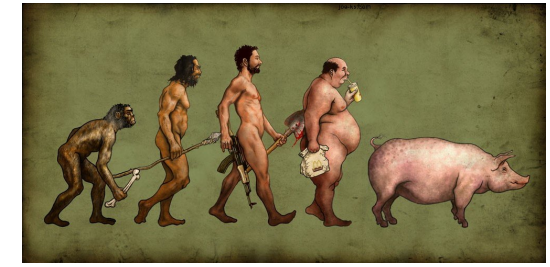
Wilkinson lecture 2010
The Art of Migraine Genetics

Joost Haan

LUMC Leiden

Rijnland Hospital Leiderdorp



The Art of Migraine
&
Migraine Genetics

Migraine Art:
First publication on this topic by Marcia Wilkinson

Migraine Genetics:
Leiden

The Art of Migraine
&
Migraine Genetics

- Art
- Genetics
- Art
- Genetics
- Art
- Genetics

Intermezzo: Migraine Art

Wilkinson and Robinson (Cephalalgia 1985;5:151-7)

Analysis of drawings and paintings entered for a migraine art competition.

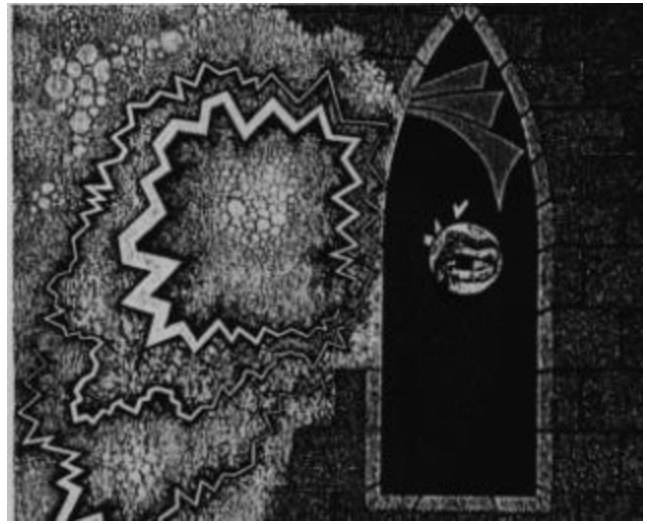
'…draw your own impression of visual disturbance or depict the effect of migraine on your life'

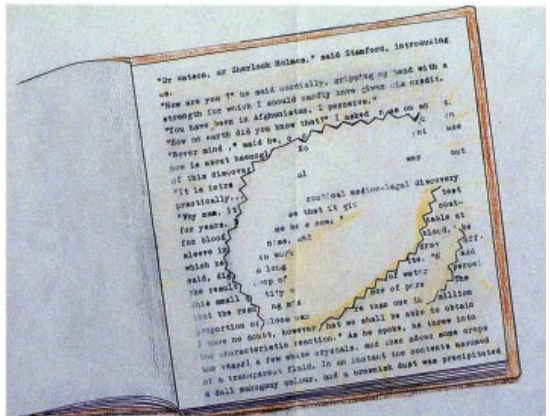
selves through the usual round of work and play, a degree
ness and a desire for rest are characteristic of
migraine. A vascular
head m
only, or even the chief, mechanism at work.
during an attack and exhibit diminished tone of skeletal
drowsy.

The relation of sle
one, and we will ha
contexts: the i
migraine (migr
migraines o
relation to
attention to t
of intense dro
the occasional abo
and the typical protracted
natural termination.

Nowhere in the literature can we find more vivid and
descriptions of migrainous stupor than in Liveing's monogr

Gowers





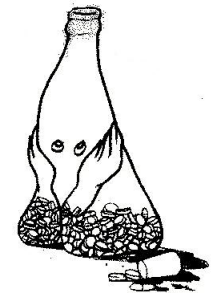


Fig. 5. Metamorphopsia. The sufferer depicts her body as a pill bottle full of tablets.

Migraine Art

Wilkinson and Robinson

- N = 207
- Spectral appearances* 70%
- Fortification spectra 48%
- Visual loss 16%
- Hemianopic loss 30%
- Pain 39%
- Metamorphopsia 16%

Uniformity of the representations

*stars, flashes.

‘…the large number of similar representations probably confirms their organic nature.’

Genetics of migraine
Studied in Leiden since 1992

- Rare autosomal dominant variants (FHM)
- Association studies (MTHFR C677T)
- Animal models (FHM KI)
- Genome-wide association studies (consortia)

McCrary Twins, Hendersonville, NC

Genetics of migraine: 1993
My personal history (I)

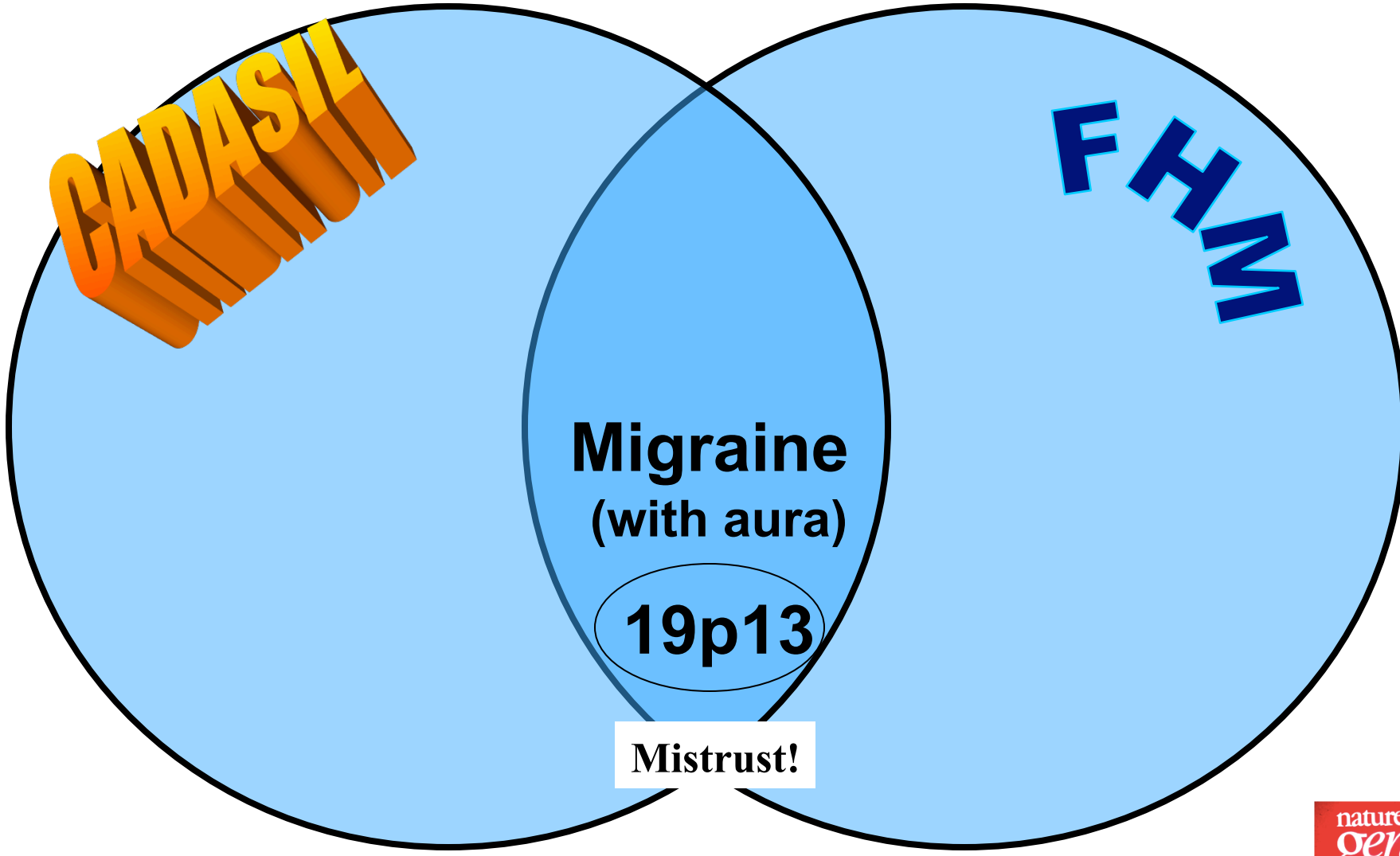
- 1990 Thesis on HCHWA-D
- Wine club 1993

  (MDF + C_2H_5OH)
- 6th IHS congress Paris 1993

  (review >100 articles)
- Secret meeting with French group (linkage FHM):

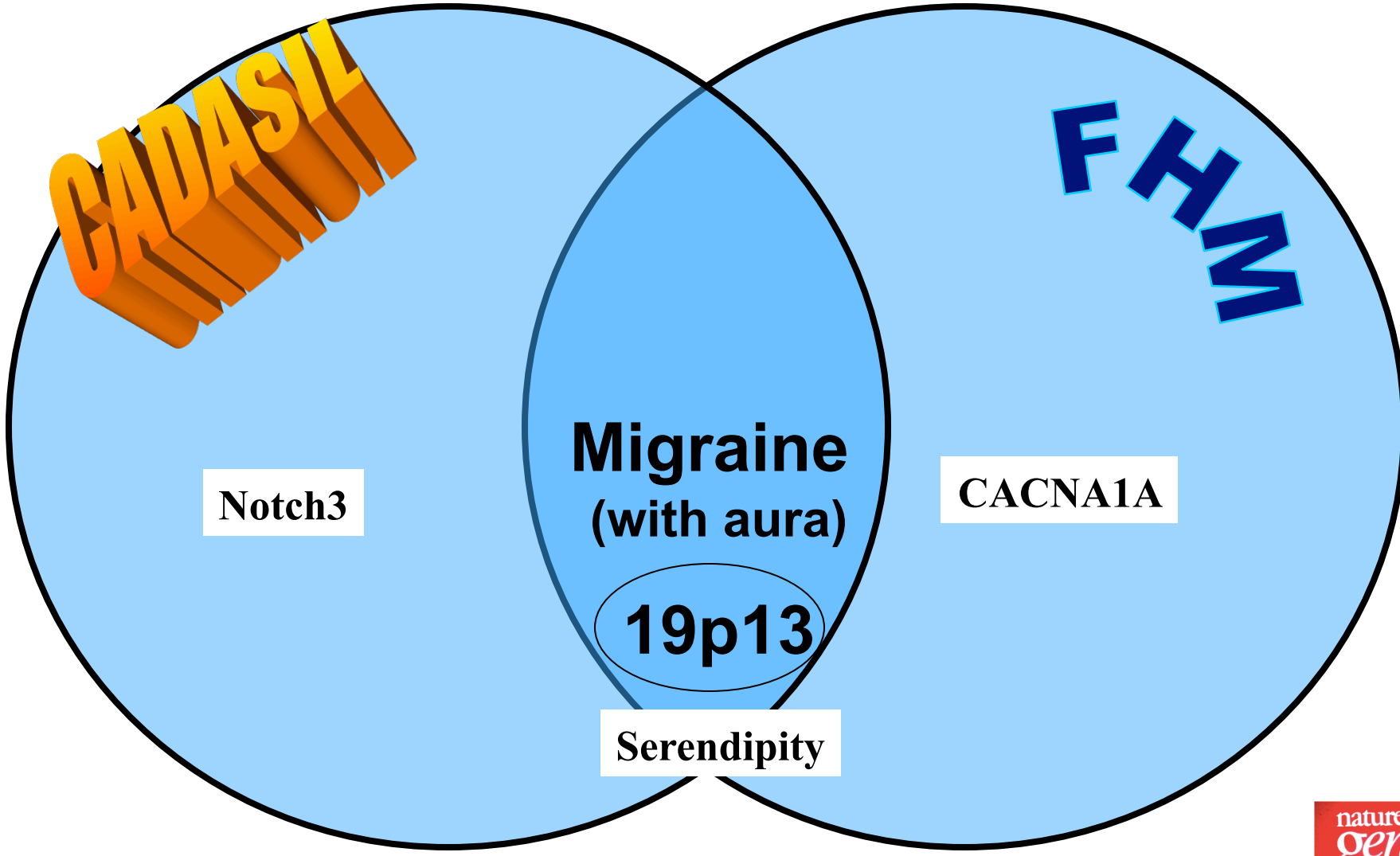
  We: ‘It is on 5’

  They: ‘It is on 19’



CADASIL: Tournier-Lasserve et al., Nat Genet 1993

FHM: Joutel A et al., Nat Genet 1993



CADASIL: Tournier-Lasserve et al., Nat Genet 1993

FHM: Joutel A et al., Nat Genet 1993

Genetics of migraine: 1994
My personal history (II)

ADMA Arundel 1994

Debate J.M.S. Pearce vs. J. Haan

There is insufficient evidence to support the belief that migraine is hereditary

Pearce:

‘I am filled with admiration for my opposing colleague Dr. J. Haan, who has so succesfully persuaded … the organizer to give him the immediately attractive role of opposing this proposition’

‘Alas, it is my sad task as the underdog to try to overcome the obvious fallacies inherent in the motion before you’

There is insufficient evidence to support the belief that migraine is hereditary

Pearce:

‘I am filled with admiration for my opposing colleague Dr. J. Haan, who has so … ive him the immediate… n’

‘Alas, it is my … the obvious fallacies inherent in the motion before you

Score Pearce – Haan

Pre 10 – 90

Post 80 - 20

Did Pablo Picasso suffer from migraine?

1) Yes
2) No
3) Don’t know

EDITORIAL COMMENT

Migraine aura, illusory vertical splitting, and Picasso

© Blackwell Science Ltd *Cephalalgia*, 2000, **20**, 686

In conclusion, we agree with Podoll and Robinson (page 228) that 'the small number of communications about illusory splitting does not reflect its true prevalence in migraine'. Besides, we think that illusory splitting as a part of bizarre visual migraine auras might have inspired Picasso to paint female faces with the characteristic vertical splitting and shift of the eyes

MD Ferrari

EDITORIAL COMMENT

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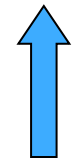
MD Ferrari & J Haan

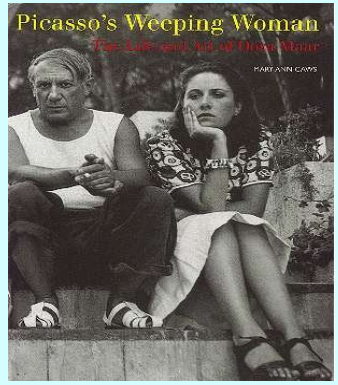


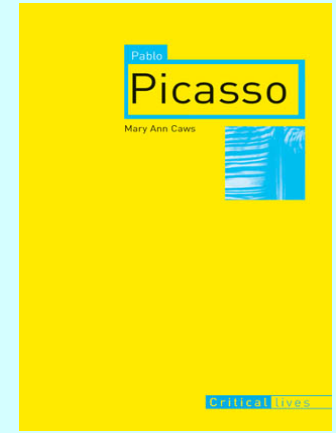
Picasso and Migraine

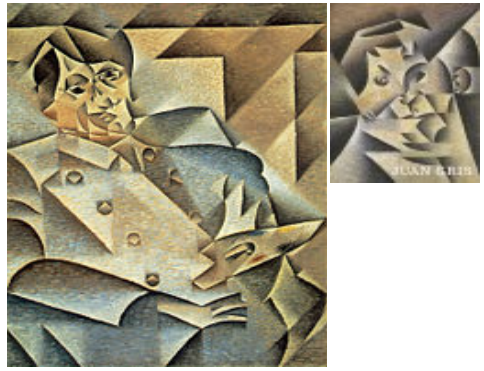
- BBC News: Monday, 4 September, 2000, 14:08 GMT 15:08 UK
- A leading Dutch neurologist is suggesting that the Spanish painter, Pablo Picasso, painted the way he did because he suffered from bizarre visual migraines.
- The Dutch neurologist, Michel Ferrari, who is presenting a paper at an international conference, conducted research in which migraine sufferers drew pictures of what they saw during an attack.
- Doctor Ferrari says these were extremely similar to Picasso's paintings from the late 1930s period.
- Google 2010: ‘Picasso and migraine’ >50.000 hits

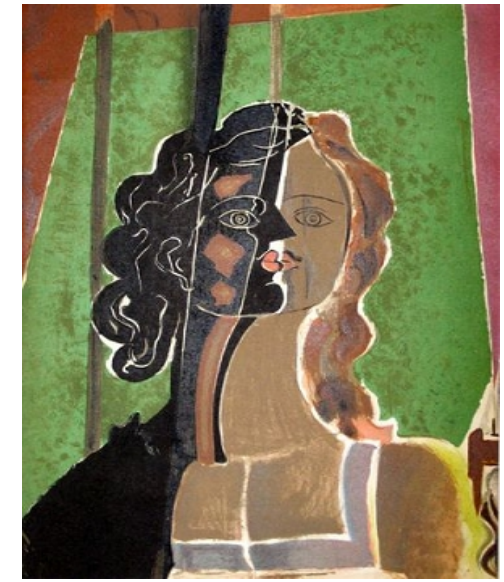
Picasso and Migraine

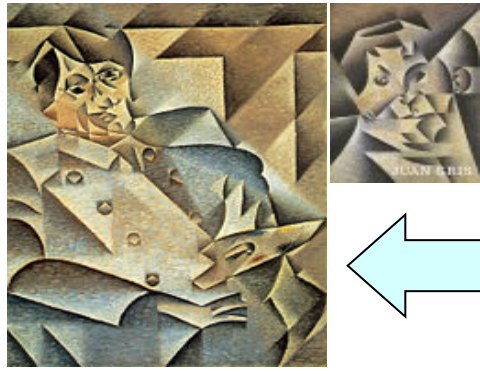
- No mention of migraine in:
  - Biographies
  - Memoirs of contemporaries
  - Letters of Picasso (eg. To Guillaume Apollinaire)






JUAN GRIS





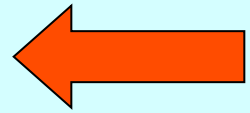
Juan Gris

Portrait of Picasso

Francis Bacon

Georges Braque

Did Pablo Picasso suffer from migraine?

1) Yes
2) No 
3) Don’t know

Migraine Genetics: CADASIL and RVCL

Migraine and genetic and acquired vasculopathies

AH Stam[1], J Haan[1,2], AMJM van den Maagdenberg[1,3], MD Ferrari[1] & GM Terwindt[1]

Departments of [1]Neurology and [3]Human Genetics, Leiden University Medical Centre, Leiden, and [2]Department of Neurology, Rijnland Hospital, Leiderdorp, the Netherlands

 Cephalalgia, 2009, 29, 1006–1017

CADASIL and Migraine: A review

Michael K Liem, Saskia AJ Lesnik Oberstein, Jeroen van der Grond, Michel D Ferrari, Joost Haan

Cephalalgia 2010, In Press.

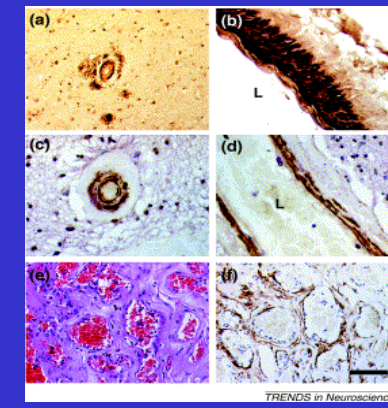
Migraine aura pathophysiology: the role of blood vessels and microembolisation

Turgay Dalkara, Ala Nozari, Michael A Moskowitz

Lancet Neurol 2010; 9: 309–17

CADASIL

Cerebral
Autosomal
Dominant
Arteriopathy with
Subcortical
Infarcts and
Leukoencephalopathy



Arteries, arterioles
GOM
Degeneration smooth muscle cells
Endothelium

CADASIL: clinical features

AAO 20-65 years

Tia's and infarcts

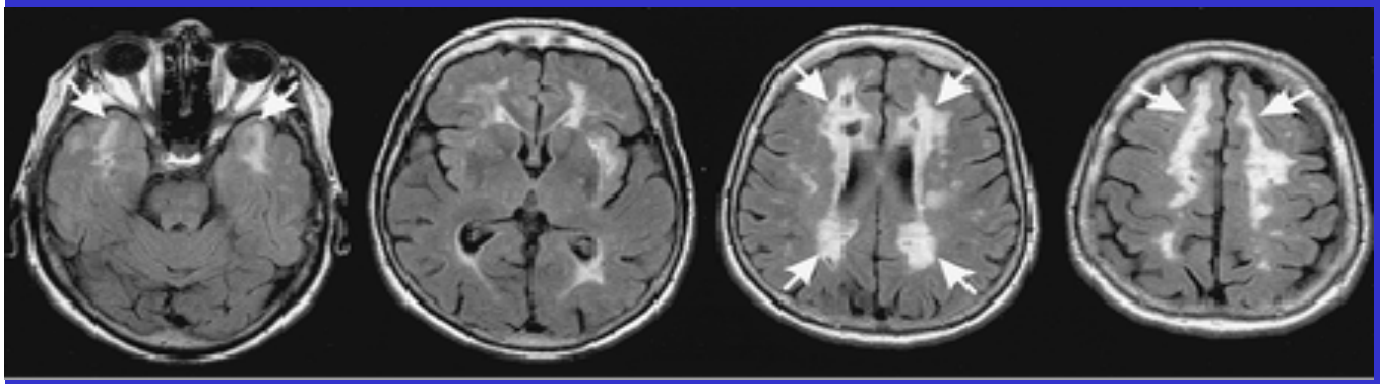
Cognitive deterioration

Migraine (with aura)*

Depression

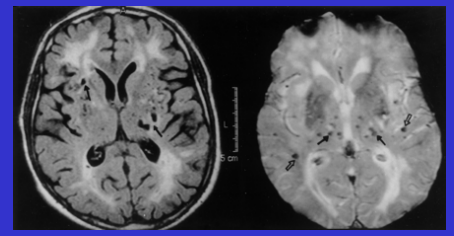
Epilepsy

MRI in CADASIL



Frontotemporal	external capsule	periventricular	frontal
(early sign)	(sens 90% spec 45%)	(not specific)	(not specific)

Microbleeds (not specific)



7 Tesla MRI

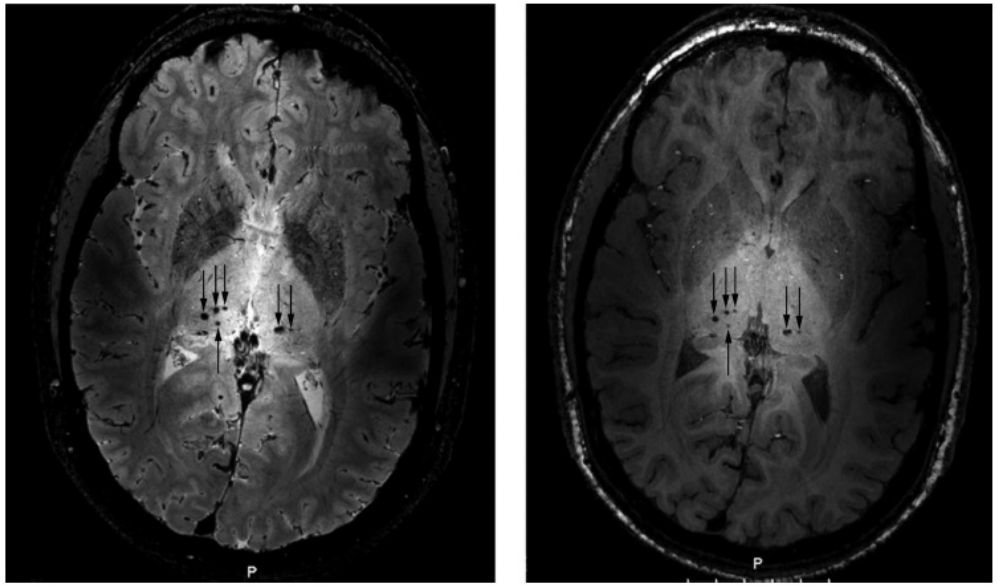


Figure 1. High resolution T2*-weighted gradient echo scan (left) and T1-weighted gradient echo scan (right) of an approximately 35 year old† CADASIL patient with focal hypointense areas (arrows) bilaterally in the thalamus.

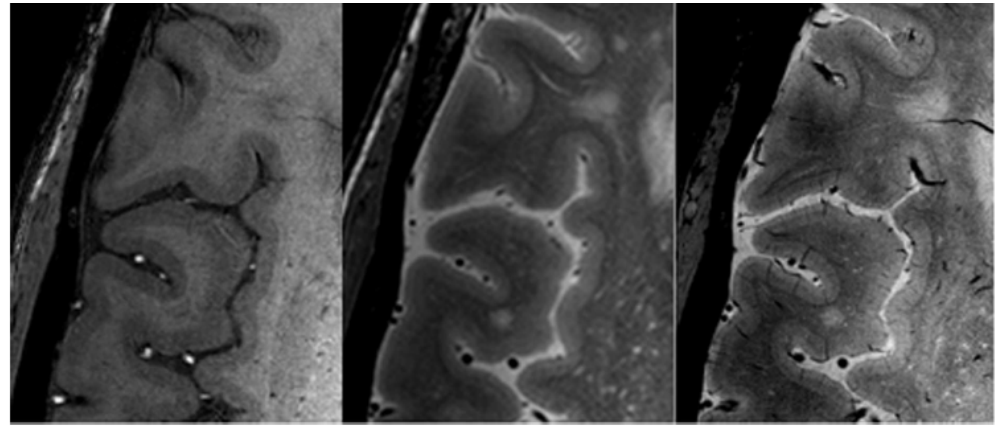
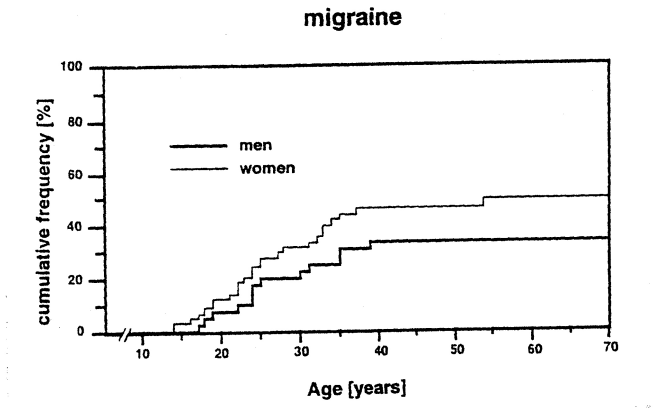
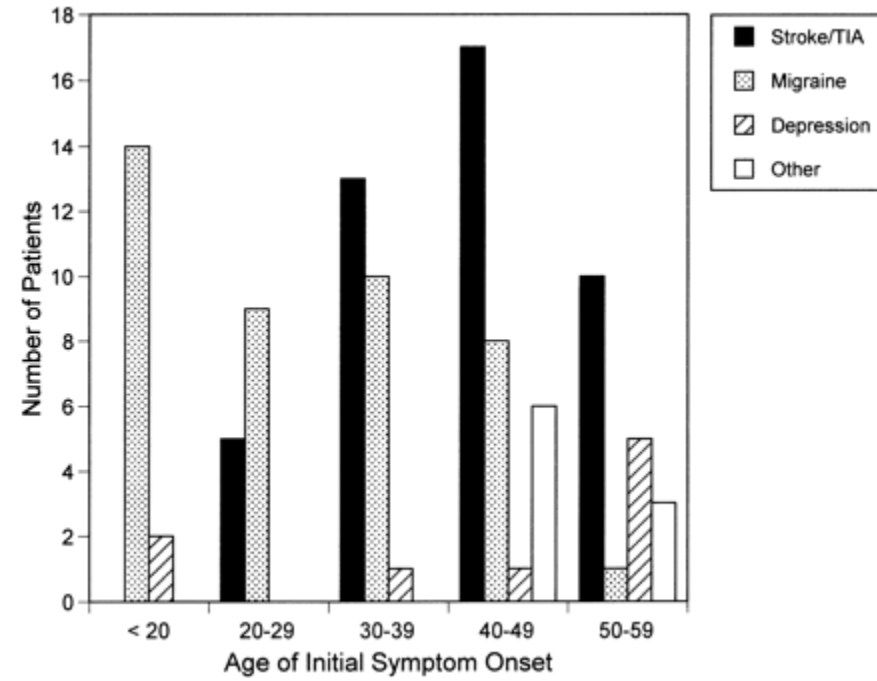


Figure 2a: High resolution images of cerebral cortex at the level of the insula, frontal and temporal lobe, in a CADASIL patient of approximately 50 years of age†, showing no focal cortical hypointensities. From left to right: 3D T1-weighted image, T2-weighted spin echo image, T2*-weighted gradient echo image.

Migraine in CADASIL

Desmond et al., Stroke 1999

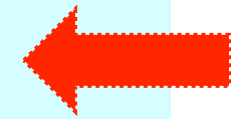




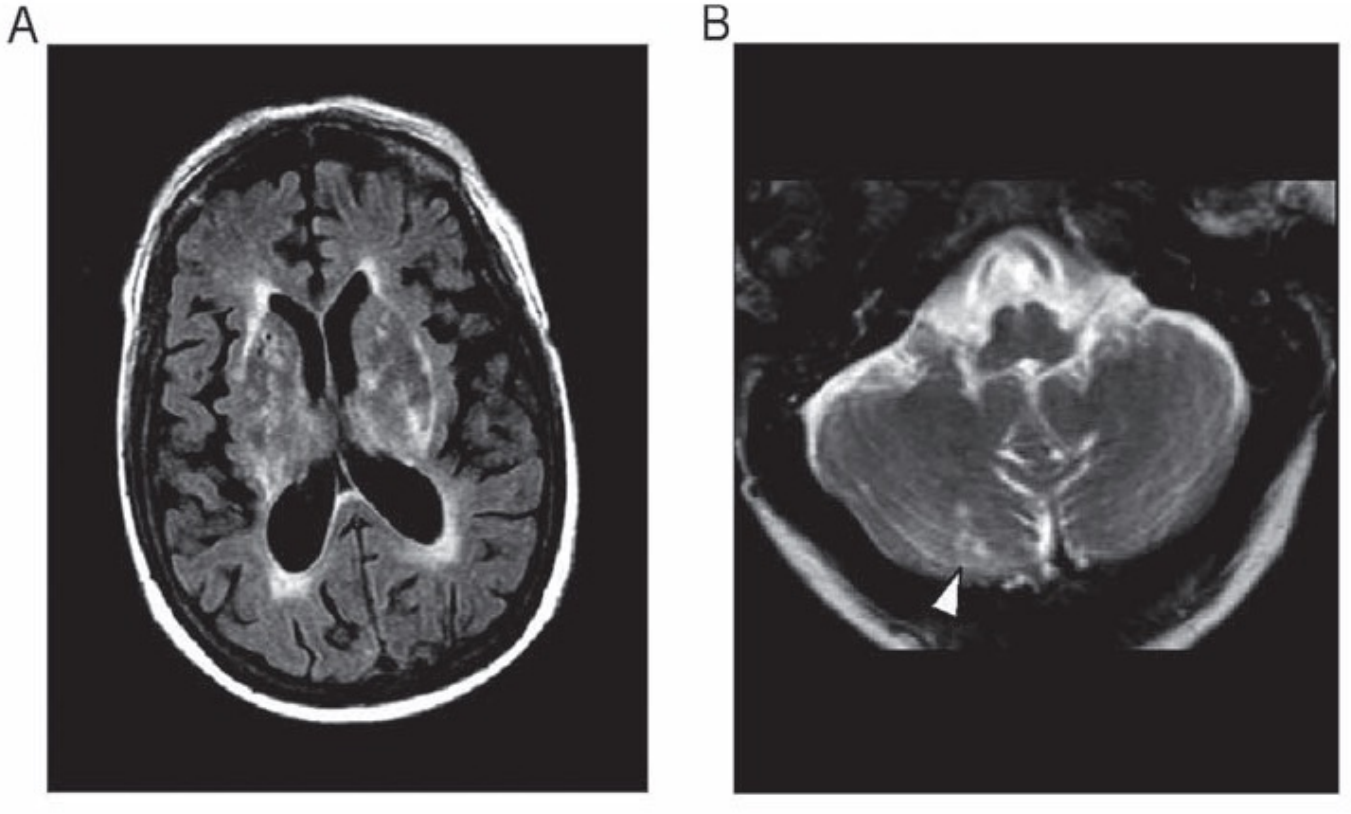
Migraine in CADASIL

Liem et al., Cephalalgia 2010 In Press

- PubMed search; 15 articles; >500 patients
- Prevalence 14-72% (overall 38%)
- 80-90% MA
- Typical aura in 44%, atypical* 56%
- No relation with genotype / MRI abnormalities



* Acute onset, >60 minutes, not visual


A
B

?

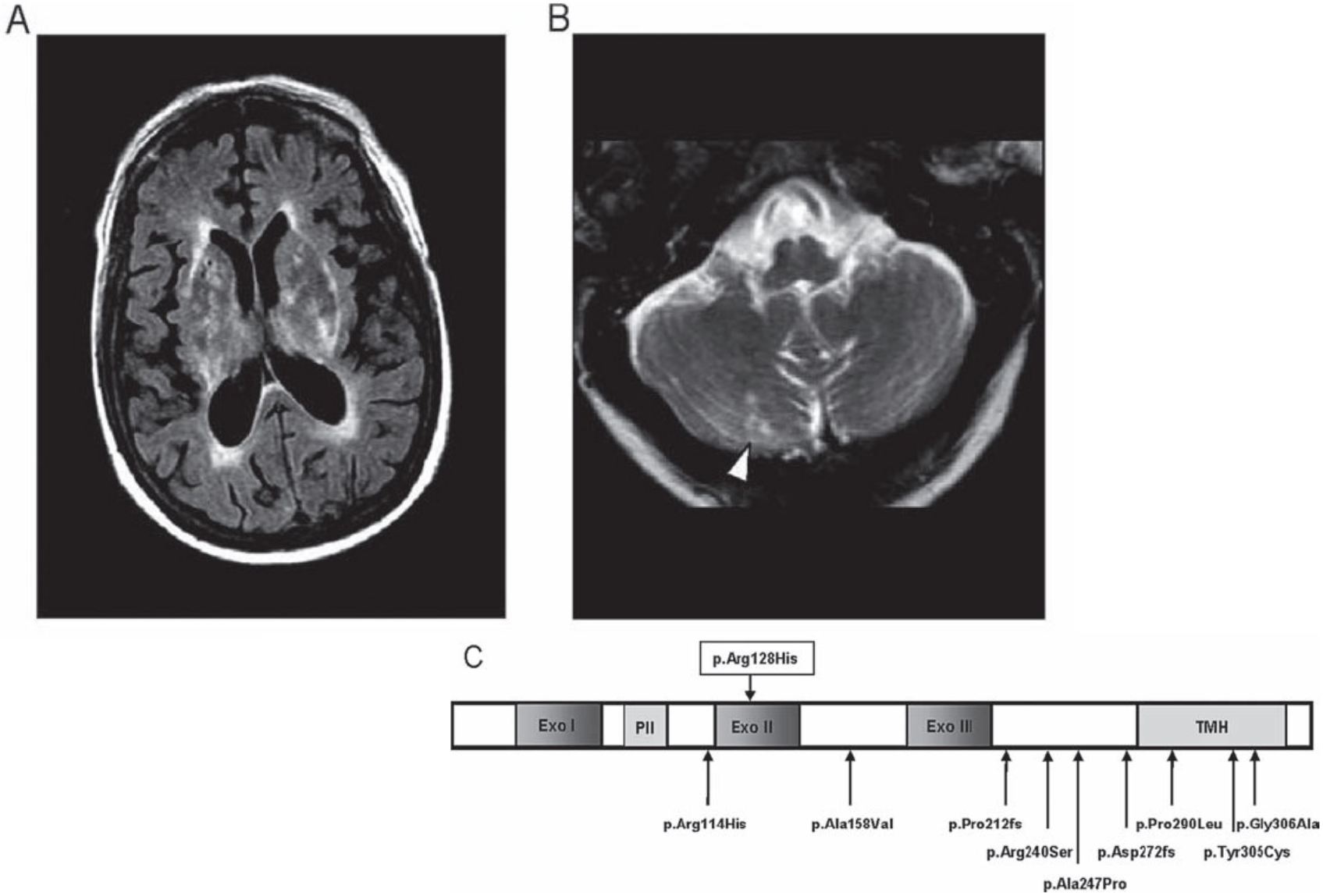


Figure 1 MRI abnormalities in the p.Arg128His *TREX1* mutation carrier with neuropsychiatric systemic lupus erythematosus. (A) FLAIR image shows symmetric white matter hyperintensities in the capsula interna, capsula externa and periventricular white matter. (B) T2-weighted image shows three small infarcts in the right cerebellar hemisphere as indicated by the white arrow. (C) Schematic representation of the TREX1 protein, showing the position of p.Arg128His as well as previously identified SLE mutations.[2] Exo I, II and III represent the exonuclease regions. PII represents the polyproline II motif and TMH the transmembrane helix.

C-terminal truncations in human 3′-5′ DNA exonuclease TREX1 cause autosomal dominant retinal vasculopathy with cerebral leukodystrophy

Anna Richards[1,22], Arn M J M van den Maagdenberg[2,3,22], Joanna C Jen[4,22], David Kavanagh[1,22], Paula Bertram[1], Dirk Spitzer[1], M Kathryn Liszewski[1], Maria-Louise Barilla-LaBarca[5], Gisela M Terwindt[3], Yumi Kasai[6], Mike McLellan[6], Mark Gilbert Grand[7], Kaate R J Vanmolkot[2], Boukje de Vries[2], Jijun Wan[4], Michael J Kane[4], Hafsa Mamsa[4], Ruth Schäfer[4], Anine H Stam[3], Joost Haan[3], Paulus T V M de Jong[8–10], Caroline W Storimans[11], Mary J van Schooneveld[12], Jendo A Oosterhuis[13], Andreas Gschwendter[14], Martin Dichgans[14], Katya E Kotschet[15], Suzanne Hodgkinson[16], Todd A Hardy[17], Martin B Delatycki[18,19], Rula A Hajj-Ali[20], Parul H Kothari[1], Stanley F Nelson[21], Rune R Frants[2], Robert W Baloh[4], Michel D Ferrari[3] & John P Atkinson[1]

Autosomal dominant retinal vasculopathy with cerebral leukodystrophy is a microvascular endotheliopathy with middle-age onset. In nine families, we identified heterozygous C-terminal frameshift mutations in *TREX1*, which encodes a 3′-5′ exonuclease. These truncated proteins retain exonuclease activity but lose normal perinuclear localization. These data have implications for the maintenance of vascular integrity in the degenerative cerebral microangiopathies leading to stroke and dementias.

RVCL
Autosomal dominant
TREX1
3′-5′ exonudease
Altered subcellular localization of Trex1 causes accumulation of DNA intermediates and abnormal immune response
Between 30–60 years
MA and MO (mainly MO)
Cognitive and psychiatric disturbances, infarcts, focal neurological symptoms
Contrast-enhancing cerebral mass lesions, calcifications, leukodystrophy
Multilayered capillary basement membranes of small cerebral vessels, skin capillaries and kidney capillaries; coagulative necrosis; obliterative vasculopathy
Vascular retinopathy, renal impairment, liver impairment, Raynaud's phenomenon, GI-bleeding

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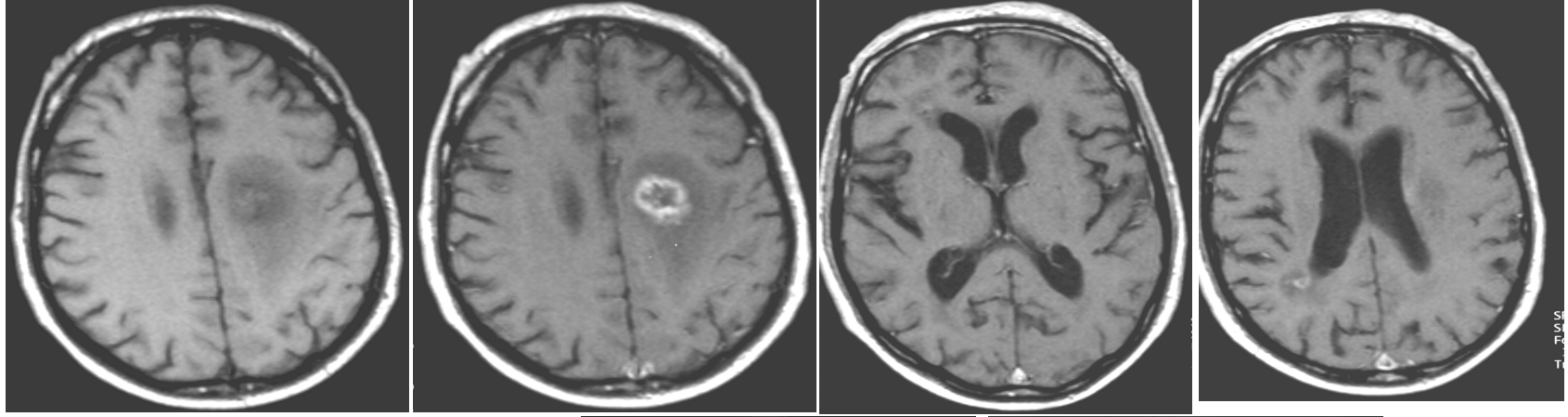
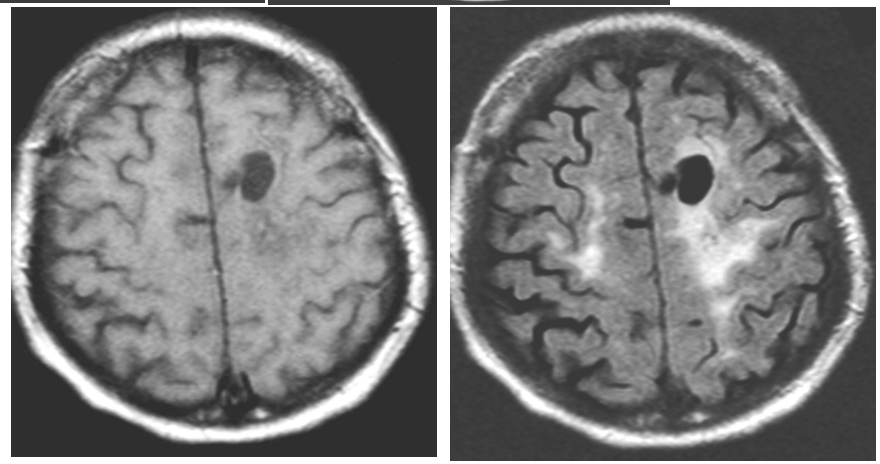
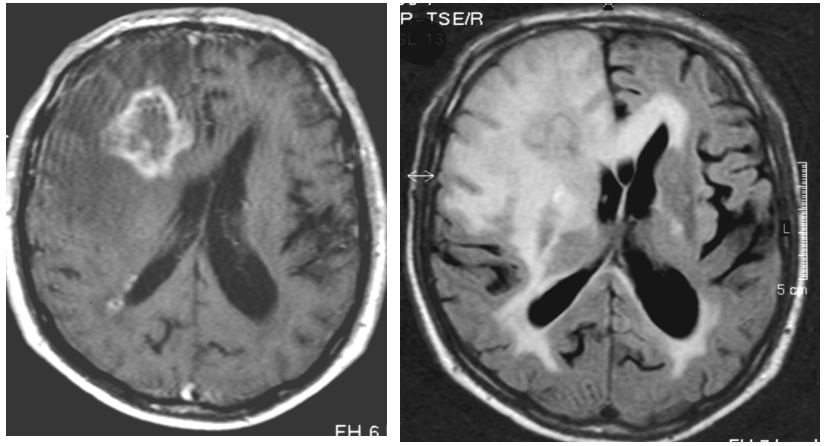


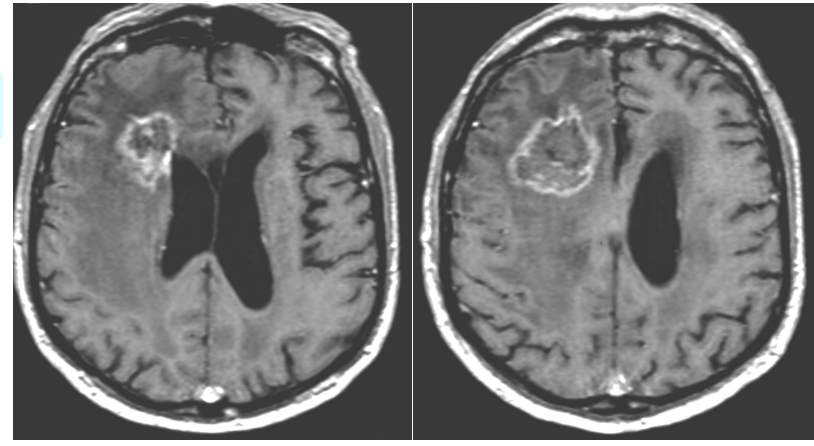
4 months

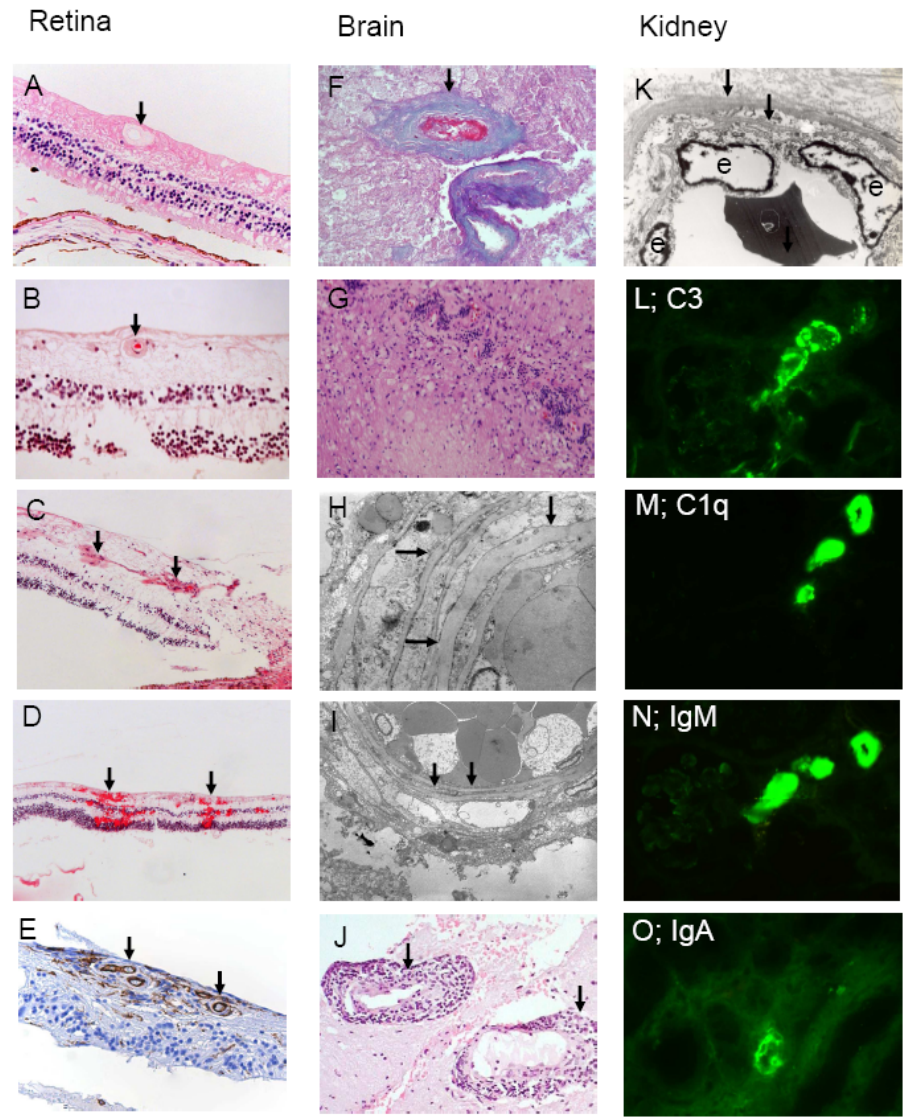


10 months



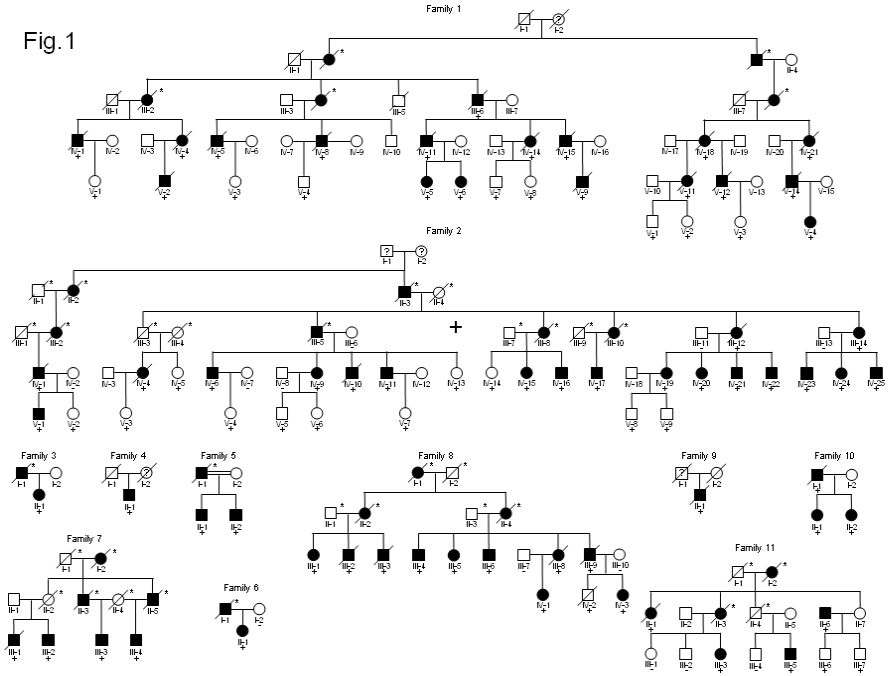
12 months

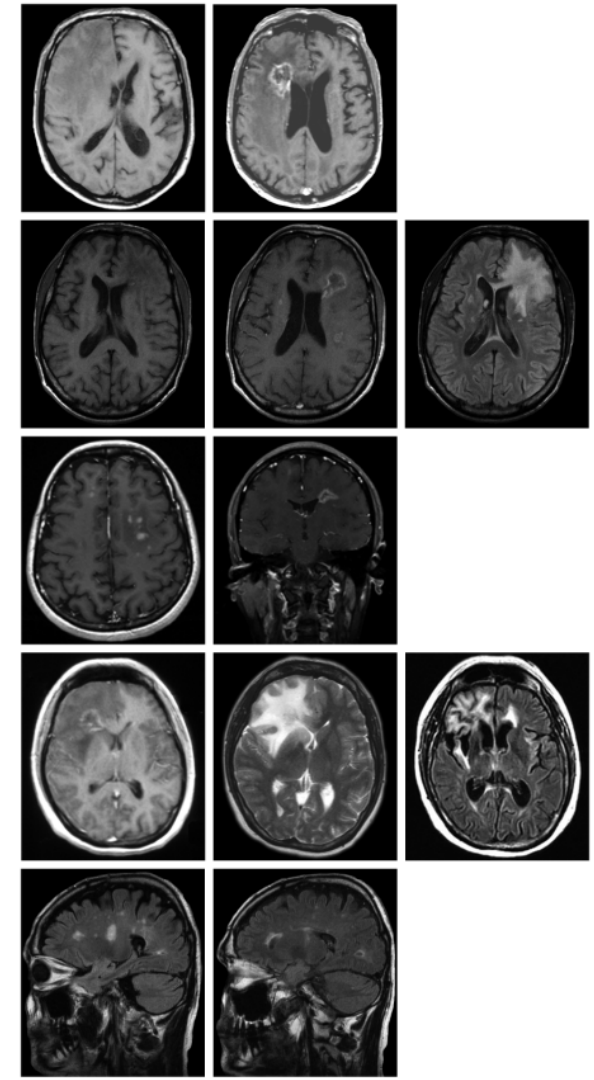




H: smooth muscle cells

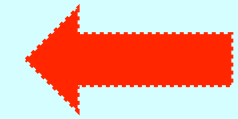
Fig.1


Family 1
Family 2
Family 3
Family 4
Family 5
Family 6
Family 7
Family 8
Family 9
Family 10
Family 11


V235fs
V236fs
T249fs
R284fs
L287fs

TREX1 and migraine

- Stam et (25) al., in preparation
  - 78 TREX1 mutation carriers from 11 families
  - 5 different mutations
  - 53% migraine
  - 86% 1st symptom
  - 70% MO / 30% MA
  - No genotype – phenotype correlation



Did Hildegard von Bingen suffer from migraine?

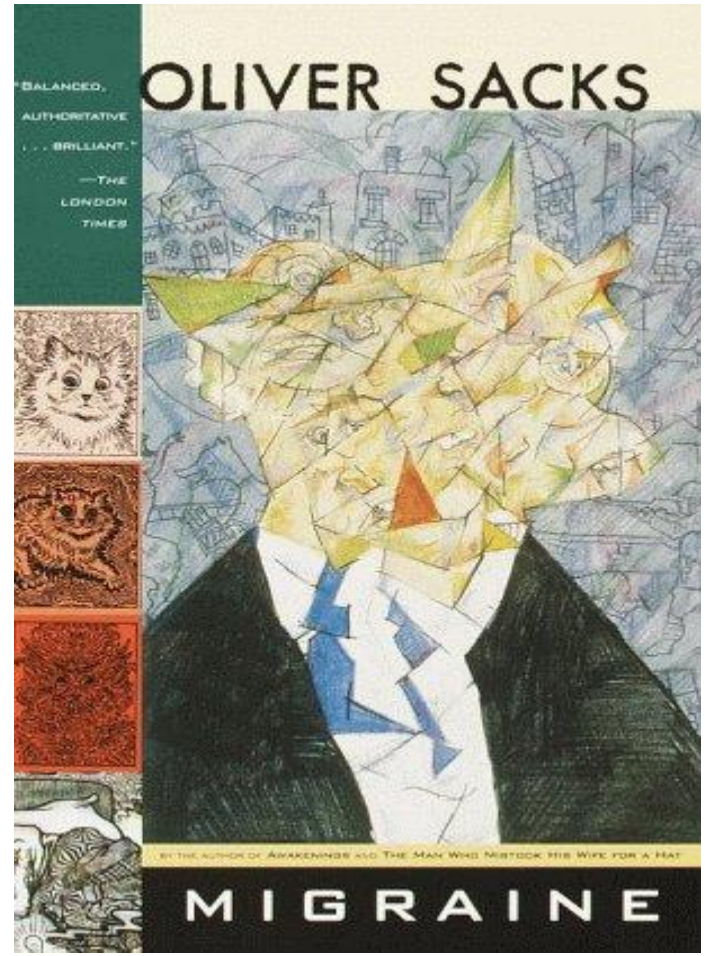
1) Yes
2) No
3) Don’t know

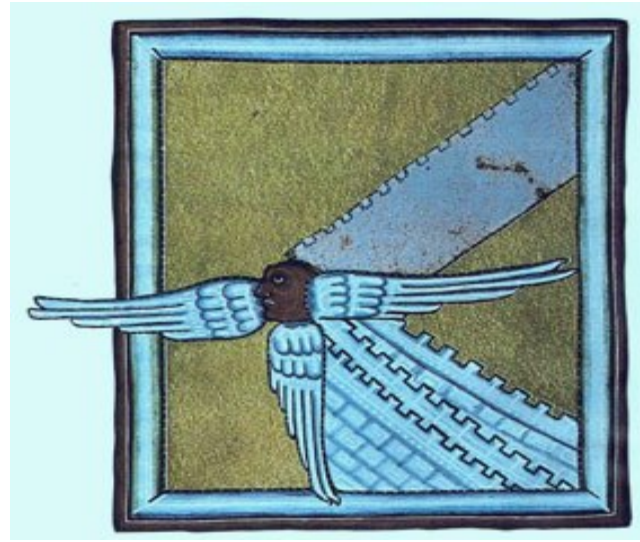
Hildegard von Bingen

- German abbess and mystic (1098-1179)
- Descriptions of her visions in:
  - Scivias
  - Liber divinorum operum simplicis hominis
- Drawings of her visions
- Composer of church music

Did Hildegard von Bingen suffer from migraine?

‘Yes’, says





D

The Visions of Hildegard of Bingen

Charles Singer

London, England

1917

I saw a great star most splendid and beautiful, and with it an exceeding multitude of falling sparks which with the star followed southward. And they examined Him upon His throne almost as something hostile, and turning from Him they sought rather the north. And suddenly they were all annihilated, being turned into black coals … and cast into the abyss that I could see them no more (*Scivias*, lib. iii, vis I; Migne, col. 565) (Frontispiece).

: migraine?

This outline of the visions Hildegard herself variously interpreted. We give examples from the more typical of these visions, in which the medical reader or the sufferer from migraine will, we think, easily recognize the symptoms of "scintillating scotoma." Some of the illuminations, here reproduced in their original colours, will confirm this interpretation.

Podoll and Robinson, 2002

Recurring painfull disease
Episodes of complete amaurosis
Bilateral pareses of the legs
Speech difficulties

doi:10.1093/brain/awl348 *Brain* (2007), **130**, 1690–1703

OCCASIONAL PAPER

Exploring the visual hallucinations of migraine aura: the tacit contribution of illustration

G. D. Schott

National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Hildegard's 'fortification figures' resemble the castellated tops of battlements, which are depicted together with human figures. To the present writer, neither Hildegard's illustrations, nor her descriptions, are at all suggestive of migraine aura, and others too have been sceptical (Levene, 1975–6; Plant, 1986; Rose, 2004). Here illustration has been instrumental in discriminating fact from fiction.

Did Hildegard von Bingen suffer from migraine?

1) Yes
2) No
3) Don’t know

Migraine aura pathophysiology: the role of blood vessels and microembolisation

Turgay Dalkara, Ala Nozari, Michael A Moskowitz

www.thelancet.com/neurology Vol 9 March 2010

Panel: **Some comorbidities of migraine with aura**

Cardiac and pulmonary

- Patent foramen ovale (associated with large openings, atrial septal aneursyms, and right-to-left shunting)
- Mitral valve prolapse
- Pulmonary arteriovenous malformations

Vascular

- Stroke
- Carotid or vertebral artery dissection
- Carotid artery puncture
- Brain arteriovenous malformations
- Hereditary disorders (CADASIL, Col4A1 mutations, AD-RVCL, hereditary vascular retinopathy)

Inflammatory

- Raynaud's phenomenon
- Sjögren's syndrome
- Antiphospholipid antibodies
- Coagulopathy
- Thrombocytosis
- Polycythemia vera

AD-RVCL=autosomal dominant retinal vasculopathy and cerebral leukodystrophy. CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

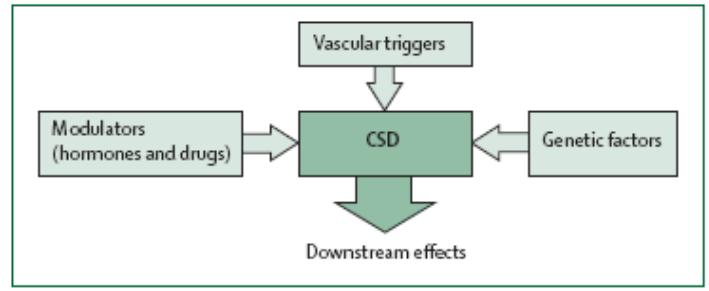


Figure 1: **CSD and factors involved in the initiation of vascularly triggered migraine aura**

CSD has a fundamental role in the genesis of migraine aura. Susceptibility to CSD is conferred by genes and modulated by hormones (ovarian and testicular) as well as by drugs that suppress CSD and prevent migraine attacks. Recently identified vascular triggers initiate CSD by causing transient, mild, and focal hypoperfusion, as determined experimentally. CSD=cortical spreading depression.

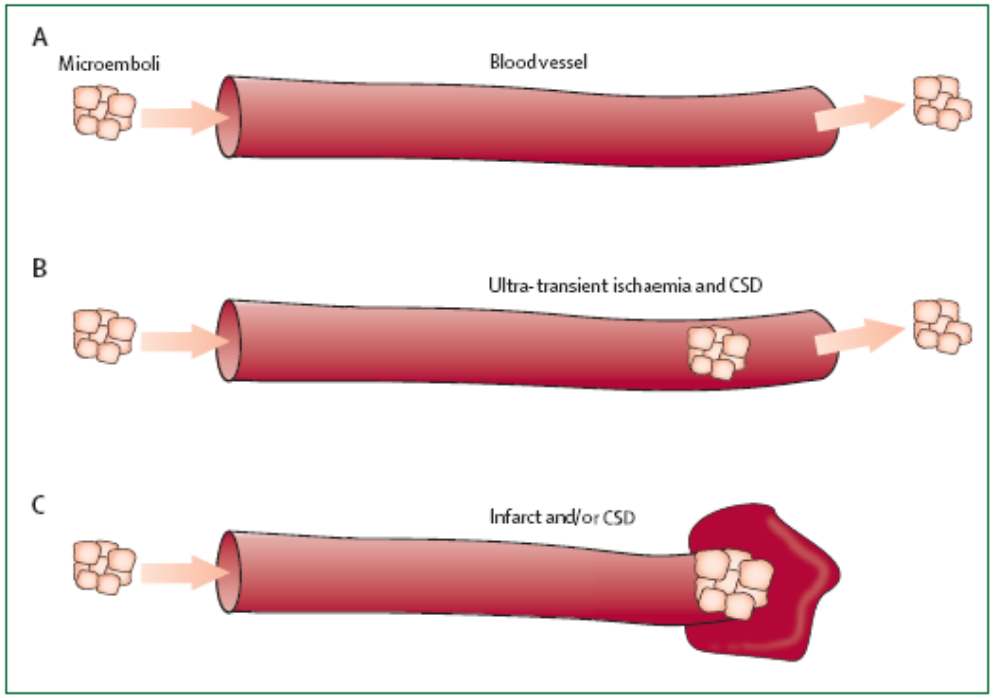


Figure 3: **The risk of developing CSD after microembolisation partly depends on the location, size, and duration of vascular occlusion**
Although some microemboli can traverse the brain microcirculation without pathophysiological consequence (A), other microemboli can transiently occlude the circulation to a critical volume of tissue to initiate CSD (B) followed by recovery; more prolonged occlusion (C) will cause tissue microinfarction. CSD=cortical spreading depression.

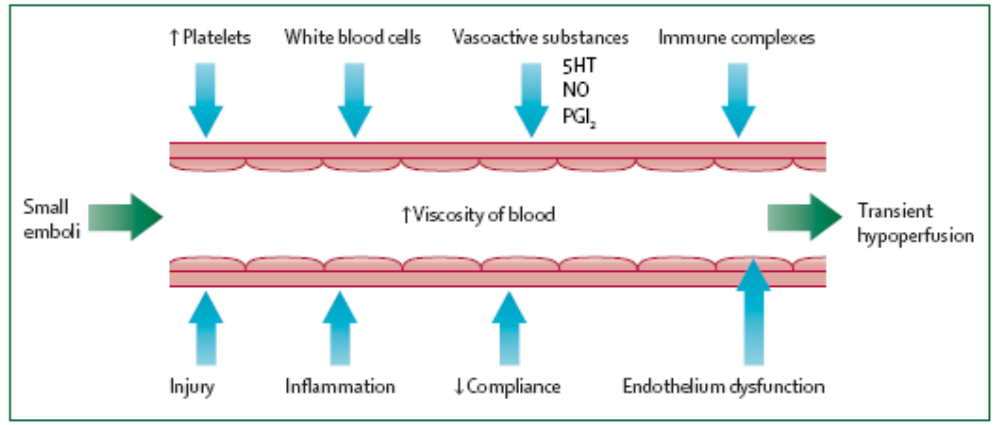


Figure 4: **Cerebral blood vessels are important for the triggering of cortical spreading depression and the pathophysiology of migraine aura**
We propose that in patients with patent foramen ovale, brief periods of local and mild hypoperfusion develop as a consequence of microemboli arising from the venous circulation, or might develop in other conditions in response to injury to the vessel wall, local release of vasoactive substances, increased blood viscosity, circulating immune complexes, endothelial dysfunction, enhanced platelet-endothelial interaction, or platelet-leucocyte interaction among other mechanisms. The potentially important astrocytes and other components of the neurovascular unit are not depicted.

Microemboli May Link Spreading Depression, Migraine Aura, and Patent Foramen Ovale

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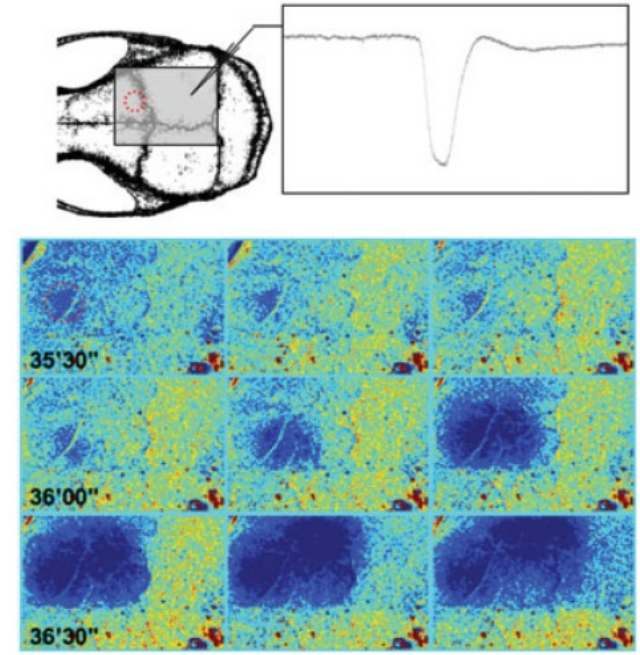

FIGURE 2: Cortical spreading depression (CSD) originates from a hypoperfused cortical focus. Representative time-lapse laser speckle images of relative cerebral blood flow changes taken approximately 35 minutes after cholesterol microembolization show the initiation of a CSD from a frontal cortical focus of hypoperfusion (red circle). A CSD was initiated from this ischemic focus after approximately 30 seconds (36′00″), and propagated throughout the ipsilateral cortex (centrifugally spreading blue hypoperfusion wave), confirmed by concurrent electrophysiological recordings using a glass micropipette (inset). Images were acquired at 0.1Hz. Laser speckle imaging field and electrode positions are shown on the upper left drawing.

Vasculopathies and migraine

- CADASIL and RVCL
  - Coincidence?
  - Shared genetic factors?
    - Notch3/Trex1 as migraine susceptibility genes?
  - Vascular?
    - Decreased CBF?
    - Microemboli from damaged blood vessels?
  - Neuronal?
    - Increased susceptibility for CSD?

Smooth muscle cells?

Vasculopathies and migraine

- CADASIL and RVCL
  - Spurious?
  - Shared gene
    - Notch3/Tre
  - Vascular?
    - Decreased
  - Neuronal?
    - Increased susceptibility for CSD?

Migraine models

7 Tesla MRI

PET

Painting as an expression of migraine?

doi:10.1093/brain/awl348 *Brain* (2007), **130**, 1690–1703

OCCASIONAL PAPER

Exploring the visual hallucinations of migraine aura: the tacit contribution of illustration

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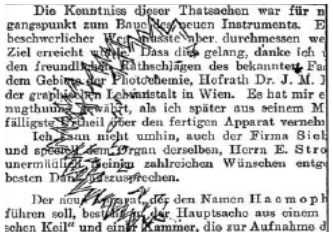
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Ziel erreicht wurde. Dass dies gelang, danke ich
den freundlichen Rathschlägen des bekannten Fa
dem Gebiete der Photochemie, Hofrath Dr. J. M.
der graphischen Lehranstalt in Wien. Es hat mir e
nugthuung gewährt, als ich später aus seinem M
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Ich kann nicht umhin, auch der Firma Siek
und speciell dem Organ derselben, Herrn E. Stro
unermüdlich, meinen zahlreichen Wünschen entge
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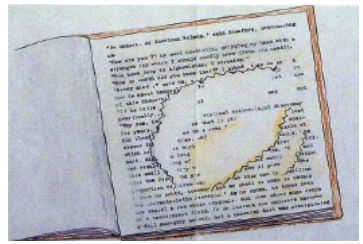

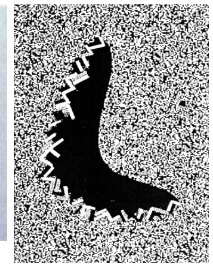

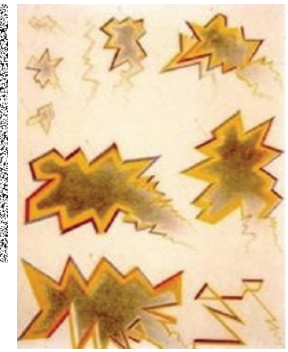

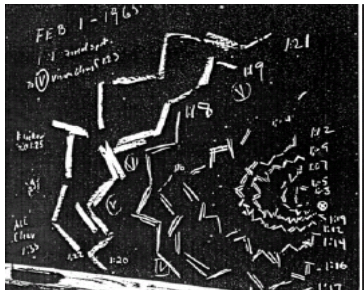

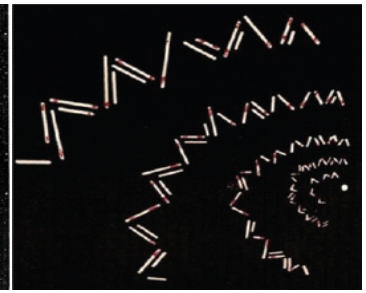

Can painting help us to better understand migraine?

The visual aura of migraine is a subjective phenomenon…

…what the migraineur experiences is necessarily inaccessible to others.

Illustration, particularly when made during the attack, provides an unusual, little used but powerful tool which uniquely allows the sufferer's subjective visual experiences to inform objective analysis. In turn, this analysis leads to insights into some of the cerebral disturbances which subserve migraine aura.

'Uniformity of the similar representations probably confirms their organic nature'
Wilkinson and Robinson, 1985