Migraine as visceral pain

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Migraine is a slow process consisting of different stages, and the pain is just the tip of the migraine iceberg.

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Fig 1—Symptoms and signs during phases of complete classic migraine attacks.

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Mechanisms of Migraine

Fig 1.—The migraine attack (Adapted courtesy Michel Ferrari, MD, PhD and Roger Cady, MD).

(Headache 2007;47 [Suppl 1]:S26-S43)

domenica 14 marzo 2010
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5. Lab work tends to be reductionist
Migraine: from theories of pathogenesis to a bio-behavioural interpretation
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Unresolved questions

- Is migraine a disease?
- What kind of pain is migraine?
- Does migraine have any meaning?
- When migraine becomes a disease?
Individuals prone to migraine have a genetic migraine threshold that renders them susceptible to a migraine attack upon exposure to some or any of a range of patient-specific trigger-factors.

Any human can suffer of a migraine headache depending from the intensity of the stimulus (hormonal milieu, stress and post-stress, lack of sleep, hypoglicaeemia, anoxia, alcohol). Concept of threshold and genetic priming.
Is migraine a disease?

The essential difference between migraineurs and the rest of the population is:

- a vulnerability to recurrent activations of the trigeminovascular and upper cervical pain systems, causing headaches that cannot be traced to infection, inflammation, a tumor or other structural abnormality or exogenous toxins.

Migraine lies somewhere between normal physiology and permanent dysfunction!!!
Bio-behavioural model for migraine:
Migraine represents bio-behaviourally based dysautonomia involving principally the intrinsic noradrenergic system and its putative orbito-frontal connections (Welch 1987)

Flaws of the model:
✓ it does not consider the Darwinian perspective
✓ it does not consider the concept of brain interoception
✓ it is focused only on the noradrenergic system
What type of pain is migraine?
.....the IH are simply the most common manifestations of the spontaneous activation of the sensory/pain transmitting afferences, decodified at the level of the integrative areas as "useless" painful and nonpainful sensations of either a visceral or a somatic type, according to the type of IH.

The adjective "idiopathic," attributed to the IH, refers to the uselessness of the sensations which dominate these syndromes. They are useless because they are not induced by harmful, environmental, or endogenous stimuli, and do not culminate in a passive or active defensive reaction.
Nature does nothing in vain!
(Aristotele, 287-212 a. C.)

"the art of discovery consist habitually searching for causes and meaning of everything that occur"
(Charles Darwin)
Pain is an enigma
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Definition of International Association for the Study of Pain:
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An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.
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- An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage

- The capacity to experience pain has a protective role; it warns us of imminent or actual tissue damage and elicits coordinated reflex and behavioural responses to keep such damage to a minimum
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Definition of International Association for the Study of Pain:

- An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.
- The capacity to experience pain has a protective role; it warns us of imminent or actual tissue damage and elicits coordinated reflex and behavioural responses to keep such damage to a minimum.
- A visceral sensation, which monitor the integrity of all tissues and elicits visceral motor and emotional responses (Saper 2000).
Modulatory mechanisms of pain show that pain perception is an active process.
Pain is both an aspect of interoception and a specific behavioral motivation.

Pain would join sensations such as hunger and thirst and itch, which are best defined as needs that signify the next probable action. Pain is an attribute assigned by the brain as a quality.

Pain is a homeostatic emotion, akin to temperature, itch, hunger and thirst.
**Types of pain**

- **Nociceptive (exteroception):**
  - Physiology: normal response
  - Anatomy: exteroceptive somatosensory system
  - High biological value

- **Visceral (interoceptive):**
  - Physiology: normal response
  - Anatomy: interoceptive system
  - High biological value

- **Neuropathic:**
  - Lesion of peripheral or CNS
  - Pathological pain
  - Maladaptive
Why “the brain-ache” is not easily classificable?
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- The only way to signal pain for the brain is by means of the trigeminal innervation of meninges and/or the trigeminovascular system.
- The brain can generate pain in the absence of input from peripheral nociceptors or the spinal cord.
- If pain is the response to a threat, the pain of brain is special since brain is at the same time the object of the threat and the subject that it has to organize the adaptive response to the threat.
Central Autonomic Network:
integration of cranial nociceptive and visceral information
Brainstem descending modulatory centers that maintain the “pain” balance: integration of pain and autonomic control by the periaqueductal gray
Anatomo-functional organization of PAG

Bandler and Shipley 1994
Distinct circuits activated by different nociceptive inputs with different behavioural significance are engaged also at the level of the hypothalamus and probably in forebrain areas such as the prefrontal cortex and the amygdala.
How does the brain react to a noxious stimulus?

Structures receiving converging nociceptive and visceral inputs from the spinal and trigeminal dorsal horns (Pain Neuromatrix)

- Anterior cingulate cortex
- Somatosensory cortex I/II
- Insula
- Praecuneus
- Thalamus
- Hypothalamus
- Amigdala
- PAG
- Putamen
- Cerebellum

It is under dynamic top-down modulation (so-called antinociceptive system) by brain mechanisms that are associated with anticipation, expectation and other cognitive factors.
As the virtual predator grew closer brain activity shifted from the ventro medial prefrontal cortex to the PAG. This shift showed maximal expression when a high degree of pain is anticipated. Moreover, imminence-driven PAG activity correlated with increased subjective degree of dread and decreased confidence of escape.
When Your Gain Is My Pain and Your Pain Is My Gain: Neural Correlates of Envy and Schadenfreude

Hidehiko Takahashi,1,2,3* Motoichiro Kato,4 Masato Matsuura,2 Dean Mobbs,5 Tetsuya Suhara,1 Yoshio Okubo6

Pain network

SSC
Thal
Ins
dACC
PAG

Reward network

VTA
VS
Amyg
VMPFC

Physical pains
Social exclusion
Bereavement
Being treated unfairly
Negative social comparison

Physical pleasures
Having a good reputation
Being treating fairly
Cooperating
Giving to charity
Schadenfreude
So what?
And Migraine?
And migraine?
And migraine?

Migraine attack is
And migraine?

Migraine attack is a transient pain.
And migraine?

Migraine attack is:

- a transient pain
- not associated with brain damage
And migraine?

Migraine attack is

- a transient pain
- not associated with brain damage
- associated with nausea, vomiting, photophobia, irritability, tiredness, and accentuated by head movements
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And migraine?

Migraine attack is:
- a transient pain
- not associated with brain damage
- associated with nausea, vomiting, photophobia, irritability, tiredness, and accentuated by head movements
- usually not localized and radiating
- associated with allodynia and hyperalgesia

domenica 14 marzo 2010
Migraine is a visceral pain!

Profound reduction of somatic and visceral pain in mice by intrathecal administration of the anti-migraine drug, sumatriptan

Tetsuro Nikai a,b, Allan I. Basbaum c, Andrew H. Ahn d,*

Pain 139 (2008) 533–540

www.elsevier.com/locate/pain
Primary headache: functional and structural evidence of different "generator centers"

During migraine attack
Brainstem activation

During CH attack and other TACs
Hypothalamic activation
Functional differences in the brainstem and the brain of 12 migraine vs. 12 healthy subjects. 

(B) Activation contrast: **Interictal migraine subjects show decreased nucleus cuneiformis (NCF) responses to stimuli relative to controls.** 
The exception is Thr+1uC on the face.
Are there the effect of the “brain in pain” or of the “pain of the brain”?
Neuroimaging analysis using structural data has begun to provide insights into the pathophysiology of headache syndromes. Several independent studies have suggested a decrease in grey matter in pain-transmitting areas in migraine patients. Most of these data are discussed as damage or loss of brain grey matter, reinforcing the idea of migraine as a progressive disease. However, given what we know about the nature of morphometric changes detectable by the methods we have to date, this interpretation is highly speculative and not supported by the data. It is likely that these changes are the consequence and not the cause of the respective headache syndromes, as they are probably not irreversible and only mirror the proportion or duration of pain suffered. Moreover, structural changes are not headache specific and have to be seen in the light of a wealth of pain studies using these methods.

Red: migraine; 
blue: cluster headache; 
yellow: tension type headache.
Migraine as visceral integrated response of a threatened brain

Threat to the brain

Pain Neuromatrix CAN Arousal System

“homeostatic afferent processing network”

Migraine
### Pattern of behavioural autonomic responses and primary headache

<table>
<thead>
<tr>
<th>Sickness Behaviour</th>
<th>Fight or flight Behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>✱ tiredness, fatigue</td>
<td></td>
</tr>
<tr>
<td>✱ motor quiescence</td>
<td></td>
</tr>
<tr>
<td>✱ avoidance of physical activity</td>
<td></td>
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<tr>
<td>✱ sleepiness</td>
<td></td>
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<tr>
<td>✱ Agitation</td>
<td></td>
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<tr>
<td>✱ Compelled of moving around</td>
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<tr>
<td>✱ Performing violent acts</td>
<td></td>
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<tr>
<td>✱ Pt aroused</td>
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</tbody>
</table>
Pattern of behavioural autonomic responses and primary headache

Sickness Behaviour
Migraine Attack
(Inescapable threat)

Fight or flight Behaviour
Cluster Headache attack
(Escapable threat)

Both may be “coping strategy” with an adaptive role in that it helps the brain to recover
Does migraine have any meaning?

Nature does nothing in vain!

Hypothesis

Migraine may have a protective role even promoting survival being a visceral response of the brain to a condition that threaten itself!!!
Which are the condition that threaten the integrity of the brain?

- Any invasion of the meninges (stimulation of the dura provokes headache)

- But when no injuries are detectable?
Neuron metabolism is primarily oxidative!!!

If the slow evolution of migraine attacks is neuronal in origin, glucose and oxygen are our main concern.

Therefore insufficient supply or excess utilisation of these chemicals should provoke migraine episodes.

What is the evidence? **Multiple triggers of the pain and strain of migraine affect the energetic metabolism of the brain.**
Migraine as a signal of a critical and still reversible metabolic situation of the brain: it deals with brain’s visceral interoception.
Views and Perspectives (Headache 2010;50:273-289)

The Primary Headaches as a Reflection of Genetic Darwinian Adaptive Behavioral Responses

Pasquale Montagna, MD; Giulia Pierangeli, MD, PhD; Pietro Cortelli, MD, PhD

MIGRAINE
External / Internal stressors: homeostatic imbalance (inescapable stress)
Cytokines (sterile inflammation?) → Activation of inescapable pain matrix (C fibers, ventrolateral PAG, etc.)

Sickness behaviour
Passive coping strategy: motor and sensory quiescence, withdrawal, fatigue, somnolence, mood depression

CLUSTER HEADACHE
External / Internal stressors: homeostatic imbalance (escapable stress)
Cytokines → Activation of escapable pain matrix (Aδ fibers, dorsolateral PAG, posterior hypothalamus, etc.)

Defense reaction
Active coping strategy: heightened alertness, motor restlessness, combativeness and rage behaviour
When migraine becomes a disease?

The Chronification of Headache

Concepts and Mechanisms of Migraine Chronification

Marcelo E. Bigal, MD, PhD; Richard B. Lipton, MD

Migraine Transformation

Episodic

Chronic

Severe Impairment

Moderate Impairment

Mild Impairment

Normal Neurological Function

Time

Depression

Muscle Pain

GI Complaints

Sleep Disorder
The double face of allostasis
Chronic migraine may be explained in an allostatic perspective.
Chronic migraine may be explained in an allostatic perspective

McEwen's basic thesis is that situations that ignite stress responses nowadays are increasingly ones for which neither fight nor flight is an option.

These stressors are often psychological in nature (e.g., working for an overbearing boss, or caring for a family member who is seriously ill, etc) and resembles many aspects of what we call triggers of migraine.

The allostatic response causes when stressors are inescapable may lead to an excessive “allostatic load.”
Chronic migraine may be explained in an allostatic perspective

Migraine attack may be the protective response of the brain threatened by an excessive allostatic load that may be interpreted by the brain as an excessive metabolic challenge but...

Repeated challenge of this adaptive mechanism in predisposed subjects, may transform migraine in a chronic condition associated with functional and structural changes of the pain matrix i.e. in a disease...
The autonomic face of migraine

Conclusions
The bio-beavioural model expanded in a Darwinian perspective with the new concept of “pain” as monitor of interoception, views the migraine attack as:
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The autonomic face of migraine

Conclusions

The bio-beavioural model expanded in a Darwinian perspective with the new concept of “pain” as monitor of interoception, views the migraine attack as:

- adaptive behavioural response engendered out of a genetic (evolutionary conserved) repertoire for the maintenance of brain homeostasis
- the neurobiological response is determined in the Central Autonomic Network which include also the Pain Neuromatrix and the Ascending Arousal System (“homeostatic afferent processing network”; “Limbic System”)
The autonomic face of migraine
Conclusions
migraine as visceral pain may signify some primarily nervous deviance from its homeostasis (brain’s interoception) and it is adaptive serving the purpose of recovering the brain’s homeostasis
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pain in different primary headaches is variously perceived according to its behavioural significance (escapable vs inescapable)
The autonomic face of migraine

Conclusions

When the “Adaptative Migraine System” is stimulated excessively may transform into disease “Chronic Migraine” (excessive allostatic load)
MIGRAINE is
OF the brain, BY the brain, FOR the brain
Future directions

Identify those characteristics of the migraine brain that, being the “real pathological factors”, trigger the development of the attack under appropriate conditions (why and how is dysregulated the “homeostatic afferent processing network”)

Identify why and how an allostatic response becomes an allostatic state (Chronic migraine view in an allostatic perspective)

Interpretation of results obtained imaging migraine
XII Congress of European Federation of Autonomic Societies (EFAS)

Giardini Naxos - Taormina, Italy, May 12 - 15, 2010
Thank you for your attention !!!