The Impact of Psychiatric Comorbidities on the Development, Course and Treatment of Epilepsy.

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Disclosures...

- None
Show of Hands...

**Only neurologists:**

How many of you screen for depression and anxiety disorders when you take the history of every patient with suspected epilepsy?
Comorbid epileptic and psychiatric disorders in animal models....
Elevated anxiety and depressive-like behavior in a rat model of genetic generalized epilepsy:

Before the onset of seizures


GAERS, n = 47

- Sucrose Preference test
- Elevated Plus Maze
- Consumption of sucrose
- Time in the open arms of the EPM

NECR, n = 73

- Open Field Arena
- Exploratory activity and time spent in the inner area of the OFA
Elevated anxiety and depressive-like behavior in a rat model of genetic generalized epilepsy:

After the onset of seizures


GAERS, n = 47
NECR, n = 73

Sucrose Preference test
Elevated Plus Maze
Open Field Arena

↓ Consumption of sucrose
↓ time in the open arms of the EPM
↓ exploratory activity and ↓ time spent in the inner area of the OFA
Morphometric abnormalities and hyperanxiety in genetically epileptic rats: a model of psychiatric comorbidity

Bouilleret et al, Neuroimage 2009.

- Adult female GAERS (n=12) and Non-Epileptic Controls (NEC; n=11).

- GAERS had: increased amygdala (right: p=0.003; left p<0.001)
- Decreased cortical volume (right: p=0.006; left p=0.012)
- Increased ventricular volumes (p=0.002)

- Hippocampal volume loss in:
  - the medial hippocampal surface immediately caudal to the hippocampal commissure,
  - the lateral hippocampal surface over the mid-portion of the septotemporal axis.
Predisposition for depression-like symptoms and epileptic seizures

**Epileptic activity**

- Genetically epilepsy-prone rat (3 and 9)
- *Innate noradrenergic and serotonergic deficits*
- ↓*pre and postsynaptic GABA activity*
- Susceptibility to seizures evoked by auditory stimuli
- Deficit in NE transmission deficit more severe in GEPR-9
- Seizures more severe in GEPR-9

**Affective-like phenomena**

- **Anhedonia**: lower consumption of water with sucrose compared to controls.

- **Behavior despair** tested by the forced swim test: >50% time in despair behavior beginning with 3rd swimming episode (not seen in controls during same time).

- Diurnal abnormalities in motor behavior.

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*Jobe & Weber, 2005.*
Psychiatric comorbidity → Epilepsy
Effects of Early Life Stress in Rodent Models of Epilepsy/Epileptogenesis

Maternal separation$^{1,2}$ or cross-fostering$^3$

Rapid amygdala Kindling to 5 or 6 class V seizures$^{1,2,3}$

↑kindling rate and ↓sz. threshold$^{1,3}$ or ↓ADT$^2$ in deprived animals

Early handled$^{1,2}$ or non-fostered$^3$

The impact of corticosterone on the kindling process

Rapid amygdala kindling

- Water
- Corticosterone
- Corticosterone + spironolactone
- Corticosterone + mifepristone
- Corticosterone + both antagonists

Mean number of stimulations required to reach the 'fully kindled state'

86.5
45.2
69.6
70.4
62.8

P <0.01
P = 0.04
NS

Kumar et al, Psychoneuroendocrinology. 2007;32:834-42
Impact of HPA on Glutamate Secretion in Depression

↓ glial cells in:
- prefrontal cortex
- subgenual
- cingulate
- dorsolateral Temporal lobe structures

↑↑↑ cortisol

↑ extracellular glutamate in:
1) Prefrontal cortex
2) Nucleus accumbens
3) Hippocampus
4) Amygdala

Toxic accumulation of extracellular glutamate

Hyperactive Hypothalamic Pituitary Adrenal Axis

Cotter et al, Arch Gen Psychiatry 2001
How big of a problem is it?
## Prevalence Rates of Psychiatric Disorders in Epilepsy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>In Epilepsy (range)</th>
<th>In the General Population (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>11%-60%</td>
<td>12%-15%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>19%-45%</td>
<td>2.5%-6.5%</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2%-8%</td>
<td>0.5%-0.7%</td>
</tr>
<tr>
<td>ADHD</td>
<td>25%-30%?</td>
<td>2%-10%</td>
</tr>
</tbody>
</table>

### Lifetime Prevalence

_Tellez-Zenteno, JF et al., Epilepsia, 2007; 48:2336-2344_

<table>
<thead>
<tr>
<th>Psychiatric Disorder</th>
<th>Controls (%)</th>
<th>Epilepsy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depressive Disorder</td>
<td>10.7 (10.2–11.2)</td>
<td>17.4 (10.0–24.9)</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>11.2 (10.8–11.7)</td>
<td>22.8 (14.8–30.9)</td>
</tr>
<tr>
<td>Mood/Anxiety Disorders</td>
<td>19.6 (19.0–20.2)</td>
<td>34.2 (25.0–43.3)</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>13.3 (12.8–13.8)</td>
<td>25.0 (17.4–32.5)</td>
</tr>
<tr>
<td>Any Psychiatric Disorder</td>
<td>20.7 (19.5–20.7)</td>
<td>35.5 (25.9–44.0)</td>
</tr>
</tbody>
</table>
Psychiatric comorbidities over time

Dx. of epilepsy

- Mood Disorders
- Anxiety Disorders
Psychiatric comorbidities over time...

- Mood Disorders
- Anxiety Disorders

Dx. of epilepsy
Psychiatric comorbidities over time

Dx. of epilepsy

- Mood Disorders
- Anxiety Disorders

Family psychiatric history
Psychiatric comorbidities over time

Dx. of epilepsy

- Mood Disorders
- Anxiety Disorders

Family psychiatric history
Psychiatric comorbidities over time

- Mood Disorders
- Anxiety Disorders

Dx. of epilepsy

Family psychiatric history

- Mood Disorders
- Anxiety Disorders
Psychiatric comorbidities over time

- Mood Disorders
- Anxiety Disorders

Family psychiatric history

Dx. of epilepsy

- Mood Disorders
- Anxiety Disorders
Psychoplasm...

- Mood Disorders
- Anxiety Disorders

Family psychiatric history

Dx. of epilepsy

- Mood Disorders
- Anxiety Disorders
Psychiatric Comorbidities That Occurred Prior to The Onset of Epilepsy

<table>
<thead>
<tr>
<th>Psychiatric Diagnosis</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=3,773)</td>
<td>(N=14,025)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>18.5%</td>
<td>13.8%</td>
</tr>
<tr>
<td>Depression</td>
<td>17.5%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>0.8% to 5.4%</td>
<td>0.1% to 2.4%</td>
</tr>
<tr>
<td>Suicidality</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Psychiatric comorbidity in children with new onset epilepsy

Jones et al., Dev Med Child Neurol, 2007

- Children aged 8 to 18 years with recent onset epilepsy (<1 yr) of idiopathic etiology ($n=53$)
- Healthy comparison group ($n=50$)
- Structured psychiatric diagnostic interview to characterize the spectrum of lifetime-to-date history of comorbid psychiatric disorder
Psychiatric comorbidity in children with new onset epilepsy

Jones et al., Dev Med Child Neurol, 2007

- Children with epilepsy exhibited significantly higher rates of:
  - Depressive disorders (22.6 vs. 4%, \( p=0.01 \)),
  - Anxiety disorders (35.8 vs 22%, \( p<0.05 \)),
  - Attention-deficit-hyperactivity disorder (26.4 vs 10%, \( p=0.01 \))

- 45% of children with epilepsy exhibited DSM-IV Axis I disorders *before the first recognized seizure.*
Psychiatric disorders as a risk factors for treatment-resistant epilepsy?
Psychiatric Predictor of Pharmacologic Treatment with AEDs

► N=780

► New-onset epilepsy

► Seizure freedom at last outcome (median, 79 months [range: 24-240])
  - Psychiatric disorder at the time of diagnosis of epilepsy: OR 2.2 ($P<.0002$) against reaching seizure freedom
  - Depressive disorders accounted for the variance

Neuropsychiatric symptomatology predicts seizure recurrence in newly treated patients

N = 138

P = 0.007

Petrovski, S. et al. Neurology 2010
The odds of failing to achieve 1-year seizure freedom were significantly higher for those with depression or treated depression preceding the onset of epilepsy.
What is the incidence of seizures in non-epileptic patients treated with psychotropic drugs?

Alper et al., Biological Psychiatry 2007

- Data from Food and Drug Administration (FDA) Phase II and III clinical trials as Summary Basis of Approval (SBA) reports that noted seizure incidence in trials of psychotropic drugs approved in the United States between 1985 and 2004.

- N = 75,873 patients.

- Comparison of seizure incidence among active drug and placebo groups in psychopharmacological clinical trials and the published rates of unprovoked seizures in the general population.
Antidepressant treatments associated with lower seizure incidence relative to placebo for all SSRIs and SNRIs

- Standardized seizure ratio: 0.48, 95% C.I. 0.36-0.61.

- The incidence of seizures among patients randomized to placebo was 19-fold higher than that of the general population.
Higher incidence of seizures in patients exposed to antidepressants than placebo:

- Clomipramine
- Bupropion immediate release (IR)
Anticonvulsant action of hippocampal serotonin is mediated by 5-HT$_{1A}$ receptors.


- The anticonvulsant effects of intrahippocampally applied 5-HT concentrations were evaluated against pilocarpine-induced seizures in conscious rats.

- 5-HT perfusions protected the rats from limbic seizures as long as extracellular 5-HT concentrations ranged 80–350% increments relative to baseline levels.

- High extracellular 5-HT (> 900% increases) concentrations worsened seizure outcome.

- The latter proconvulsant effects were associated with significant increases in extracellular glutamate.
Impact of presurgical psychiatric history on post-surgical outcome

- Higher likelihood of persistent seizures after epilepsy surgery with antero-temporal lobectomies (?)
  - Kanner et al., Neurology 2009 ........... YES
  - Cleary et al., Epilepsia 2012 ............ YES
  - De Araujo et al., Epilepsia 2012 ........ YES
  - Adams et al., Epilepsia 2013 ............. NO
  - Kock Stoecker et al., Epilepsia 2017 .. YES
Seizure Outcome After Anterior Temporal Lobectomy: Effect of LT History of Depression

- 100 consecutive patients with anterior temporal lobectomy.
- Presurgical evaluation for lifetime psychiatric history.
- Outcome: seizure frequency at 2 years post surgery
- Mean post-op f/u: 8.3±3.1 years.

Kanner et al, Neurology 2009

Relationship between no mood disorder history and outcome:
- Class IA: OR =19.4 (95% CI=7.0-64.7)
- Class IA + IB: OR=7.2 (95% CI=3.0-19.0)
- Class IA, IB, IC: OR=5.1 (95% CI=1.5-2.5)
Germany: Data from the Epilepsy Center Bethel

Koch Stocker et al., Epilepsia 2017

Description of the study group:
- 378 adult patients, between 18 and 70 years old
- Mean age 37 years
- Not mentally retarded (IQ > 70)
- 185 men, 193 women
- 172 left, 206 right temporal
- Operated on between 1992 and 2006
- Followed up for two years

Pathology:
- MTS: 55%
- Gangliogliomas + DNET: 14%
- Other: 31%

Seizure outcome:
- Engel 1: 64% (MTS: 70%)
- Engel 1A: 43% (MTS: 49%)

Preoperative psychiatric interview for all patients
## Psychiatric Categories for the Study

### Categories of Psychiatric syndromes:
1. Depression during assessment-time - no matter what kind
2. Psychosis active or in remission - no matter what kind
3. Other clinical syndrome (anxiety disorder, adaptation disorder, PTSD …)

### Categories of Personality disorders (PD):
1. Cluster A DSM IV (paranoid, schizoid, schizotypical)
2. Cluster B DSM IV (Borderline, histrionic, narcissistic, antisocial)
3. Cluster C DSM IV (dependent, avoidant, obsessive-compulsive)
4. “Organic” PD (irritability, slowing of mental activity, impaired judgements…)
5. Other (immature…)
Psychiatric Syndromes
of 378 adult pts. with TL-resection

- Depression (n=98) 26%
- Psychosis (n=26) 7%
- Other (n=53) 14%
- No (n=201) 53%
Percentage of seizure freedom in psych. syndrome groups

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Engel 1A</th>
<th>Engel 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression (38/51 of 98 pts)</td>
<td>39%</td>
<td>52%</td>
</tr>
<tr>
<td>Psychosis (7/10 of 26 pts)</td>
<td>27%</td>
<td>38%</td>
</tr>
<tr>
<td>other (18/30 of 53 pts)</td>
<td>34%</td>
<td>57%</td>
</tr>
<tr>
<td>no ps. syndrome (101/151 of 201 pts)</td>
<td>50%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Exact Fisher Test: p < 0.001, **Engel 1**
p < 0.024, **Engel 1A**
Percentage of seizure-free patients in different PD groups

Cluster B: 17(23) of 49 pts
Cluster C: 26(42) of 70 pts
organic: 9(14) of 43 pts
no PD: 107(155) of 200 pts

Exact Fisher Test: p < 0.001, Engel 1
p < 0.001, Engel 1A
Seizure freedom 2y after TL-surgery (n=378)

- Double diagnosis (ps syndr plus PD): 24(38) of 93 pts (26%)
- Personality disorder only: 33(49) of 85 pts (39%)
- Psychiatric syndrome only: 39(53) of 84 pts (46%)
- No diagnosis: 68(102) of 116 pts (59%)

Engel 1a: 41%
Engel 1: 88%
Bad seizure outcome: **Engel 4** (n=36 pts.)

- Double diagnosis: 14% (13 of 93 pts)
- Personality disorder: 12% (10 of 85 pts)
- Psych syndrome: 10% (8 of 84 pts)
- No diagnosis: 4% (5 of 116 pts)
Impact on the potential anticipation of seizures triggered by stress: clinical and research implications
Impact of stress on epilepsy

- Stress influences epilepsy at multiple levels:
  - affects seizure occurrence
  - seizure frequency
Stressful events are not random...

- Prodromal depressive symptoms predispose to stressful life events and depression (Kendler et al., 1999).

- Variables that predict stressful events:
  - Lower social class
  - Drug and alcohol abuse
  - Personality factors:
    - low self-esteem
    - impulsivity
    - poor frustration tolerance
    - risk taking

- Family history of psychiatric disorders predicts an increased occurrence of stressful events (Breslau et al., 1991)
Stress-related seizures

- N = 71 subjects returned 15,179 complete diary days. One-unit increments of anxiety (on a 10-point scale) were associated with an increased risk of seizure the following day (OR 1.07; 95% CI 1.02, 1.12).

  Haut et al., Neurology 2007

- N = 19 subjects reported 244 eligible seizures. Self-prediction appeared to be driven by mood and premonitory symptoms. Favorable change in mood (0.82; CI 0.67-0.99).

  Haut et al., Epilepsy & Behavior 2012
Impact on the tolerance of AEDs…
## Adverse Events Profile

During the past four weeks, have you had any of the problems or side-effects listed below?

<table>
<thead>
<tr>
<th>Problem</th>
<th>Always</th>
<th>Sometimes</th>
<th>Rarely</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsteadiness</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Tiredness</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Restlessness</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Feelings of aggression</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nervousness and/or aggression</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hair loss</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Problems with skin, e.g. acne, rash</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Double or blurred vision</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Upset stomach</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Difficulty in concentrating</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Trouble with mouth or gums</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Shaky hands</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Weight gain</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Memory Problems</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Disturbed sleep</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Baker et al, Epilepsia, 1994.*
**Impact of Psychiatric Disorders on Perception of AED-Related Adverse Events**  
*Kanner et al., Epilepsia, 2012*

<table>
<thead>
<tr>
<th>Psychiatric Dx.</th>
<th>N</th>
<th>AEP Score: all items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>103</td>
<td>32.2 (±7.6)</td>
</tr>
<tr>
<td>Sub-syndromic depressive episode</td>
<td>26</td>
<td>45.1 (±9.6)</td>
</tr>
<tr>
<td>Major depressive episode</td>
<td>10</td>
<td>49.6 (±9.3)</td>
</tr>
<tr>
<td>Anxiety Disorders</td>
<td>28</td>
<td>45.5 (±10.8)</td>
</tr>
<tr>
<td>MDE + Anxiety Disorders</td>
<td>21</td>
<td>52.8 (±9.2)</td>
</tr>
</tbody>
</table>

\[ p = \frac{F = 38.3, <0.0001}{1} \]
Increased risk of psychiatric iatrogenic adverse events

- Mula et al., Epilepsia 2003, 2007
- Kanner AM, 2016
Dx. of epilepsy

- Mood Disorders
- Anxiety Disorders

Iatrogenic Symptoms
- Pharmacologic
- Surgical

Family psychiatric history

Time
Psychiatric comorbidities over time

- Mood Disorders
- Anxiety Disorders

Dx. of epilepsy

- Mood Disorders
- Anxiety Disorders

Family psychiatric history

Iatrogenic symptoms
- Pharmacologic
- Surgical

Time
Psychiatric comorbidities over time

- Mood Disorders
- Anxiety Disorders

Dx. of epilepsy

- Mood Disorders
- Anxiety Disorders

Iatrogenic symptoms
- Pharmacologic
- Surgical

Family psychiatric history

Time
Psychiatric symptoms as an expression of a iatrogenic effect…

1. Introduction of AED with negative psychotropic properties *in vulnerable patients*.

2. Increase dose of AED with negative psychotropic properties.

3. Withdrawal of AED with positive psychotropic properties *in vulnerable patients*.

4. Pharmacokinetic interaction between enzyme-inducing AED and concomitant psychotropic drug.
### AEDs with psychotropic properties that can cause iatrogenic psychiatric episodes

<table>
<thead>
<tr>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Barbiturates</td>
<td>➢ Carbamazepine</td>
</tr>
<tr>
<td>➢ Benzodiazepines</td>
<td>➢ Valproic acid</td>
</tr>
<tr>
<td>➢ <strong>Levetiracetam</strong></td>
<td>➢ Oxcarbazeptine</td>
</tr>
<tr>
<td>➢ Topiramate</td>
<td>➢ Lamotrigine</td>
</tr>
<tr>
<td>➢ Zonisamide</td>
<td>➢ Gabapentin</td>
</tr>
<tr>
<td>➢ Vigabatrin</td>
<td>➢ Pregabalin</td>
</tr>
<tr>
<td>➢ Tiagabine</td>
<td>➢ Benzodiazepines</td>
</tr>
<tr>
<td>➢ Perampanel</td>
<td></td>
</tr>
</tbody>
</table>
Post-surgical depression /anxiety

- Post-surgical major depressive and/or anxiety episodes are likely to occur in approximately 30% of patients undergoing an ATL.
- Most depressive/anxiety episodes are diagnosed within the first three to six months after surgery.
- Symptoms may appear after the first two weeks.
- They may persist for periods ranging between six and twelve months.
- Up to 15% of patients are likely to suffer from a persistent depressive episode, which may be severe and fail to remit to various therapeutic interventions.

- While some authors have associated persistent post-surgical symptoms of depression with failure to achieve a seizure-free state, this has not been a uniform finding.

- A pre-surgical history of mood and anxiety disorder was associated with an increased risk of post-surgical depressive episodes in most studies.
Can patients at risk of postsurgical recurrence or exacerbation of mood / anxiety be identified?

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Recurrence/exacerbation</th>
<th>Risks Identified Presurgically</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrench et al.</td>
<td>60</td>
<td>+</td>
<td>Presurgical Hx. of depression</td>
</tr>
<tr>
<td>Quig et al.,</td>
<td>107</td>
<td>+</td>
<td>Presurgical Hx of depression</td>
</tr>
<tr>
<td>Barbieri et al.</td>
<td>150</td>
<td>+</td>
<td>Presurgical Hx of depression</td>
</tr>
<tr>
<td>Kohler et al.</td>
<td>60</td>
<td>+</td>
<td>Ictal fear</td>
</tr>
<tr>
<td>Kanemoto et al.</td>
<td>52</td>
<td>+</td>
<td>Postictal psychosis</td>
</tr>
</tbody>
</table>
## De- Novo mood / anxiety episodes

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Prevalence rates</th>
<th>Type of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrench et al.</td>
<td>62</td>
<td>13% 17%</td>
<td>ATL and ETL</td>
</tr>
<tr>
<td>Ring et al.,</td>
<td>60</td>
<td>22%</td>
<td>ATL</td>
</tr>
<tr>
<td>Glosser et al.</td>
<td>44</td>
<td>31%</td>
<td>ATL</td>
</tr>
<tr>
<td>Blumer et al.</td>
<td>50</td>
<td>16%</td>
<td>ATL and ETL</td>
</tr>
<tr>
<td>Kanner et al.</td>
<td>100</td>
<td>15%</td>
<td>ATL</td>
</tr>
</tbody>
</table>
Post-surgical Psychosis…

- Reported postop incidence from 3-35%
- Mean incidence 7-10%
- Hallucinations, paranoia, agitation or withdrawal, hostility, violence
- Most patients with postop psychosis have family hx of psychosis or other severe psychiatric disease
- May be more common in patients who are older at the time of surgery
Psychiatric disorders as risk factors for epilepsy?
Population, N = 10 595 709 patients in The Health Improvement Network

N = 229 164 (2.2%) developed depression
N = 97 177 (0.9%) developed epilepsy.

Incident epilepsy was associated with an increased hazard of developing depression (HR: 2.04 [95% CI, 1.97-2.09]; P < .001).

Incident depression was associated with an increased hazard of developing epilepsy (HR, 2.55 [95% CI, 2.49-2.60]; P < .001)
Association of Depression and Treated Depression With Epilepsy and Seizure Outcomes: A Multicohort Analysis

Josephson et al., JAMA Neurology 2017

- **Incremental hazard to develop epilepsy according to depression treatment type:**
  - lowest risk for those receiving counselling alone (HR, 1.84 [95% CI, 1.30-2.59]; \( P < .001 \)),
  - Intermediate risk for those receiving antidepressants alone (HR, 3.43 [95% CI, 3.37-3.47]; \( P < .001 \)),
  - highest risk for those receiving both (HR, 9.85 [95% CI, 5.74-16.90]; \( P < .001 \)).
### Psychiatric Comorbidities That Occurred Prior to The Onset of Epilepsy

<table>
<thead>
<tr>
<th>Psychiatric Diagnosis</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=3,773)</td>
<td>(N=14,025)</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>18.5%</td>
<td>13.8%</td>
</tr>
<tr>
<td>Depression</td>
<td>17.5%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicidality</td>
<td>0.8% to 5.4%</td>
<td>0.1% to 2.4%</td>
</tr>
</tbody>
</table>

Trends in the incidence rate ratio for epilepsy versus controls with 95% confidence intervals for depression in the 3 years before and 3 years after epilepsy diagnosis.

Trends in the incidence rate ratio for epilepsy versus controls with 95% confidence intervals for anxiety in the 3 years before and 3 years after epilepsy diagnosis.
Trends in the incidence rate ratio for epilepsy versus controls with 95% confidence intervals for suicidality in the 3 years before and 3 years after epilepsy diagnosis.
Trends in the incidence rate ratio for epilepsy versus controls with 95% confidence intervals for psychosis in the 3 years before and 3 years after epilepsy diagnosis.

Bidirectional relation between schizophrenia and epilepsy

- Population based study in Taiwan
- Patients with epilepsy had a 7-fold higher risk of developing schizophrenia
- Patients with primary schizophrenia had a 6-fold higher risk of developing epilepsy.
Common pathogenic mechanisms?

1) Genetics?

2) Neurotransmitter disturbances:
   - Serotonin
   - Glutamate
   - GABA

3) Endocrine disturbances
   - Hypothalamic-pituitary-adrenal hyperactivity

4) Inflammatory disturbances
Serotonin
Decreased 5HT$_{1A}$ Receptor Binding in Patients with Primary Depression and Temporal Lobe Epilepsy

Major Depressive Disorder

Temporal Lobe Epilepsy

* A decrease in postsynaptic 5-HT$_{1A}$ receptor availability may be a trait marker of recurrent depression$^3$

* independent of hippocampal atrophy$^2$

*independent of hippocampal atrophy*

*independent of hippocampal atrophy*²
Glutamate
Glutamate in Depressive Disorders

1) High glutamate plasma and CSF concentrations

2) Dysfunction of glutamate transporter proteins (identified in animal models of depression).

3) Increased Cortical Glutamate identified in brain MRS.

4) Antidepressant effects of NMDA antagonists.

2. Levine K et al., Increased cerebrospinal fluid glutamine levels in depressed patients. Biol Psychiatry, 2000.
GABA
GABA disturbances

1) Decreased CSF concentrations

2) Decreased cortical concentrations in:
   - Post-mortem studies of patients with mood disorders
   - Brain MRS studies.
   - Normalization of GABA concentrations has been demonstrated with antidepressant therapy\(^5\) and electroshock therapy\(^6\)

3) Decreased \(\text{GABA}_A\) activity identified in studies with TMS:
   - Reduced silent period
   - Reduced intra-cortical inhibition.

3. Sanacora et al., Arch Gen Psychiatry 1999; 4. Sanacora et al., Arch Gen Psychiatry 2004
↑HPA
Increased Salivary Cortisol in Patients Who Have Recovered from Depression … Suggests HPA Axis Activity Abnormality

HPA in Patients with Epilepsy

- 16 patients with Temporal Lobe Epilepsy
- 16 patients with Major Depressive Disorder
- 16 healthy controls

Lack of inhibitory control of the HPA system in patients with epilepsy and major depression

Depression But Not Age Predicts Hippocampal Volume Loss in Recurrent Depression


10% to 20%
Structural changes in frontal lobe

Atrophy of:

Cingulate
Orbito-frontal cortex

The magnitude of prefrontal volume changes related to severity of the depression.

Neuropathological abnormalities in primary major depressive disorders

**In cingulate gyrus:**
- Significant ↓ in glial densities
- ↓neuronal size

**In the rostral orbito-frontal region:**
- ↓Cortical thickness
- ↓Neuronal sizes
- ↓Neuronal densities in layers II, III, and IV

**In the caudal orbito-frontal cortex:**
Significant ↓ in glial densities in cortical layers V and VI associated with decreases in neuronal sizes

Cotter et al, Arch Gen Psych, 2001
Bowley et al, Biol Psych 2001
Neuropathological abnormalities in primary major depressive disorders

In the dorsolateral prefrontal cortex:

A ↓ in neuronal and glial density and size in all cortical layers.
Neuropathological abnormalities in primary major depressive disorders

↓ in glial cell density in amygdala
Inflammatory Mechanisms...
Inflammatory Mechanisms

► Pro-inflammatory cytokines, in particular interleukin-1β (IL-1β), IL-2, IL-6, interferon-γ (IFN-γ) and tumor necrosis factor-α have been identified as pathogenic mechanisms in animal models of depression and in clinical studies in patients with mood disorders\(^1\).

► IL-1β, has been found to have pro-convulsant properties\(^2\).

► All three found to be over-expressed in human brains of patients with TLE, cortical dysplasias and tuberous sclerosis.

2. Vezzani et al., J Neuroscience, 1999
Mechanisms responsible for IL-1β proconvulsant properties

- ↑ glutamate concentrations resulting from:
  1) reduction in glutamate uptake by glial cells
  2) enhanced release from glial cells mediated by TNF-α.
Neuroimaging changes in mesial temporal lobe epilepsy are magnified in the presence of depression.

Salgado et al., Epilepsy Behav. 2010

- To investigate differences in gray matter volume between patients with mesial temporal lobe epilepsy (MTLE) with and without depression using voxel-based morphometry.

- 96 neurologically healthy adult subjects and 48 people with MTLE participated in this study.

- 24 patients had MTLE with and 24 without major depression.

- The number of areas of gray matter volume loss was higher in patients with MTLE with depression than in those with MTLE without depression.
# Areas with Significant Greater Cortical Thinning in Depressed Patients with TLE

<table>
<thead>
<tr>
<th>Anatomical structure</th>
<th>Laterality</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesial structures</td>
<td>Bilateral</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Left</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferior &amp; Superior Temp Gyrus</td>
<td>Bilateral</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferior &amp; Middle Frontal Gyrus</td>
<td>Bilateral</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Middle occipital gyrus, cuneus, fusiform gyrus</td>
<td>Left</td>
<td>0.016</td>
</tr>
<tr>
<td>Caudate body</td>
<td>Right</td>
<td>0.023</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>Left</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Pathogenic mechanisms of schizophrenia

- Reduced neuropil
  - Reduced soma, dendritic branching and spine formation.
  - Neuronal atrophy of pyramidal neurons

- Loss of inhibitory neurons
  - Impaired functioning of parvalbumin neurons (low GAD-67).
“...melancholics ordinarily become epileptics, and epileptics melancholics: of these two states, what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy.”
The perfect storm?

↓ GABA + ↓ 5HT and NE + Glutamate and cortisol

vulnerability for epileptic seizures

Inflammatory mechanisms
however....

...most patients with mood and anxiety disorders do not develop seizures or epilepsy...
Conclusions

- Psychiatric disorders and epilepsy share common pathogenic mechanisms.
- These common pathogenic mechanisms may explain:
  - the bidirectional relation,
  - high comorbidity between psychiatric disorders and epilepsy
  - the negative impact of psychiatric disorders on epilepsy.
...so...

...if there is a bidirectional relation between psychiatric disorders and epilepsy...

…can neurologists and psychiatrists please establish a bidirectional relation?