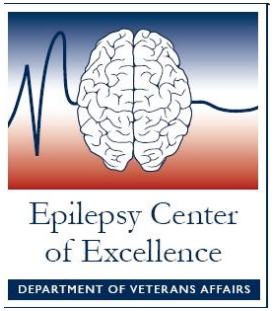


Depression & Epilepsy

Dr. Hamada Hamid
Co-Director, Connecticut VA Epilepsy Center of Excellence,
Assistant Professor
Department of Neurology & Psychiatry
Yale School of Medicine

Outline

- Impact of Mood in Epilepsy
- The Brain, Mood & Epilepsy
- Medicine, Mood & Epilepsy
- The Mind, Mood & Epilepsy

“So What?”

- Why should you care about the relationship between depression and seizures?
  - Depression impacts QOL
  - Depression associated with worse seizure control
  - People with epilepsy DIE from suicide

Clinical Relevance

- 35 year old woman carries a 15 year h/o epilepsy
  - Recent attempted suicide (O.D.) after breaking up with boyfriend
  - In psychiatry ward had multiple tonic clonic seizures, requiring multiple stat Ativan
  - Rx: Keppra 1500mg , Dilantin 300mg, Lexapro 20mg
  - PE: neurologically normal, dysphoric, No SI/HI

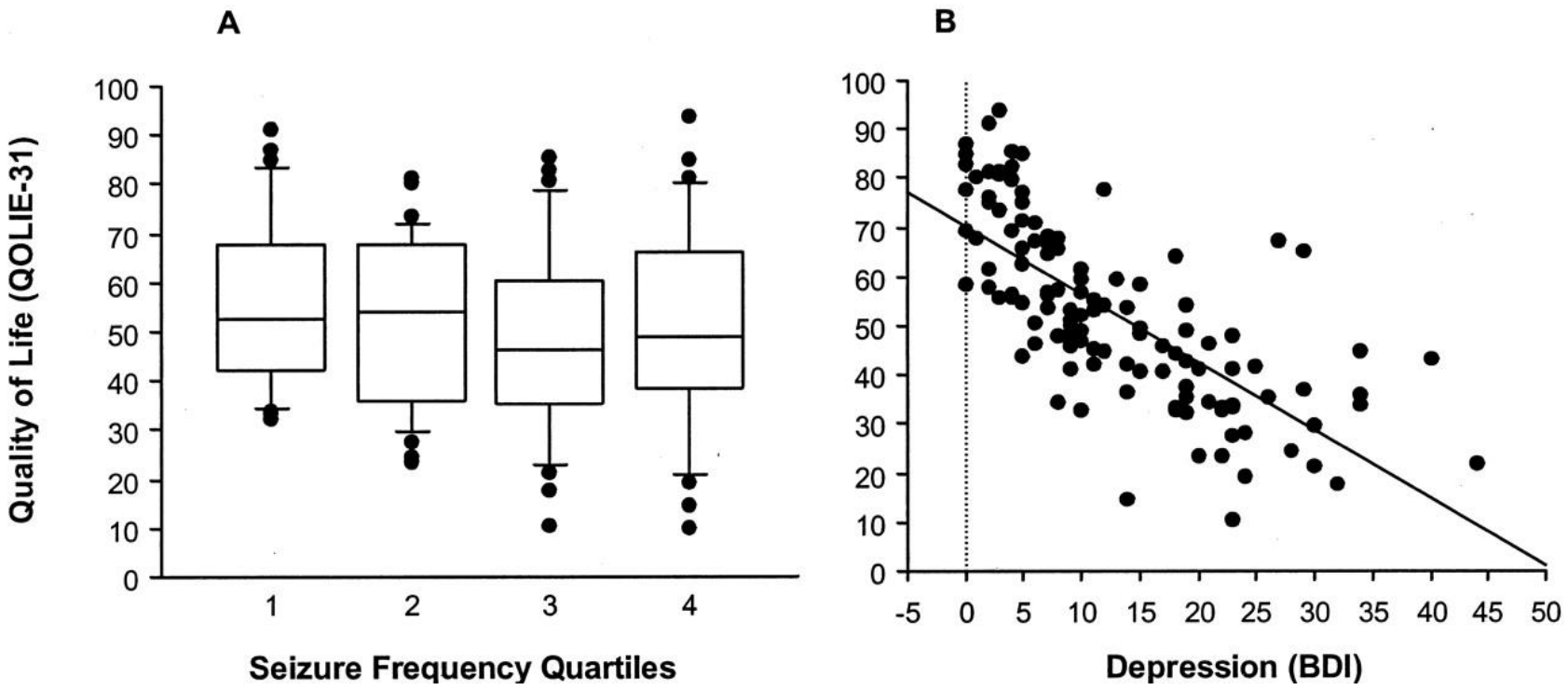
Clinical Relevance

- Does Lexapro (anti-depressants) worsen seizures?
- Does Keppra (anti-convulsants) worsen depression?
- Is uncontrollable seizures a significant risk for suicide?

Three reasons you should care

- 1. Suicide!
- 2. Quality of Life
- 3. Seizure Control?

Quality of life vs seizure frequency or depression



Boylan, L. S. et al. Neurology 2004;62:258-261

QOL Associated W/ Depression

- Depression impacts QOL
  - Not seizure frequency
  - Not anxiety/anticipation
  - Not social functioning
  - Not seizure stigma

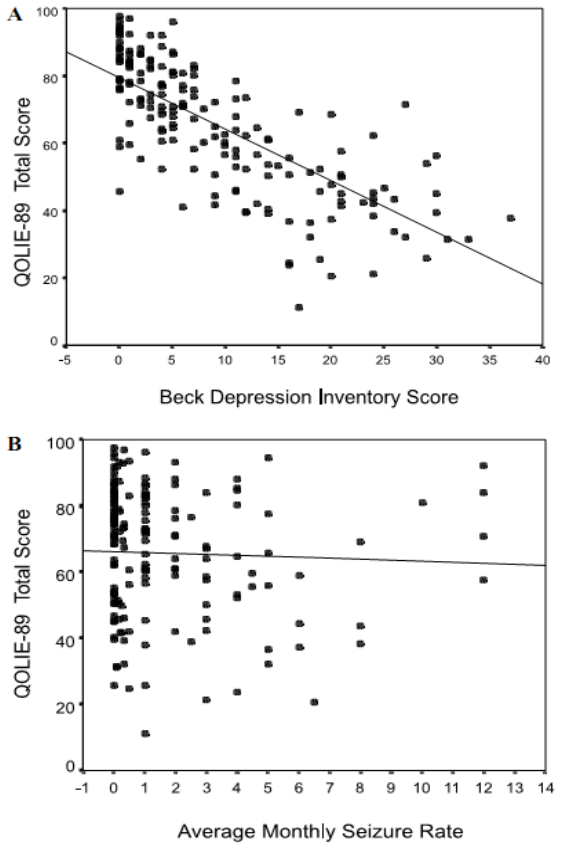


Fig. 1. (A) Scatterplot of correlation of health-related quality of life (Quality of Life in Epilepsy-89 global score) with depression symptoms ($r = -0.49$, $P < 0.001$) ($n = 200$) [17]. (B) Scatterplot of correlation of average monthly seizure rate with depression symptoms ($r = -0.01$, $P = 0.93$) ($n = 200$) [17].

Tracy 2007, Boylan 2004, Gilliam 2002

Bidirectional Relationship

- Depression 3x more likely → Epilepsy
- Suicide 5x more likely → Epilepsy
- People enrolled in anti-depressant clinical trials who were taking placebo were 17X more likely to experience a seizure than general population

Impact of mood disorders on seizure control

- Predictors of Rx resistant epilepsy:
  - Traumatic Brain Injury OR: 3.26 (1.97 – 5.40)
  - Psychiatric co-morbidity OR: 2.35 (1.48 - 3.73)
  - Family History of Epilepsy OR: 2.02 (1.30 - 3.13)
  - Substance abuse OR: 4.76 (2.37 - 9.58)
  - > 10 Seizures before Rx OR: 2.71 (1.99 – 3.69)
- Predictors of Excellent Epilepsy Surgery Outcome
  - Large surgical resection OR: 4.6 (1.6 – 15.3)
  - No psychiatric history OR: 13.1 (4.4 – 45.3)

(Hitris et al 2007, Kanner et al 2009)

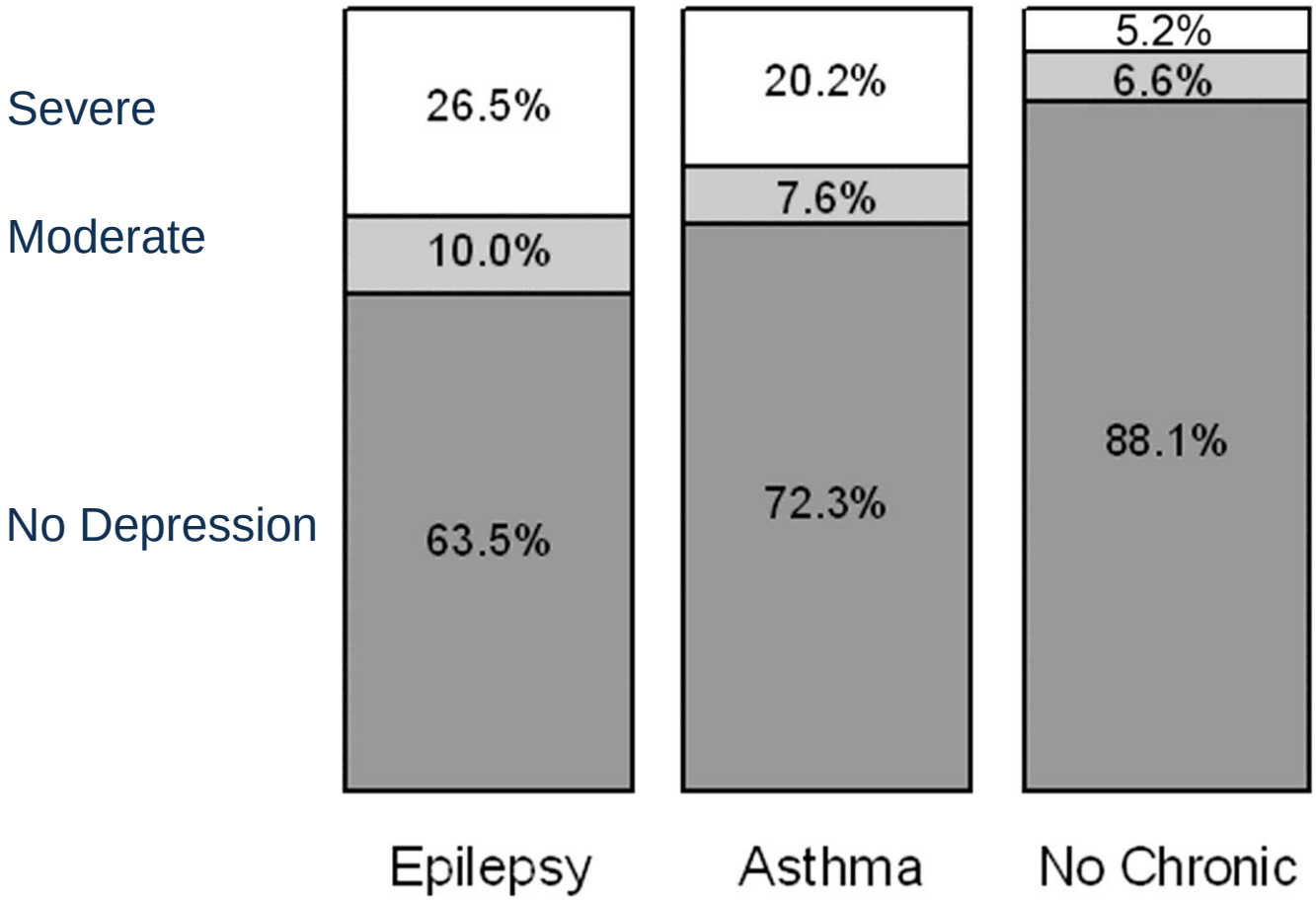
Risk of Suicide in People with Epilepsy

- 6-25x greater risk of suicide in people with epilepsy
- 5.3 x greater risk within 6 months of initial diagnosis
- >20x greater risk with co-morbid psychiatric disease
- 7-13x greater risk after epilepsy surgery

Depression in Epilepsy
Co-morbidity

- Standard DSM Definition of Depression:
  - 24% (Jones 2005)
- National Community Based Survey
  - 3x more than non-epilepsy controls (Kobau 2006)
  - 37% of Epilepsy > 28% of Asthma > 12% Healthy Controls (Ettinger2004)

Depression as Co-Morbidity



Ettinger A et al. Neurology 2004;63:1008-1014

Anything Special About Epilepsy: Temporal Relation to Seizure?

- Interictal Dysphoric Disorder
  - Labile depression: depressed, anergia, pain, insomnia
  - Labile affective symptoms: fear, anxiety
  - Paroxysmal irritability and euphoric moods
- Due to periodicity, may be misdiagnosed as bipolar d/o
- Case reports describe good response to SSRI, TCAs

(Mula 2008, Blumer 2004, Mula 2010)

Outline

- Impact of Mood in Epilepsy
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- Medicine, Mood & Epilepsy
- The Mind, Mood & Epilepsy

Deconstructing the Anatomy of Depression

1. Depressed mood often
2. Anhedonia
3. Change in weight
4. Change in sleep
5. Psychomotor agitation
6. Fatigue/loss of energy
7. Worthlessness/Guilt
8. Concentration problems
9. Suicidal ideation

Vegetative-Somatic

Attention-Cognition

Primary Depression Anatomy

- Hippocampal Atrophy most common finding
- Decrease by 8% on Left and 10% on Right

(Videbech & Ravnkilde 2004)

FIGURE 2. Standardized Mean Difference of Right Hippocampal Volume in Patients With Depression Relative to Comparison Subjects From a Meta-Analysis of 12 MRI Studies[a]

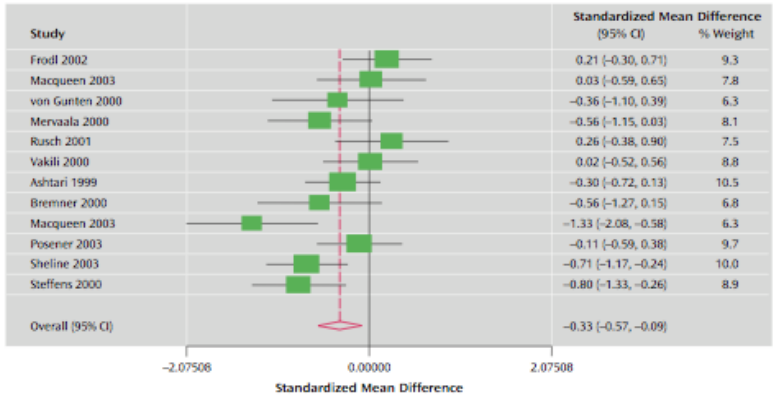
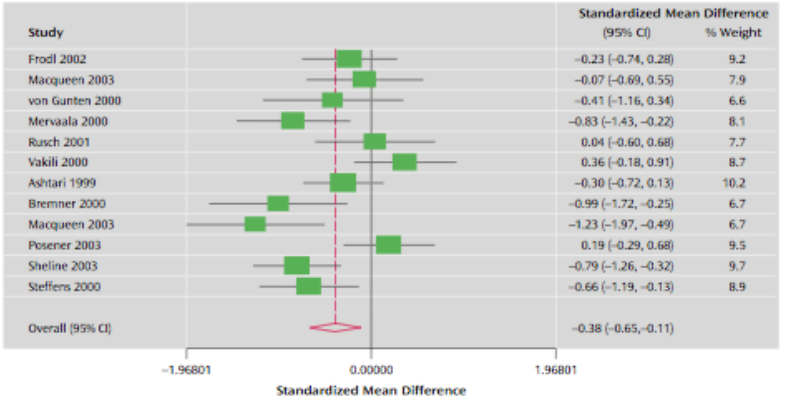


FIGURE 1. Standardized Mean Difference of Left Hippocampal Volume in Patients With Depression Relative to Comparison Subjects From a Meta-Analysis of 12 MRI Studies[a]



Primary Depression Anatomy

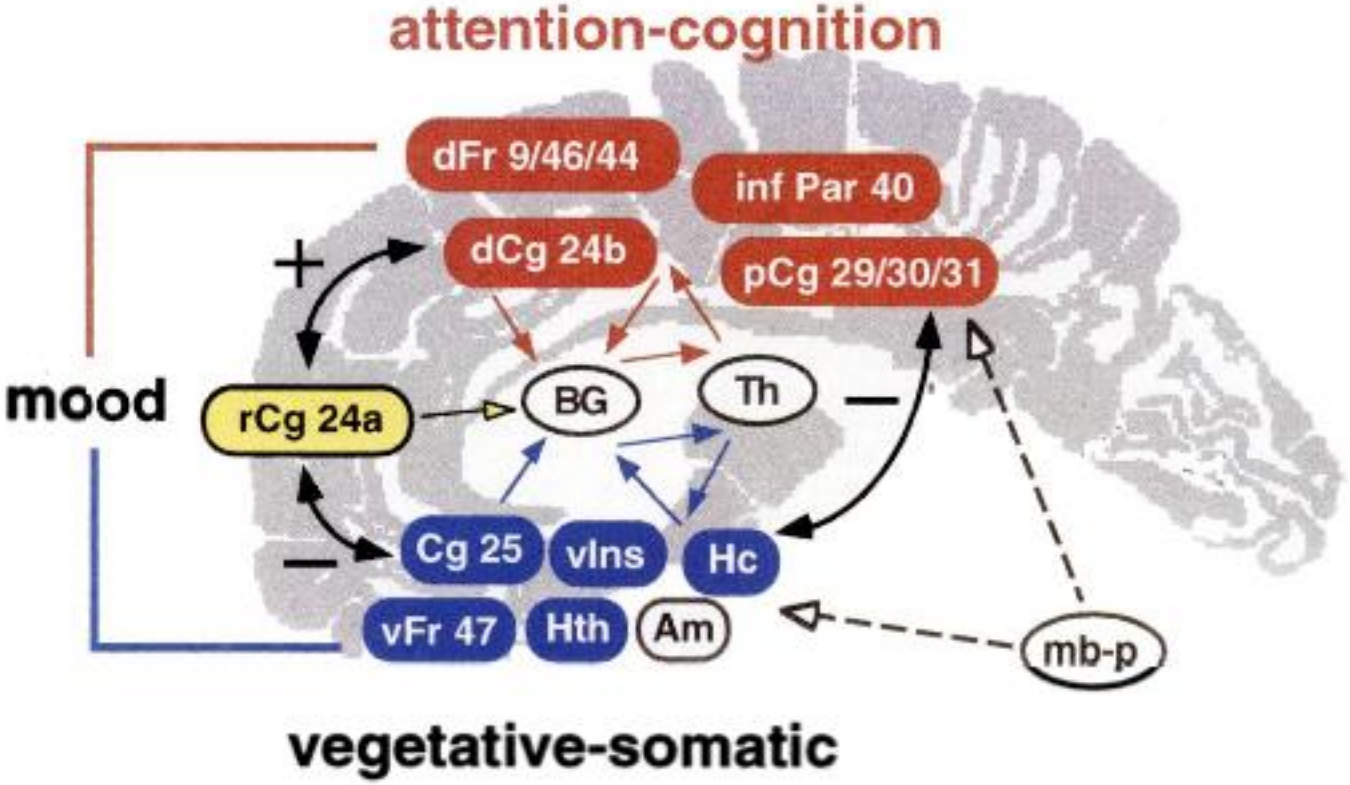
- Connections: Decreased Frontal and Temporal White Matter

Table 2. Data Analysis and Results

Study	Diagnosis	Data Analysis				Results	
		Method	Anisotropy	Diffusivity	ROI/Tract	Significant Difference in Anisotropy	Significant Difference in Diffusivity
Adler *et al.* (2004) (57)	BP	ROI	FA	TADC	Frontal	↓ Frontal	No significant differences
Adler *et al.* (2006) (56)	BP	ROI	FA	TADC	Frontal, posterior	↓ Frontal (L)	No significant differences
Bae *et al.* (2006) (58)	MD	ROI	FA	ADC	Frontal, CC, IC	↓ Frontal (L, R)	No significant differences
Beyer *et al.* (2005) (62)	BP	ROI	FA	ADC	Frontal	No significant differences	↑ Frontal
Frazier *et al.* (2007) (68)	BP	ROI	FA	NA	Frontal, CC, SLF	↓ Frontal (L, R), CC (R), SLF (L, R)	NA
Haznedar *et al.* (2005) (53)	BP	ROI	RA	NA	Frontal, SLF, FOF, IC	↓ IC (L, R), FOF ↑ Frontal (R)	NA
Houenou *et al.* (2007) (59)	BP	Tractography	FA	ADC	Frontal, Temporal, UF Pons, Cerebellum, P-C	No significant differences	No significant differences
Li *et al.* (2007) (10)	MD	ROI	FA	NA	Frontal	↓ Frontal (L, R)	NA
McIntosh *et al.* (2008) (64)	BP	Tractography	FA	NA	UF, ATR	↓ UF, ATR	NA
Nobuhara *et al.* (2004) (94)	MD	ROI	FA	NA	Frontal, Temporal, CC	↓ Frontal, Temporal	NA
Nobuhara *et al.* (2006) (95)	MD	ROI	FA	NA	Frontal, Temporal, Parietal, Occipital, CC	↓ Frontal, Temporal	NA
Pavuluri *et al.* (2009) (63)	BP	ROI	FA	ADC	CC, IC, SLF, ILF, ACR, CG	↓ ACR	↑ CC
Steele *et al.* (2005) (96)	MD	ROI	FA	NA	Brainstem	No significant differences	NA
Sussmann *et al.* (2009) (65)	BP	ROI	FA	NA	IC, UF	↓ IC (L), UF (L, R)	NA
Taylor *et al.* (2001) (60)	MD	ROI	FA	ADC	Frontal, Parietal, Caudate, Thalamus	No significant differences	No significant differences
Taylor *et al.* (2004) (97)	MD	ROI	FA	NA	Frontal, Occipital	↓ Frontal (R)	NA
Taylor *et al.* (2007) (69)	MD	Tractography	FA	NA	UF	No significant differences	NA
Wang *et al.* (2008) (71)	BP	ROI, VBA[a]	FA	NA	CC	↓ CC	NA
Wang *et al.* (2008) (70)	BP	ROI	FA	NA	CG	↓ CG	NA
Yang *et al.* (2007) (98)	MD	ROI	FA	NA	Frontal, Temporal, CC	↓ Frontal (L, R), Temporal (R)	NA
Yurgelun-Todd *et al.* (2007) (54)	BP	ROI	FA	Tr	CC	↑ CC	No significant differences

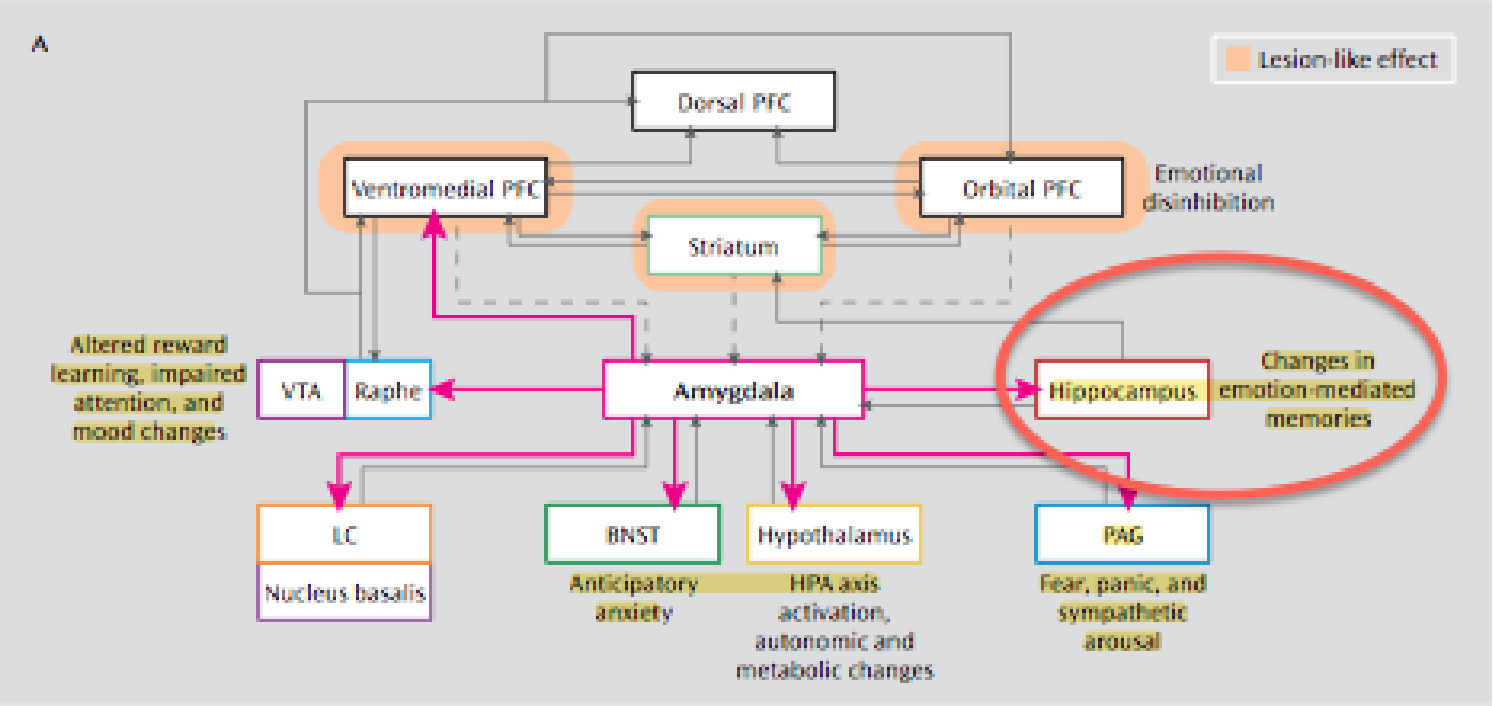
Primary Depression Networks

- Mayberg 1997



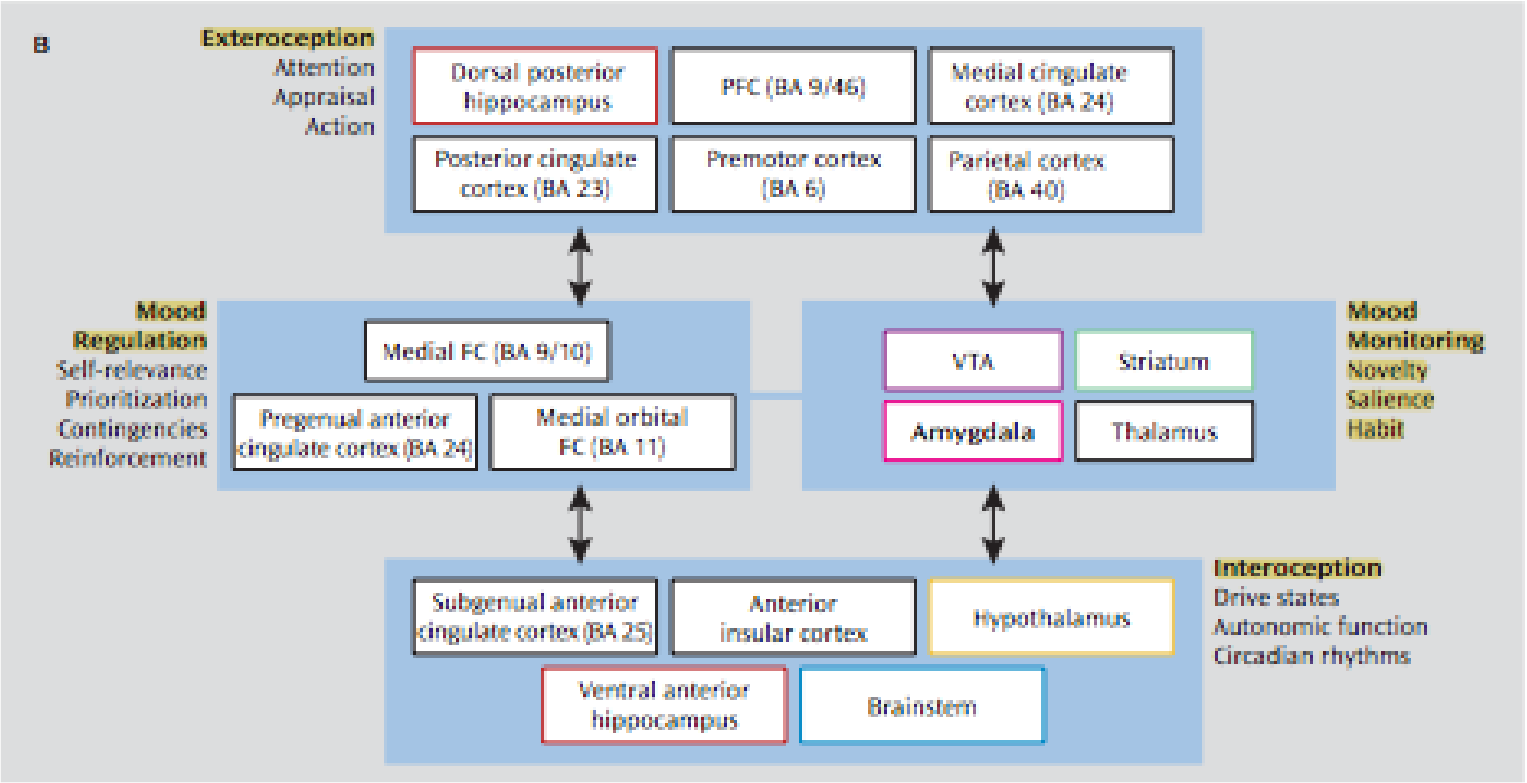
Primary Depression Networks

- Amygdala Centric “Lesion Model”

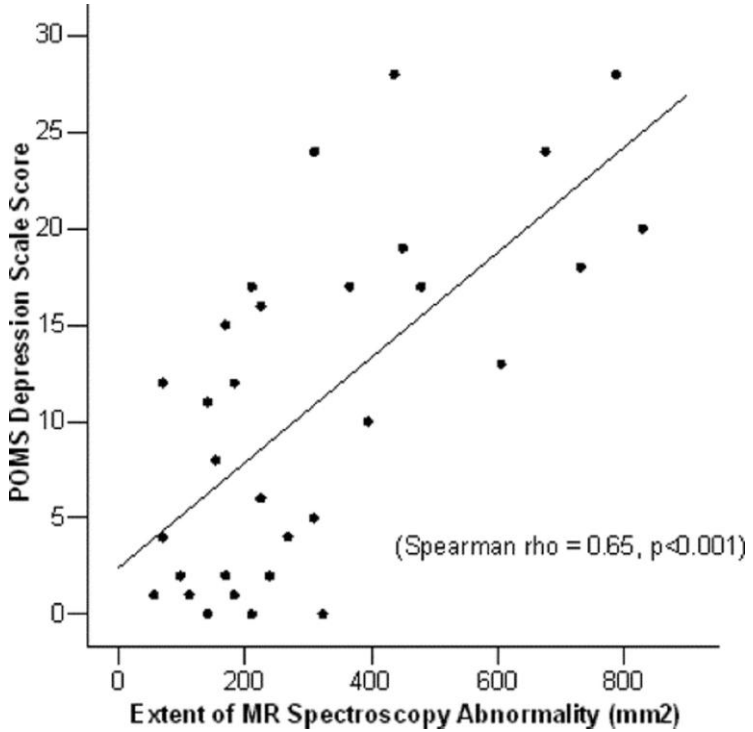


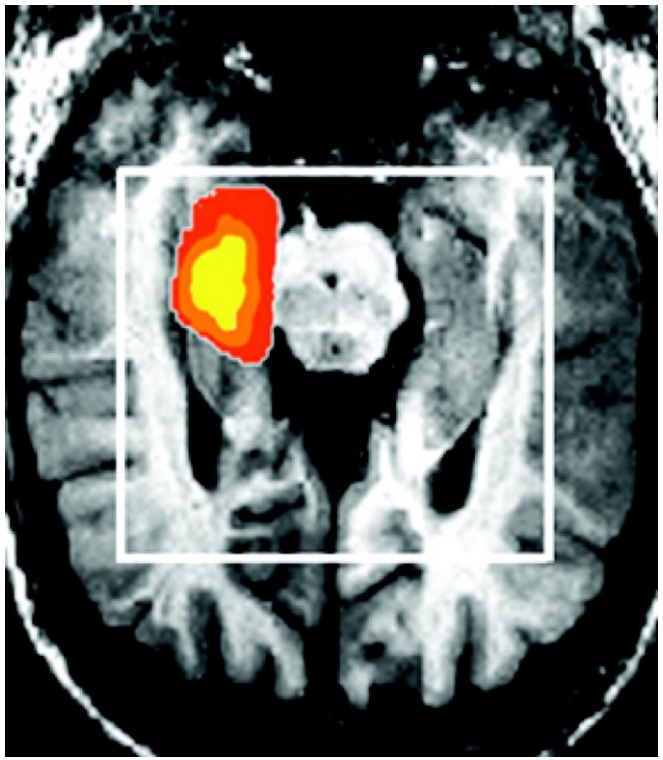
Primary Depression Networks

- Circuit Model- Clusters of cognitive/emotional function



Temporal Lobe Epilepsy and Mood



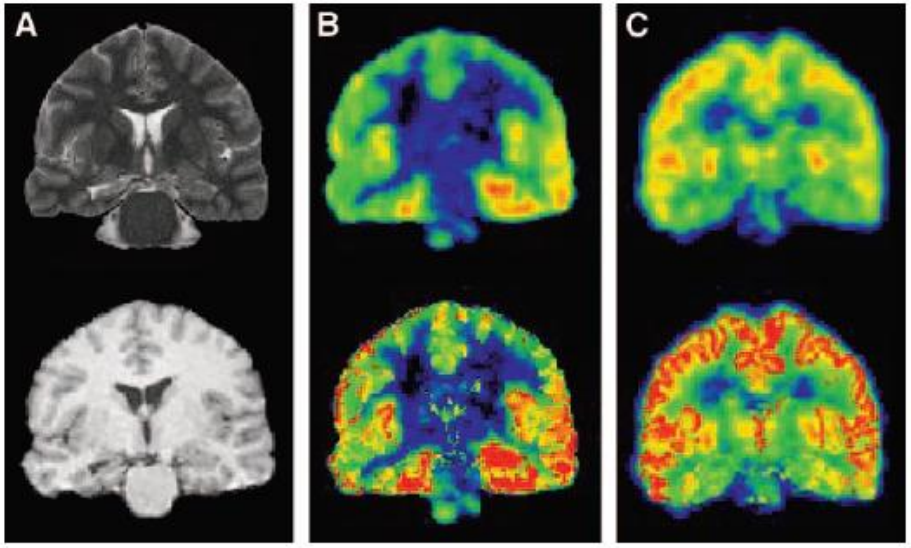


Gilliam, F. G. et al. Neurology 2007;68:364-368

Temporal Lobe Epilepsy and Mood

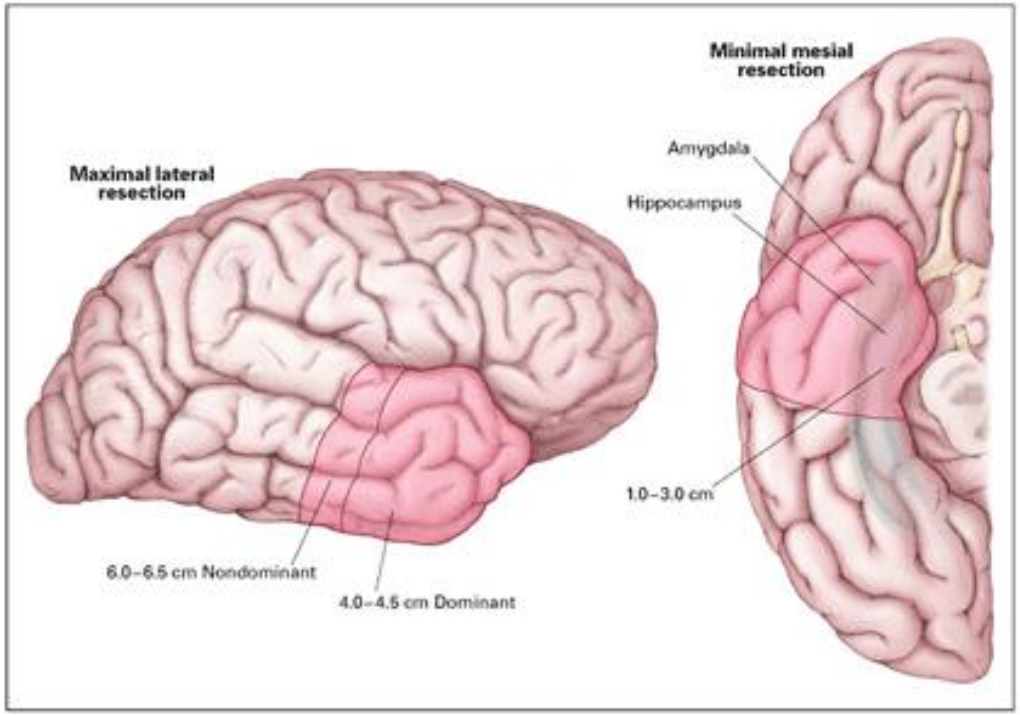
- somatic symptoms → epileptogenic hippocampus/ parahippocampal regions
- anhedonia → cingulate gyrus
- negative cognitions → insula

(Lothe et al 2004)



Anatomy of Depression in Epilepsy

What happens to mood when a large piece of brain (which is involved in the depression network) is removed?



Depression 5 years after surgery

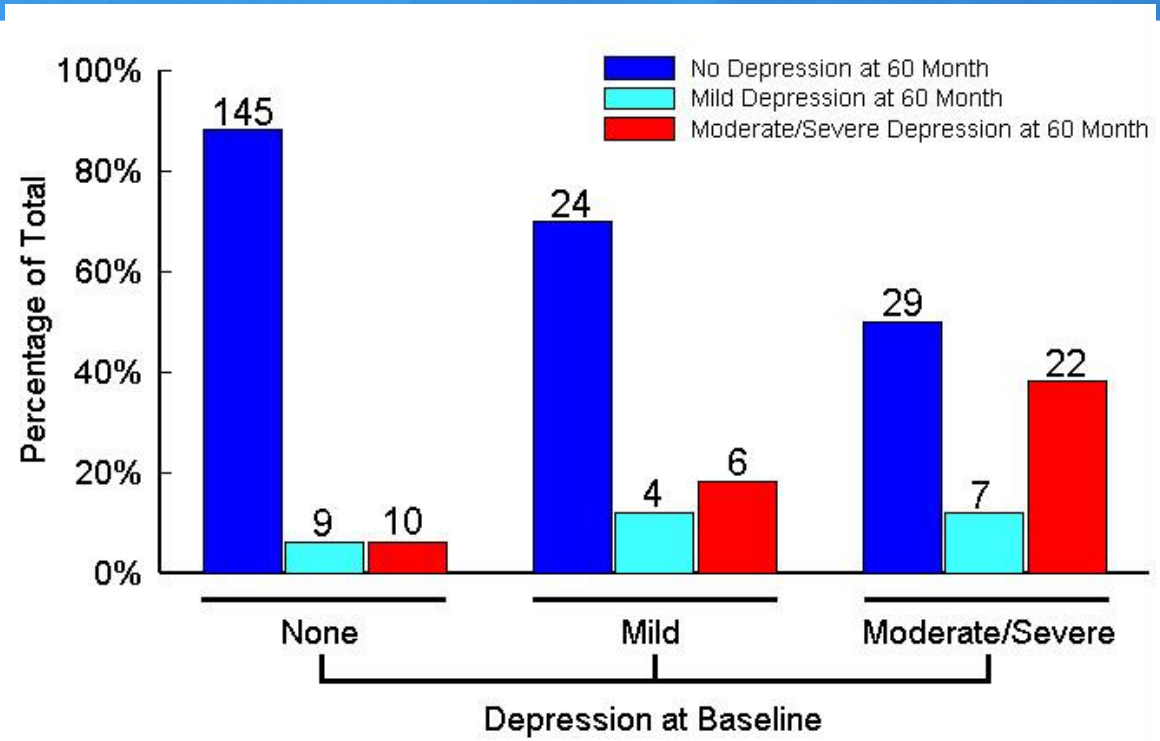
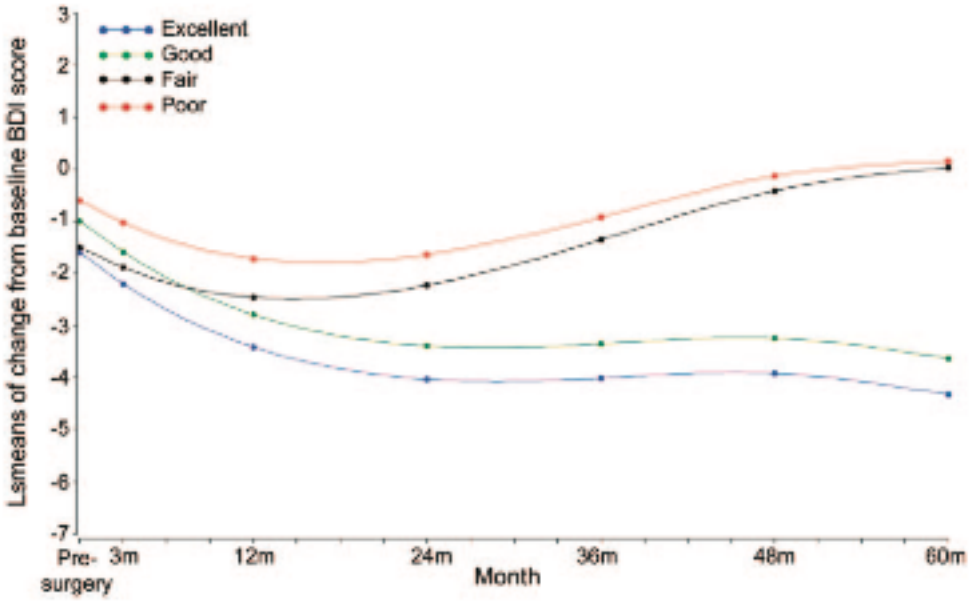


Figure 1. Percentage of patients scoring in the not depressed, mildly depressed, and moderate to severe depression range pre-surgically versus five years post-surgically. Number of respective patients in each category labeled within the columns.

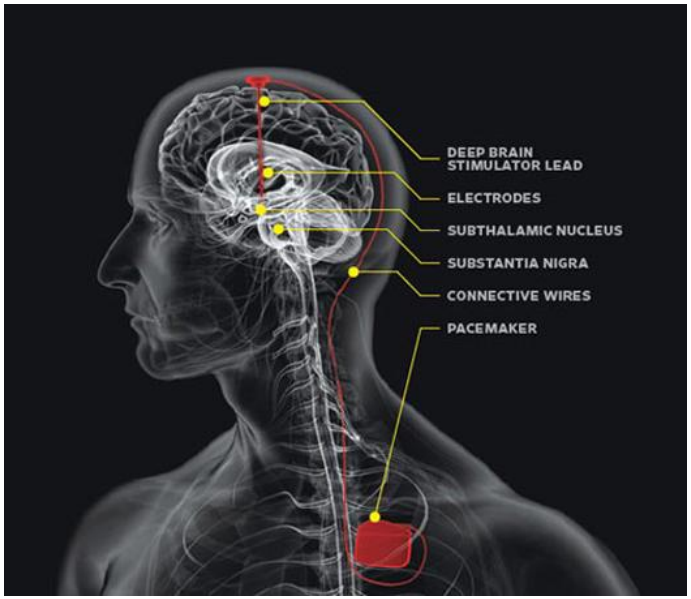
Note: Out of the 379 adult subjects in the study, 256 subjects had both baseline and five year follow up depression score summarized above. A total 123 subjects were excluded: 101 with baseline depression score only; n=7 with five year depression score only and 15 missing both baseline and five year depression scores.

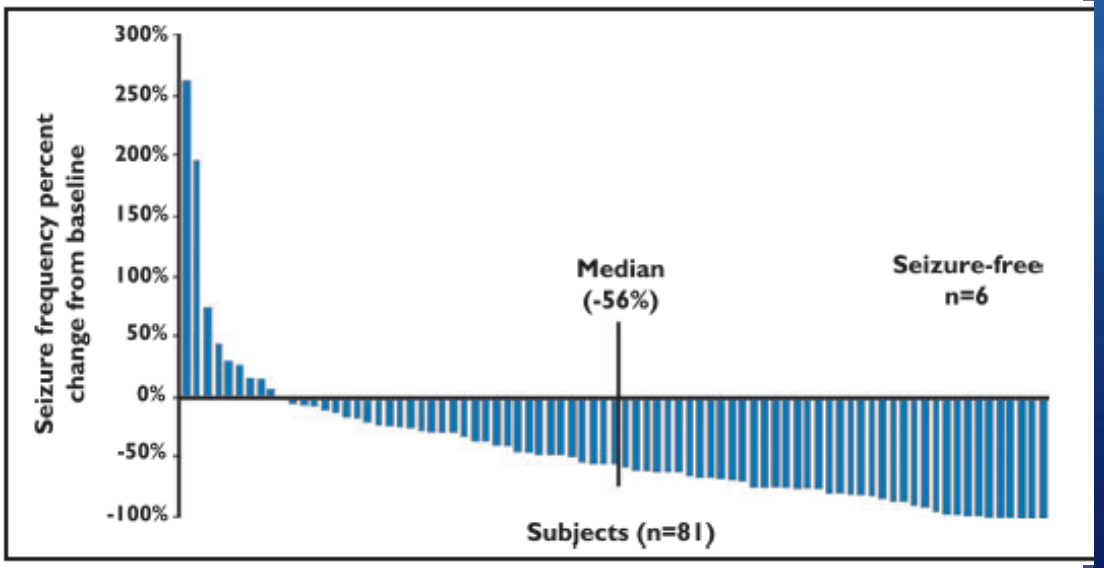
Depression 5years after surgery

- Long term depression outcomes after epilepsy surgery



Epilepsy- Deep Brain Stimulation





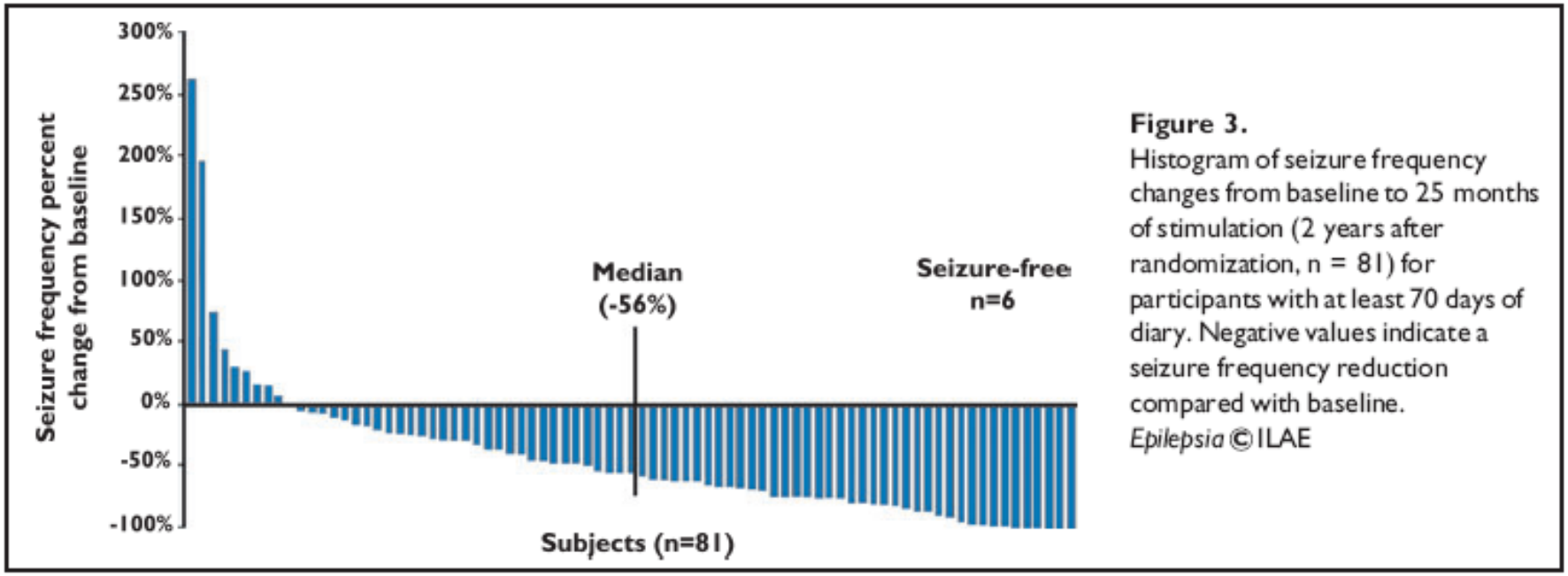


Figure 3.
Histogram of seizure frequency changes from baseline to 25 months of stimulation (2 years after randomization, n = 81) for participants with at least 70 days of diary. Negative values indicate a seizure frequency reduction compared with baseline.

DBS Anterior Thalamus- Depression?

Table 3. Adverse events occurring in >5% of subjects in either the active or control group during the Blinded Phase, ordered by difference between groups

	Active		Control			
Preferred term	Number of subjects	% (n = 54)	Number of subjects	% (n = 55)	Difference[a]	p-value[b]
Depression	8	14.8%	1	1.8%	13.0%	0.0162[c]
Memory impairment	7	13.0%	1	1.8%	11.1%	0.0316[c]
Confusional state	4	7.4%			7.4%	0.0568
Anxiety	5	9.3%	1	1.8%	7.4%	0.1130
Paraesthesia	5	9.3%	2	3.6%	5.6%	0.2706
Influenza	3	5.6%			5.6%	0.1182
Partial seizures with secondary generalization[d]	5	9.3%	3	5.5%	3.8%	0.4890
Simple partial seizures[d]	3	5.6%	1	1.8%	3.7%	0.3634
Complex partial seizures[d]	5	9.3%	4	7.3%	2.0%	0.7420
Anticonvulsant toxicity	3	5.6%	4	7.3%	−1.7%	1.0000
Dizziness	3	5.6%	4	7.3%	−1.7%	1.0000
Headache	2	3.7%	3	5.5%	−1.8%	1.0000
Excoriation	1	1.9%	3	5.5%	−3.6%	0.6180
Contusion	1	1.9%	4	7.3%	−5.4%	0.3634
Nasopharyngitis	1	1.9%	5	9.1%	−7.2%	0.2057
Upper respiratory tract infection			4	7.3%	−7.3%	0.1182
Injury	1	1.9%	6	10.9%	−9.1%	0.1130

[a]Positive, more frequent in the active group; negative, more frequent in the control group.
[b]Fisher's exact test.
[c]Statistically significant.
[d]New or worse seizures, or seizures meeting serious adverse event criteria.

Outline

- Impact of Mood in Epilepsy
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- The Mind, Mood & Epilepsy

Anti-convulsants implicated as depressive

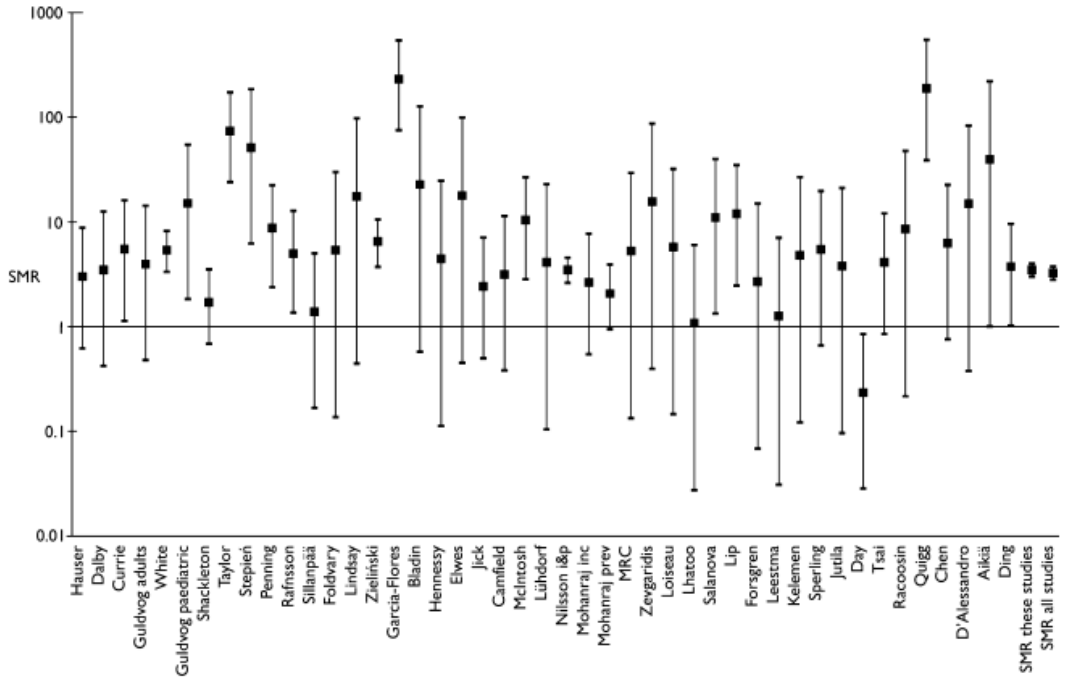
- Potentially Depressogenic:
  - Phenobarbital
  - Primidone,
  - Tiagabine,
  - Vigabatrin,
  - Felbamate,
  - Topiramate,
  - Levetiracetam,
  - Zonisamide

Anti-Epileptic Drugs & Suicide

- FDA Meta-analysis:
  - 199 studies
  - >27,000 subjects
  - 11 AEDs used for seizure control, psychiatric or 'other' indications.
  - TPM and LEV only significant increase risk SI.
  - 4 completed suicides + AEDs
  - 0 suicides placebo.
- Odds ratio for suicidal behavior or ideation was 1.8 (95% CI 1.24, 2.66),
- FDA Black Box warning: "Patients being treated with antiepileptic drugs for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior"

Suicide and Seizures

Figure 1.
Standardized mortality ratios (SMRs) (with 95% confidence intervals) for death by suicide in studies of people with epilepsy. The figure includes only those cohorts with any deaths due to suicide. inc, incidence; prev, prevalence; i&p, incidence and prevalence.
Epilepsia © ILAE



Bell 2009

What medications anti-depressants are most appropriate?

Seizure Incidence in Psychopharmacological Clinical Trials: An Analysis of Food and Drug Administration (FDA) Summary Basis of Approval Reports

Kenneth Alper, Kelly A. Schwartz, Russell L. Kolts, and Arif Khan

BIOL PSYCHIATRY 2007;62:345–354

- Incidence rate of seizures controlling for years on Rx:
  - SSRI = 0.48
  - Bupropion IR only = 1.58
  - Antipsychotics = 2.05
  - Antipsychotics (excluding clozapine) = 1.35)
  - Clozapine only = 9.50

Alper 2007

My Recommendations

- MUST ask about Anxiety & Mania
- Pick Two SSRI (one generic)
  - Celexa/Lexapro (QT syndrome)
  - Zoloft
  - Effexor (more activating, HTN)
  - Welbutrin SR (more activating, no sexual dysfunction)

Outline

- Anatomy of Mood & Epilepsy
- Pharmacology of Mood & Epilepsy
- Psychology of Mood & Epilepsy

Outline

- Impact of Mood in Epilepsy
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Psychological State

- Coping Styles
  - Negative
    - Escape Avoidance
    - Distancing
    - Self-controlling
    - Confrontational
  - Positive
    - Seeking support
    - Accepting responsibility
    - Planful problem solving
    - Positive appraisal

Even if Epilepsy if Epilepsy is Cured: Burden of Normality

- After living with chronic disease, feeling disabled, building a network around your epilepsy…. now you are cured!

Psychological	Affective	Behavioral	Sociological
Sense of loss Grieving for epilepsy	Mood Elevation	Excessive Activity	New family dynamics
Proof of Normality	Anxiety	Increased Sex drive	New vocational expectations
Increased Expectations	Depression	Shirking behavior-	New social skills
The Lost Years- To make up for		Other somatization	

What can a person do?

Case study

- 35 year old woman carries a 15 year h/o epilepsy
  - Recent attempted suicide (O.D.) after breaking up with boyfriend
  - In psychiatry ward had multiple tonic clonic seizures, requiring multiple stat Ativan
  - Rx: Keppra 1500mg , Dilantin 300mg, Lexapro 20mg
  - PE: neurologically normal, dysphoric, No SI/HI