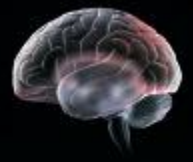
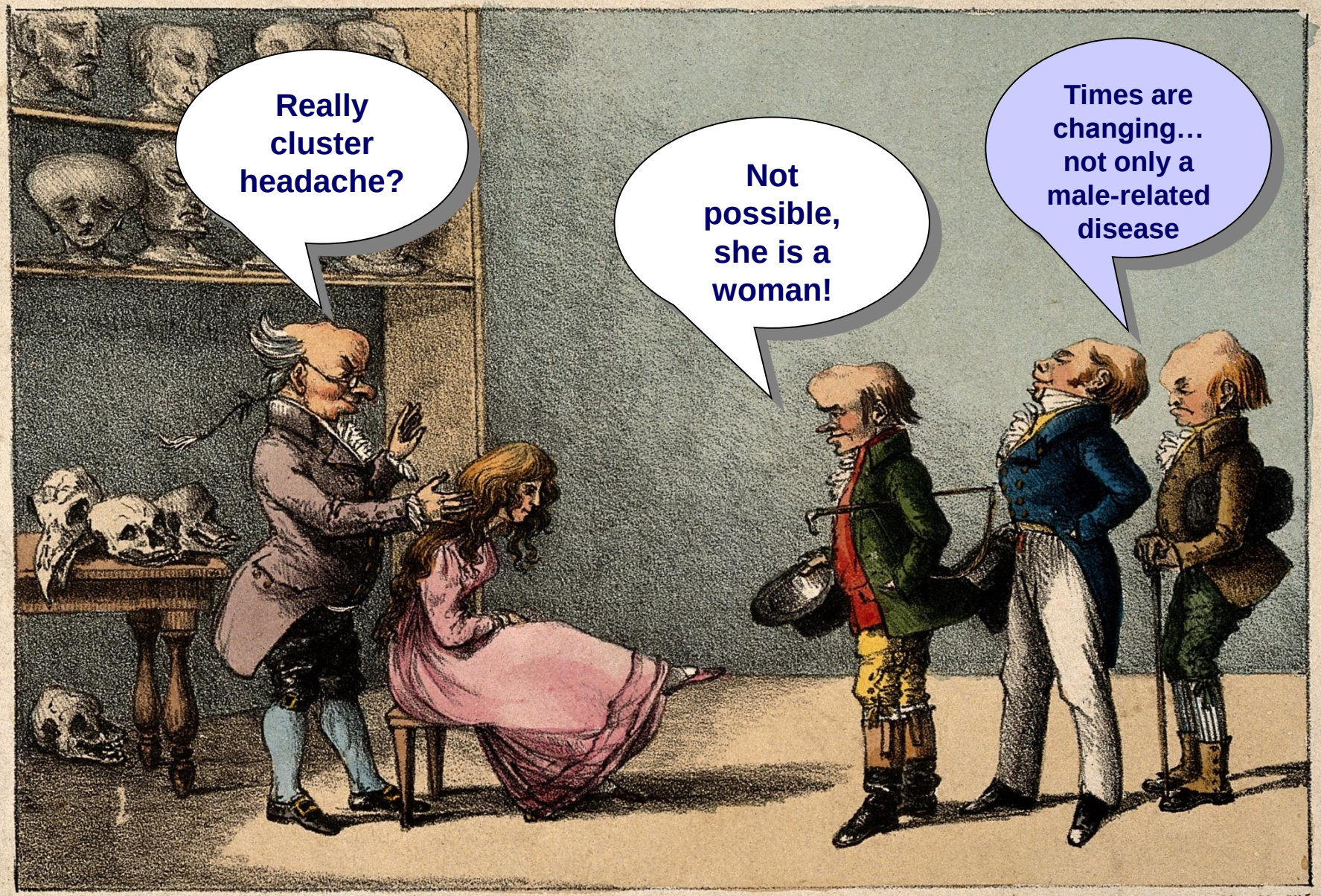
V Congresso Nazionale Medicina di Genere
Torino, 5 aprile 2019



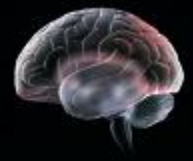
CEFALEA A GRAPPOLO E GENDER

Innocenzo Rainero, MD, PhD
Neurology I – Department of Neuroscience
University of Torino, Italy

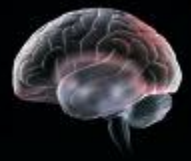
AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino


Really cluster headache?
Not possible, she is a woman!
Times are changing… not only a male-related disease
Drawn on Stone by E. H.
London Pub.d by Rowe & Walter 49 Fleet St. 1825.
THE PHRENOLOGIST.

OUTLINE

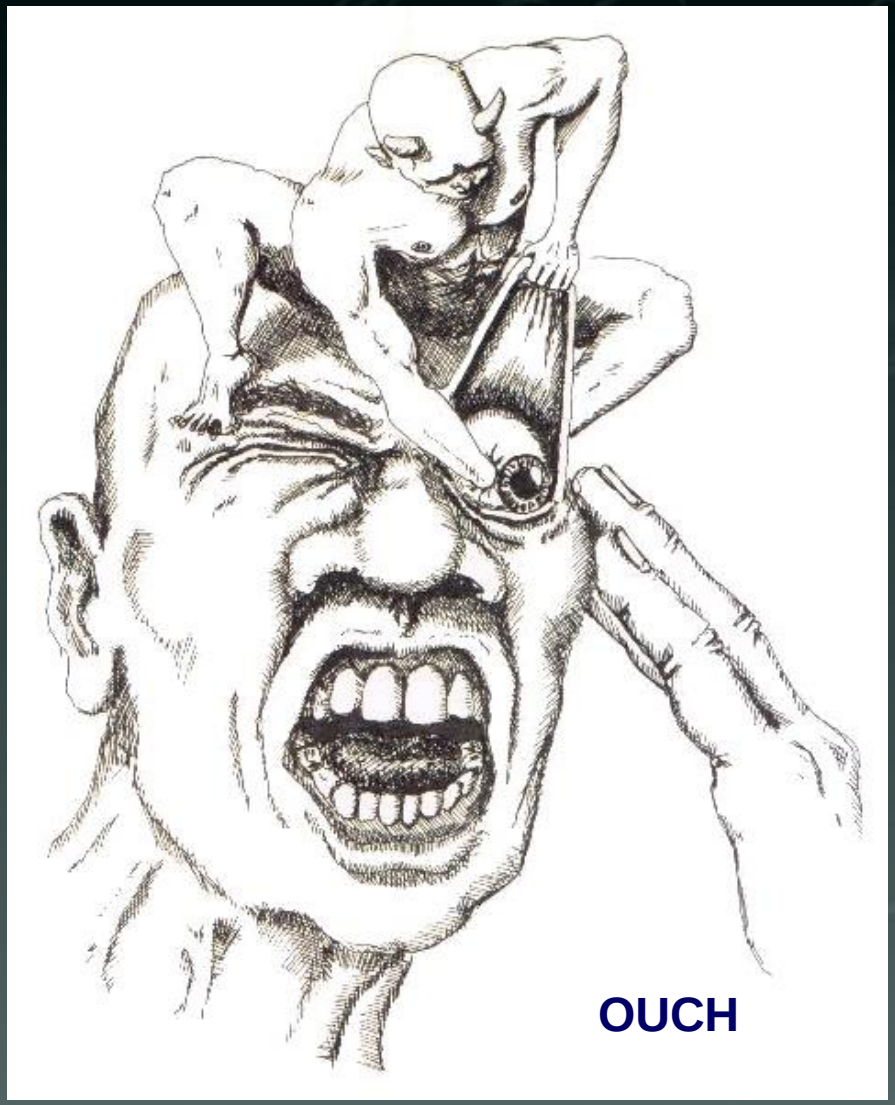


- Cluster headache: the symptoms
- Cluster headache: the pathogenesis
- Cluster headache and gender
- Potential neurobiological mechanisms in gender differences
- Therapeutic approaches and gender
- Future perspectives



Cluster headache: the symptoms

The cluster headache attack



Cluster headache is one of the most painful conditions known to mankind.

Attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal or in any combination of these sites, lasting 15-180 minutes and occurring from once every other day to eight times a day.

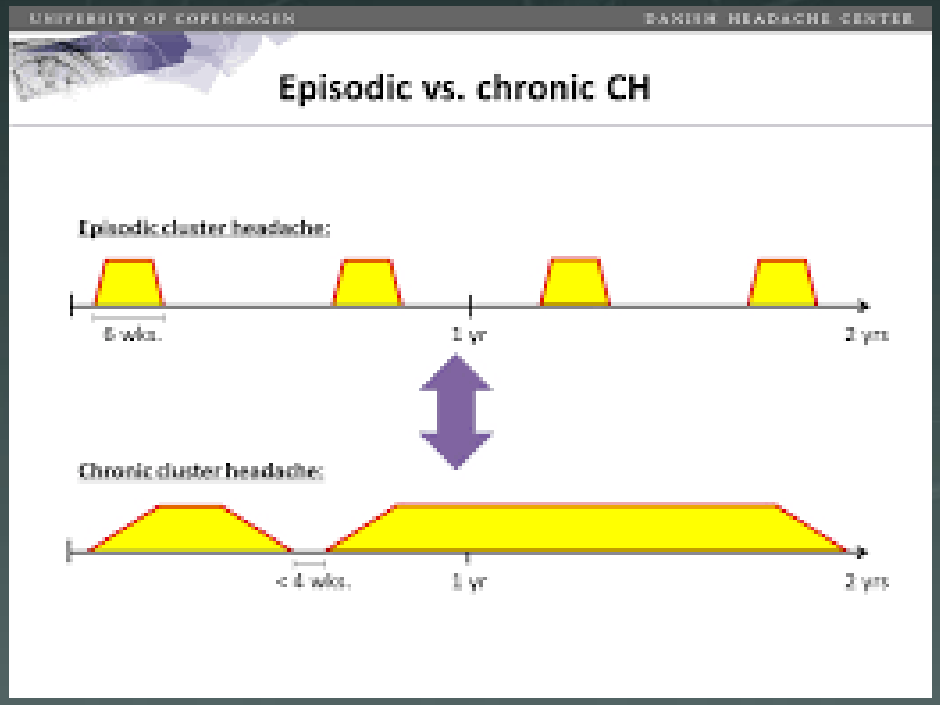
CH attack: accompanying symptoms

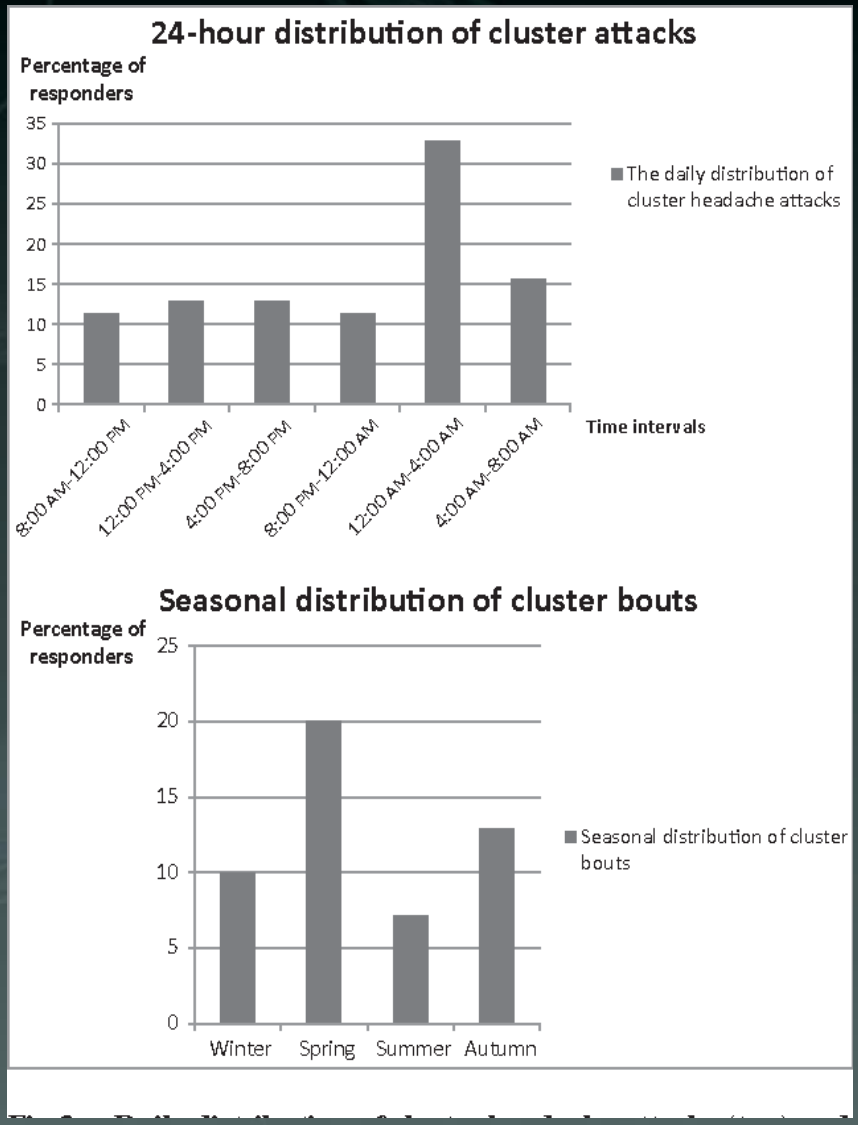
- Conjunctival injection and/or lacrimation
- Nasal congestion and/or rhinorrhea
- Eyelid oedema
- Forehead and facial sweating
- Miosis and/or ptosis

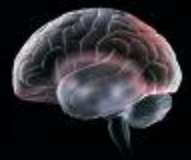
- A sense of restlessness or agitation

CH: the periodicity

Attacks occur in series lasting for weeks or months (so-called cluster periods or bouts) separated by remission periods usually lasting months or years.

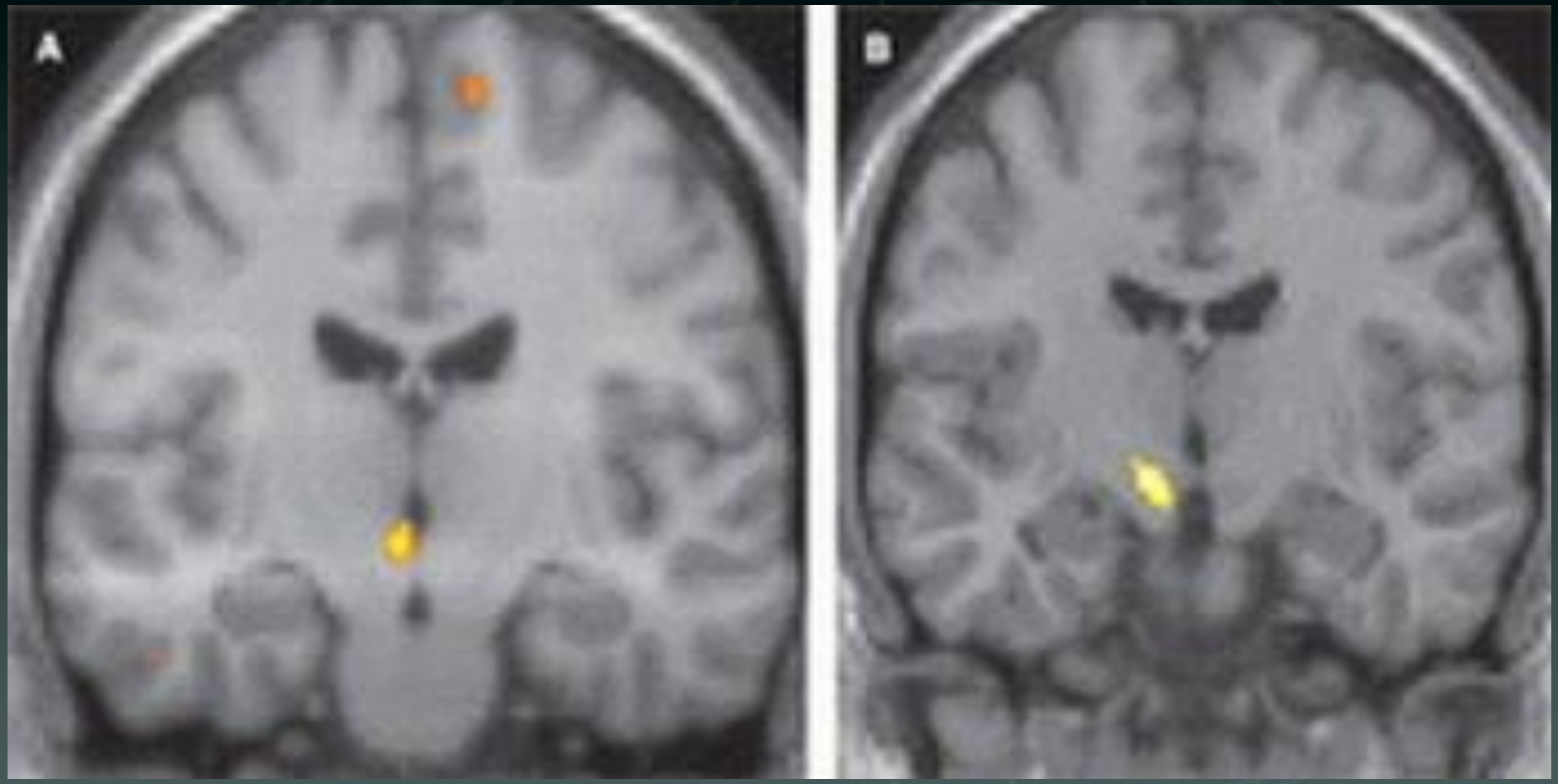






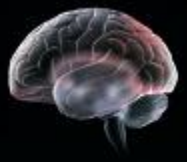
Cluster headache: pathogenesis

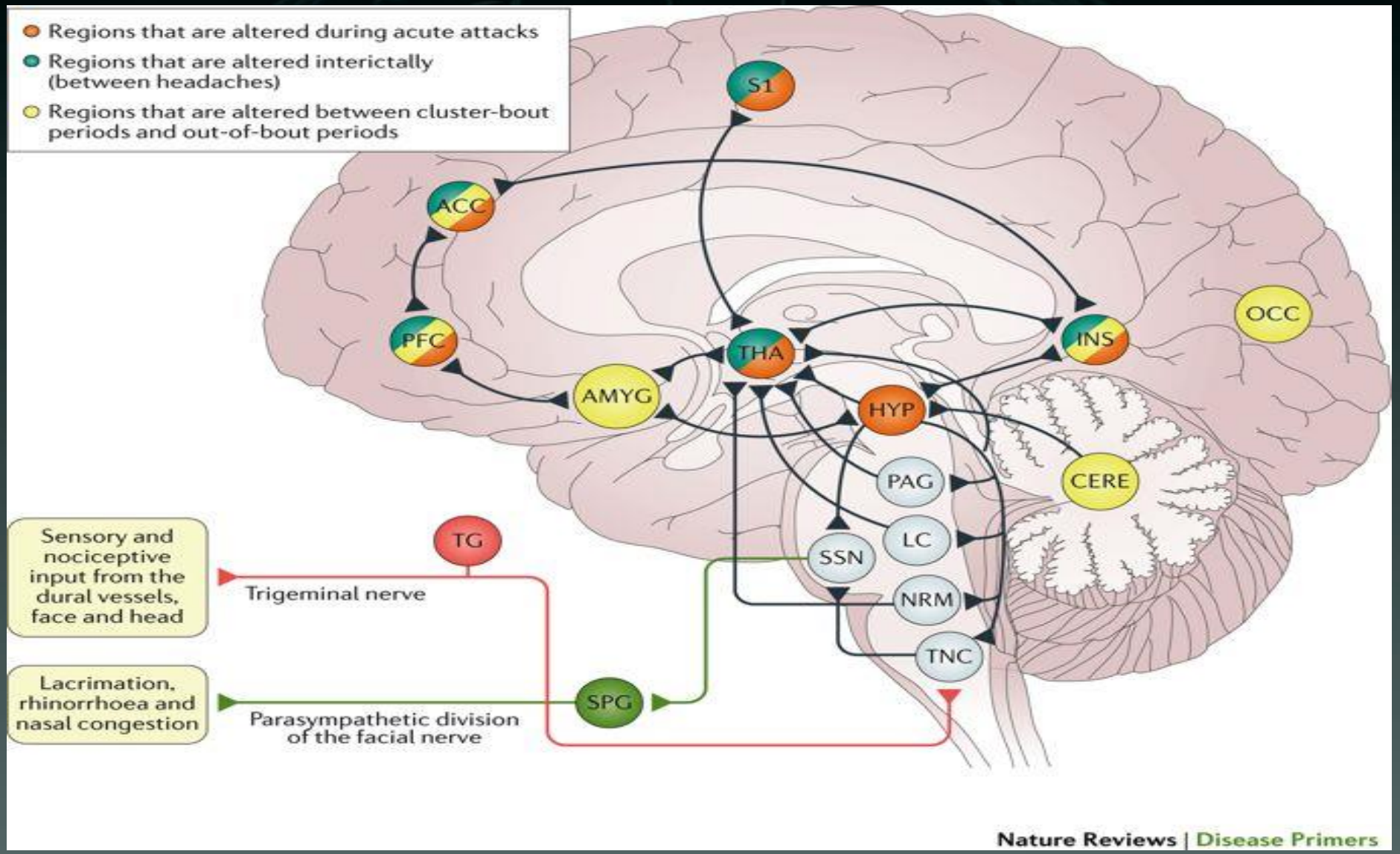
Cluster headache and gender



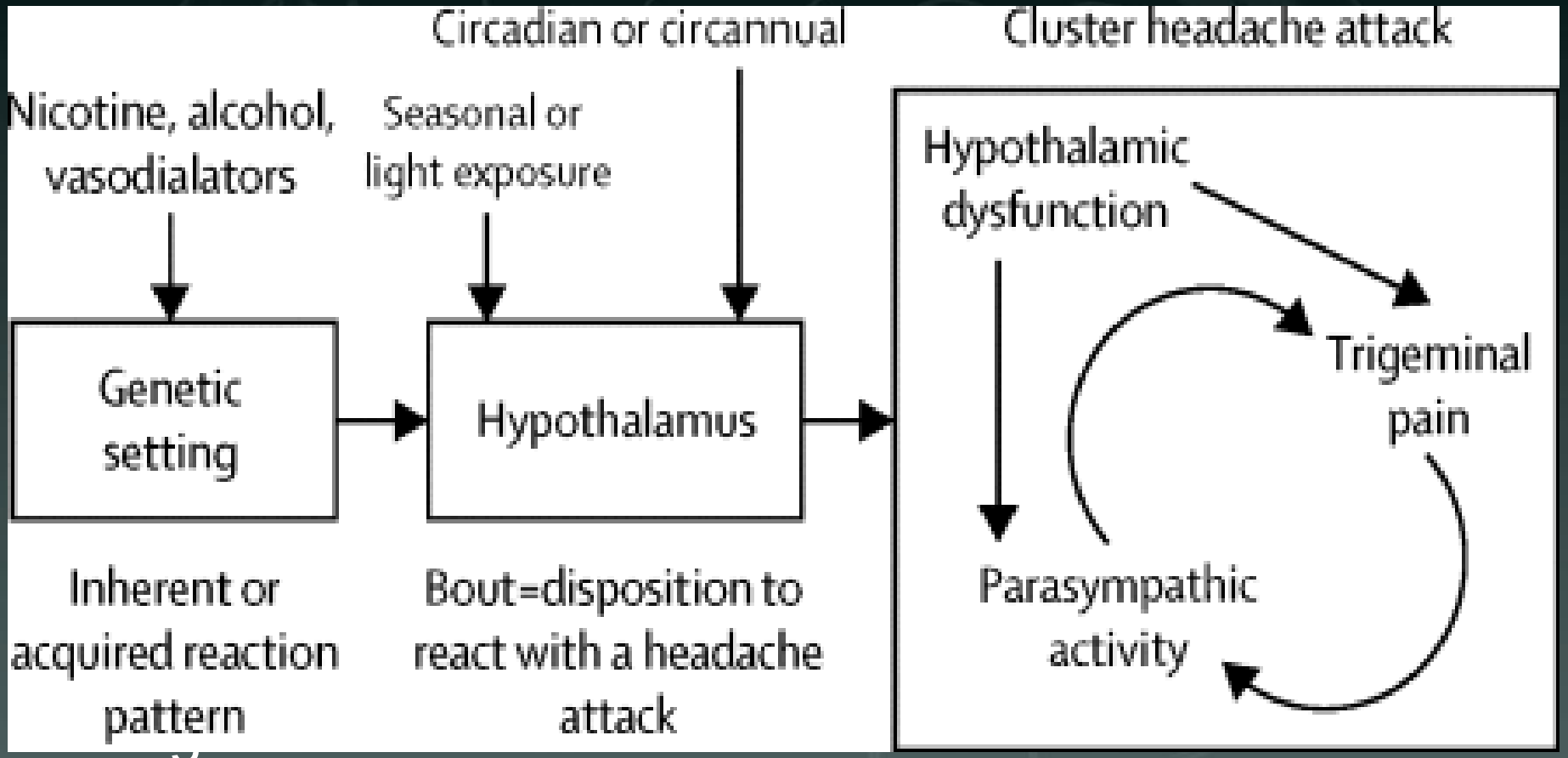
Hypothalamic activation in cluster headache, Goadbsy et al., 1998

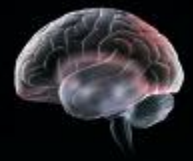
Cluster headache and gender





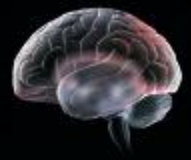
Cluster headache: the causes





Cluster headache and gender

Are there gender related differences in CH?



A. **Family history**: woman cluster headache sufferers are more likely to have a family history of both cluster headache and migraine.

B. **Age of onset:** women develop cluster headache at an earlier age than men.

C. **Pain location:** women are significantly more likely to experience cluster headache pain in the jaw, cheek and ear than men.

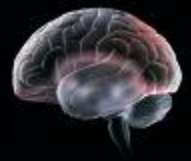
D. **Triggers:** women with cluster headache are much less likely to have alcohol trigger a headache, but are significantly more likely to have "migrainous" triggers for their cluster headaches than men.

E. **Smoking issues:** women are much less likely to have a smoking history than male cluster headache sufferers.

F. **Comorbid conditions:** female cluster headaches sufferers are significantly more likely to experience depression and have asthma than males.

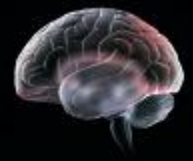
United States Cluster Headache Survey, 2012

Male preponderance of CH



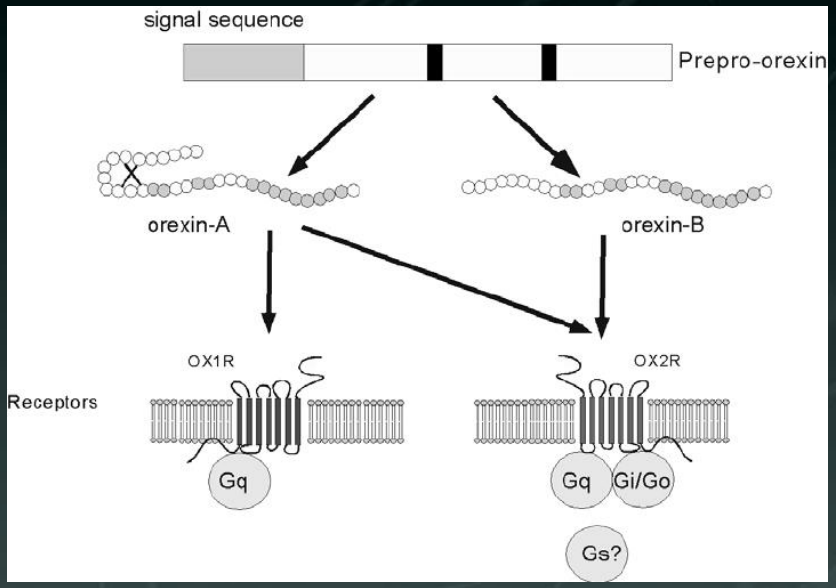
- Cluster headache has been historically considered to have a male preponderance, with a high male-to-female ratio.
- The overall sex ratio is 4.3 (male to female), higher in chronic cluster headache (15.0) compared with episodic cluster headache (3.8).
- Several studies observed that, recently there is a **downward trend in male preponderance** over this period. In Italy, the M/F ratio has fallen from 6.2:1 for patients with CH onset before 1960, to 5.6:1, 4.3:1, 3.0:1, and 2.1:1 for patients with CH onset in the 1960s, 1970s, 1980s, and 1990s, respectively.
- Some authors suggested that the decreasing male-to-female ratio reflects the change in women's lifestyle over the decades, possibly related to **cigarette smoking and alcohol use**.

Cluster headache and gender

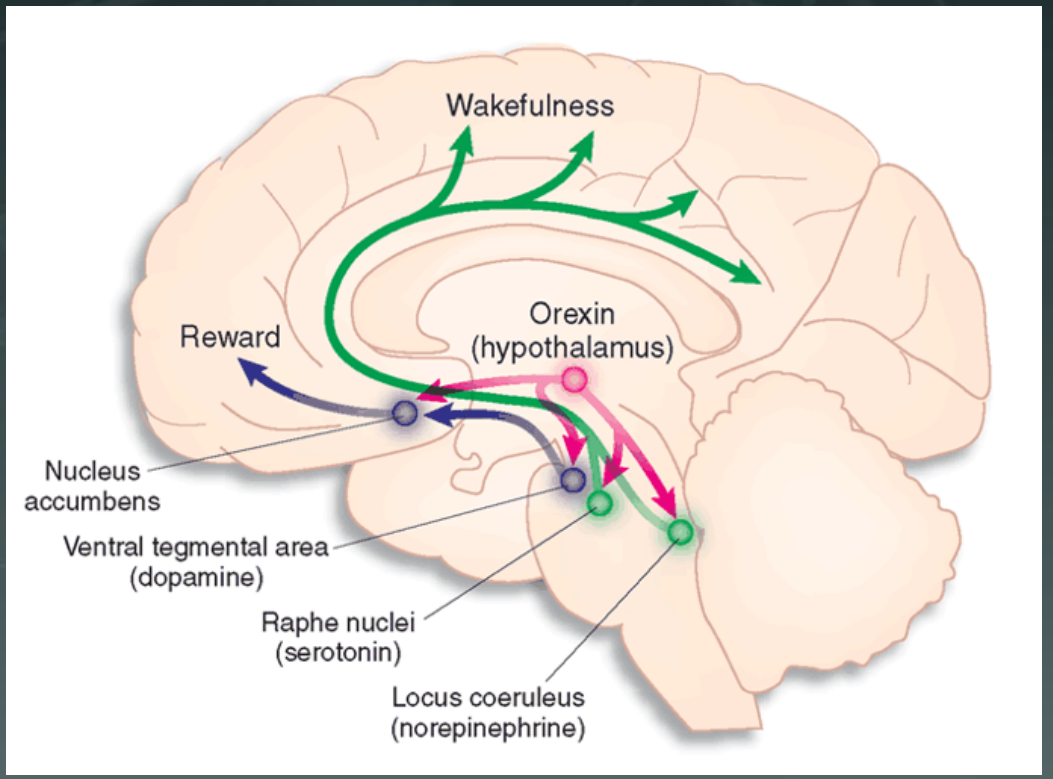


Potential neurobiological mechanisms in gender differences

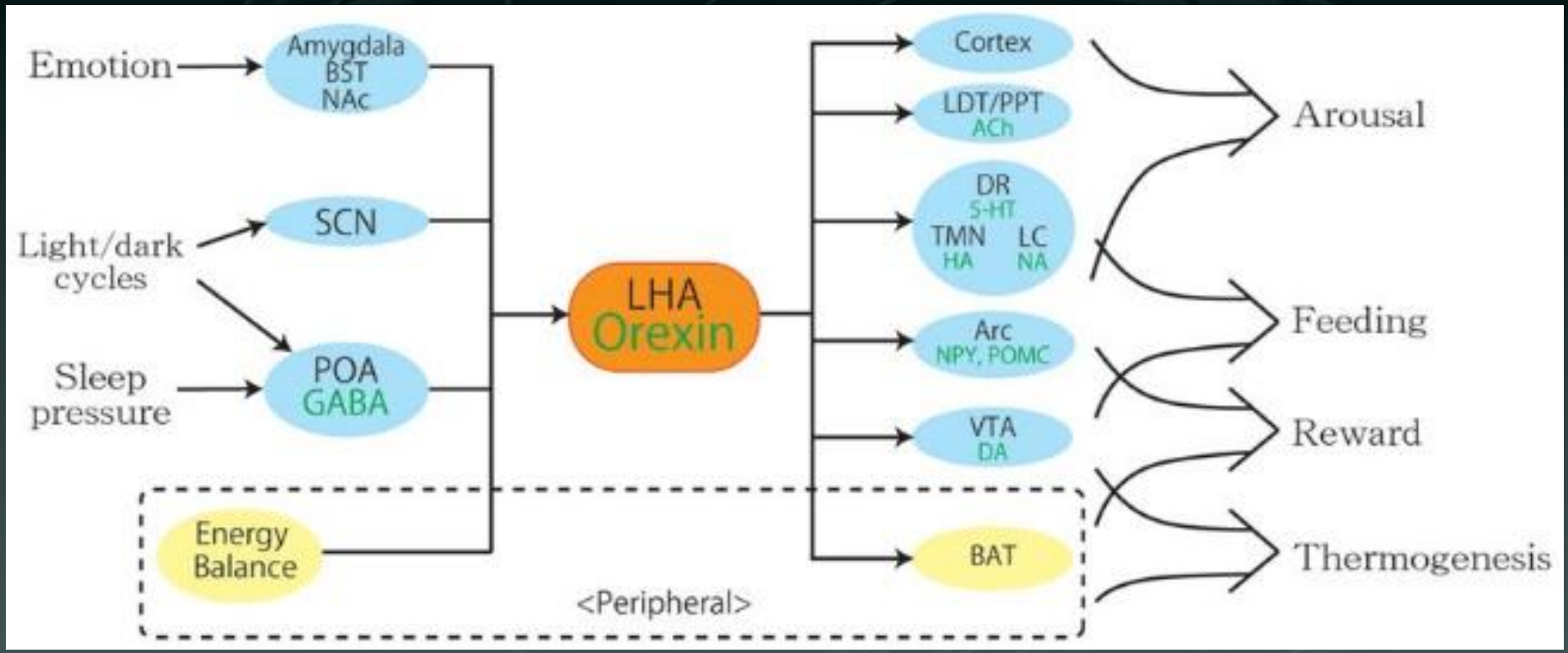
Gender differences and orexins



There are significantly higher levels of PPO mRNA in the hypothalamus of female rats compared to male rats, suggesting **gender-specific** functions of orexins.

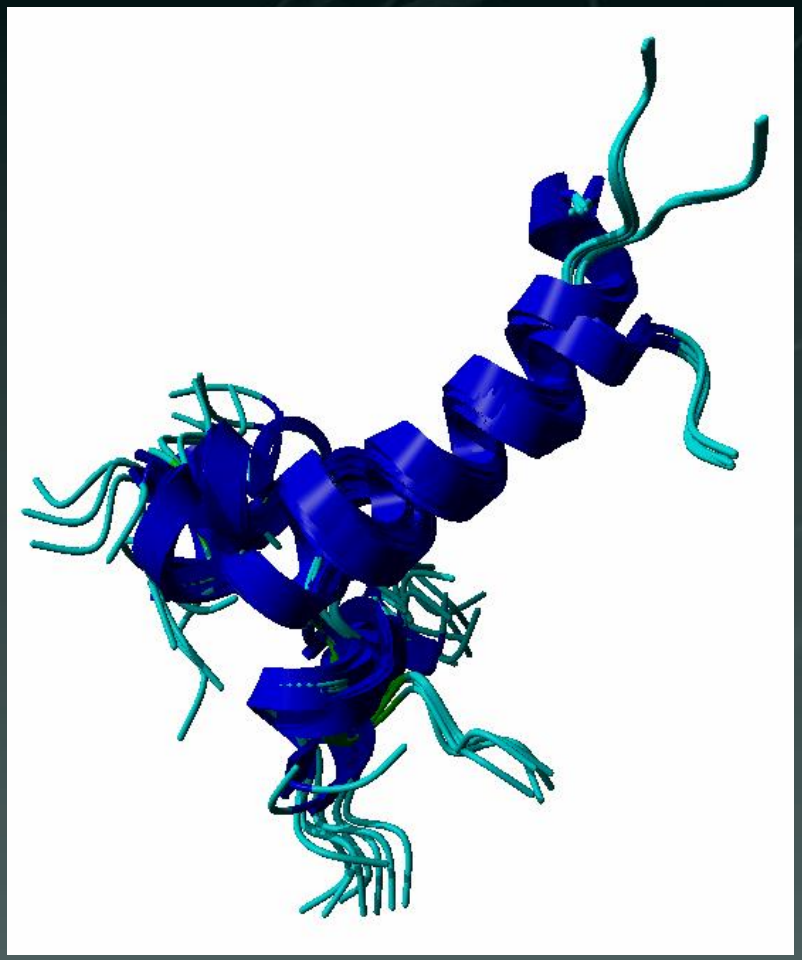


Gender differences and orexins



The orexin system regulates multiple physiological functions

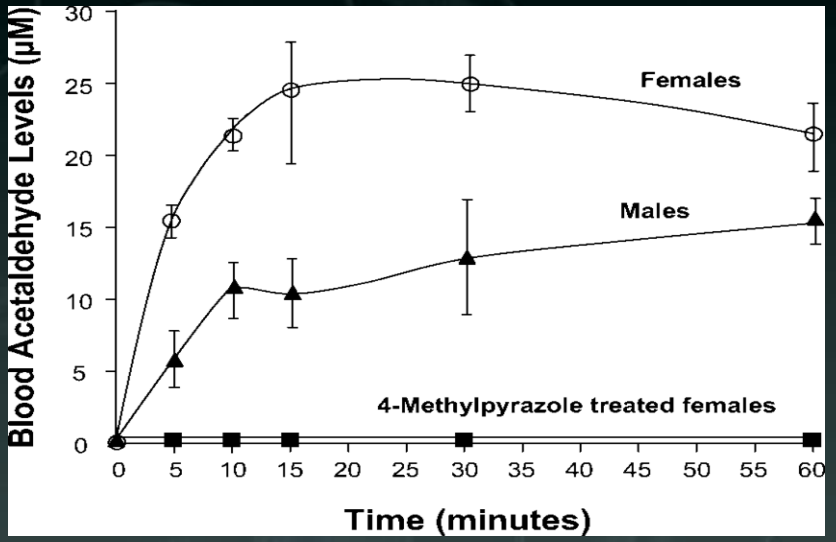
HCRTR2 gene and cluster headache

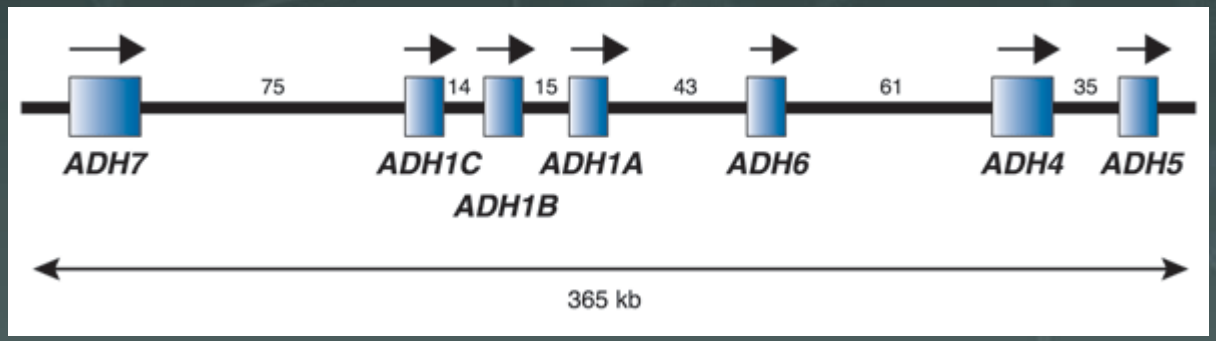


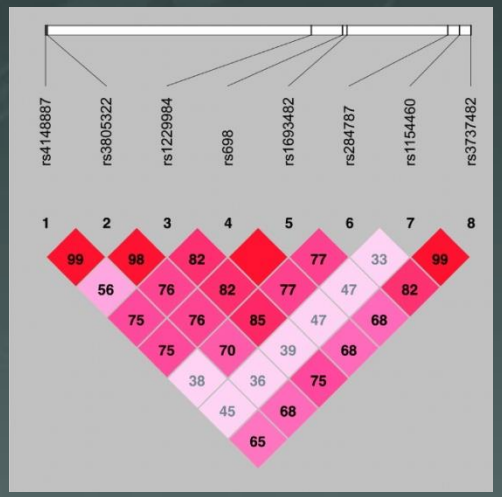
Haplotype	Haplotype sequence	Frequency (%)
haplo1	ACTCGGTCATG	1.6
haplo2	TATTGGTCATG	0.4
haplo3	AATTGGTCTTG	11.0
haplo4	AATTAATTACG	11.8
haplo5	ACTTGGTCTTG	0.8
haplo6	ACTTAATTACG	1.6
haplo7	AATTGGTCATG	13.4
haplo8	TCTCGGTCATC	2.4
haplo9	TCTCGGTCATG	53.3
haplo10	ACGCGAACATG	3.7

For rs2653349, a marginal statistically significant difference between genders was found ($p = 0.080$) for A:A versus G:G and G:A genotypes (OR = 2.78), indicating a higher representation of male homozygotes for the protective mutant A:A allele than female

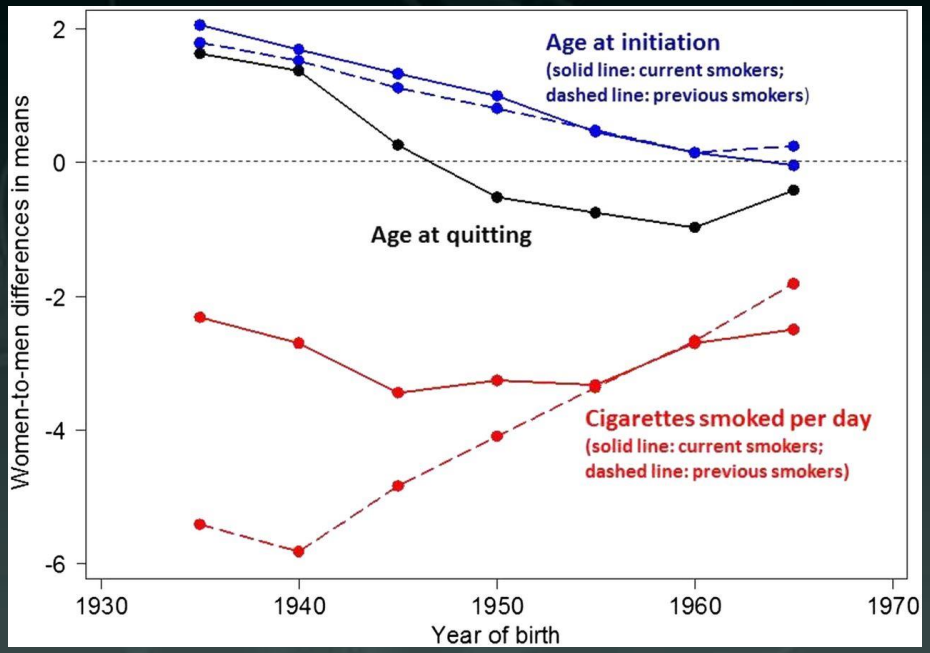
Alcohol and gender differences in CH



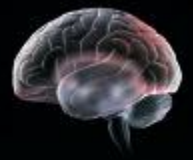




Smoke and gender differences in CH



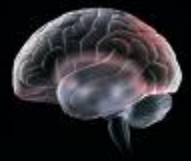
Linking Cigarette Smoking and Cluster Headache: a New Theory



The hypothesis theory will include several principles:

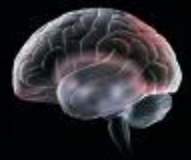
1. the need of double lifetime tobacco exposure,
2. that cadmium is possibly the primary agent in cigarette smoke that leads to hypothalamic-pituitary-gonadal axis toxicity promoting cluster headache,
3. that the estrogenization of the brain and its specific sexually dimorphic nuclei is necessary to develop cluster headache with tobacco exposure,
4. that the chronic effects of smoking and its toxic metabolites including cadmium and nicotine on the cortex are contributing to the morphometric and orexin alterations that have been previously attributed to the primary headache disorder itself.

Rozen TD. Headache 2018;58(7):1096-1112.



Therapeutic approaches and gender

Treatment and gender



A. **Diagnostic delay:** there remains a significant diagnostic delay for cluster headache patients in both sexes but women were more likely to be diagnosed after 10 years of symptom onset than males.

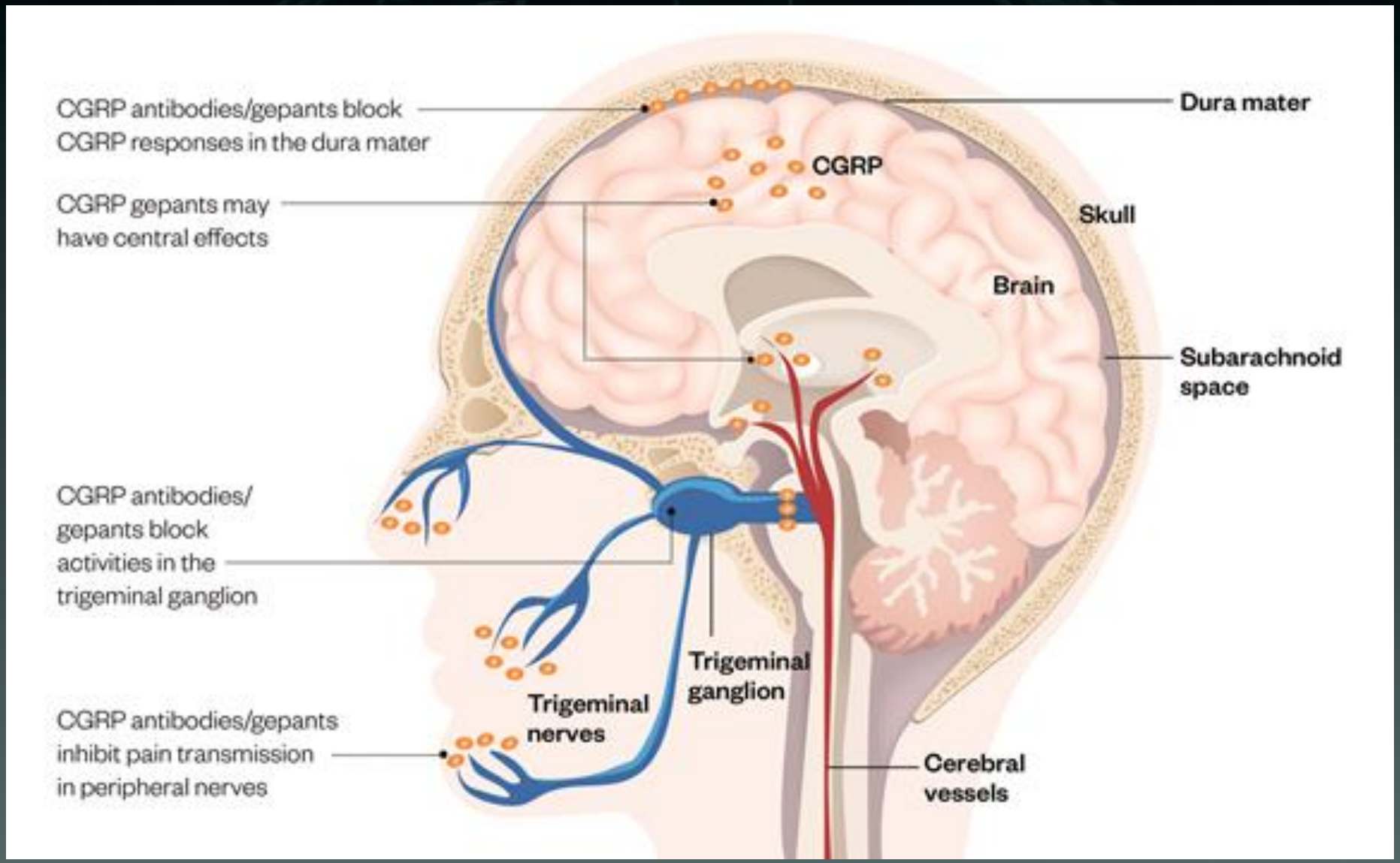
B. **Acute treatment:** women statistically were less response to sumatriptan injectable and nasal spray than men. There was equal efficacy in the sexes to inhaled oxygen

C. **Preventive therapy:** overall women were less responsive to almost all preventives than men.

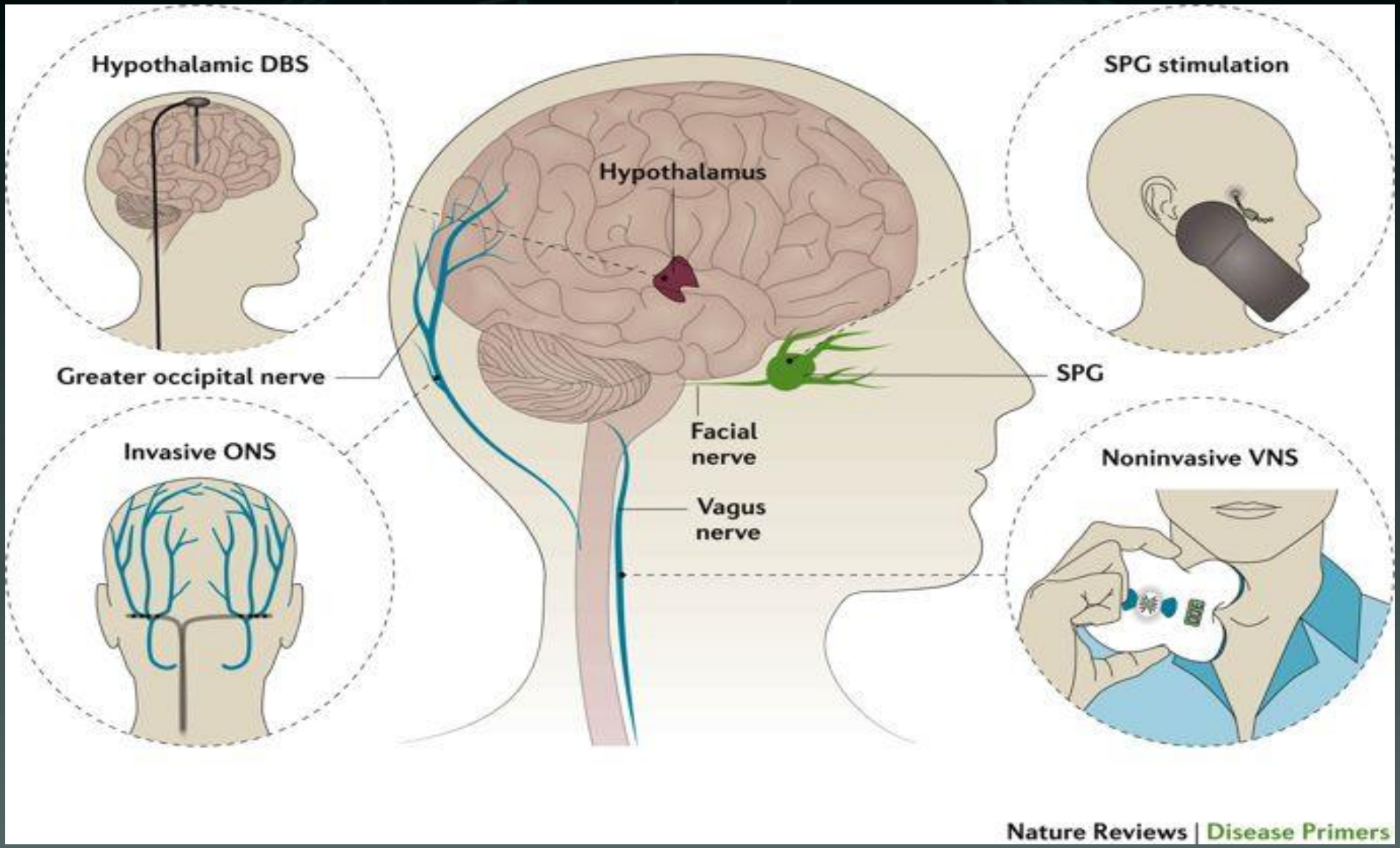
D. **Personal burden:** cluster headache causes significantly more personal burden in women than men with more loss of employment and/or need of disability, as well as more homebound days.

United States Cluster Headache Survey, 2012

anti-CGRP in cluster headache



Neurostimulation in cluster headache



Future directions

- In the past 20 years, great advances in our understanding of the pathophysiology of cluster headache have come from genetic and neuroimaging studies.

- A large number of studies clearly showed that cluster headache is a gender related disease. Intriguingly, the male/female ratio is changing, probably in relation with different lifestyles.

- There is an urgent need of new, gender related studies, in order to better understand the complex pathophysiology of this disease and to plan, according to a personalized medicine strategy, a tailored treatment for individuals suffering for cluster headache.


Thank you for your attention