Contribution of **Neuroimaging & Neurophysiology** to the understanding of **Epilepsy Comorbidities**

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What shall we expect ?

✓ **Better understand the pathophysiology of epilepsy comorbidities:**

- ✓ similarities / differences with the « morbidities » not associated with epilepsy (e.g. depression)
- ✓ might help develop more effective strategy to prevent or treat comorbidities (major impact on quality of life)

✓ **Better understand the pathophysiology of epilepsy**

- ✓ investigating links between mechanisms of epilepsy and its comorbidities
- ✓ benefit from knowledge and expertise from other research fields (e.g. depression)

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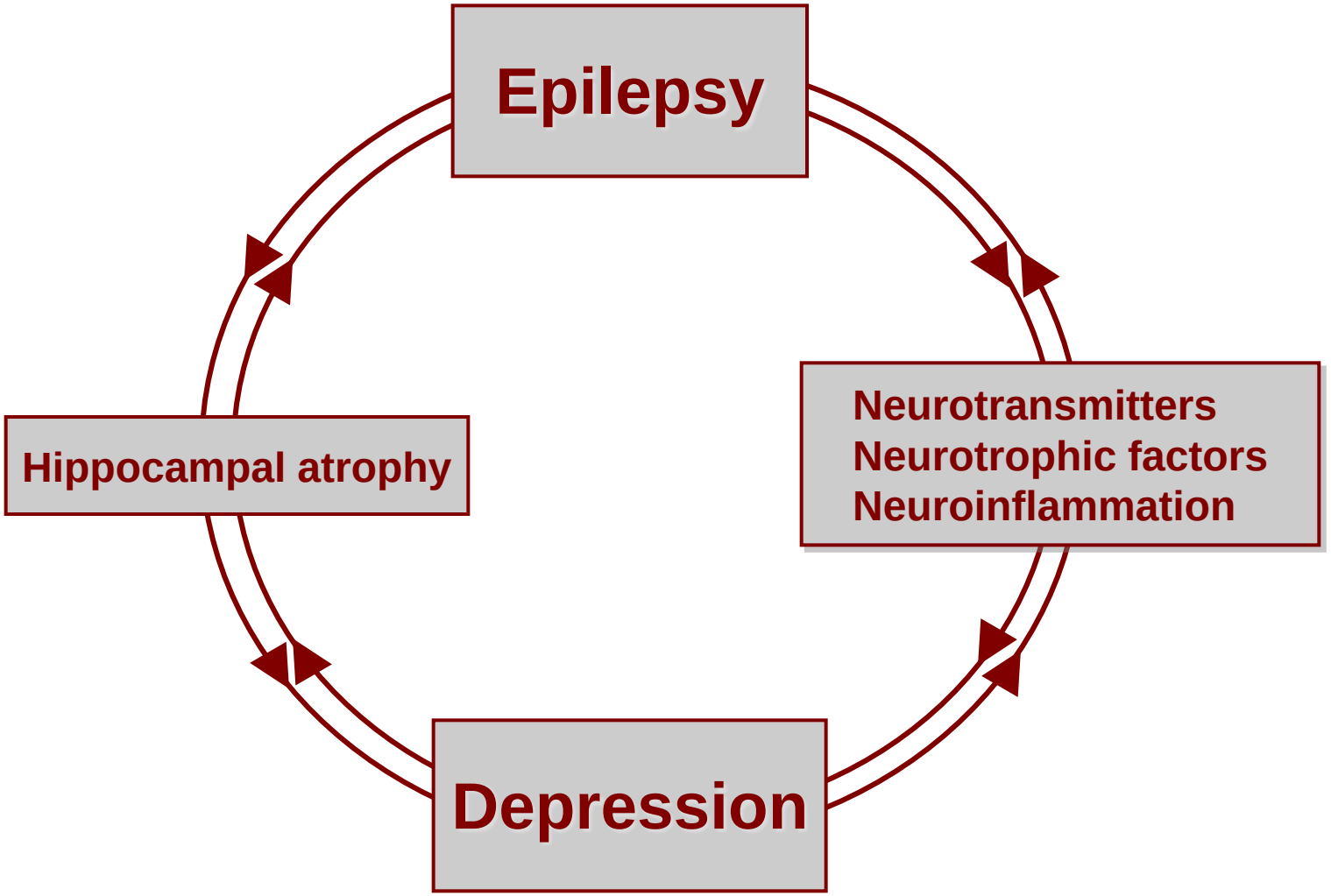
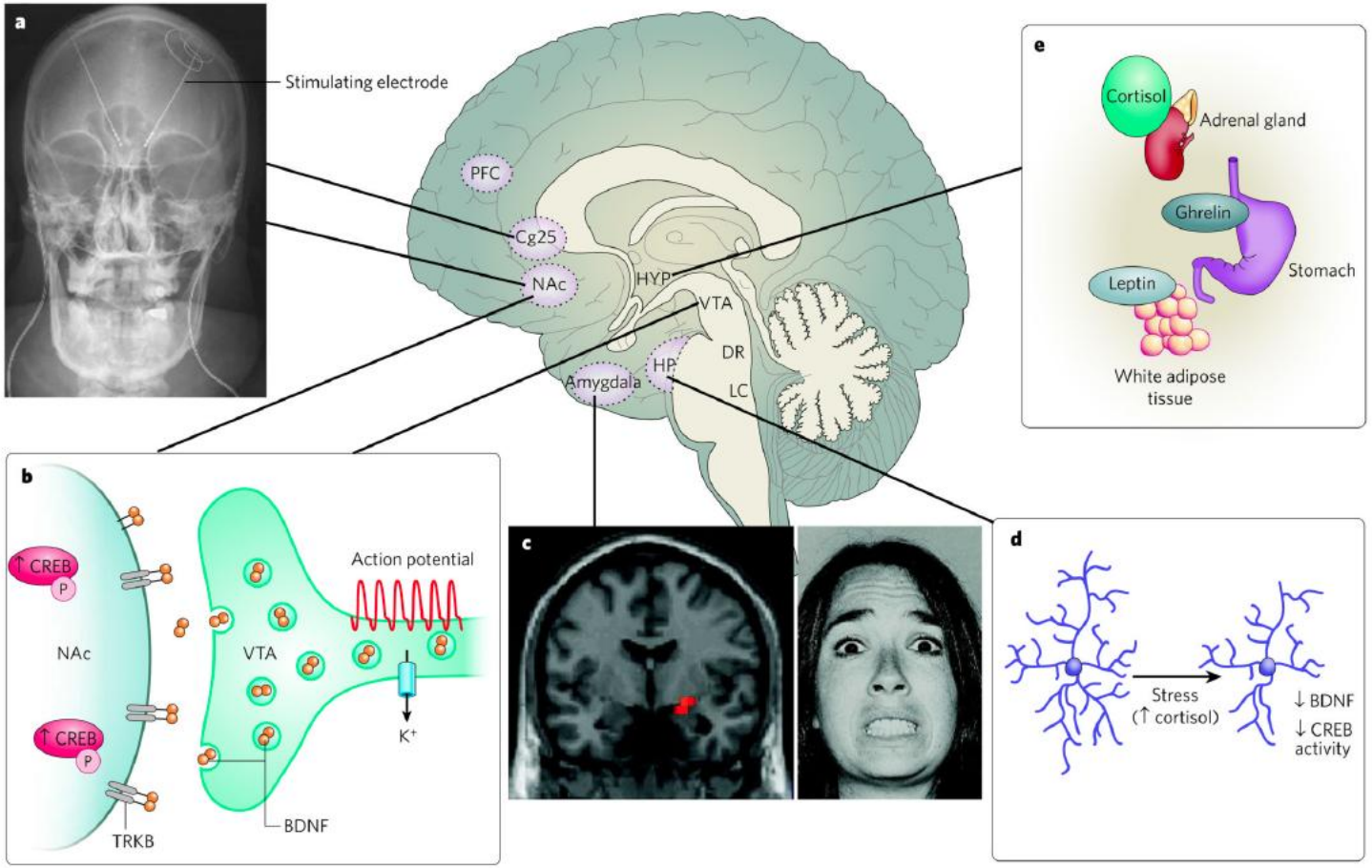
Deprelepsy

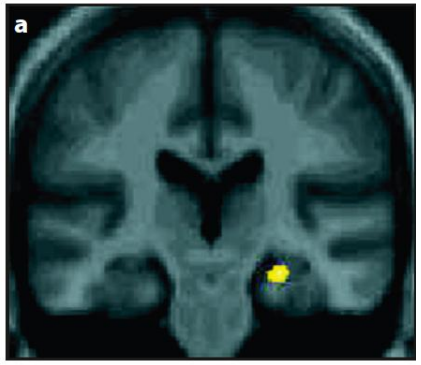


The example of depression

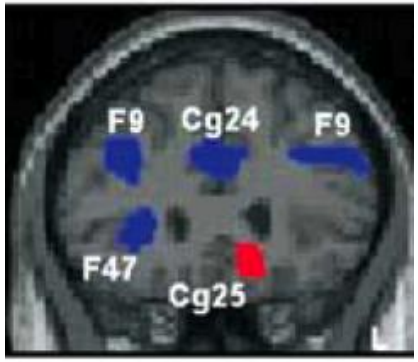


Krishnan and Nestler Nature 2008

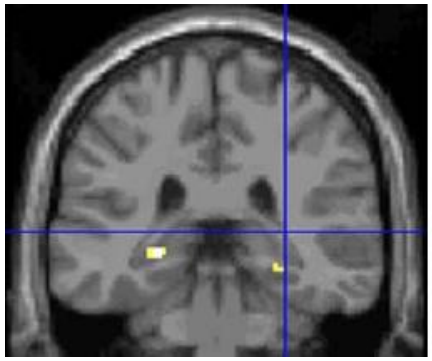
The example of depression



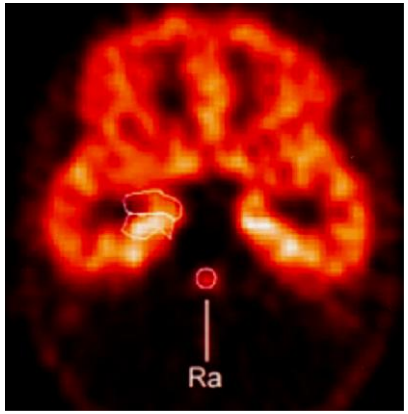
MRI – VBM [1]
Hippocampal atrophy



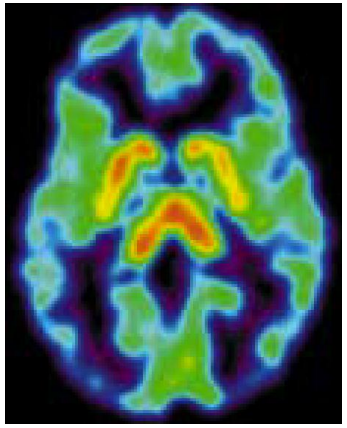
FDG-PET [2]
Altered metabolism



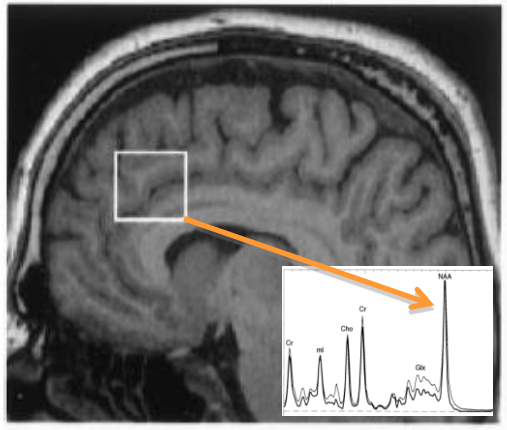
FMZ-PET [3]
↘ BZD receptors



WAY-PET [4]
↘ 5-HT1A receptors



DASB-PET [5]
↗ 5-HTT



MR spectroscopy [6]
Altered GABA/glutamate

[1]Bell-McGintry et al. Am J Psychiatry 2002, [2]Mayberg et al. Neuron 2005,
[3]Klumpers et al. Eur J Nucl Med Mol Imaging 2010, [4]Drevets et al. Biological Psychiatry 1999,
[5]Meyer et al. Am J Psychiatry 2001, [6]Auer et al. Biological Psychiatry 2000,

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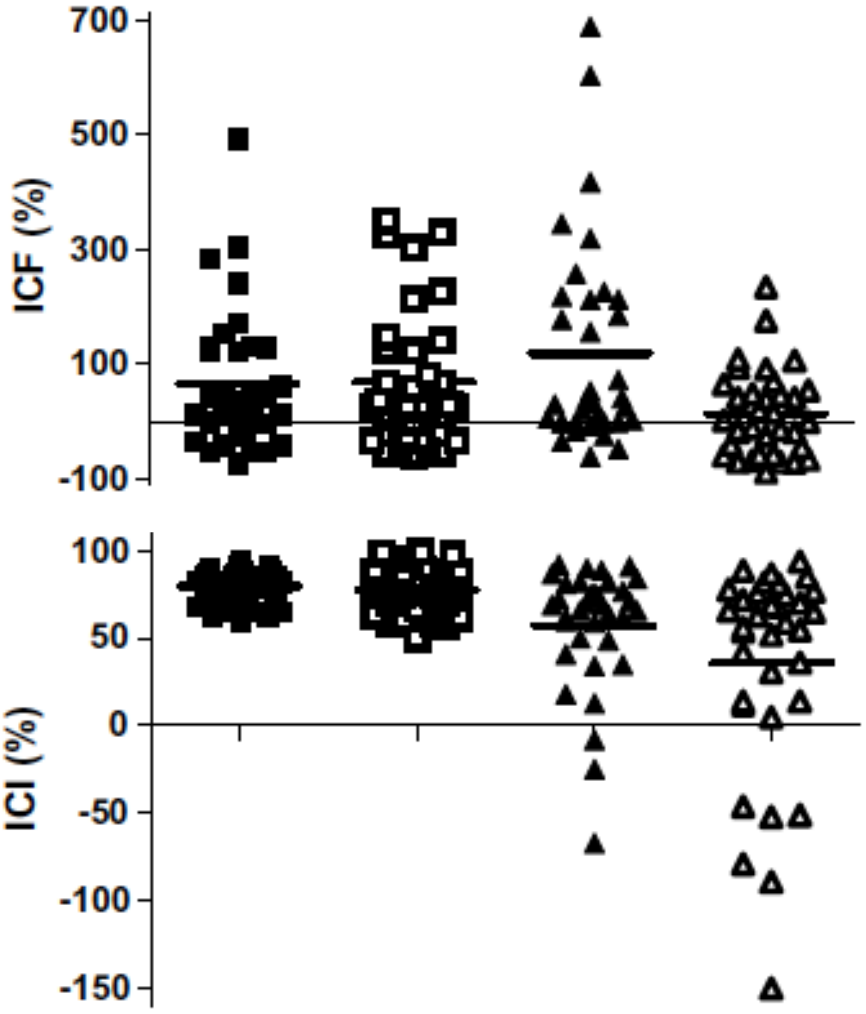
The example of depression

Transcranial Magnetic Stimulation



Left decrease in intra-cortical **facilitation**

Healthy controls ■ right □ left

Patients ▲ right △ left

Bilateral decrease in intra-cortical **Inhibition**

Lefaucheur et al. Journal of Psychiatric Research 2008

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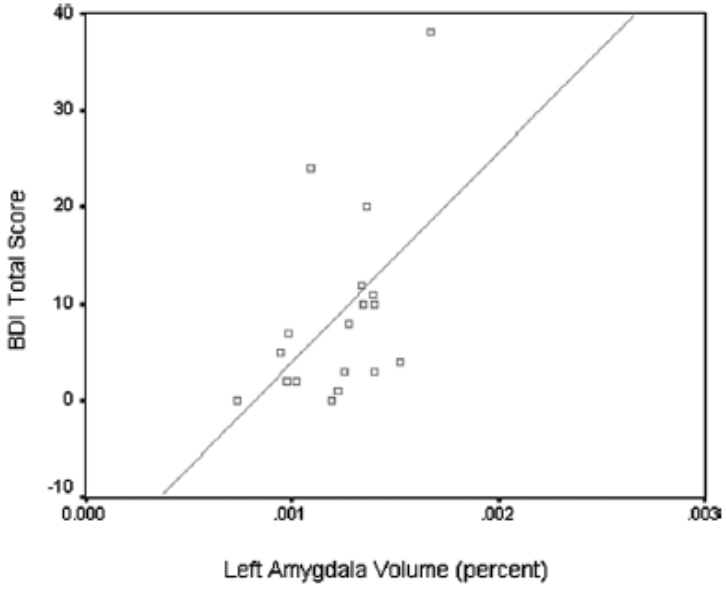
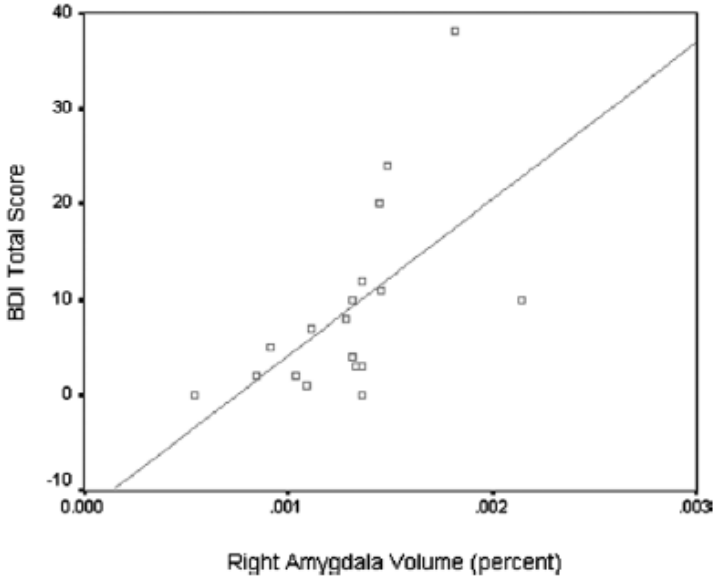
Translation in epilepsy

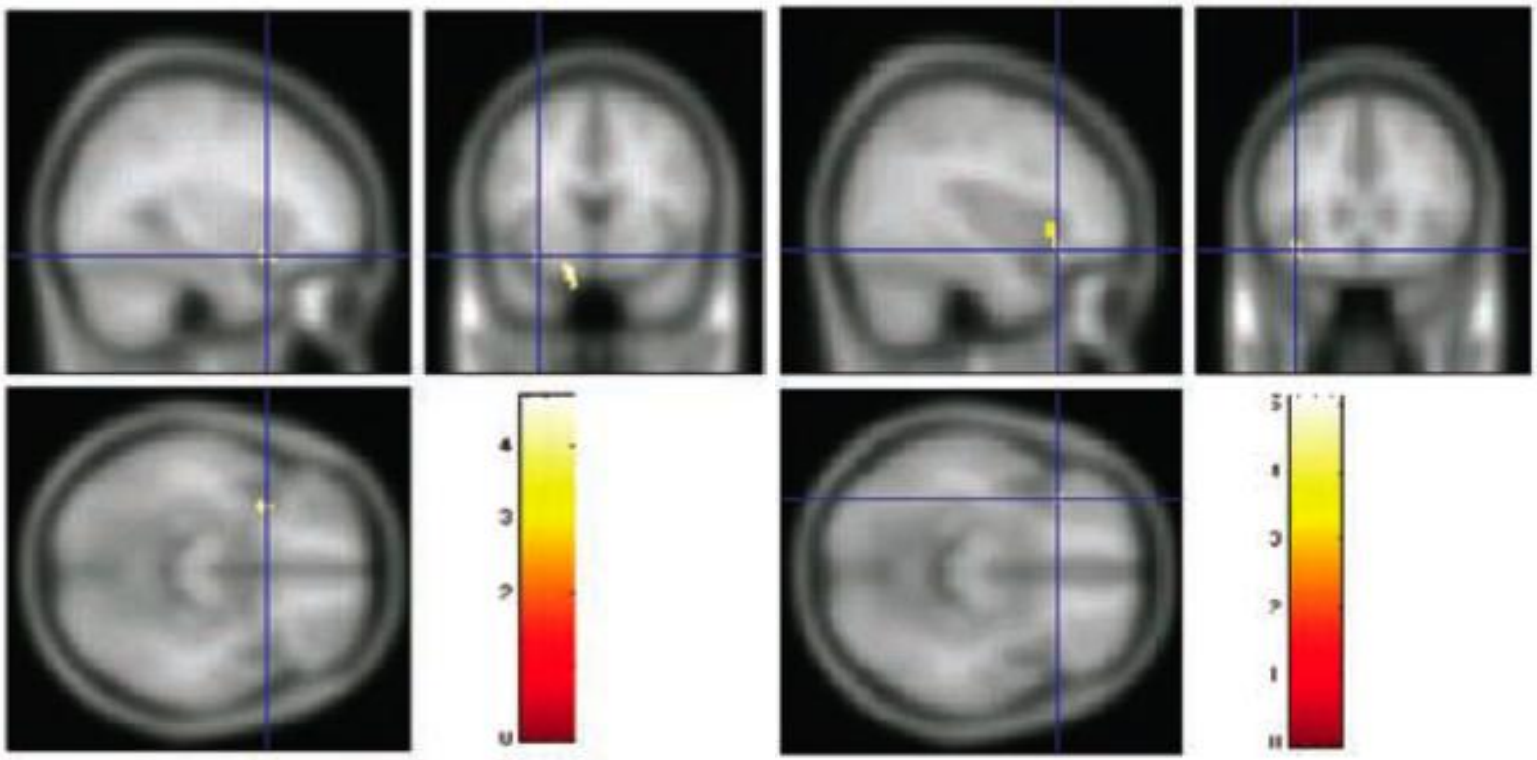




Richardson et al. Epilepsy and Behavior 2007;10:242–249

Translation in epilepsy

[^{18}F]FDG-PET in patients with TLE with or without depression



Hypometabolism in TLE patients with life-time history of depression

Hypometabolism in TLE patients who develop post-op depression

Salzberg et al. Epilepsia 2006;47:2125–2130

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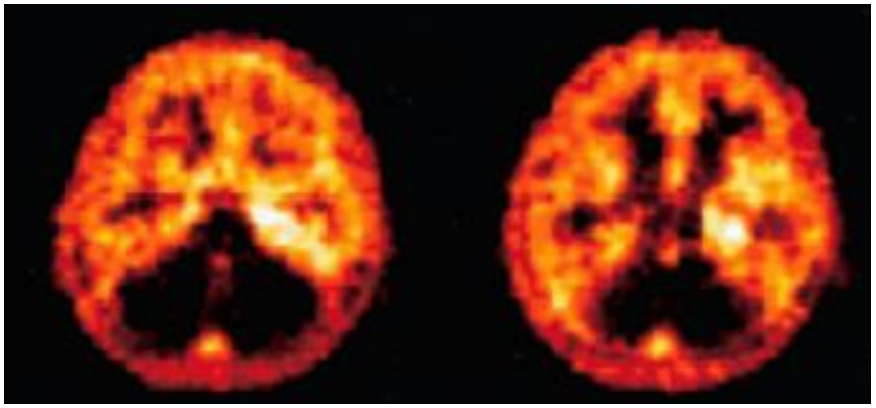
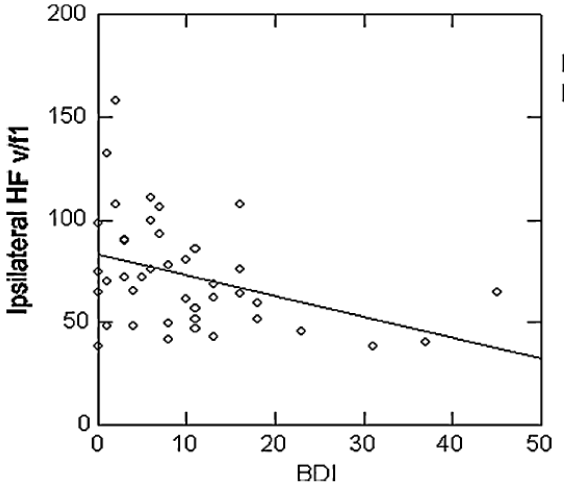
Translation in epilepsy

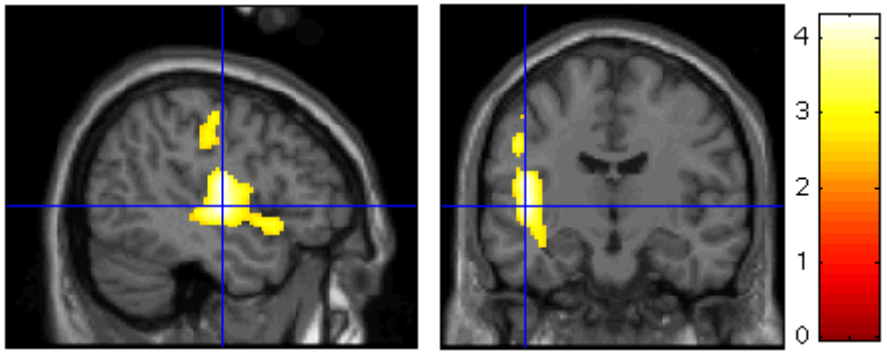
[^{18}F]FCWAY-PET: Decreased uptake in TLE with comorbid depression

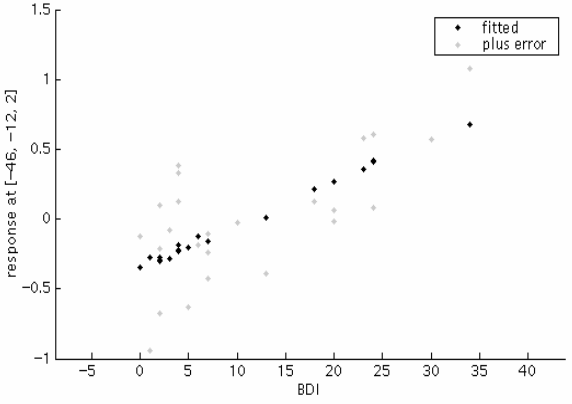




(Theodore et al. Epilepsia 2007)

[^{18}F] MPPF-PET: Increased uptake in TLE with comorbid depression





(Lothe et al. Brain 2008)

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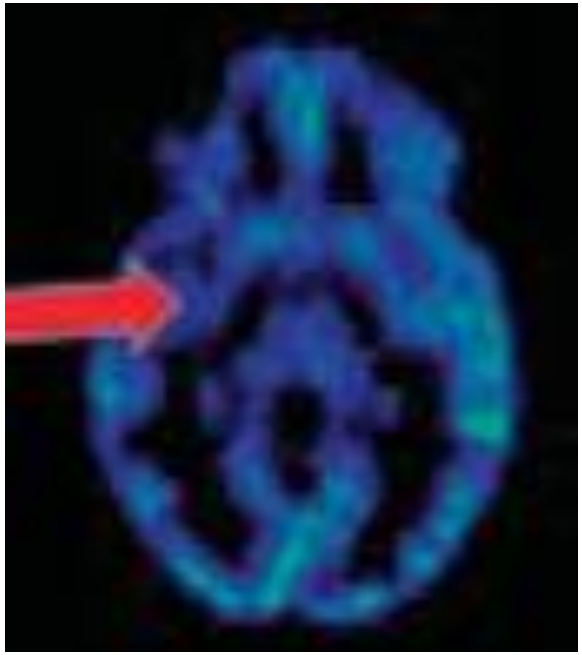
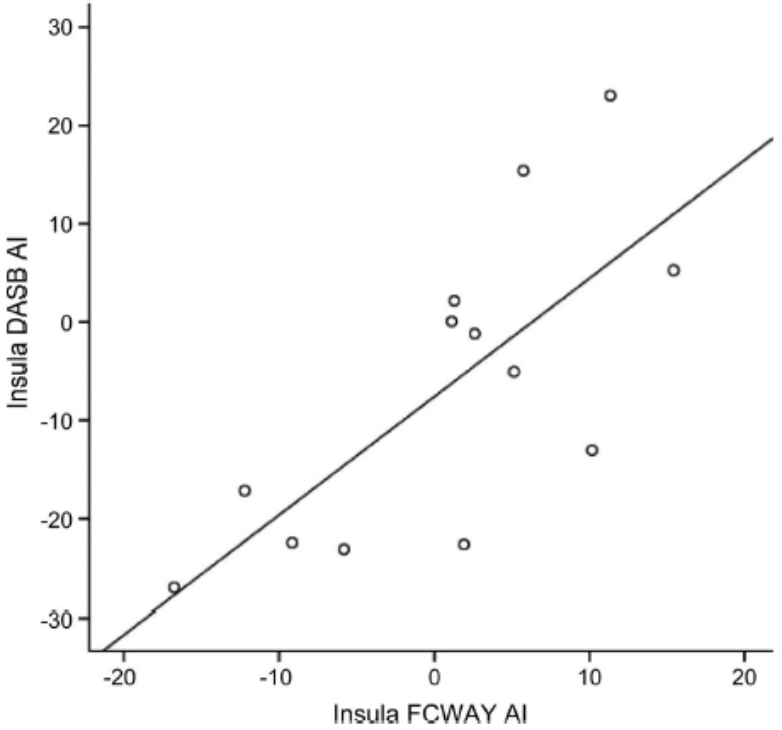
Translation in epilepsy

[^{11}C]DASB and [^{18}F]FCWAY-PET in TLE +/- comorbid depression

13 patients, including four with depression

Increased asymmetry in the insula in depressed patients





Martinez et al. Neurology 201380:1465–1471

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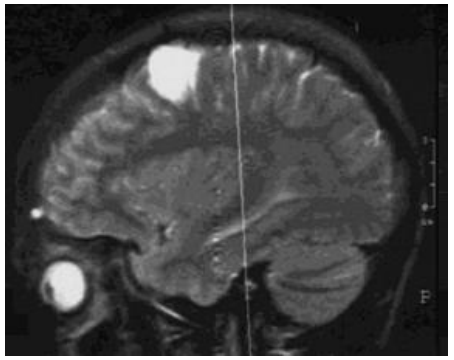
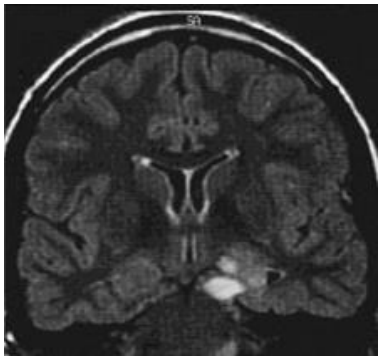
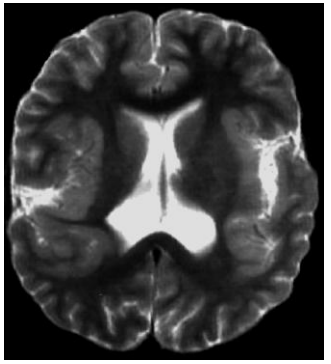
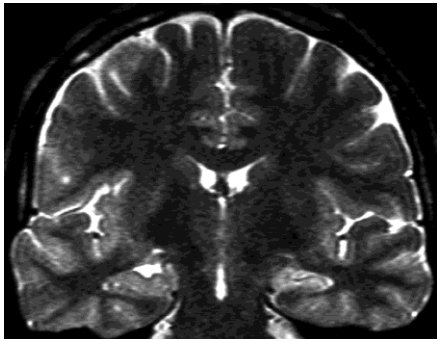
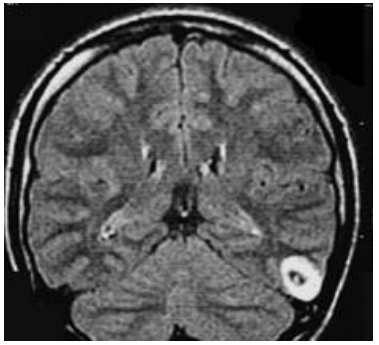
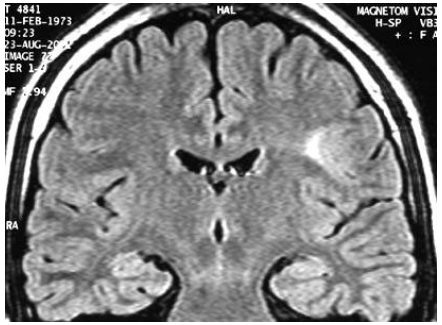
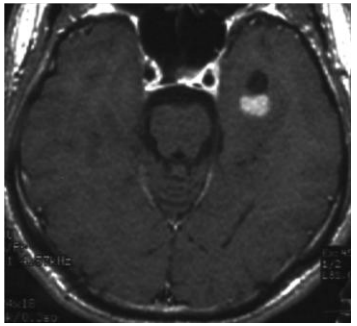
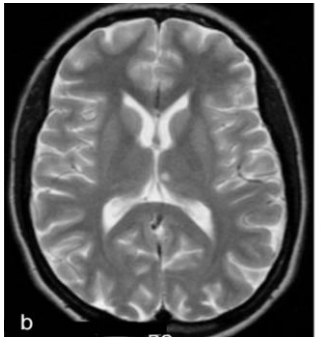
Epilepsy Heterogeneity



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Other limitations

- ✓ **Ambiguous interpretation** of Neuroimaging and Neurophysiological data
- ✓ Lack of understanding of **dynamic changes** over time
- ✓ **Limited sample size**

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Other limitations

Power failure: why small sample size undermines the reliability of neuroscience

Katherine S. Button[1,2], John P. A. Ioannidis[3], Claire Mokrysz[1], Brian A. Nosek[4], Jonathan Flint[5], Emma S. J. Robinson[6] and Marcus R. Munafò[1]

Abstract | A study with low statistical power has a reduced chance of detecting a true effect, but it is less well appreciated that low power also reduces the likelihood that a statistically significant result reflects a true effect. Here, we show that the average statistical power of studies in the neurosciences is very low. The consequences of this include overestimates of effect size and low reproducibility of results. There are also ethical dimensions to this problem, as unreliable research is inefficient and wasteful. Improving reproducibility in neuroscience is a key priority and requires attention to well-established but often ignored methodological principles.

"Low power therefore has an ethical dimension — unreliable research is inefficient and wasteful"

Button et al. Nature Reviews Neuroscience 2013;14:365–376

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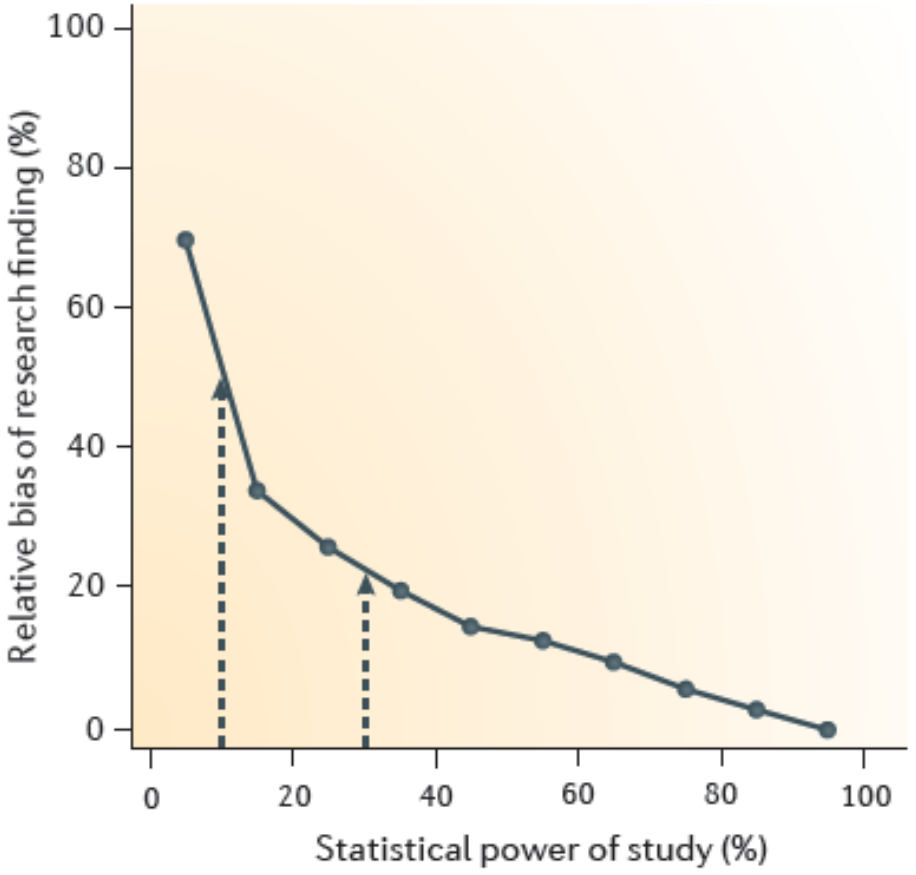
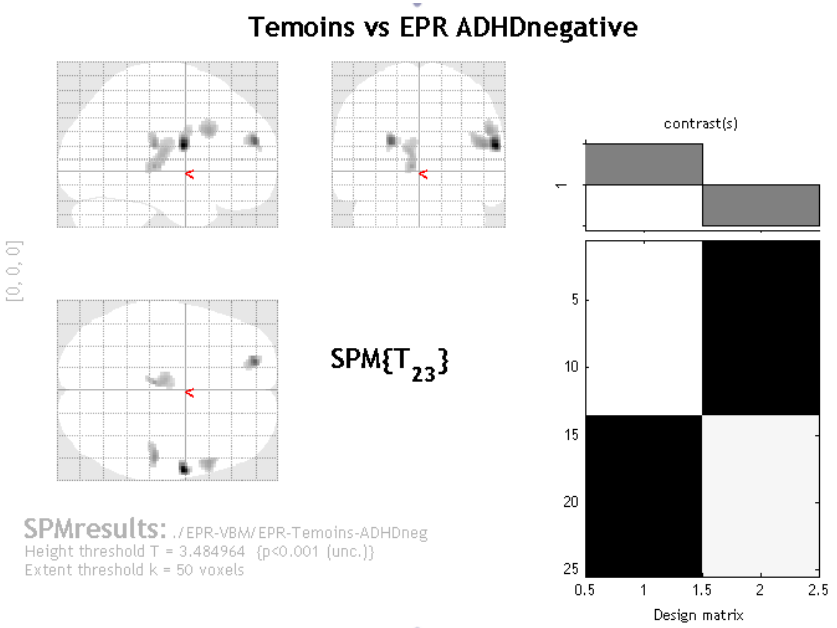
Other limitations

Neuroimaging studies: *"median statistical power of these studies was 8% across 461 individual studies contributing to 41 separate meta-analyses"*



Button et al. Nature Reviews Neuroscience 2013;14:365–376

Other limitations



Statistics: *p-values adjusted for search volume*

set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_e)	p_{uncorr}			
0.025	5	0.314	0.591	98	0.018	0.004	0.021	8.11	5.52	0.000	60	-2	20
		0.618	0.787	66	0.045	0.191	0.522	6.00	4.61	0.000	-22	54	22
		0.497	0.703	77	0.032	0.724	0.976	5.06	4.10	0.000	50	-24	20
		0.352	0.591	93	0.020	0.906	0.976	4.74	3.92	0.000	54	18	30
		0.120	0.521	140	0.006	0.906	0.976	4.73	3.92	0.000	-6	-24	4
						0.988	0.976	4.40	3.71	0.000	-6	-18	12
						1.000	0.976	3.96	3.42	0.000	-4	-14	22

Height threshold: T = 3.48, p = 0.001 (1.000)
Extent threshold: k = 50 voxels, p = 0.076 (0.803)
Expected voxels per cluster, <k> = 16.019
Expected number of clusters, <c> = 1.63
FWEp: 6.751, FDRp: 8.113, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 23.0]
FWHM = 11.5 11.7 11.2 mm mm mm; 5.8 5.8 5.6 {voxels}
Volume: 2510496 = 313812 voxels = 1584.6 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 187.54 voxels)

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Other limitations

✓ **Ambiguous interpretation** of Neuroimaging and Neurophysiological data

✓ **Limited sample size**

✓ Lack of understanding of **dynamic changes** over time

Prospective longitudinal multimodal assessment of deeply phenotyped large cohort of patients where neuroimaging/neurophysiological data should primarily aim at refining a relevant systems biology framework

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And what about SUDEP ?

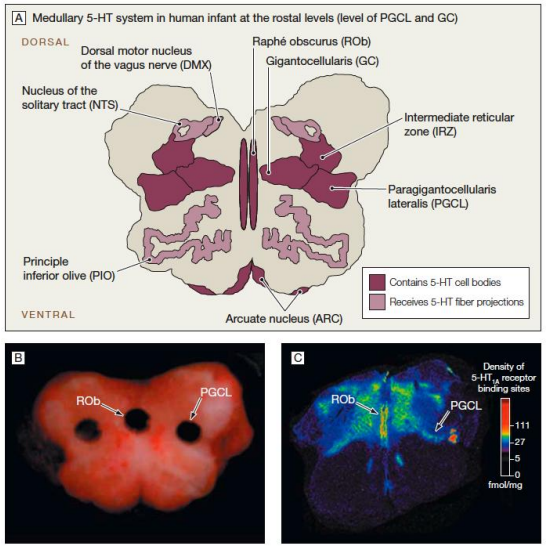
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

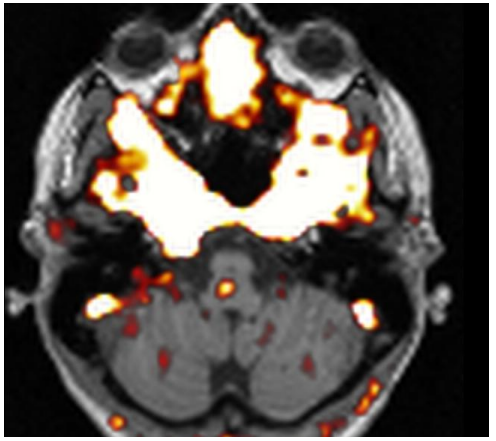
Long-Term Mortality in Childhood-Onset Epilepsy

Matti Sillanpää, M.D., Ph.D., and Shlomo Shinnar, M.D., Ph.D.

> 20% of patients with uncontrolled childhood onset epilepsy die of SUDEP



5-HT abnormalities in SIDS



In vivo PET measurement of $5HT_{1A}$ receptors in caudal raphe

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