



Affective and Anxiety Disorders in Epilepsy

Never Stand Still

Medicine

Department of Developmental Disability Neuropsychiatry

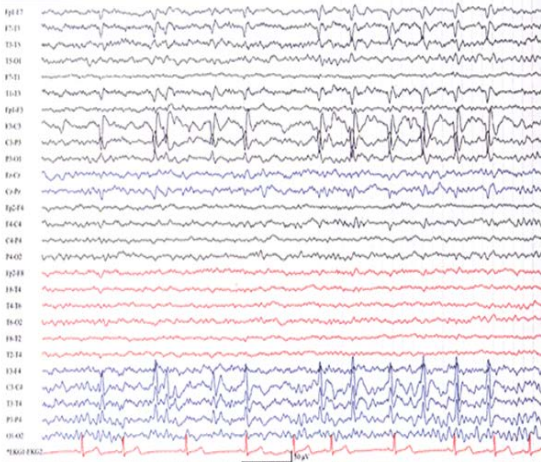
Professor Julian Trollor

Chair, Intellectual Disability Mental Health

Head, 3DN

School of Psychiatry, UNSW Australia

j.trollor@unsw.edu.au





"Looking good!"

Outline

- Introduction & relevance
- Significance of Affective and Anxiety Syndromes in Epilepsy
- Peri-ictal Affective and Anxiety Syndromes
- Interictal Affective Symptoms
- Special Situations and Issues
 - Post-surgical depression
 - VNS
 - ECT
 - Mania

Depressive Syndromes in Epilepsy: Importance

- Depression- the most frequent psychiatric comorbidity in epilepsy
- Associated with:
 - reduced quality of life on standardized measures (Cramer, Blum et al. 2003) (Tracy, Dechant et al. 2007)
 - increased health service utilization (Cramer, Blum et al. 2004)
 - seizure severity and slower recovery from seizures (Cramer, Blum et al. 2003)
 - suicide and deliberate self harm at a staggering rate of 4-5 times that of the general population (Harris and Barraclough 1998)
- Recognition and treatment of mood disorders in individuals in this context is often delayed or inadequate (Ettinger, Reed et al. 2004)

Anxiety Syndromes in Epilepsy: Importance

- Anxiety- the second most frequent psychiatric comorbidity in epilepsy (10-25% in community samples)
- Rates higher in medically intractable samples
- Probable increased rates of PAN/GAD/OCD
- Overlap and association with depression

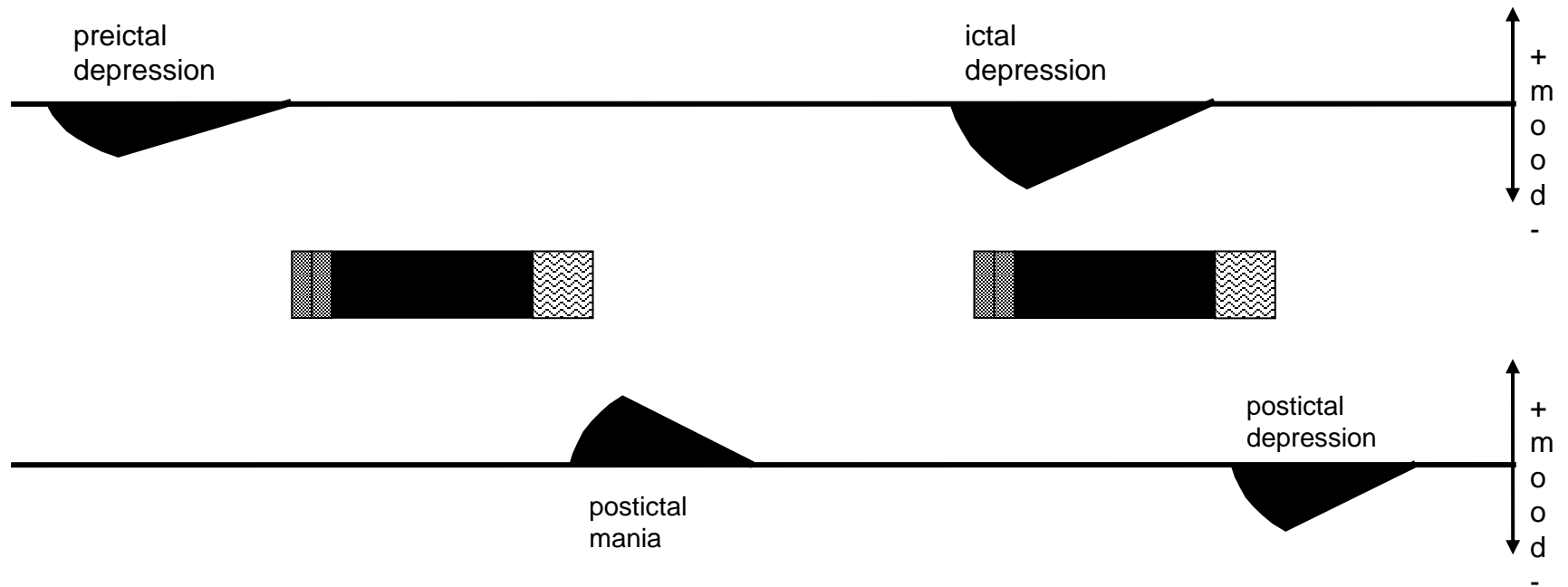
Risk Factors for Depression in Epilepsy

Psychosocial	Low income and unemployment Negative Attributional style Lower sense of self efficacy and problem solving
Demographic	Family history of affective disorder
Seizure-related	Left-hemisphere focus Temporal lobe epilepsy/Complex partial seizures Absence of secondary generalized tonic clonic seizures Treatment resistance
Treatment Related	Polypharmacy Certain AEDs eg phenobarbital, primidone, phenytoin, vigabatrin, topiramate Folate deficiency Temporal lobectomy
Other	Neurological disorder Frontal lobe dysfunction

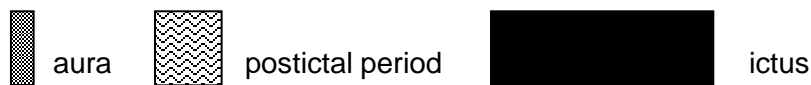
What Approach Should We Take

- The use of antidepressants and anxiolytics needs to be understood in the context of a broader framework of management
 - Embracing a holistic approach
 - Biological, psychological and behavioural approaches have merit
 - Emphasis on management determined by the various aetiological and clinical aspects in formulation of the patient's problems

Peri-ictal Anxiety & Affective Disorders 1



Legend



Peri-ictal Affective & Anxiety Disorders 2

- Aims include:
 - optimising seizure control
 - Provision of psychoeducation & support to patient and carer/s
- Pharmacological intervention not commonly required

Peri-ictal Affective and Anxiety Symptoms: Potential Mechanisms

- Structural Hypothesis
 - Local site (limbic)
 - Product of sz activity in these (abnormal) regions
 - Template of abnormal microstructure and function eg aberrant sprouting of mossy fibres
 - Distant Site (frontal)
 - Excitation or inhibition of specific (normal) regions
- Functional Hypothesis
 - Vulnerability conferred by tonic alterations in regional rCBF/metabolism
 - Mood change precipitated by further sz activity
- Neurotransmitter Hypothesis
 - Acute changes associated with sz

Peri-ictal Affective & Anxiety Disorders 3

- The lack of clear understanding of risk factors, pathophysiological mechanisms and modifying effect of biological (eg AED), psychological and environmental influences over its expression makes a rational pharmacological approach difficult

Peri-ictal Affective & Anxiety Disorders 4

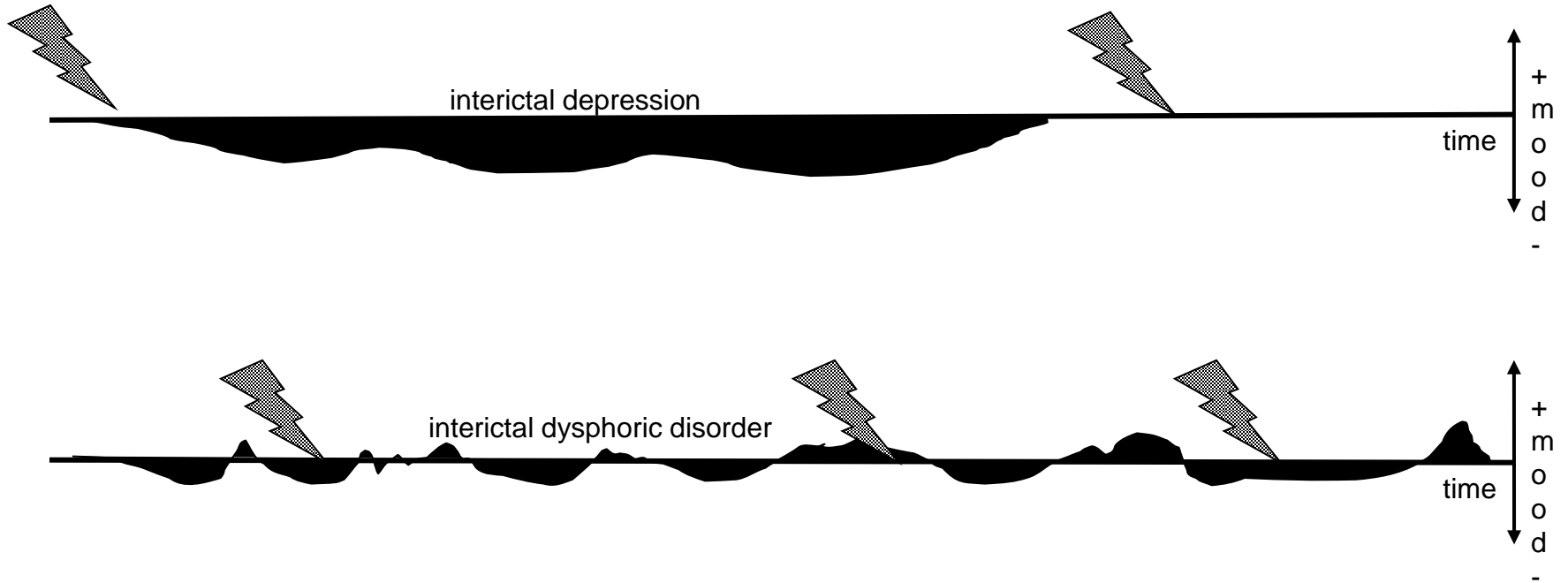
- Helpful Strategies in Clinical Practice
 - Single dose or short-term regular benzodiazepines for protracted anxiety, where agitation is severe or where anxiety/agitation is a prodrome for psychosis
 - Considering SSRI for protracted or complicated post-ictal depression
- Many Unknowns
 - Prophylactic ability of antidepressants eg SSRIs in peri-ictal disorders
 - The effectiveness or otherwise of behavioural or psychological interventions for pre/postictal affective & anxiety syndromes

Peri-ictal Affective & Anxiety Disorders 4

- Some Risks of Benzodiazepine Use
 - Long-term benzodiazepine use (dependence, withdrawal)
 - Compounding cognitive disorder
 - Contributing to mood disorder



Interictal Depressive Disorders



Legend



Antidepressants and Risk of Seizures

- History
- Sz reported with most classes of antidepressants at therapeutic and toxic doses
- Most concerning are clomipramine, bupropion

Depression and Epilepsy- a Bidirectional Relationship

- Pre-existing depression increases the risk of seizures by 3-4 X, (Hesdorffer, Hauser et al. 2006) (Hesdorffer, Hauser et al. 2000) (Forsgren and Nystrom 1990)
 - a particularly elevated risk for partial seizures (Forsgren and Nystrom 1990)
- Temporal relationship between depressive symptoms and first seizure has been noted (Hesdorffer, Hauser et al. 2000)
- Epidemiological work suggests that:
 - Depression itself is associated with increased sz risk
 - ie those taking antidepressants have elevated rates of seizures above general population
- Evidence of a shared pathogenesis

Serotonin and Seizures

- ↑ 5-HT levels (such as through 5-HT reuptake blockers), inhibit seizures (Loscher 1984; Prendiville and Gale 1993; Yan et al. 1994)
 - ↓ 5-HT lowers the threshold for a variety of experimentally induced seizures (Browning et al. 1978; Statnick et al. 1996)
 - A number of AEDs increase 5HT release or levels (Valproic acid, lamotrigine, carbamazepine, phenytoin, zonisamide Okada et al.1992; Dailey et al. 1996; Ahmad et al. 2005)
- Acute administration of SSRIs increase seizure threshold/decrease severity
- For an excellent review see Bagdy G et al Journal of Neurochemistry 2007;100:857–87

Antidepressants and Seizure

Models

- Antidepressants do not lower sz threshold in epilepsy prone animals
- Genetically epilepsy prone rats have deficits in NA and 5HT; which if exacerbated, worsen sz; and if improved, reduce sz predisposition
- Several antidepressants, esp fluox & citalopram have demonstrated anticonvulsant properties

Data on Antidepressants and Seizures

- Alper K Biol Psych 2007
 - FDA data from psychotropic drug trials 1985-2004.
 - “The incidence of seizures was significantly lower among patients assigned to antidepressants compared to placebo (standardized incidence ratio .48; 95% CI, .36- .61)
 - In patients assigned to placebo, seizure incidence was greater than the published incidence of unprovoked seizures in community nonpatient samples
 - **Conclusions:** Proconvulsant effects are associated with a subgroup of psychotropic drugs. Second-generation antidepressants other than bupropion have an apparent anticonvulsant effect. Depression, psychotic disorders, and OCD are associated with reduced seizure threshold.”

What Does This Data Mean?

- We can and should use antidepressants where clinically appropriate
- With few exceptions our concern about seizure induction should be put aside



Interictal Depression: Drug Treatment

- Aim for optimal seizure control
 - Consider 'helpful' AEDs such as VPA, CBZ, LTG
 - Avoid PB, PHT, VGB
- In choice of antidepressant some things to consider:
 - Level of evidence
 - Side- effects (including effect of antidepressant on seizure threshold) & AED levels
 - Drug interactions
 - Ease of use and patient acceptability
 - Lethality in overdose

Potential Interactions between AEDs and Antidepressants

- PB, PHT & CBZ enhance metabolism of TCA's & mianserin
- VPA can inhibit metabolism of TCA's
- TCA's can increase PHT levels
- Fluoxetine & fluvoxamine increase levels of VPA & CBZ
- Sertraline escitalopram & citalopram low risk

Other Concerns with Antidepressant Use

- Somatic S/E
- Cognitive S/E
- Behavioural S/E
- Adverse effect on mood

A Clinical Approach

- 1st Line: citalopram, escitalopram, sertraline
 - Commenced at ½ dose; slow titration
 - Measure AED level 2 & 4 weeks after commencing
- 2nd Line venlafaxine, duloxetine
 - Commenced at ½ dose; slow titration
 - Measure AED level 2 & 4 weeks after commencing

Special Situations and Issues

- Post-surgical depression
- VNS
- ECT
- Mania in Epilepsy

Affective Disorder Following Epilepsy Surgery 1

- Development, exacerbation or improvement of mood disorder in the postoperative period determined by complex interplay between vulnerability factors present prior to surgery and those which become a feature of the post-surgical recovery period
- Issues:
 - For many individuals a transient phenomenon
 - Some individuals at higher risk



Affective Disorder Following Epilepsy Surgery 2

- Is there a role for prophylaxis in certain individuals?
- No, but may become a reality if clearer predictors of postoperative depression identified

Vagus Nerve Stimulation 1

- VNS causes:
 - reduction in sz frequency in ST & LT (Schachter 2002)
 - improvement in mood in patients with epilepsy (Harden, Pulver et al. 2000) (Elger, Hoppe et al. 2000)
 - Improvement in mood in treatment resistant major depression (TRD) in ST (Rush, George et al. 2000) (Rush, Marangell et al. 2005) & LT (Nahas, Marangell et al. 2005) (Rush, Sackeim et al. 2005)

Vagus Nerve Stimulation 2

- VNS associated with LT increase in the firing rate of the dorsal raphe nucleus and locus coeruleus (Dorr and Debonnel 2006) in animals, and in humans increases the CSF concentration of the dopamine metabolite homovanillic acid (HVA) (Carpenter, Moreno et al. 2004)
- Effect on sz in rats is blocked by lesioning LC & DRN
- Probable that effects on NE and 5HT pivotal to both anticonvulsant & antidepressant properties

Vagus Nerve Stimulation 3

- Patients with both epilepsy and depression
 - Presence of depression does not preclude VNS
 - Both seizures and depression may be assisted
 - Should we consider VNS more actively in this group?
 - data in TRD insufficiently strong at present

Electroconvulsive Therapy

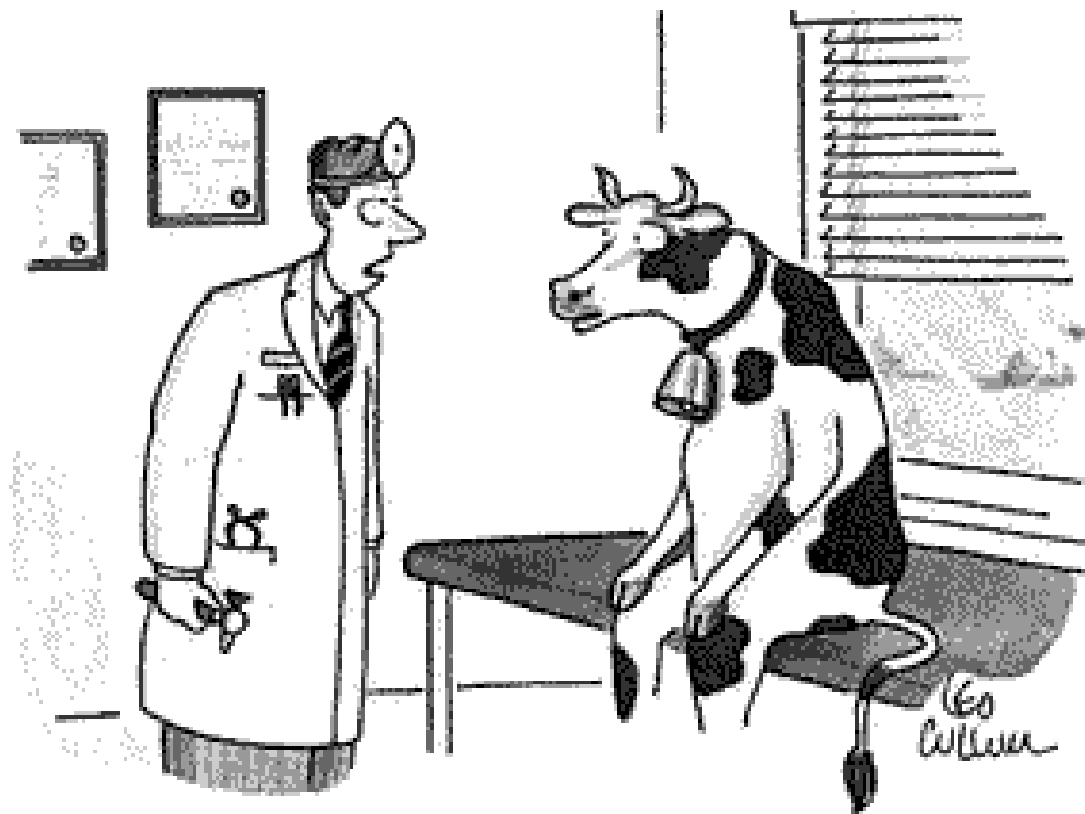
- ECT indicated for:
 - Severe depression with melancholia especially psychotic depression
 - Depression preferentially responsive to ECT
 - Depression with catatonic features
 - Emergency treatment for depressive stupor
- Epilepsy not a contraindication per se but caution required:
 - Risk of prolonged seizure
 - Seizure induction may be difficult in context of AED prescription

Mania in Epilepsy

- Most manic episodes occur either as:
 - postictal phenomenon
 - following surgery for epilepsy (10%) of patients undergoing temporal lobectomy (Schmitz 2005). Risks- right-sided surgery and bilateral involvement (Carran, Kohler et al. 2003)
- Ettinger 2005:
 - bipolar symptoms evident in 12.2% of epilepsy patients
 - predictor = family history

Antidepressants and Risk of Mania in Epilepsy Patients

- No data
- Theoretically protected by some AEDs
- Consider screening carefully for:
 - past history of spontaneous or secondary manic episodes
 - Family history bipolar disorder
- Think about additional risks
 - following surgery for epilepsy
 - right-sided surgery and bilateral involvement
- Consider lower initial dose, slower titration
- Screen for frequent mood shifts (rapid & ultra rapid cycling bipolar)

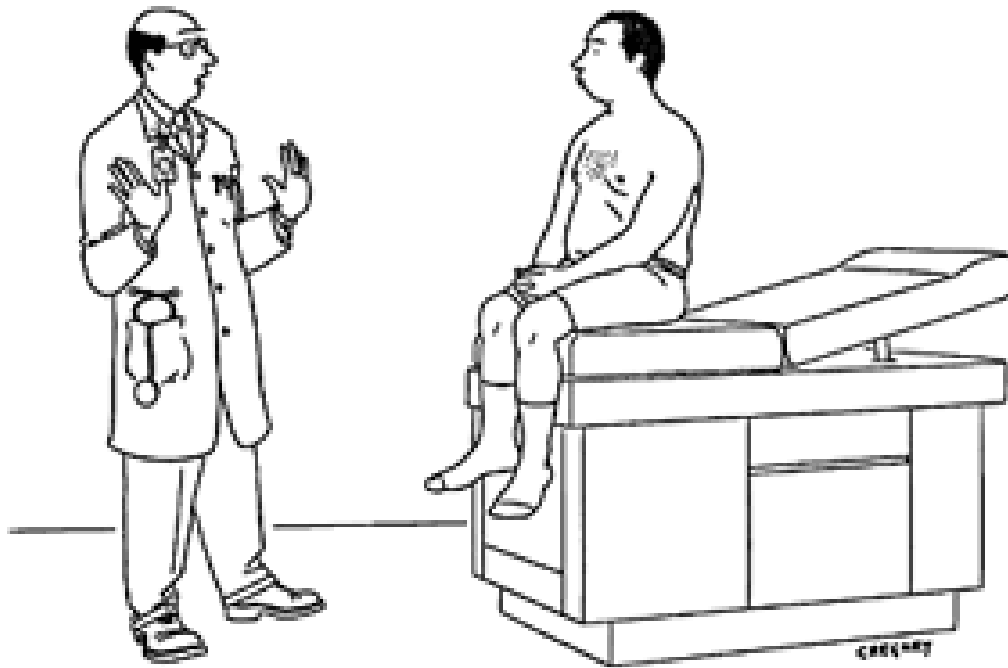


“The ringing in your ears—I think I can help.”

“The ringing in your ears- I think I can help”

Conclusions

- Affective & Anxiety syndromes are prominent in patients with epilepsy and have a significant bearing on QOL
- The perception of the effect of antidepressants on seizure threshold is changing
- Pharmacotherapy has a role but must be considered as a component of comprehensive clinical care






“Whoa—way too much information!”

Preictal Depression: Observations

- Minutes to days before a seizure
- Range of affective disturbances (dysphoria, irritability, elation, anxiety)
- Rare in primary generalized seizures



Preictal Depression: Mechanisms

- Mechanism unknown
- Subclinical sz activity  mood disturbance?
- Suppression of sz activity  mood disturbance?
- Negative life events  low mood and increased likelihood of seizures

Ictal Depression: Observations

- Approx 10% of patients with TLE
- No association with laterality of seizure focus
- With SPS or CPS
- May continue beyond duration of observable seizure

Ictal Depression: Mechanisms

- Speculative
- Local Sz activity  mood disturbance?
 - Some support from intracranial stimulation studies eg Smith JR et al 2006
- Distal excitation or inhibition disturbance?  mood

Lateralisation of Affect

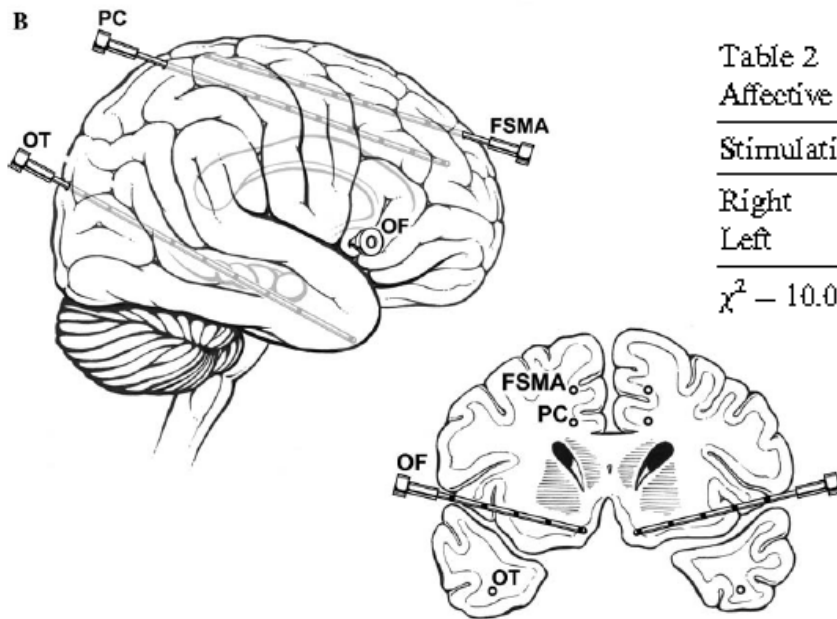


Table 2
Affective responses related to mesial frontal stimulation

Stimulation side	Dysphoric response	Euphoric response
Right	10	0
Left	0	1

$\chi^2 = 10.0, P = 0.0016.$

Smith JR et al *Epilepsy and Behaviour* 2006;8:534-541

Postictal Depression: Observations

- Immediately following seizure
- Unclear relationship to laterality
- Must distinguish from delirium, postictal psychosis

Postictal Depression: Mechanisms

- Post-ictal inhibition of neuronal function
- Local or regional
- Possible Correlates
 - Reduction in CBF/metabolism post seizure

Factors Influencing Psychopathology in Epilepsy

- Clinical:
 - Age of onset, length of illness, severity, frequency and type of seizure disorder
- Social:
 - Socioeconomic impact, educational impact, stigma, impact on driving, family response
- Psychological:
 - Impact on self esteem, illness attitudes and behaviour
- Biological:
 - Neuropathology in limbic, frontal and basal ganglia circuits
 - Emotional and cognitive side-effects of AEDs & surgery

Associations Between Psychiatric Disorders & Epilepsy

- Two unrelated co-morbid conditions
- Underlying pathological substrate predisposing to both epilepsy and psychiatric disorder
- Epilepsy predisposing to psychiatric disorder:
 - Biological, psychological & social factors
- Psychiatric disorder secondary to treatment for epilepsy
- Psychiatric disorder predisposing to epilepsy

Depression & Seizures: Direction of Relationship

- 3 controlled studies suggest that in newly diagnosed adults with epilepsy, depression pre-exists more often than in controls:
 - 3x, 17x risk for partial seizures (Forsgren 1990)
 - 3.7x (Hesdorffer 2000)
 - 4x risk (Hauser 2000)
- Depressed subjects rate higher on seizure severity & poorer on seizure recovery (Cramer '03)

Interictal Depression: Prevalence

- Community Samples:
 - Variable rates.
 - 9% (Jacoby '96)
 - 55% (Mendez '86)
- Medically Intractable Samples:
 - Higher rates.
 - Lifetime prevalence 60% (Victoroff '90)
 - Point Prevalence ~ 20-30%
- Higher prevalence compared to neurological and health controls (Mendez 1986)

Interictal Depression: Taxonomy

- Major Depression v's Interictal Dysphoric Disorder
 - About ½ cases of depression in epilepsy are atypical (Mendez et al 1986)
 - Dysthymia-like disorder of epilepsy (Kanner)
 - Interictal Dysphoric Disorder: Chronic dysthymia, fluctuating, intermixed with brief euphoric, irritable or anxious moods; often associated with somatic symptoms

Is Interictal dysphoric disorder a valid entity?

- No systematic studies
- No data to specifically link this syndrome with limbic epilepsy



What could determine such fluctuations?

- Seizure activity.....but relationship to seizures unclear
- Inhibitory activity.....no data on suppression of EEG
- Biochemical changes
 - Endogenous opiate systems?
 - Fluctuations in cortisol secretion?
 - Other?

Depression & Epilepsy

“Melancholics ordinarily become epileptics and epileptics melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy”

Hippocrates ~ 400 BC



Interictal Depression: Observations 1

- Gender M>F
- Sinistrality
- Family History
- Neurological Conditions
- Intellectual Function and Learning Disorder

Interictal Depression: Observations 2

- Seizure Characteristics

- No clear relationship with age or duration of epilepsy
- CPS/TLE association tenuous
- Laterality L>R
- Increased risk with frontal dysfunction

Interictal Depression: Observations 3

- Increased risk with:
 - Polypharmacy (Mendez 93, Fiordelli 93)
 - Certain AEDs e.g. PB; primidone, PHT, VGB
 - Folate deficiency
 - Tryptophan depletion

Interictal Depression: Psychosocial Determinants

- Epilepsy has multiple effects on lifestyle, vocational opportunities and financial security
- Handicap that arises is in part determined by social skills and emotional resources
- Attributional style may be important

Mania and Epilepsy

- Mania rare
- Exceptions
 - Postictal psychosis
 - Post temporal lobectomy ~10%

Alternative Psychosis: Forced Normalisation

- 1860/70's Sant, Falret & Morel observed reciprocal relationship between psychiatric disorder and epilepsy
- Landolt 1953 “forced normalisation is the phenomenon characterised by the fact that, with the occurrence of the psychotic state, the EEG becomes more normal or entirely normal as compared with previous and subsequent EEGs”
- Tellenbach 1965 coined term “Alternative Psychosis”

Alternative Psychosis: Forced Normalisation

- Proposed Mechanisms:
 - Biological antagonism between psychosis and seizures
 - Continuing limbic seizures
 - Propagation of seizure along unusual pathways
 - Interaction between hippocampus (inhibited post seizure) and the RAS (activated)
 - Reaction of the healthy brain against the abnormal seizure focus

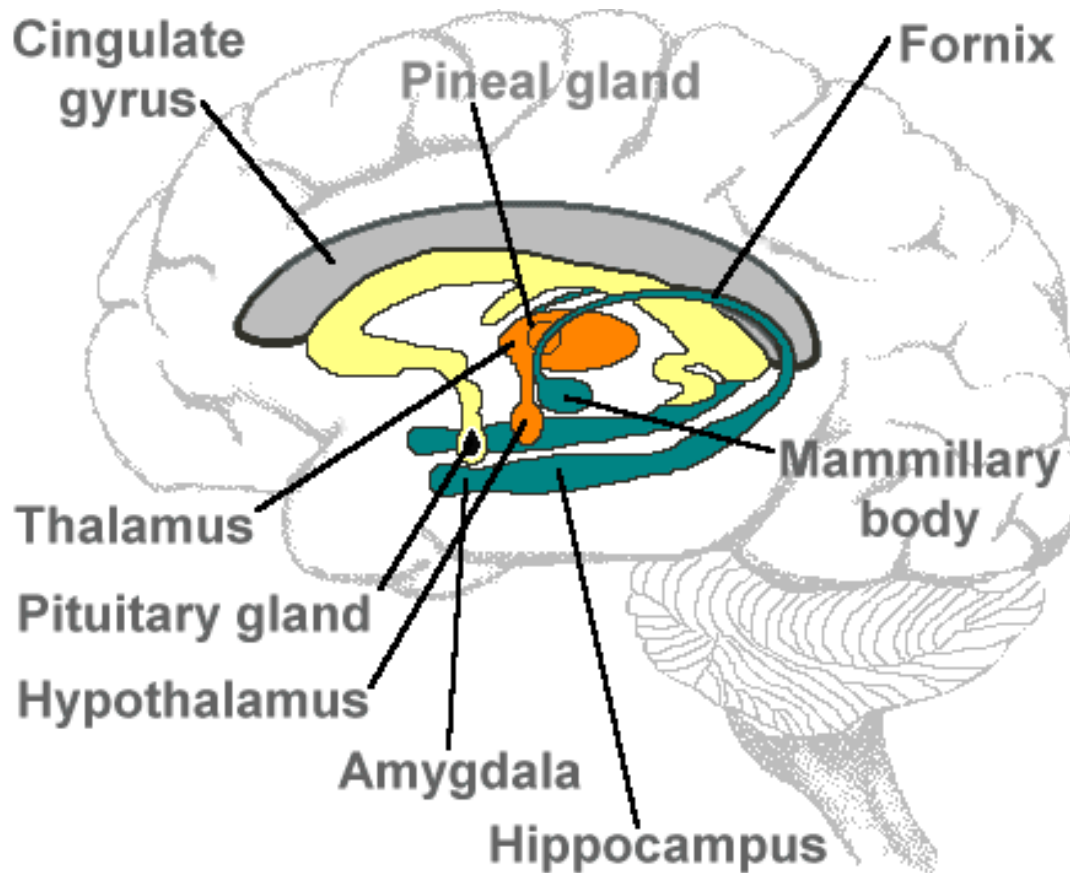


Kindling

- Brief high frequency trains of electrical impulses produce a change in response to the stimulus such that there is gradual progression of the electrical and behavioural response culminating in a seizure
- Electrical and pharmacological models
- Kindling may be involved in secondary epileptogenesis at sites that receive synaptic input from the origin
- Secondary neurochemical changes may kindle behavioural response (eg \uparrow DA turnover) and serve to inhibit seizures (DA is anticonvulsant), such that the behavioural response (eg psychosis) then predominates



The Limbic System



The Limbic System

Limbic System: Relevance -I

- Centres of functional relevance for human emotion
- Direct connections with other regions of importance for emotional regulation
- Hippocampus is the most common site of localisation related epilepsy
- Surrounding regions:
 - Parts of parahippocampal cx & amygdala are most rapidly kindled structures in human brain
 - Contain regions with lowest seizure threshold in human brain

Limbic System: Relevance -II

- Susceptible to development of epileptiform activity.
- Distant seizure prone regions with projections to the MTL also may result in MTL epileptiform activity and behavioural/emotional disturbance

Psychosurgery, DBS, the Limbic System and Mood

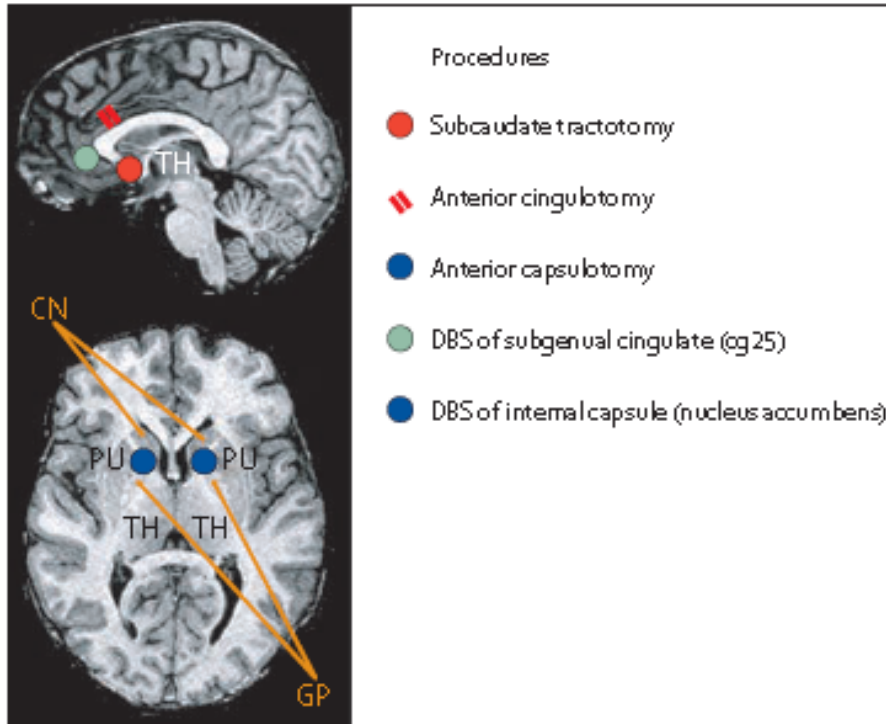
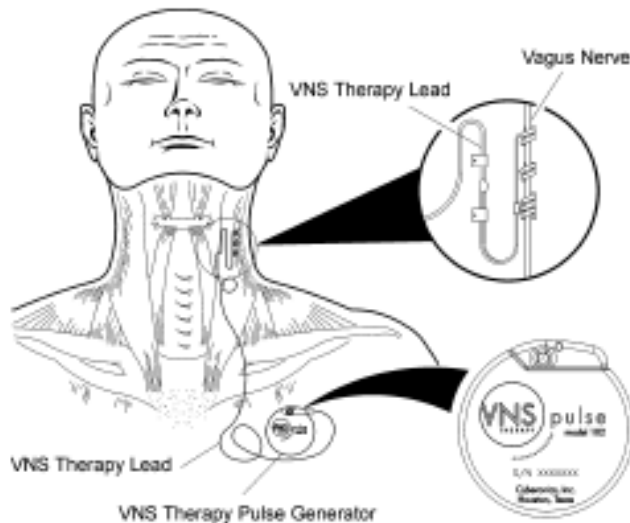


Figure: Neurosurgical targets for treatment of refractory obsessive-compulsive disorder and major depression

TH=thalamus, CN=caudate nucleus, PU=putamen, DBS=deep brain stimulation. Historically a multitargeted procedure, termed limbic leucotomy, combining anterior cingulotomy and subcaudate tractotomy (both procedures in light red in figure), has been used for intractable depression, obsessive-compulsive disorder and some other forms of severe anxiety disorders.

- “Depression...conceptualised as systems level disorder... involving selected cortical, subcortical and limbic sites and their related neurotransmitter and molecular mediators” (Mayberg et al 2005)
- Converging evidence from DBS & antidepressant studies that subgenual cingulate important in regulating negative mood states
- Limbic system critically involved

VNS Therapy for Epilepsy and Depression



- VNS increases CSF levels of GABA, 5-HIAA, HVA
- VNS activates LC
- VNS stimulation acutely increases CBF in medulla, thalamus, hypothalamus, insula, postcentral gyrus
- VNS acutely decreases CBF in hippocampus, amygdala, cingulate. (cf DBS)

Depression in Epilepsy: a 'Hypofrontality'?

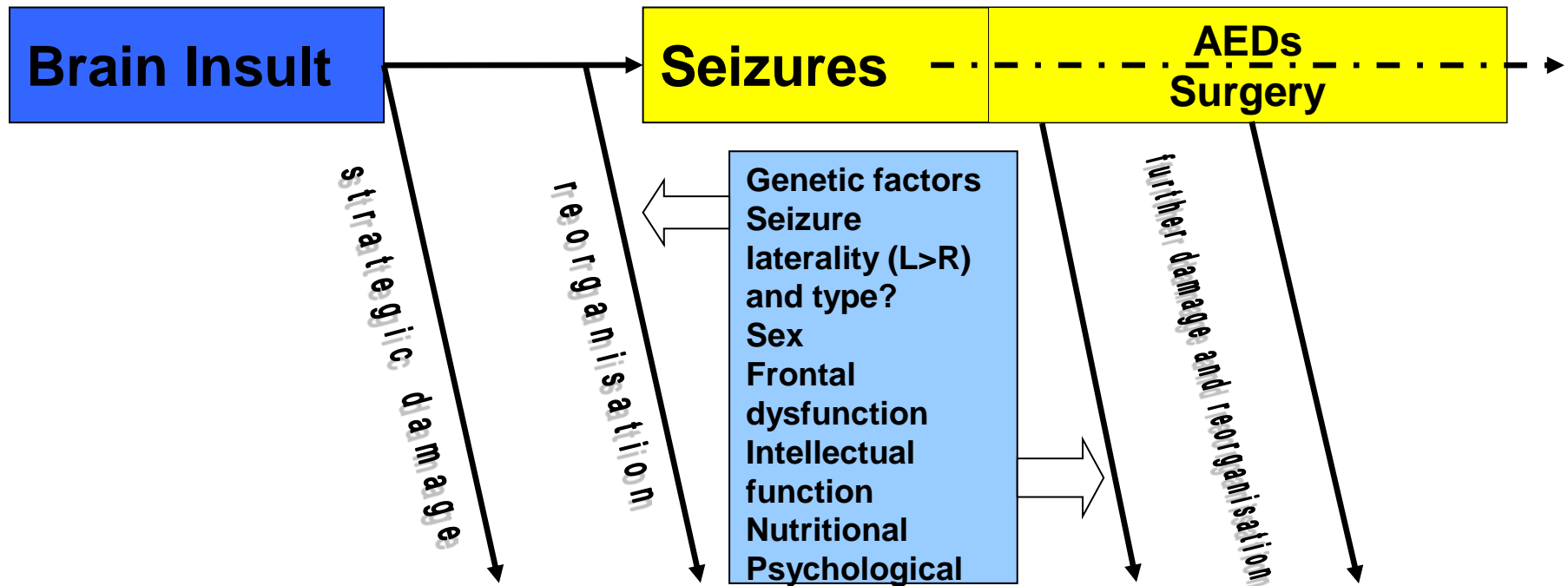
- Depression more common in those with CPS
- CPS most commonly arise from limbic structures
- Reduced rCBF in prefrontal cortex in those being investigated for focal epilepsy with left sided focus (Schmitz et al, 1997)
- Common findings in rCBF and rCMRglu studies of depression and depression secondary to other neuropsychiatric disorders (Stroke, IPD, AD, etc)
- 'Frontal' neuropsychological dysfunction correlates with depression in those with L sided seizure focus (Hermann et al 1991)

Depression in Epilepsy: Other Biological Correlates

- Opioid Hypothesis (Engel 2002)
 - Reciprocal connections between limbic structures and brainstem nuclei with opioid projections to forebrain
 - Endogenous opioids are increased during seizures
 - Mu opiate receptor binding is increased in epileptic temporal lobe
 - Affective symptoms could conceivably represent opiate withdrawal when:
 - seizures are infrequent
 - There is a dramatic reduction in sz frequency (surgery, AEDs)
- Core Amine Deficit
 - Reciprocal connections between limbic structures and brainstem nuclei with amine projections to forebrain
 - Epilepsy-prone mice (genetic model); baboons
 - Innate NA & 5HT deficit; Seizures blocked by SSRI and MAOI

Affective Disorders and Epilepsy

(model after Majak & Pitkanen 2004)



Affective and Anxiety Syndromes

Conclusions

- Affective syndromes are prominent in patients with epilepsy and have a significant bearing on QOL
- Neurobiological mechanisms of peri-ictal affective syndromes remain speculative and hard to elucidate
- The status of specific epilepsy associated depressive subtype is uncertain but worthwhile exploring
- Interictal affective syndromes are amenable to study

Future Directions

- Enhanced screening tools and guidelines for management of depression in epilepsy
- Further longitudinal evaluation of nature/course of depression in epilepsy
- Need for studies examining biological, psychological and social correlates of depression in epilepsy
- Focussed examination of imaging correlates of depression