels, intracellular calcium and nitric oxide (NO) have been proposed to account for the effect of CO_2 on the cerebral vasculature, but the main mechanism appears to be mediated by a direct effect of the extracellular fluid [H+] on cerebrovascular smooth muscle in the arterioles.

BOLD Activations due to pain stimulation



BOLD Activations due to motor task



A - activation under normocapnia

B - activation under hypocapnia

-8.00

Application of voluntary breath holding for FMRI study of serotonergic system in humans brainstem

482

P. Terekhin, C. Forster

Institute of Physiology and Pathophysiology, University of Erlangen-Nürnberg

University of Erlangen-Nuernberg

Introduction

Serotonin or 5-HT is a biogenic amine which acts as a neurotransmitter. Most of serotonergic neurons are located within the midline raphe nuclei (RN) which can be divided into two groups. The caudal group of the nucleus has descending projections and influences breathing, cardiovascular control, autonomic output, and pain processing. The rostral group of the pons and midbrain projects throughout the forebrain, and is associated with arousal, anxiety, and control of cerebral blood flow. It has been shown, that many of 5-HT neurons are chemosensitive (>70% cell subset). They have widespread connections and might mediate also nonrespiratory responses induced by changes in pH.

The aim of the study was to investigate the feasibility of BOLD sensitive fMRI to detect changes of the activity in the RN due to an increased of blood pCO_2

Schematic representation of the reticular formation and brain serotonergic system

Hm ... Aha...interesting... Well, let me see...

Activation Map - Breath holding (Coronal EPI slices)

Wow!!! Looks good....come on!

Time courses obtained from NR and cortex

OK...it sounds good, but what about anatomical variability of brainstem?

Co-registration of the brainstem images

Well, Show me...

Activation Map - Breath holding (saggital slices)

Time courses obtained from RN and cortex

Wunderful!!! Great!!!! Cool!!!.. But...

Generalized increase of BOLD signal due to pCO, stimulation

But... how can you distinguish the neuronal activation from the general vascular effect???

Verification of BOLD activations in ROI

Conclusions

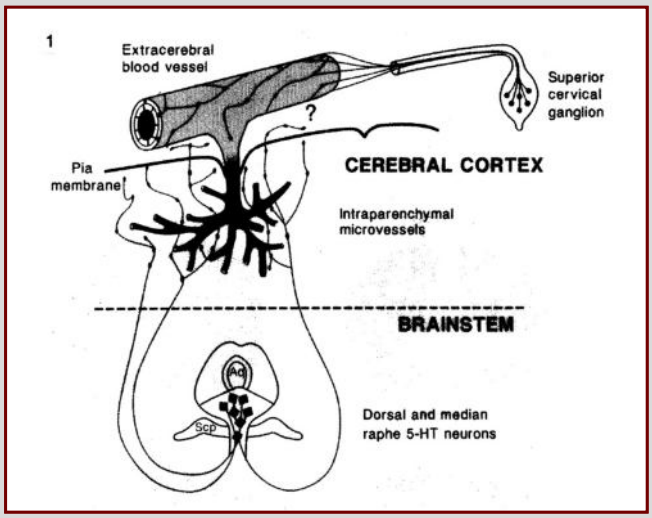
- BOLD sensitive fMRI can be used to study the activation of small brainstem nuclei, even under strong generalized BOLD changes during a respiratory induced vasodilatation.
- Increase of pCO2 due to voluntary breath holding produces detectable BOLD responses in brainstem areas where the Raphe nucisi are located.
- The activations confirm the chemosensitivity of 5-HT neurons in the Raphe nuclei.
- The breath holding task will activate the motor respiratory suppression network. Thus, we can't fully exclude input from central respiratory network to the rostral and caudal Raphe nuclei which are involved in respiratory control.

Acknowledgments: Thanks Socrates for bitter Debate (and Plato for his "Dialogues")...

Presented at the 38th Annual Meeting of the Society for Neuroscience, Washington, DC, 2008

Contact: terekhin@physiologie1.uni-erlangen.de

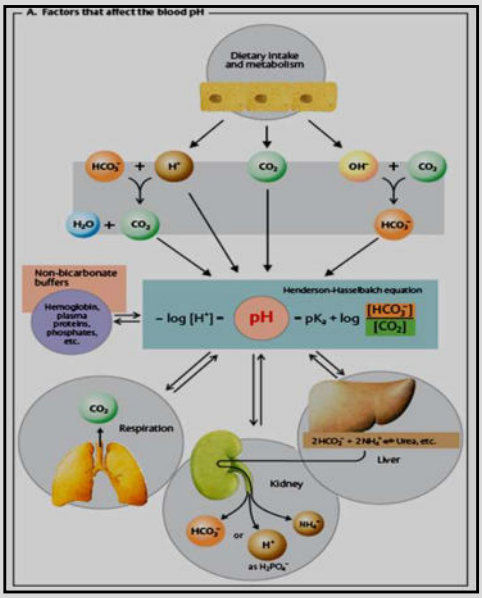
Schematic representation of extracerebral and intraparenchymal blood vessels and of the origin of their respective 5-HT innervations.



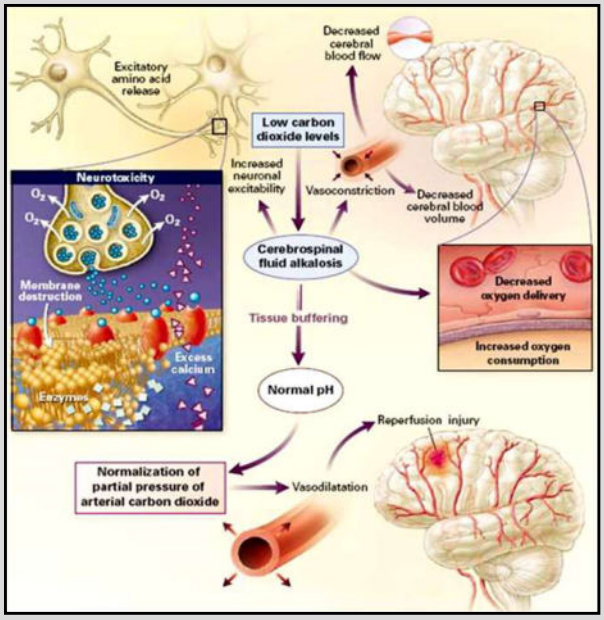
Cohen et al., 1996

Causes of Hypocapnia

- **Hypoxemia**
  High altitudes, pulmonary disease, Pulmonary disorders, Pneumonia, interstitial pneumonitis, fibrosis, edema, pulmonary embolism, vascular disease, bronchial asthma, pneumothorax
- **Cardiovascular disorders**
  Congestive heart failure, hypotension
- **Metabolic disorders**
  Acidosis (diabetic, renal, or lactic), hepatic failure
- **Central nervous system disorders**
  Psychogenic or anxiety-induced hyperventilation, central nervous system infection, central nervous system tumors
- **Drugs**
  Salicylates, methylxanthines, b-adrenergic agonists, progesterone
- **Miscellaneous**
  Fever, sepsis, pain, pregnancy



Neurologic Effects of Hypocapnia.



ADVERSE NEUROLOGIC AND MYOCARDIAL EFFECTS OF HYPOCAPNIA

- Brain injury in neonates
- Cerebral infarction
- Reactive hyperemia and hemorrhage
- Impairment of cerebral function in adults
- Increased time to regain consciousness, increased reaction times
- Poorer psychomotor performance, diminished higher intellectual functions
- Personality changes
- Myocardial effects
- Decreased myocardial oxygen supply
- Reduced coronary flow and collateral flow
- Increased coronary microvascular leakage
- Increases in platelet count and aggregation
- Increased myocardial oxygen demand
- Increased (and later decreased) contractility
- Increased intracellular calcium concentration
- Increased systemic vascular resistance
- Myocardial ischemia
- Reperfusion injury

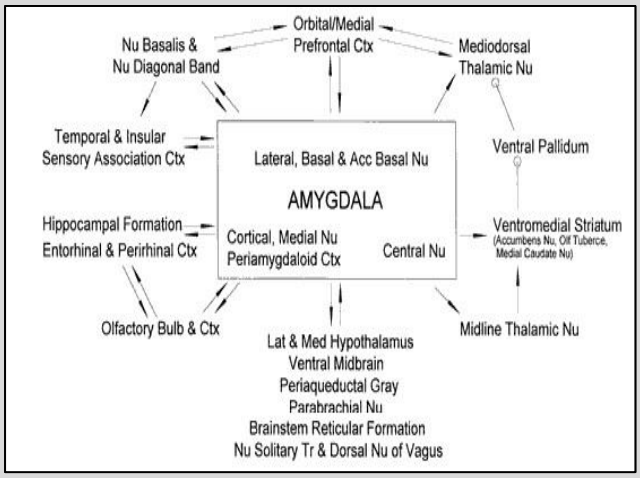
PANIC DISORDER PROJECT

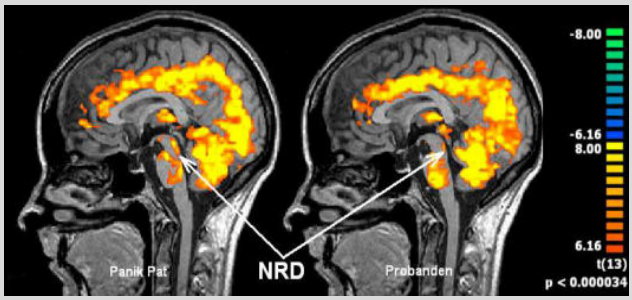
Panic disorder (PD) is a chronic illness characterized by the occurrence of spontaneous, unprovoked, and intense episodes of fear accompanied by typical symptoms of autonomic overactivity including sweating, palpitations, flushing, dizziness, and psychological symptoms including depersonalization, fear of dying, and fear of losing control. Hyperventilation and paresthesia are also common symptoms of a panic attack. Moreover, hyperventilation has been considered to be a cause, a correlate and a consequence of panic.

One of the hypotheses *("suffocation false-alarm")*, suggested that one of the central point neurobiology of PD is dysfunction of brainstem structures (noradrenergic (NE) and serotonergic (5-HT) nuclei) and high sensitivity to carbon dioxide levels in blood. There are different types of 5-HT chemosensitive neurons: ones is that stimulated by increased carbon dioxide, and another that is inhibited by the same stimulus. Most of 5-HT from dorsal raphe were found to increase their firing rate in response to acidosis.

Alternative hypothesis is that patient with PD inherit an especially sensitive central nervous system mechanism that has its center the central nucleus of the amygdala and includes the hippocampus, thalamus, and hypothalamus, as well as the periaqueductal gray matter (PAG), locus ceruleus (LC) and other brainstem sites.

The main point of the second hypothesis is that a trigger for PD is located in amygdala (central nucleus) and based on hypersensitivity to different homeostasis challenges of this structure.





Increase in BOLD signal during breath-holding in patients with panic disorder (left) and healthy controls. In most regions, a stronger BOLD response is observed in the controls, except in the Nucleus Raphe Dorsalis (NRD).

- Compared to healthy individuals, the weaker CVR in the nucleus raphe dorsalis, together with a greater extent of activation, is consistent with earlier findings of an enlarged volume of this nucleus in patients with panic disorder
- This nucleus may have an inhibitory influence on the CVR of many brain regions. The weaker activation of this region in patients with panic disorder could therefore promote the higher CVR in other brain regions and thereby amplify activity within the "fear network." In addition, an increased sensitivity of serotonergic neurons to CO_2 changes could modulate activations in the sense of reinforcing the network during CO_2 reduction (hyperventilation)
- The data show that a central brain area involved in the processing of anxiety states, the amygdala, is influenced much more strongly by breathing maneuvers in patients than in healthy individuals. This may also be a consequence of altered modulation by brainstem nuclei
- However, an altered sensitivity of the amygdala itself to CO_2 must also be taken into consideration.

To summarize the summary of the summary:

«All you really need to know for the moment is that the universe is a lot more complicated than you might think, even if you start from a position of thinking it's pretty damn complicated in the first place.»

„Don't Panic!“

Douglas Adams
“The Hitchhiker's Guide to the Galaxy“

References

1.Chechko N, Wehrle R, Erhardt A, Holsboer F, Czisch M, Sämann PG Unstable prefrontal response to emotional conflict and activation of lower limbic structures and brainstem in remitted panic disorder. PLoS One. 2009 May 20;4(5):e5537

2.de Carvalho M, Dias GP, Cosci F et al. Current findings of fMRI in panic disorder: contributions for the fear neurocircuitry and CTB effects. Expert Rev. Neurother. 10(2), 291-303 (2010)

3.Esquivel G, Schruers KR, Maddock RJ et al. Acids in the brain: factor in the panic? Journal of Psychopharmacology 24(5) 2010 639-647

4.Gorman JM, Kent MD, Sullivan GM et al. Neuroanatomical hypothesis of panic disorder, revised. Am J Psychiatry 2000; 157:493-505

5.Ho-Ling Liu, ju-Chuan Huang, Chien-Te Wu, Yuan-Yu Hsu. Detectability of blood oxygenation level-dependent signal changes during short breath hold duration. Magnetic Resonance Imaging 20 (2002) 643-648

6.Jacobs BL, Azmitia EC. Structure and function of the brain serotonin system. Physiological reviews, v. 72-1, 1992 pp.165-229

7.Klein DF False suffocation alarms, spontaneous panics, and related conditions: an integrative hypothesis. Arch Gen Psychiatry 1993; 50:306-317

8.McKay LC, Adams L, Frackowiak RSJ, Corfield R. A bilateral cortico-bulbar network associated with breath holding in humans, determined by functional magnetic resonance imaging. NeuroImage 40(2008) 1824-1832

9.Nardi AE, Valenca AM, Nascimento I, Zin WA. Hyperventilation challenge test in panic disorder and depression with panic attack. Psychiatry Reseach 2001, 105:57-65

10.Protopopescu, Pan et al., Increased brainstem volume in panic disorder: a voxel-based morphometric study. BrainImaging, V. 17-4, pp.361-363

11.Richerson GB. Serotonergic neurons as carbon dioxide sensors that maintain pH homeostasis Nature reviews Neuroscience 2004, Vol.5, 449-461

12.Sitker A, Freska E, Braun IM et al. The role of hyperventilation-hypocapnia in the pathomechanism of panic disorder. Rev Bras Psiquiatr. 2007; 29(4):375-9

13. Terekhin P, Forster C.: Hypocapnia related changes in pain-induced brain activation as measured by functional MRI. Neurosci Lett. 2006 May 29;400(1-2):110-

14. Terekhin P.I Clinical aspects of the use of magnetic encephalography. Human Physiology, Volume 30, Number 2, March 2004, pp. 251-252(2). Agadjanian N.A.,

15. Terekhin P.I.: Physilogical mechanisms of respiratory phenomena at anxiety and depressive disorders. Human physiology, v.28. N3-77, 2002

16. Terekhin *P.I.* The role of hypocapnia in inducing altered states of consciousness. Human physiology. V. 22. N6. P.100-105, 1996

17. Sikter A, Faludi G, Rihmer Z. The role of carbon dioxide (and intracellular pH) in the pathomechanism of several mental disorders. Are the diseases of civilization caused by learnt behaviour, not the stress itself? Neuropsychopharmacol Hung. 2009 Sep;11(3):161-73.