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# Stroke affecting the limbic system

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Acknowledgement: José Ferro, MD, Lisbon



Centre
Cérébrovasculaire

UNIL | Université de Lausanne

# Stroke in the limbic system (LS)

## Menu


- Complexe cerebral function/dysfunction
- Potential symptoms from stroke in the LS
- Observed symptoms from stroke in the LS
- Amnesia and stroke
- TGA (and stroke)


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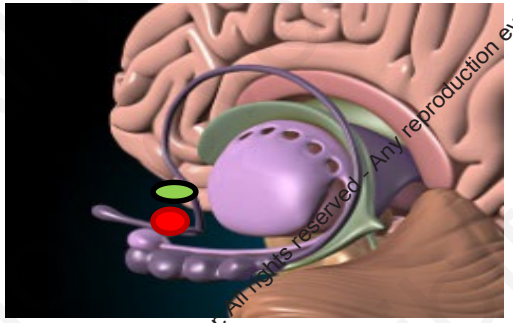
# Complexe cerebral function and dysfunction

## Traditional model



Limbic system

Vegetative

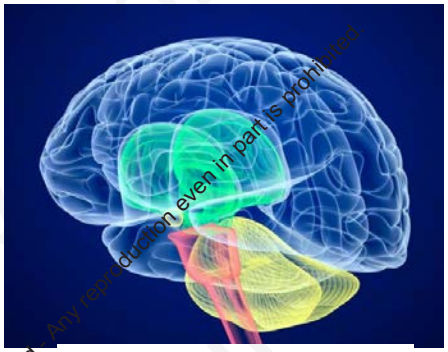
Emotions

Cognition

Behaviour

Perception

Mouvements / Reward



Basal ganglia & Frontal lobe

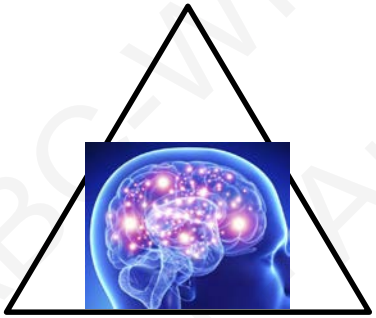
Cortex

# Complexe cerebral function and dysfunction

## Traditional model

Vegetative

Emotions



Limbic system

Basal ganglia & Frontal lobe

PowerPoint

P. Michel

Cognition

Behaviour

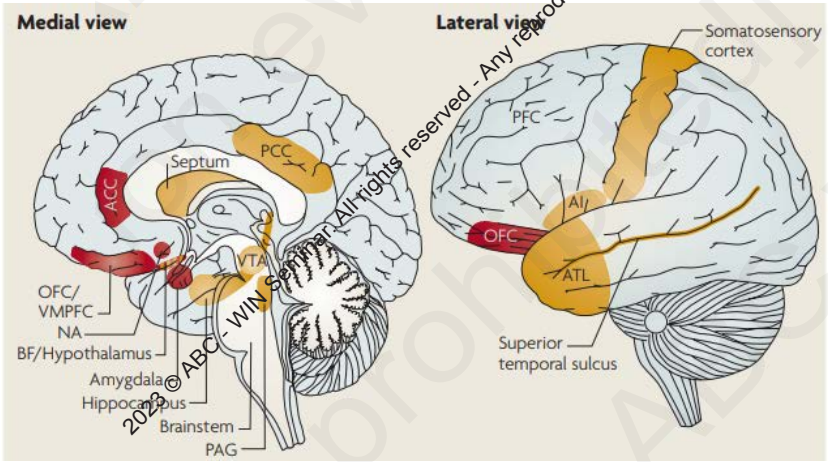
tion

Mouvements / Reward

Cortex

# LS = « The emotional brain » ?

## Functions potentially attributed to the limbic system




Red: «Core emotional brain»

Yellow: «Extended emotional brain»

Pessoa Nature Rev Neurosci 2007

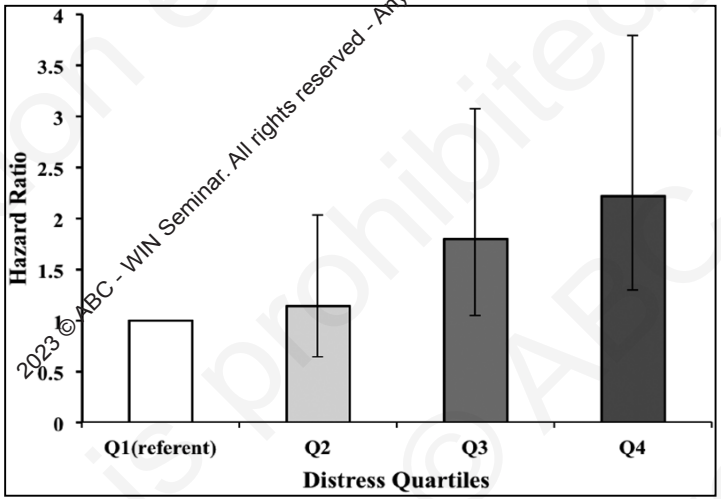
Potential / probable functions of the limbic system :

- Emotional/neuropsychiatric
- Behavioural
- Vegetative/olfactory
- Memory

# Chronic emotions cause stroke

## Chronic stress

Stroke probability




Chicago Health and Aging Project
Henderson Stroke 2013

## Stress per geographics

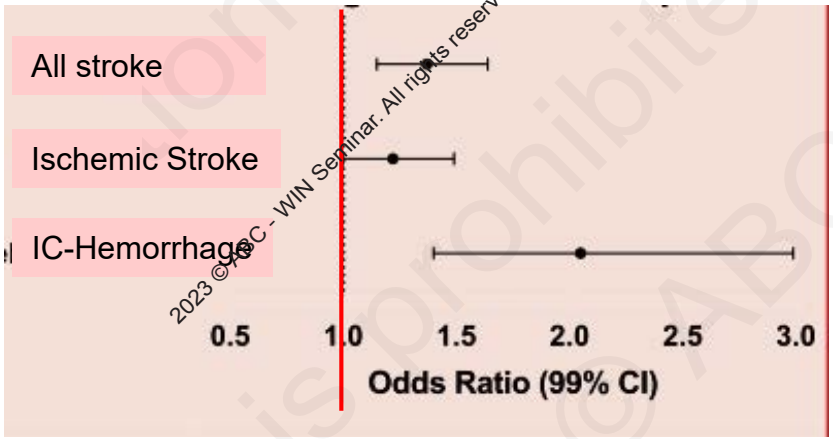

→ Stroke

Overall OR =2.20 (1.78-2.72)

INTERSTROKE/ODonnell Lancet 2016

# Acute emotions cause stroke

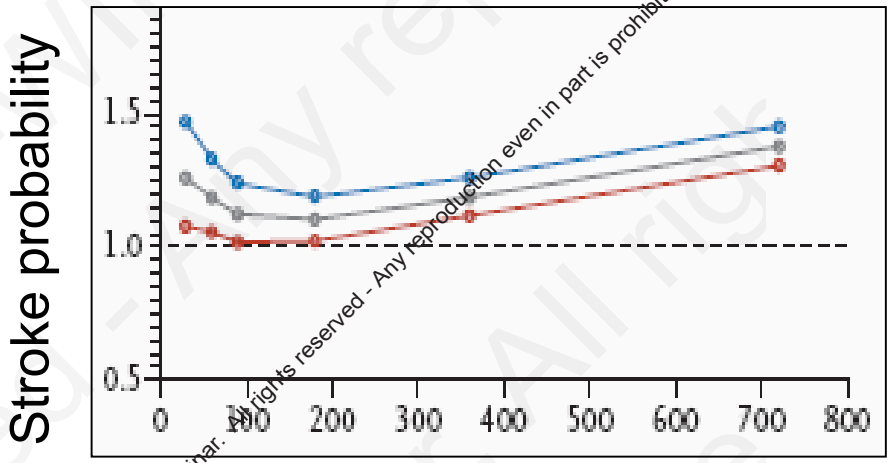
## Anger or emotional upset during last 60 min.




→ Anger/upset present

INTERSTROKE/Smyth Eur Heart J 2022

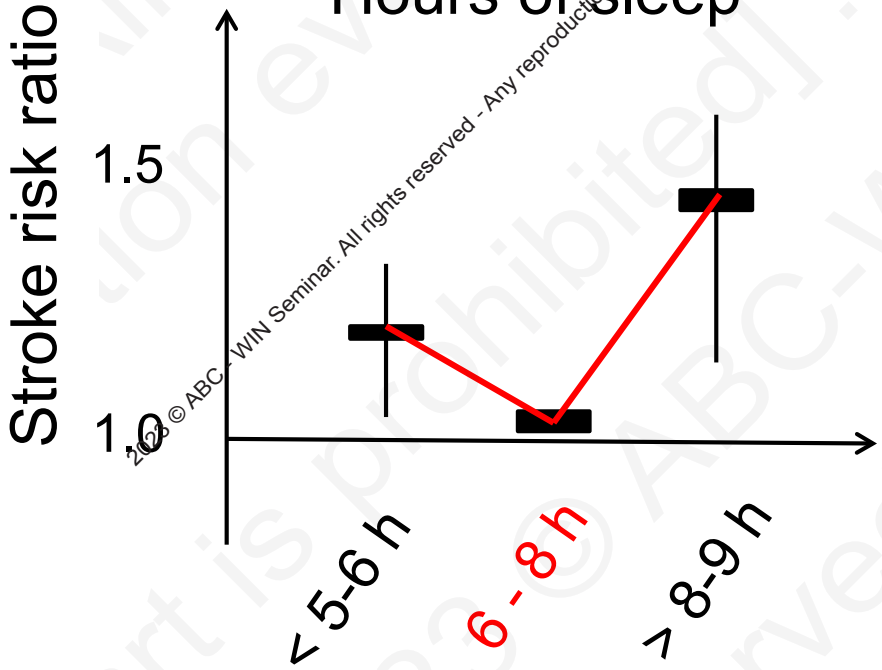
## Stroke in men following hospitalisation of wife




Christakis NEJM 2006

# Behavioural habits cause stroke

## Hours of sleep




Leng Neurology 2015

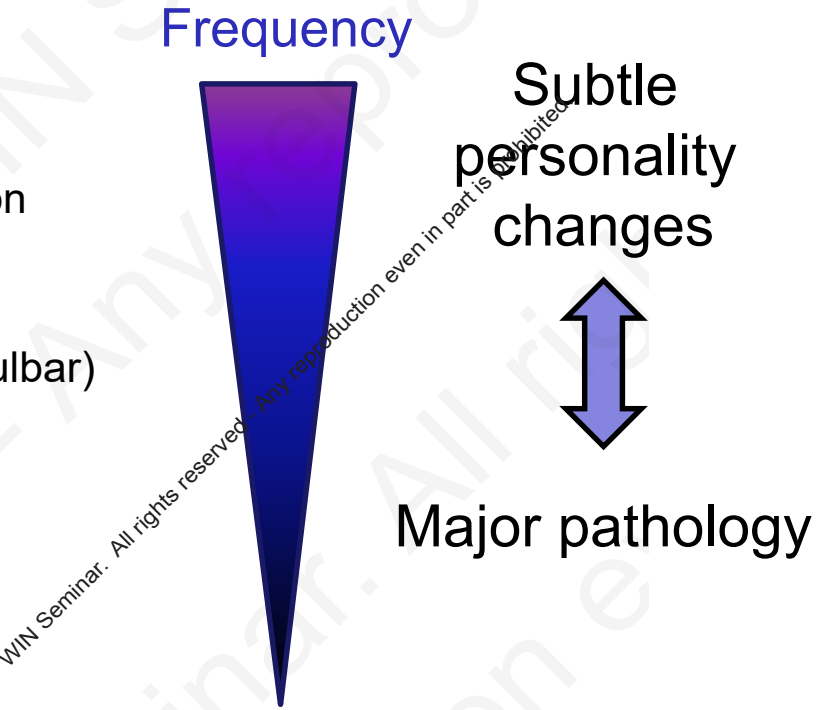
## Dark chocolate


↓ 27% stroke risk

Buitrago-Lopez BMJ 2011; WHI/Greenberg Am Nutr 2018

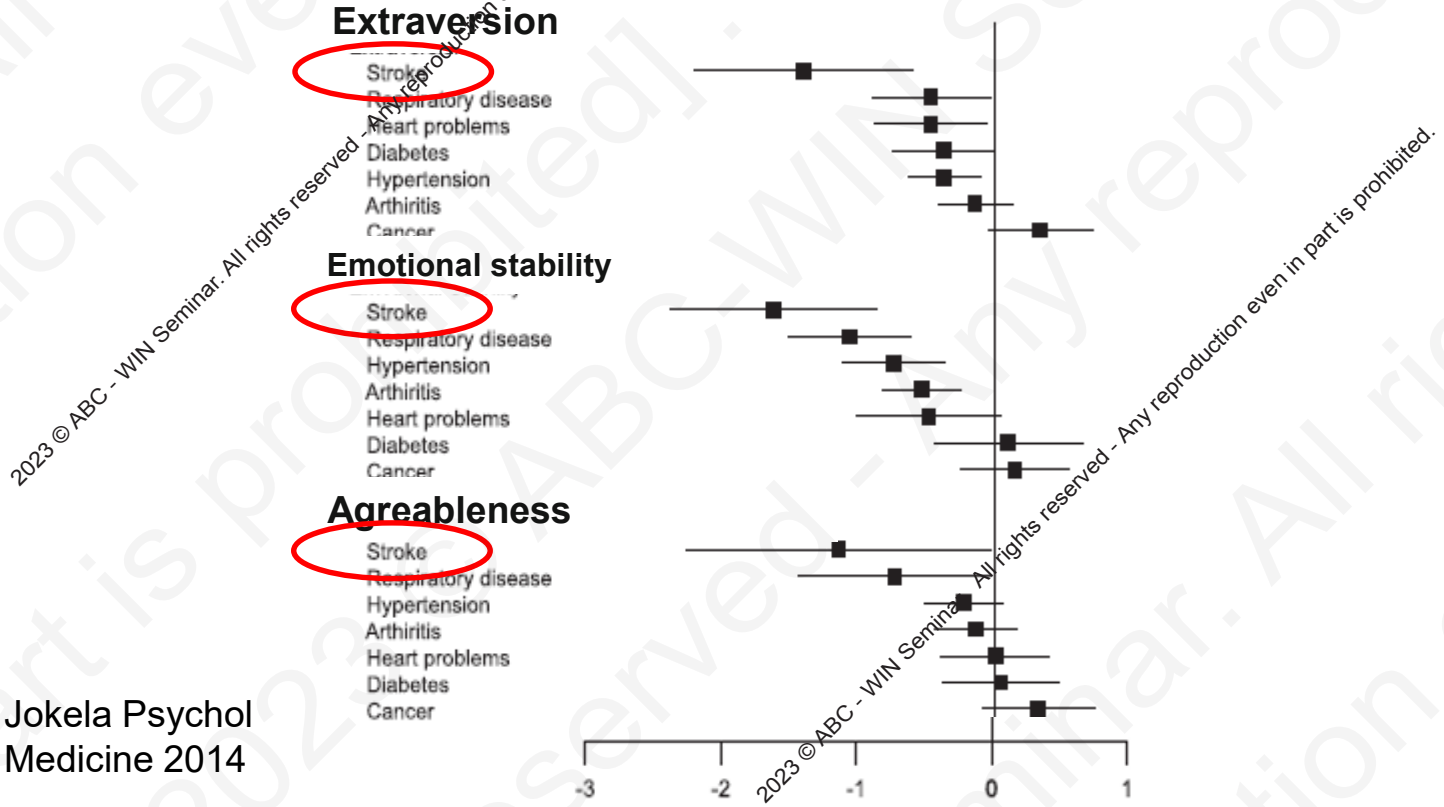
# After stroke: emotional and behavioural problems are multiple and frequent

- Depression (→ rarely suicidality)
- Apathy
- Anxiety, phobias
- Emotional instability, catastrophic reaction
- Irritability, impulse control disorders
- PTSD
- Pathological laughter & crying (pseudobulbar)
- Compulsion, OCD, «Witzelsucht»
- Agression
- Lack of empathy
- Psychosis
- Mania
- Hypersexuality



# After stroke : emotional and personality changes

## are more frequent than in other chronic illness




Jokela Psychol Medicine 2014

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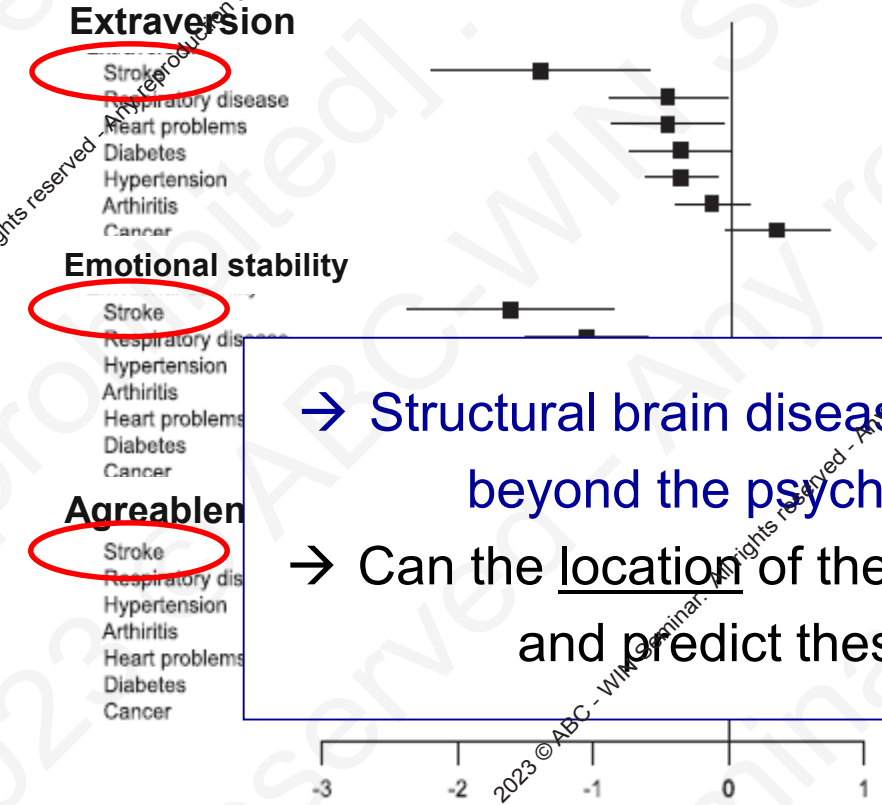


→ Structural brain disease changes humans beyond the psychological impact

→ Can the location of the brain lesion explain and predict these changes ?

Jokela Psychol Medicine 2014

# Stroke in the limbic system (LS)

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Emotions


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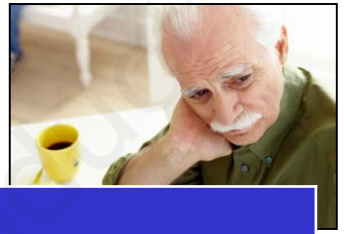
# Potential LS manifestations of stroke



| Emotion | Stroke localisation |
|---|---|
| Depression | Not specific; networks more important<br>Left basal ganglia and left PFC (?) |
| Anxiety | Not specific.<br>Anterior circulation, right frontal (?) |
| Mania | Right hemispheric including (para)-limbic<br>Orbitofrontal/basotemporal; caudate nucleus/thalamus regions |
| PTSD | Not specific / unknonwn |
| Emotional lability/ laughter/ crying | Frontal lesions; frontal-lenticular-pontine base |
| Catastrophic reaction | Left hemispheric (?) |
| Lack of empathy | Not specific (networks more important) |

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Behaviour


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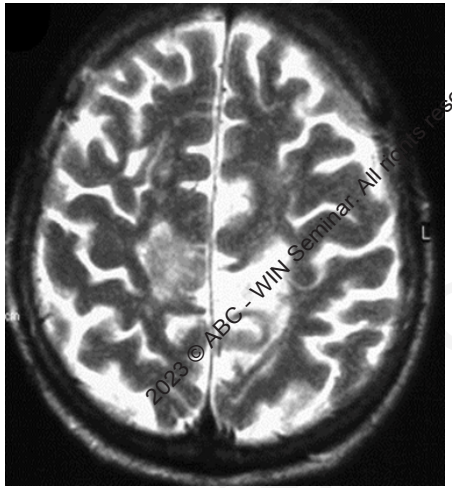
# Potential LS manifestations of stroke

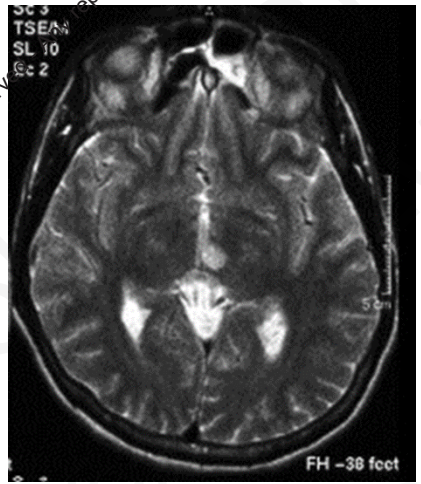
| Behaviour | Stroke localisation |
|---|---|
| Aggression, anger, disinhibition | Not specific.<br>Orbitofrontal/ventromedial/lenticulo-capsular/basal pontine areas |
| Apathy, lack of motivation | Not specific, not lateralized<br>Anterior cingulate–pallidum–thalamic circuit; bilateral lesions |
| Psychosis | Right hemispheric-cortical |
| Compulsion, OCD, «Witzelsucht» | Cortico-striato-thalamo-cortical circuits |
| Hypersexuality (part of Klüver–Bucy syndrome) | Amygdala/mesiotemporal lobe; cingulate |

# Example: apathy after stroke

## independent of stroke types; stroke localization of limited value



Right ACA




Right paramedian thalamus


Deep venous thrombosis

Right caudate and intraventricular ICH

Slide courtesy: J. Ferro

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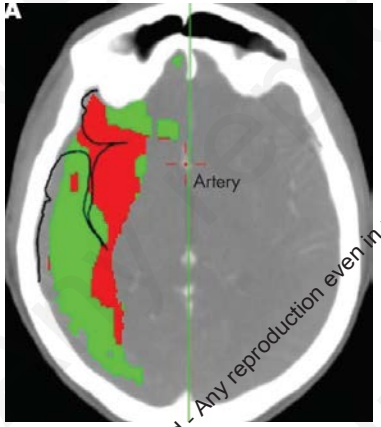
Vegetative, olfactory

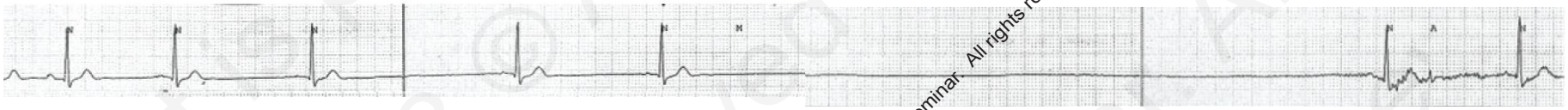
# Vignette : 42 yo. lady, right MCA stroke (ESUS)

- Between 7 and 20h after onset:
  - Five episodes of asystolia of 10 sec.
  - Each accompanied by brief loss of consciousness




→ Major <u>insular</u> involvement

→ Not really “limbic”!



Rey & Michel, JNNP 2008

# Potential LS manifestations of stroke

| Vegetative & olfactory manifestation | Stroke localisation |
|---|---|
| Tachycardia/bradycardia/arrythmis | Insular cortex, other ? |
| Sleep apnea (central, obstructive) | Not specific (severity may matter)<br>Udine's curse: bilateral lateral medulla |
| Sweating | General: not specific<br>Rare focal hyper/hypo in brainstem. |
| Fatigue | Not specific. Posterior circulation (?) |
| Horner's syndrome | Dorsal brainstem<br>Thalamus, subcortical WM |
| Olfactory | Non-specific anterior circulation |

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Amnesia


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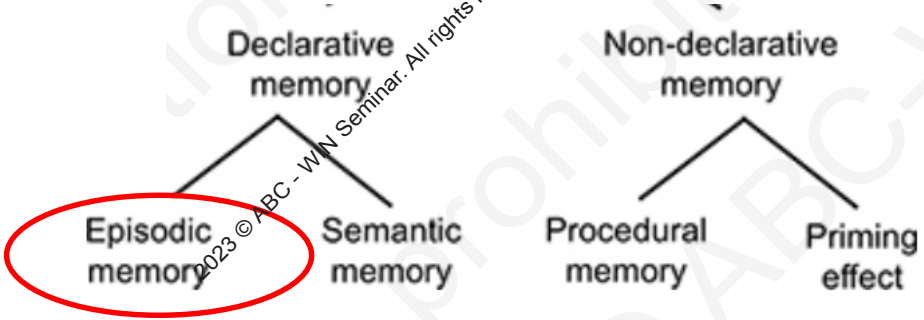
# Potential LS manifestations of stroke

Amnesia

## Memory types




## Memory processes

- Memorizing (encoding)
- Retention (storage)
- Regeneration (recall)

→ Hippocampal-diencephalic and parahippocampal-retrosplenial networks

Review: Maeshina & Osawa, In: Stroke. Dehkharghani S (Editor). Exon Publications, 2021

# Potential LS manifestations of stroke

| Amnesia (usually episodic) | Stroke localisation |
|---|---|
| Anterograde amnesia (=encoding) | Anywhere in Papez' circuit<br>Also para-limibic system (retrosplenial, ....) |
| Retrograde amnesia (= retrieval) | Hippocampus, parahippocampus |
| - but often OK with clues | - basal forebrain, caudate |
| Retention (=storage = old memories) | Rarely affected by stroke |
| Attentional problems/forgetfulness | Anywhere supratentorial (also Infratentorial ?) |
| Learning | Any of the above |

Memory deficits : L hemispheric: more verbal; R hemispheric: more visual

# Intermediate conclusion

## Pit-stop 1


Red Bull electric car

«Limbic symptoms» ⇏ Structural limbic lesion

# Stroke in the limbic system (LS)

## Menu

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- **Clinically observed symptoms from stroke in the LS**
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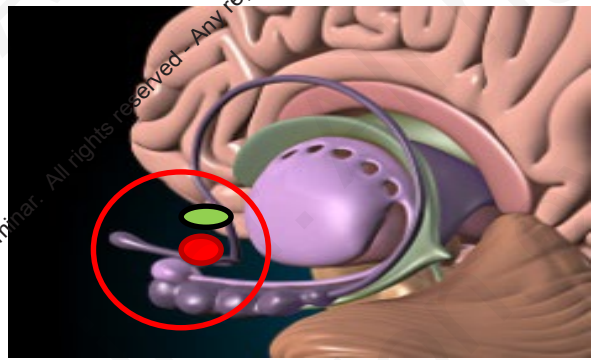
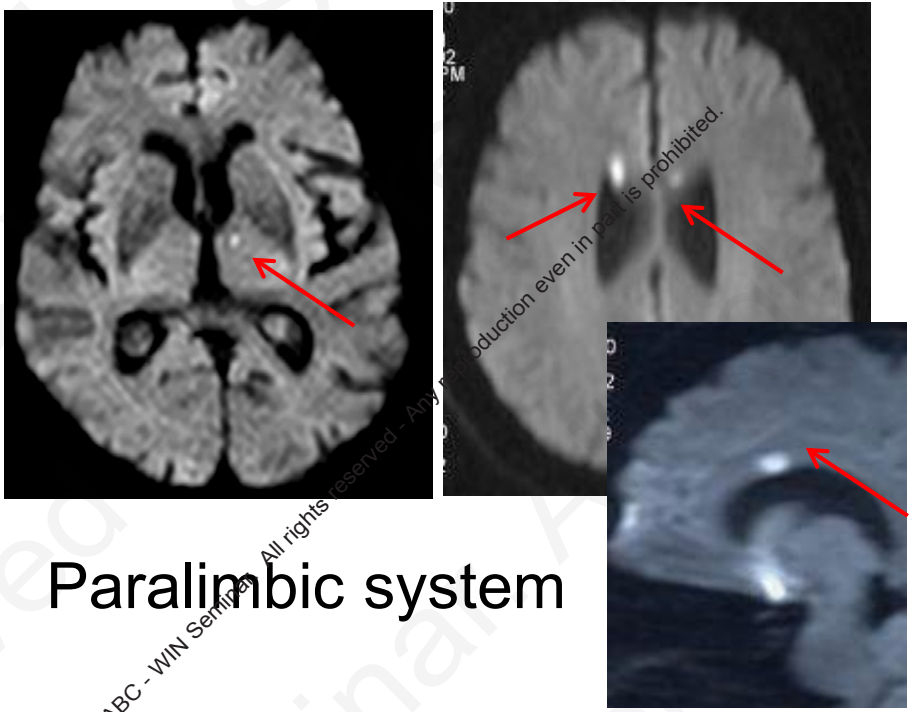


# Examples of strokes in the limbic system

Core limbic system



Paralimbic system

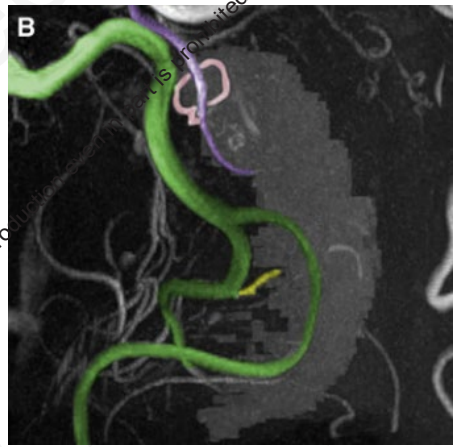
# Clinically observed manifestations of damage to LS

| Limbic structure | Manifestations |
|---|---|
| Amygdala | Isolated stroke: not described (?!)<br>(Potentially: anterograde > retro amnesia, altered decision making, altered fear response, anxiety, aggression, irritability, ↑ or ↓ sex drive) |
| Hippocampus | Short >> long term episodic memory loss (initially disorientation) |
| Hypothalamus | Rare: somnolence, hypothermia, Horner's<br>(Potentially: changes in weight, hyperhidrosis, ↑ or ↓ sex drive, aggression, stress, fatigue, altered biol. rhythm) |
| **Paralimbic / associated structures** | |
| Cingulate gyrus, anterior thalamus, VTA, prefrontal cortex/basal forebrain, basal ganglia CC, fornix, Ncl. acumbens | Episodic amnesia<br>Multiple and often unspecific cognitive/ memory/ emotional/ behavioural deficits |

Hypothal. stroke: Matsubara BMC Neurol 2019;

# Clinically observed manifestations of damage to LS are rare. Why ?

- Pubmed/internet: isolated stroke of ...
  - Amygdala : 0 cases
  - Hippocampus : 0 - 5% of hippocampus-involving strokes
  - Hypothalamus : 6 cases
- Why are such isolated stroke in the core limbic system so rare ? Likely because of ...
  - Abundant vascularization from multiple sources
  - for phylogenetically reasons
  - (and its dysfunction is rapidly compensated?)




Perosa Brain 2020

Hypothal. stroke: Matsubara BMC Neurol 2019; hippo-involving: Szabo Stroke 2009; Förster Int J Stroke 2016

# Intermediate conclusion

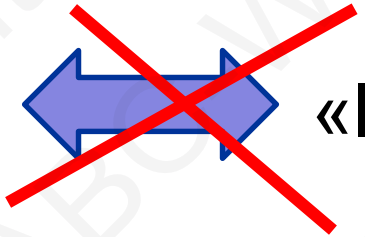
## Pit-stop 2


Red Bull electric car

Limbic lesion ⇏ «limbic» symptoms

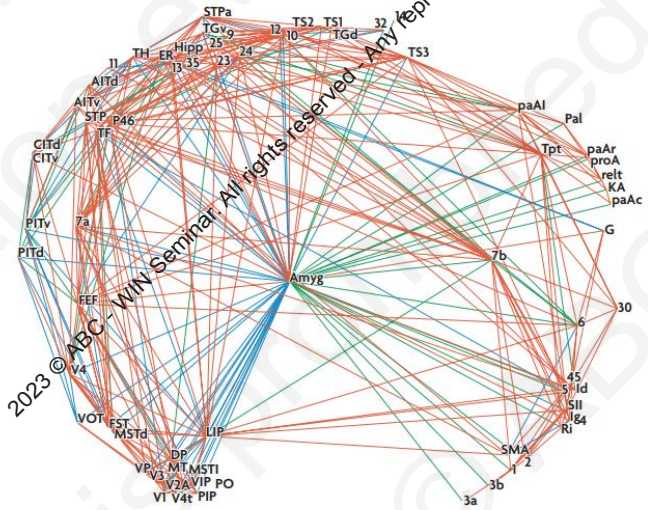
# Why this mismatch

## between «limbic» stroke symptoms and limbic stroke ?

Limbic lesion  «limbic» symptoms

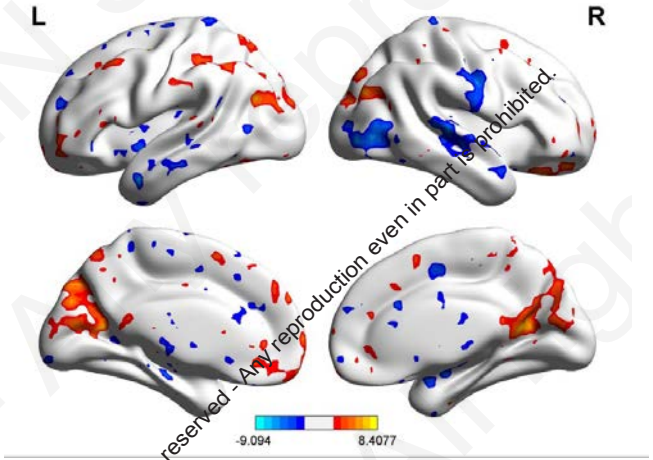
# Complexe cerebral function/dysfunction happen in widely distributed networks

## Exemple : amygdala




Connectivity of the amygdala

Young Rev Neurosci 1994 and Heller Cogn Emot 1997



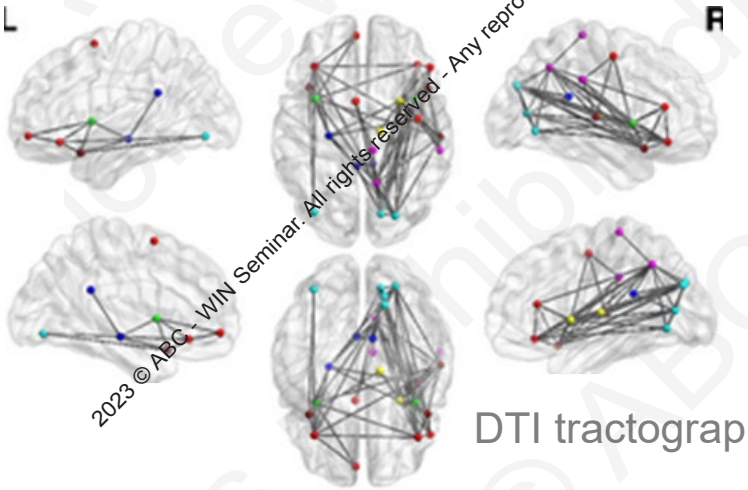

Functional connectivity by resting state fMRI

## Post-stroke depression: Changes of amygdala connections

Zhang Am J Phys Med Rehabil 2019

# Complexe cerebral function/dysfunction happen in widely distributed networks

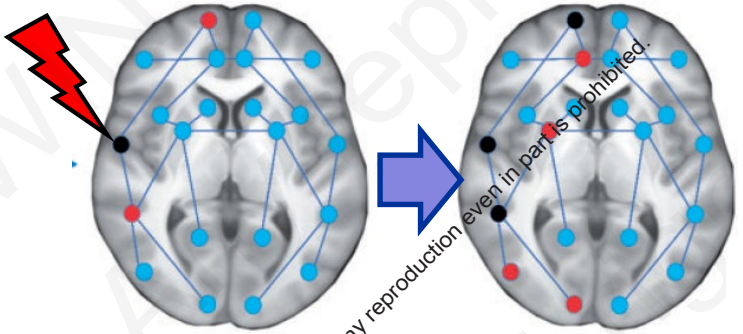
## Exemple : apathy post-stroke




DTI tractography

Post-stroke apathy:
Disconnection of complex sub-network of regions

Yang Eur J Neurol 2014



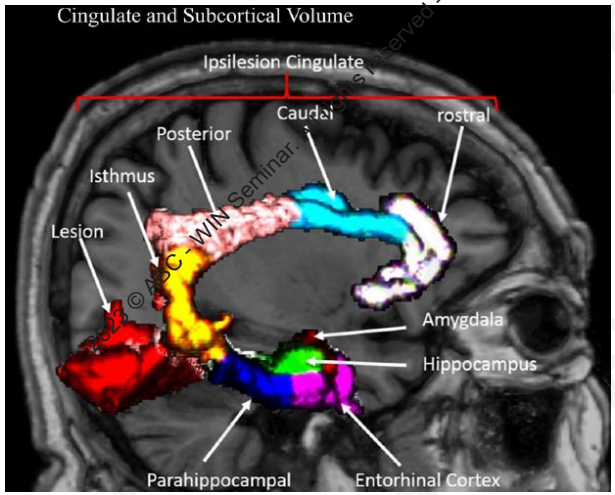
**Red**: funct. diaschisis
**Black**: 2° degeneration

Apathy model:
Disruption of key networks

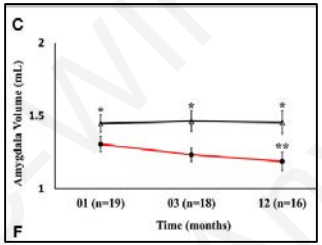
Tay IntJStroke 2021

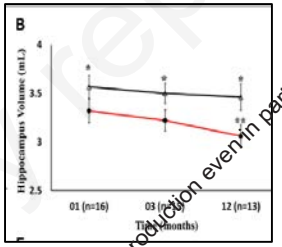
# Complexe cerebral function/dysfunction happen in widely distributed networks

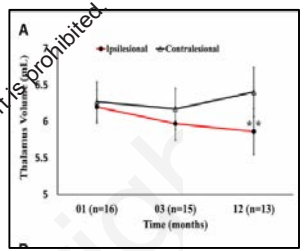
## Non-limbic stroke : effect on limbic volume over time




3T-DTI volume measurements




Amygdala Hippocampus Thalamus

→ Limbic and paralimbic volume decrease («degenerate») with time from remote effects of strokes

Haque & Savitz, Front Neurol 2019

# Intermediate conclusion

## Pit-stop 3


Red Bull electric car

→ Limbic system is heavily connected

→ Limbic stroke causes «diffuse», non-specific compexe brain dysfunctions, and vice-versa

→ Limbic stroke: any exception to these «non-specific» effects ?

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# Acute non-traumatic amnesia

## Differential diagnosis

- Transient global amnesia (TGA)
- Strategic TIA or stroke = ischemic amnesia
- Focal epileptic seizure = epileptic amnesia
- Migraine with amnestic aura = migrainous amnesia
- Gayet-Wernicke syndrome (thiamine deficiency)
- Limbic encephalitis
- Functional amnesia (dissociative, psychogenic)


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# Acute amnesia from stroke/TIA

- Isolated amnesia from stroke: very rare
  - ➢ 0.2% of all ischemic strokes
- Often: misdiagnosed as transient global amnesia (TGA)
  - → and therefore stroke missed
  - ➢ Very rarely: ischemic amnesia clinically identical to true TGA
- Often: some red flags (next slide)

# Acute amnesia: red flags for stroke rather than TGA

- Higher age, presence of ++ vascular risk factors
- Very short (minutes)
- Partial (not global)
- Additional symptoms or signs :
  - Visual, sensory, motor, ↓ consciousness, aphasia etc.


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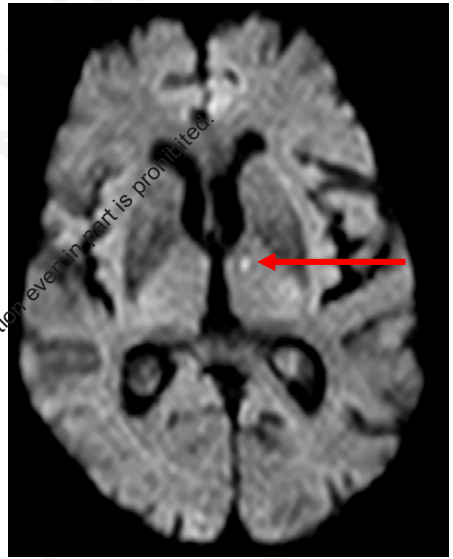
# Isolated amnesia from stroke

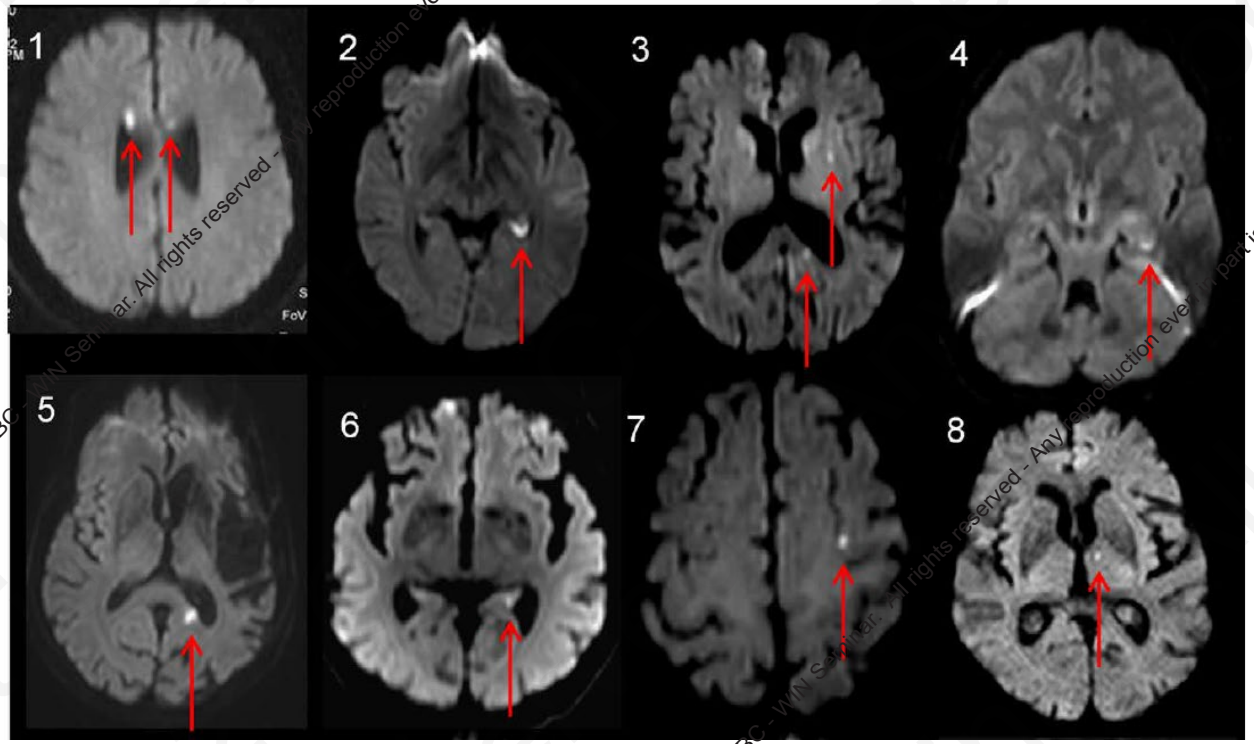
## Radiology and lesion location

- Mostly limbic and paralimbic system (Papez' circuit)
  - Anterior thalamus (posterior comm. art.)
  - Hippocampus (mesio-temporal)
  - Splenium/fornix
- Clincally : Unilateral stroke
  - → Transient episodic amnesia (and red flag symptoms)
- Bilateral strokes
  - → Persistent amnesia, partial or severe (and red flags)



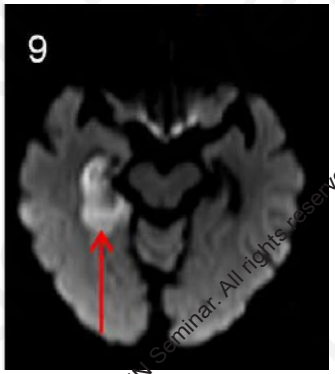
Anterior thalamic
Radiology CHUV

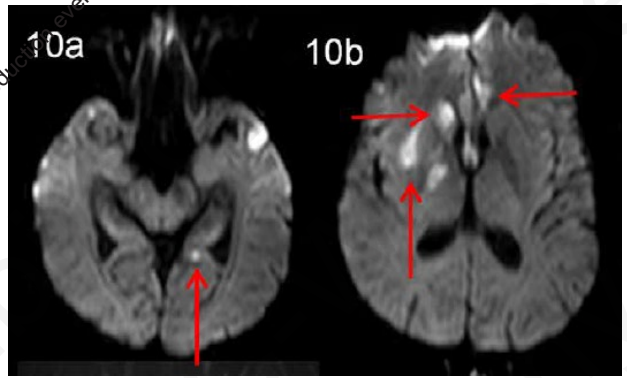
# Isolated ischemic amnesia (N=13) : Radiology - 1

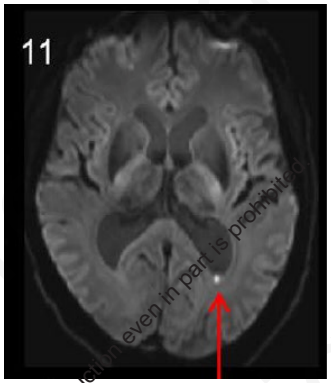


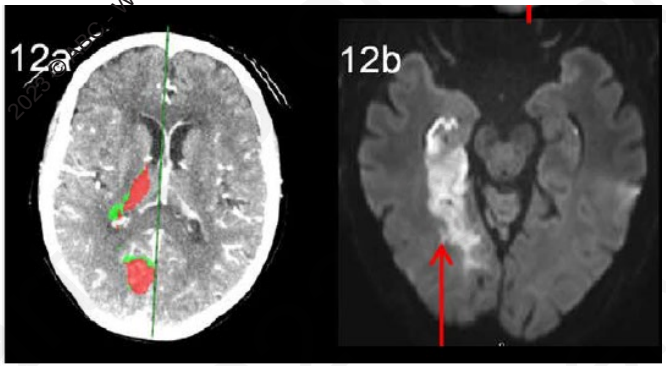

Michel Stroke 2017

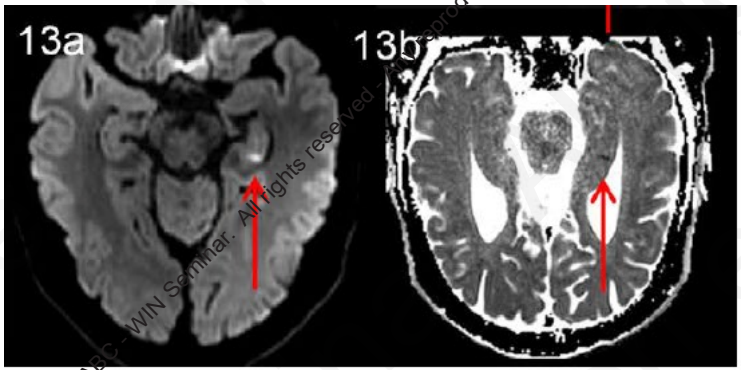
# Isolated ischemic amnesia (N=13) : Radiology - 2



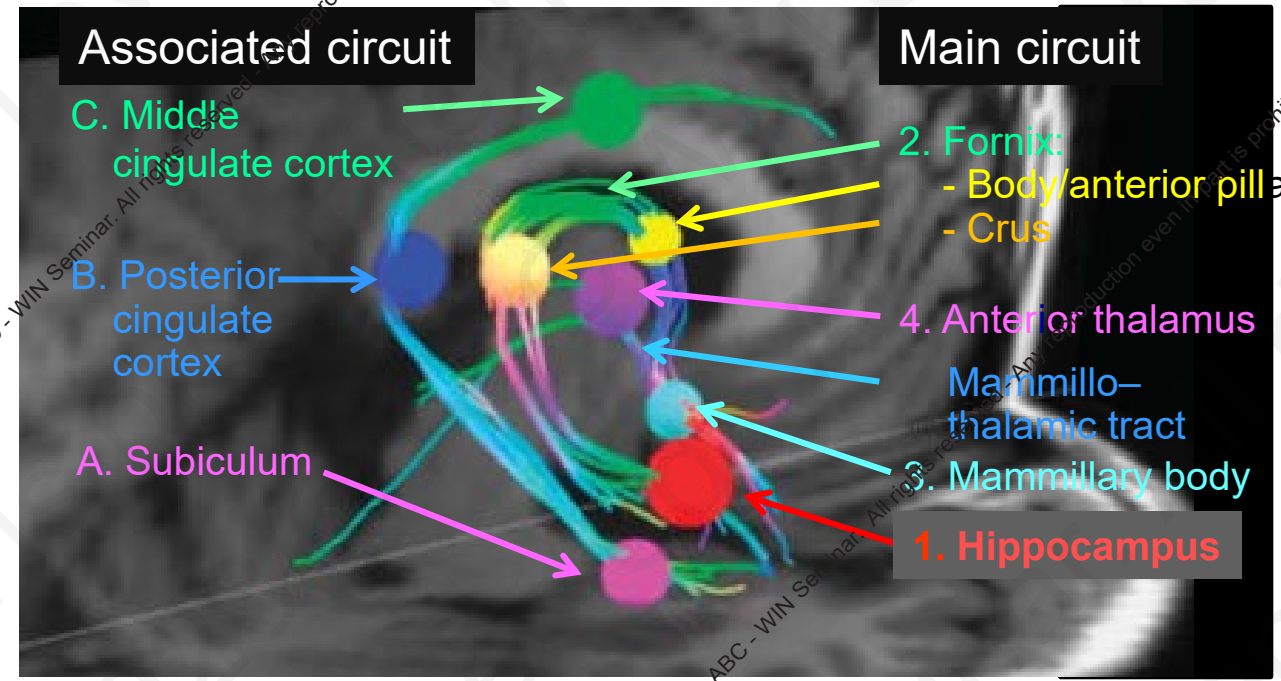




Michel Stroke 2017

# Anatomy of Papez circuit visualized in vivo

## by MR diffusion spectrum imaging of fiber tracts

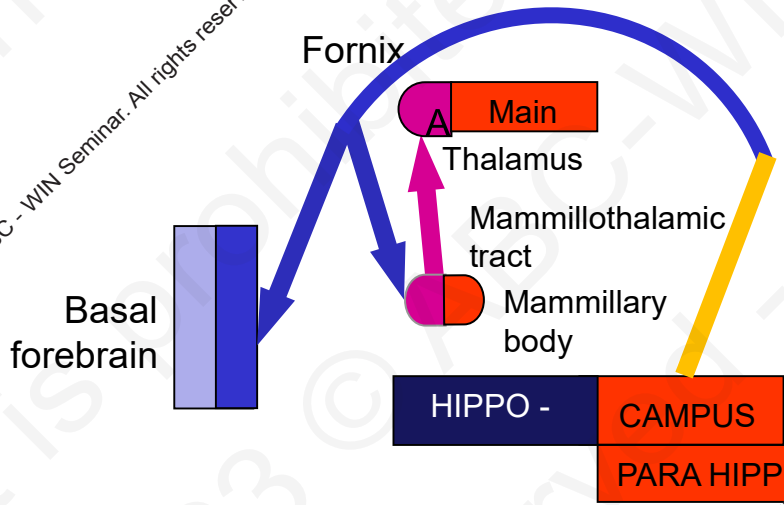
Posterior ← Brain → Anterior




Granziera NeuroReport 2011

# Vascularisation of the Papez' circuit

- Anterior cerebral artery
- Anterior choroidal artery
- Anterior communicating artery
- Posterior cerebral artery
- Posterior choroidal artery
- Posterior communicating artery




→ Mosty posterior circulation

Slide: courtesy J. Ferro, Lisbon

# Intermediate conclusion

## Pit-stop 4


Red Bull electric car

→ Stroke in seral parts of the (extended) limbic system can cause a quite specific episodic, mostly transient memory deficit


# Stroke in the limbic system (LS)


## Menu

- Complexe cerebral function/dysfunction
- Potential symptoms from stroke in the LS
- Observed symptoms from stroke in the LS
- Amnesia and stroke
- TGA (and stroke)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# What is TGA ?

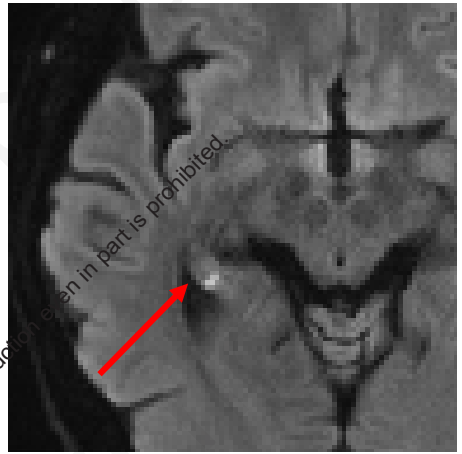
## (transient global amnesia)

- Pure antero- & retrograde amnesia
- Often repetitive questions, anxiety, headache, nausea, dizziness
- No other neurological signs&symptoms; preserved identity
- Lasting < 24 hours at bedside
- Triggers present in 50-70% (physical and/or emotional)

Criteria : Caplan L, in Vinken/Bruyn/Klawans: Handbook of Clinical Neurology 1985
Hodges and Warlow JNNP 1990

# What is TGA ?

## Radiology and prognosis



- 50-70% with vanishing hippocampal DWI-pixel
  - 10% multiple/bilateral
  - Best timing of DWI : 12-48 hours
- TGA is not a (classical, arterial) stroke or TIA
  - Not increased stroke risk
  - No further stroke work-up needed if typical
- Pathogenetic hypotheses
  - Hypoxic-ischemic
  - Transient venous hypertension
  - Stress-induced functional disorder of hippocampus

# TGA triggers are present in 50-70 %

**Systemic (physical) triggers**

- Strenuous physical activity
- Acute temperature change
- Hypertensive crisis
- Sexual intercourse
- Acute cardiovascular events
- Medical interventions
- and others

**Psychological triggers**

- Acute emotional stress
- Surprise
- Acute pain
- Sexual intercourse
- and others

**Spontaneous occurrence**

- No trigger
- Unidentified trigger

**Acute neurological disease triggers***

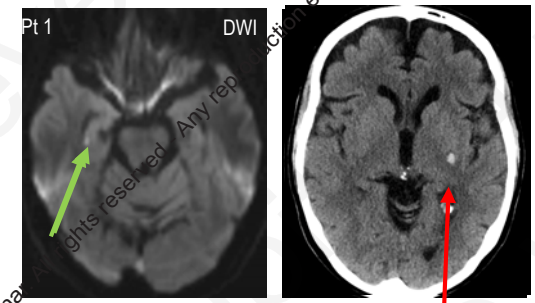
- **Ischemic stroke**
- **Intracerebral haemorrhage**
- **Subarachnoid haemorrhage**
- Reversible cerebral vasoconstriction syndrome
- Seizure/encephalitis
- Peripheral vertigo
- Migraine

## Transient Global Amnesia

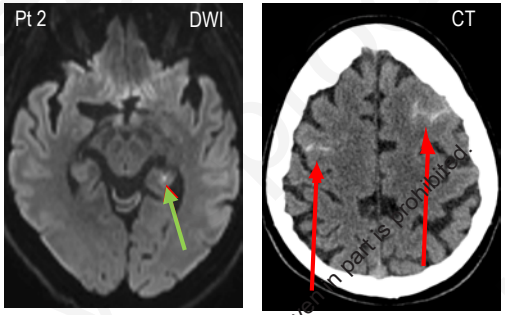
* Piffer S, Nannoni S, & Michel. Neurol Sci 2022

# TGA triggered by / associated with

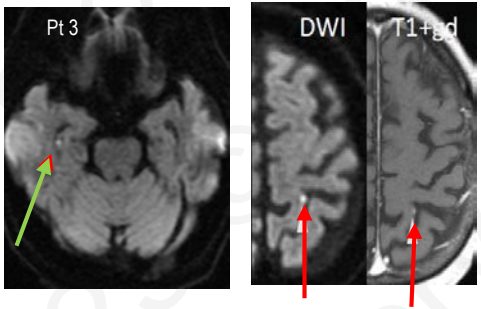
## acute cerebrovascular events



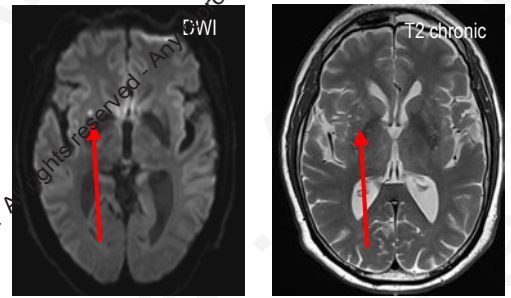

Intracereb. hemorrhage (contralat.)




Bilat. convexity SAH



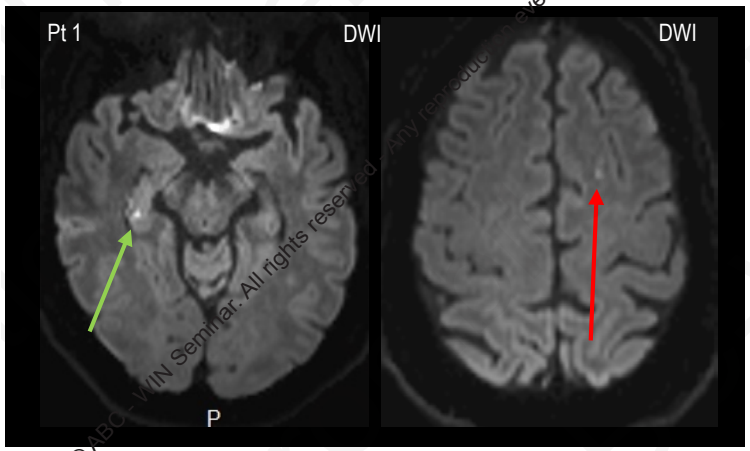

Ischemic stroke (contralat.)



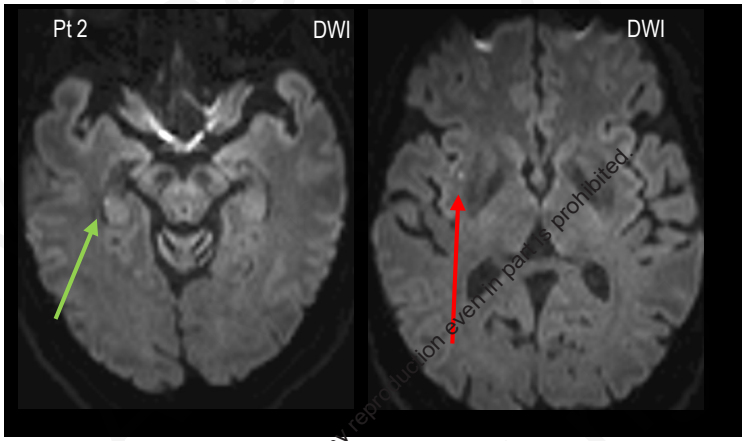

Ischemic stroke (ipsilat.)

Piffer S*, Nannoni S*, & Michel. Neurol Sci 2022

# TGA: unexpected radiological findings




Clinical TGA




Clinical TGA

→ Additional vanishing pixels outside hippocampus

(usually in the hemispheric WM) have been observed in otherwise typical TGA

# Triggers of TGA

- **Systemic (physical) triggers**
- **Psychological triggers**
- **Spontaneous occurrence**
- **Acute neurological disease triggers**

## Transient Global Amnesia







Piffer S*, Nannoni S*, & Michel. J Neurol Sci 2022

# Triggers of TGA

| Systemic (physical) triggers | Psychological triggers | Spontaneous occurrence | Acute neurological disease triggers |
|---|---|---|---|

## Transient Global Amnesia – Hippocampal Punctate DWI Lesion **Spectrum**

| | Typical radiological findings | | Atypical radiological findings |
|---|---|---|---|
| | HPDL | No PDL | Extra-HPDL (with/without HPDL) |
| Typical clinical TGA | **« Classical » TGA** with HPDL | **« Classical » TGA** without PDL | **« Classical » TGA** with extra-HPDL |
| Atypical clinical manifestation | **TGA - plus** with HPDL | **TGA - plus** without PDL | **TGA - plus** with extra-HPDL |
| Atypical clinical manifestation | **Non-amnesic neurological manifestations** with HPDL | **Non-amnesic neurol. manifestations** without PDL | **Non-amnesic neurological manifestations** with extra-HPDL |

Piffer S*, Nannoni S* & Michel. J Neurol Sci 2022

# Intermediate conclusion

## Pit-stop 5


Red Bull electric car

→ TGA is TGA (and not stroke)

→ But sometimes ....

- Stroke triggers a TGA
- TGA is not as typical as we wish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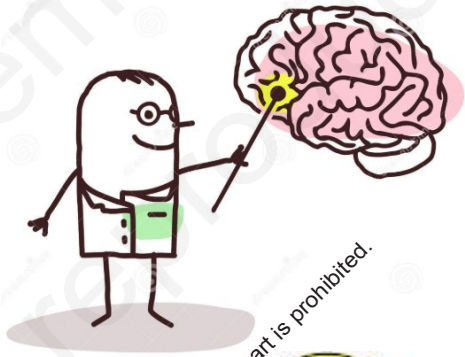
# The finish line ...

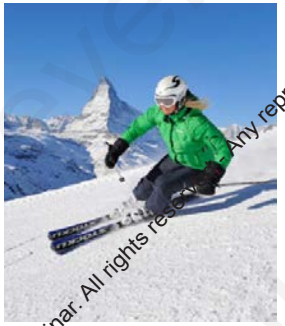


« Neurologists: 100% accurate,
but completely useless »

« The best stroke treatment
is stroke prevention »

→ 6 Swiss secrets
how to prevent strokes

# Swiss secrets how to prevent strokes



## Lots of sport

Lee Stroke 2003

## Relax with friends

Henderson Stroke 2013


## Black chocholate

Buitrago-Lopez BMJ 2011

## Vegetables & fruits

He Lancet 2006

## Low-fat milk products

Larsson Stroke 2012/ Dehghan Lancet 2018


## 3-5 cups/day

Ding Circulation 2013

# Stroke in the limbic system


- Rare in isolation; symptoms little specific
- Network effect from and on limbic system
- Exception: episodic memory loss, often transient
- Differentiate ischemic amnesia from TGA







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