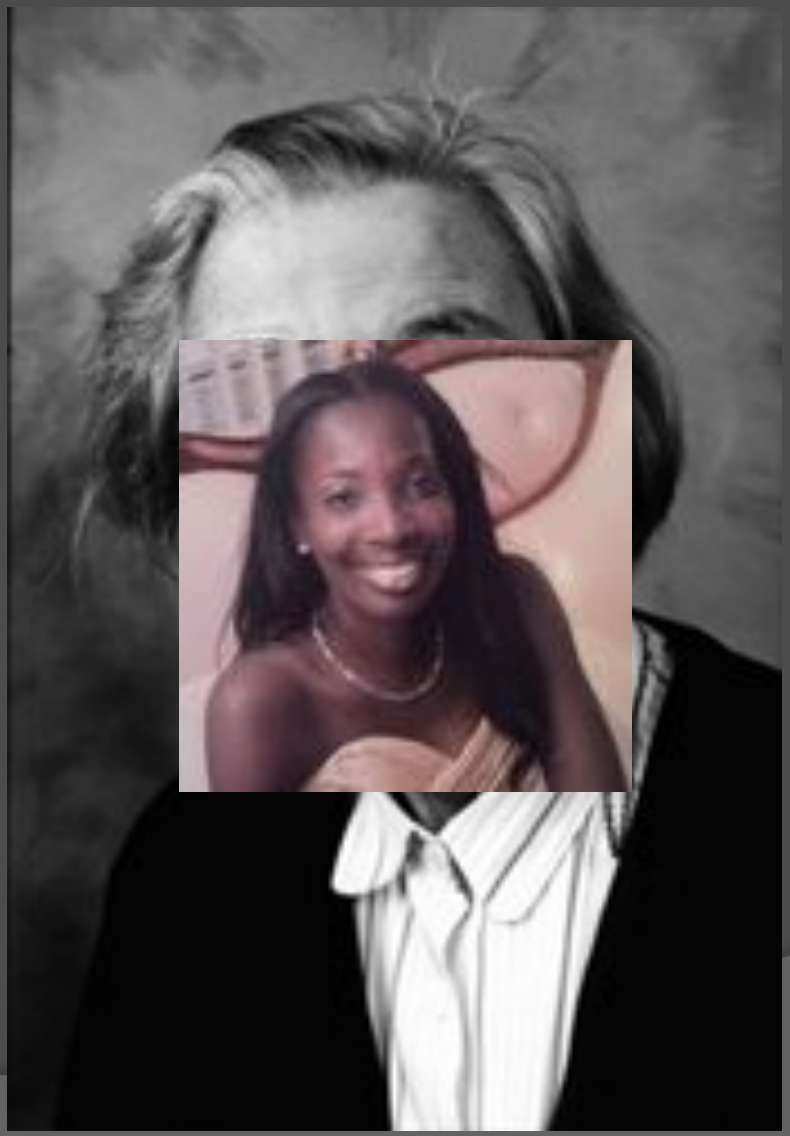
Wim Mulleners
Canisius-Wilhelmina Hospital Nijmegen

CORTICAL DYSEXCITABILITY

Science and semantics

Conflicts of interest

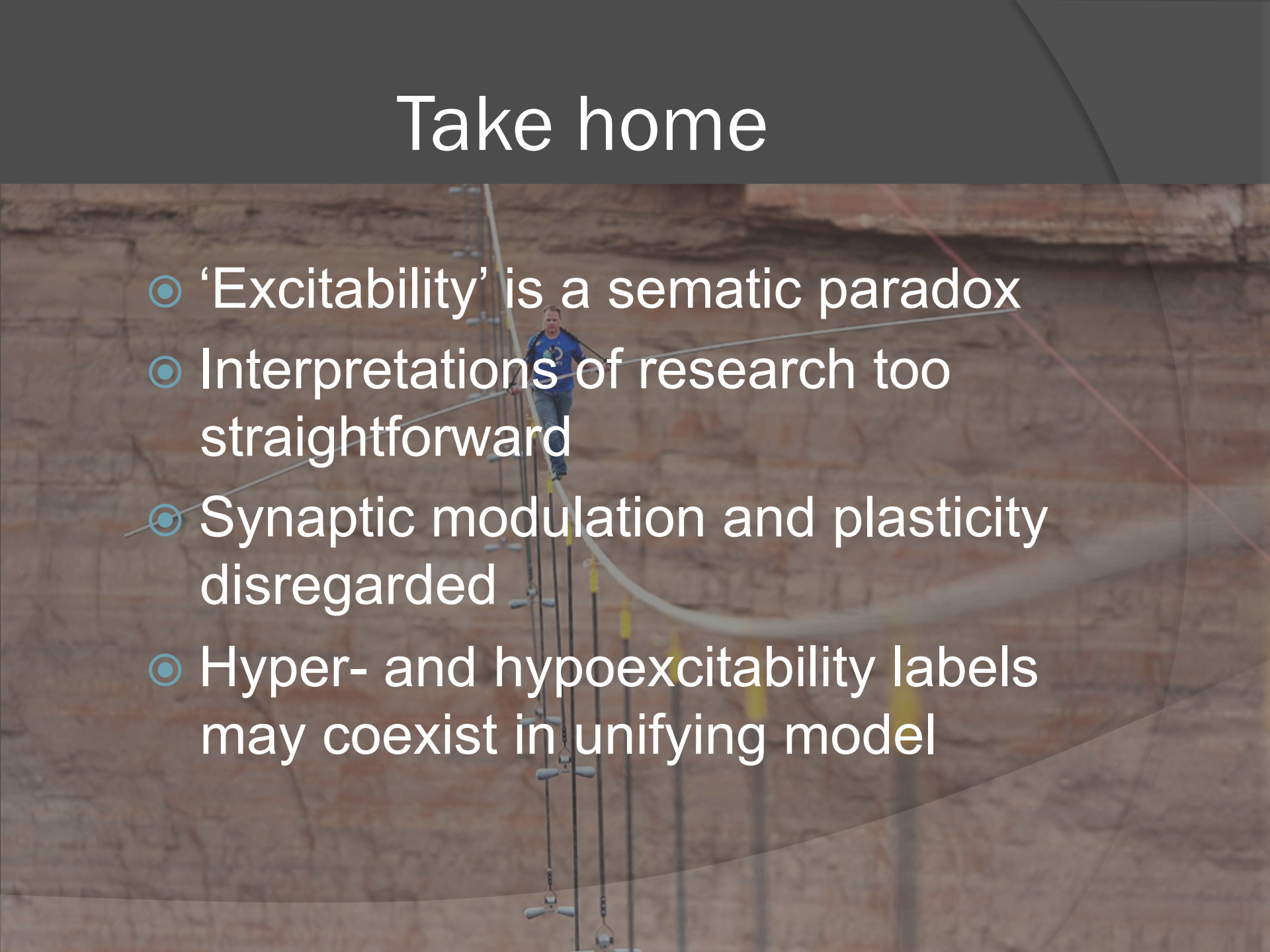
Marcia Wilkinson Lecture



Hypo- or hyperexcitable?

Take home

Take home



- ‘Excitability’ is a sematic paradox
- Interpretations of research too straightforward
- Synaptic modulation and plasticity disregarded
- Hyper- and hypoexcitability labels may coexist in unifying model

Outline

- Review of spreading depression
- Psychophysical evidence
- Neurophysiological evidence
- Neurobiological evidence
- Conclusions

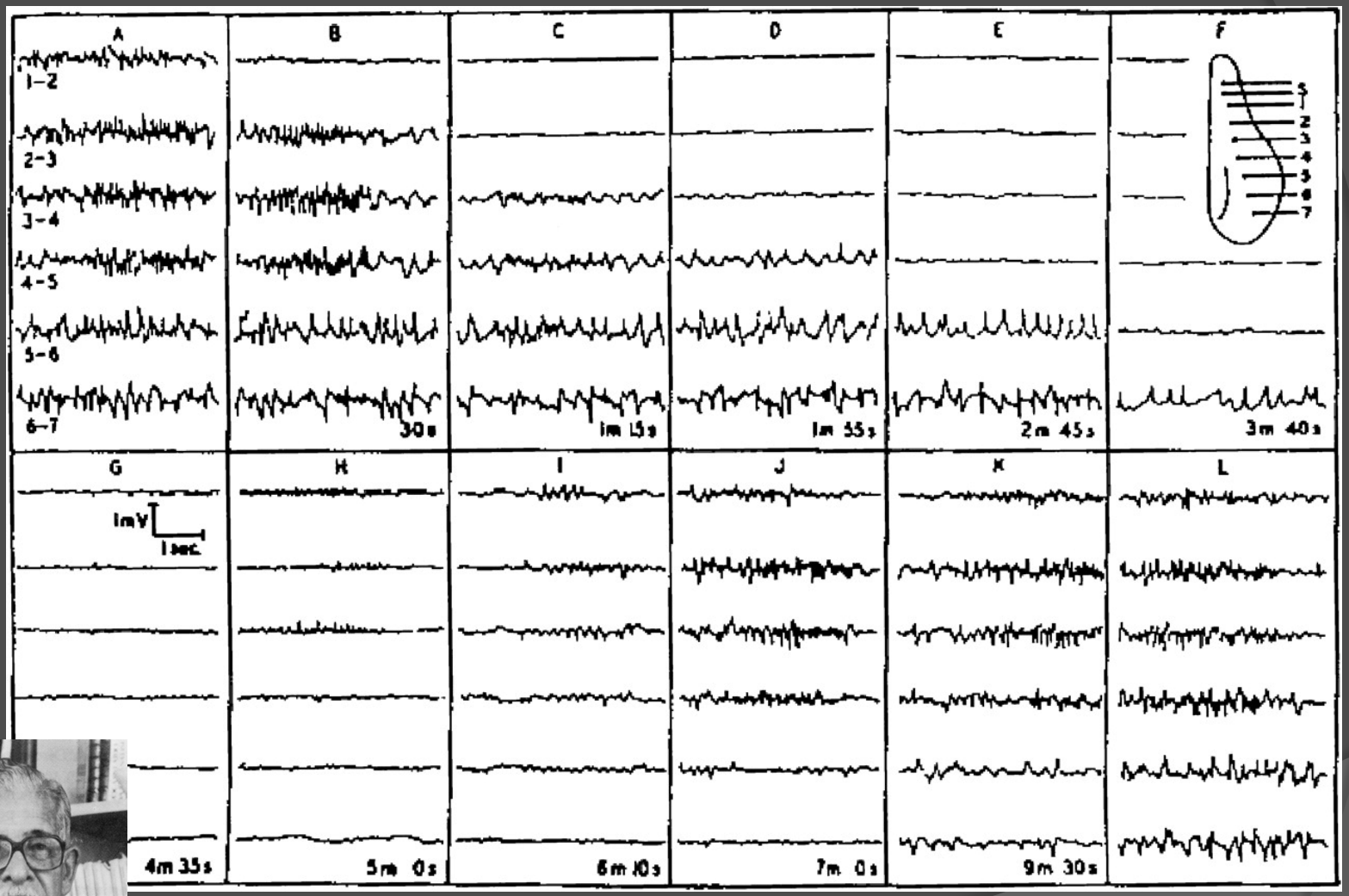
Who cares?

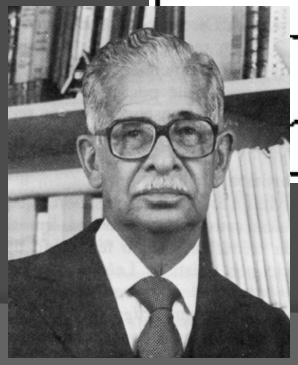
Headache 0733–8619/90 $0.00 + .20

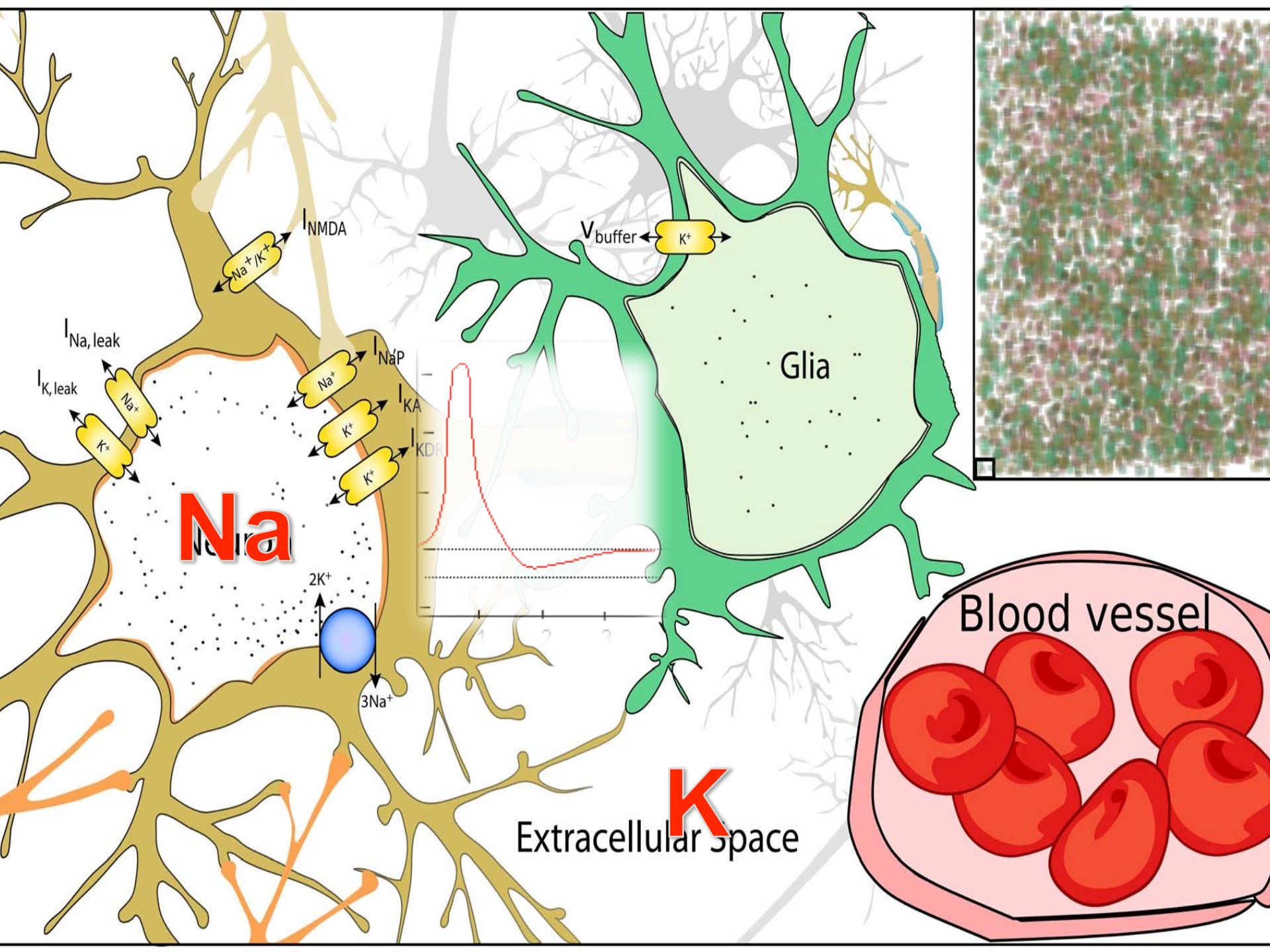
The Concept of Migraine as a State of Central Neuronal Hyperexcitability

K. M. A. Welch, MD, G. D'Andrea, MD,†*
N. Tepley, PhD,‡ G. Barkley, MD,§
and N. M. Ramadan, MD ¶

Leão's original illustration of spreading depression.



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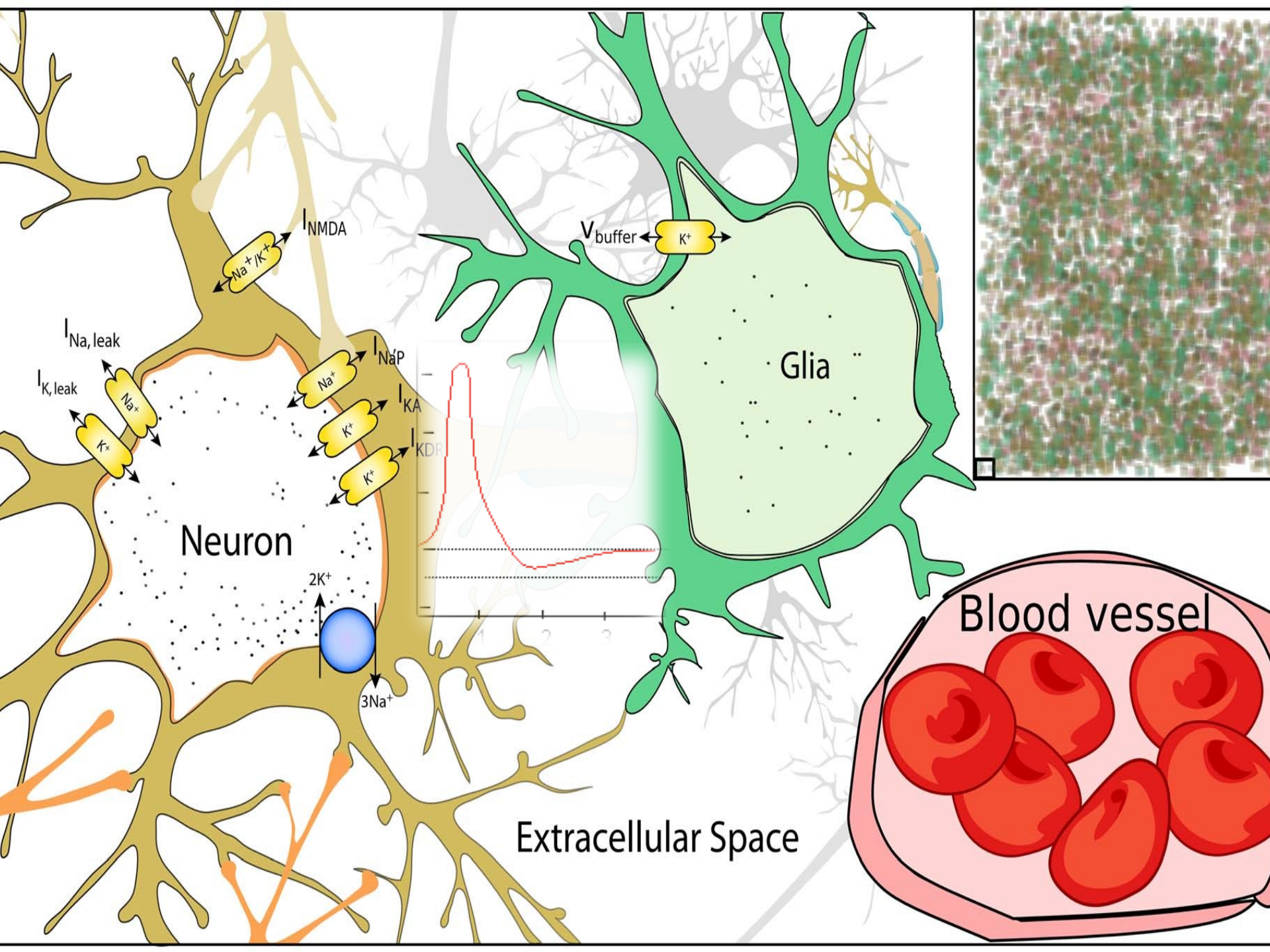
Na^+/K^+
$I_{Na, leak}$
$I_{K, leak}$
Na^+
K^+
I_{NaP}
I_{KA}
I_{KDR}
V_{buffer}
K^+
Glia
Na
$2K^+$
$3Na^+$
K
Extracellular Space
Blood vessel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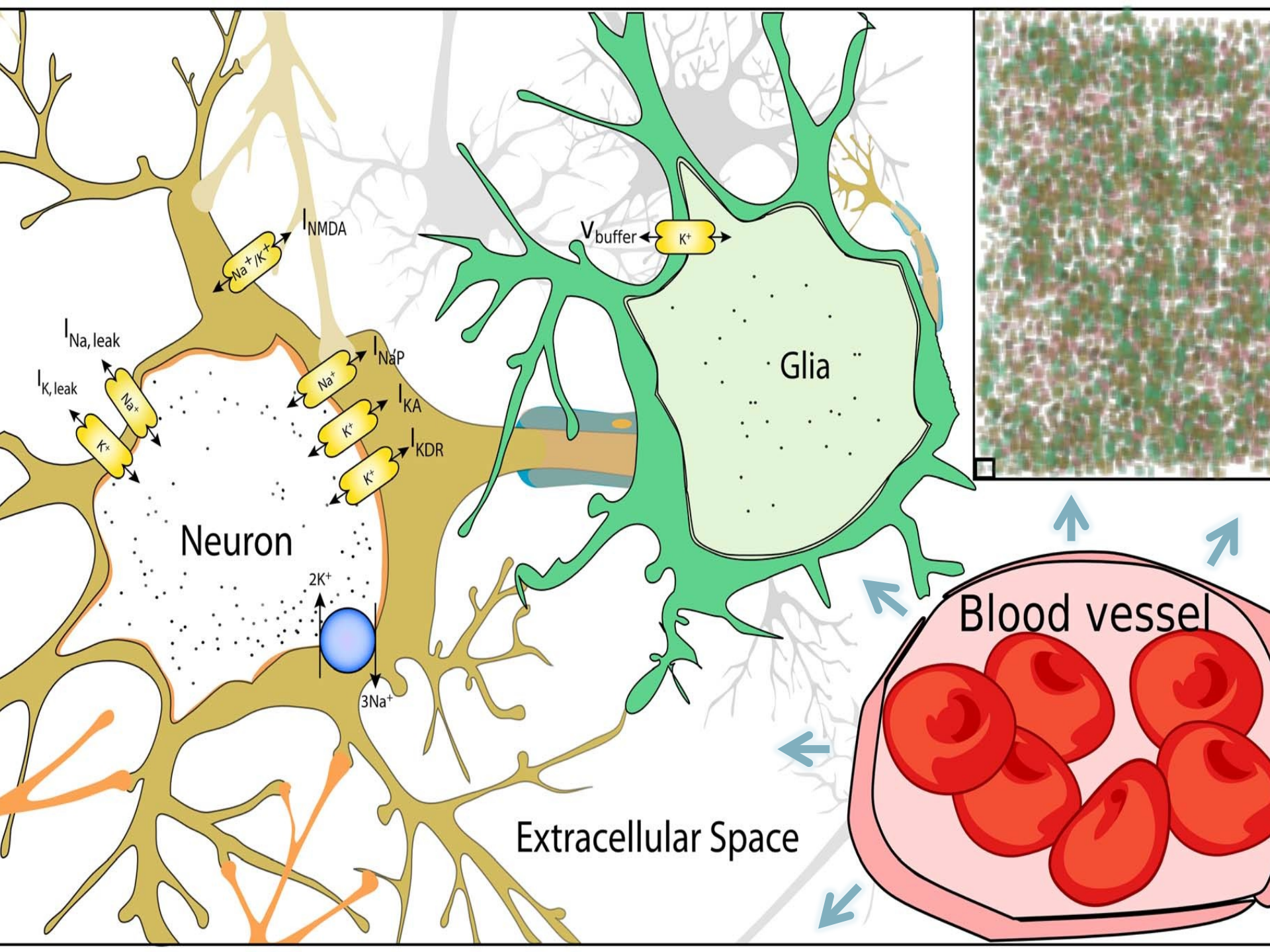
$I_{Na, leak}$
$I_{K, leak}$
Na^+
K^+
I_{NaP}
I_{KA}
I_{KDR}
Neuron
$2K^+$
$3Na^+$
V_{buffer}
K^+
Glia
Blood vessel
Extracellular Space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$I_{K, leak}$
Na^+
K^+
I_{NaP}
I_{KA}
I_{KDR}
Neuron
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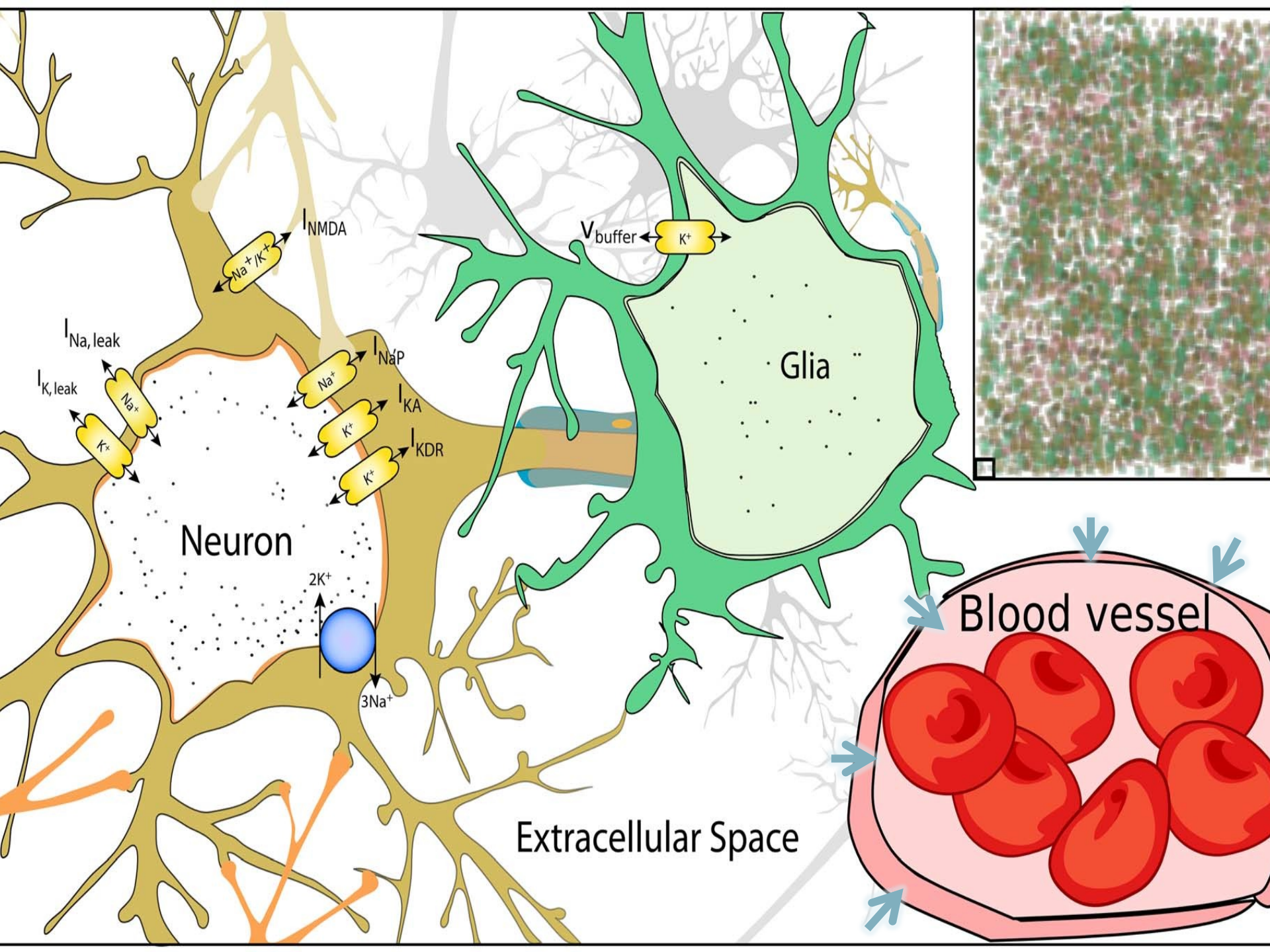
K^+
Glia
Blood vessel
Extracellular Space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$I_{Na, leak}$
$I_{K, leak}$
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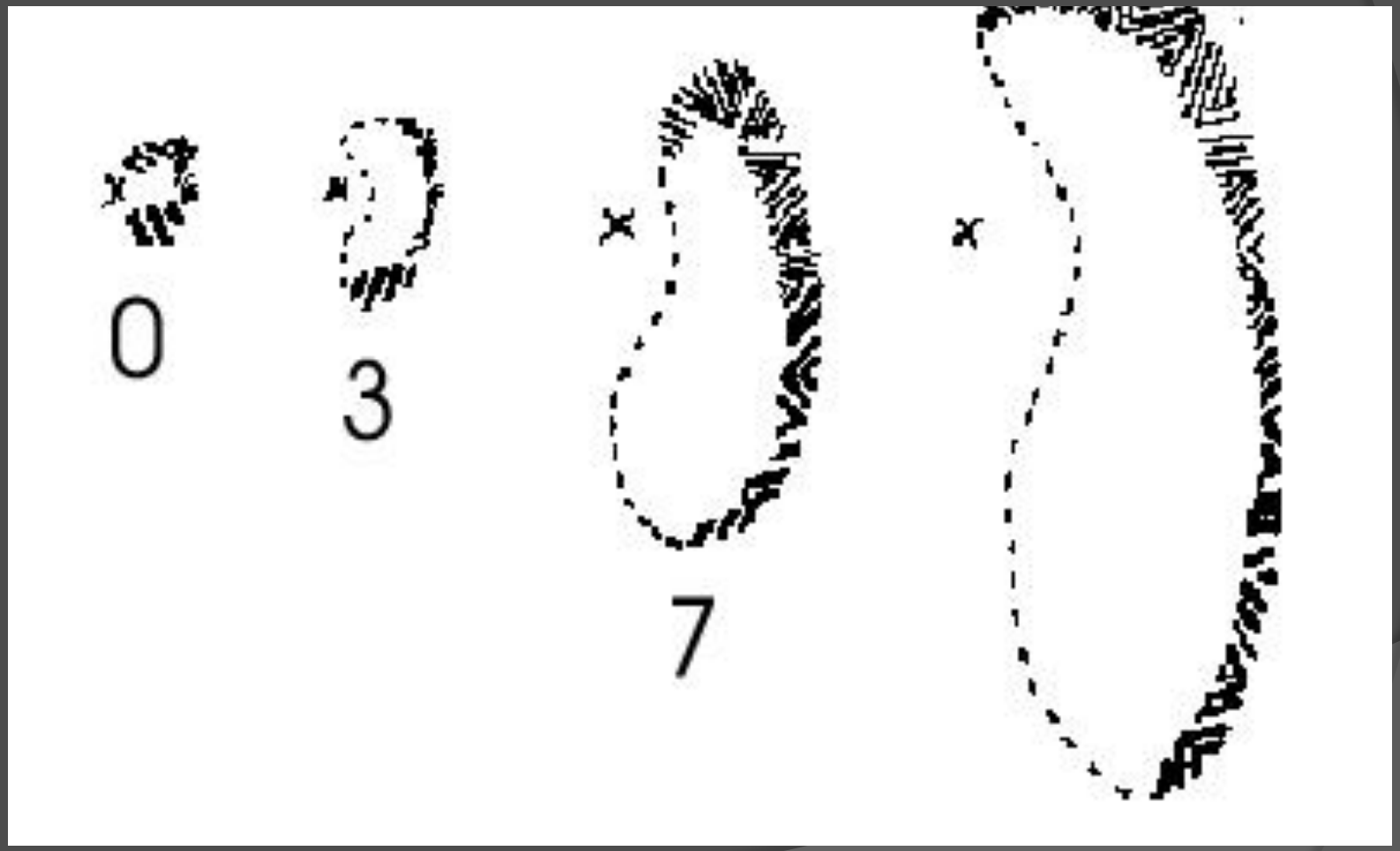
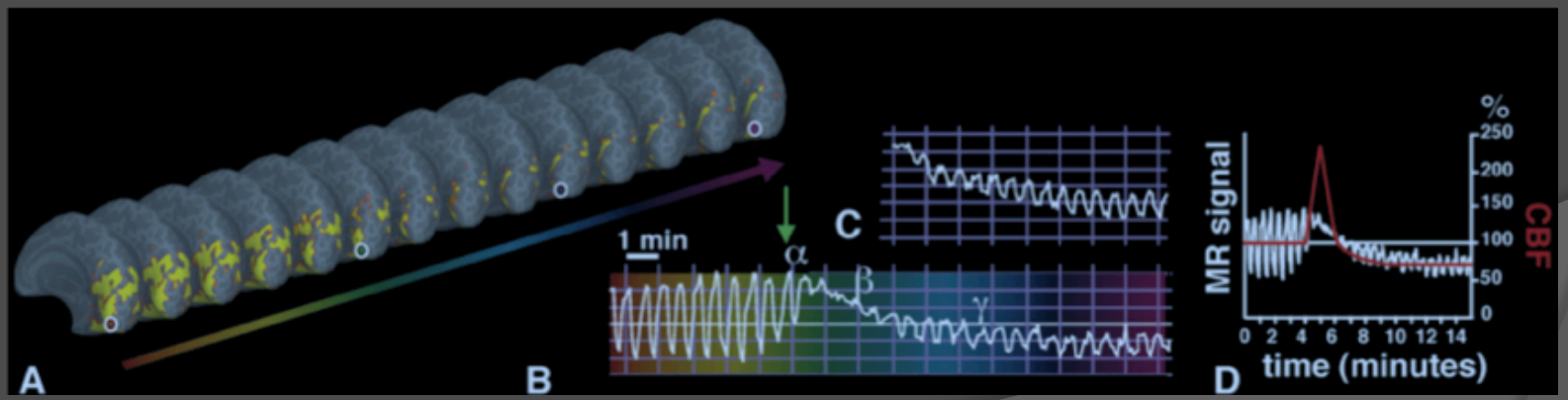
K^+
I_{NaP}
I_{KA}
I_{KDR}
Neuron
$2K^+$
$3Na^+$
V_{buffer}
K^+
Glia
Blood vessel
Extracellular Space

Milner



Spreading oligaemia

Olesen 1981



Hadjikhani 2001

MEG

- Prolonged DC shifts comparable to SD-eperimental MEG-changes
- Prolonged attenuation of spontaneous activity
- Large amplitude waves representing spontaneous neural depolarizations

MEG

- Prolonged DC shifts comparable to SD-eperimental MEG-changes
- Prolonged attenuation of spontaneous activity
- Large amplitude waves representing spontaneous neural depolarizations

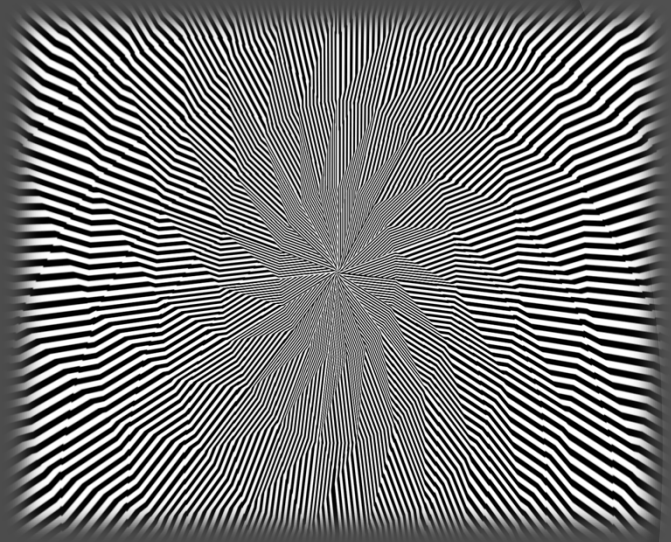
CSD

MEG

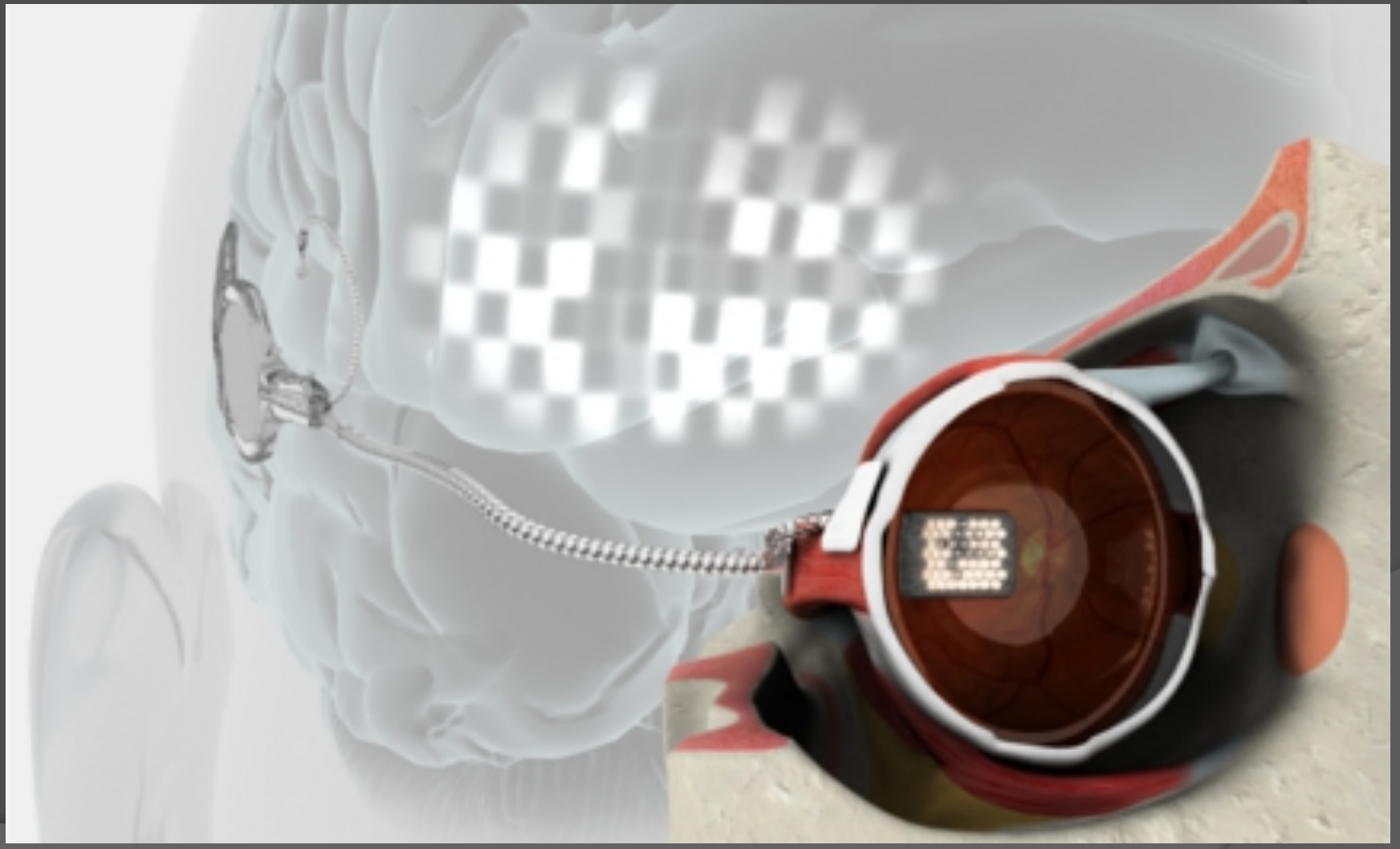
- Prolonged DC shifts comparable to SD-eperimental MEG-changes
- Prolonged attenuation of spontaneous activity
- Large amplitude waves representing spontaneous neural depolarizations

HYPEREXCITABILITY

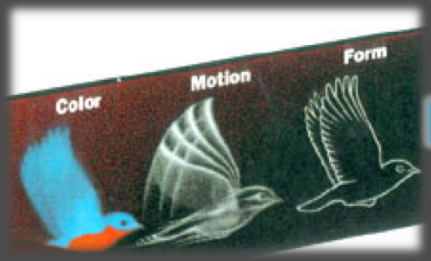
Visual stress

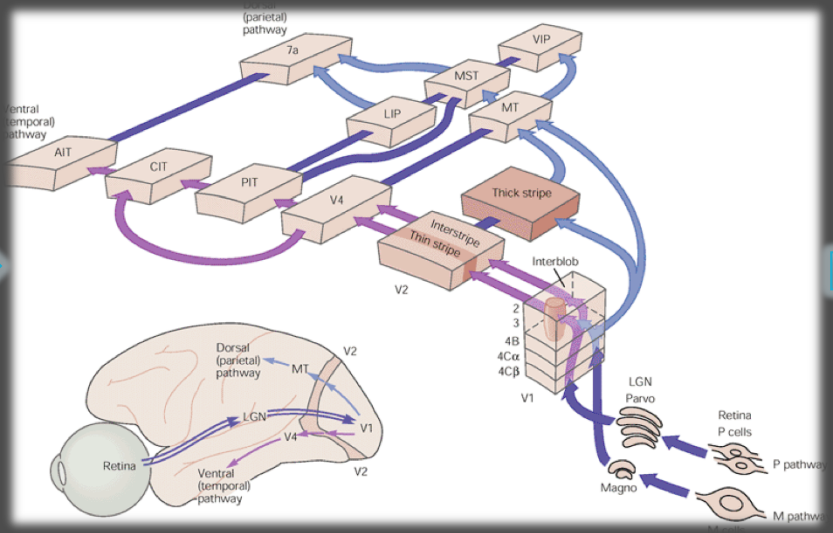


Visual psychophysics



Visual processing





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Baker
Research
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Binocular
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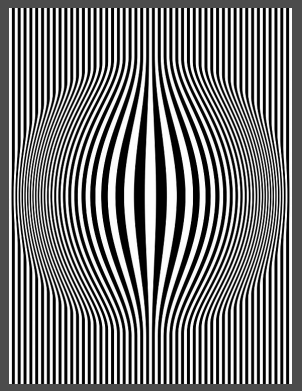
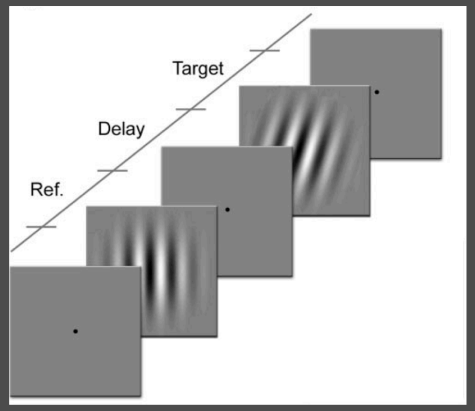
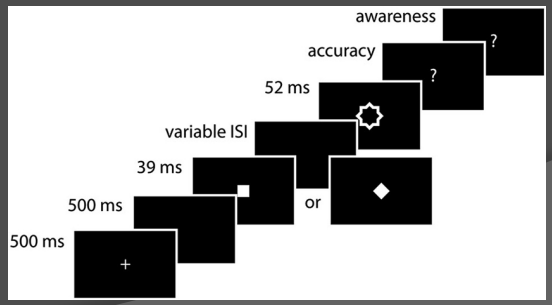
image
level

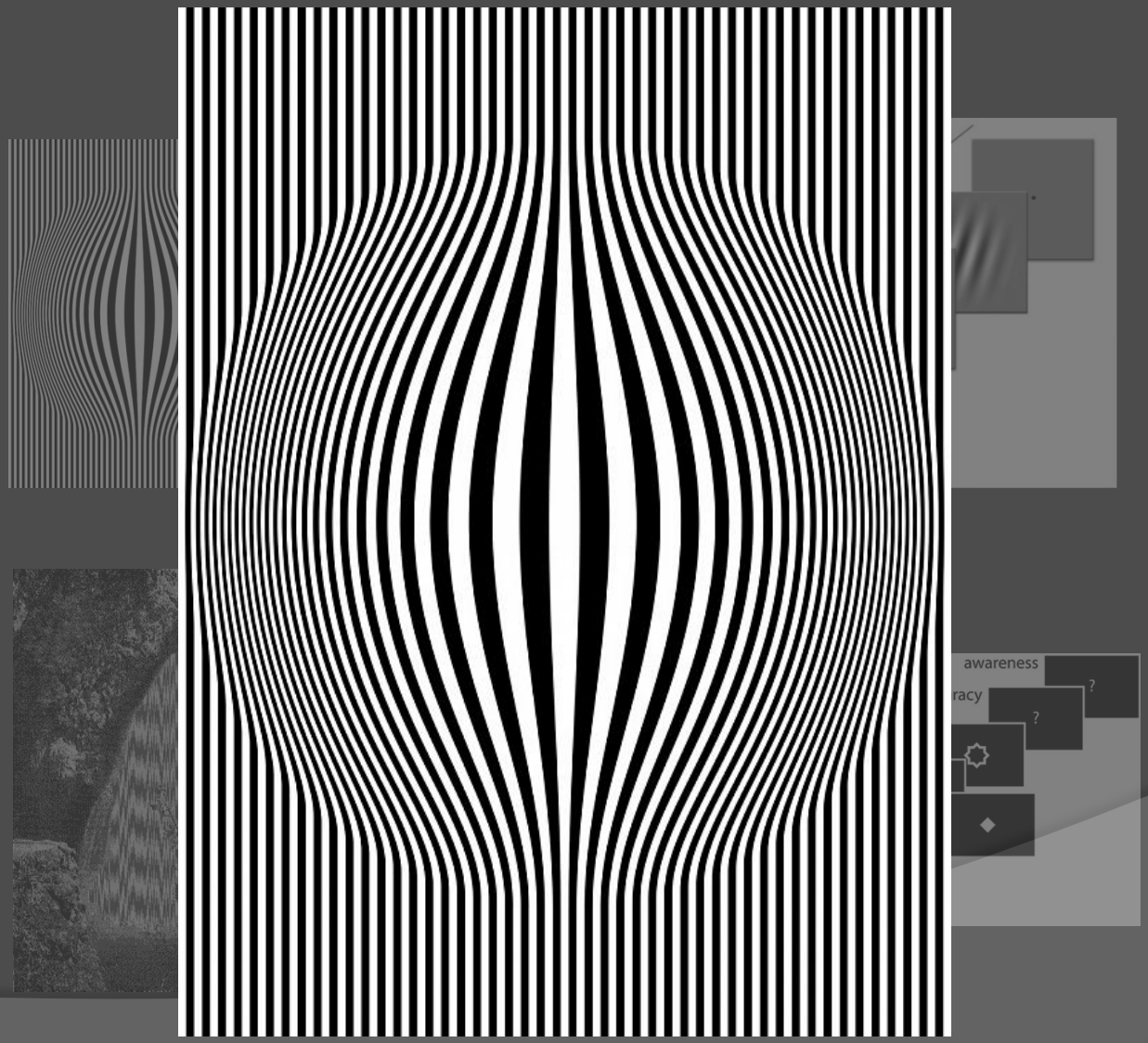
Psychophysical paradigms



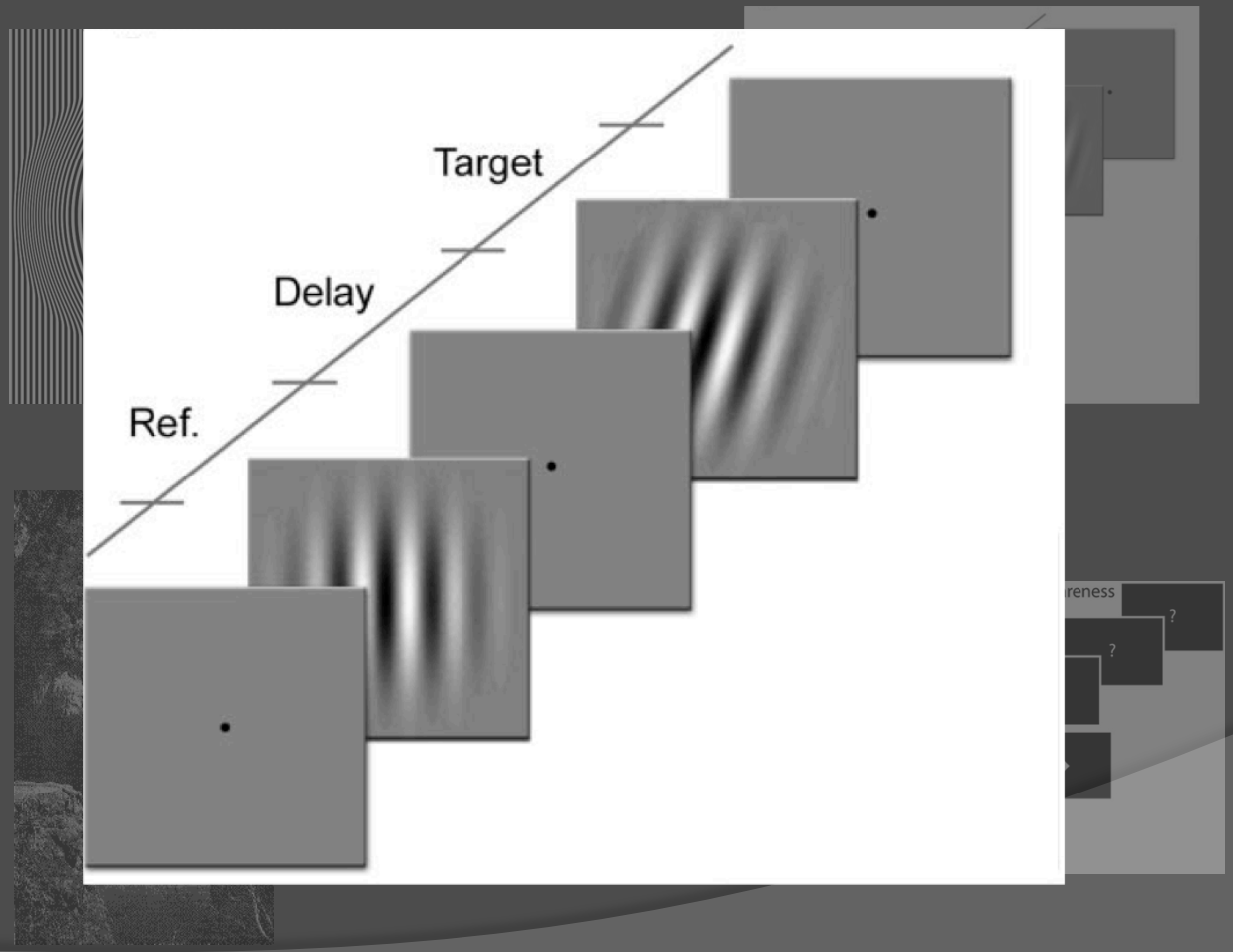




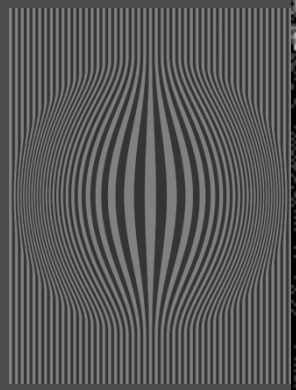
Psychophysical paradigms

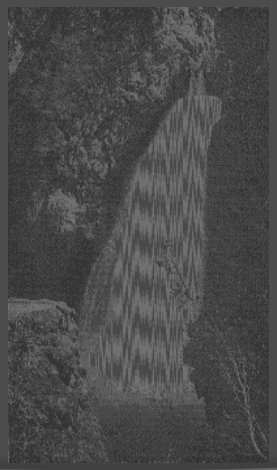


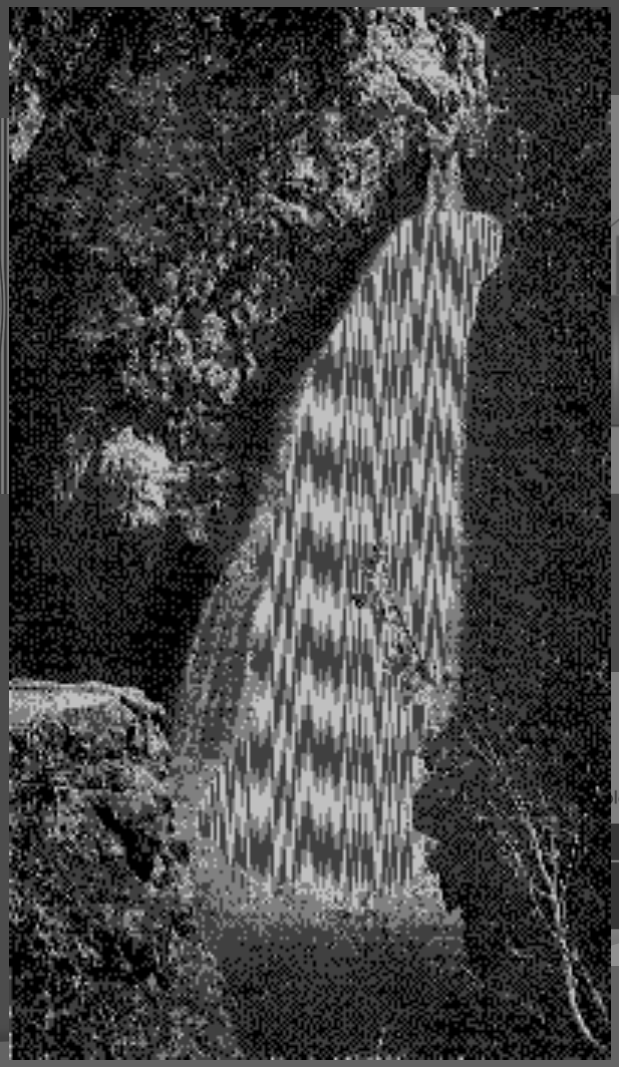
Psychophysical paradigms

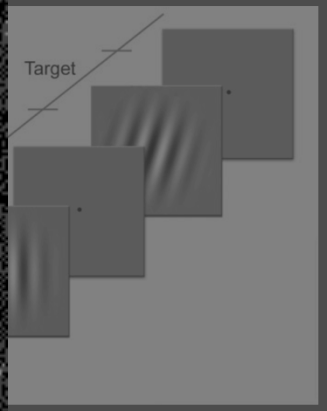


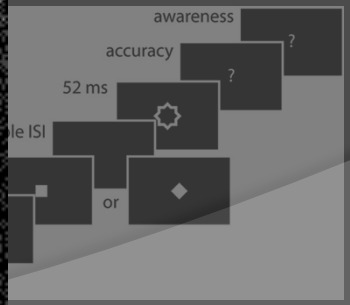
Psychophysical paradigms



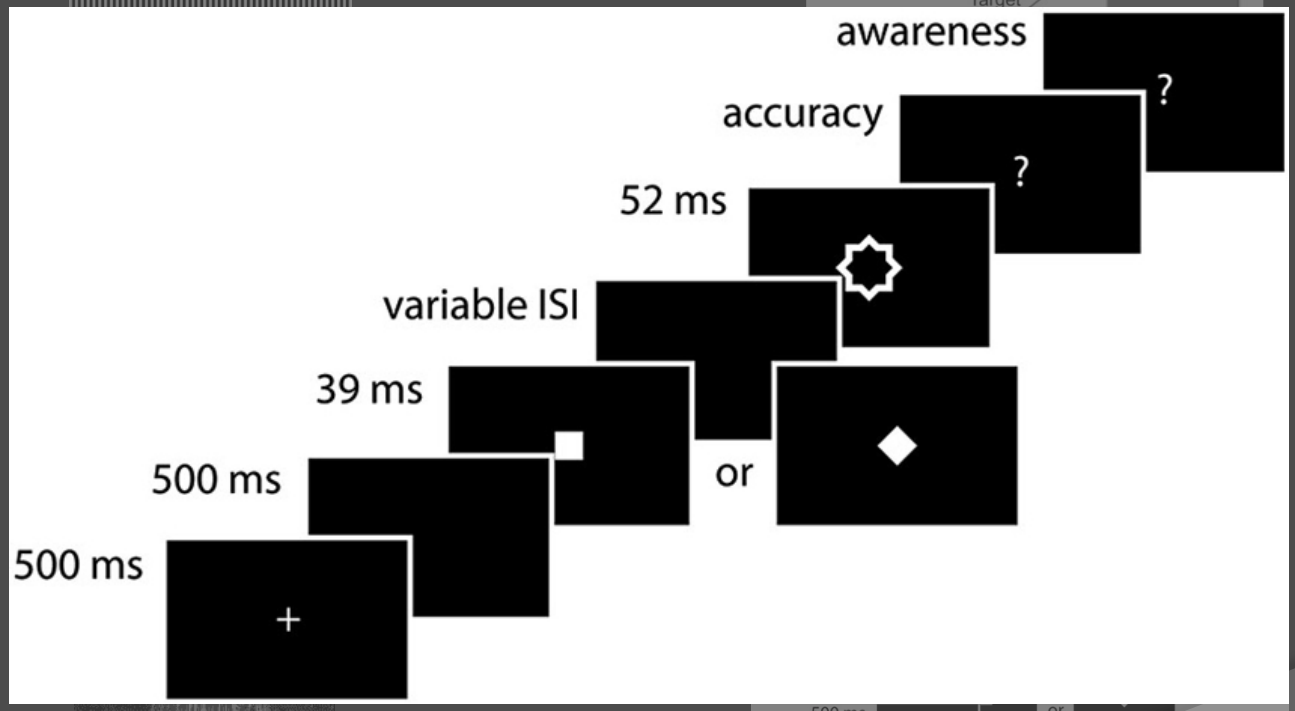








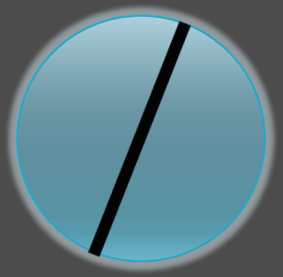
Psychophysical paradigms

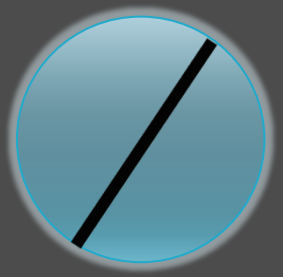


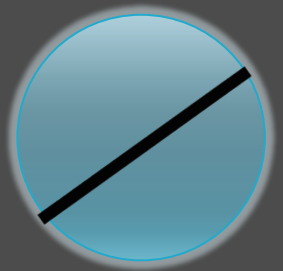
Summary

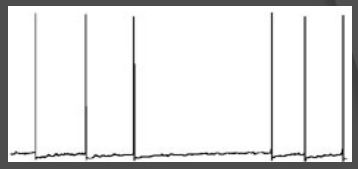
Current psychophysical studies are unable to catch enhanced visual responsiveness under one header of hyper- or hypoexcitability, or impaired inhibition

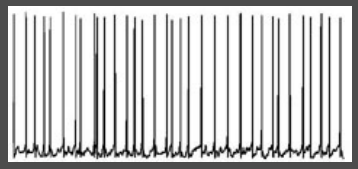
Narrow-band tuning

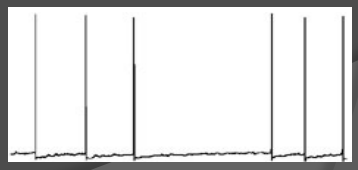






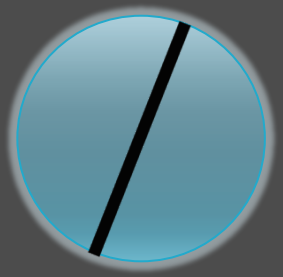


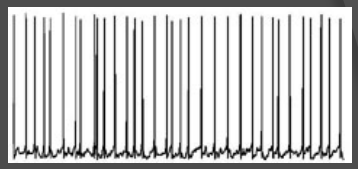


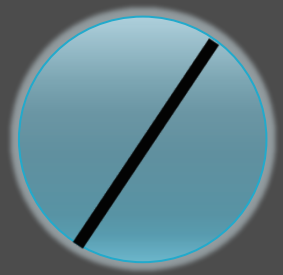


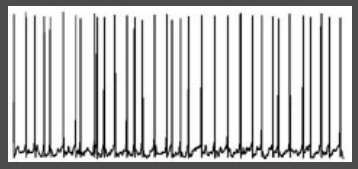
Discrimination high

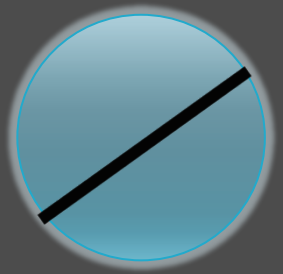
Broad-band tuning

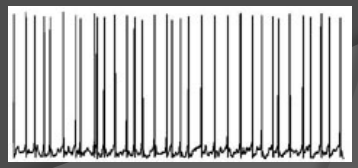












Discrimination low

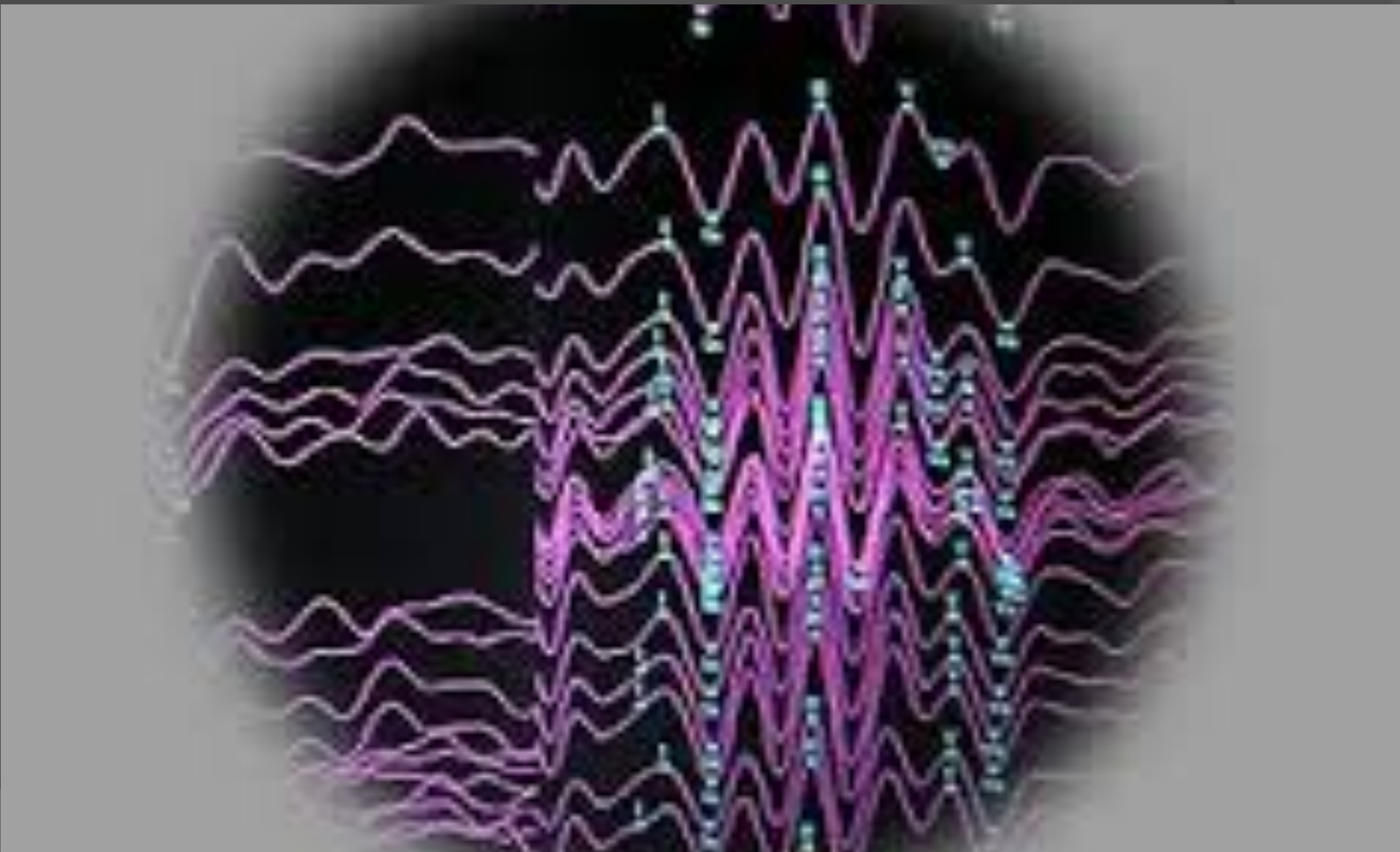
Regional excitability differences & predicted outcomes

Affected population	*Hyperexcitable*		*Hypoexcitable*	
	SNR	*Outcome*	*SNR*	*Outcome*
Proportional change	-	-	-	-
Non-target > target	<	DET: < DISC: <	>	DET: > DISC: <
Target > non-target	>	DET: > DISC: <	<	DET: < DISC: <

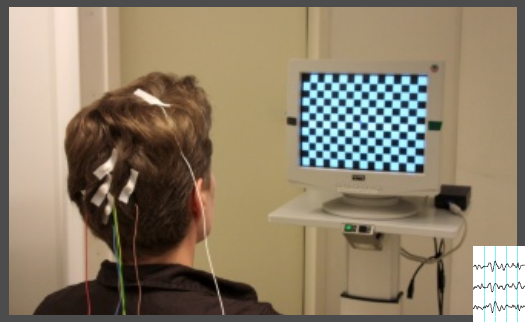
Conclusion

- Psychophysics does not allow solid inferences on excitability without knowing the differential effects on the various neuronal populations
- Short-term and long-term dynamics of synaptic function needs to be taken into account

Neurophysiology



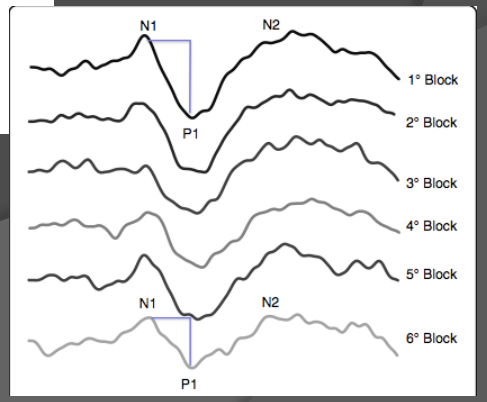
Evoked potentials



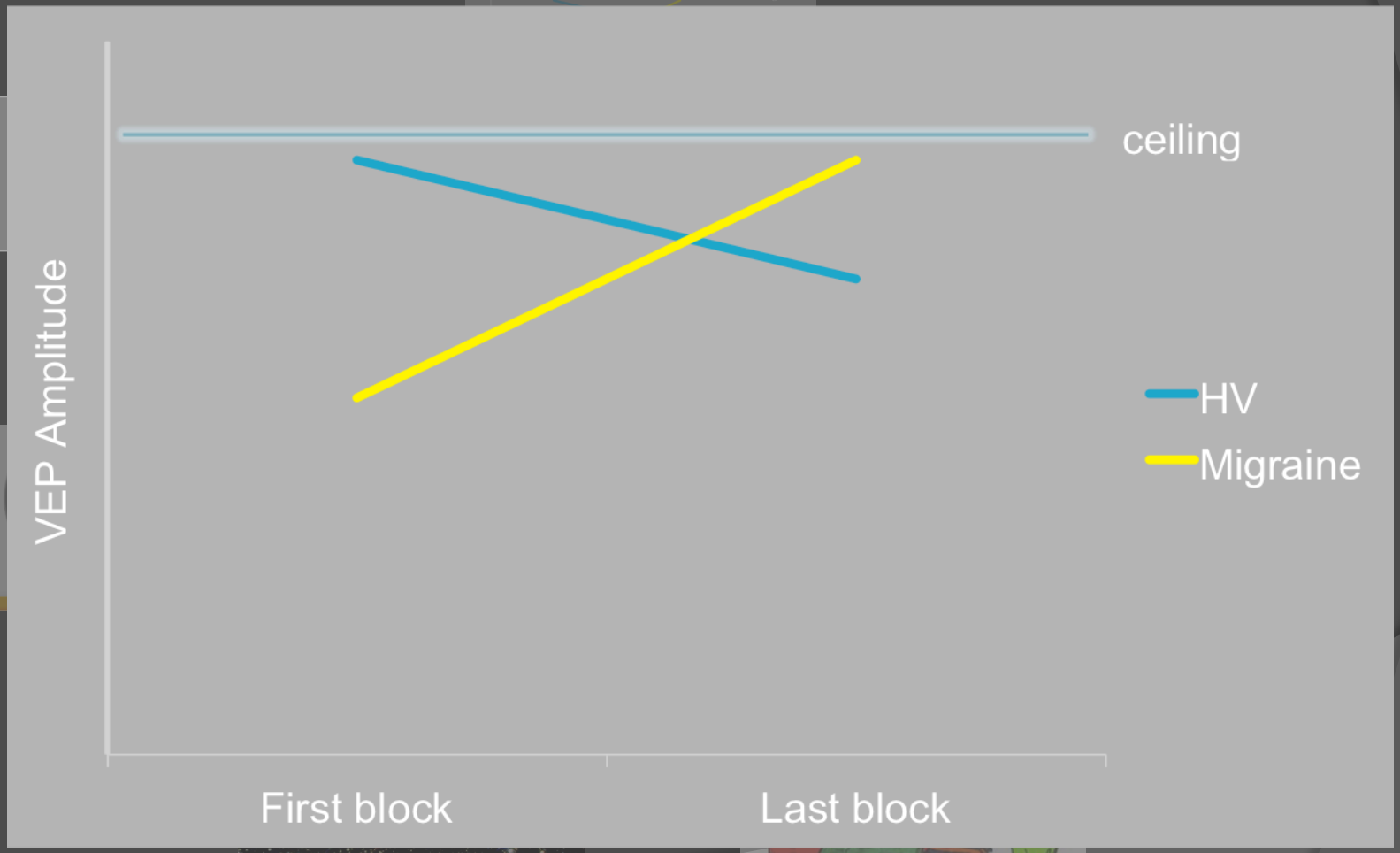
Averaging

&

Filtering

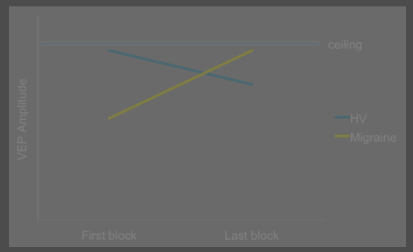


Ceiling theory

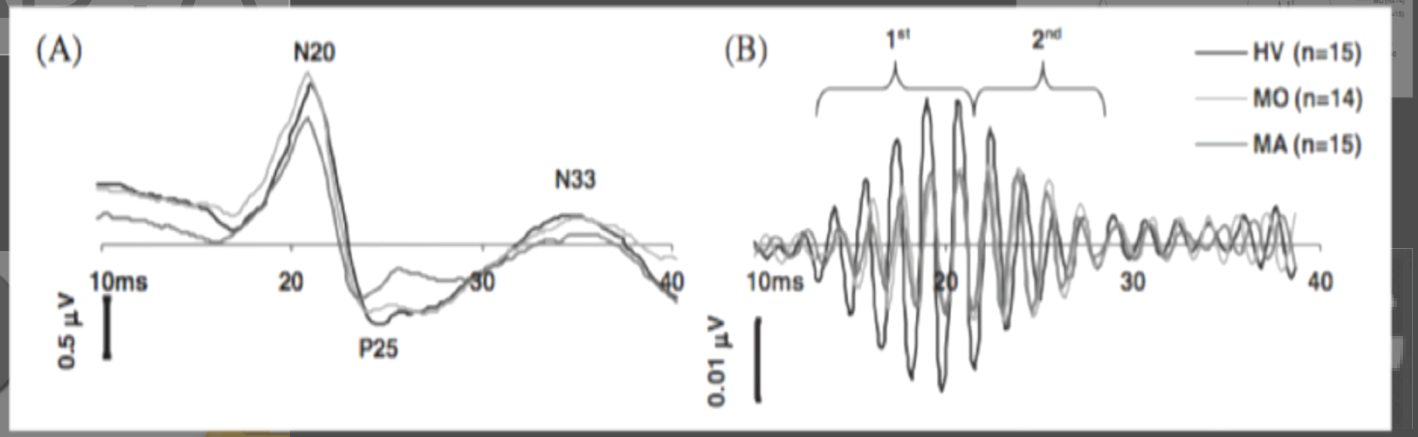


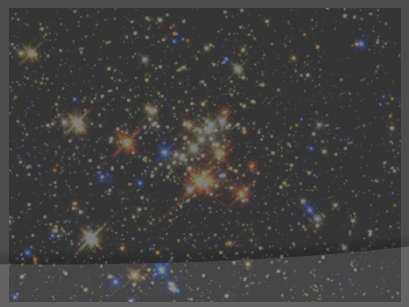
Reduced cortical pre-activation

High frequency oscillations

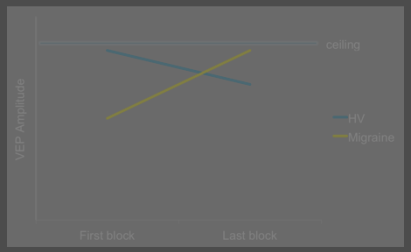


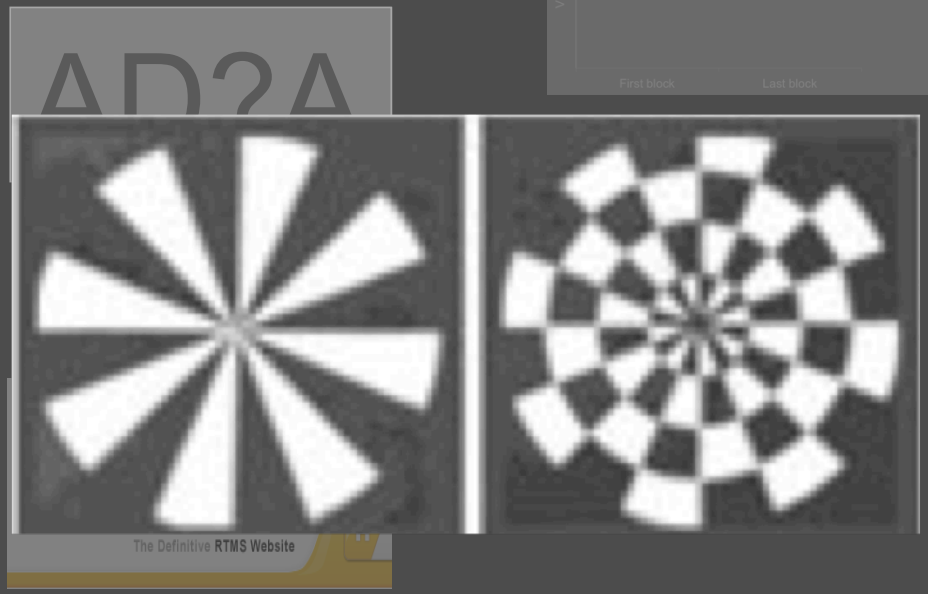
AD?A

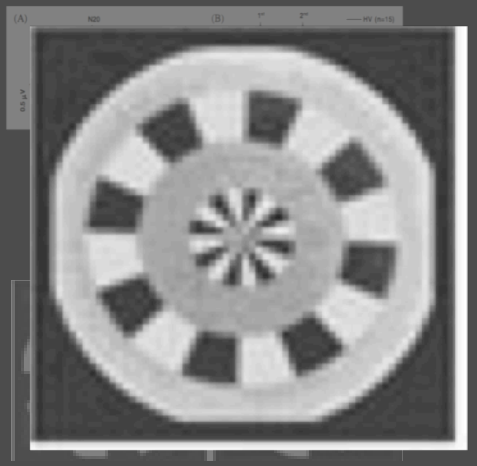




Dartboard & windmill



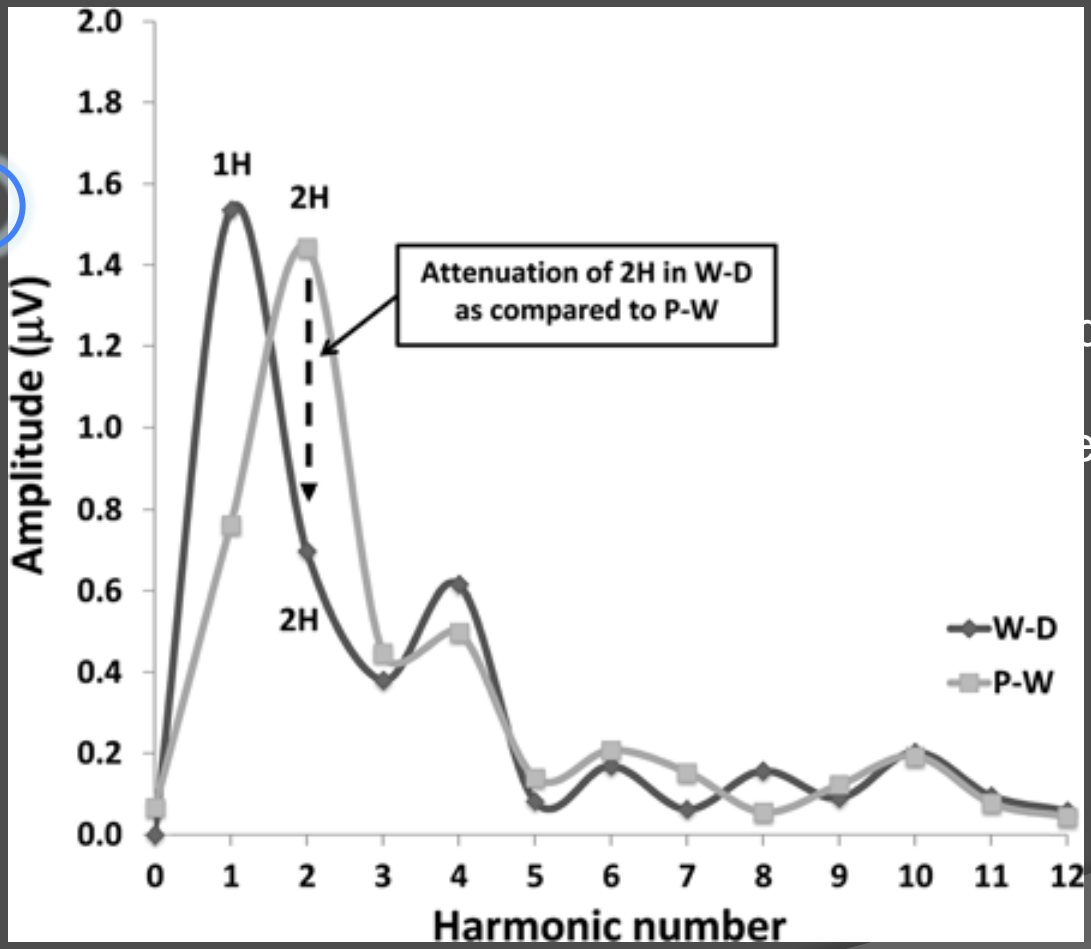




Windmill-dartboard

Partial windmill

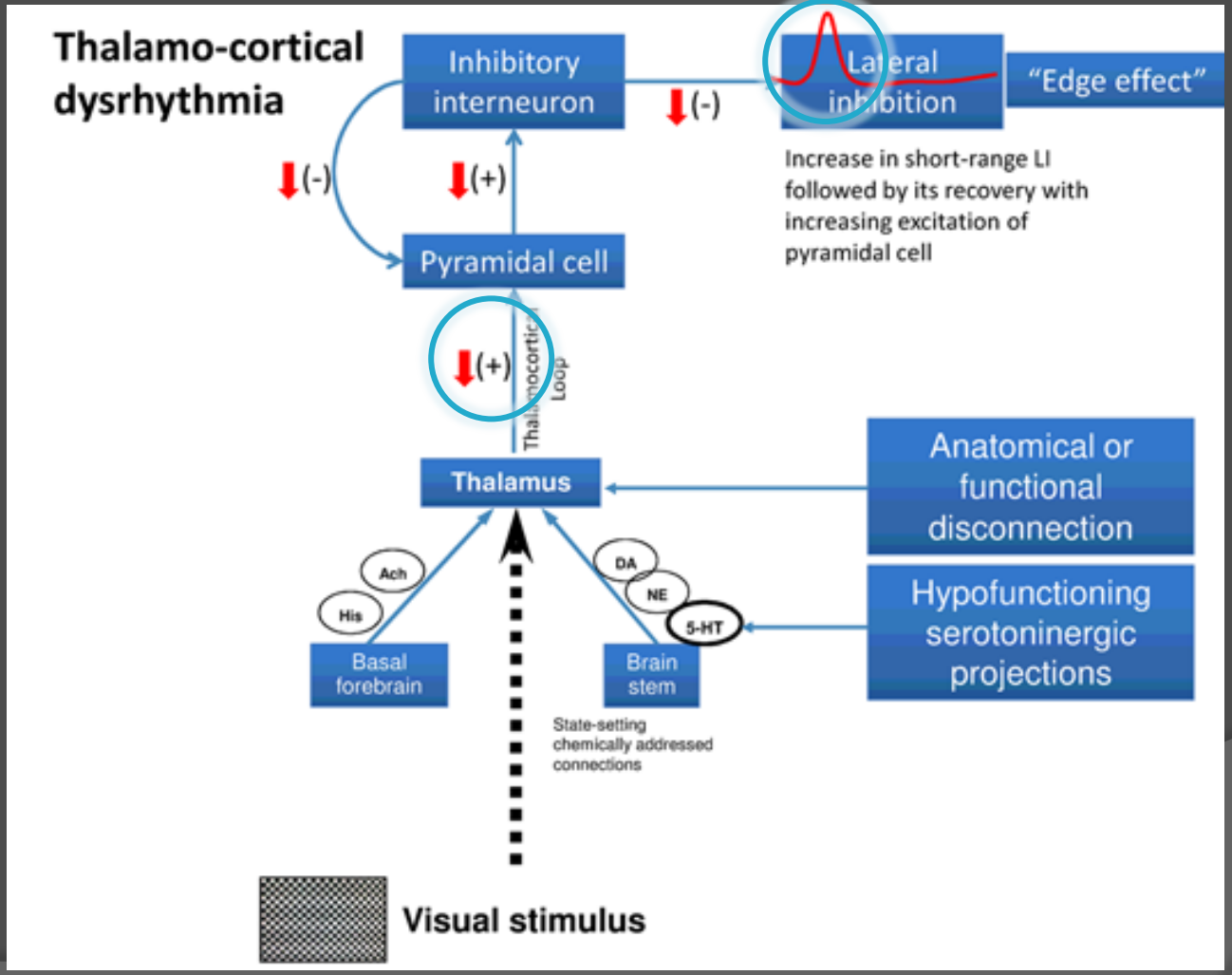
Increased short-range lateral inhibition



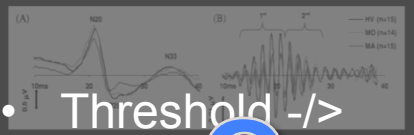
d amplitude

es over time

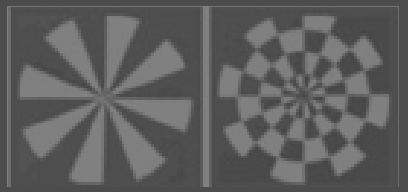
Thalamo-cortical dysrhythmia

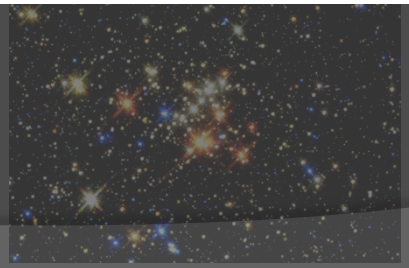


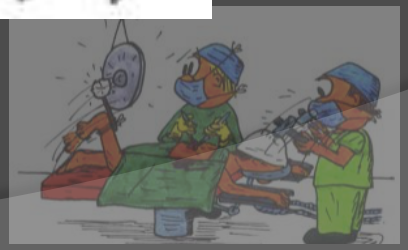
Motor cortex stimulation



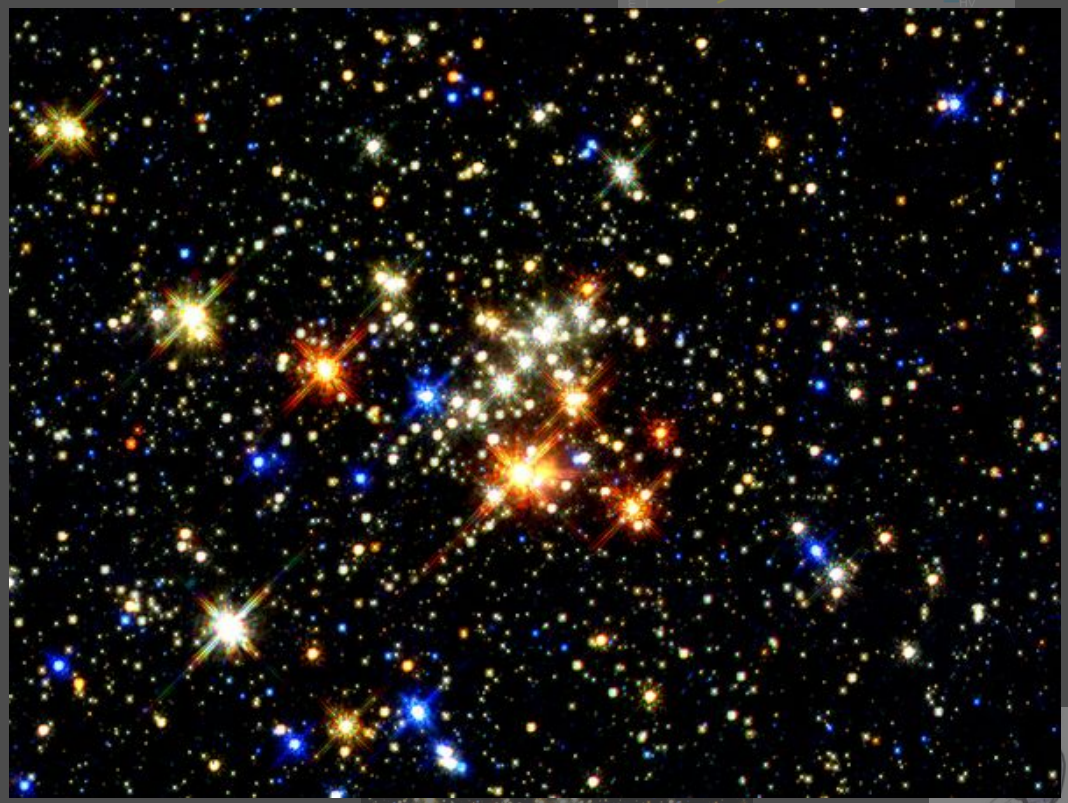
- Threshold -/>
- Amplitude -> (FHM)
- Intracortical inhibition <?

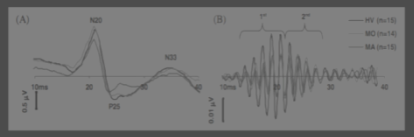




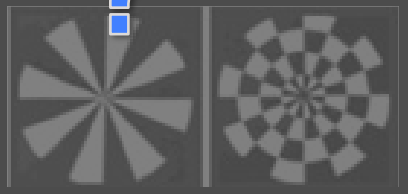


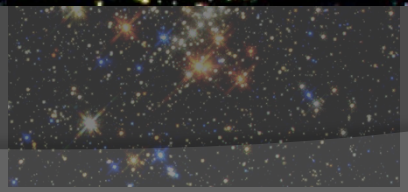
Phosphenes



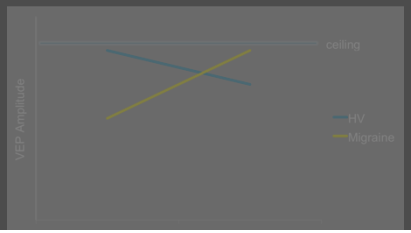


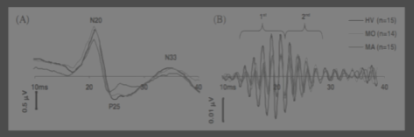
- Threshold </-/>



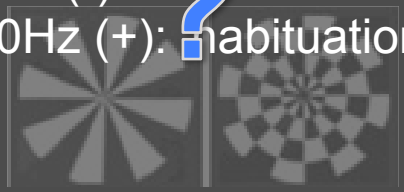


rTMS

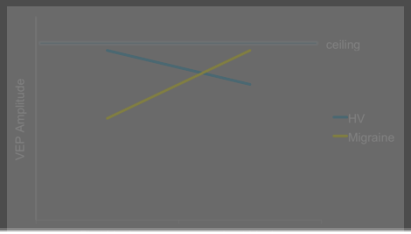


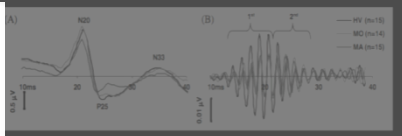


- 1Hz (-): ?T <
- 10Hz (+): habituation restored

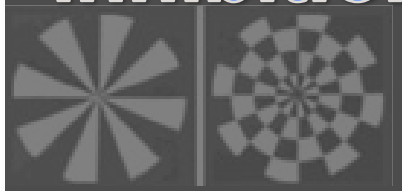


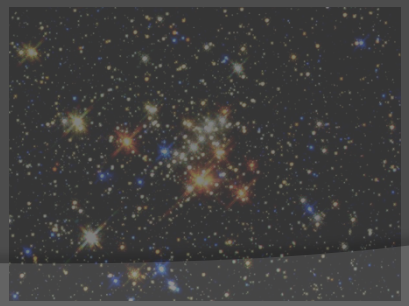
Suppression of perception





- inhibition ↓





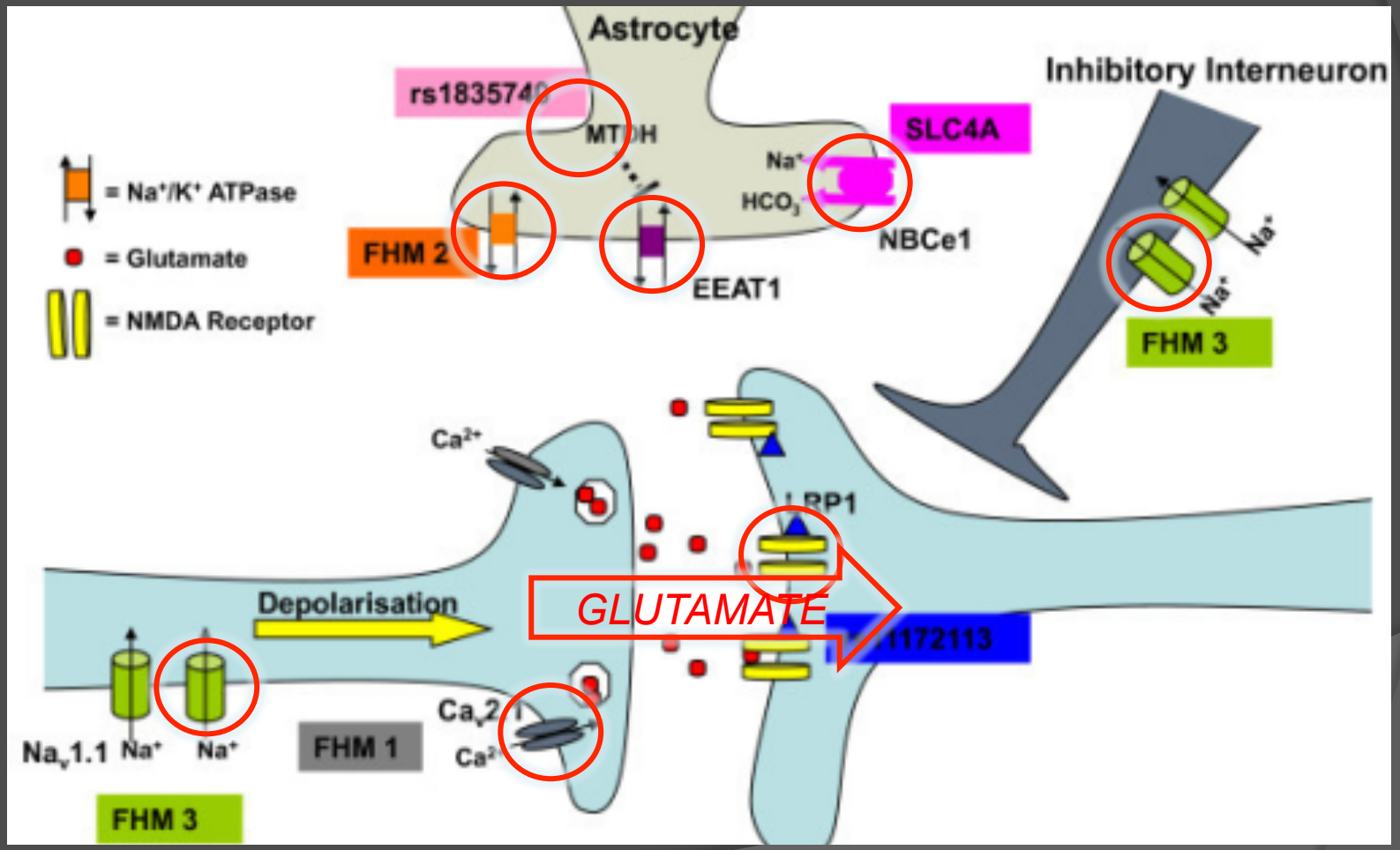
Conclusion

Neurophysiology research:

- Differences are not unidirectional
- Results are not uniform
- Result of dynamic shifts in neuronal physiology

Neurobiology

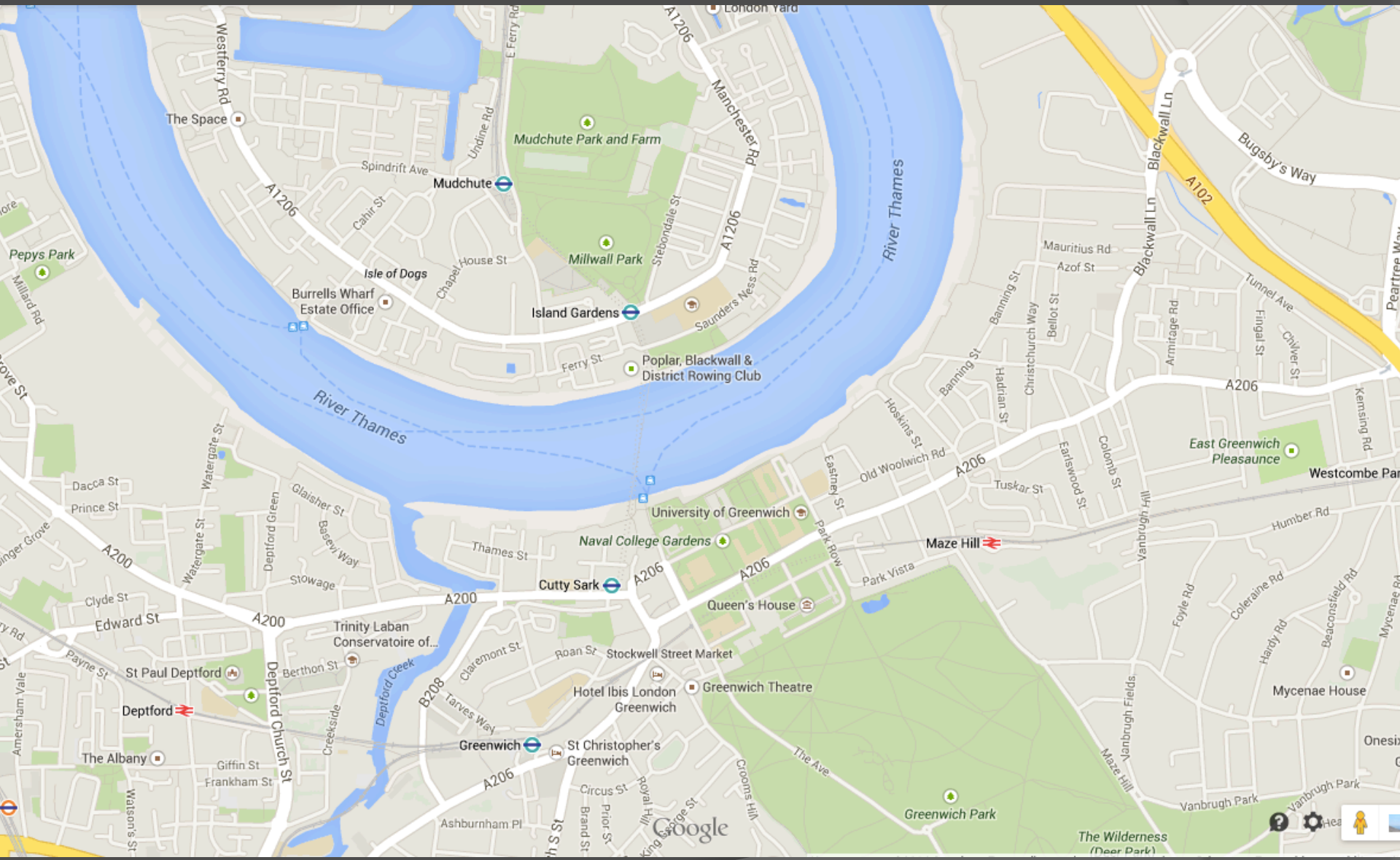
Functional genetics



Conclusions

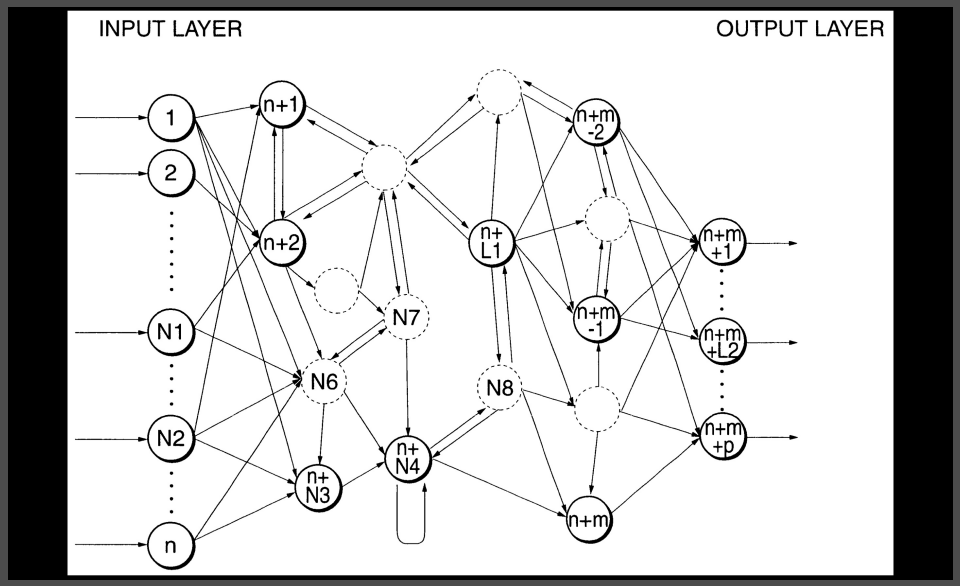
- cellular ≠ functional dysexcitability
- ↑ glutamate = ↑ excitability
- generic/uniform or regional/differential?
- hyperexcitability and reduced pre-activation may co-exist
- mind the 5 dimensions: 3-D network, synaps and plasticity
- don’t forget the glia!

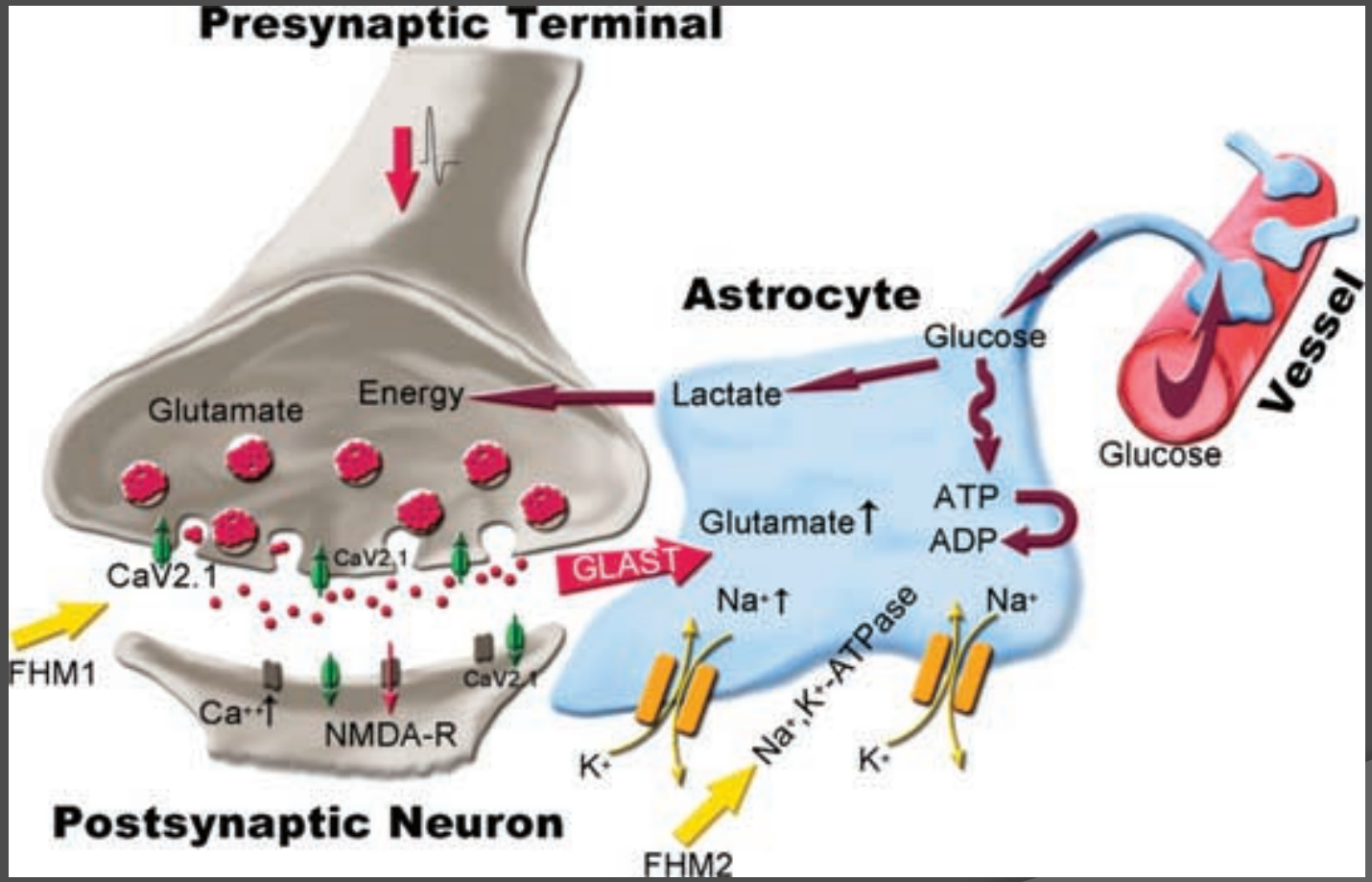

Special fares apply
Watford Junction
Watford High Street
Bushey
Carpenders Park
Hatch End
Headstone Lane
Harrow & Wealdstone
Kenton
Preston Road
Northwick Park
Wembley Park
Neasden
Dollis Hill
Willesden Green
Kilburn
West Hampstead
Kilburn High Road
Queen's Park
Kensal Rise
Kensal Green
Brondesbury
Brondesbury Park
Willesden Junction
Harlesden
Stonebridge Park
Wembley Central
North Wembley
South Kenton
North Harrow
Pinner
Northwood Hills
Northwood
Rickmansworth
Moor Park
Croxley
Watford
Chorleywood
Chalfont & Latimer
Chesham
Amersham
Uxbridge
Hillingdon
Ickenham
Ruislip
Ruislip Manor
Eastcote
West Ruislip
Ruislip Gardens
South Ruislip
Northolt
Greenford
Perivale
Hanger Lane
Park Royal
North Ealing
Ealing Broadway
Ealing Common
Acton Central
South Acton
Acton Town
South Ealing
Northfields
Boston Manor
Osterley
Hounslow East
Hounslow Central
Hounslow West
Heathrow Terminals 1, 2, 3
Heathrow Terminal 4
Heathrow Terminal 5
Hatton Cross
Chiswick Park
Turnham Green
Stamford Brook
Ravenscourt Park
Shepherd's Bush Market
Goldhawk Road
Shepherd's Bush
Wood Lane
White City
East Acton
North Acton
Hammersmith
Barons Court
West Kensington
Earl's Court
Gunnersbury
Kew Gardens
Richmond
Olympia
West Brompton
Fulham Broadway
Parsons Green
Putney Bridge
East Putney
Southfields
Wimbledon Park
Wimbledon
Ladbroke Grove
Latimer Road
Westbourne Park
Royal Oak
Paddington
Edgware Road
Marylebone
Baker Street
Great Portland Street
Euston
Euston Square
Warren Street
Regent's Park
Oxford Circus
Bond Street
Lancaster Gate
Marble Arch
Queensway
Notting Hill Gate
Holland Park
High Street Kensington
Hyde Park Corner
Green Park
Knightsbridge
Gloucester Road
South Kensington
Sloane Square
St. James's Park
Victoria
Westminster
Piccadilly Circus
Leicester Square
Charing Cross
Embankment
Waterloo
Pimlico
Vauxhall
Oval
Kennington
Lambeth North
Southwark
Borough
London Bridge
Bermondsey
Canada Water
Canary Wharf
Heron Quays
South Quay
Crossharbour
Mudchute
Island Gardens
Blackfriars
Temple
Mansion House
Cannon Street
Monument
Tower Hill
Tower Gateway
Aldgate
Aldgate East
Liverpool Street
Bank
St. Paul's
Chancery Lane
Holborn
Russell Square
Goodge Street
Tottenham Court Road
Covent Garden
Barbican
Moorgate
Old Street
Angel
Farringdon
King's Cross St. Pancras
Caledonian Road
Holloway Road
Arsenal
Finsbury Park
Highbury & Islington
Canonbury
Essex Road
Dalston Junction
Haggerston
Hoxton
Shoreditch High Street
Whitechapel
Shadwell
Wapping
Limehouse
Westferry
Poplar
All Saints
East India
Bromley-by-Bow
Bow Road
Bow Church
Mile End
Stepney Green
Bethnal Green
Pudding Mill Lane
Stratford
West Ham
Star Lane
Canning Town
Royal Victoria
Custom House for ExCeL
Prince Regent
Royal Albert
Beckton Park
Cyprus
Gallions Reach
Beckton
London City Airport
King George V
Woolwich Arsenal
Pontoon Dock
West Silvertown
Silvertown
Emirates Royal Docks
Emirates Greenwich Peninsula
North Greenwich
Cutty Sark for Maritime Greenwich
Greenwich
Deptford Bridge
Elverson Road
Lewisham
New Cross Gate
New Cross
Brockley
Honor Oak Park
Forest Hill
Sydenham
Penge West
Anerley
Norwood Junction
West Croydon
Crystal Palace
Queens Road Peckham
Peckham Rye
Denmark Hill
Brixton
Clapham Junction
Wandsworth Road
Clapham High Street
Clapham North
Clapham Common
Clapham South
Balham
Tooting Bec
Tooting Broadway
Colliers Wood
South Wimbledon
Morden
Kew Gardens
Kew Bridge
Gunnersbury
Chiswick Park
Acton Town
Ealing Broadway
Ealing Common
Acton Central
South Acton
Acton Town
Hammersmith
Barons Court
West Kensington
Earl's Court
Olympia
Kensington (Olympia)
Shepherd's Bush Market
Goldhawk Road
Shepherd's Bush
Wood Lane
White City
East Acton
North Acton
Ealing Broadway
Ealing Common
Acton Central
South Acton
Acton Town
Hammersmith
Barons Court
West Kensington
Earl's Court


Westferry Rd
The Space
Undine Rd
E Ferry Rd
London Yard
A1206
Manchester Rd
Mudchute Park and Farm
Spindrift Ave
Mudchute
A1206
Cahir St
Millwall Park
Stebondale St
A1206
River Thames
Blackwall Ln
A102
Bugsby's Way
Pepys Park
Isle of Dogs
Chapel House St
Burrells Wharf Estate Office
Island Gardens
Saunders Ness Rd
Mauritius Rd
Azof St
Banning St
Christchurch Way
Bellot St
Armitage Rd
Tunnel Ave
Fingal St
Chilver St
Ferry St
Poplar, Blackwall & District Rowing Club
River Thames
A206
Hoskins St
Old Woolwich Rd
Hadrian St
Eastney St
Earlswood St
Colomb St
Kemsing Rd
East Greenwich Pleasaunce
Westcombe Par
Dacca St
Prince St
Watergate St
Deptford Green
Glaisher St
Basevi Way
Tuskar St
University of Greenwich
Naval College Gardens
Thames St
Park Row
Maze Hill
Humber Rd
Vanbrugh Hill
A200
Stowage
Cutty Sark
A206
A206
Park Vista
Queen's House
Clyde St
Edward St
A200
Trinity Laban Conservatoire of...
Foyle Rd
Coleraine Rd
Hardy Rd
Beaconsfield Rd
Payne St
St Paul Deptford
Berthon St
Claremont St
Roan St
Stockwell Street Market
Deptford Church St
Deptford Creek
B208
Tarves Way
Hotel Ibis London Greenwich
Greenwich Theatre
Mycenae House
Deptford
Creekside
Greenwich
St Christopher's Greenwich
The Albany
Giffin St
Frankham St
A206
The Ave
Vanbrugh Fields
Maze Hill
Vanbrugh Park
Vanbrugh Park
Circus St
Royal Hill
Prior St
Brand St
Crooms Hill
Greenwich Park
Ashburnham Pl
Google
The Wilderness (Deer Park)

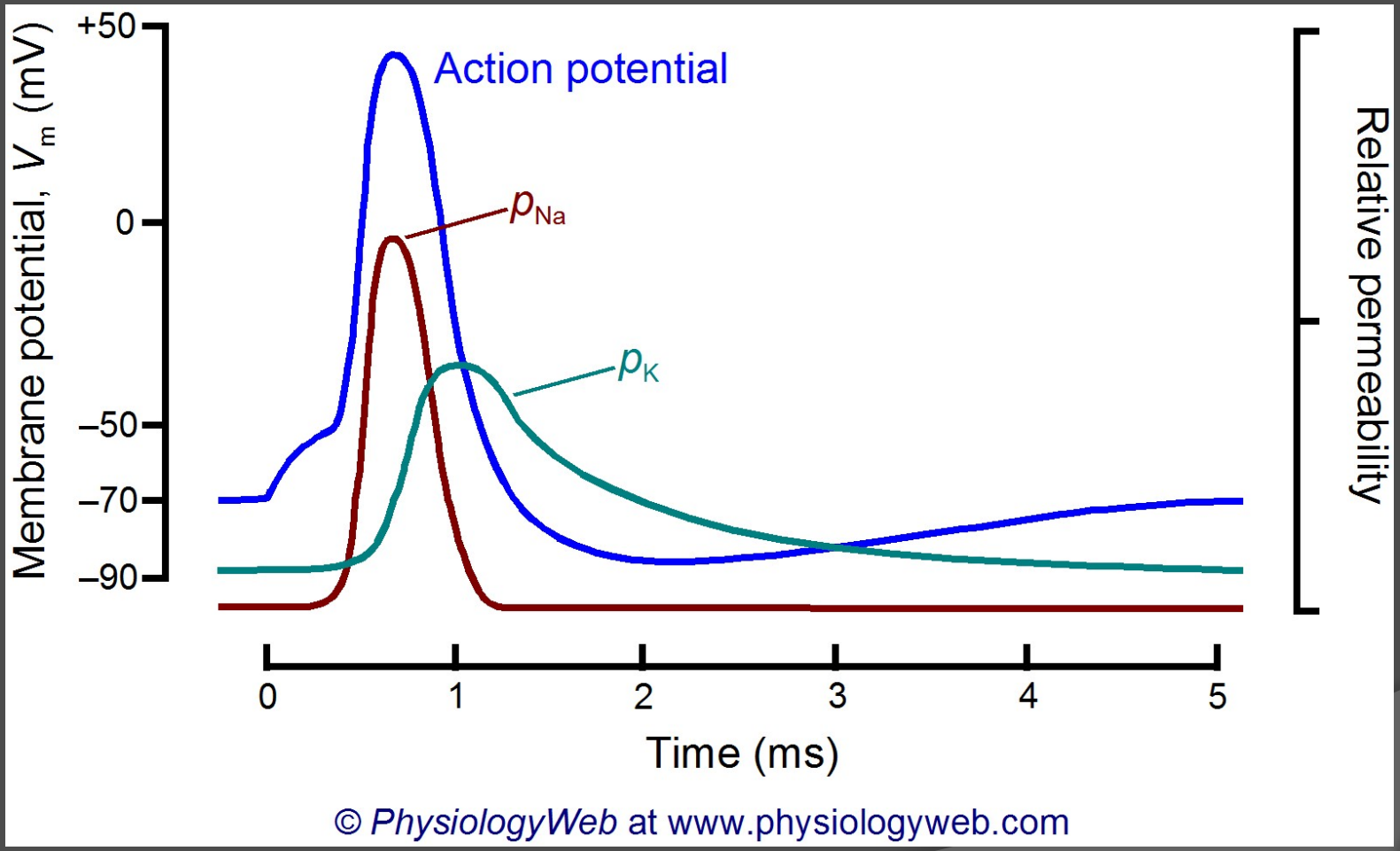

Cockspur Street
Strand
The Mall
A3212 Whitehall
15
13 M
25 min
11:01
11:26
30 mph
A206 Romney Road
TOMTOM


Thank you

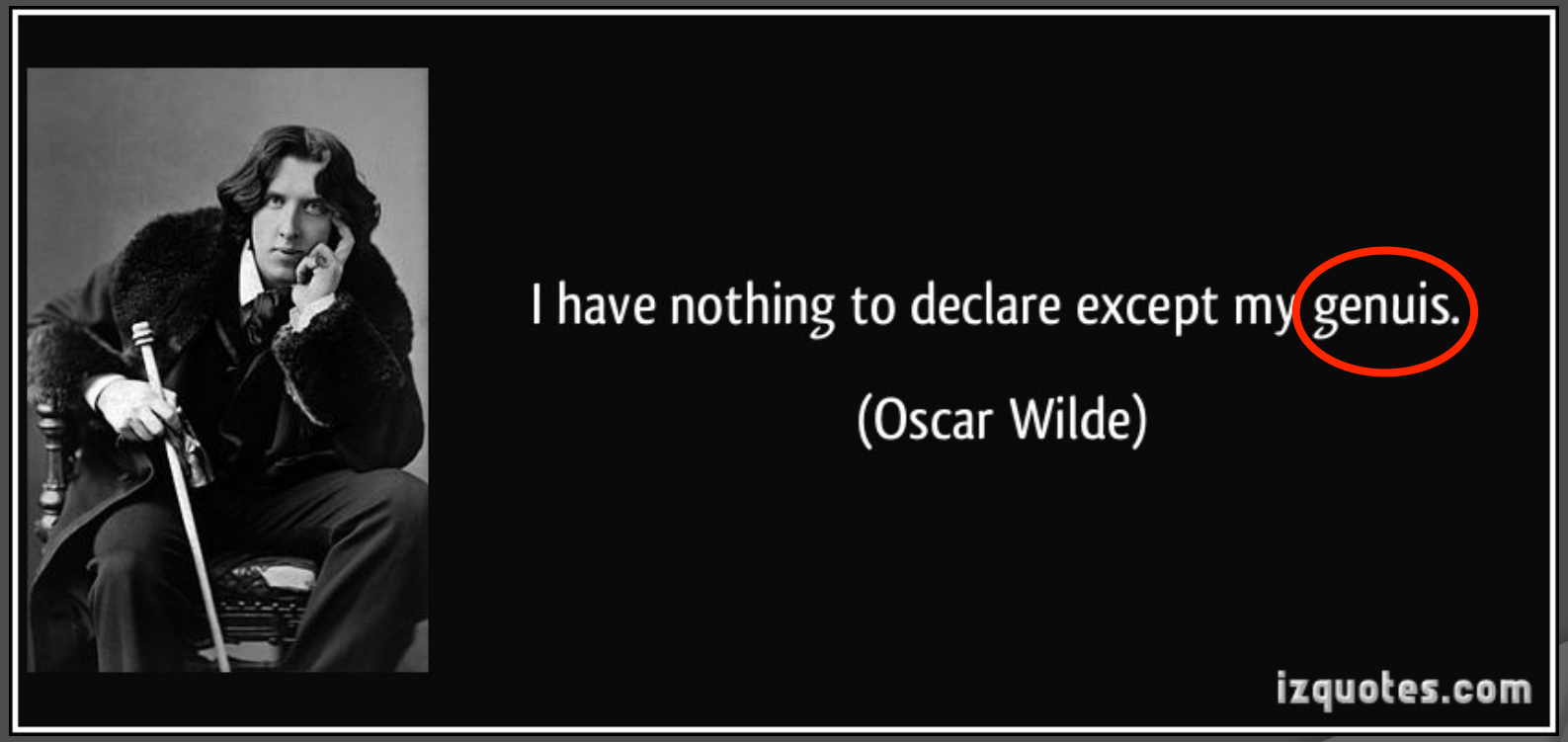

INPUT LAYER
OUTPUT LAYER
1
2
N1
N2
n
n+1
n+2
N6
n+ N3
N7
n+ N4
n+ L1
N8
n+m -2
n+m -1
n+m
n+m +1
n+m +L2
n+m +p


Presynaptic Terminal
Astrocyte
Glucose
Vessel
Glucose
Energy
Lactate
Glutamate
ATP
ADP
Glutamate↑
CaV2.1
CaV2.1
GLAST
Na⁺↑
Na⁺
FHM1
Ca⁺⁺↑
NMDA-R
CaV2.1
Na⁺,K⁺-ATPase
K⁺
K⁺
Postsynaptic Neuron
FHM2

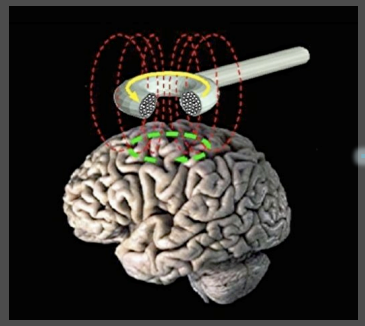

VISUAL
HUMAN
PSYCH
PSYCHOPHYSICS
FACTORS
DEPT
WICHITA
STATE


Membrane potential, V_m (mV)
+50
0
–50
–70
–90
Action potential
p_{Na}
p_K
Relative permeability
0
1
2
3
4
5
Time (ms)
© PhysiologyWeb at www.physiologyweb.com

Conflicts of interest



Transcranial magnetic stimulation



- Threshold -/>
- Amplitude > (FHM)
- Intracortical inhibition <?

- Threshold </-/>

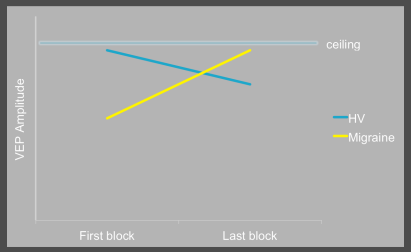
- 1Hz (-): PT <
- 10Hz (-): habituation restored

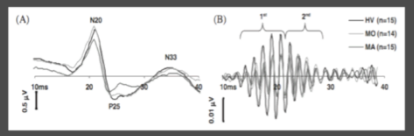
AD?A

inhibition ↓

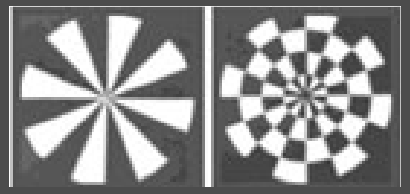
- Letter recognition

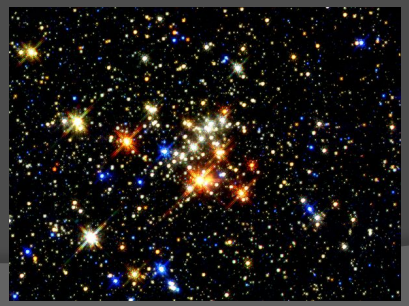
AD?A


ceiling
HV
Migraine
VEP Amplitude
First block
Last block

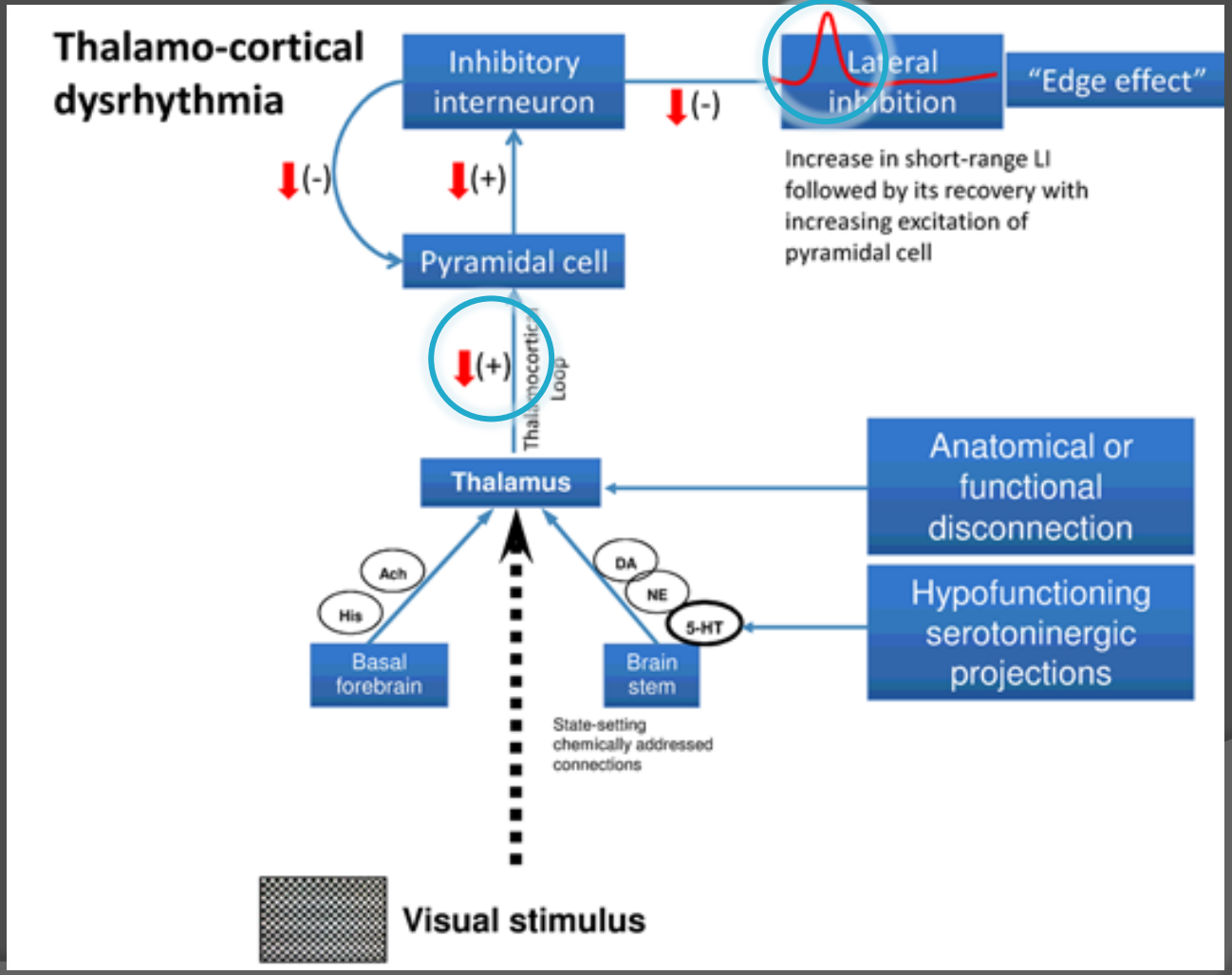

(A)
N20
N33
P25
10ms
(B)
1st
2nd
10ms

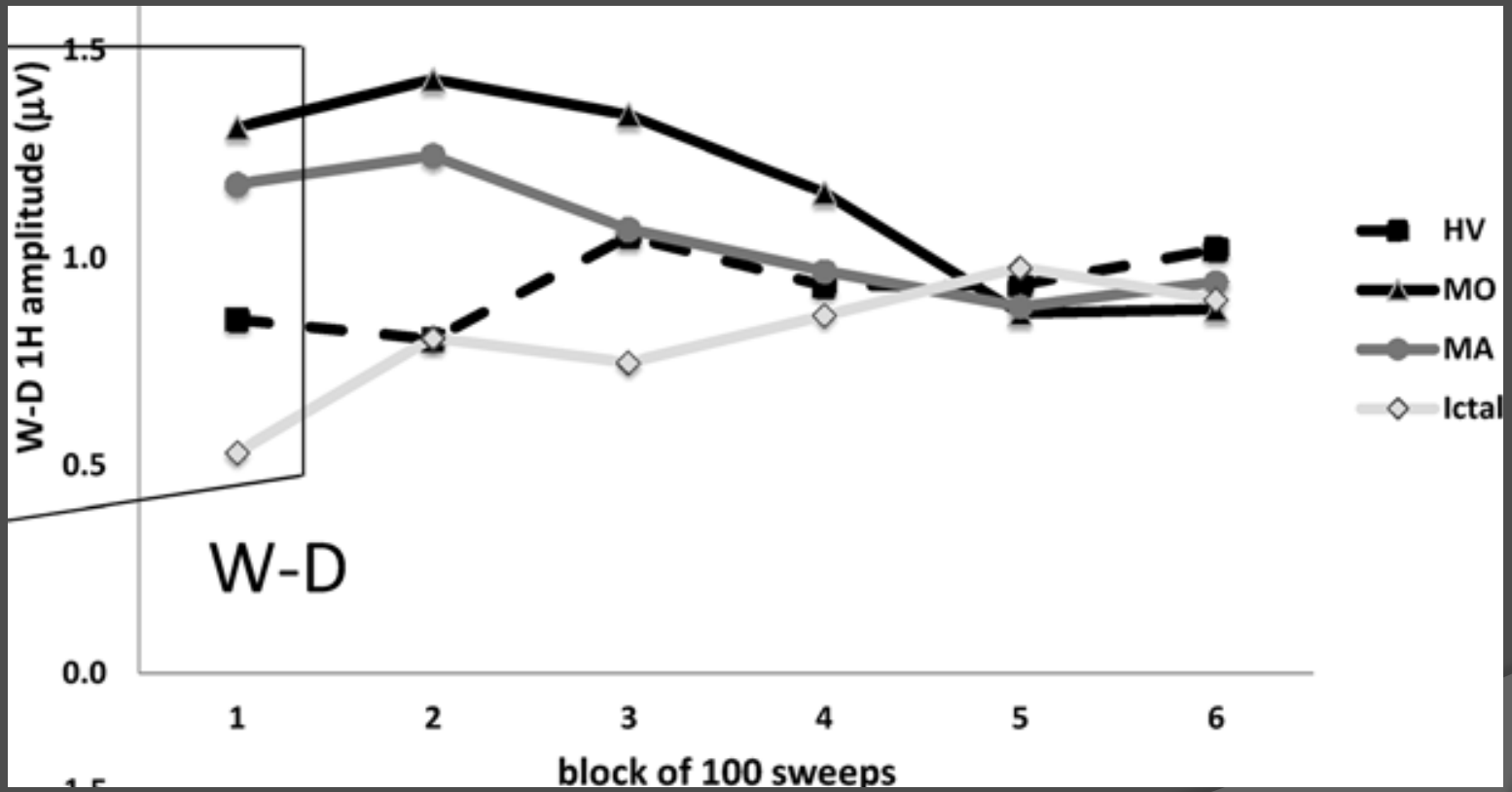

Road Transport Management System
RTMS
Driver Wellness • Safety • Loading • Productivity
The Definitive RTMS Website



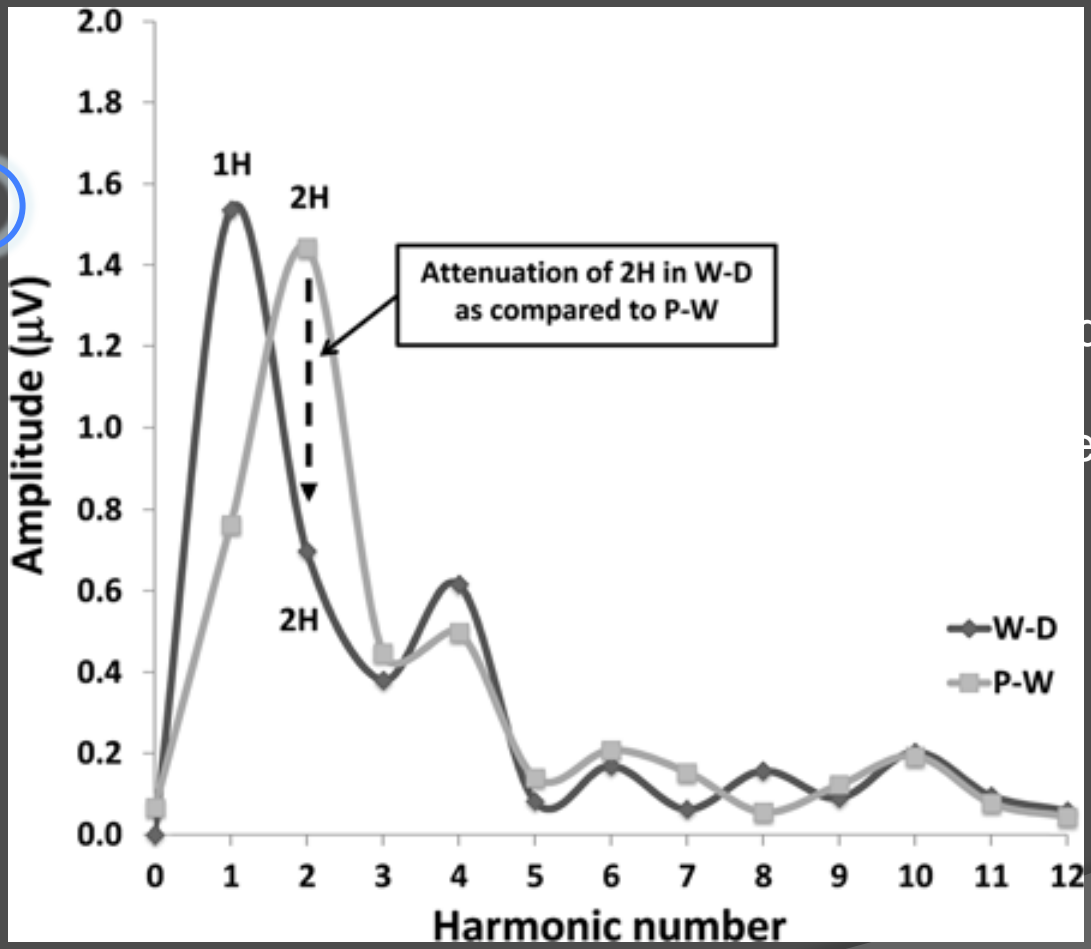


Thalamo-cortical dysrhythmia



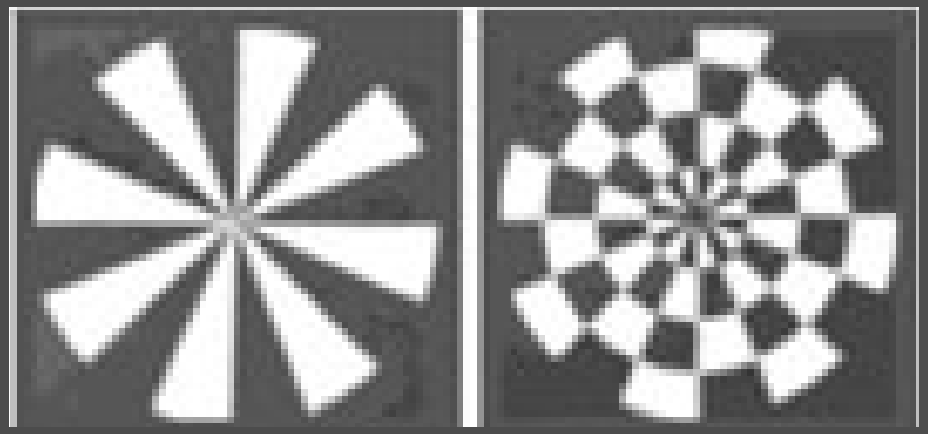

W-D 1H amplitude (µV)
1.5
1.0
0.5
0.0
W-D
1
2
3
4
5
6
block of 100 sweeps
HV
MO
MA
Ictal

Increased short-range lateral inhibition

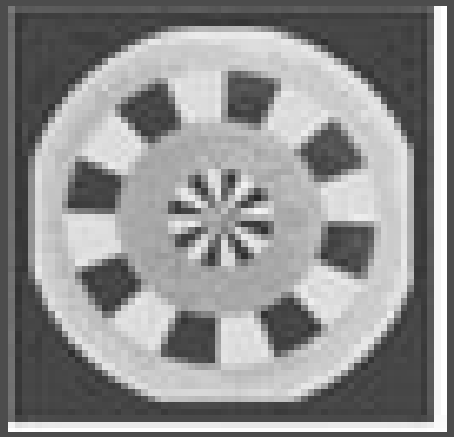


d amplitude

es over time

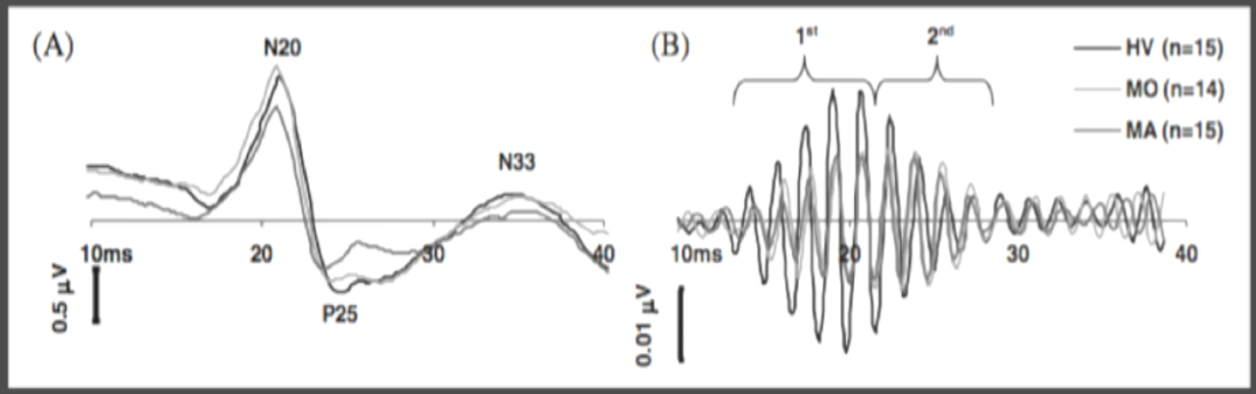


Windmill-dartboard

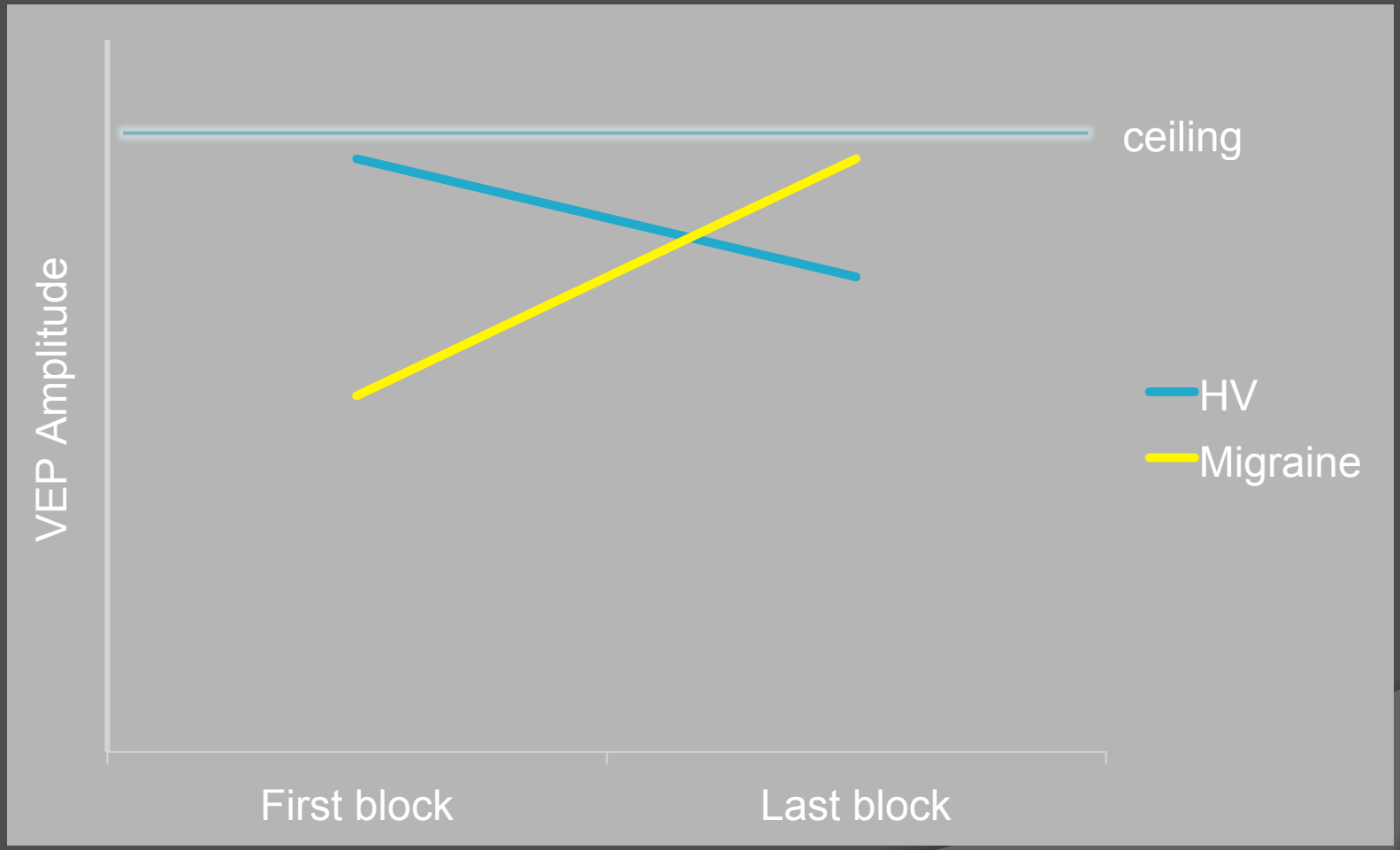


Partial windmill

High frequency oscillations

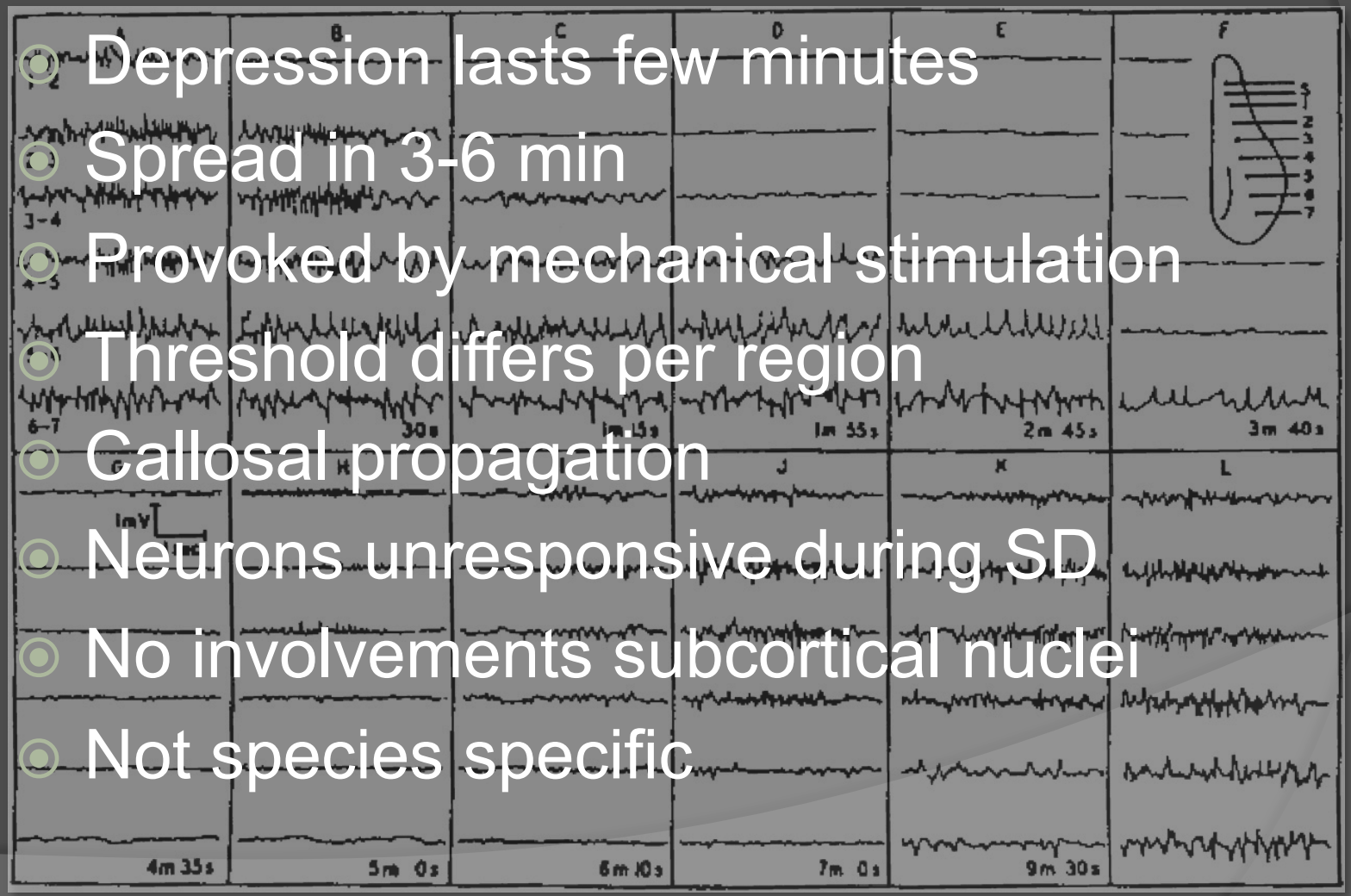


Ceiling theory



Reduced cortical pre-activation

Characteristics of SD



- Depression lasts few minutes
- Spread in 3-6 min
- Provoked by mechanical stimulation
- Threshold differs per region
- Callosal propagation
- Neurons unresponsive during SD
- No involvements subcortical nuclei
- Not species specific