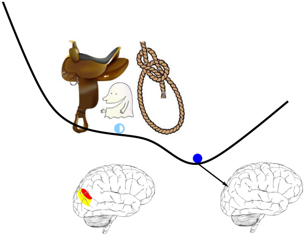
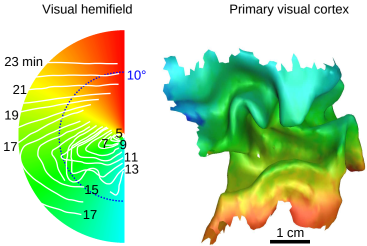
Ghost behavior: Transient **localized** patterns of CSD in the gyrencephalic human cortex

Markus A. Dahlem

HU Berlin, Research group: Dynamics and Neuromodulation of Migraine





Workshop 1, July 9, 2014

Outline

What is the question?

Generic (off–the–shelf) reaction–diffusion models in 2D

Predictions

- Cortical hot spots and labyrinths
- Migraine subform (with and w/o aura / headache)
- (Towards therapeutic intervention)

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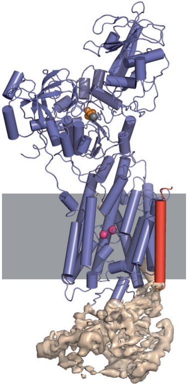
Multiscale phenomenon: From molecules to entire brain

Functional mutations



(e.g. FHM2: sodium-potassium pump)

Maagdenberg, et al., *Ann. Neurol.*, **67** (2010)

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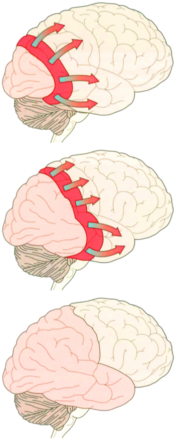
Freilinger, et al. *Nature Genetics* **44** (2012),

Dahlem, et al *PeerJ*, **2**,379 (2014)

Spreading depression (SD)

during a migraine attack



Atlas of Migraine and Other Headaches, Silberstein et al (Editors)

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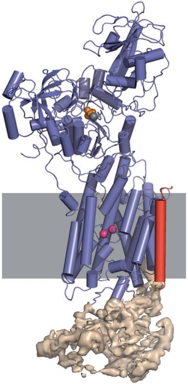

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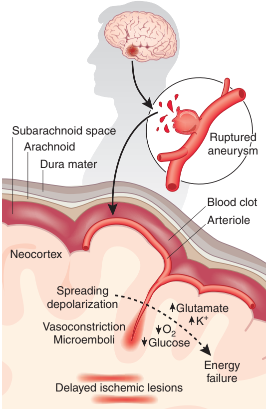
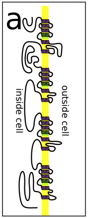
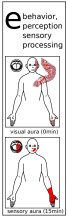


Iadecola, "Killer waves ..." *Nature Medicine* **15** (2009)

Models fill the ‘gaps’ in the multiscale framework





(a) Functional mutations, either FHM, CADASIL, ... or GWAS.

(e) Throbbing pain, aura symptoms, mental dysfunctions, impared sensory and cognitive processing.

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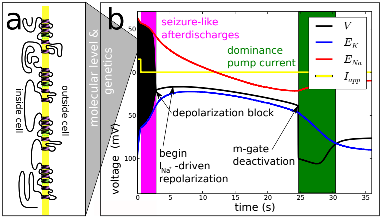

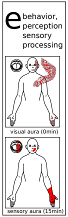

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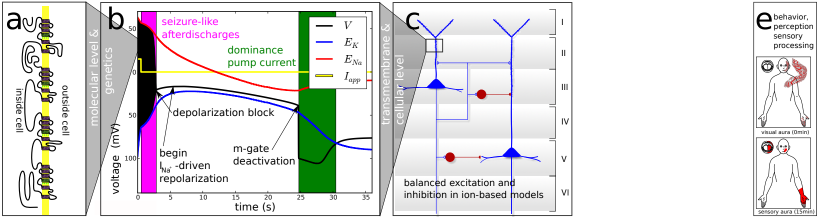

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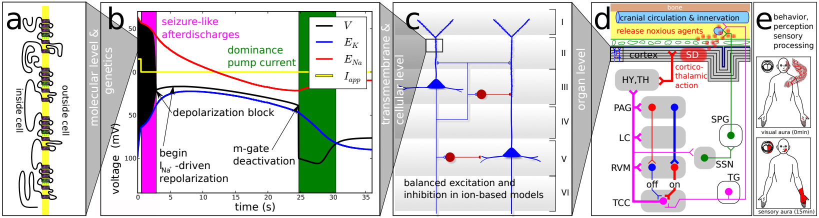

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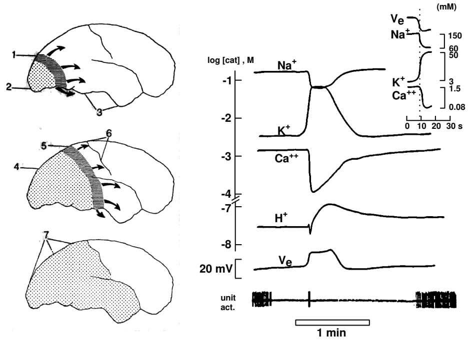
(c) Cortical circuits, subpopulations with specific synaptic receptor distribution, towards neural mass/fields population models.

(d) Generic reaction-diffusion, neuropetides CGRP, cytokines TNF, ... and larger networks (migraine generator network).

(e) Throbbing pain, aura symptoms, mental dysfunctions, impared sensory and cognitive processing.

What is cortical spreading depression on macro-scale?

Homeostatic insult self-organzied as 2D patterns in gray matter.



M. Lauritzen, *Trends in Neurosciences* **10**,8 (1987).

A controversial debate but

"...essential view of a reaction-diffusion process still holds ..."

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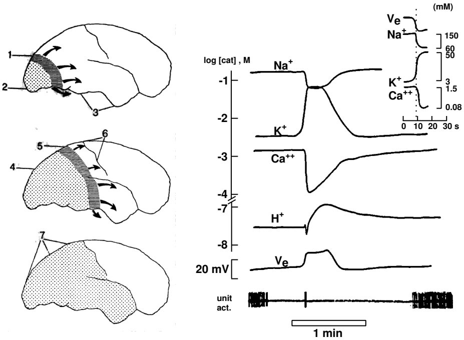

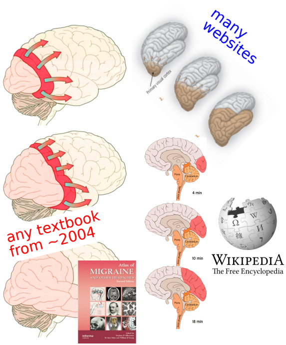

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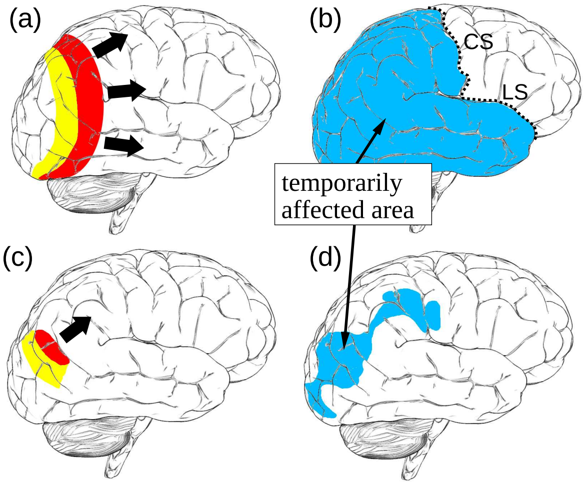
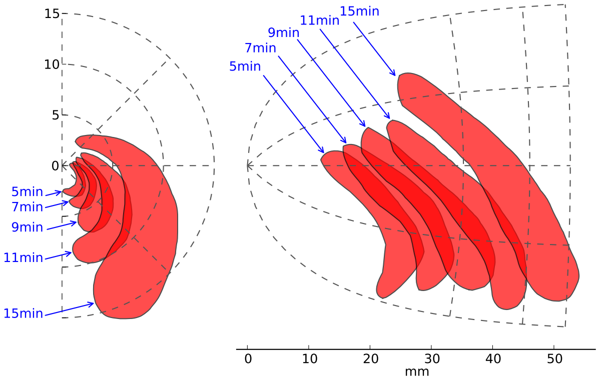
Migraine full-scale attack is more confined



- M. A. Dahlem and S. C. Müller, *Reaction-diffusion waves in neuronal tissue and the window of cortical excitability*, Ann. Phys. **13**, 442 (2004). Festschrift for H.-G. Purwins.
- M. A. Dahlem et al. "2D wave patterns ... ". *Physcia D* **239** (2010) Special issue: Emerging Phenomena.Festschrift for S.C. Müller.

Migraine visual field defects reported in 1941 by K. Lashley

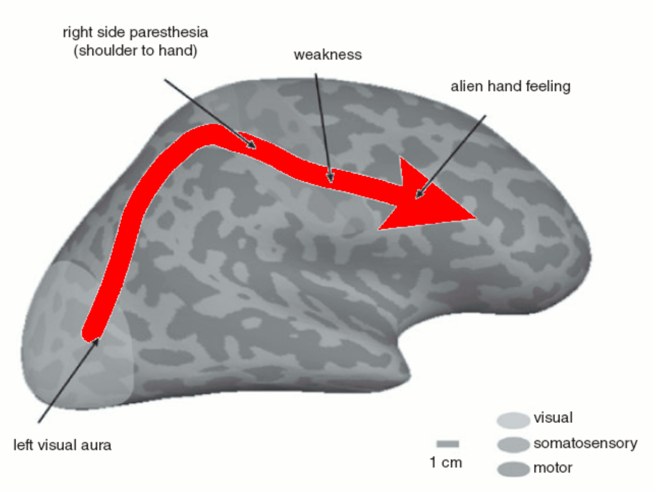
visual field defect pattern on primary visual cortex



Only about 2-10% but not 50% cortical surface area is affected!

- M. A. Dahlem & N. Hadjikhani, Migraine aura: retracting particle-like waves in weakly susceptible cortex, PLoS ONE **4**: e5007, 2009.

Tracking migraine aura symptoms



Vincent & Hadjikhani (2007) Cephalagia **27**

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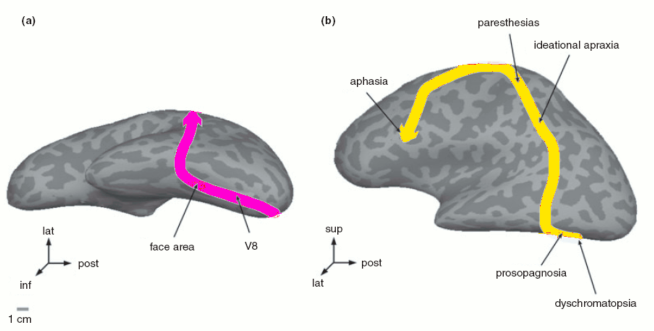

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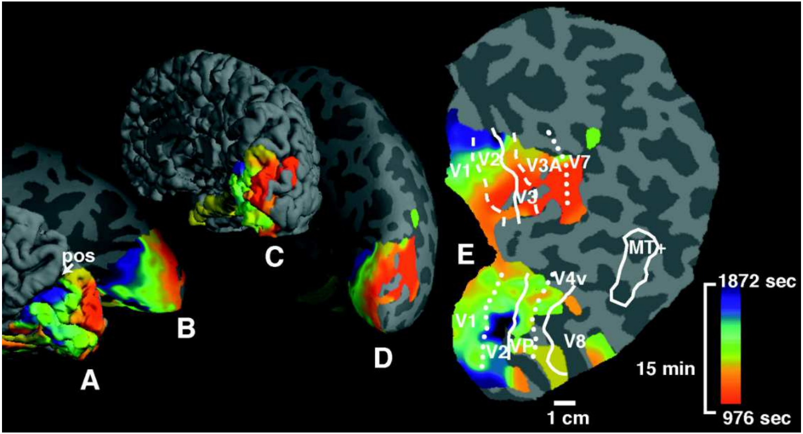
Confined spatial patterns of spreading depression



Hadjikhani et al. (2001) PNAS

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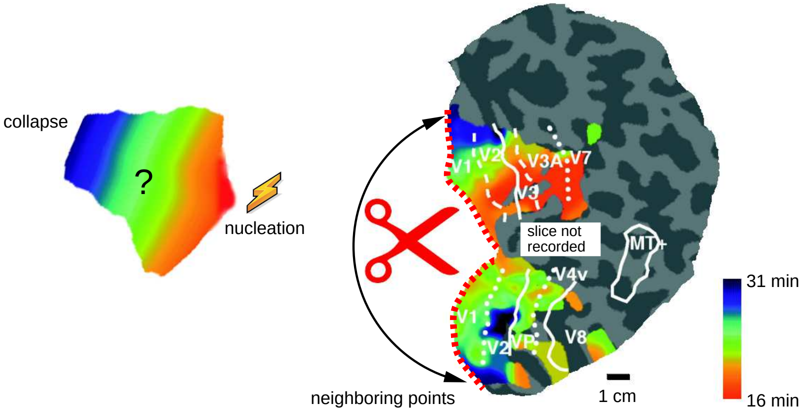

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How can we build a generic reaction–diffusion model?

Generic reaction-diffusion model

The Hodgkin-Grafstein model
of SD (1963)

(cf. Zeldovich-Frank-Kamenetskii
(1938), ... Schlögl (1972))

$u = [K^+]_e$

$$\dot{u} = k\,(u - u_{rest})\,(u - u_{ceiling})\,(u - u_{max}) + D\nabla^2 u \qquad (1)$$

Generic reaction-diffusion model

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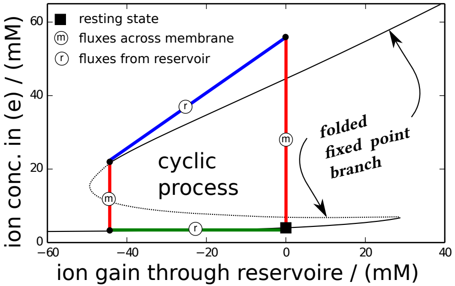

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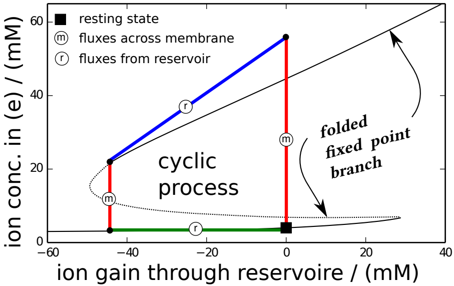

$$\dot{u} = k\,(u - u_{rest})\,(u - u_{ceiling})\,(u - u_{max}) + D\nabla^2 u \qquad (1)$$

'Obvious' (off–the–shelf) extensions:
add inhibitors ...

$$\dot{u} = u - \frac{u^3}{3} - v + D_u \nabla^2 u \qquad (1a)$$

$$\dot{v} = \varepsilon\,(u + \beta - \gamma v) \qquad (2)$$

$$\dot{w} = \ldots \qquad (3)$$

Three-species reaction–diffusion model

One activator (u), two inhibitors (v and w)

$$\frac{\partial u}{\partial t} = u - u^3 - k_3 w - k_2 v - k_1 + \nabla^2 u \tag{1}$$

$$\phi \frac{\partial v}{\partial t} = u - v + D_v \nabla^2 v \tag{2}$$

$$\theta \frac{\partial w}{\partial t} = u - w + D_w \nabla^2 w. \tag{3}$$

cf. H.-G. Purwins' original work on pattern formation in planar DC gas-discharge systems.

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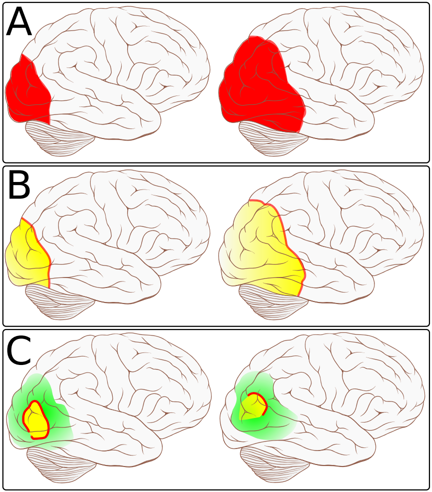
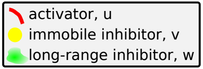
Three-species reaction–diffusion model



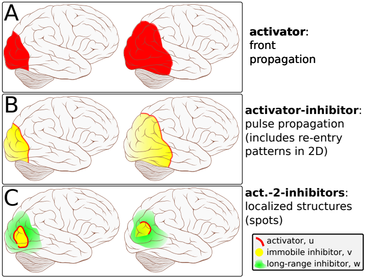
activator:
front
propagation

activator-inhibitor:
pulse propagation
(includes re-entry
patterns in 2D)

act.-2-inhibitors:
localized structures
(spots)



Dissipative solitons: model variants



Generic off–the-shelf RD model to study principal effects.

fast diffusing second inhibitor

$$
\begin{aligned}
\partial_t u &= f(u) - k_3 w - k_2 v - k_1 + \nabla^2 u \\
\phi\, \partial_t v &= u - v + D_v \nabla^2 v \\
\theta\, \partial_t w &= u - w + D_w \nabla^2 w.
\end{aligned}
$$

mean field inhibition

$$
\begin{aligned}
\varepsilon \partial_t u &= f(u) - v + \nabla^2 u \\
\partial_t v &= u + \beta_0 + K \int H(u)\, dA.
\end{aligned}
$$

Krischer, K. and Mikhailov, A. , *Phys. Rev. Lett.* **73**, 3165 (1994)

see also e.g.

N. Akhmediev, & A. Ankiewicz (eds), *Dissipative solitons: from optics to biology and medicine*, Springer, 2008

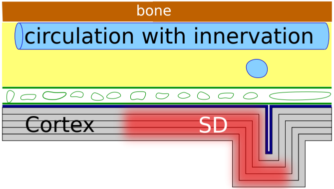
A. W. Liehr, *Dissipative Solitons in Reaction Diffusion Systems. Mechanism, Dynamics, Interaction*, Springer, 2013

We know the spatio–temporal pattern and have designed a generic reaction–diffusion model accordingly.

What is the physiological basis of the global/long–range inhibitory feedback?

Model of SD in gray matter

Model of SD in gray matter or in the brain?



Circulation outside the parenchyma

• M. A. Dahlem, Migraine generator network and spreading depression dynamics as neuromodulation targets in episodic migraine. *Chaos*, **23**, 046101 (2013)
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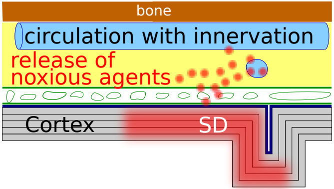

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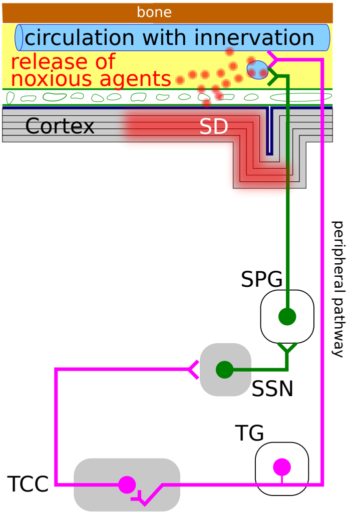

Circulation outside the parenchyma
parasympathetic control

TG: trigeminal ganglion
TCC: trigeminocervical complex
SSN: superior salivatory nucleus
SPG: sphenopalatine ganglion

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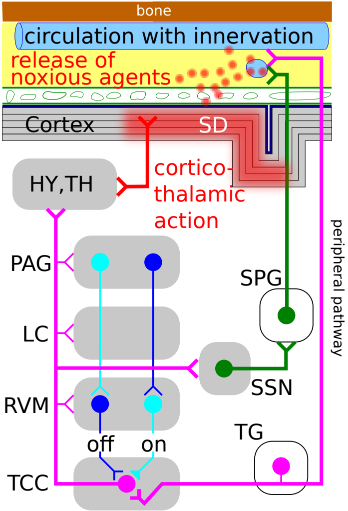

Circulation outside the parenchyma
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TG: trigeminal ganglion
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decending modulatory control and
further subcortical structures

RVM: rostral ventromedial medulla
LC: locus coeruleus
PAG: periaqueductal gray
TH: thalamus
HY: hypothalamus

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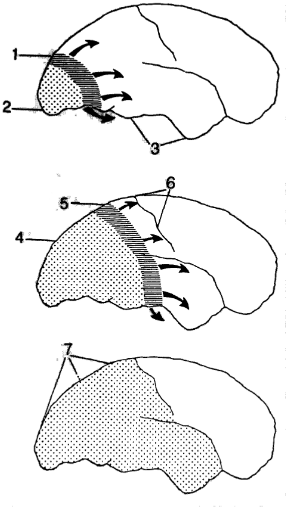
SD in gray matter: engulfing and re-entry waves forms

Canonical RD eqs.

(in weak limit, β large but not too large)

$$\begin{aligned} \partial_t u &= f(u) - v + \nabla^2 u \\ \partial_t v &= \varepsilon(u + \beta) \end{aligned}$$



Localized waves are unstable critical nuclei (mass)

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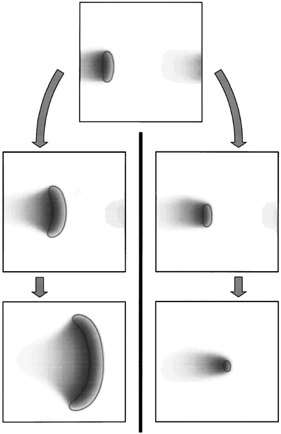

Schenk et al. *Phys. Rev. Lett.* **78**, 3781 (1997)

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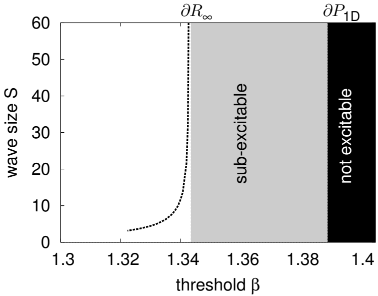
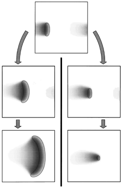
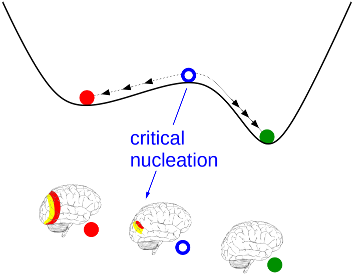
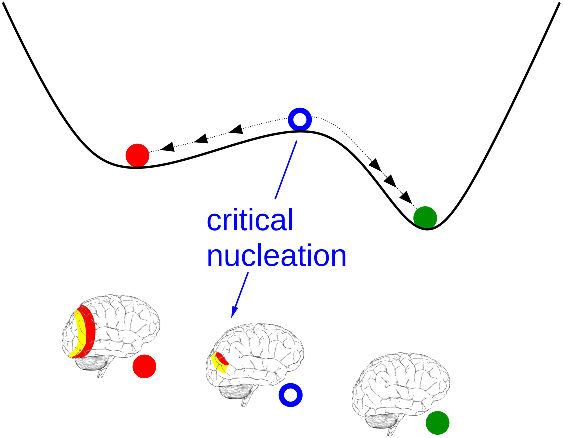


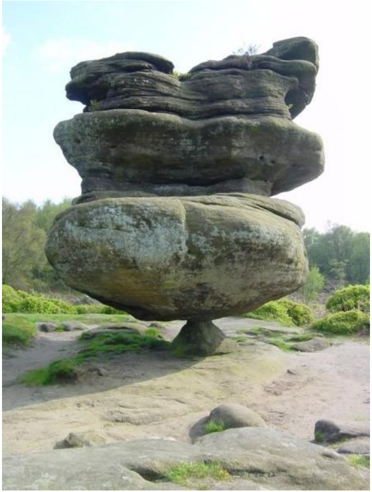




SD in migraine looks like a unstable nucleation process



What are we missing?



We already know are what we missing to explain localized wave forms: inhibitory long–range/mean field coupling.

If we fill in this missing piece, what are the predictions?

Prediction with regard to cortex gyrification (see talk tomorrow by Frederike Kneer!)

Predictions with regard to migraine subform, i.e., with and w/o aura / headache.

Predictions with regard to migraine therapie.

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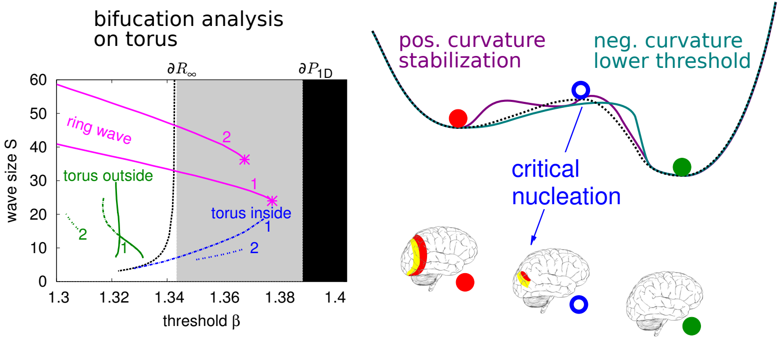
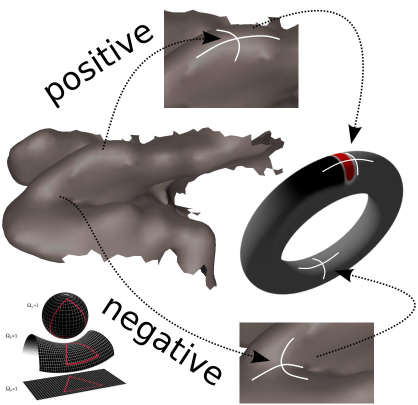
Effect of intrinsic curvature of the medium

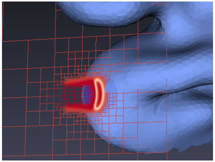
1. Lower threshold for SD if cortex is (intrinsically) negatively curved.
2. Stable wave segments: center being at positive curvature while the open ends extend into negative curvature.

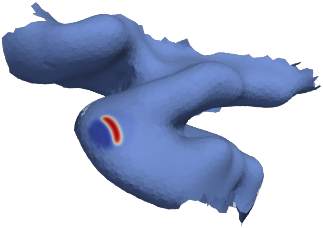


- F. Kneer, E. Schöll & M. A. Dahlem, *New J Phys*, **16** 053010 (2014)

Individual 'hot spots' and 'labyrinths' determine attack







Principles

- simulations on simpler shapes
- analytical results with isothermal

coordiantes (toroidal coordinates)

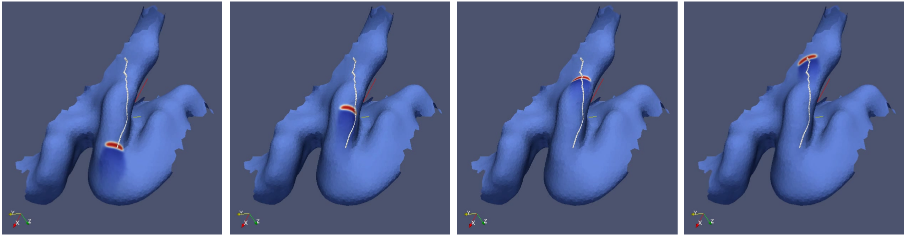
Validate

- uploading patient's MRI scanner readings
- finite element analysis
- polygon mesh processing

Excitation waves on curved surfaces

Paradigmatic SD model on gyrified cortex.

$$
\begin{aligned}
\frac{\partial u}{\partial t} &= u - \frac{1}{3}u^3 - v + D_u \frac{1}{\sqrt{g}} \frac{\partial}{\partial \alpha^i} \left(g_{ij} \sqrt{g} \frac{\partial u}{\partial \alpha^i} \right) \\
\frac{\partial v}{\partial t} &= \epsilon (u + \beta + K \int H(u) d\alpha^i)
\end{aligned}
$$

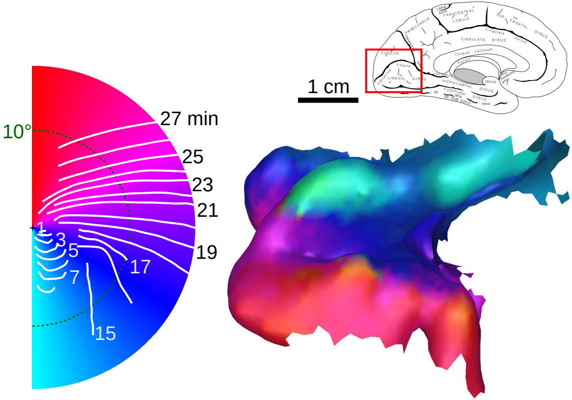


SD in weakly excitable cortex posses critical properties.

First approximation: localized SD follows shortest path.

Mapped visual symptoms on cortex via fMRI retinotopy

Visual hemifield | Primary visual cortex



- Dahlem & Hadjikhani (2009) PLoS ONE **4**: e5007.

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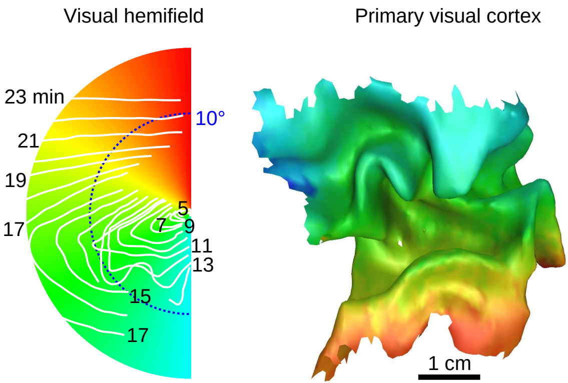
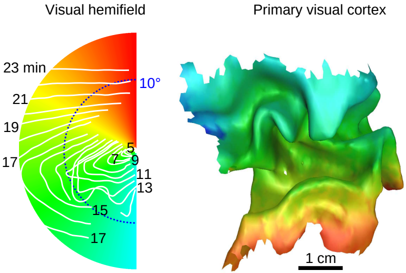
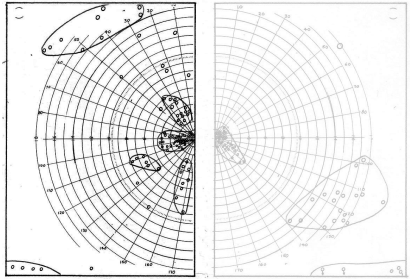


- Dahlem & Hadjikhani (2009) PLoS ONE **4**: e5007.

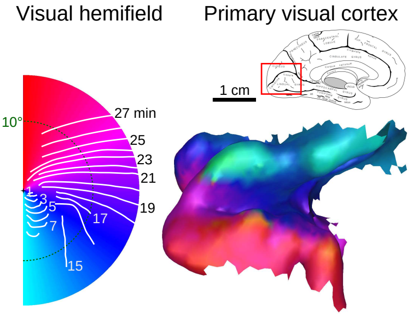
Hot spots left visual field

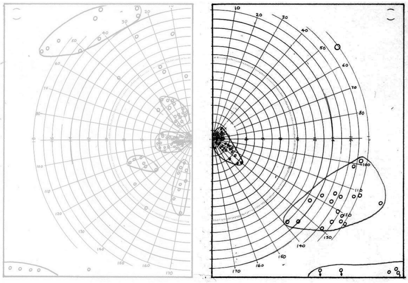




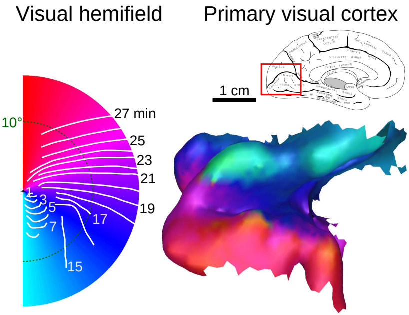
Cooperation with Andrew Charles, UCLA.

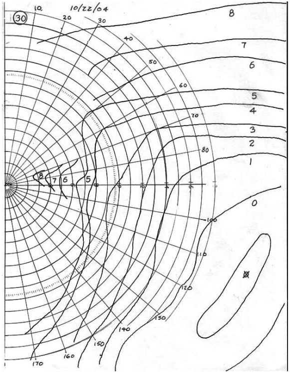
Hot spots right visual field



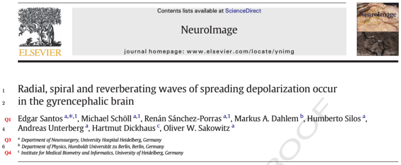


Labyrinth path in reverse direction





Oberserved wave forms of SD in the gyrencephalic brain


Contents lists available at ScienceDirect
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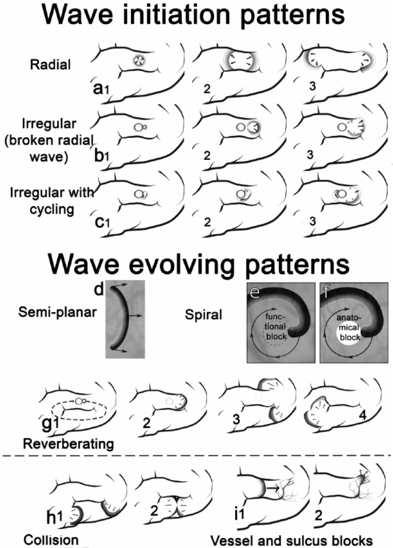
journal homepage: www.elsevier.com/locate/ynimg

Radial, spiral and reverberating waves of spreading depolarization occur in the gyrencephalic brain

Edgar Santos [a,*,1], Michael Schöll [a,1], Renán Sánchez-Porras [a,1], Markus A. Dahlem [b], Humberto Silos [a], Andreas Unterberg [a], Hartmut Dickhaus [c], Oliver W. Sakowitz [a]
[a] Department of Neurosurgery, University Hospital Heidelberg, Germany
[b] Department of Physics, Humboldt Universität zu Berlin, Berlin, Germany
[c] Institute for Medical Biometry and Informatics, University of Heidelberg, Germany



- E. Santos, et al., Radial, spiral and reverberating waves of spreading depolarisation occur in the gyrencephalic brain, *NeuroImage* **Epub ahead of print**.

Outline

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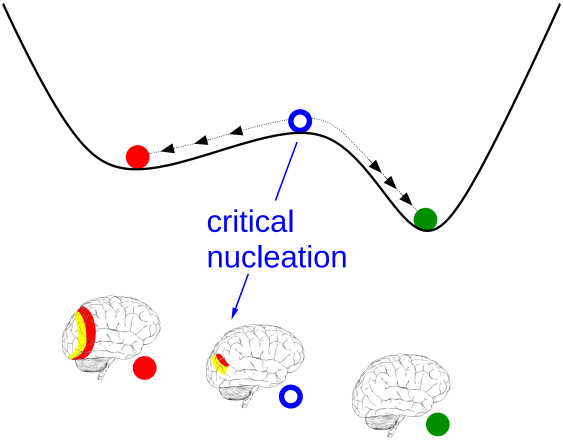
Generic (off–the–shelf) reaction–diffusion models in 2D

Predictions

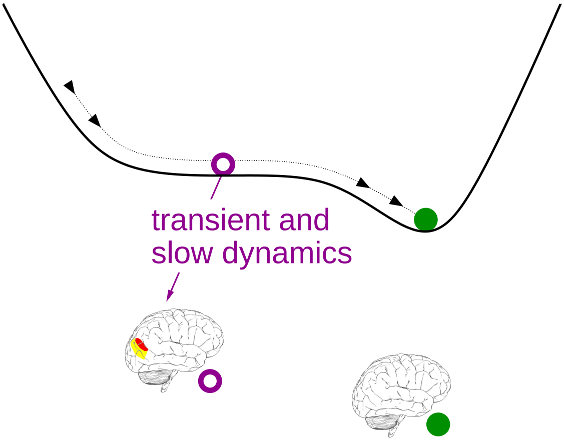
- Cortical hot spots and labyrinths
- Migraine subform (with and w/o aura / headache)
- (Towards therapeutic intervention)

Cortical homeostasis is excitable (bistabe)



Inhib. global feedback: long transient (ghost behavior)

Hypothesis: Cortical susceptibility to SD depends on the size of the momentarily affected tissue.



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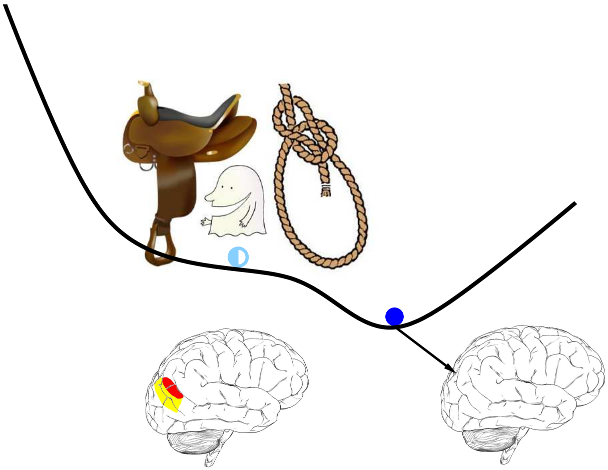
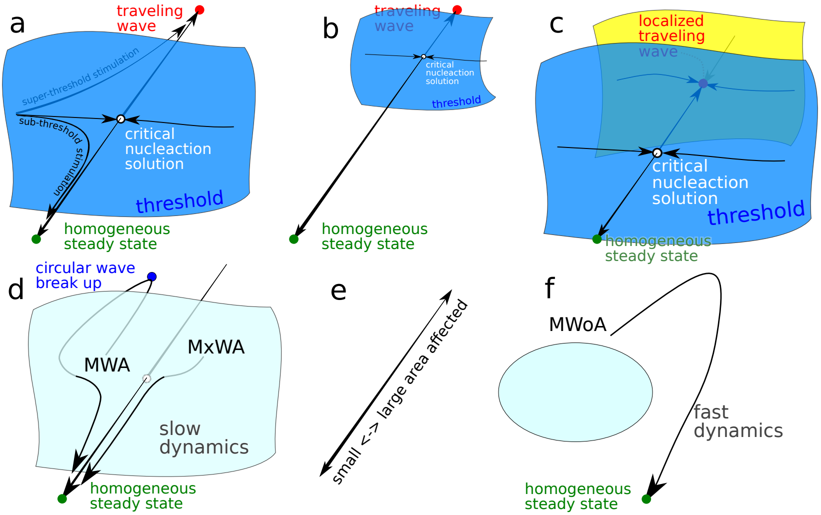


Mean field inhibition



Reaction-diffusion with global inhibition

The extended Hodgkin-Grafstein model (1963) of SD
+ canonic (i.e., FHN) inhibitor equations + nonlocal term

$$\begin{aligned} \dot{u} &= \left(u - \frac{u^3}{3} - v\right) + D\nabla^2 u \\ \varepsilon^{-1}\dot{v} &= (u+\beta) + KF[u] \end{aligned} \tag{4}$$

Global control

$$F[u] = S_u(t-\tau) - S_0$$

$$S_u(t) = \int H(u(\mathbf{r},t) - u_e)\, d\mathbf{r},$$

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Global control

$$F[u] = S_u(t \qquad) - S_0$$

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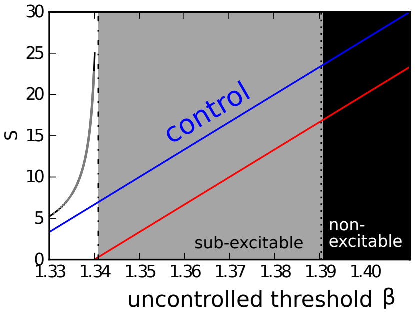
cf. K. Krischer and A. Mikhailov, (1994) *PRL* **73**, 3165

Sakurai *et al.*, (2002) *Science* **296**, 2009

Mean field inhibition can cause ghost behavior



$$
\begin{aligned}
\varepsilon \partial_t u &= f(u) - v + \nabla^2 u \\
\partial_t v &= u + \beta_0 + K \int H(u)\, dA.
\end{aligned}
$$

with "wave size S":

$$S = \int H(u)\, dA,$$

- Dahlem & Isele, Transient localized wave patterns and their application to migraine. *J. Math. Neurosci.* **3**,7 (2013)

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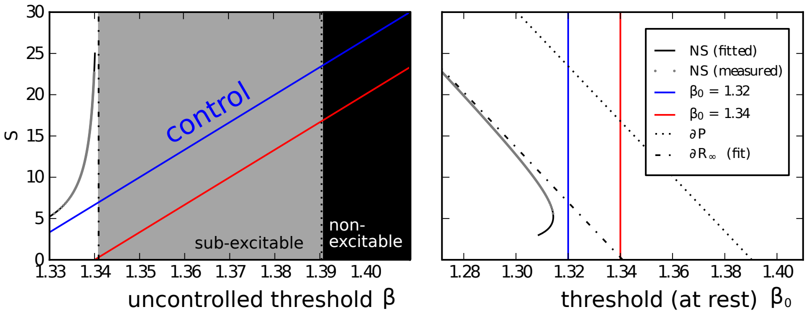

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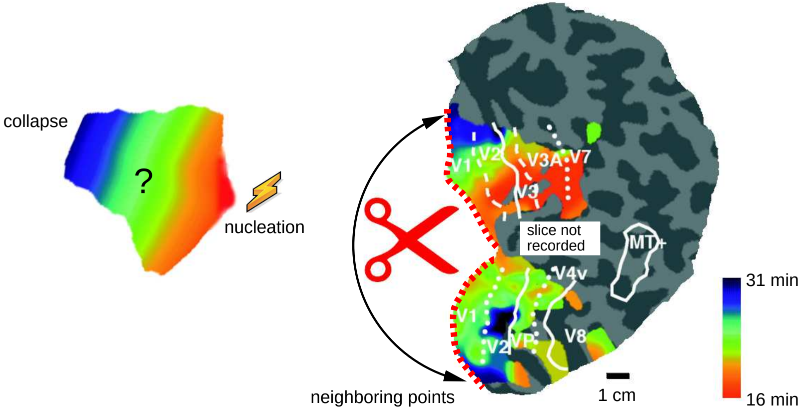
Confined spatial patterns of spreading depression



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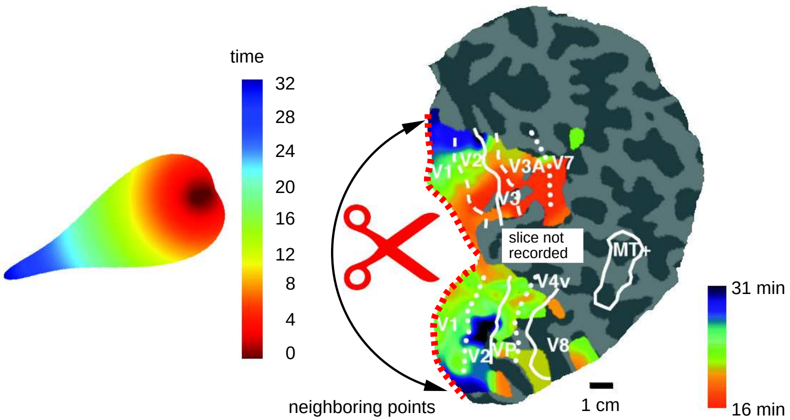

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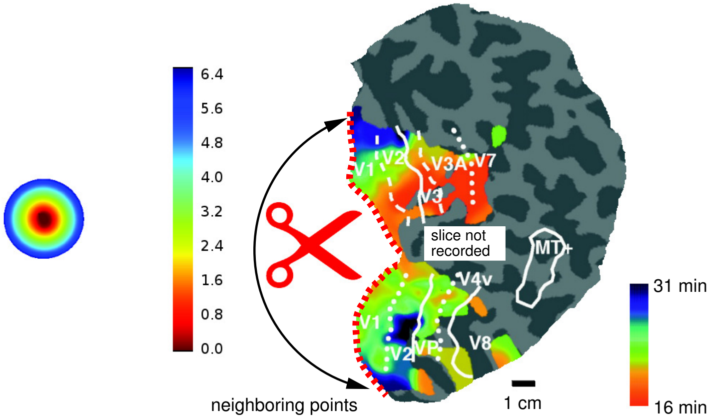

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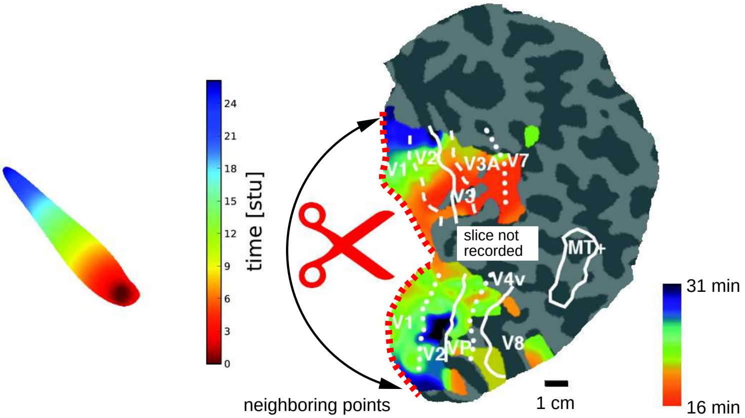

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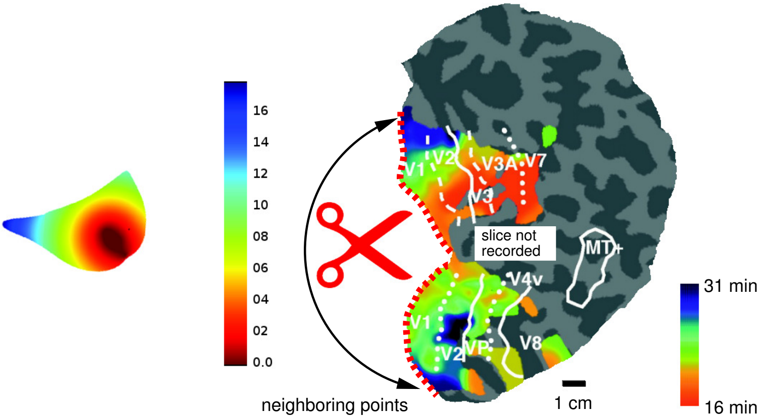
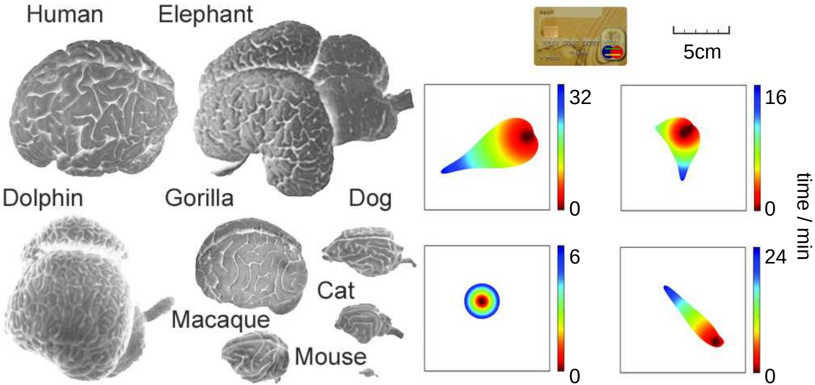
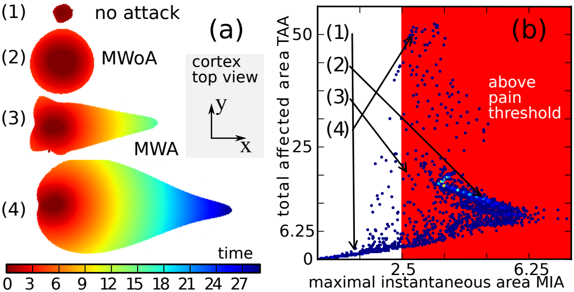
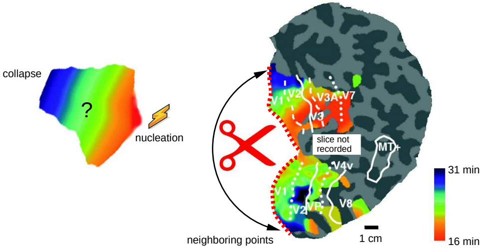


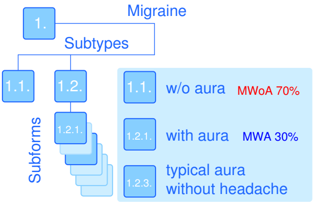
Confined spatial patterns of spreading depression



Modeled spatio-temporal signatures

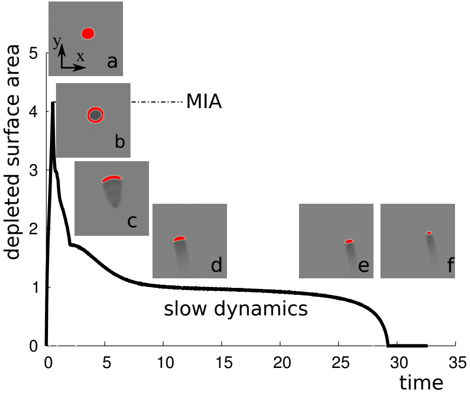






- M. A. Dahlem & T. M. Isele: *J. Math. Neurosci.* **3**,7 (2013).

Pain comes from the meninges not the cortex



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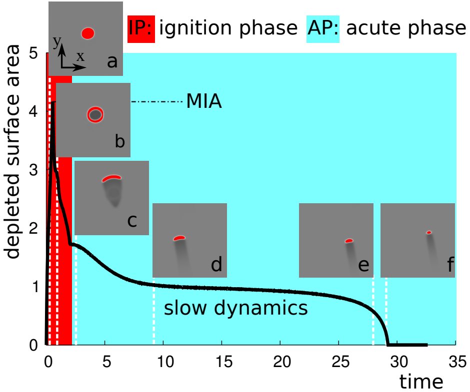

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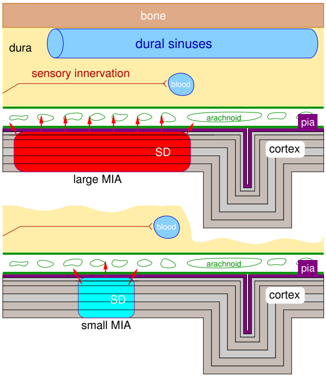
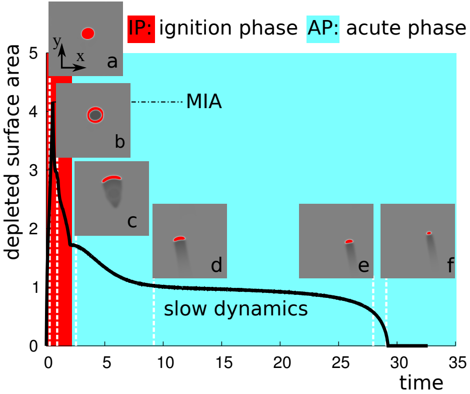
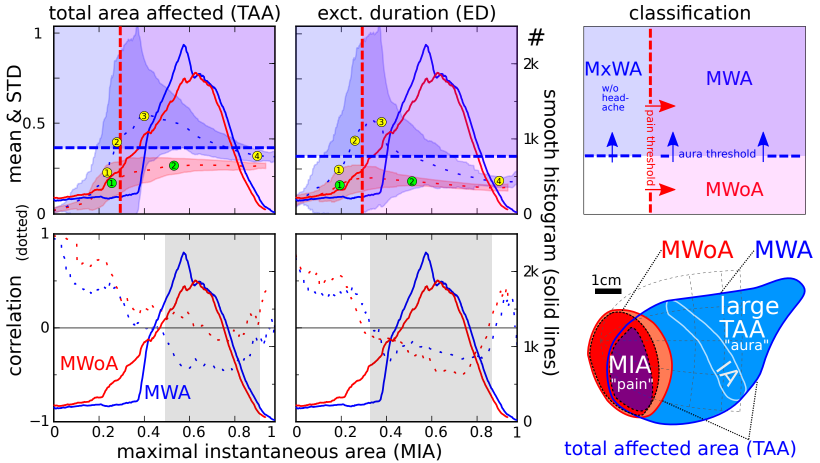




For example, can a sulcal pial siphoning of K^+ lead to focally raised concentration in the meninges?

Hypoth.: pain ∼ instantaneous area, aura ∼ long duration



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- (Towards therapeutic intervention)

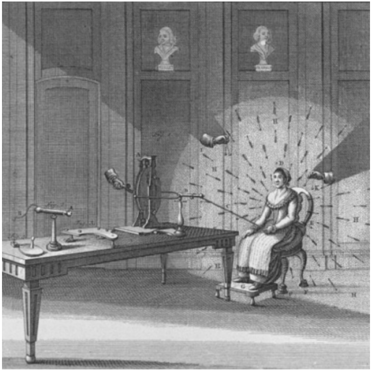
History of electrical & magnetic stimluation

Non-drug treatment for headaches (AD 47)

Scribonius Largus, court physician to the Roman emperor Claudius 47 AD used the black torpedo fish (electric rays) to treat migraine.

History of electrical & magnetic stimluation

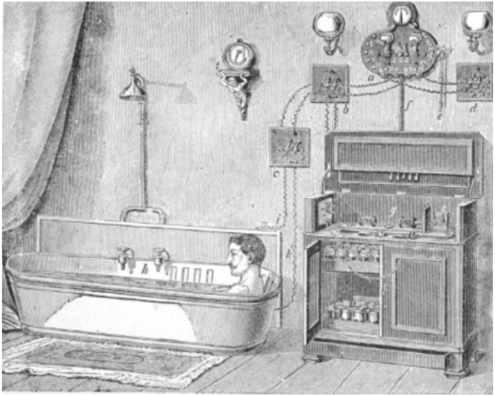
Non-drug treatment for headaches (1788)



P. J. Koehler and C. J. Boes, A history of non-drug treatment in headache, particularly migraine. *Brain* **133**:2489-500. 2010

History of electrical & magnetic stimluation

Non-drug treatment for headaches (1887)



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History of electrical & magnetic stimluation

Non-drug treatment for headaches (1896)

First steps in miniaturization

History of electrical & magnetic stimluation

Non-drug treatment for headaches (1961)

(1985) Zeitschrift EEG-EMG, Georg Thieme Verlag Stuttgart

History of electrical & magnetic stimluation

Non-drug treatment for headaches (2013)

Courtesy eNeura Inc. USA
Disclosure: Conflict of interest

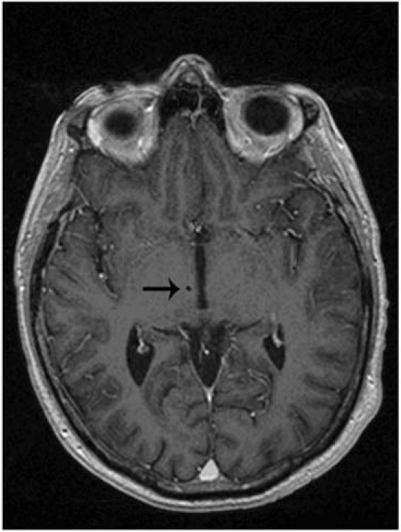
Consulting services in 2013 for Neuralieve Inc. (trading as eNeura Therapeutics)

History of electrical & magnetic stimluation

Non-drug treatment for headaches (2014)

Courtesy Cerbomed GmbH, Germany

Modern neuromodulation (invasive)



Modern neuromodulation (invasive)

Courtesy Autonomic Technologies, Inc.

Modern neuromodulation (invasive)

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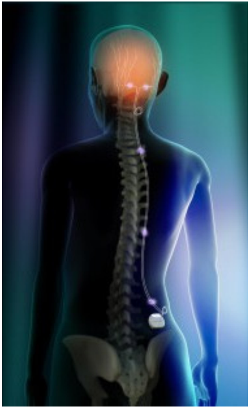
Modern neuromodulation (invasive)

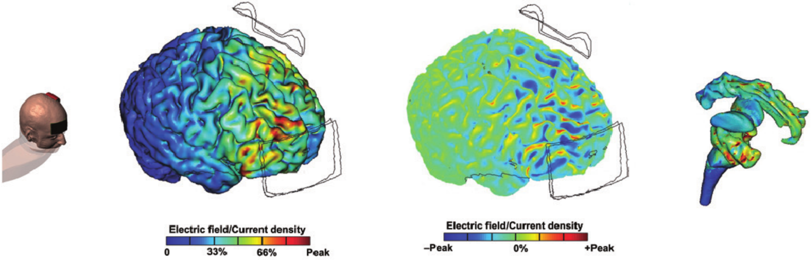
Courtesy St. Jude Medical Inc.

Modern neuromodulation (invasive)

Courtesy St. Jude Medical Inc.

Neuromodulation in migraine



- hypothalamic deep brain stimulation (hDBS),
- sphenopalatine ganglion stimulation (SPGS)
- occipital nerve stimulation (ONS),
- cervical spinal cord stimulation (cSCS),
- hypothalamic deep brain stimulation (hDBS),
- vagus nerve stimulation (VNS),
- transcutaneous electrical nerve stimulation (TENS),
- transcranial magnetic stimulation (TMS),
- transcranial direct current stimulation (tDCS),
- transcranial alternate current stimulation (tACS).

Old problems remain

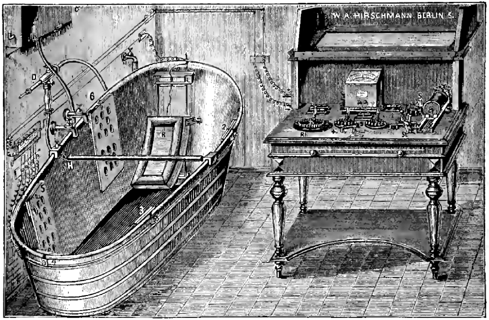
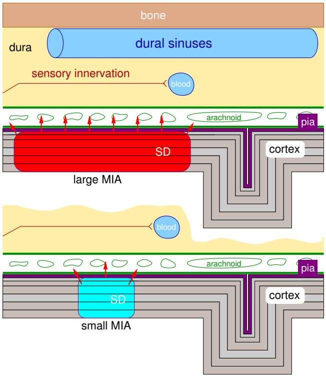


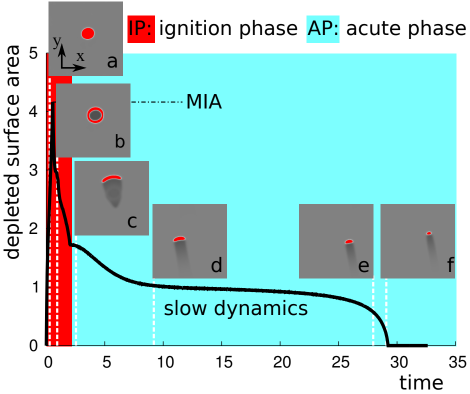
Fig. 21. Einrichtung eines elektrischen Bades nach EULENBURG.

"Über die physiologischen Wirkungen der elektrischen Bäder liegen eine Reihe von Angaben [...] vor.
[...]
Im allgemeinen haben faradische Bäder einen erfrischenden Einfluß, galvanische sollen müde machen.
Es kommt für die Wirkung entschieden auf die Dauer der Bäder an, kürzere werden mehr anregend, längere mehr erschlaffend wirken.
Durchsichtig ist jedenfalls die physiologische Begründung dieser Bäder durchaus nicht, man wird sich vorstellen, daßsie im allgemeinen die eines indifferenten Bades, mit dem ein milder Hautreiz verbunden ist, haben.
Es mögen dadurch Aenderungen in unseren Allgemeingefühlen, also Wohlbehagen, Erfrischung oder Müdigkeit bedingt werden. Nach meiner Ansicht liegt aber die Hauptwirkung dieser elektrischen Bäder in erster Linie auf suggestivem Gebiete, und das rechtfertigt ihre Anwendung und ihre unleugbaren Erfolge auf dem Gebiete der nervösen Allgemeinleiden, wie Hysterie, Neurasthenie etc."

(Lehrbuch der klinischen Hydrotherapie, Max Matthes)

Phase-dependend neuromudulation





cf. Karatas H et al., Spreading depression triggers headache by activating neuronal Panx1 channels. *Science*, **339**:1092-5 (2013).
cf. Charles AC, Baca SM., Cortical spreading depression and migraine. *Nat Rev Neurol.* **9**:637-44, (2013)
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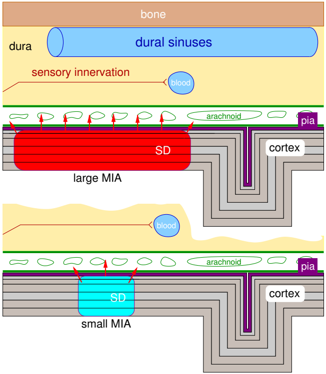

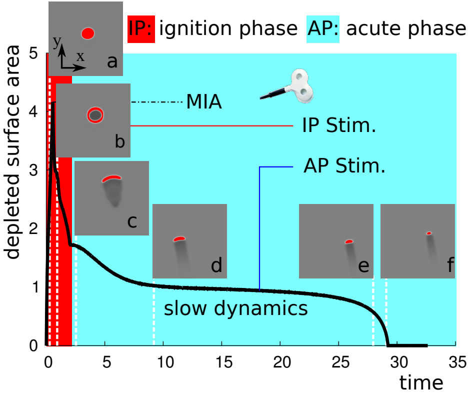

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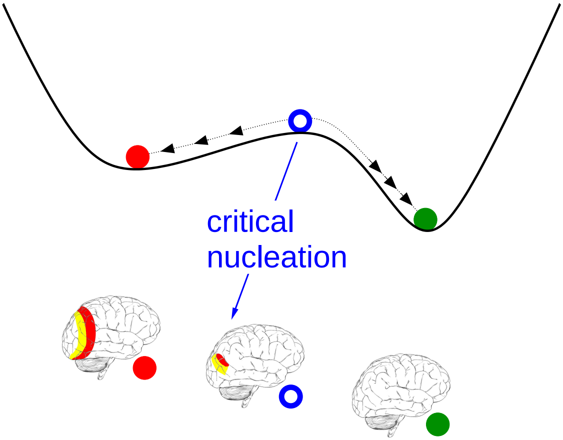
Cortical homeostasis is excitable (bistabe)



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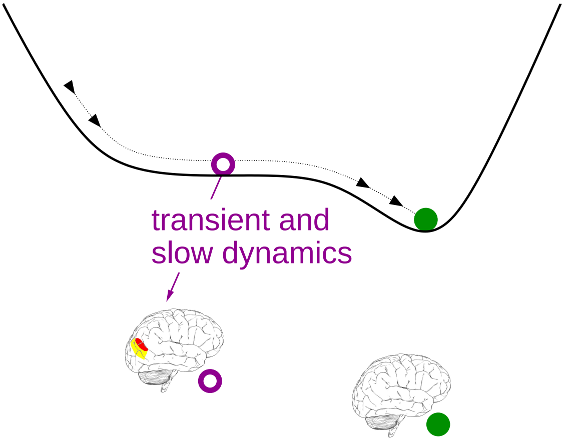

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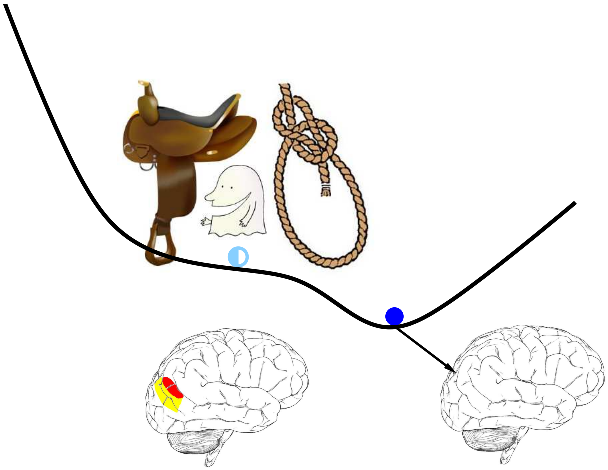
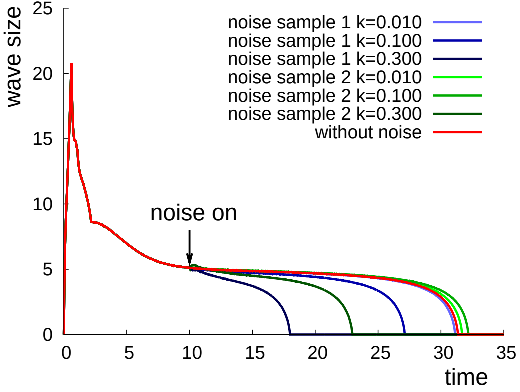
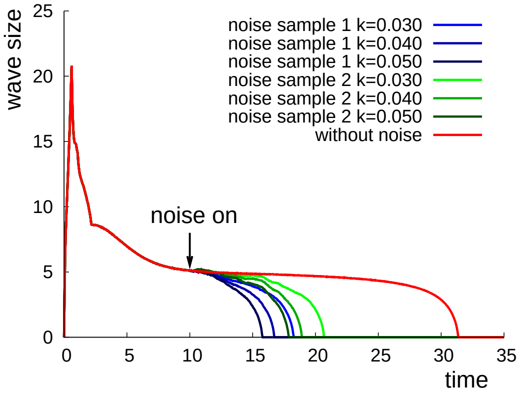


Single pulse stimulation (current TMS strategy)

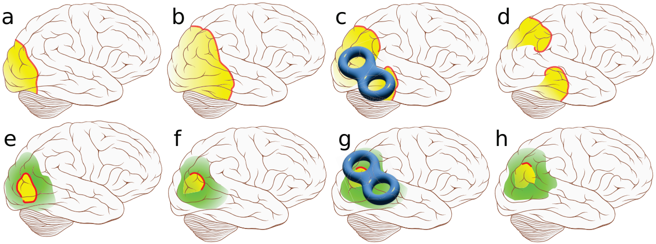


Constant noise stimulation



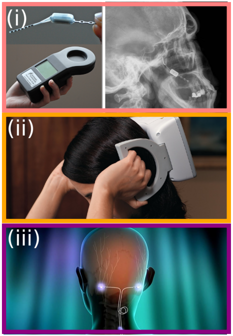
Spatio-temporal waves need spatio-temporal control

Old paradigm



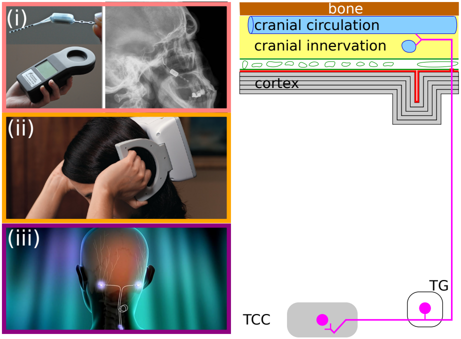
New paradigm: opens up new strategies, eg, transcranial random noise stimulation (tRNS) at special locations

Migraine Generator Network & Dynamical Network Biomarker



• M. A. Dahlem, Migraine generator network and spreading depression dynamics as neuromodulation targets in episodic migraine. *Chaos*, **23**, 046101 (2013).

Migraine Generator Network & Dynamical Network Biomarker



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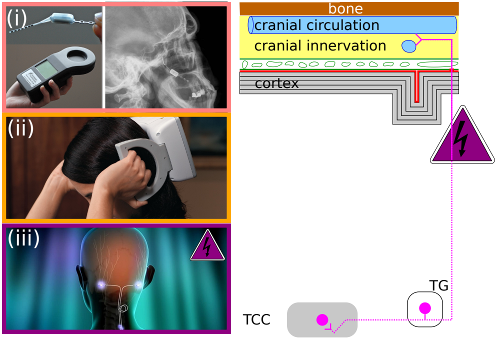

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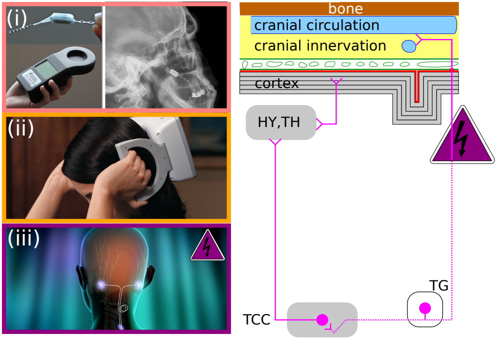

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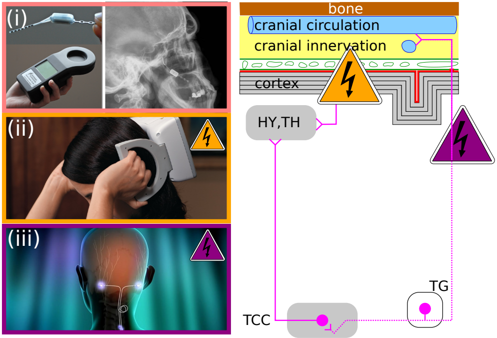

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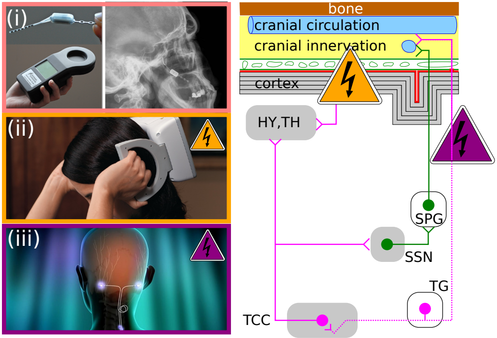

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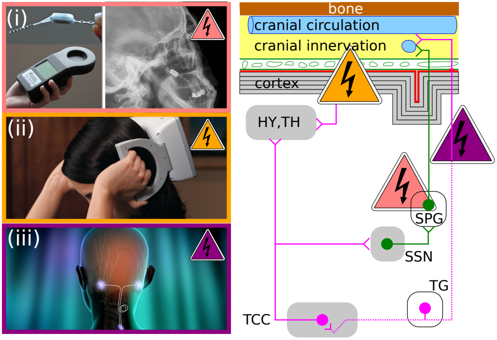

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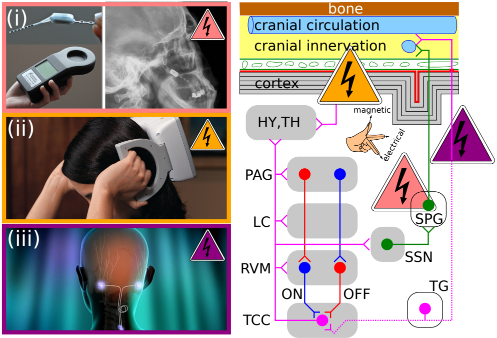

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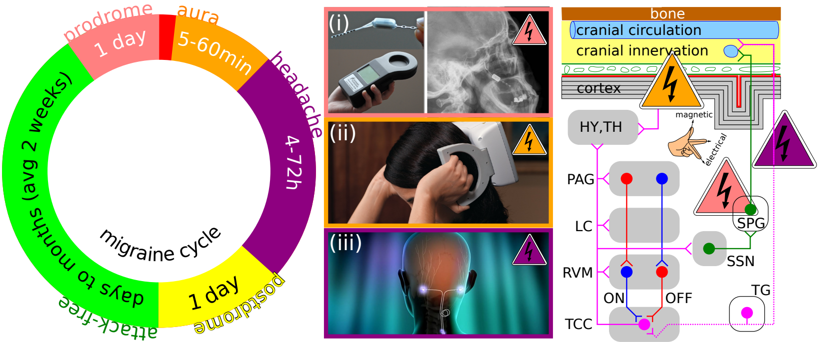

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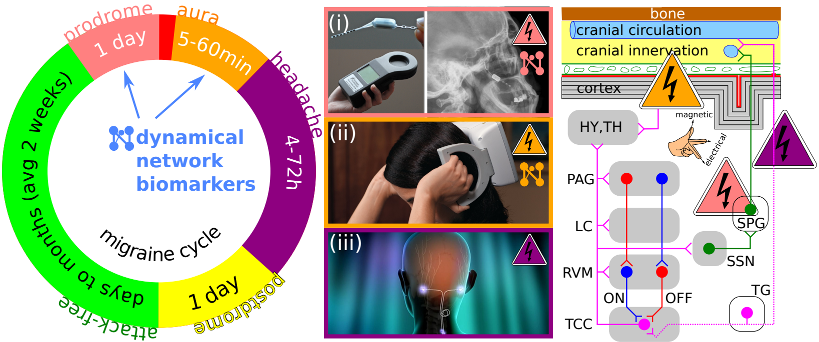

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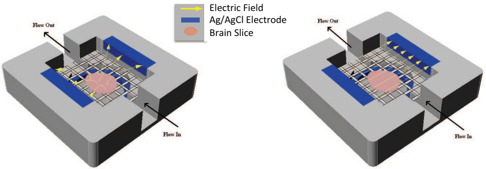
Feedback control of spreading depression

From bench

to bedside



Cooperation with Stephen Schiff & Bruce Gluckman

Dept. Biomedical Engineering, Penn State (CRCNS)

Courtesy Neuralieve

Feedback control with Kalman filter

TMS (external forcing)

“Dynamical disease”

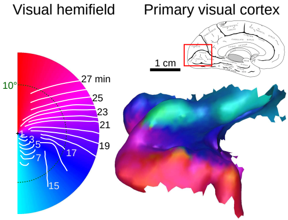
Leon Glass and Michael Mackey coined the term **dynamical disease** to identify diseases that occur due to an abrupt change in the natural rhythms of the body and rhythms become abnormal. In particular, chronic disorders with episodic manifestations.

“The significance of identifying a dynamical disease is that it should be possible to develop therapeutic strategies based on our understanding of dynamics combined with manipulations of the physiological parameters back into the normal ranges.”

(Bélair, Glass, an der Heiden, & Milton, *Chaos*, **5**, 1995)

Conclusions

- **We need more non-invasive imaging data of migraine with aura to test predictions.**
- Sef-organizing patterns provide a unifying concept including *silent* aura, migraine w or w/o headache/aura
- Dynamical cocepts may refine neuromodulation strategies:
  - Being close to a saddle-node bifurcation ("ghost" plateau)
  - Design (feedback) control to intelligently target certain properties of SD in migraine



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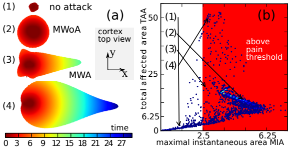

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Cooperation & Funding

Niklas Hübel, Frederike Kneer,
Thomas Isele, Julia Schumacher
Bernd Schmidt

Steven Schiff
(Penn State Center for Neural Engineering)

Eckehard Schöll
(Department of Theoretical Physics, TU Berlin, Berlin)

Jens Dreier
(Department of Neurology, Charité; University Medicine, Berlin)

GEFÖRDERT VOM
Bundesministerium
für Bildung
und Forschung

bccn berlin

GRK1558 research training group

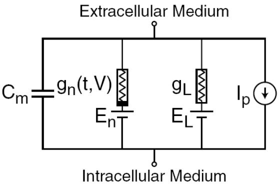
NATIONAL INSTITUTES OF HEALTH

Migraine Aura Foundation

MIGRÄNE AURA

Additional slides

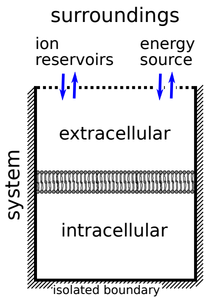
HH-type conductance-based



$$
\begin{aligned}
C\frac{\partial V}{\partial t} &= -I_{Na} - I_K - I_{leak} \qquad +I_{app} \quad (1) \\
I_{Na} &= \bar{g}_{Na} m^3 h(V - E_{Na}) \\
I_K &= \bar{g}_K n^4 (V - E_K) \\
I_{leak} &= g_{leak}(V - V_{rest}) \\
\frac{\partial n}{\partial t} &= \alpha_n(1-n) - \beta n, \quad \frac{\partial h}{\partial t} \cdots \quad (2)-(4)
\end{aligned}
$$

HH: Hodgkin-Huxley

From HH-type conductance-based to conductance- & ion-based models (2^{nd} generation model)

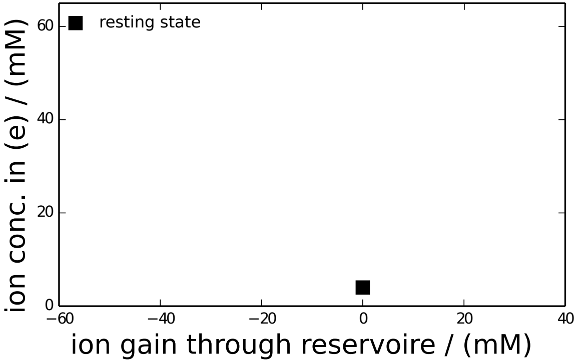


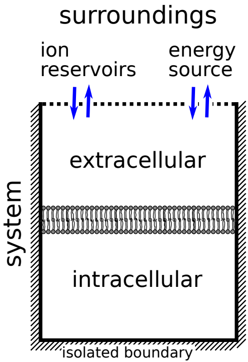
$$
\begin{aligned}
C\frac{\partial V}{\partial t} &= -I_{Na} - I_K - I_{leak} - I_{pump} + I_{app} \quad (1)\\
I_{Na} &= \bar{g}_{Na} m^3 h (V - E_{Na})\\
I_K &= \bar{g}_K n^4 (V - E_K)\\
I_{leak} &= g_{leak}(V - V_{rest})\\
\frac{\partial n}{\partial t} &= \alpha_n (1-n) - \beta n, \quad \frac{\partial h}{\partial t} \cdots \quad (2)-(4)\\
\frac{\partial [ion]_e}{\partial t} &= -\frac{A}{FVol_o} I_{ion}\\
\frac{\partial [ion]_i}{\partial t} &= \frac{A}{FVol_i} I_{ion} \qquad (5) - \cdots
\end{aligned}
$$

HH: Hodgkin-Huxley

The neuron in analogy to a heat engine

Four processes make up a spreading depression "cycle"





- Dreier et al., *Neuroscientist* **19**, (2012)
- Hübel et al., *PLOS Comp. Biology.* **10**, e1003551 (2014)
- Hübel & Dahlem, arXiv:1404.3031 (under review in *PLOS Comp. Biology*)

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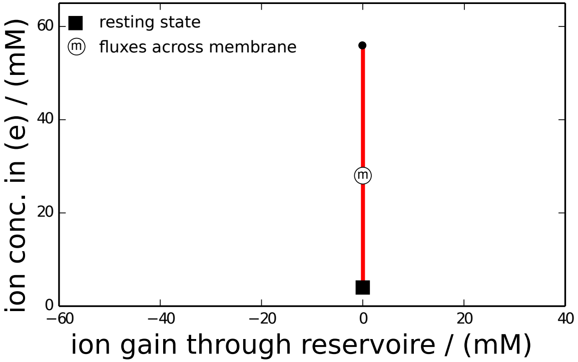

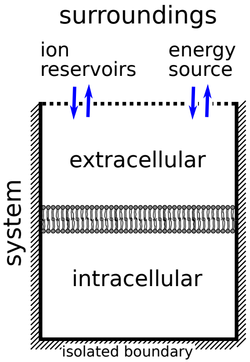

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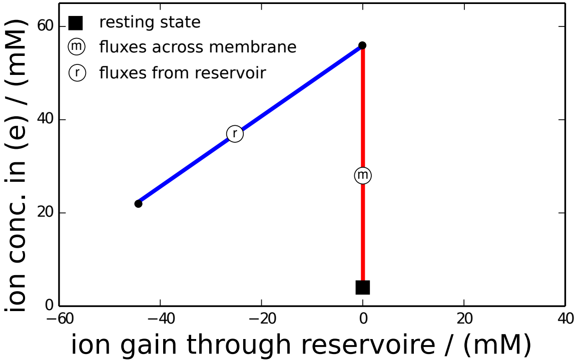

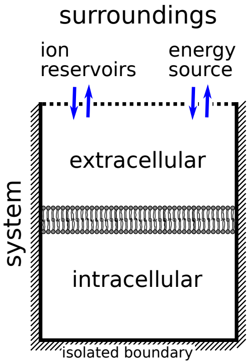

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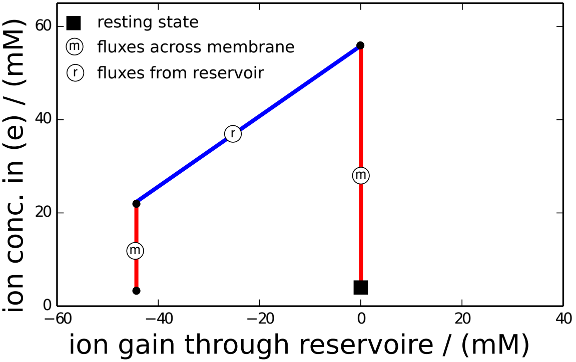

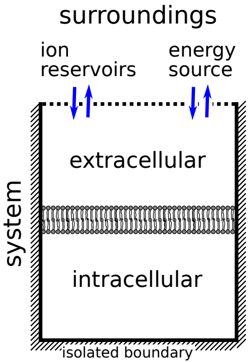

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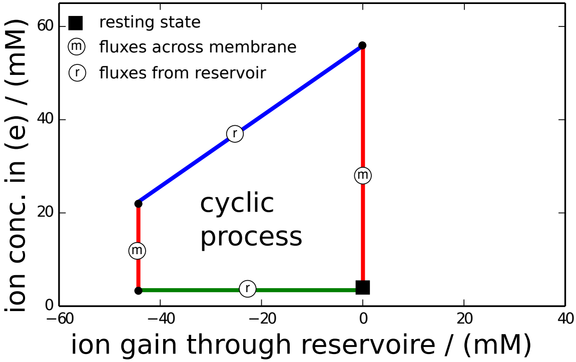

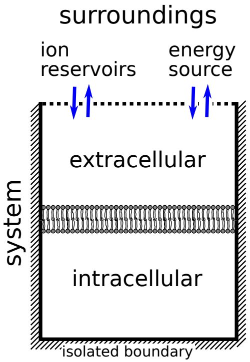

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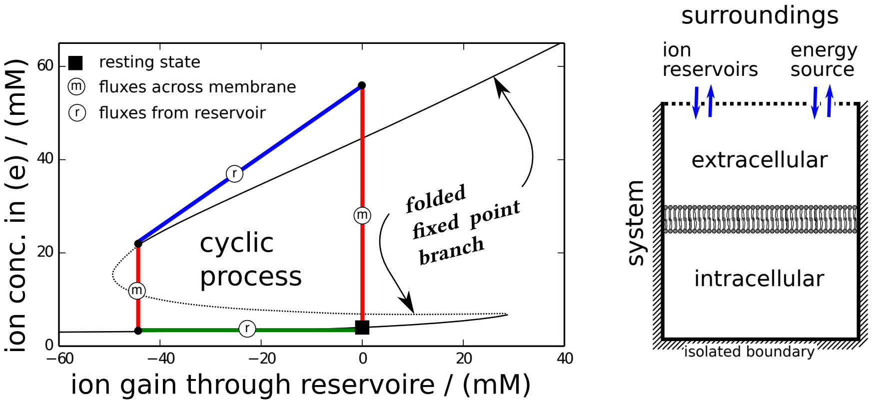

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Many, many, parameters, but most fixed by experiments

Table : Parameters for ion–based model – Part 2

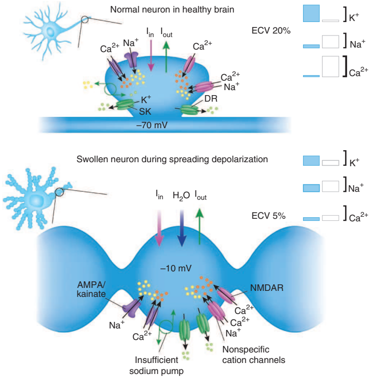
Name	Value & unit	Description
C_m	1 μF/cm^2	membrane capacitance
ϕ	3/msec	gating time scale parameter
g^l_{Na}	0.0175 mS/cm^2	sodium leak conductance
g^g_{Na}	100 mS/cm^2	max. gated sodium conductance
g^l_K	0.05 mS/cm^2	potassium leak conductance
g^g_K	40 mS/cm^2	max. gated potassium conductance
g^l_{Cl}	0.02 mS/cm^2	chloride leak conductance
Na^0_i	25.23 mM/l	intracell. sodium conc.
Na^0_e	125.31 mM/l	extracell. sodium conc.
K^0_i	129.26 mM/l	intracell. potassium conc.
K^0_e	4 mM/l	extracell. potassium conc.
Cl^0_i	9.9 mM/l	intracell. chloride conc.
Cl^0_e	123.27 mM/l	extracell. chloride conc.
E^0_{Na}	39.74 mV	sodium Nernst potential
E^0_K	-92.94 mV	potassium Nernst potential
E^0_{Cl}	-68 mV	chloride Nernst potential

Including cell swelling

Electrophysiology

break down of ion grandients

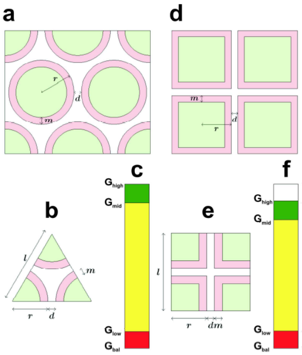
cell swelling



J.P. Dreier *Nature Medicine* **17** 2011

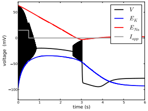
Thermodynamics

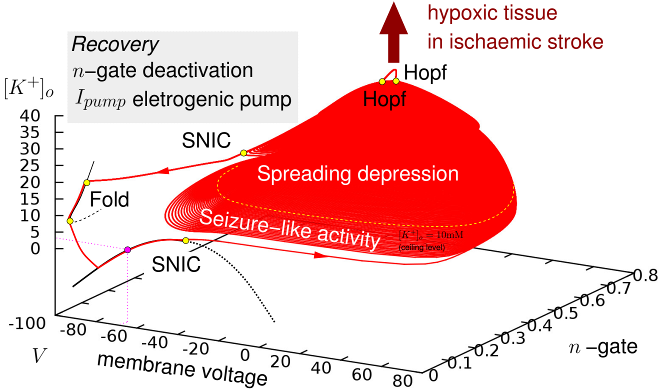
massive release of Gibbs free energy



J.P. Dreier et al. *Neuroscientist* **19** 2012

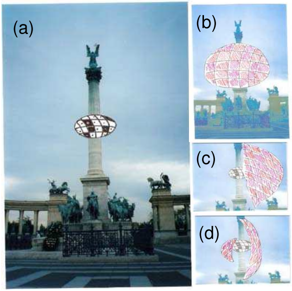
Modeling the migraine aura–ischemic stroke continuum



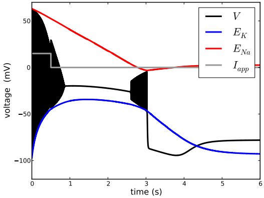


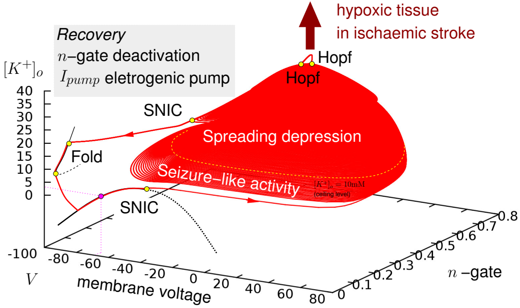
Modeling the migraine aura–ischemic stroke continuum

- Ischemia-induced migraine,
- Migrainous infarction,
- Persistent migraine w/o infarction (see below).



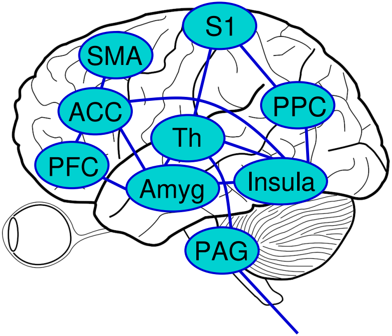
Dahlem et al. *Physica D* **239**, 889 (2010)



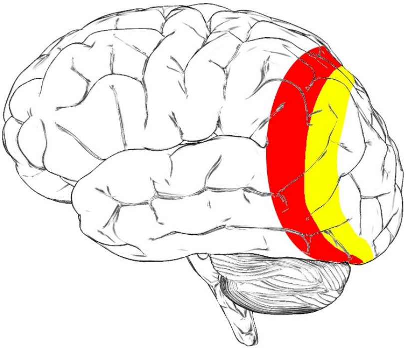


Mainly two neural theories of migraine

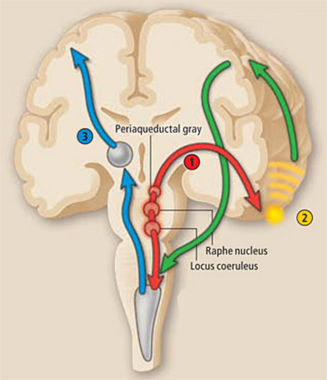
"Migraine generator"-theory

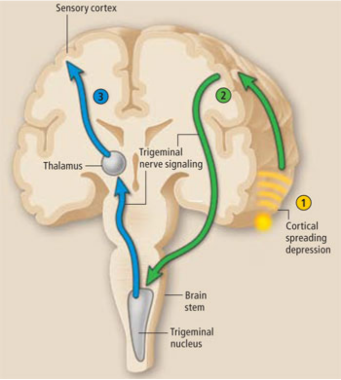


"Spreading depression"-theory



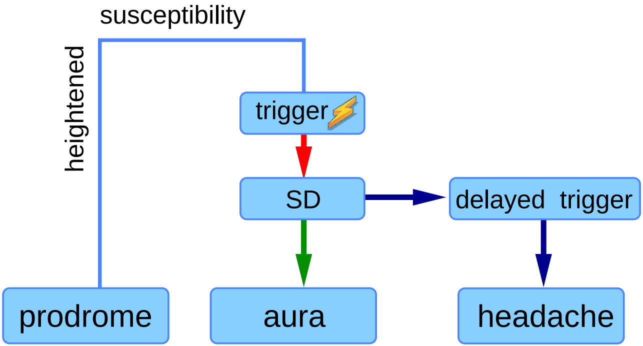
SD triggers trigeminal meningeal afferents, ie, headache





see e.g.: Bolay et al. *Nature Medicine* **8**, 2002
Review: Eikermann-Haerter & Moskowitz, *Curr Opin Neurol.* **21**, 2008
Figure: Dodick & Gargus *SciAm*, August 2008

Common etiology or 2 mechanisms in MWoA and MWA?



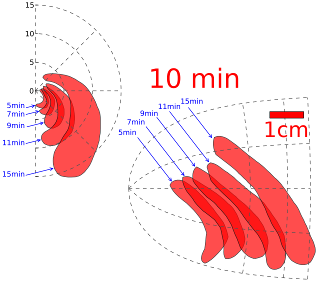
1. Only one upstream trigger?

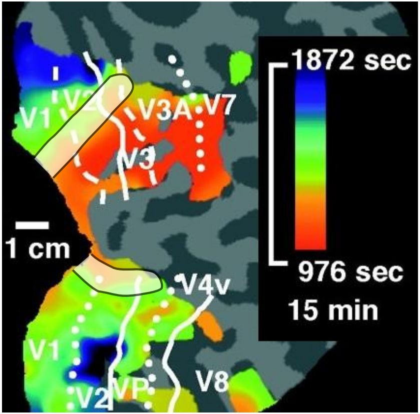
2. MWoA & MWA share same pain phase? **3.** Silent aura? **4.** Even prevalent?

5. Delayed headache link? **6.** Missing the pain phase?

SD: Spreading Depression, see next slide

SD does *not* curl-in in human cortex





Only about 2-10% but not 50% cortical surface area is affected!

right: modified from Hadjikhani et al. *PNAS* **98**:4687 (2001).

- Dahlem & Hadjikhani, *PLoS ONE*, **4**: e5007 (2009).

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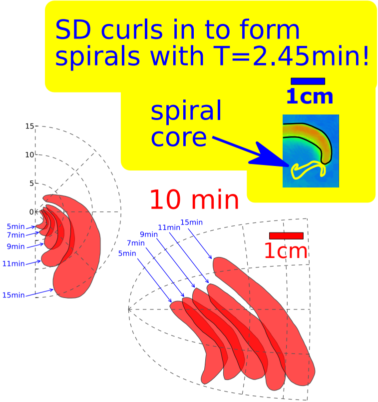

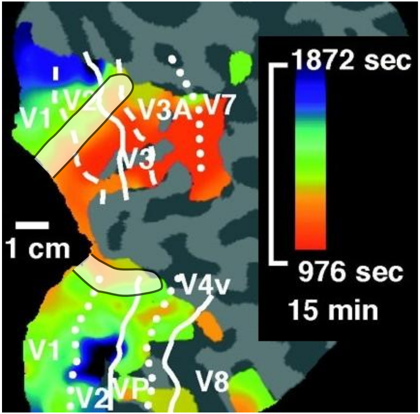

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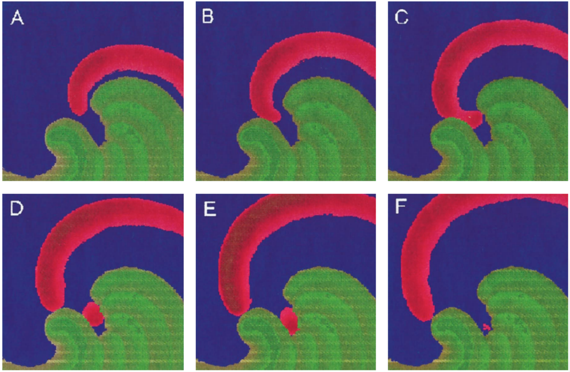
- Dahlem & Müller, *Exp. Brain Res.* **115**,319, (1997).

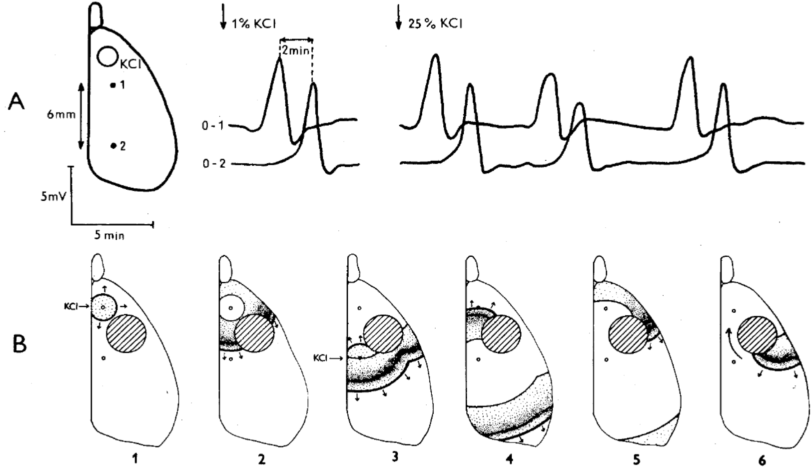
Re-entrant SD waves with functional block

Z-type rotation causes a wave break in the spiral core.



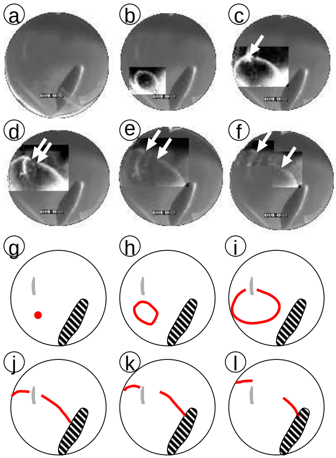
Dahlem & Müller (1997) *Exp. Brain Res.* **115**:319

Re-entrant SD waves with anatomical block



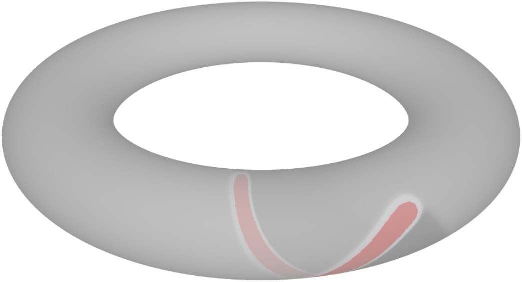
Reshodko, L. V. and Bureš, J *Biol. Cybern.* **18**,181 (1975)

Drugs adjust excitability:retracting & collapsing waves

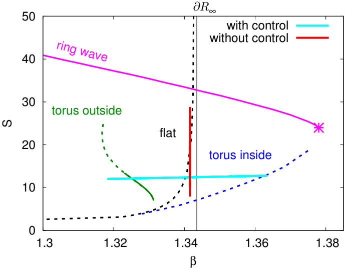


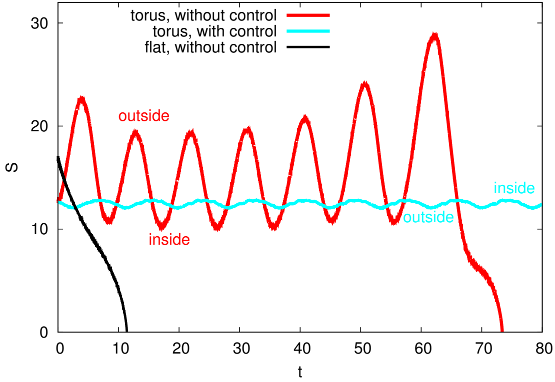
Dahlem et al. *2D wave patterns ...* . (2010) *Physcia D*

Nucleation failure on torus



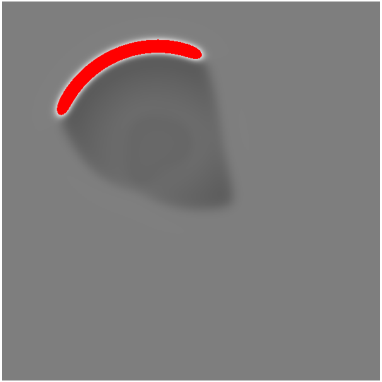
Transient times in flat and curved geometry



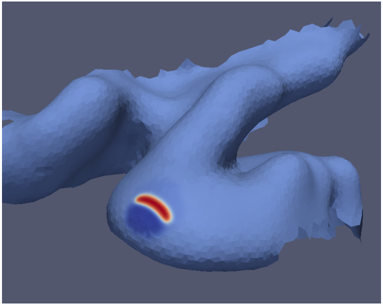


Simulation of transient SD wave segment

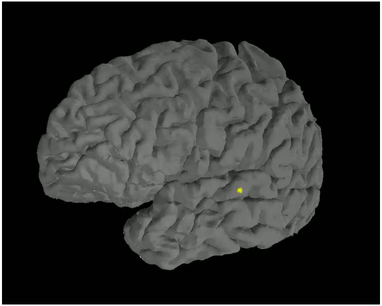
gray = cortical surface; red = SD wave



Simulation of an engulfing SD wave

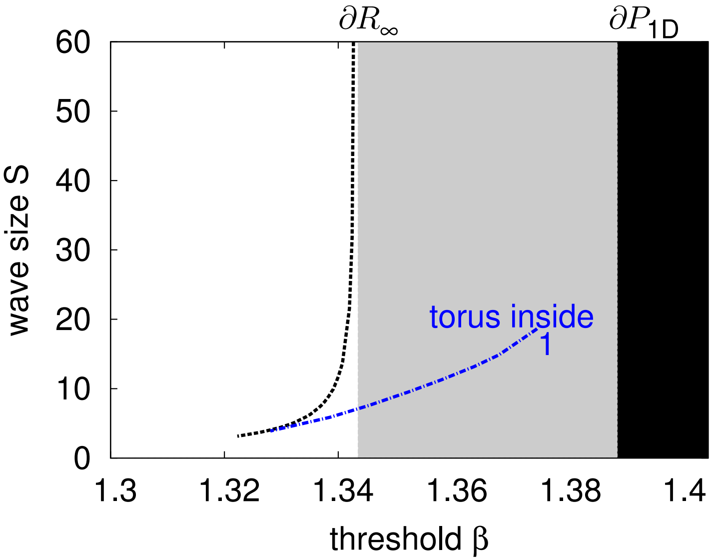


In cooperation with Bernd Schmidt, Magdeburg

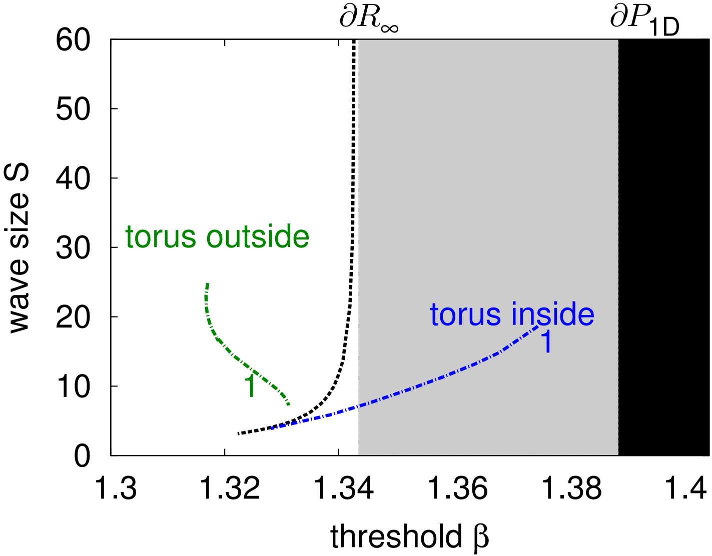


In cooperation with Jens Dreier & Denny Milakara, Charité

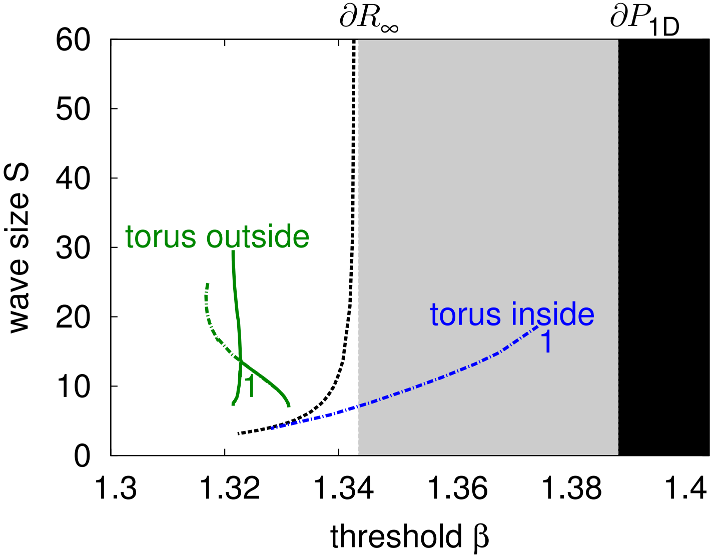
Minimum threshold in a flat geometry



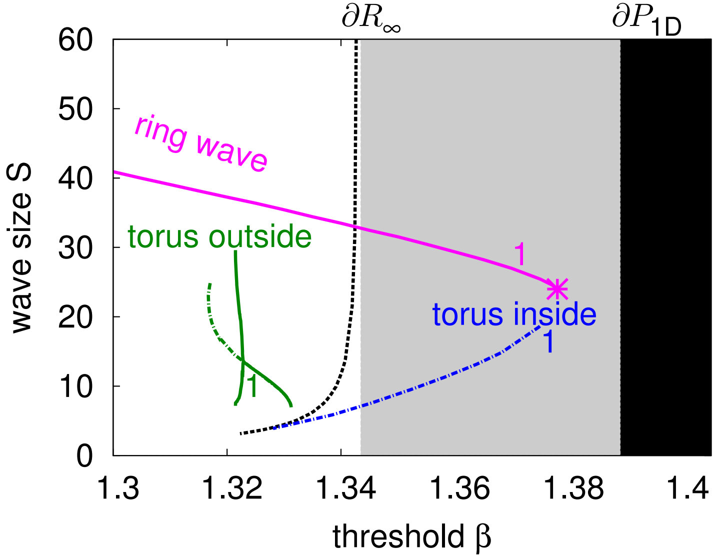
Minimum threshold in a flat geometry



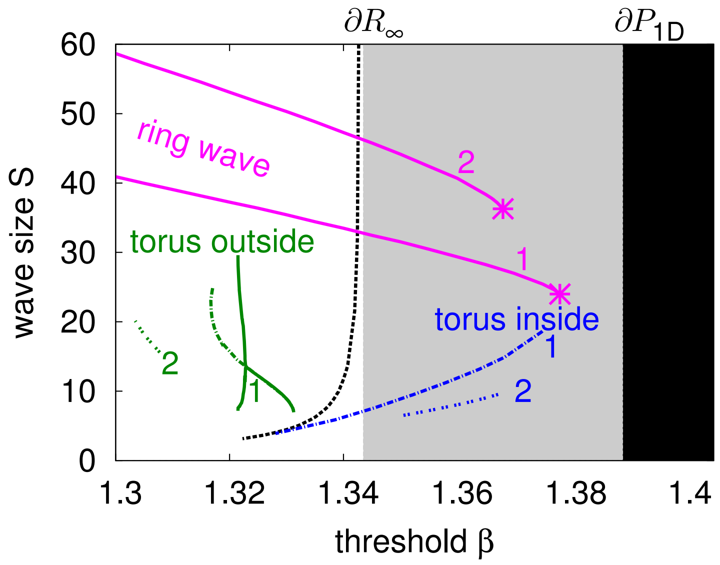
Minimum threshold in a flat geometry



Minimum threshold in a flat geometry

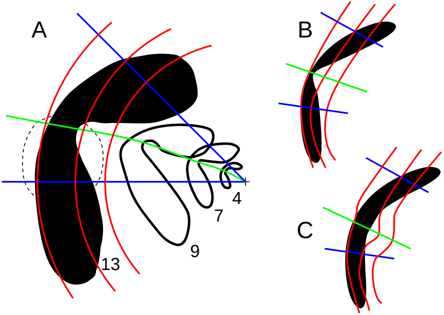


Minimum threshold in a flat geometry



Migraine scotoma reveal functional properties

Pattern matching



- Dahlem & Tusch, *J. Math Neuroscie.* **2**,14 (2012)

Migraine scotoma reveal functional properties

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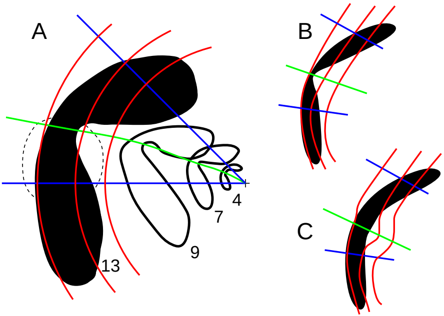
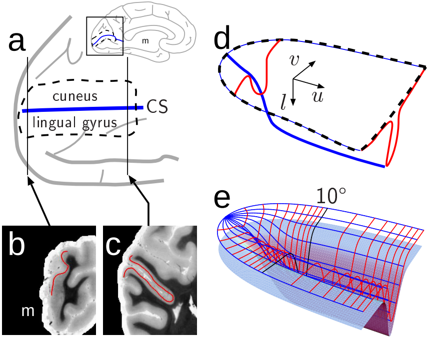


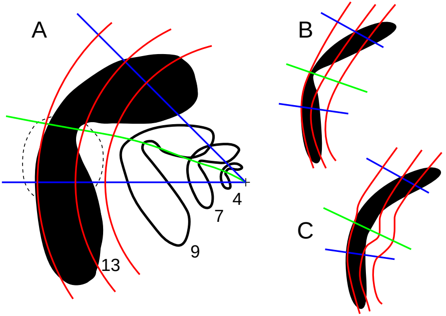
"Curved" retinotopic mapping



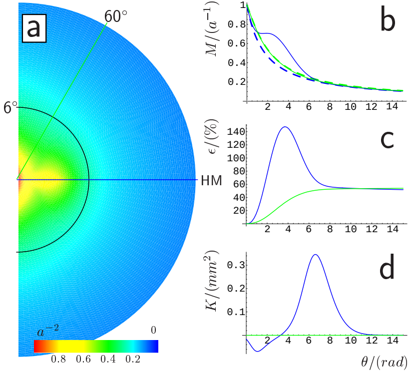
- Dahlem & Tusch, *J. Math Neuroscie.* **2**,14 (2012)

Migraine scotoma reveal functional properties

Pattern matching



"Curved" retinotopic mapping



- Dahlem & Tusch, *J. Math Neuroscie.* **2**,14 (2012)