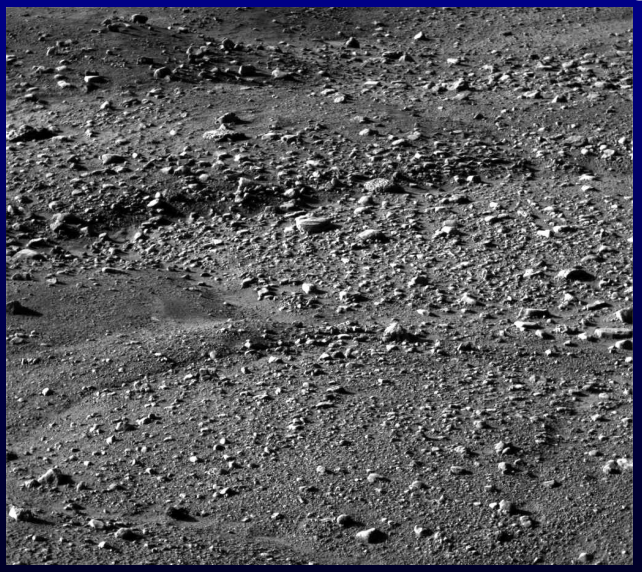
Cluster Headache
2025

Summer Conference 2025
Royal Victoria Infirmary

Organisation for Understanding Cluster Headache- UK



8th June 2024

Professor Peter J. Goadsby

Cluster Headache

- Historical Background/Definition
- Oxygen for Cluster Headache
  - Does the demand valve quicker than high flow mask (Diana Wei)?
- Brain anatomy
  - Where is the problem/what is he problem?
- What have we learned from the Help Line
- Travel and Cluster Headache
- Biochemistry of cluster headache

Cluster headache history

- Migrainous neuralgia (of Wilfred Harris)
- Histaminic cephalalgia
- Petrosal neuralgia
- Sphenopalatine neuralgia
- Hemicrania periodic neuralgiformis
- Erthroprosopalgia of Bing
- Horton's headache (cephalalgia)
- 'a particular variety of headache' (Symonds)

Trigeminal Autonomic Cephalalgias (TACs)*

3.1 **Cluster Headache**
- **a. Episodic (> 3 months break; no Rx)**
- **b. Chronic (≤ 3 months break; no Rx)**

3.2 Paroxysmal Hemicrania
- a. Episodic
- b. Chronic

3.3 SUNCT (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing)/SUNA

3.4 Hemicrania continua

3.5 Probable TAC

*Goadsby & Lipton Brain 1997;120:193
ICHD-3 Cephalalgia 2018;38:1

Cluster Headache

A. Headache ≥ 5 attacks fulfilling criteria B-D
B. Severe or very severe pain lasting 15-180 minutes (untreated)
C. Either or both of the following:
   1. At least one of the following symptoms or signs, ipsilateral to headache:
      a. Conjunctival injection, lacrimation, or both
      b. Nasal congestion, or rhinorrhoea, or both
      c. Eyelid oedema
      d. Forehead and facial sweating
      e. Miosis, or ptosis, or both
      f. Sense of aural (ear) fullness
      g. Forehead/facial flushing
   2. Associated with sense of restlessness or agitation
D. Frequency: every other day to eight per day
E. Not better accounted for by another ICHD-3 diagnosis

Episodic: At least two cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥3 months.

Chronic: Occurring without a remission period, or with remissions lasting <3 months, without preventive treatment, for at least 1 year.

ICHD-3 Cephalalgia 2018;38:1

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Evaluating the treatment of cluster headache – ETCHO-1

Study cohort: South-Central England and Scotland
n = 200

Table 1. Highlighted clinical findings from questionnaire in both regions

	Scotland	South-Central England
Median number of CAS	5 (IQR: 6-4)	6 (IQR: 6-3)
Median time to diagnosis	2 (IQR: 10-1) months	3 (IQR: 8-1) months
Top three preventives	Verapamil	Verapamil
	Lithium	Lithium
	Greater occipital nerve injection	Greater occipital nerve injection

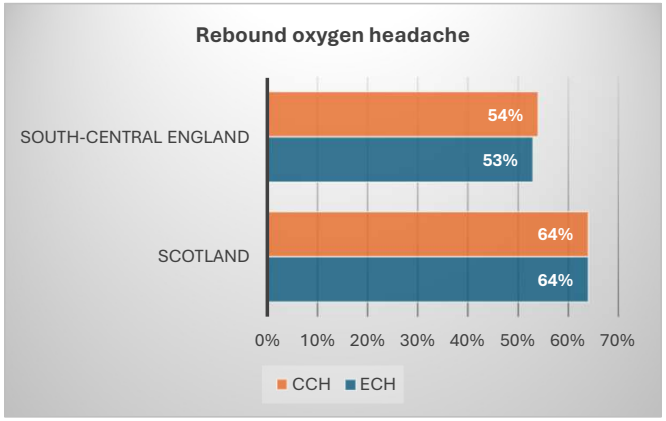
→ Lacrimation

→ Neurologist

→ Verapamil

In the Scotland cohort, **significant association between oxygen as the most effective acute treatment and taking verapamil as a preventive** was seen for ECH patients. We conducted Fisher's exact test with a $P < 0.001$.

Figure 1. Proportion (%) of patients with rebound oxygen headache in both regions. ECH = episodic cluster headache, CCH = chronic cluster headache



Final stages → Move to online data collection via OUCH UK website *(subject to ethics approval)* - - → Final analysis of all data and subsequent publications

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Oxygen in CH

Dr Diana Wei

Consultant Neurologist

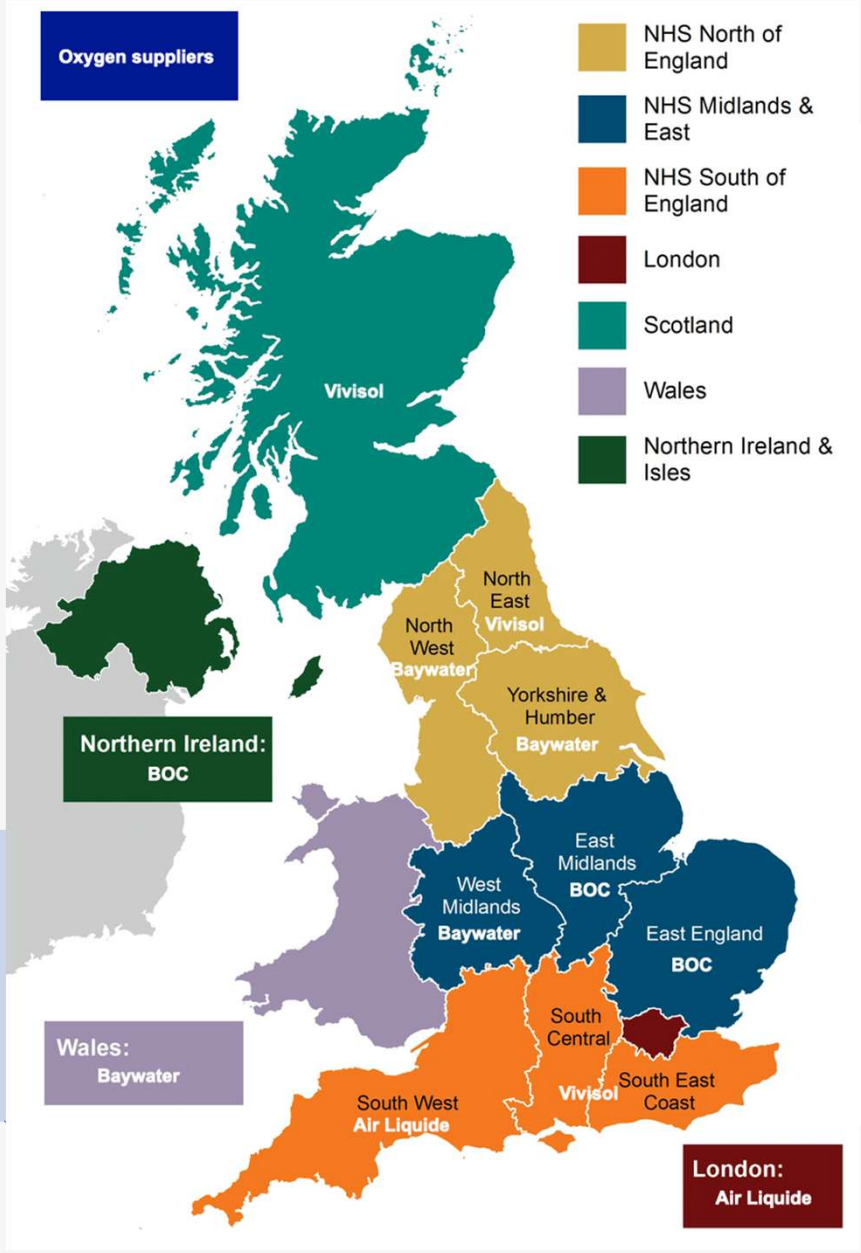
Senior Lecturer

1952 First description of oxygen use in histaminic cephalgia

1981 First systematic study on oxygen for CH

1985 Crossover study showed oxygen was more effective than room air

2009 Oxygen at 12l/min was proven to be more effective than room air



Oxygen Suppliers

Air Liquide

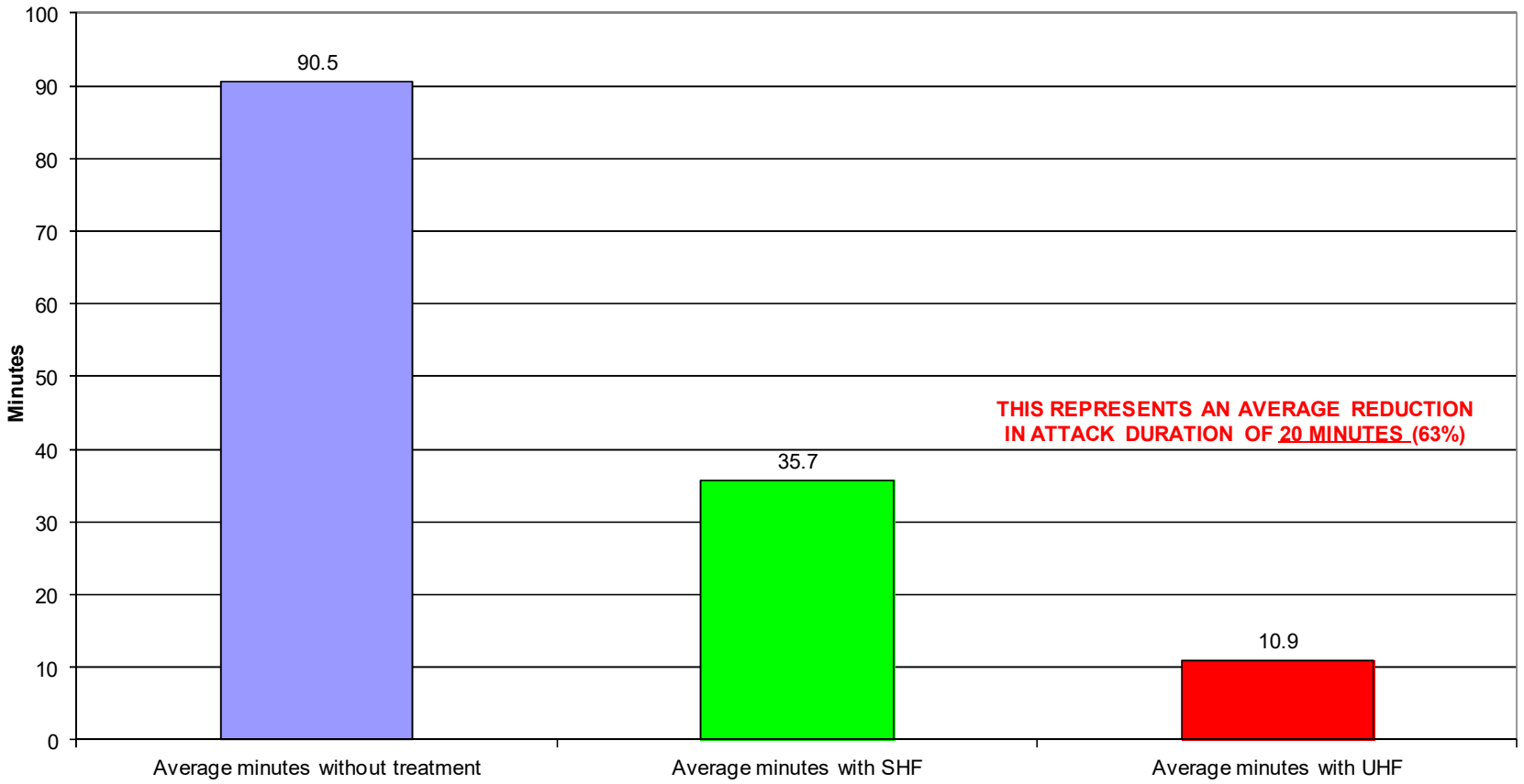
BOC
A Linde company

baywater
HEALTHCARE

VIVISOL
Home Care Services


Demand valve
vs
standard treatment

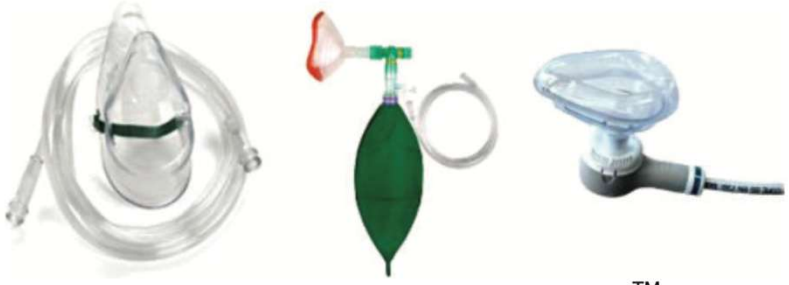
AVERAGE ATTACK DURATION FOLLOWING TREATMENT
Average Minutes (N=23)



Goadsby, Bahra, Silver & Hobbs Cephalalgia Reports 2025;8:1

Simple mask vs O2ptimask vs Demand valve

	Simple mask	O_2ptimask	DVO (100% O_2)	DVO (placebo)	*p* values comparing: DVO to SM[1] DVO to OM[2] DVO to placebo[3]
Primary endpoint					
Pain relief (15 minutes)	8/28(29%)	13/32 (40%)	15/31 (48%)	5/11 (45%)	0.119[1] 0.535[2] 0.867[3]



Simple open mask

O_2PTIMASK™

Ultraflow™ Oxygen Demand Valve

Petersen *et al.* (2017) Cephalalgia

Proposed study design

PHASE 1 Double-blind, randomised, placebo-controlled crossover trial
4 attacks treated in random order by all permutations of oxygen vs air (blinded) and demand valve vs non-rebreather bag and mask

Participants are provided with 4 cylinders blinded, 2 containing oxygen and 2 containing air (placebo), each attached with either a non-rebreather mask or demand valve mask

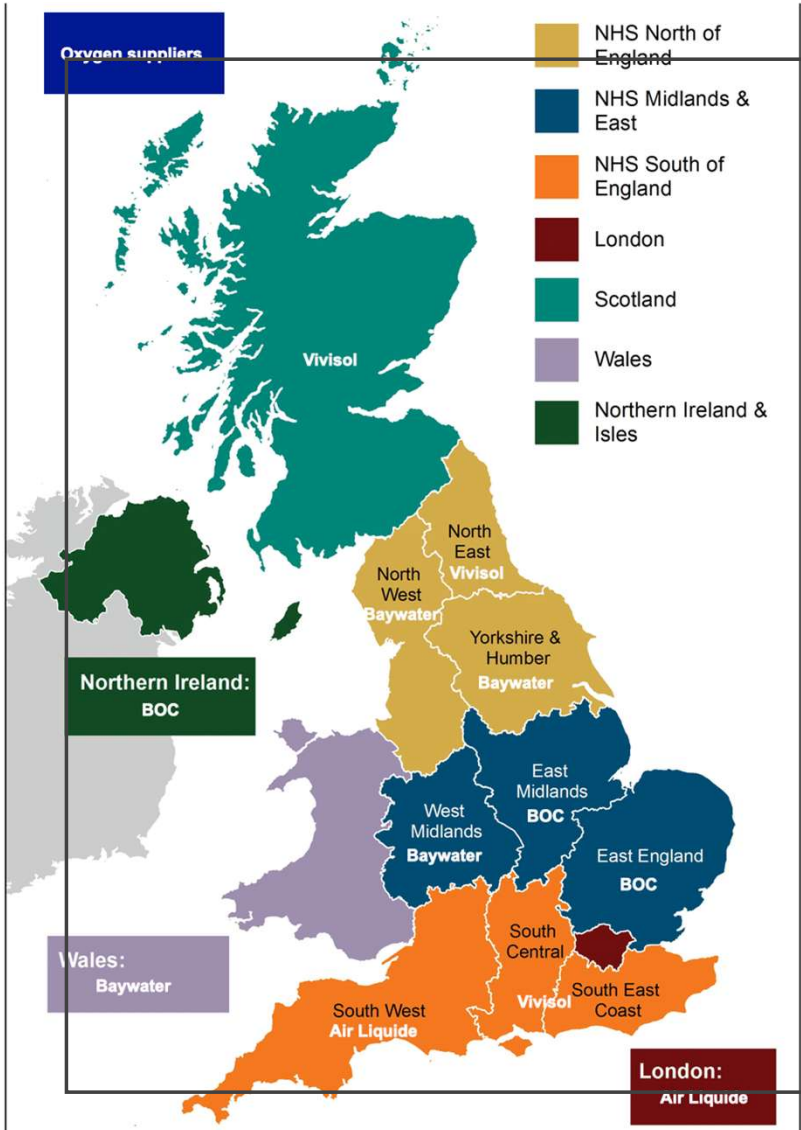
Attack 1	Attack 2	Attack 3	Attack 4
TREATMENT A Oxygen cylinder with non-breather mask	TREATMENT B Oxygen cylinder with demand valve mask	TREATMENT C Air cylinder with non-breather mask	TREATMENT D Air cylinder with demand valve mask
			

Treatment order will be randomised for each participant

PHASE 2 Patient preference (blinded)
Cylinder and oxygen delivery method of choice for the remainder of the cylinder

Measuring time to meaningful relief


Demand valve
vs
standard treatment


Oxygen suppliers
NHS North of England
NHS Midlands & East
NHS South of England
London
Scotland
Wales
Northern Ireland & Isles
Vivisol
North East
Vivisol
North West
Baywater
Yorkshire & Humber
Baywater
Northern Ireland:
BOC
East Midlands
BOC
West Midlands
Baywater
East England
BOC
South Central
Vivisol
South East Coast
South West
Air Liquide
Wales:
Baywater
London:
Air Liquide


Health
Equity

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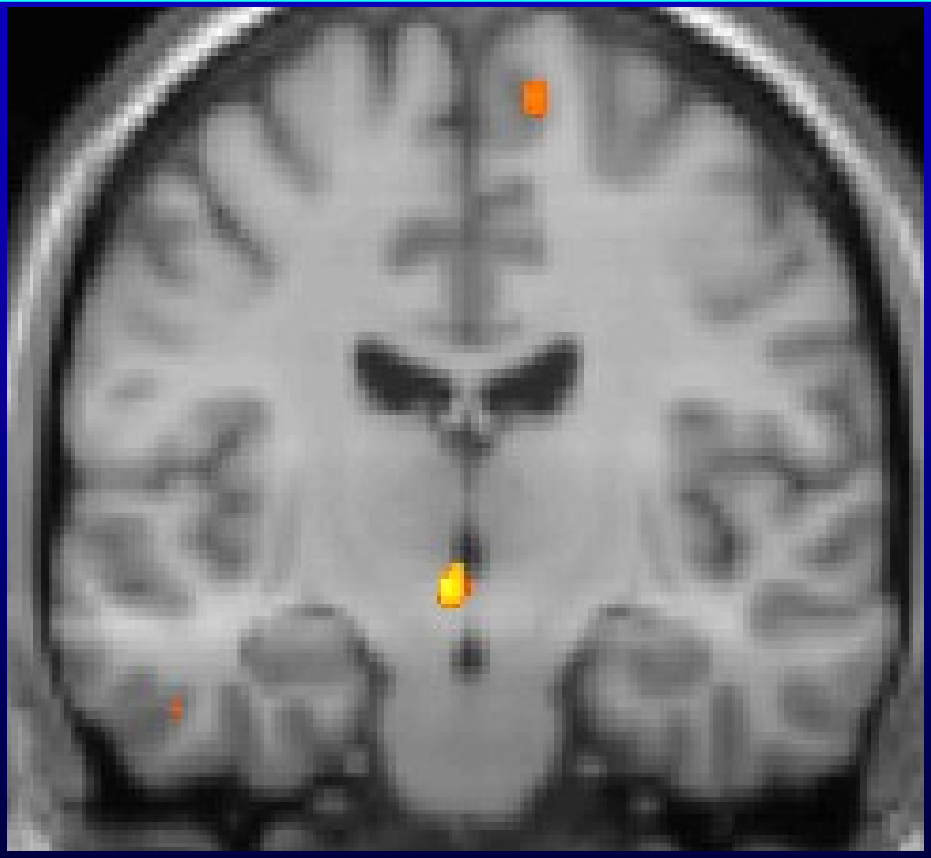
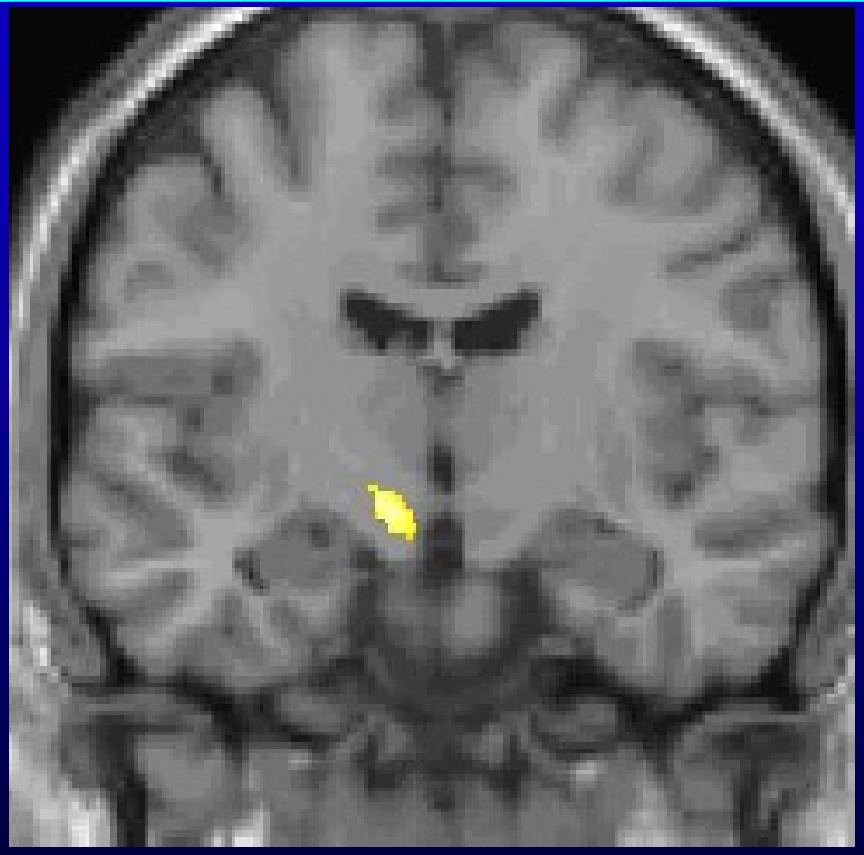
Cluster headache: structure and function

(From OUCH Conference 16th June 2002)



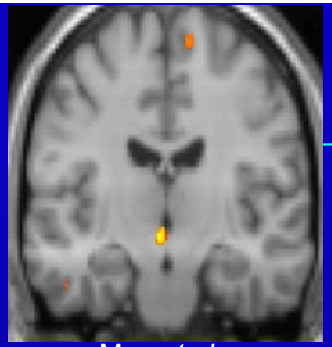
PET- functional activity

(Lancet 1998; 351:275-278)



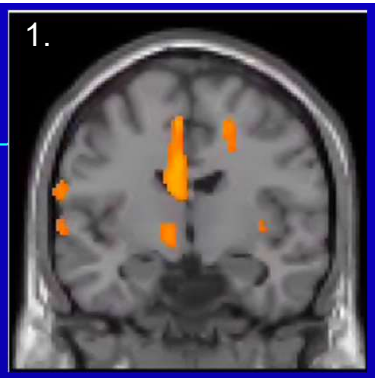
Voxel-based morphometry

(Nature Med 1999; 5:836-838)

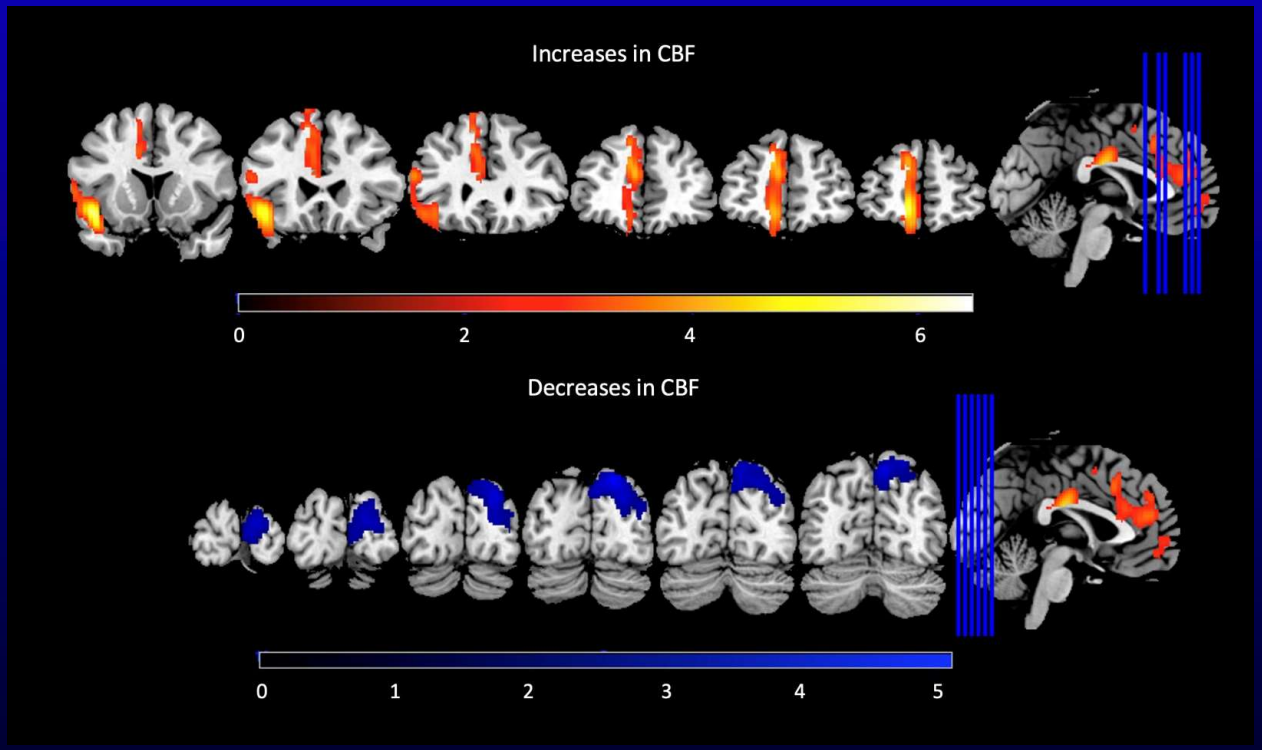


May *et al.*,
Lancet 1998; 351:275

Cluster headache



- Episodic and chronic cluster headache (*n* = 33)
- Nitroglycerin-triggered/placebo attacks imaged 3T MRI pCASL CBF
- Analysis:
  - Normalise images to standard symmetric template and flip
  - 2x2 factorial and RoI

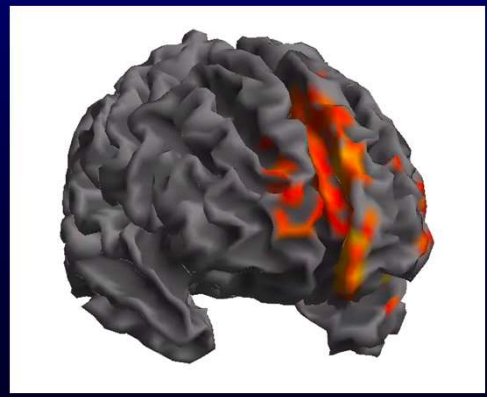


ANOVA

- Increased activations
  - Left medial frontal gyrus: pain anticipation
  - Left superior/inferior frontal gyrus: pain processing
  - Left anterior cingulate gyrus: affective pain
  - Right medial frontal gyrus
- Decreased activations
  - Right precuneus: reduced default mode activation
  - Right cuneus: ?photophobia
  - Right occipital gyrus

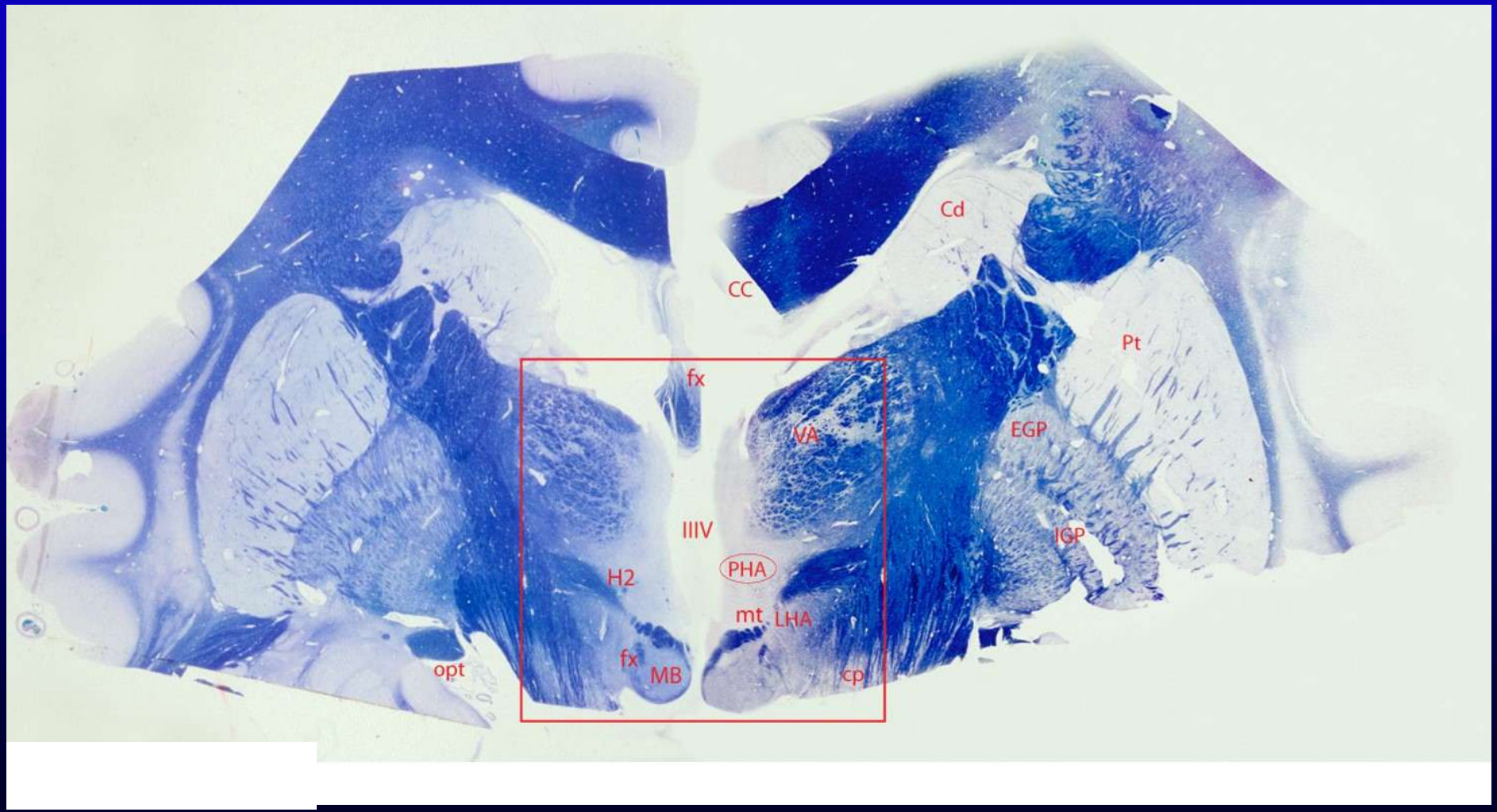
RoI

- Hypothalamus
- Ventral pons



1. Wei *et al.*, Neuroimage Clin 2022;33:102920

Cluster Headache- *which part of the brain?*



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A Patient with Cluster Headache: Issues & Primary Care Solutions in the UK
Analysis of OUCH Patient call Log.

Dr Ravindra Inaththappulige, Elizabeth Kelly,
Professor Peter Goadsby.

Objectives:

- Explore patient experiences and challenges.
- Identify gaps in UK primary care.
- Discuss practical and systemic solutions.

Patient Case Study

Sam:

38-year-old, Delivery Driver

2-year history of severe headaches.

Symptoms : Left-sided eye pain, lacrimation, nasal congestion.

Initial Misdiagnosis : Migraine.

Consequences : Sleep deprivation, job loss, depression.

Outcome

Insufficient access to urgent care or neurology

- Delay in referral to Neurology
- Delay in Diagnosis
- No neurologist Review

Underuse of evidence-based treatments

- Delay in initiation of treatment (e.g., high-flow O_2/ nasal or Subcutaneous sumatriptan)

Issues

- Lack of GP awareness of CH symptoms
- Misinterpretation of symptom patterns

June 2024-November 2024							
	June	July	August	September	October	November	Total (June-November)
No of Calls	25	27	18	24	25	23	142
No of Issues	29	34	21	26	31	24	166
General Query	5	3	1	0	1	0	10
Referral Query	0	0	0	1	0	0	1
Delay in Referral	0	0	1	1	1	2	5
Delay in Review	0	0	1	0	1	0	2
Delay in Diagnosis	3	2	0	2	1	0	8
No Neurologist Review	0	2	0	1	0	0	3
Request for Neurologist Recommendation	1	1	1	0	1	1	5
No Clear Diagnosis	1	7	3	4	2	2	19

Suggestion

- Early referral to neurology on suspicion of CH, for early diagnosis, with emphasis on cranial autonomic symptoms.
- Addressing myths and beliefs (over emphasis on laterality, gender).
- Recommendations for primary care while awaiting Neurology appointment
  - Acute treatment and transitional treatment
  - Oxygen
  - Sumatriptan
  - Steroids

How Can We Improve Knowledge and Understanding of Cluster Headache

Why GPs make diagnostic errors?

- Pattern recognition used as an important reasoning strategy
- Audit on knowledge of cluster headache in primary care
- Better GP - Specialist communication : eg: consultant connect
- Mass media, leaflets

Challenges Faced by the Patient

Delayed Diagnosis: Average 5 years

Mismanagement: Repeated migraine meds

Access Barriers: Long GP wait times, poor referral systems

Psychosocial Impact: Isolation, anxiety, suicide risk (high in CH)

NICE Guidelines

Diagnosis:

Clinical; MRI to exclude secondary causes.

Acute Treatment

High-flow oxygen (12–15 L/min).
Subcutaneous or intranasal sumatriptan.

Prevention : Verapamil (first-line), lithium.
Referral : **Urgent** neurology referral recommended.

June 2024-November 2024							
	June	July	August	September	October	November	Total (June-November)
Oxygen Related	1	0	0	0	0	0	1
General Query on Oxygen	3	1	1	1	0	1	7
Holiday / Portable Oxygen	0	1	2	0	1	1	5
Difficulty / Delay	0	0	0	2	1	1	4
Demand Valve	3	0	2	3	2	3	13
Oxygen and Smoker	0	0	1	2	0	0	3
Triptans: Unhelpful GP	0	1	0	0	2	1	4
Only Tablets Prescribed	0	1	0	0	1	1	3
Only Nasal Triptans Prescribed	0	0	0	0	0	1	1
Less Nasal Triptans Prescribed	0	0	0	0	0	1	1
No of Triptans (Unspecified)	1	0	0	0	0	0	1
No Injections	1	0	0	1	1	0	3
Less Injections	0	0	0	1	1	0	2
Misconceptions on Triptans	1	1	0	0	1	0	3
Side Effects of Triptans	0	0	1	0	0	0	1

Treatment-related

Acute Treatment:

Sumatriptan: type prescribed

Number of injections prescribed

Myths on Sumatriptan: medication overuse in cluster

Oxygen and DV : Not prescribing, changes in area setting, lack of awareness on the pathway and prescription

Treatment pathways for different preventatives and abortive medications

Transitional Treatment:

When to use

GON block availability and competence (Secondary and Tertiary Care)

Underutilisation of short course on Steroids recommending

Preventive

Verapamil related:

GP is reluctant to prescribe despite suggested by secondary/ tertiary care

Clear identification of suitable patients,

What exactly GP should look at on ECG/ and clinical monitoring if they happy to take over the care

Patient Reach services during a bout.

Suggestion:

Regional Headache Units can offer a diagnosis of the attack, and provide treatment ” Cluster Bluster Units”/ Adhoc GON Clinics.

How GP can support: (minimum 2-3 weeks of support)

Steroids

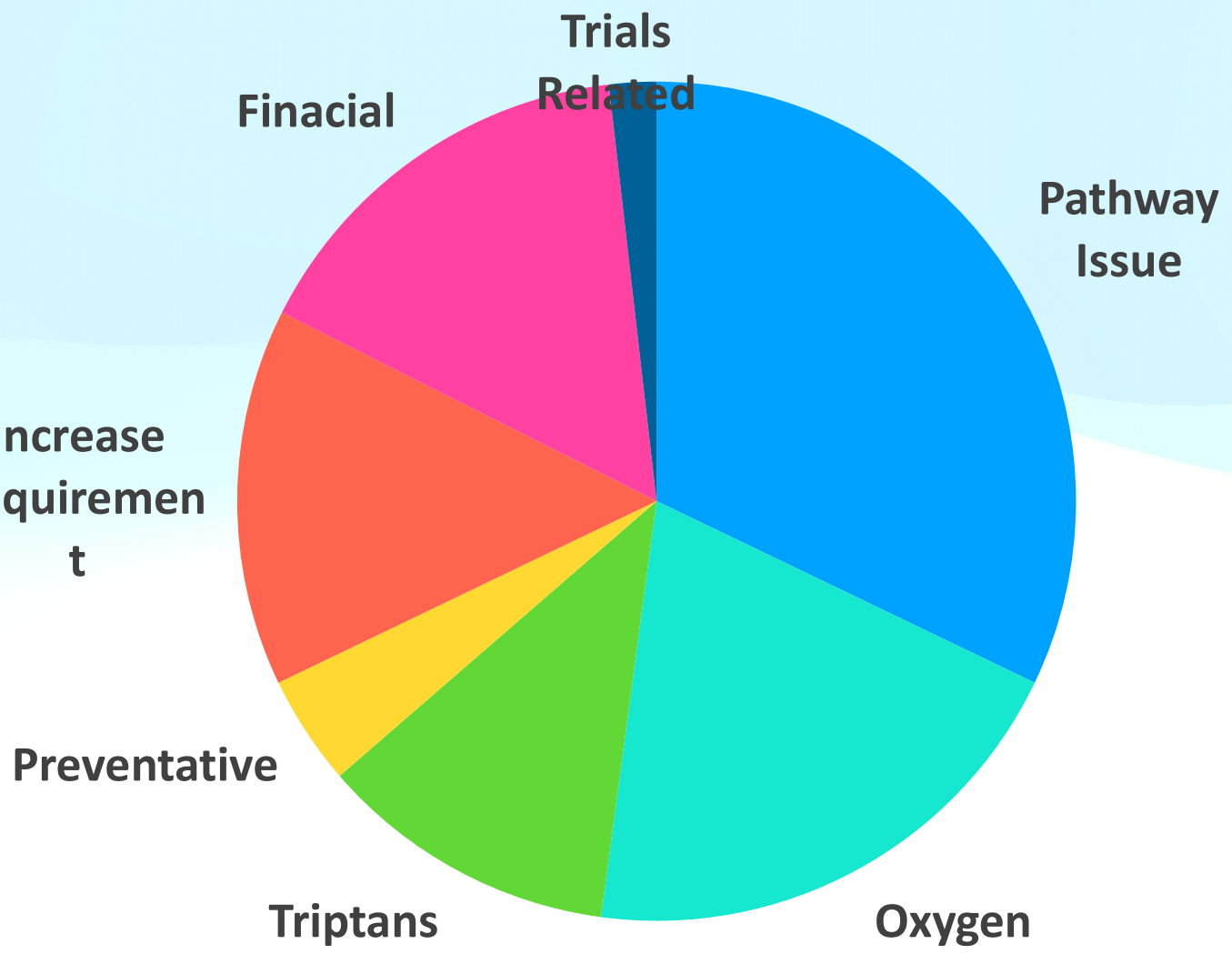
June 2024-November 2024							
	June	July	August	September	October	November	Total (June-November)
General Benefits Query	0	0	0	0	0	1	1
PIP	1	2	1	3	6	0	13
Universal Credit	0	0	0	1	0	0	1
Employment	1	2	0	0	2	3	8
Housing	0	1	2	0	0	0	3
Trials Related	0	1	1	0	1	0	3

Patient Concern with Work, Finances and Housing

- PIP related
- Benefits and income
- Occupation
- Housing

Recommendation of a support letter concerning disability and impact
Clinician and patient awareness of support systems

	June-November 2024
Pathway Issue	53
Oxygen	33
Triptans	19
Preventative	7
Increase Requirement	24
Finacial	26
Trials Related	3



Thank You!

We would like to express our gratitude to all team members involved in the OUCH call log process.

Special appreciation goes to Elizabeth Kelly and Professor Peter Goadsby.

Lastly, a BIG thank you to all our patients who have reached out and educated us about their journey.

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ECCOT: Effect of Chronic Cluster from Overseas Travel

Why

We know cluster headache can **switch "on" and "off",** this may be influenced by **environmental factors** but there are a paucity of studies exploring all of these factors

Who

Patients with **chronic cluster headache** who are **travelling overseas in the next 12 months**

What

We will be conducting a study to identify whether **overseas travel changes the pattern of cluster headaches** as well as exploring which factors about overseas travel i.e. **change in time-zone, altitude or climate are most associated with changes** in cluster headache patterns

This will involve the **collection of headache diary and geographical data** from chronic cluster headache patients **one month before and one month after** overseas travel

In doing so, **we hope to gain more insight into the factors that drive cluster headache, as well as factors that may alleviate it**

Please contact Dr Usman Ashraf for any questions:
usman.ashraf@kcl.ac.uk

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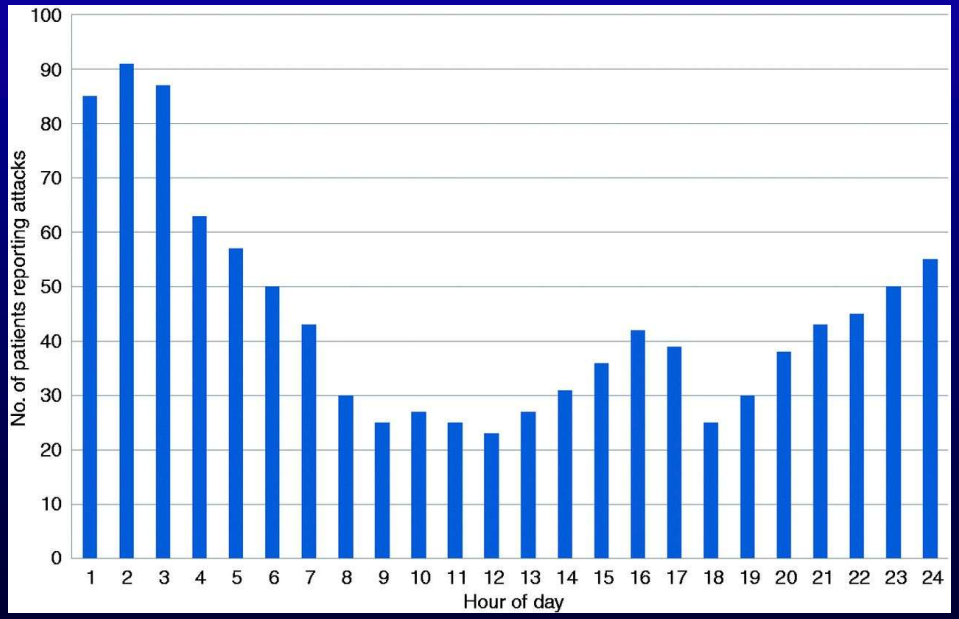
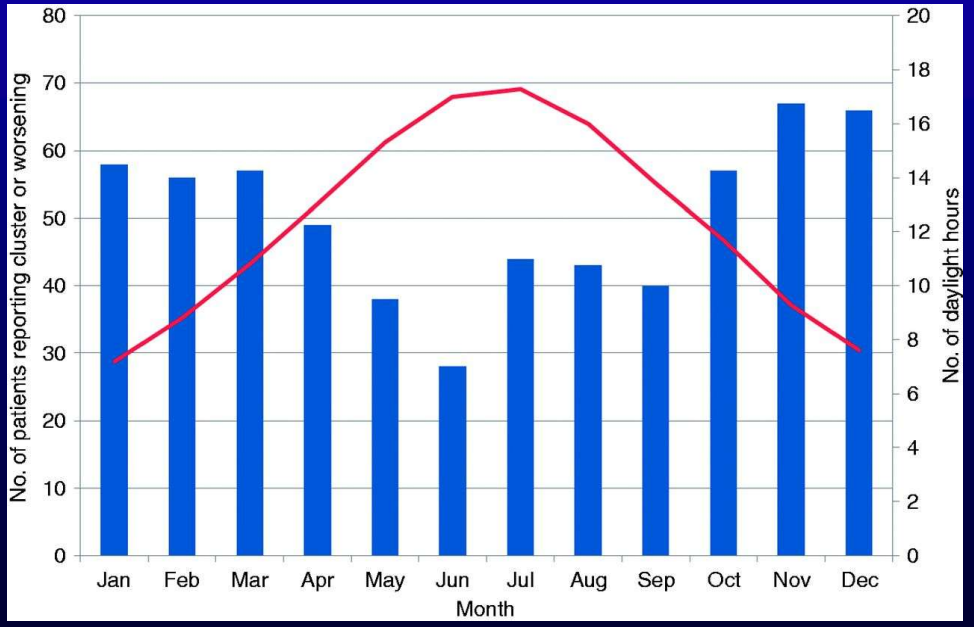
Cluster headache
Sleep and chronobiology

- Study of CH patients (*n* = 275)
  - Diurnal: 82%
  - Annual: 56%

Circadian



Circannual



Barloese *et al*. Cephalalgia 2015;35:969

Biochemistry of Cluster Headache

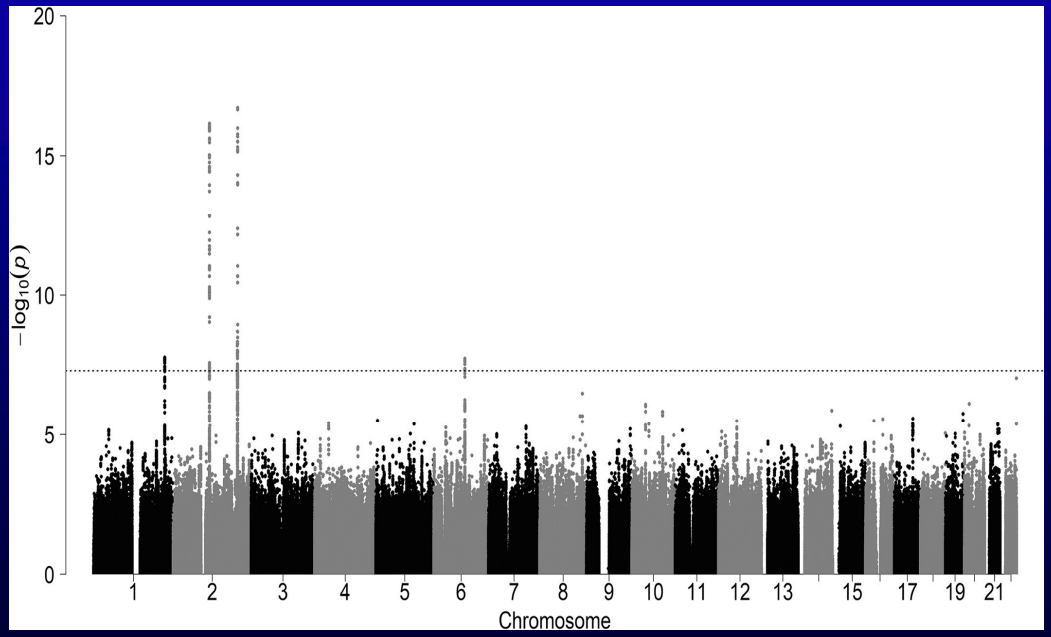
What substances can we measure in the blood and saliva to point to new treatments?

- Study in cluster headache
- Participants come to King's Clinical Research Facility
  - Reimburse travel
  - Per diem allowance for time
- Stay overnight from 4pm until 4pm the next day
- Sample blood and saliva
  - Every two hours
  - During and after attack treatment with usual acute treatment
- Record attack symptoms

Backup Slides

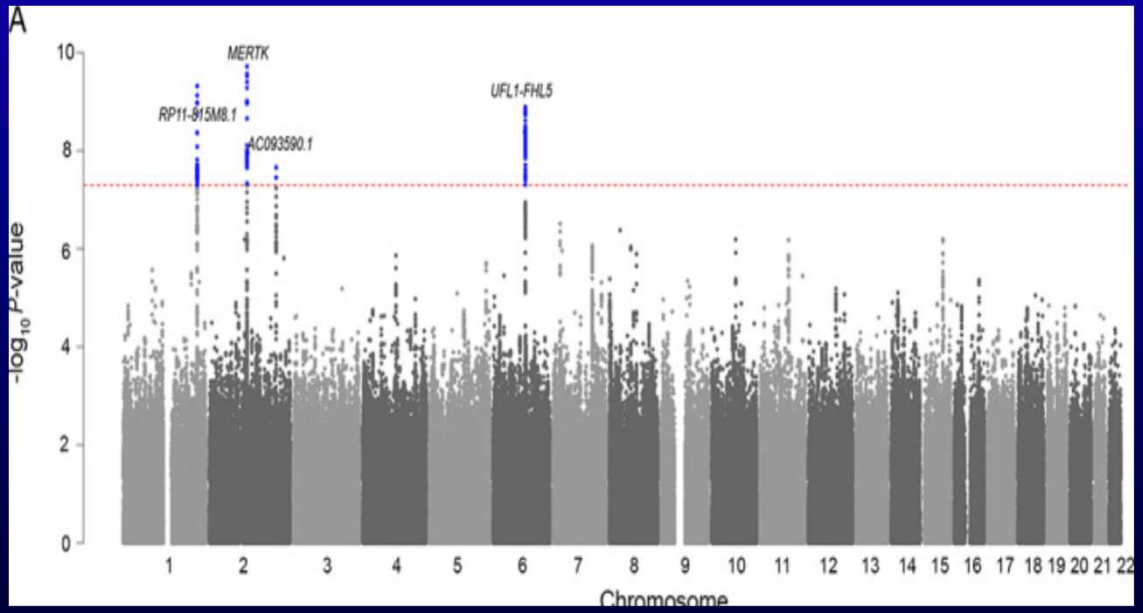
Genetics of Cluster Headache

- Genome-wide association study
  - UK: *n* = 852; Sweden: *n* = 591
- Results
  - Chromosome 2: LINC01877 (intergenic) & MERTK (microglial)
  - Chromosome 1 and 6



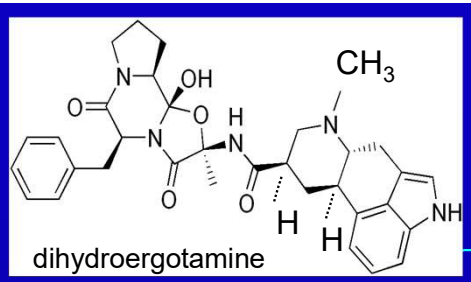
O'Connor *et al*., Ann Neurol 2021;90:193

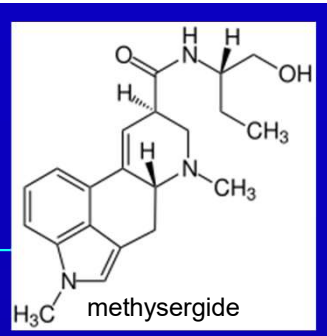
- Genome-wide association study (7% variance)
  - The Netherlands: *n* = 840; Norway: *n* = 144
- Results
  - Chromosome 2: MERTK & AC093590.1
  - Chromosome 1 and 6



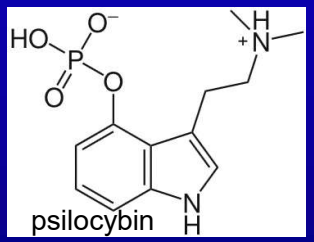
Harder *et al*., Ann Neurol 2021;90:203

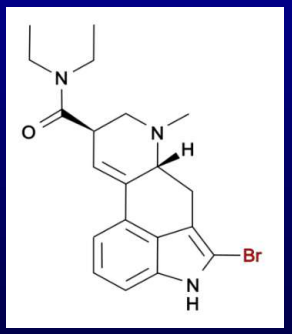
Cluster Headache & Hallucinogens

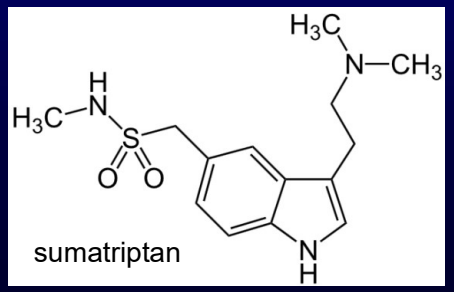

dihydroergotamine


methysergide

- Hallucinogens: altered state of consciousness, eg lysergic acid diethylamide (LSD)
  - Psychedelics
    - alter perception, emotion & cognition without memory loss or delirium
    - 5-HT_{2A} receptor agonists
  - Dissociative: ketamine, PCP
  - Delirium: scopolamine
- Psilocybin (psilocin; 5-$HT_{2A/2B}$)[1]
  - Naturally occurring indole produced by mushrooms with psychedelic effects
  - Reports of use in cluster headache
- 2-bromo-LSD (5-HT_{2A})[2]
  - Pharmacology: unclear
  - Participants felt: “slightly tipsy”, “flabby feeling”
  - One ECH- better; Four CCH- reduced frequency
- Other *options*
  - 5-MeO-DALT (*N,N*-diallyl-5-methoxytryptamine; 5-$HT_{2A\ \&\ 2B}$)
  - 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT; psychedelic, $5HT_{1A\ \&\ 2A}$)


psilocybin

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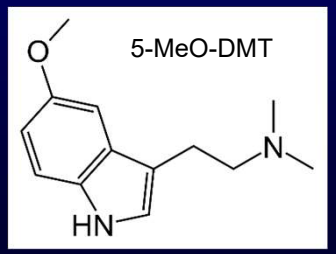
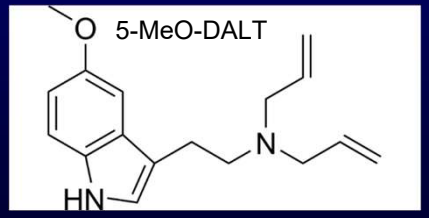
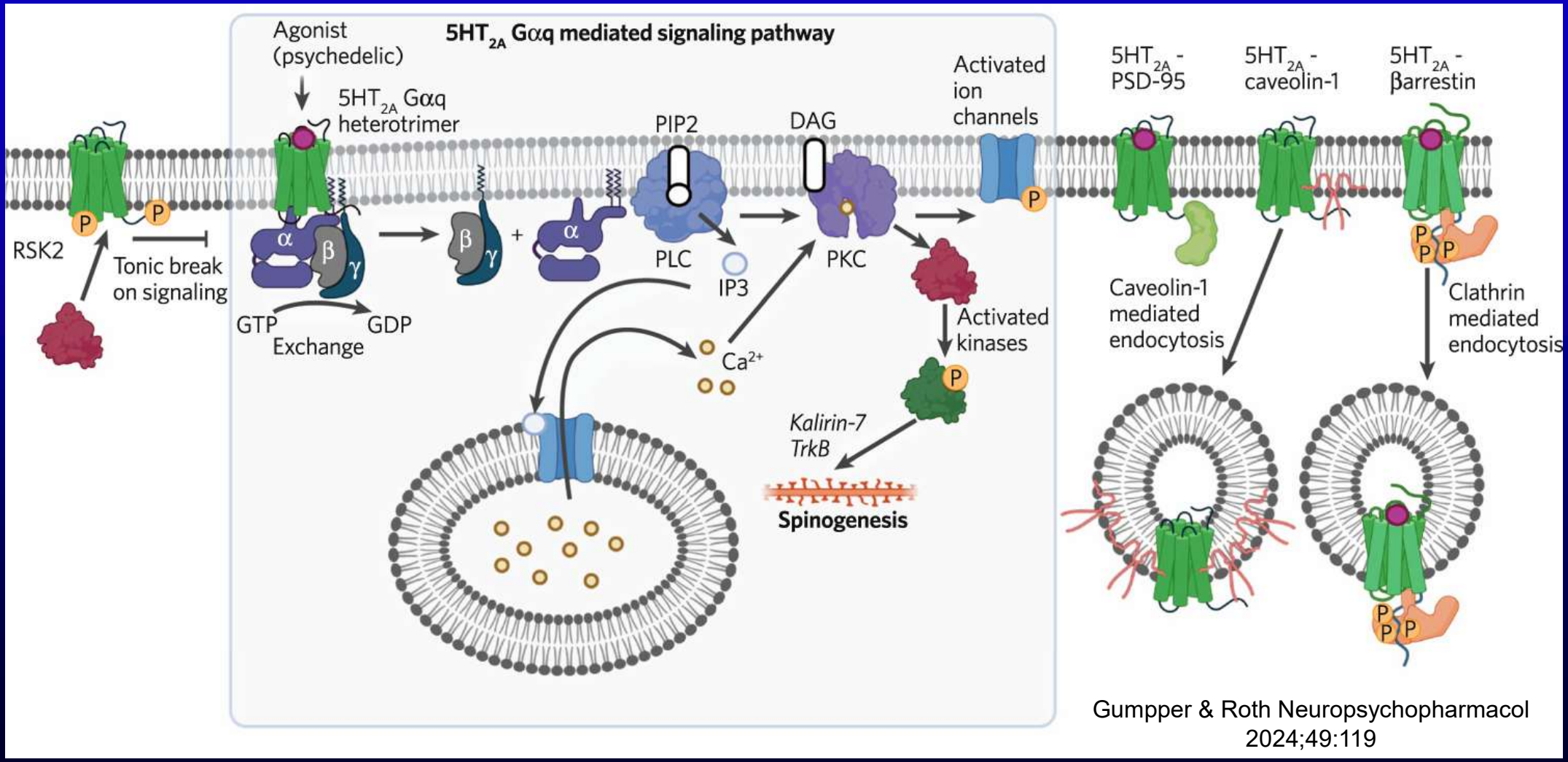

5-MeO-DMT


5-MeO-DALT

5-$HT_{1B/1D}$

1. McClure-Begley & Roth Nat Rev Drug Discov 2022;21:463
2. Sewell *et al*., Neurology 2006;66:1920
3. Karst *et al*., Cephalalgia 2010;30:1140

5-HT$_{2A}$ Receptor



Gumpper & Roth Neuropsychopharmacol 2024;49:119