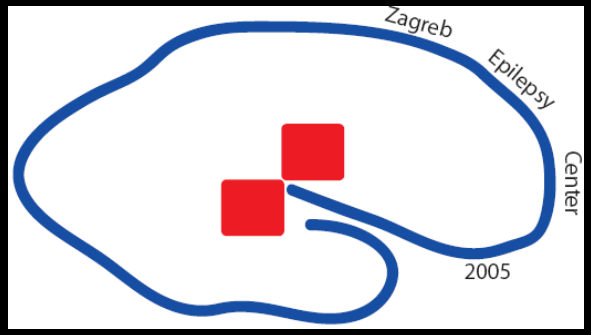
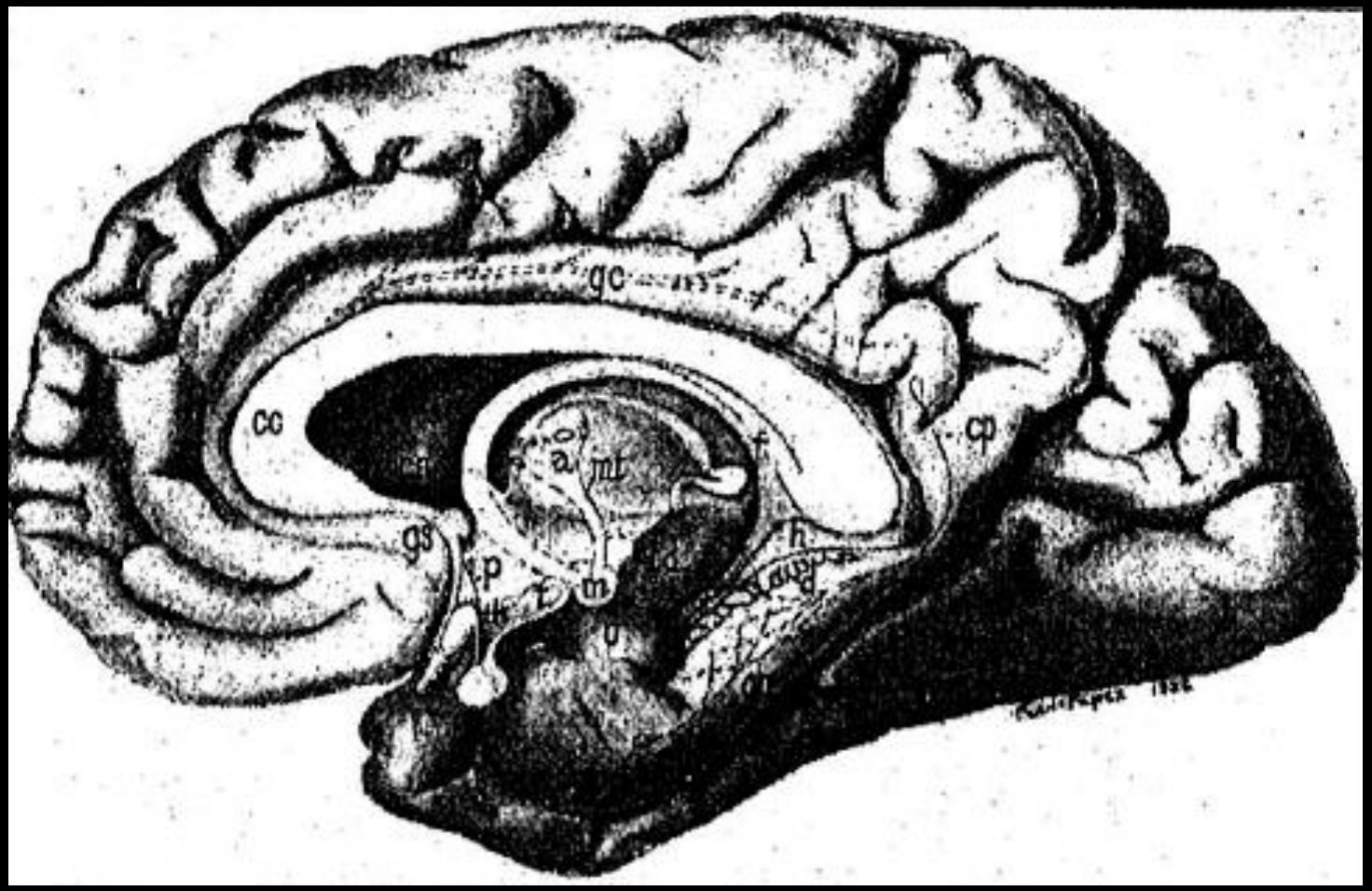
# CLINICAL MODEL OF NEURAL NETWORKS

Hrvoje Hećimović, MD PhD
Zagreb Epilepsy Center
Croatia



# Papez' Circuit of Emotion




Papez JW. Archives of Neurology and Psychiatry. 38: 725-734, 1937

# A PROPOSED MECHANISM OF EMOTION

JAMES W. PAPEZ, M.D.

ITHACA, N. Y.

For centuries the functional significance of the hippocampus has remained unknown. The hippocampus is by no means a vestigial structure; it may vary greatly in development in different persons. Retzius,[17] commenting on this, stated that the varied development of the hippocampus is independent of age, sex or special prominence of any known psychic function. Ferrier [18] was the first to test the matter experimentally. He destroyed the hippocampus in monkeys and described the depressive effect it produced on cutaneous sensibilities. He expressed the belief that it is the center for these sensibilities. What

leaving the functions of the hippocampus in obscurity

Subsequent observations have placed the zone of cutaneous sensibility in the parietal lobe, leaving the functions of the hippocampus in obscurity.

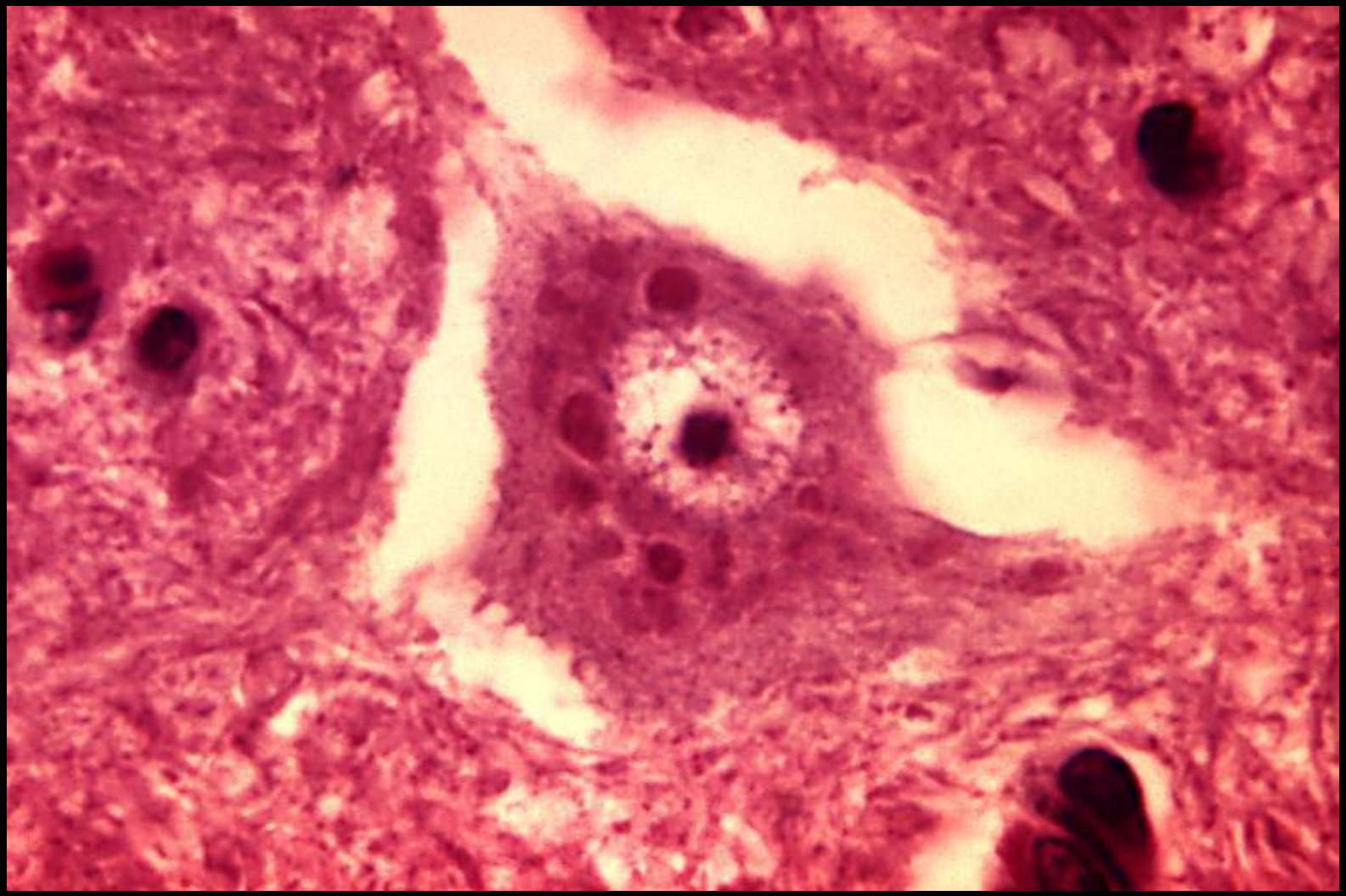
Since the Negri bodies, the essential lesions of rabies, or hydrophobia, have their site of predilection in the hippocampus and the cere-

intense emotional, convulsive, and paralytic symptoms

clue to the probable location of the emotive mechanism. The premonitory symptoms—insomnia, irritability and restlessness—usher in the stage of excitement and profound emotional perturbation. There is extreme

Archives of Neurology and Psychiatry. 38: 725-734, 1937.

# Negri Bodies in Ammon's Horn

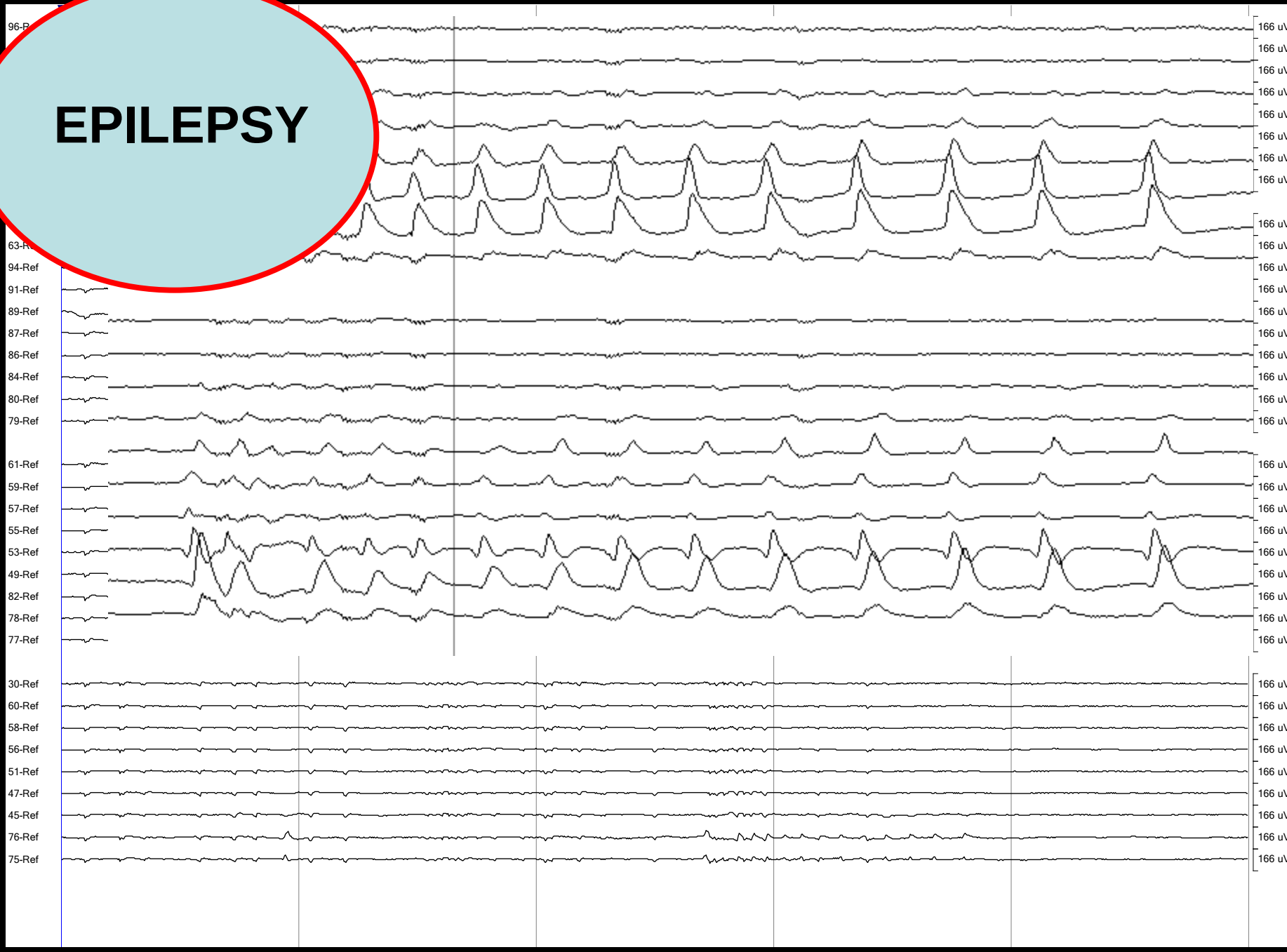


# Rabies Encephalitis

## Hippocampal Hyperexcitibility?

Burton et al. *Arch Neurolology 2005;62:873-882*

# EPILEPSY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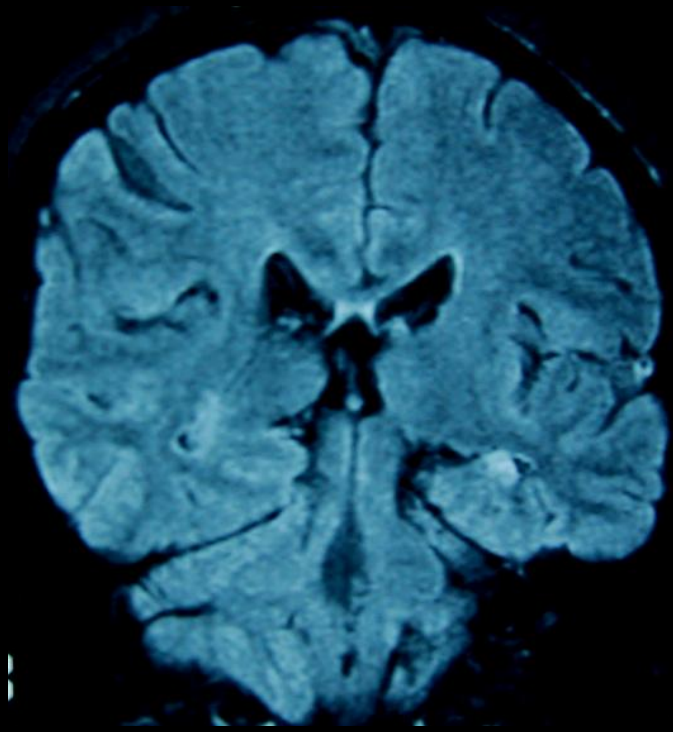
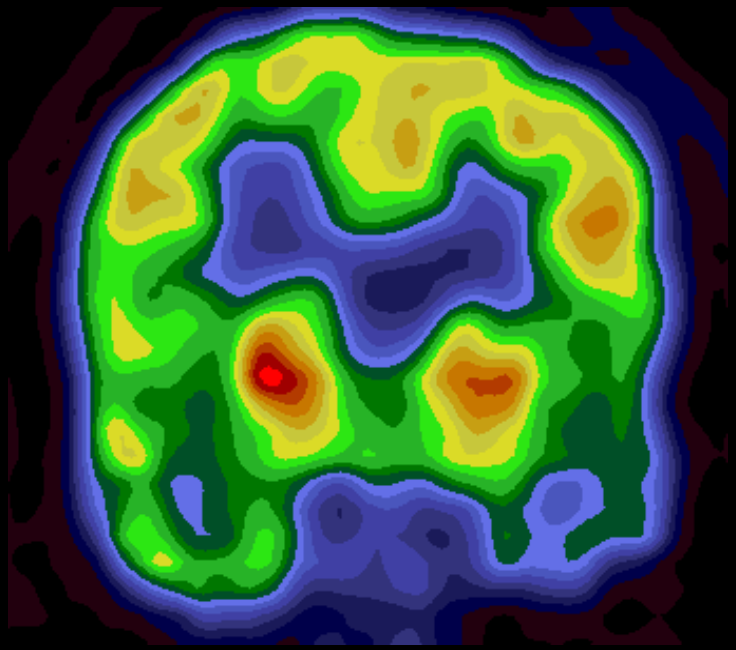
166 uV

# Inversion Recovery

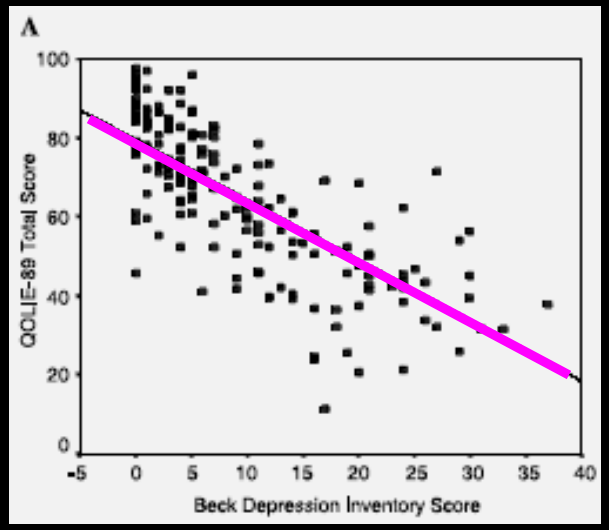



FLAIR

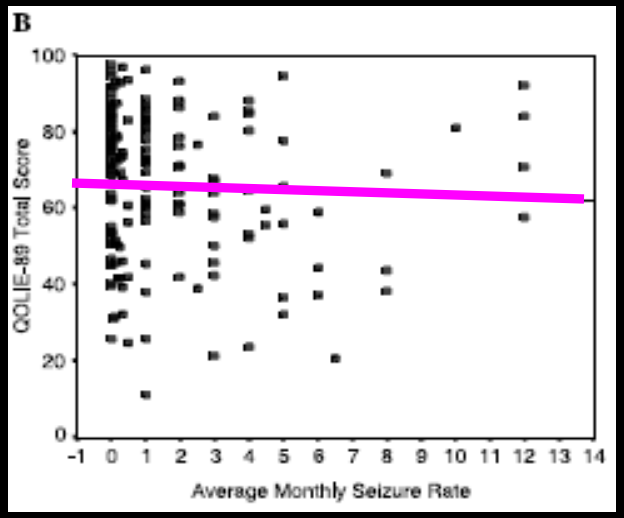


FDG-PET

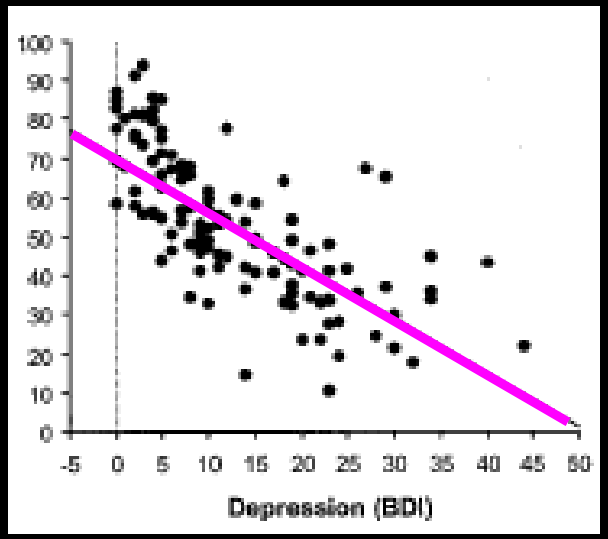
# Depression and Health Status in Epilepsy



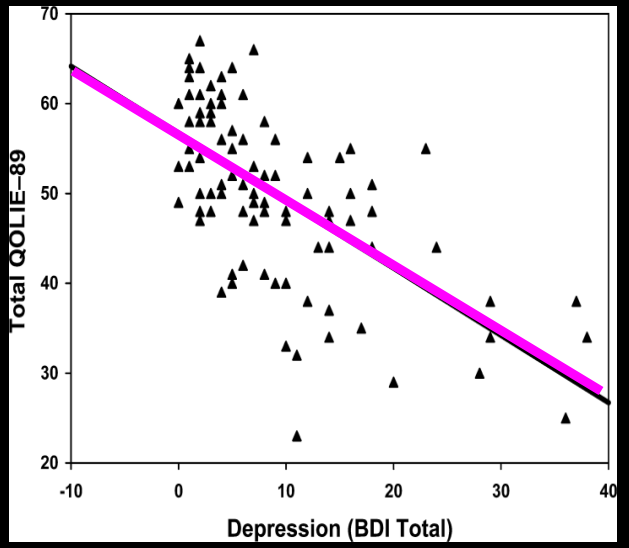

Gilliam et al, 1997, 2002




Gilliam et al, 1997, 2002

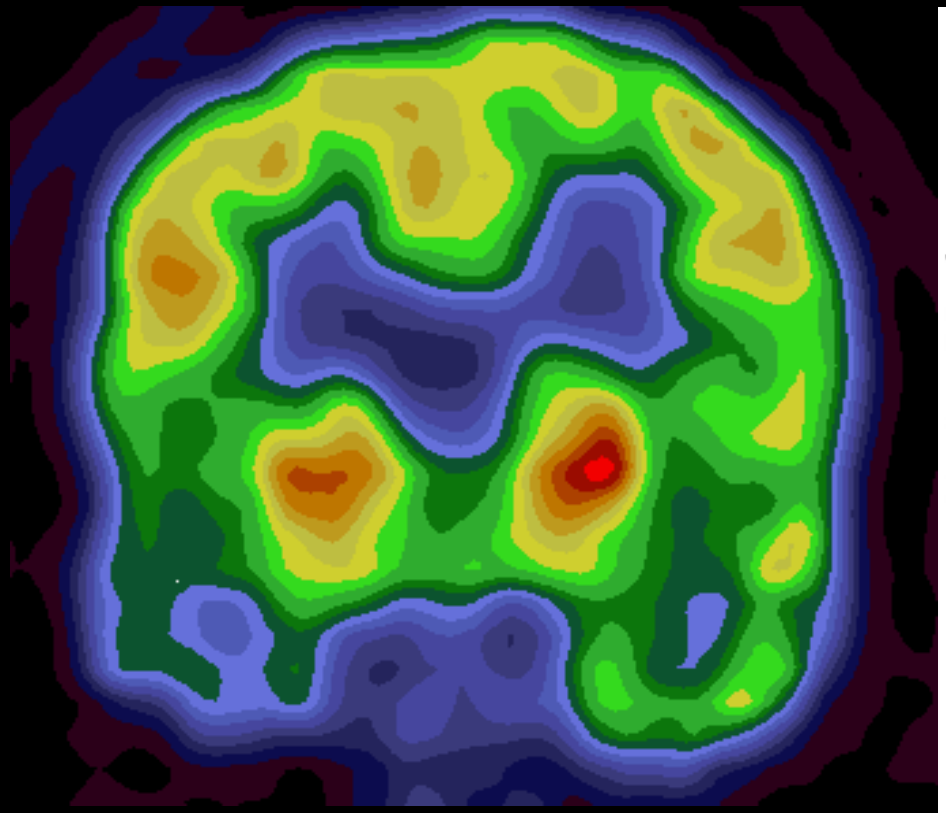


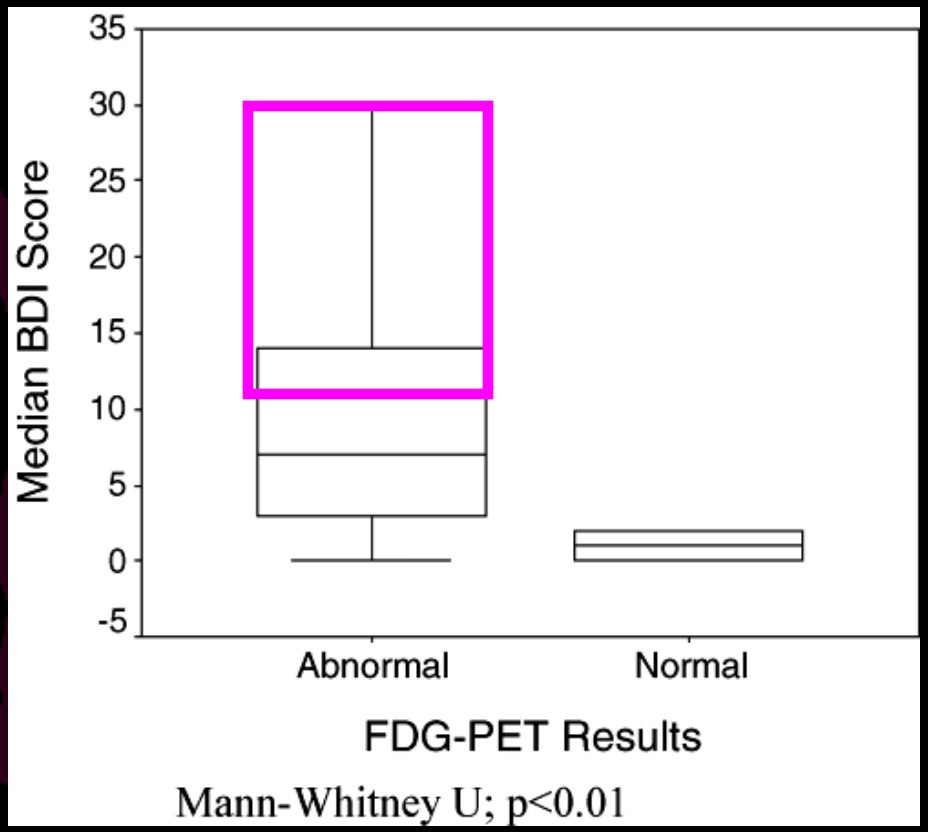

Boylan et al, 2004

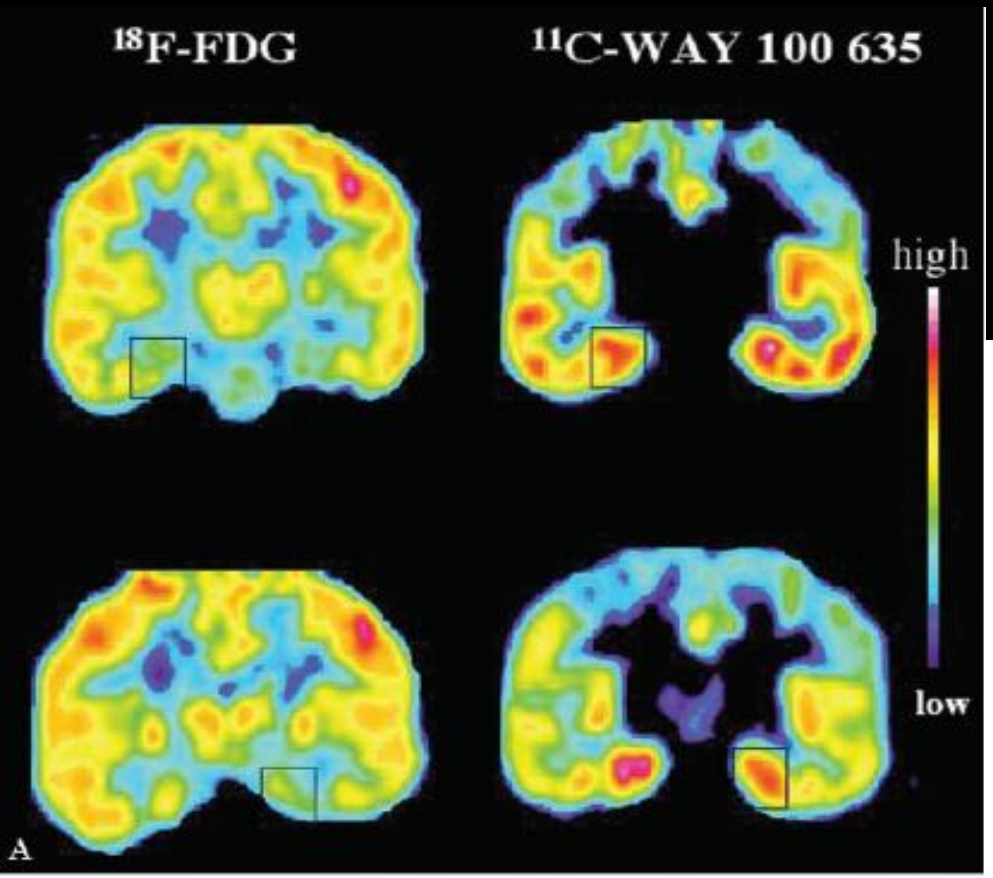


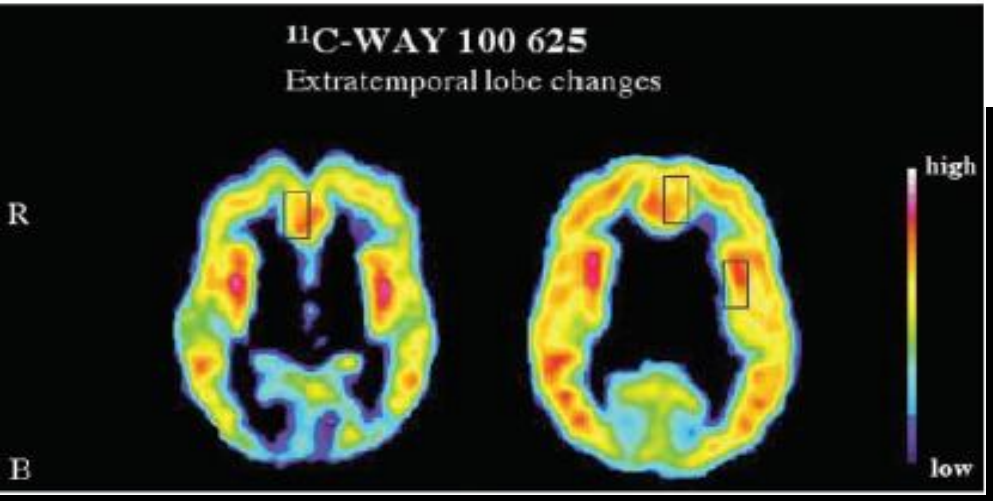

Jones et al, 2002

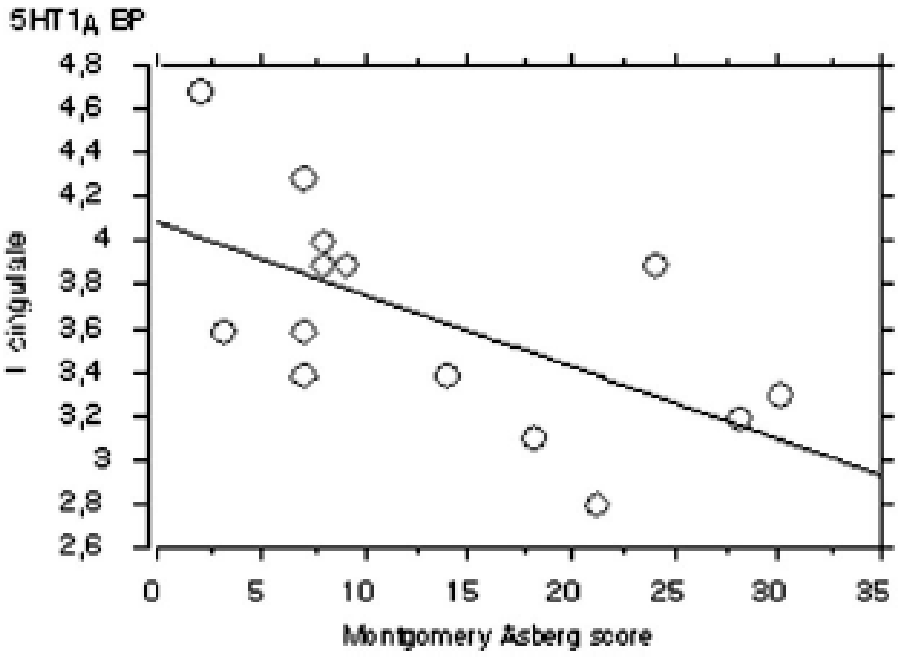
# FDG-PET and Depression in Epilepsy





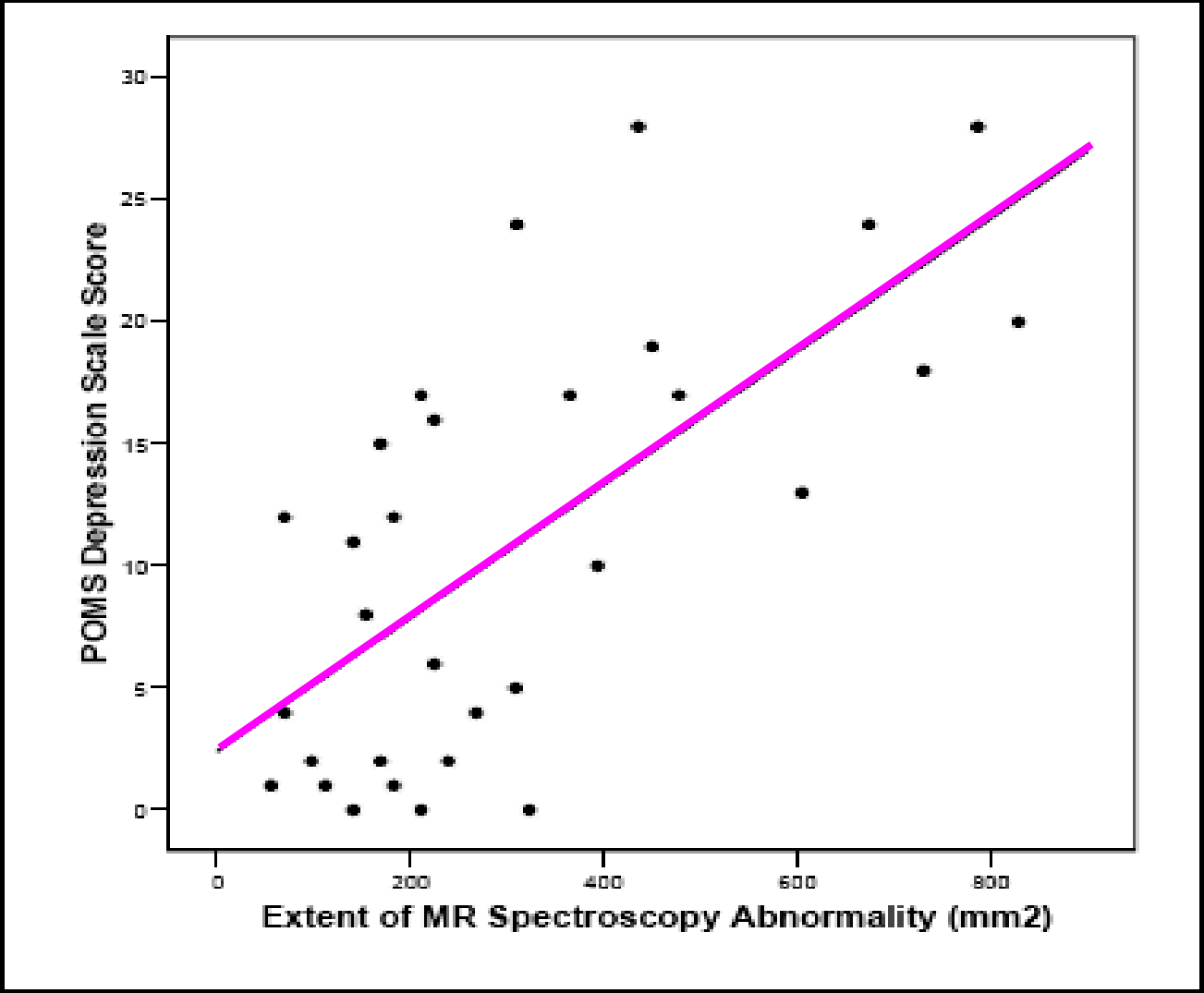



Savic et al, Neurology 2004

# $^{1}$H-MR Spectroscopy and Depression in TLE

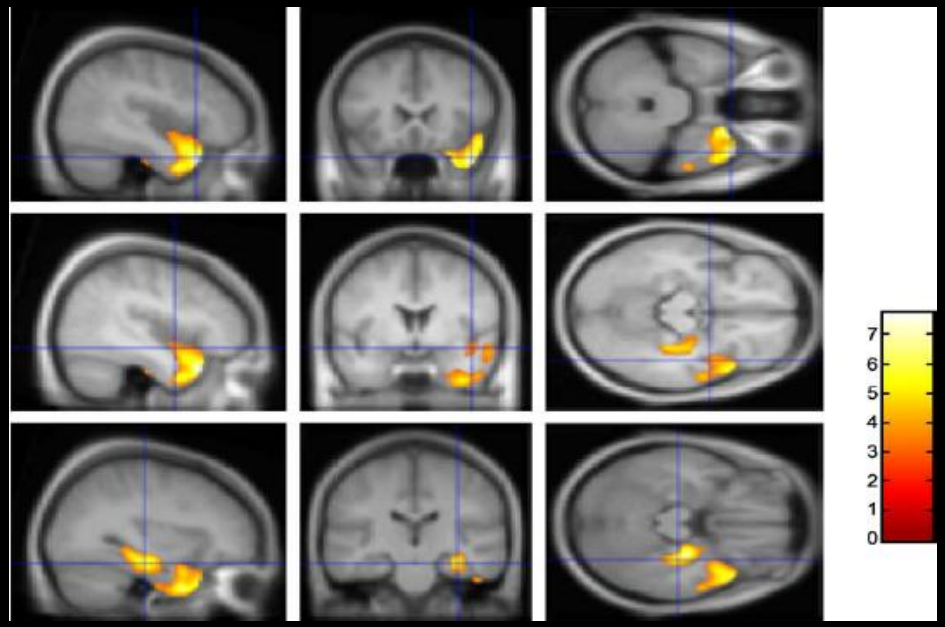


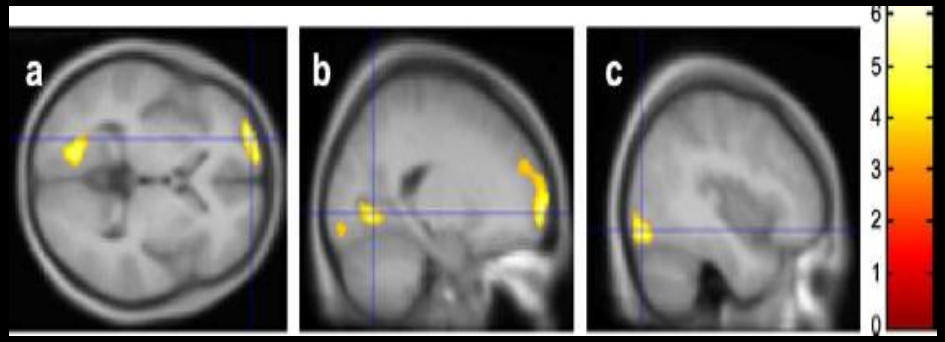

Spearman rho = 0.65, p<0.001

Gilliam et al. *Neurology*, 2007

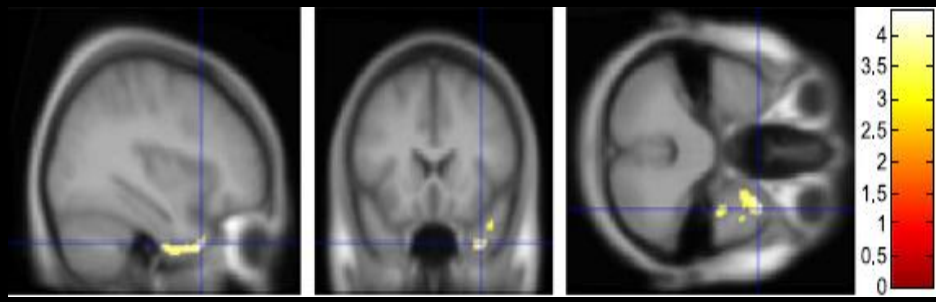
# HIPPOCAMPAL ATROPHY AND RELATED SEROTONERGIC CHANGES

**A) MTLE patients with HA**




**B) MTLE patients without HA**



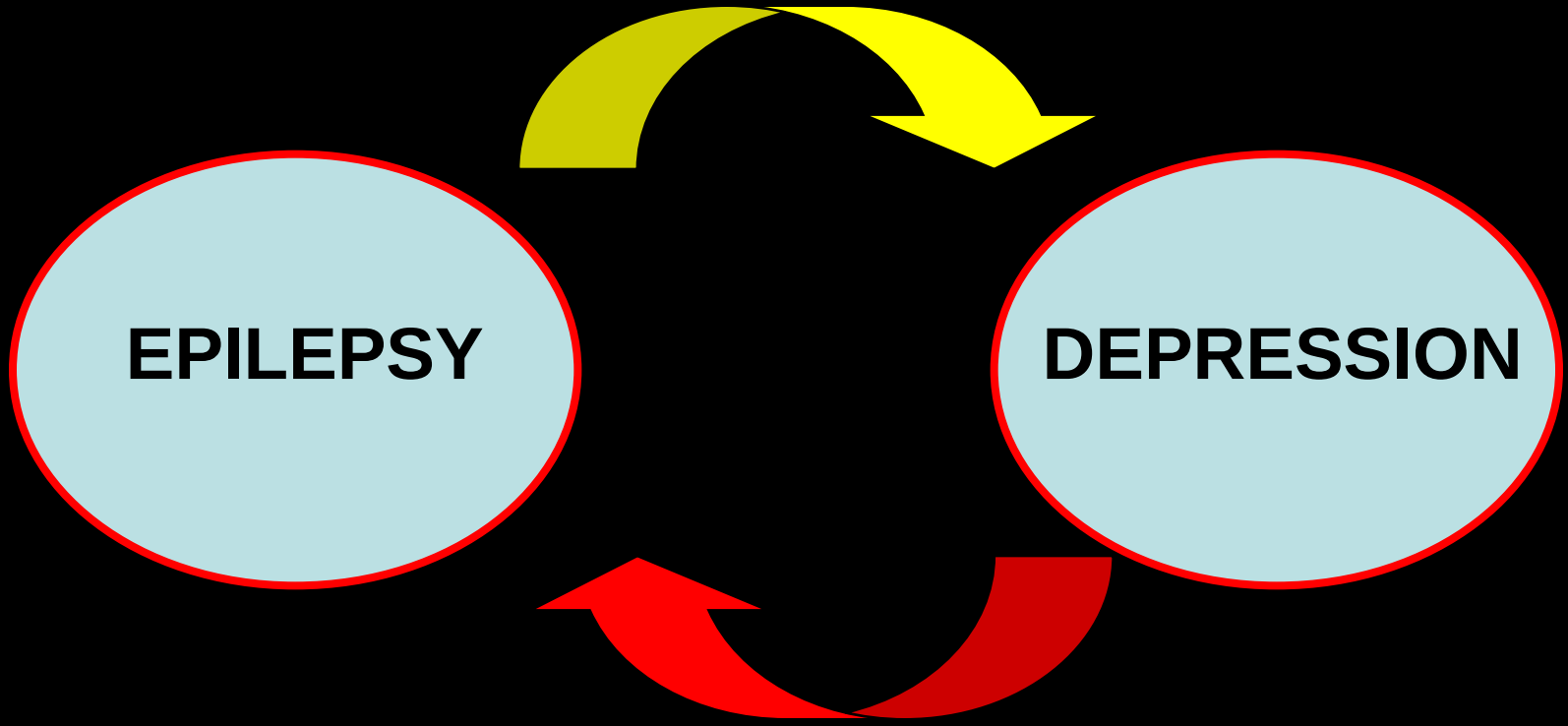

Merlet et al, Neuroimage 2004

# Prevalence of psychiatric comorbid diseases in epilepsy patients

| | In Epilepsy (range) | In the General Population (range) |
|---|---|---|
| **Depression** | **11%–60%** | **2%–4%[1]** |
| **Anxiety** | **19%–45%** | **2.5%–6.5%[2]** |
| **Psychosis** | **2%–8%** | **0.5%–0.7%[3]** |
| **ADHD** | **25%-30%?** | **2%–10%[4,5]** |

[1]Anthony, et al. *Epidemiol Rev.* 1995;17:240-242. [2]Weissman, et al. *J Clin Psychopharmacol.* 1986;Suppl 6:11-17. [3]Kessler, et al. *Arch Gen Psych.* 1994;51:8-19. [4]Costello EJ. *J Am Acad Child Adolesc Psychiatry.* 1989;28:836-841. [5]Rutteret al.,1970.

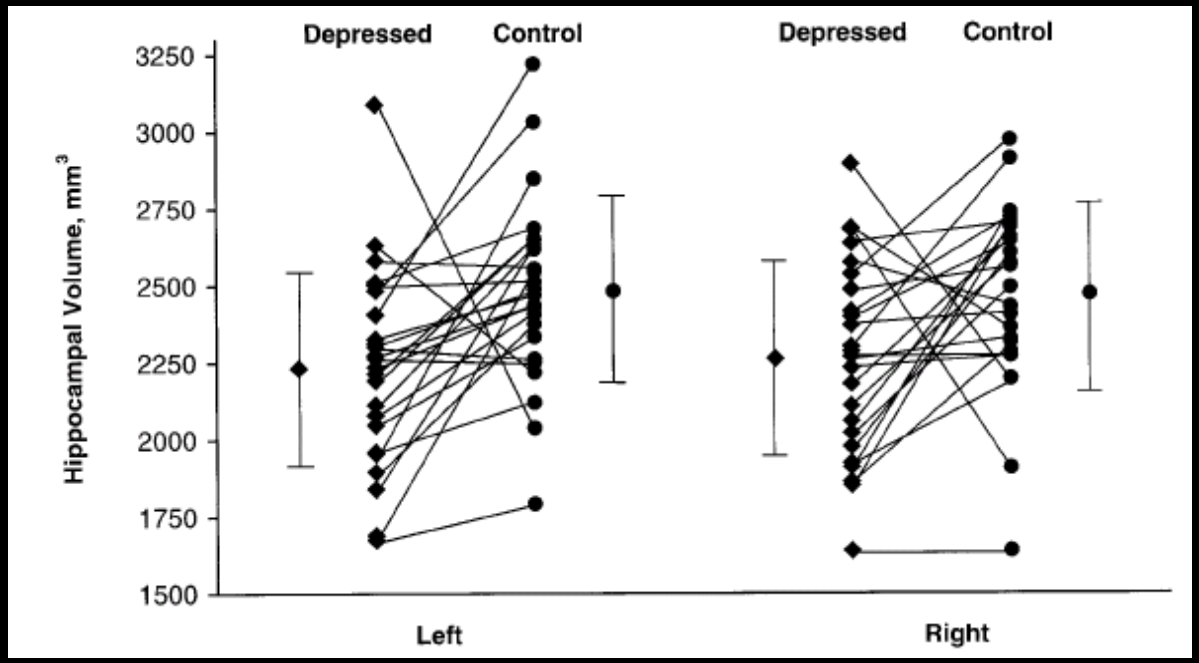
Kanner, with permission

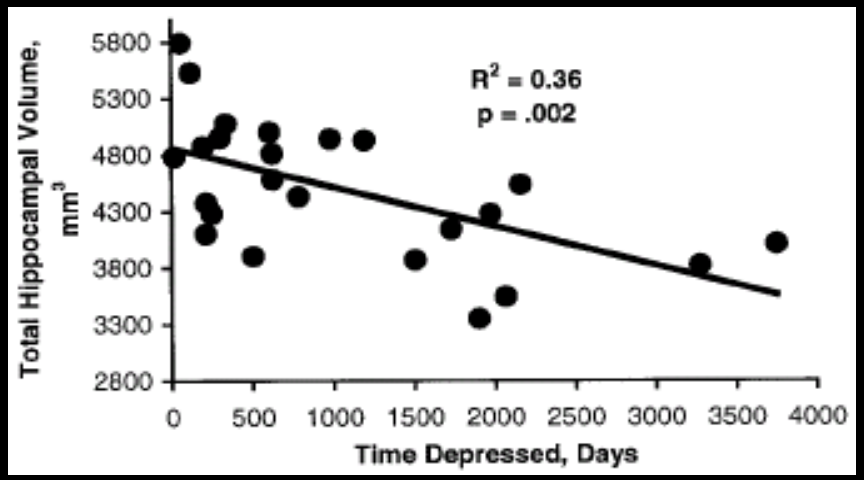

EPILEPSY
DEPRESSION

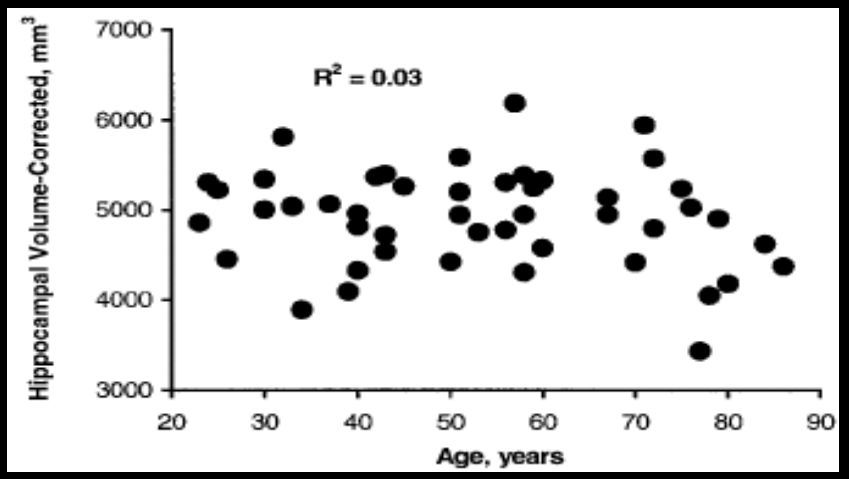
# Major Depression is a Risk Factor for Seizures

- Hippocrates (400 AD): “Melancholic people often have seizures, and epilepsy patients commonly become melancholic”
- Fosgren and Nystrom (1990): patients with major unipolar depression are **7x** more likely to get seizures during the course of illness
- Hesdorffer and Hauser (2000): patients with depression have **3.7x** increased risk for their first seizure

# STRUCTURAL CHANGES IN DEPRESSED

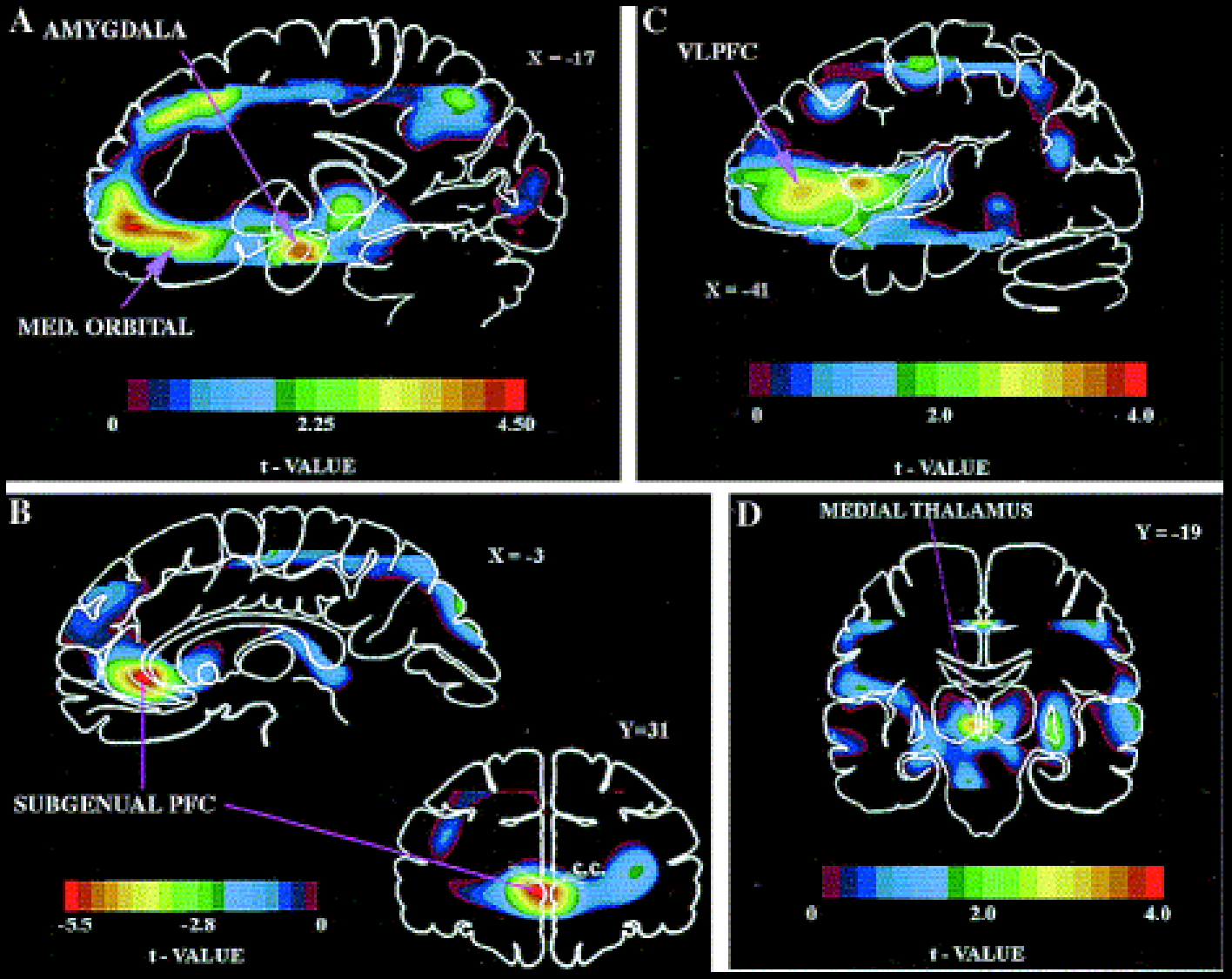


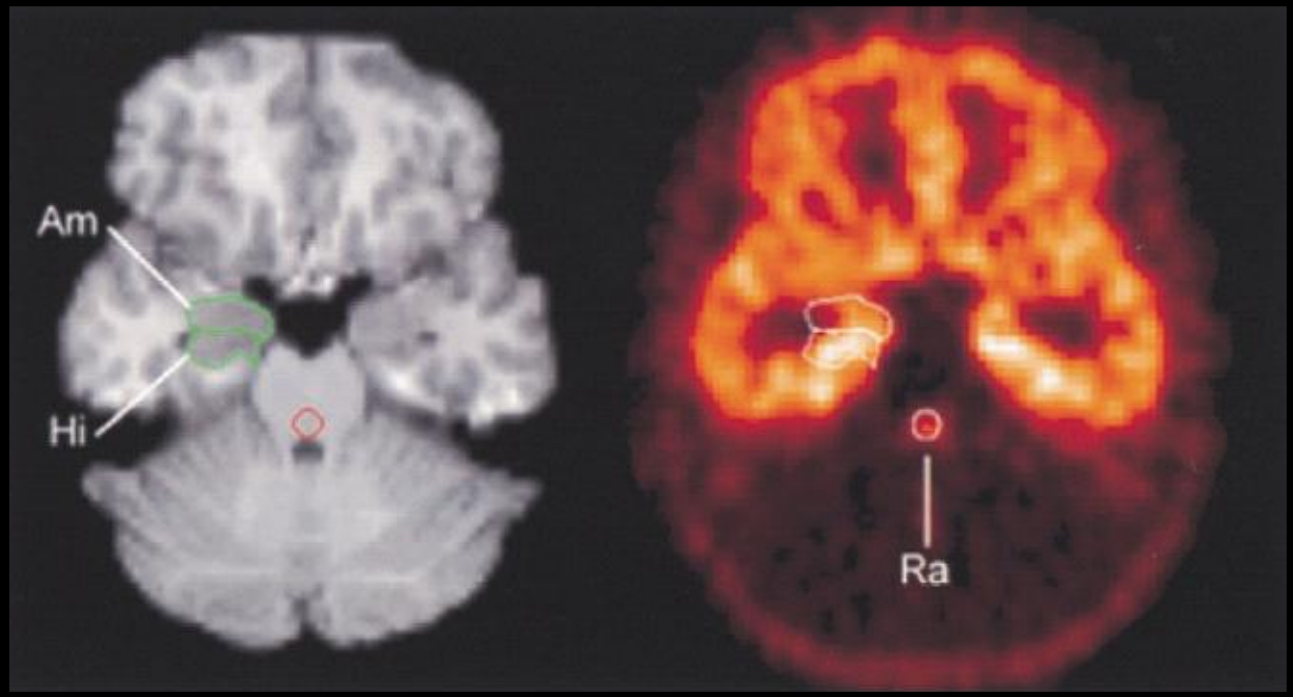

Sheline et al, J Neurosci 1999

# FRONTO-LIMBIC NETWORK CHANGES IN DEPRESSED



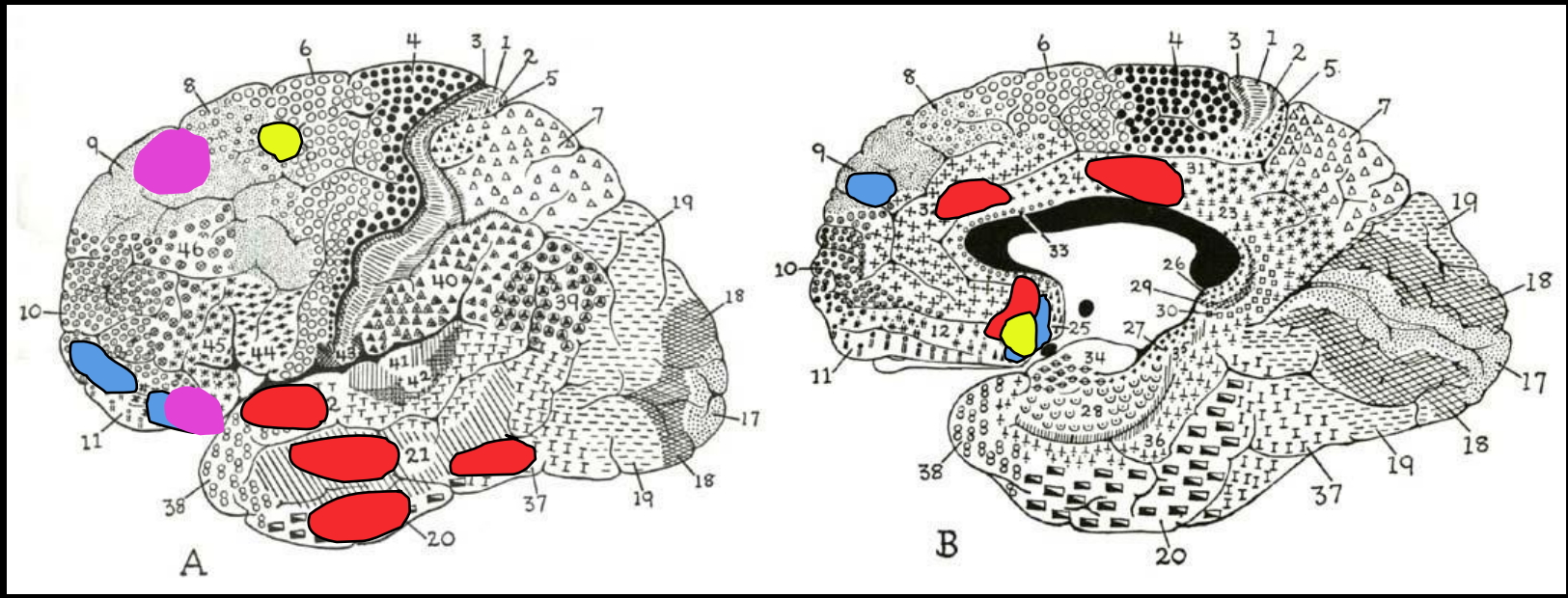

Drevets et al, Ann NY Acad Sci 1999

# Functional imaging of serotonin 1A receptor binding in depression



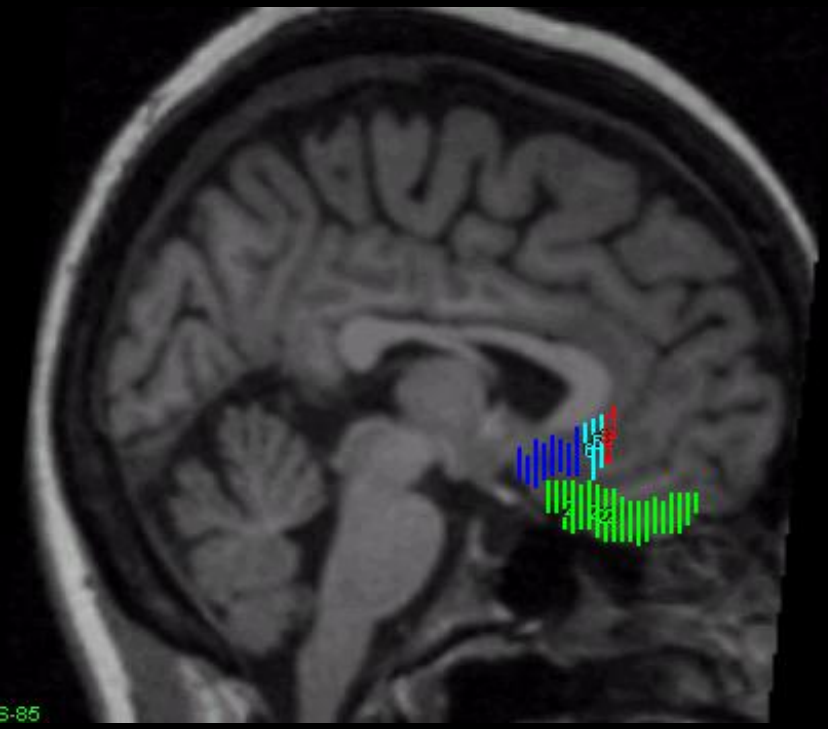

Drevets et al, Biol Psychiatry 1999

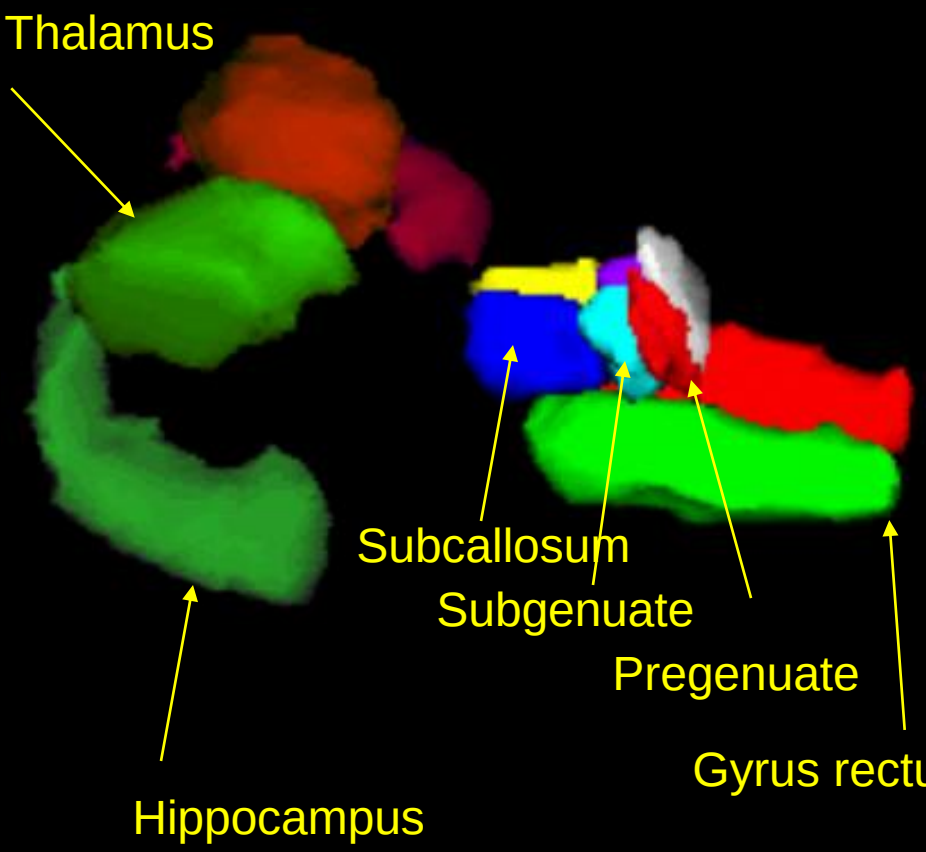
# Areas of FDG-PET change in Depression




= Gilliam et al., submitted
= Mann et al., 2005
= Drevets et al., 2004
= Mayberg et al., 1999

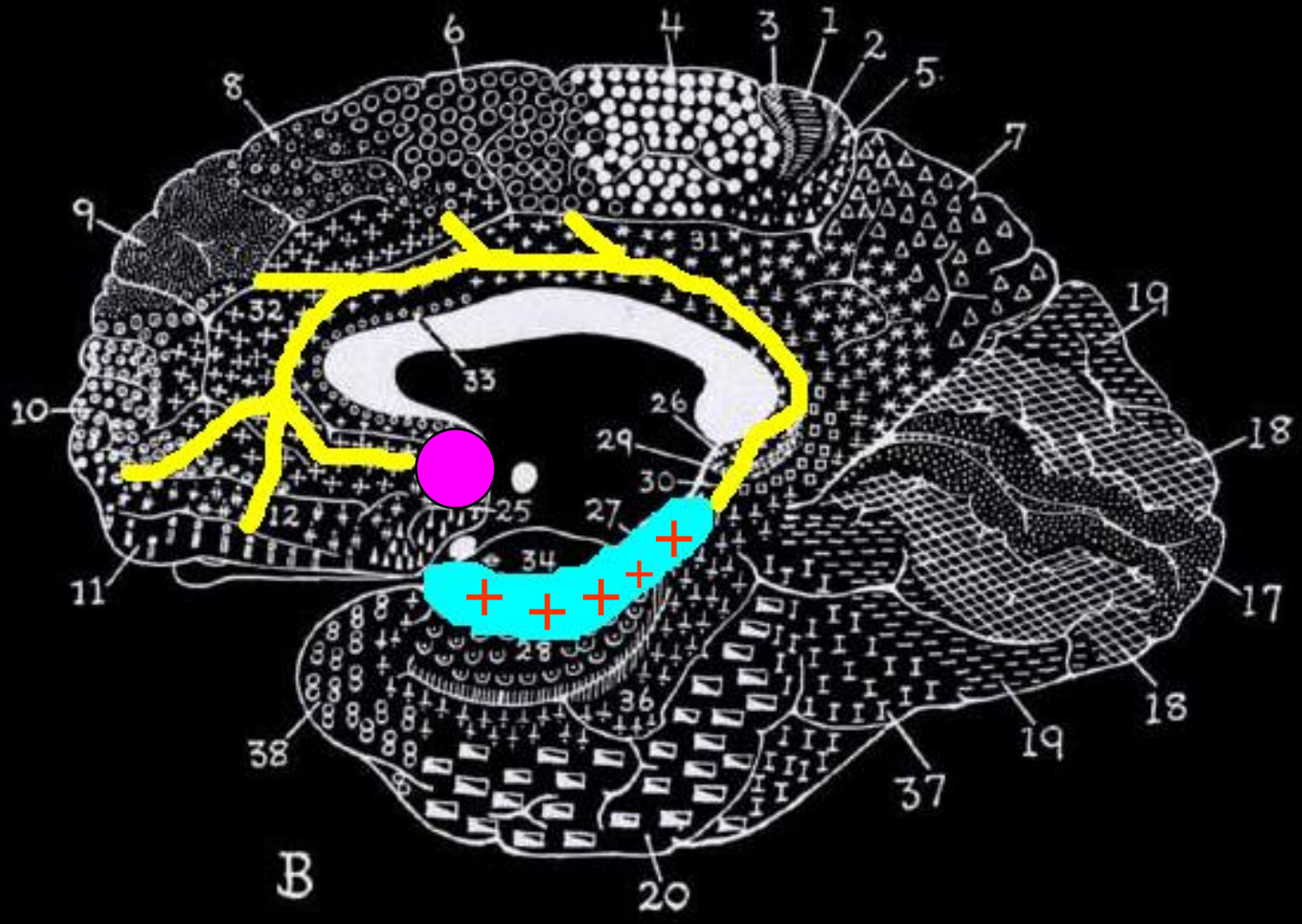
# Limbic-prefrontal network



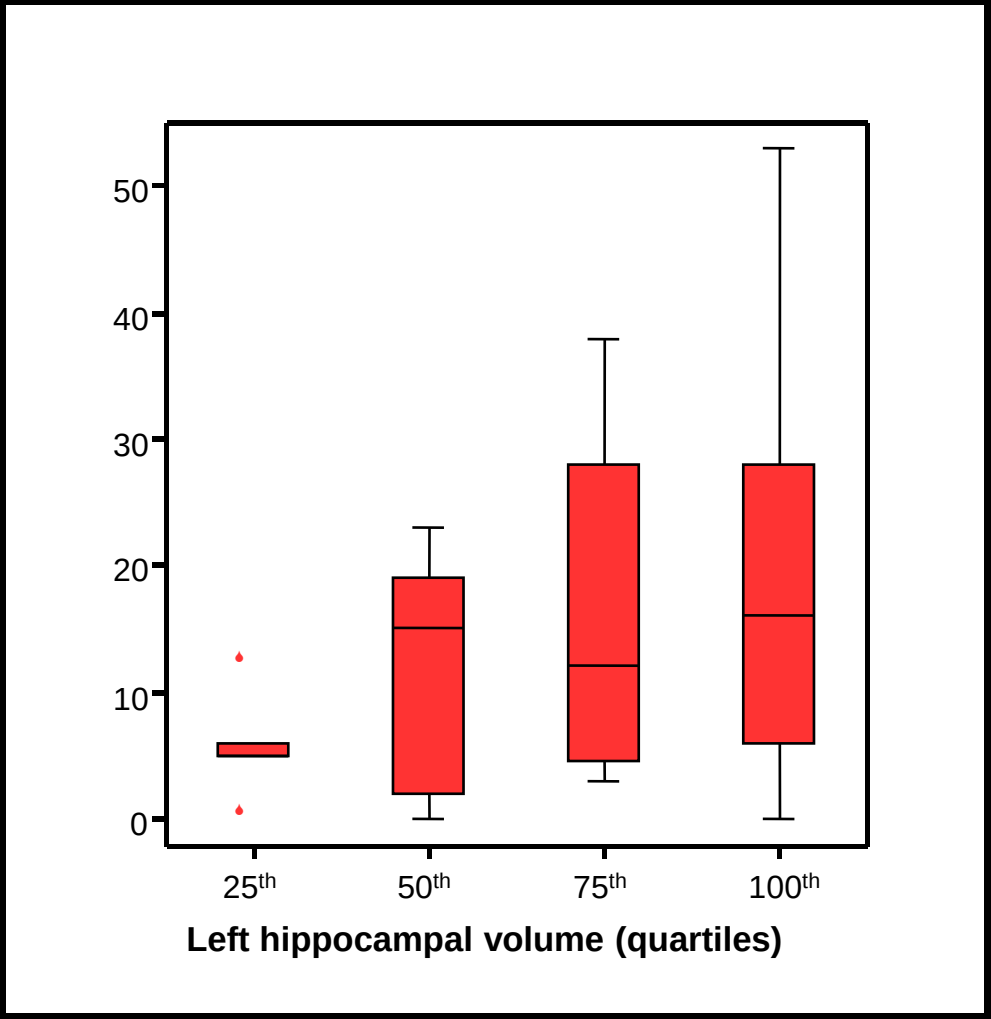


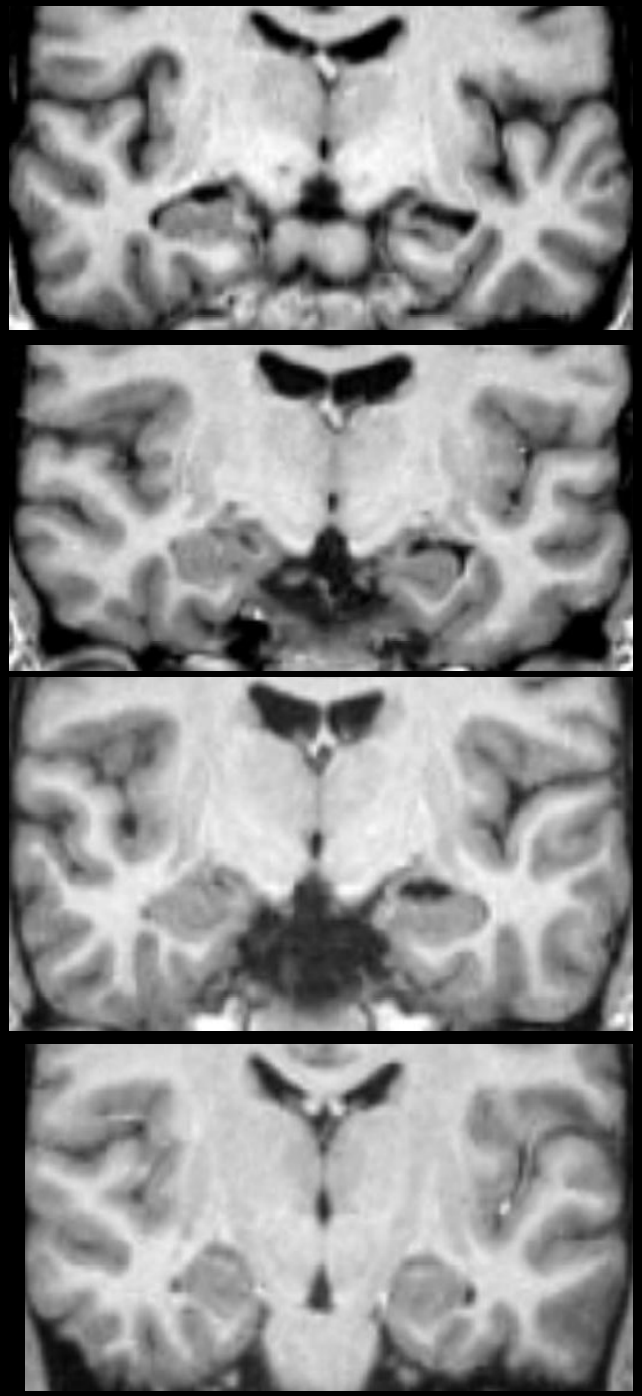

Hecimovic, Santos, Gilliam

# Hyperexcitable Hippocampal Effects on BA 25 in Temporal Lobe Epilepsy



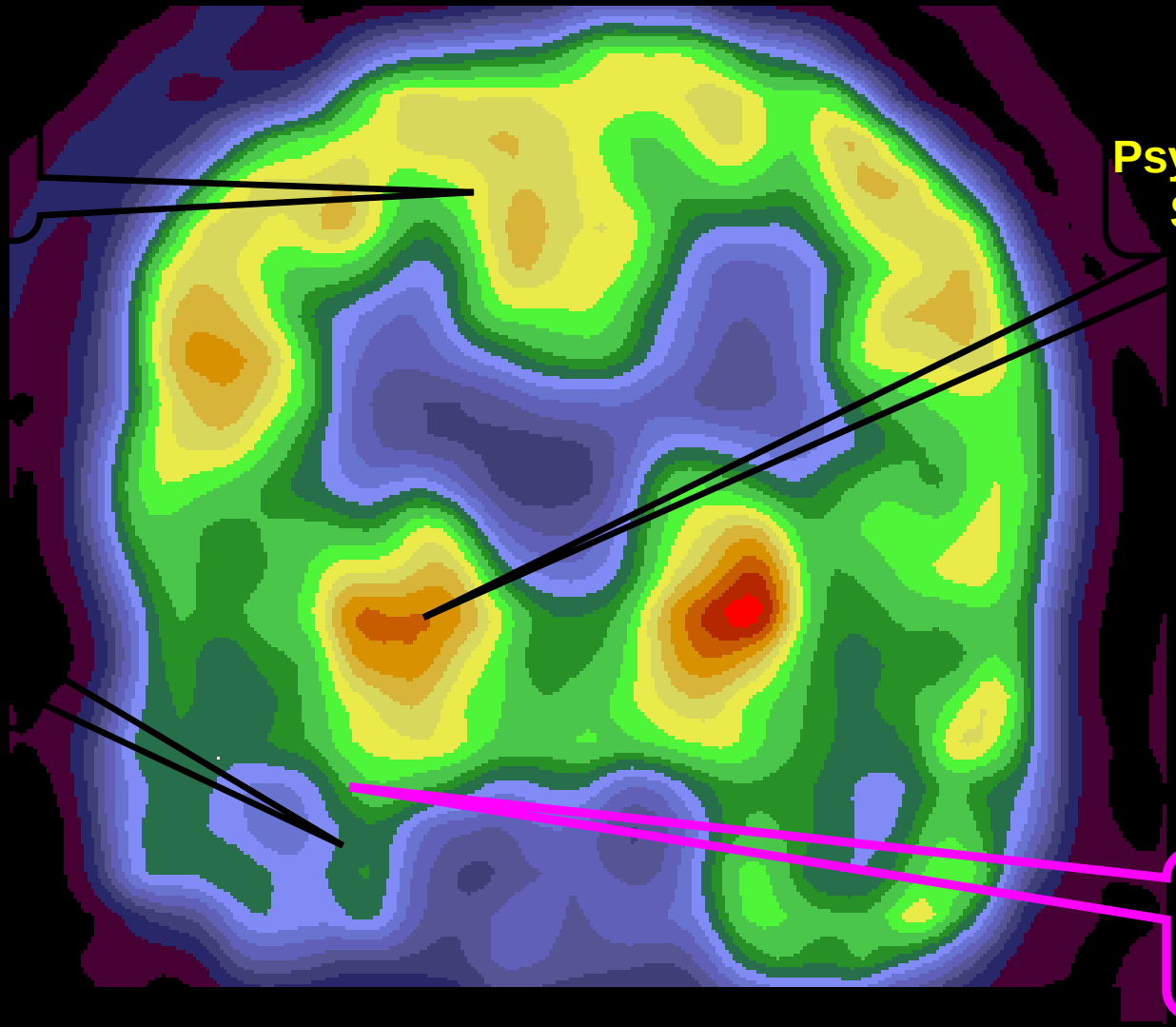
# Degree of hippocampal injury modulates expression of depressive symptoms in TLE



Hecimovic et al, submitted

# Energy Dysmetabolism and the Interictal State



*J. Neurol. Neurosurg. Psychiat.*, 1957, **20**, 11.

# LOSS OF RECENT MEMORY AFTER BILATERAL HIPPOCAMPAL LESIONS

BY

**WILLIAM BEECHER SCOVILLE and BRENDA MILNER**

*From the Department of Neurosurgery, Hartford Hospital, and the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute, Canada*

FIG. 1.—Area removed bilaterally from the medial temporal lobes demonstrating 5 cm. as well as 8 cm. removals through supra-orbital trephines.

seizures in our temporal-lobe resecti
pared with fractional lobotomies in oth
operation was carried out with the u
and approval of the patient and his f
hope of lessening his seizures to som
operation the medial surfaces of both te
were exposed and recordings were taken from both surface and depth electrodes before any tissue was removed; but again no discrete epileptogenic focus was found. Bilateral resection was then carried out, extending posteriorly for a distance of 8 cm. from the temporal tips.

"whose cheerful placidity does not differ from his preoperative status"

## Results

The psychiatric findings bearing upon the treatment of schizophrenia have already been reported (Scoville and others, 1953). Briefly, it was found that bilateral resections limited to the medial portions of the temporal lobes were without significant therapeutic effect in psychosis, although individual patients (including the one with the most radical removal) did in fact show some improvement. There have been no gross changes in personality. This is

and severity of seizures in the epileptic patient were sharply reduced for the first year after operation, and although he is once again having both major and minor attacks, these attacks no longer leave him stuporous, as they formerly did. It has therefore been possible to reduce his medication considerably. As far as general intelligence is concerned, the epileptic patient has actually improved slightly since operation, possibly because he is less drowsy than before. The psychotic patients were for the most part too disturbed before operation for finer testing of higher mental functions to be carried out, but certainly there is no indication of any general intellectual impairment resulting from the operation in those patients for whom the appropriate test data are available.

There has been one striking and totally unexpected

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Epilepsy & Behavior
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Controversies in Epilepsy and Behavior

# Is major depression a neurologic disorder with psychiatric symptoms?

Andres M. Kanner*

*Department of Neurological Sciences, Rush Medical College, Rush Epilepsy Center, Rush University Medical Center, Chicago, IL, USA*

Received 9 July 2004; accepted 9 July 2004

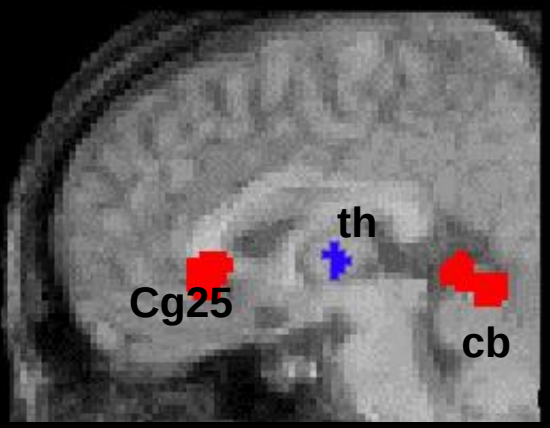
*Epilepsia*, **45**(Suppl. 2):28–33, 2004
Blackwell Publishing, Inc.


# Depression in Epilepsy: Ignoring Clinical Expression of Neuronal Network Dysfunction?

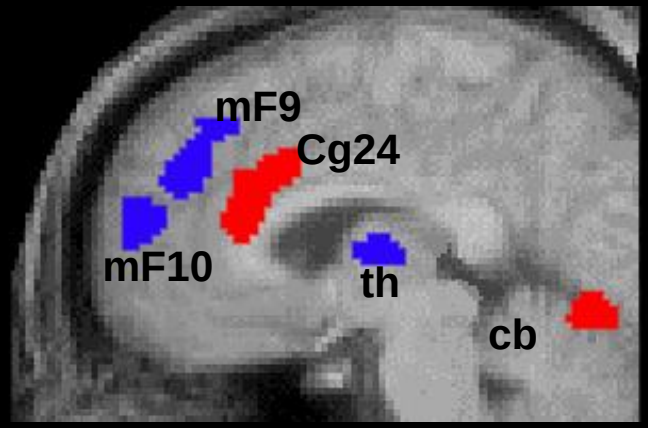
Frank G. Gilliam, Juan Santos, Victoria Vahle, Jewell Carter, Kelly Brown, and Hrvoje Hecimovic

*Department of Neurology, Washington University, St. Louis, Missouri, U.S.A.*

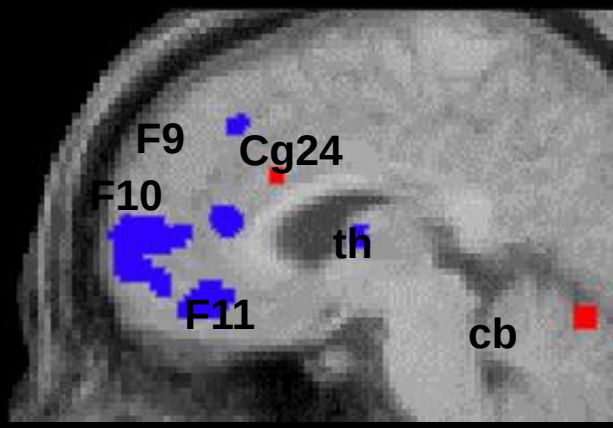
# BIOLOGICAL MARKER OF LIMBIC SYSTEM INJURY?




Control



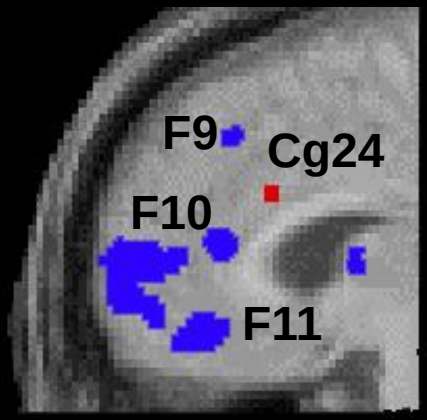

Depressed



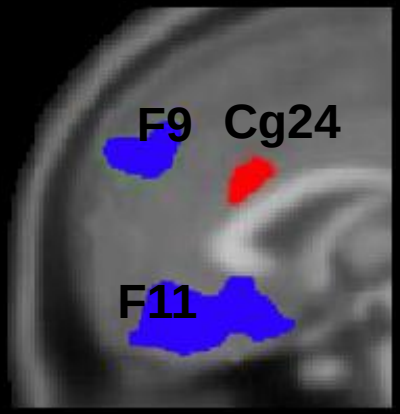

Remitted depression

Liotti et al, Am J Psych 2002

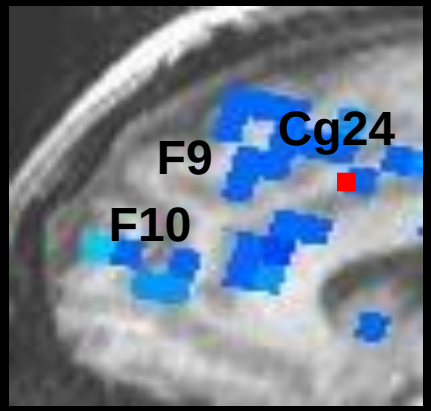
# Common Medial Frontal Changes
# UP, BP, PD



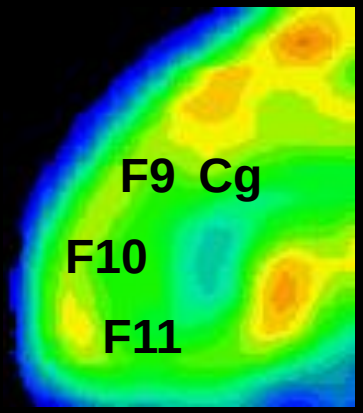

UP Rem




BP Rem




DBS induced
Sad in PD



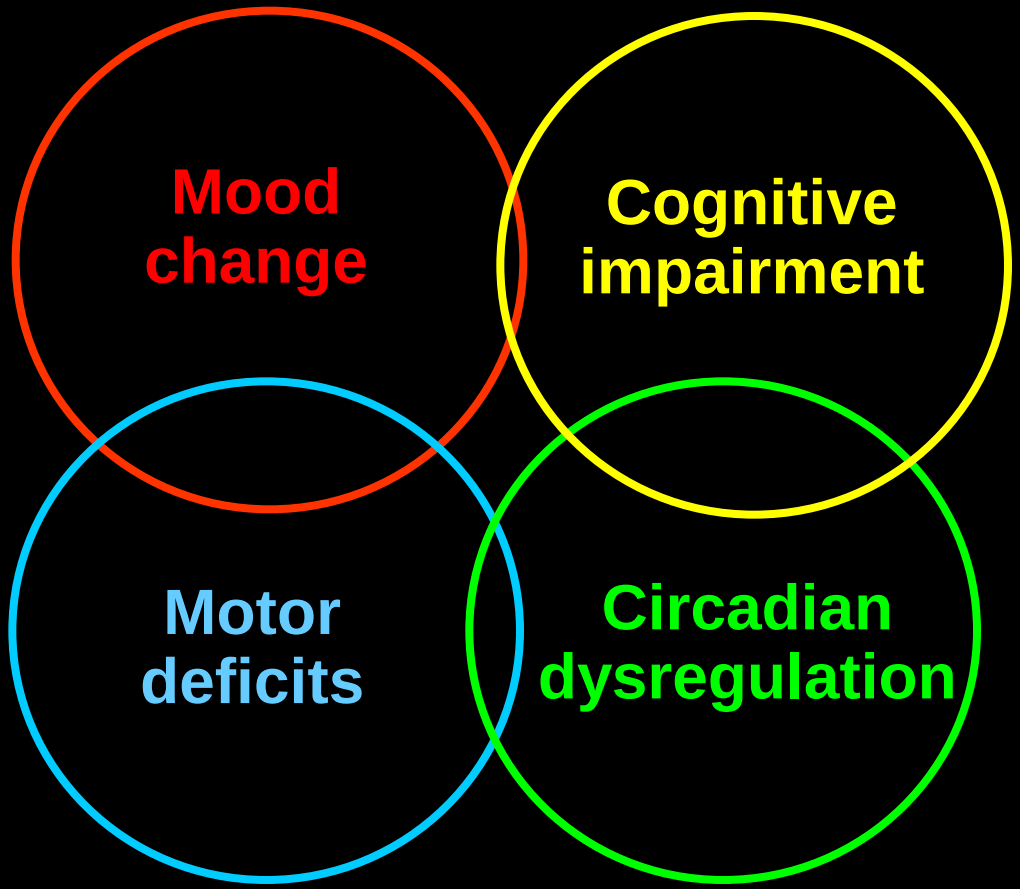

Resting CBF
Active Dep

**Vulnerability Marker?**

Liotti et al Am J Psych 2002
Krueger et al Biol Psych 2003

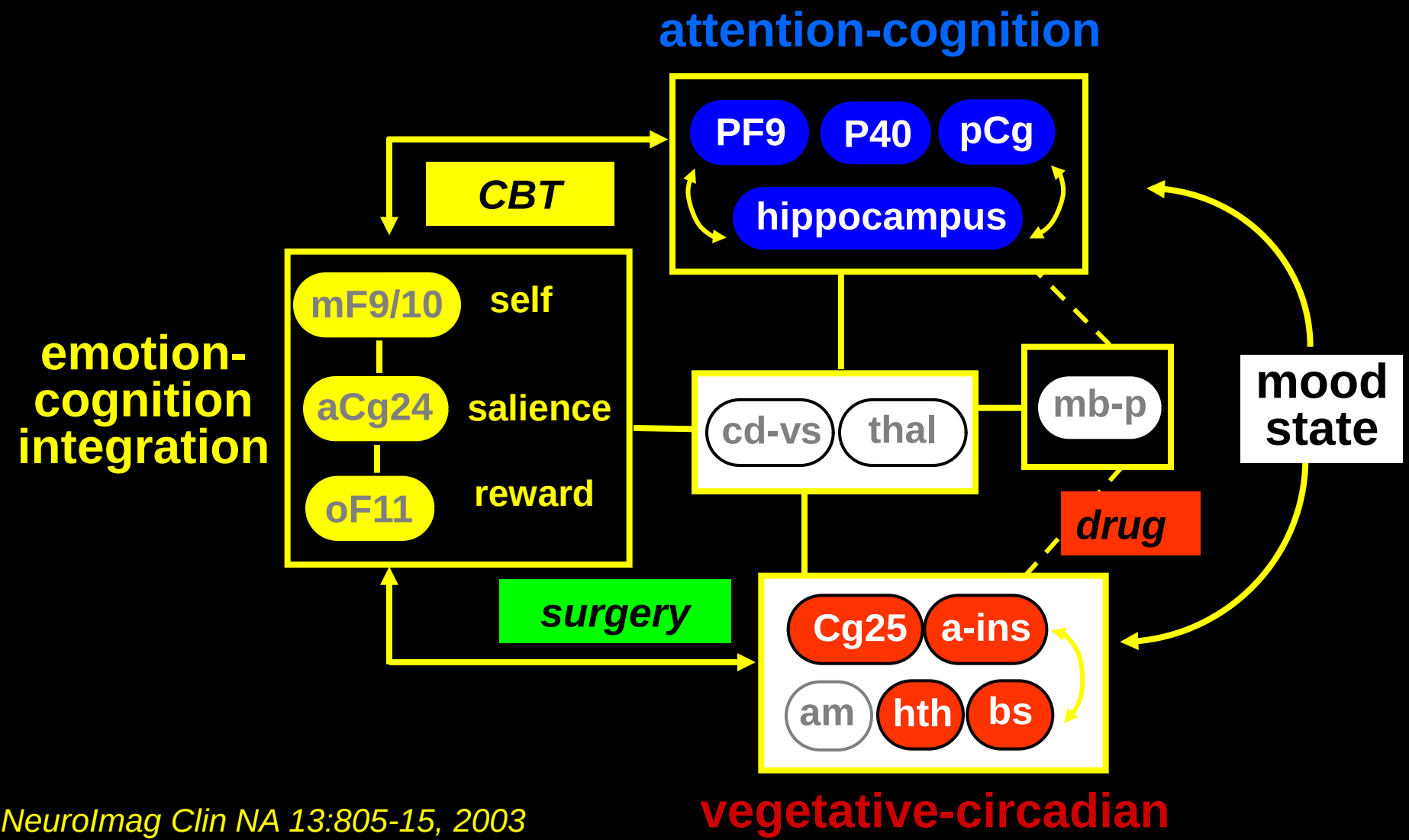
Stefurak et al Mov Dis 2003
Mayberg et al J Nuc Med 1994

# Clues to Specific Circuits in Depression: Clinical Dimensions



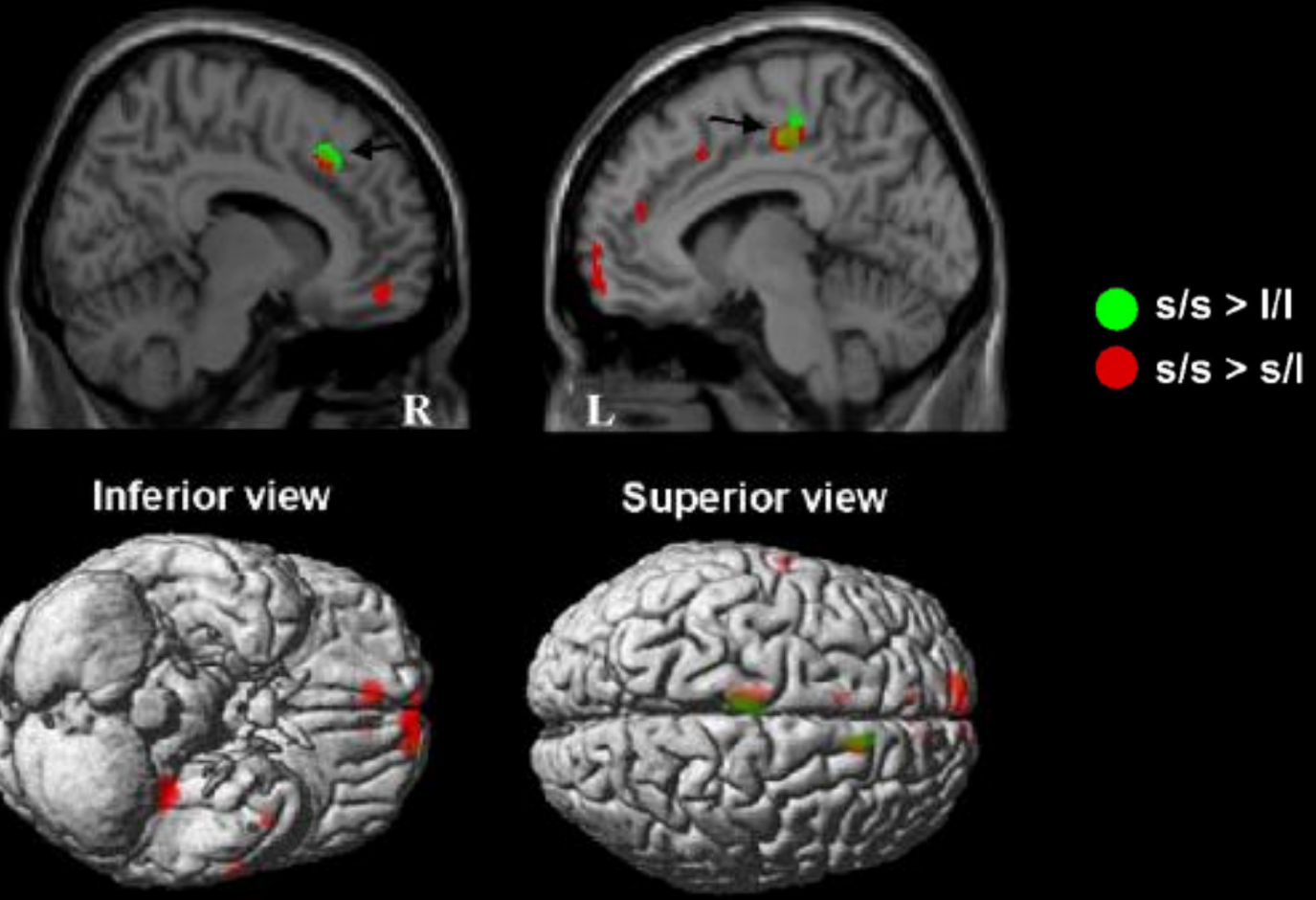

Mayberg, 2004

# Goal: Optimized Treatment



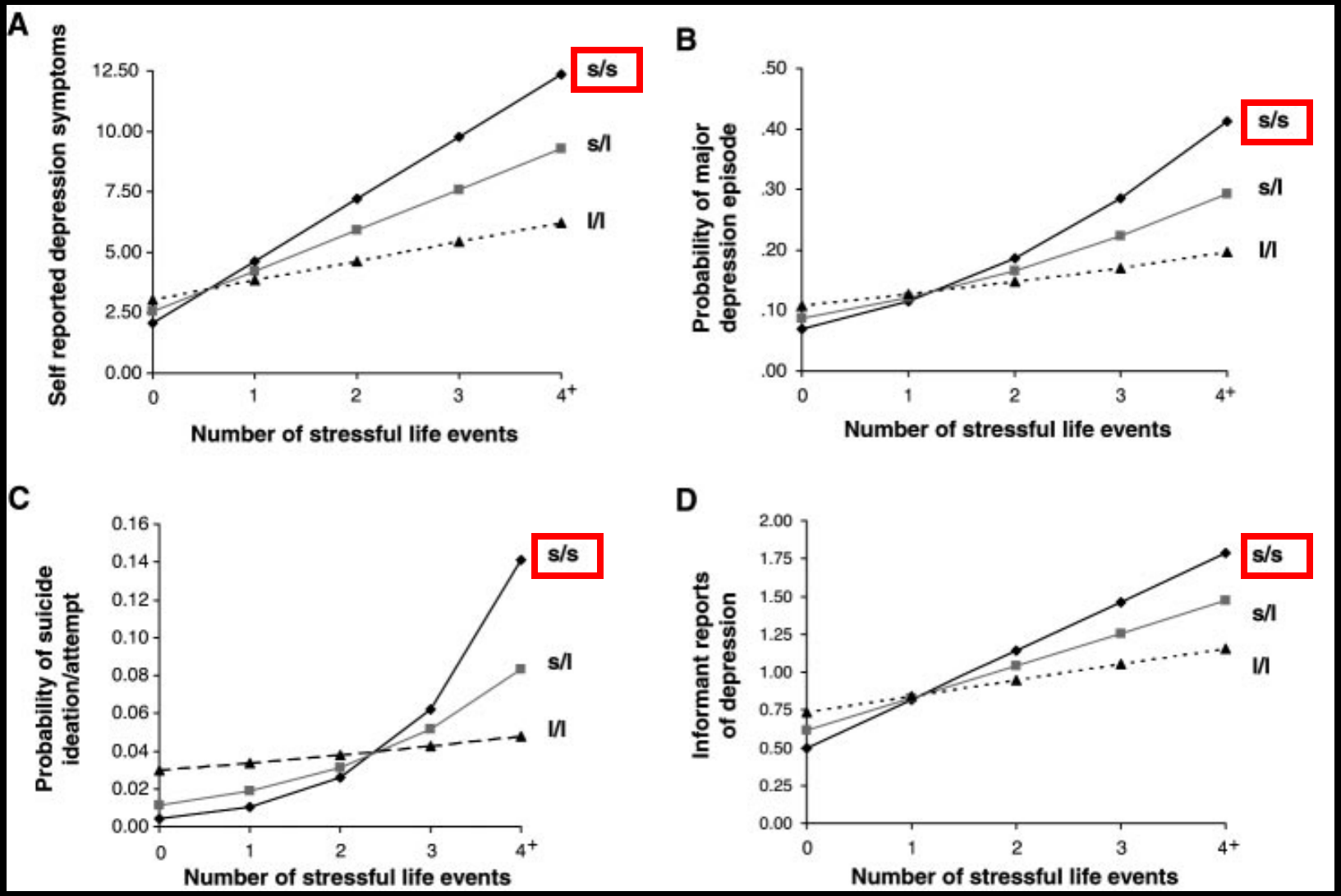

*NeuroImag Clin NA 13:805-15, 2003*

# Genotype and changes in glucose brain metabolism




Graff-Guerrero et al, Neuroimage 2005

# Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene



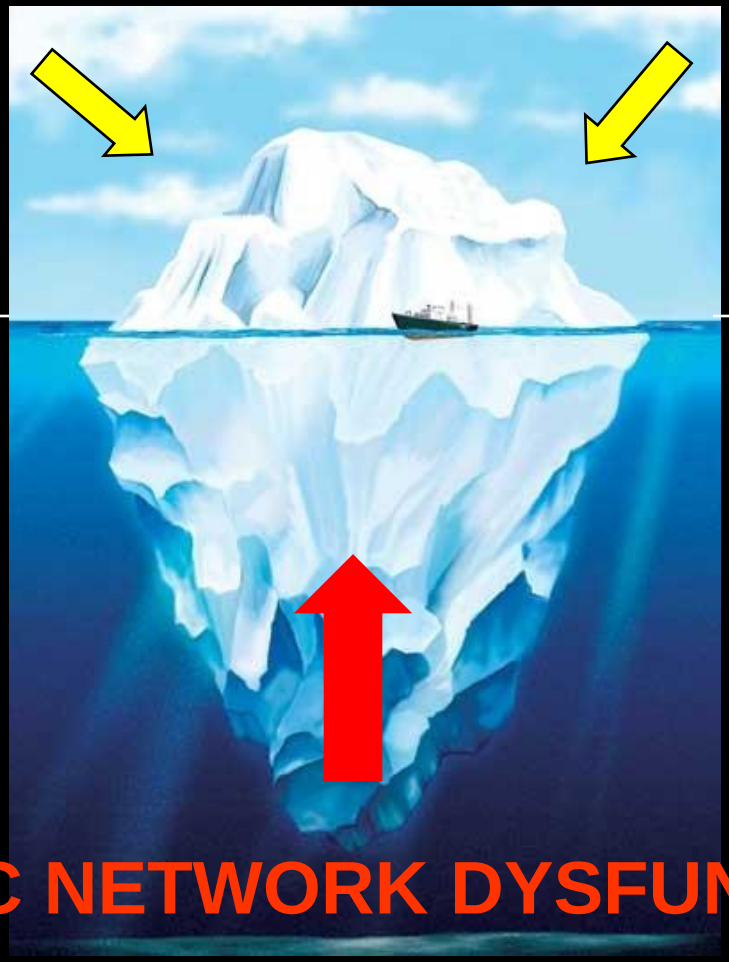

Caspi et al, Science 2003

Seizures

AED

Depression

Cognitive problems



**LIMBIC NETWORK DYSFUNCTION**