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Chulalongkorn Comprehensive Epilepsy Centre

Drug-resistant epilepsy: Definition and Consequences

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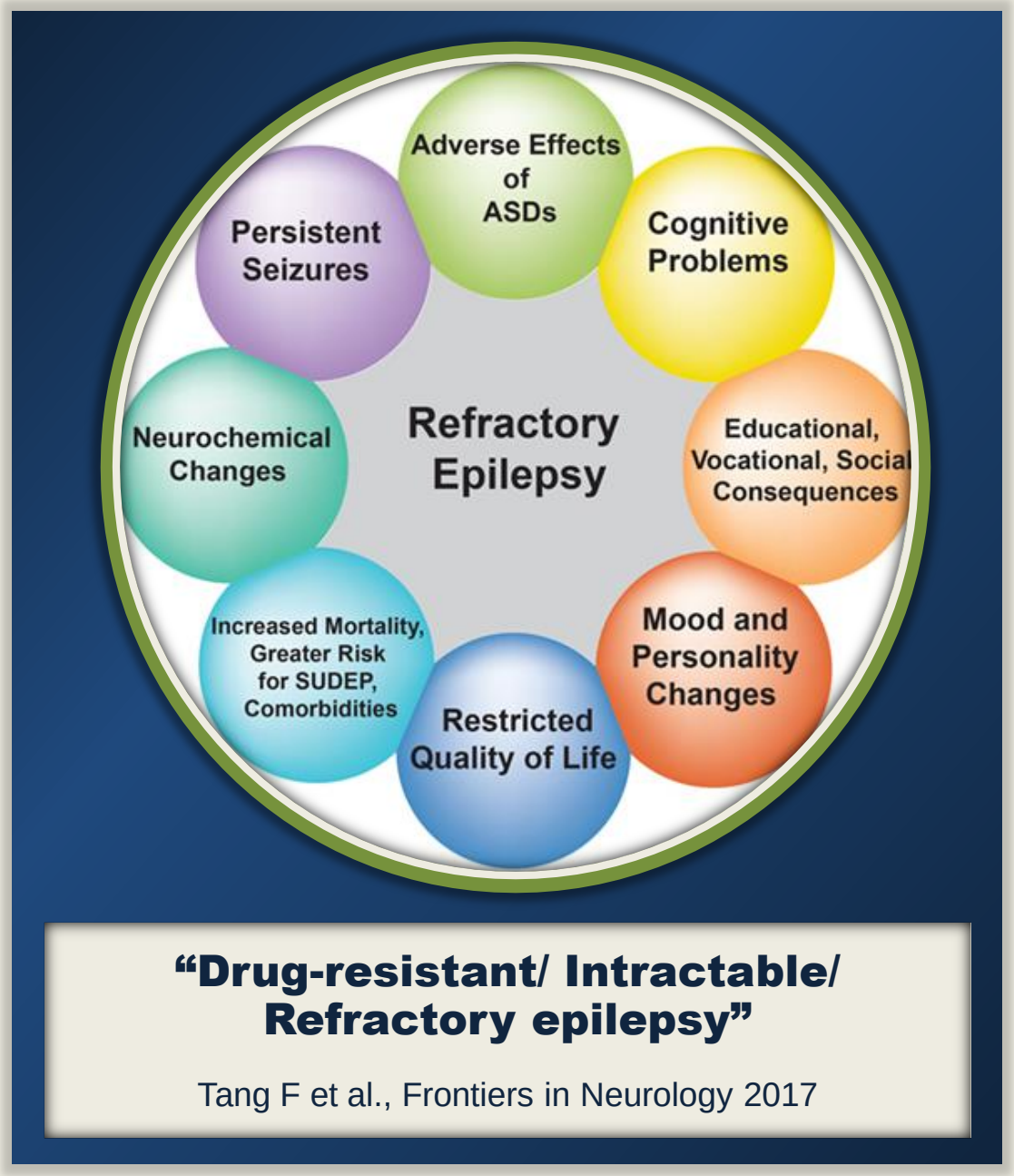
Talk overview

- **Patterns of treatment response in newly diagnosed epilepsy**
- **Defining drug-resistant epilepsy**
  - ❖ ***ILAE definition***
- **Predictors of drug-resistant epilepsy**
- **Consequences of drug-resistant epilepsy**



"Drug-resistant/ Intractable/ Refractory epilepsy"

Tang F et al., Frontiers in Neurology 2017

Patterns of treatment response in newly diagnosed epilepsy

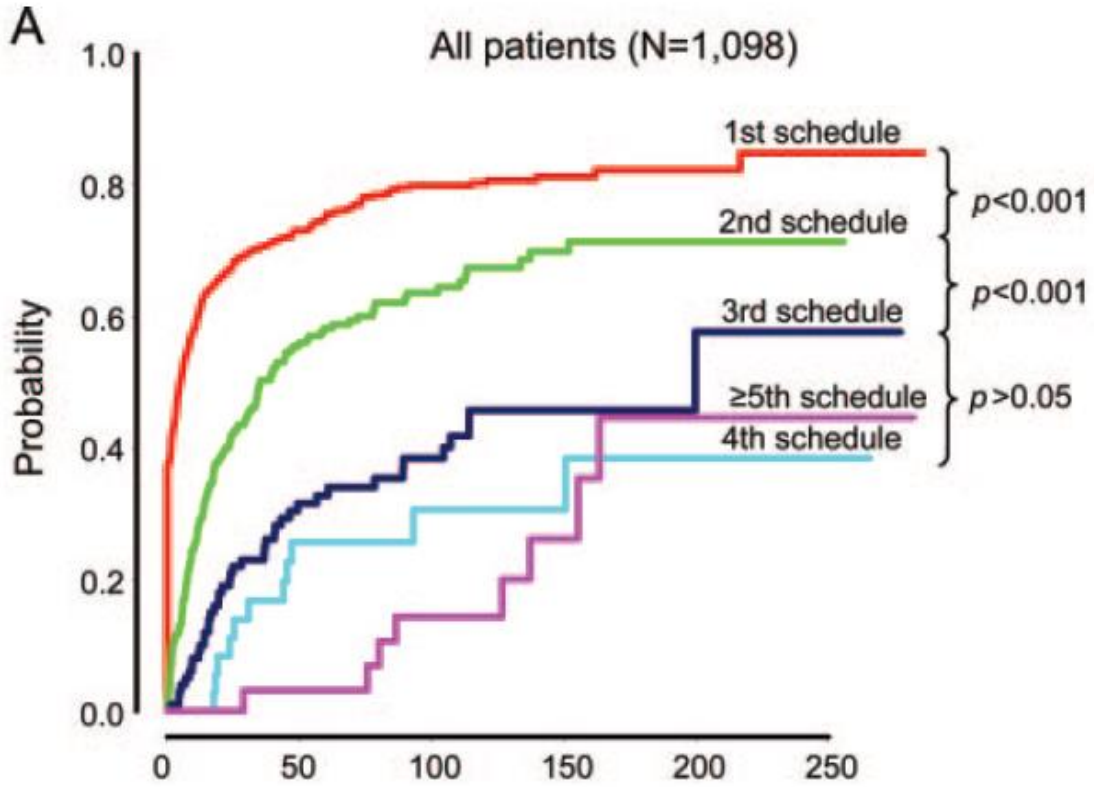
Seizure-free rates with successive AED regimens

There was a higher probability of seizure freedom in patients receiving 1 compared to 2 drug regimens, and 2 compared to 3 regimens ($p < 0.001$)

Table 1 Seizure-

Drug regimens	No. of patients	% Seizure-free on regimen
First	1,098	49.5
Second	398	36.7
Third	168	24.4
Fourth	68	16.2
Fifth	32	12.5
Sixth	16	12.5
Seventh	9	22.2
Eighth	3	0.0
Ninth	2	0.0

Figure 2 Cumulative probability of being seizure-free by time from start of treatment and number of antiepileptic drug regimens tried



Brodie MJ et al.; Neurology 2012

4 patterns of treatment response (1,098 pts)

A) Early and sustained seizure freedom	**37%**
B) Delayed but sustained seizure freedom	**22%**
C) Fluctuation between periods of seizure freedom and relapse	**16%**
D) Seizure freedom never attained	**25%**

Seizure freedom was defined as no seizures for 1 year at last follow-up

Drug responsiveness of a patient's epilepsy should be regarded as a
"dynamic process rather than a fixed state"

The classification of a patient's epilepsy as drug resistant at a given point in time is valid only at the time of the assessment and does not necessarily imply that the patient will never become seizure-free on further manipulation of AED therapy

Brodie MJ et al.; Neurology 2012

Defining drug-resistant epilepsy

Defining Intractability: Comparisons among Published Definitions

- **Individual studies use different definitions, creating difficulties for comparisons of results across studies**
- **This study was designed to detect the appearance of intractable seizures early in the course of the disorder**
- Study subjects are members of the **Connecticut Study** of Epilepsy, a prospective**, community-based cohort of 613 children** who were recruited during 1993 through 1997 at the time they were **first diagnosed with epilepsy**

Berg AT & Kelly MM; Epilepsia 2006

Definitions of intractable epilepsy

TABLE 1. *Published criteria used for determining intractable epilepsy*

Study/Citation	Criteria		Comments/qualifications
	Minimum AEDs failed	Seizures	
Connecticut (2)	2	1 seizure per mo for ≥18 mo and ≤3 mo seizure free during that time	The outcome had to be met within 3 years of diagnosis
Holland (1)	Not specified	At 6 mo after diagnosis, failure to be ≥3 mo seizure free	Published criteria were not modified. This is an indicator of risk and not a criterion for intractability per se.
Philadelphia (3)	2	At 2 yr after diagnosis, failure to be ≥6 mo seizure free	Criteria were used as published without modification
Canada (5)	3	≥1 seizure every 2 mo in last year of follow-up	Modified to be assessed at 5 yr after initial diagnosis
Scotland (6)	2	<1 yr seizure free at last follow-up	Modified to be assessed at 5 yr after initial diagnosis
Surgery (4)	2	Not explicitly stated	The outcome had to be met within 3 yr of diagnosis

Berg AT & Kelly MM; Epilepsia 2006

Definitions of intractable epilepsy

TABLE 2. *Proportion of children who met each of the different definitions of intractability or poor outcome*

Criteria (n = number with unclassified outcomes due to insufficient follow-up)	Did not meet criteria	Met criteria
Connecticut (n = 10)	546 (91%)	57 (9%)
Dutch (n = 4)	461 (76%)	148 (24%)
Philadelphia (n = 14)	530 (88%)	69 (12%)
Canadian (n = 48)	514 (91%)	51 (9%)
Scottish (n = 48)	491 (87%)	74 (13%)
Surgery (n = 0)	510 (83%)	103 (17%)

- The epilepsy of **9–24%** of children was considered intractable
- Kappa ranged from low of **0.45 to 0.79**

Berg AT & Kelly MM; Epilepsia 2006

TABLE 4. *Associations between intractability criteria and longer-term outcomes of 2- and 5-year remission*

Criteria	In 2-yr remission at last follow-up for those followed up for ≥7 yr (n = 549)	In 5-yr remission at last follow-up for those followed up for ≥10 yr (n = 210)
Connecticut		
Not intractable	386/502 (77%)	133/193 (69%)
Intractable	4/47 (9%)	1/17 (6%)
RR	9.0 (8.3–9.9)	11.7 (10.3–13.3)
Holland		
Not at increased risk	340/424 (80%)	122/173 (71%)
At increased risk	50/125 (40%)	12/37 (32%)
RR	2.0 (1.8–2.2)	2.2 (1.8–2.6)
Philadelphia		
Not intractable	377/489 (77%)	131/189 (69%)
Intractable	13/60 (22%)	3/21 (14%)
RR	3.6 (3.2–4.0)	4.9 (4.1–5.7)
Canadian		
Not intractable	388/499 (77%)	134/195 (69%)
Intractable	2/50 (4%)	0/15 (0)
RR	14.4 (13.5–15.5)	~20.6 (18.4–23.1)
Scotland		
Not intractable	380/478 (79%)	134/190 (71%)
Intractable	10/71 (14%)	0/20 (0)
RR	5.6 (5.2–6.2)	~28.2 (25.7–31.0)
Surgery		
Not intractable	364/459 (79%)	130/184 (71%)
Intractable	26/90 (29%)	4/26(15%)
RR	2.7 (2.5–3.0)	4.6 (3.9–5.4)

1 seizure per mo for ≥18 mo and ≤3 mo seizure free during that time
2 Minimum AEDs failed

≥ 1 seizure every 2 mo in last year of follow-up
3 Minimum AEDs failed

Berg AT & Kelly MM; Epilepsia 2006

Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies

*[1]Patrick Kwan, †Alexis Arzimanoglou, ‡Anne T. Berg, §Martin J. Brodie, ¶W. Allen Hauser, #[2]Gary Mathern, **Solomon L. Moshé, ††Emilio Perucca, ‡‡Samuel Wiebe, and §§[2]Jacqueline French

Kwan P et al.; Epilepsia 2010

Goals

- Aid nonspecialists in recognizing patients with drug resistant epilepsy for prompt referral to specialist centers for evaluation

- Facilitate comparison and meaningful synthesis of results across studies

Drug resistant epilepsy may be defined as **failure of adequate trials of two tolerated and appropriately chosen and used AED schedules** (whether as monotherapies or in combination) to achieve sustained seizure freedom

The consensus to adopt the failure of two (rather than greater numbers) AED schedules in the definition represents a testable hypothesis and aims to avoid unnecessary delay in evaluation, and **may be revised as more high quality data become available**

Drug resistant epilepsy may be defined as **failure of adequate trials of two tolerated and appropriately chosen and used AED schedules** (whether as monotherapies or in combination) to achieve sustained seizure freedom

Appropriately chosen

For instance, ethosuximide would usually not be considered an appropriate intervention for focal seizures.

Under most circumstances, a trial of this drug in a patient with focal epilepsy would not "count" toward being defined as "drug resistance."

Adequate

- Application of the intervention at adequate strength/dosage for a sufficient length of time

- This **may not be the case** in some circumstances, for example**, when a drug is withdrawn before it has been titrated to its clinically effective dose range because of an adverse effect**

For adults, reference may be made to the **World Health Organization (WHO)'s defined daily dose (DDD),** which is the assumed average maintenance dose per day for a drug used for its main indication (World Health Organization, 2008)

Kwan P et al.; Epilepsia 2010

https://www.whocc.no/atc_ddd_index/

Drug-responsive epilepsy
Epilepsy in which the patient receiving the current AED regimen has been **seizure-free for a minimum of three times the longest preintervention interseizure interval or 12 months**, **whichever is longer**

Seizure freedom
Freedom from all types of seizures for 12 months or three times the preintervention interseizure interval, whichever is longer

A patient was newly started on **carbamazepine after two partial seizures in 9 months**. He has had no seizures for **12 months** since

Undefined
The pretreatment interseizure interval was 9 months.
Although the patient has had no seizure for 12 months, the duration is less than three times the pretreatment interseizure interval, hence outcome to treatment is undetermined and drug responsiveness of epilepsy is **undefined**

A patient had **one seizure in January 2006 and two seizures in October 2006**. After starting treatment in November 2006 he has been **seizure free for 30 months** with no adverse effect

Drug responsive
The longest pretreatment interseizure interval was 9 months (January–October 2006).
The patient has had no seizure for more than three times the pretreatment interseizure interval and for more than 12 months

Kwan P et al.; Epilepsia 2010

Predictors of drug-resistant epilepsy

Predictors of refractory epilepsy (multivariate analysis)

A total of **780 patients living in the West of Scotland** diagnosed with epilepsy and prescribed their first AED in the Epilepsy Unit of the Western Infirmary in Glasgow, Scotland, between July 1982 and May 2001 were included in this analysis

Predictors	Odds ratio	95% CI
Family history	1.89	1.15 – 3.00
Febrile convulsions in infancy	3.36	1.58 – 7.18
Traumatic brain injury	2.73	1.59 – 4.69
Psychiatric comorbidity (particularly depression)	2.17	1.33 – 3.55
Recreational drug use	4.26	2.03 – 8.94
More than 10 seizures before treatment	2.77	1.98 – 3.89

Hitiris N et al.; Epilepsy Res 2007

Consistent predictors of refractory epilepsy

- Early response to medication
- Underlying etiology
  - ✓ Epilepsies relating to structural brain abnormalities are less likely to enter remission compared that occurring in patients with structurally normal brains
  - ✓ Lower remission rate for symptomatic epilepsies (both partial and generalised) compared to idiopathic epilepsy syndromes in children
- Number of seizure prior to treatment

Mohanraj R & Brodie M; Seizure 2013

Consequences of drug-resistant epilepsy

Increased mortality

Table 1
Risks of premature death in individuals with epilepsy compared with those in population controls and unaffected siblings.
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	Odds ratio for death compared with population controls (aOR [95% CI])	Odds ratio for death compared with unaffected sibling controls (aOR [95% CI])
All-cause mortality	11.1 (10.6–11.6)	11.4 (10.4–12.5)
Natural causes	15.5 (14.6–16.4)	16.7 (14.9–18.7)
Neoplasms	11.2 (10.3–12.2)	11.3 (9.4–13.7)
Nervous system	71.1 (57.3–88.4)	86.9 (54.3–139.1)
External causes	3.6 (3.3–4.0)	3.2 (2.7–3.7)
Suicide	3.7 (3.3–4.2)	2.9 (2.4–3.6)
All accidents	3.6 (3.1–4.1)	3.6 (2.9–4.5)
Vehicle	1.4 (1.1–1.8)	1.5 (1.1–2.2)
Other	5.5 (4.7–6.5)	6.3 (4.6–8.8)
Drug poisoning	5.1 (3.9–6.5)	5.7 (3.3–9.7)
Fall	8.5 (5.3–13.7)	10.0 (2.9–33.8)
Drowning	7.7 (4.7–12.7)	9.5 (3.5–25.7)
Other and unspecified	4.9 (3.6–6.5)	5.2 (3.2–8.5)
Assault	2.8 (1.6–4.8)	1.7 (0.9–3.3)

Data are adjusted odds ratios (aOR) of external deaths compared with population controls (matched for age and sex, and adjusted for income, and marital and immigration status) or unaffected sibling controls (adjusted for age and sex).

Laxer KD et al.; Epilepsy & Behav 2014

Mortality is greater for those with epilepsy than for those without

Within epilepsy, mortality is greatest for those with refractory epilepsy

SUDEP (sudden, unexplained death in epilepsy)

- The average incidence is **1/1,000** patients with epilepsy per year

- In **refractory epilepsy**, the incidence is **6 /1,000** patients per year, and the lifetime incidence is 7% to 35%, with the greater end of this range applying to childhood-onset refractory epilepsy

- Risk of SUDEP in those with epilepsy is approximately **16-times** that of the general population, after adjustment for multiple factors, including age, sex, and psychiatric and neurologic disease

Increased risk of neuropsychiatric impairment

How are epilepsy and neuropsychiatric conditions related ?

Could be

1) Seizure activity itself

Patients with **chronic seizures** experience greater rates of cognitive deficits, emotional problems, physical and psychiatric disease, health care utilization, educational and occupational underachievement, failure in fulfilling normal social roles, and reduced quality of life

2) Structural and functional abnormalities often precede the onset of seizures and medication use

It is increasingly clear that **neuropsychiatric comorbidities are evident prior to the onset of observable seizure activity**, or sufficiently soon after onset that they are unlikely to have been caused by seizure activity itself.

Conditions with greater degree present at, before, or soon after onset of seizures

- ADHD
- Depression
- Behavioral problems
- Cognitive difficulties

Laxer KD et al.; Epilepsy & Behav 2014

Drug-Resistant Epilepsy: Multiple Hypotheses, Few Answers

*Fei Tang[1,2], Anika M. S. Hartz[3,4] and Björn Bauer[2,5]**

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Tang F et al.; Frontiers in Neurol 2017

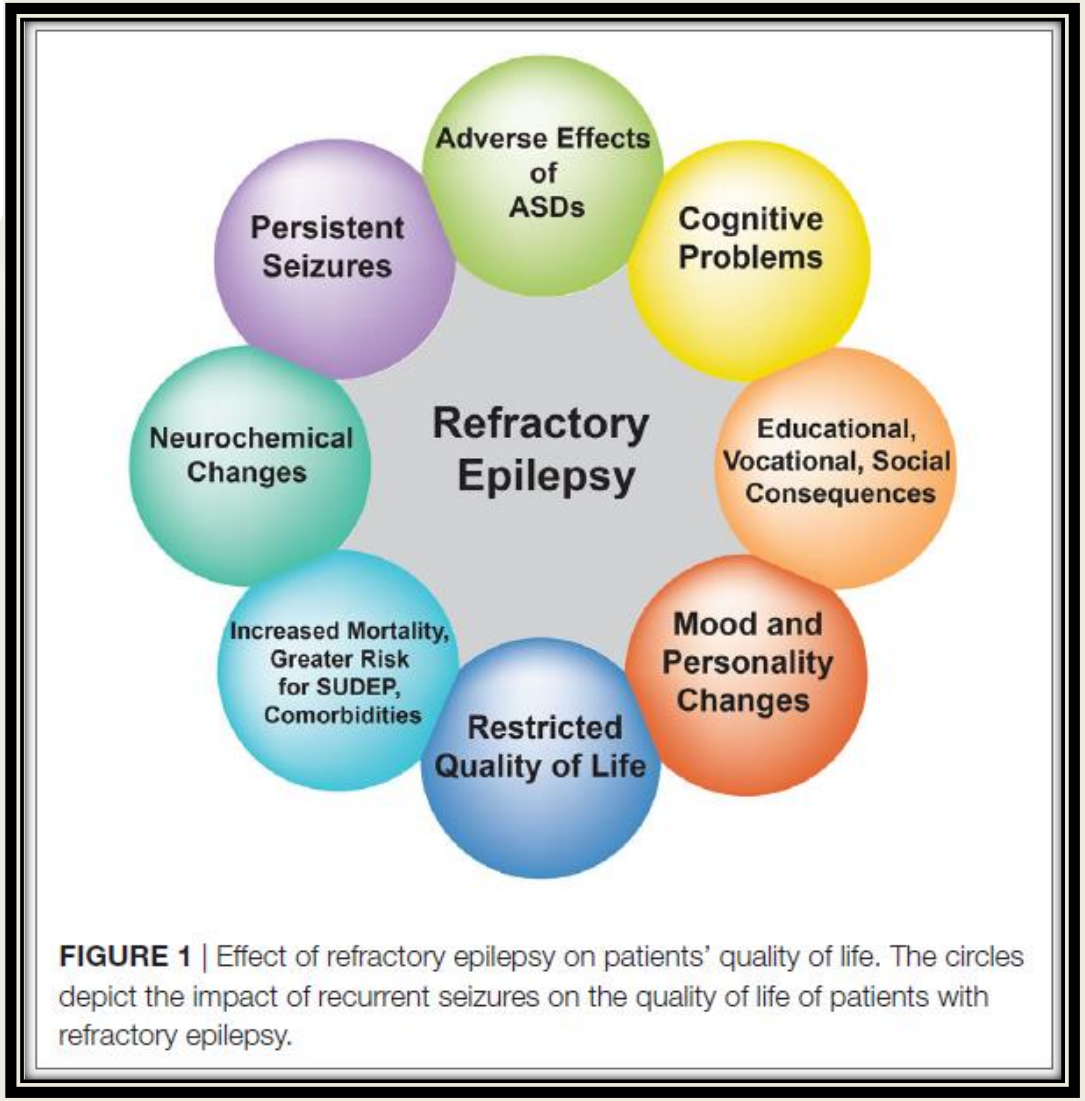
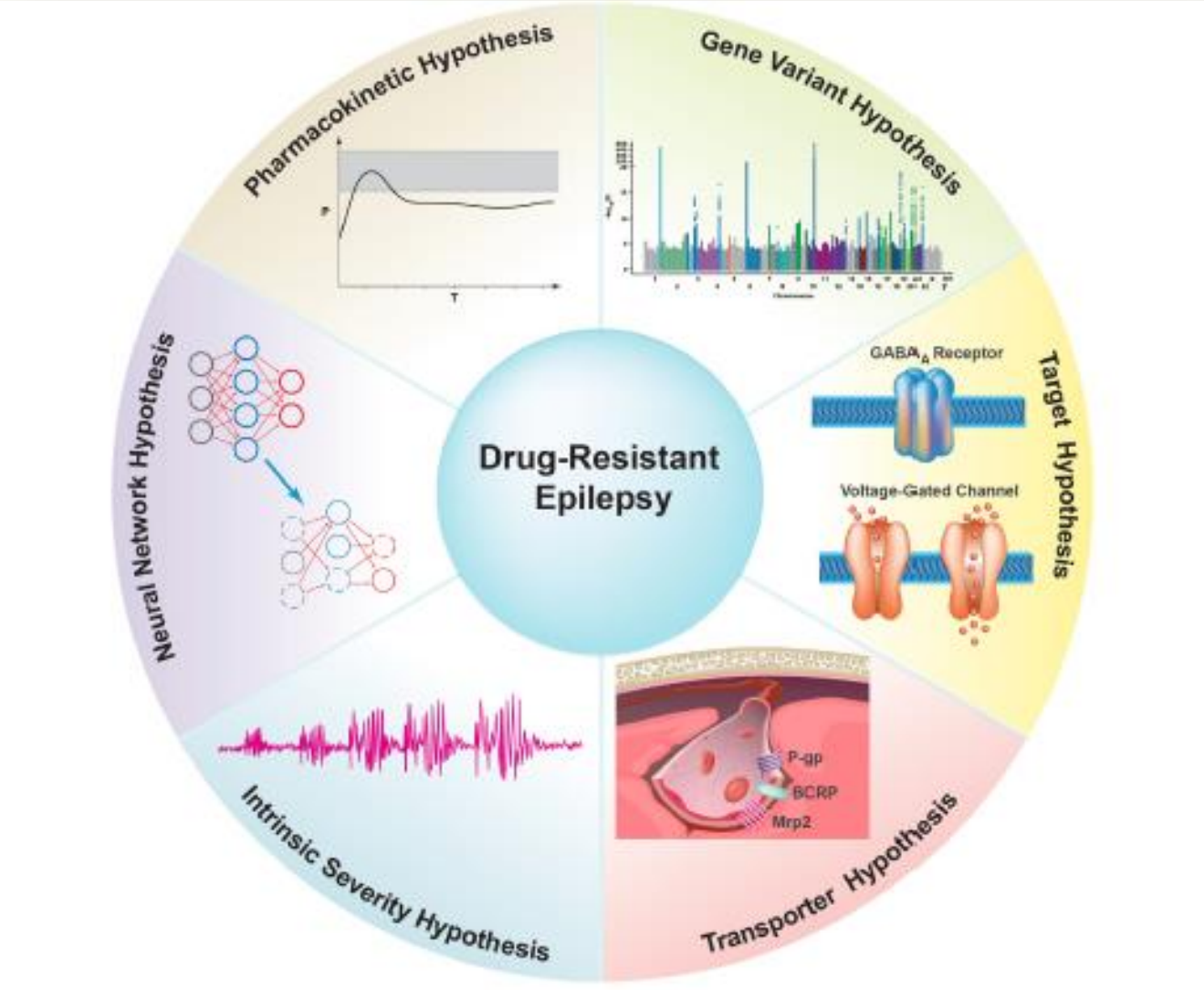


FIGURE 1 | Effect of refractory epilepsy on patients' quality of life. The circles depict the impact of recurrent seizures on the quality of life of patients with refractory epilepsy.

Potential mechanisms of drug resistance



The "**Target hypothesis**" and "**Transporter hypothesis**" are the most cited theories of ASD resistance, but neither fully explains the neurobiological basis of this phenomenon

The mechanism(s) of refractory epilepsy is/are most likely **multifactorial**, involving **environmental, genetic, as well as disease- and drug-related factors**

Tang F et al.; Frontiers in Neurol 2017

Pharmacokinetic hypothesis proposes that

- **Overexpression of efflux transporters in peripheral organs** such as intestine, liver, and kidney decreases ASD plasma levels in refractory epilepsy patients, thereby reducing the amount of ASD available to cross

- **Low plasma levels of AEDs, coincided with increased P-glycoprotein (P-gp) protein expression levels** in endothelial cells, astrocytes, and neurons from the patient's resected brain tissue

Neural Network Hypothesis

The neural network hypothesis, which states that **seizure-induced degeneration and remodeling of the neural network suppress the endogenous antiseizure system** and inhibit ASDs from accessing neuronal targets.

i.e., **Neurogenesis and Astrogliosis** in TLE could contribute to the development of abnormal neural networks and eventually ASD resistance

The gene variant hypothesis

Variations in genes associated with ASD pharmacokinetics and pharmacodynamics cause inherent pharmacoresistance. Specifically, variations in genes that encode enzymes that metabolize ASDs or ion channels and neurotransmitter receptors targeted by ASDs can potentially affect ASD response

Intrinsic severity hypothesis

- Common neurobiological factors contribute to both epilepsy severity and pharmacoresistance
- High pretreatment seizure frequency is an important predictor for refractory epilepsy

Tang F et al.; Frontiers in Neurol 2017

Target hypothesis

Alterations in the properties of ASD targets, such as compositional changes in voltage-gated ion channels and neurotransmitter receptors, result in decreased drug sensitivity and thus lead to refractoriness

Tang F et al.; Frontiers in Neurol 2017

Transporter hypothesis

(1) Overexpression of efflux transporters correlates with pharmacoresistance in epilepsy and

(2) ASDs are subject to active transport by efflux transporters

The best understood efflux transporters are members of **the ABC (ATP-binding cassette)** superfamily subfamilies B, C, and G, specifically **P-gp (*ABCB1 or MDR1*)**, the **multidrug resistance-associated proteins** (MRP1, *ABCC1*; MRP2, *ABCC2*), and breast cancer resistance protein (BCRP, ABCG2)

Neuroimaging of drug resistance in epilepsy

Memory circuit reorganization in the pre-op and post-op periods in drug-resistant TLE

Clinical study

Memory loss and memory reorganization patterns in temporal lobe epilepsy patients undergoing anterior temporal lobe resection, as demonstrated by pre-versus post-operative functional MRI

Chusak Limotai [a,b,c,1], Richard S. McLachlan [a], Susan Hayman-Abello [a], Brent Hayman-Abello [a], Suzan Brown [a], Frank Bihari [a], Seyed M. Mirsattari [a,d,e,f,*]

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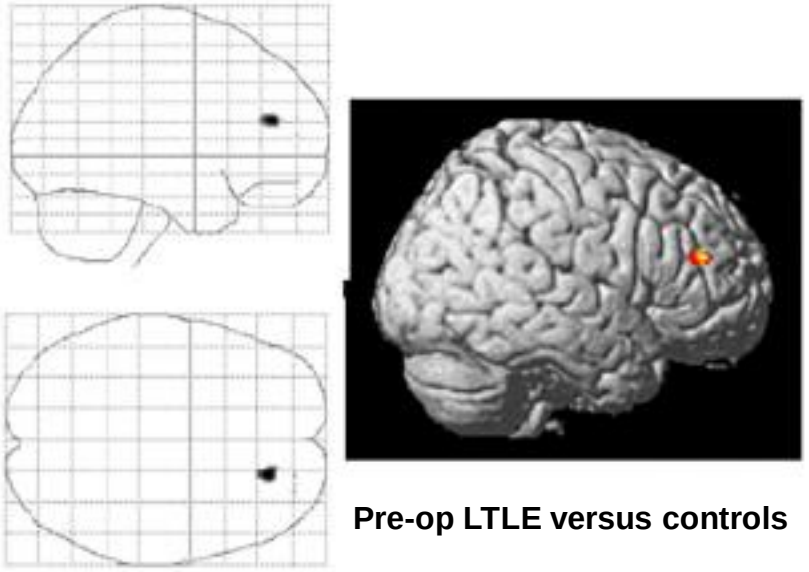
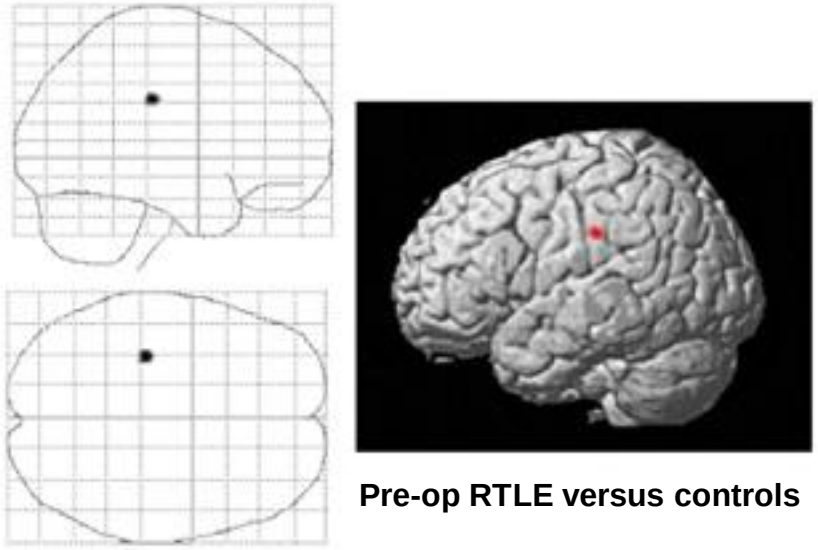
Limotai C et al.; J Clin Neurol 2018



Pre-op LTLE versus controls

(A)



Pre-op RTLE versus controls

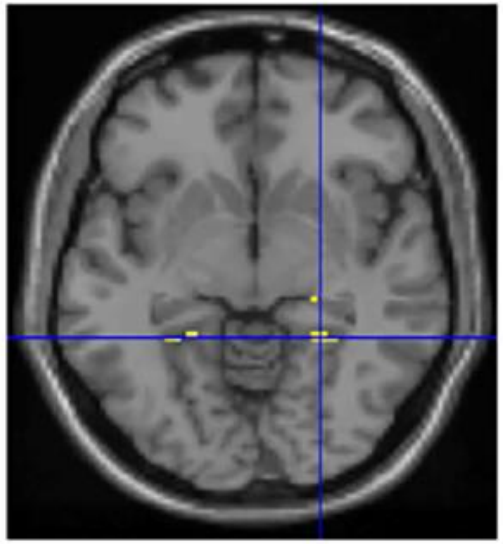
Nineteen patients with medically-intractable TLE (10 left TLE, 9 right TLE) and 15 healthy controls were enrolled

Group analyses were conducted pre- and post-ATL of a **novelty complex scene-encoding paradigm** comparing areas of BOLD signal activations on fMRI

Extra-temporal activations were detected pre-operatively in both LTLE and RTLE, particularly in the frontal lobe

Limotai C et al.; J Clin Neurol 2018

L



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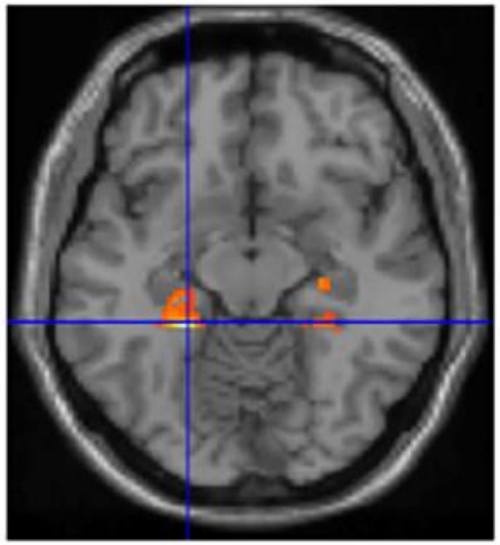
Pre-op LTLE versus controls

(E)

L



R

Pre-op RTLE versus controls

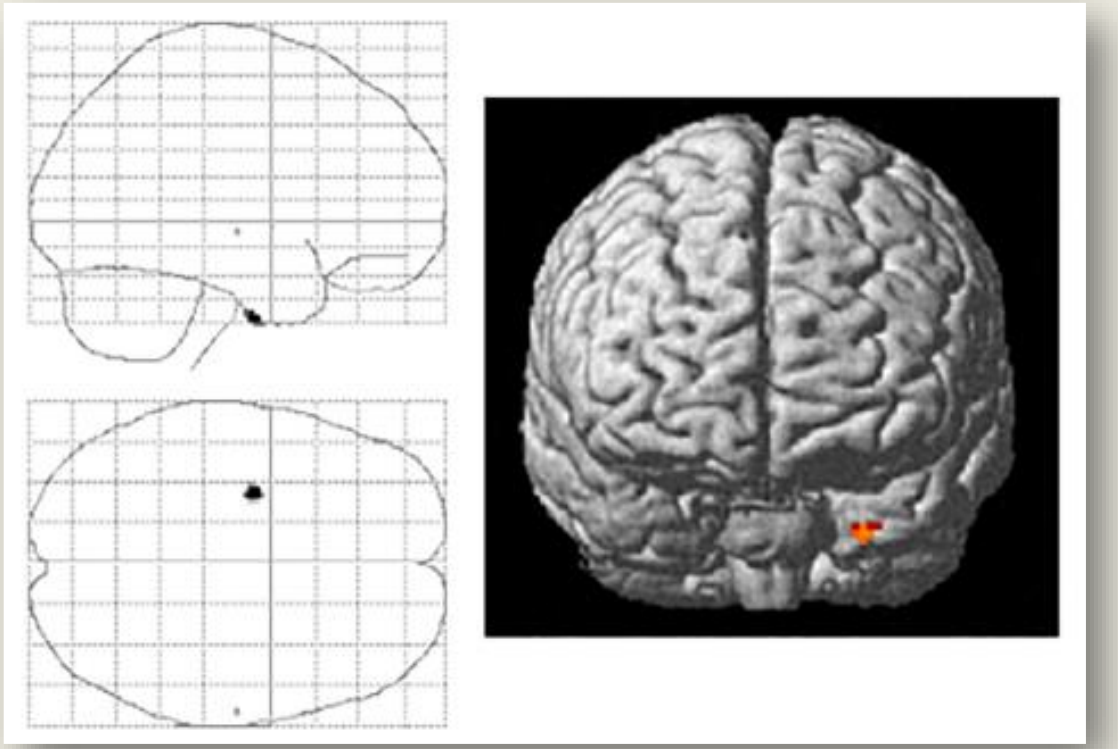
Greater activations also were noted in the contralateral hippocampus and parahippocampus in LTLE and RTLE

Signal changes in the left HC/PHC (R^2 = 0.513 (p = 0.025) for verbal memory (AdDel score)

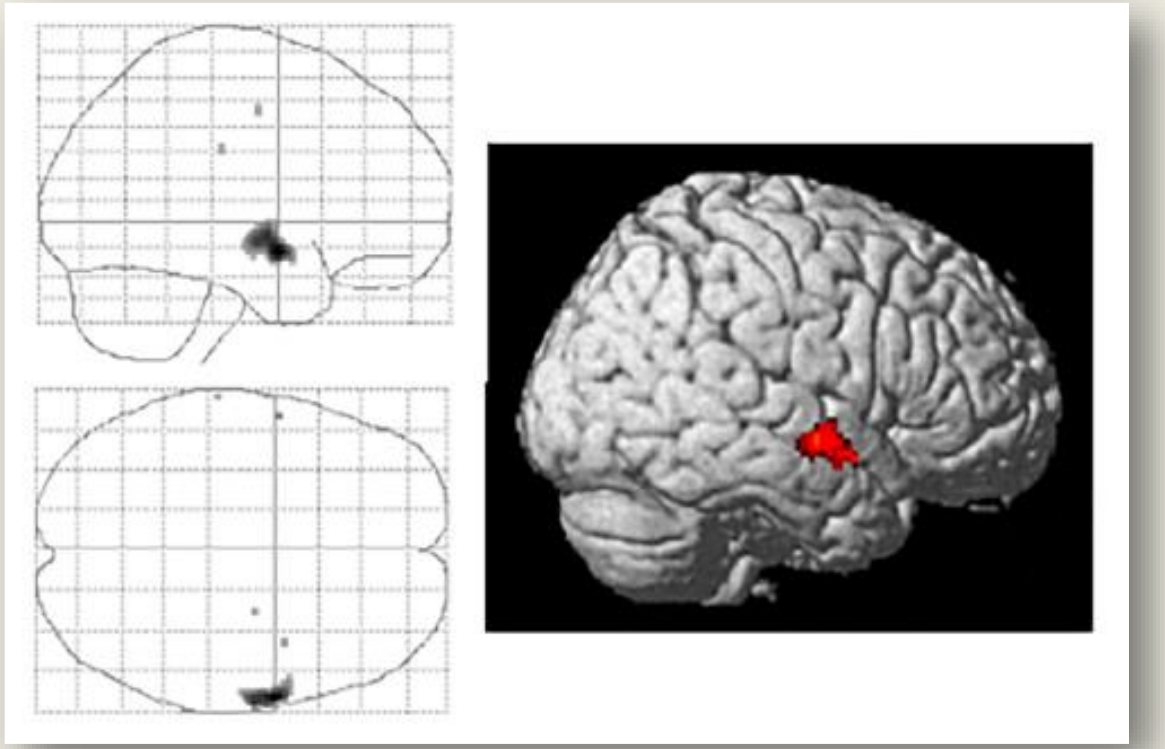
fMRI provides evidence for importance of **"Functional adequacy of ipsilateral structures"** rather than functional reserve of the contralateral hemisphere

Limotai C et al.; J Clin Neurol 2018
Koepp MJ; Curr Opin Neurol 2014

Whole-brain memory circuit reorganization at post-operative period



LTLE Post-op versus Pre-op



RTLE Post-op versus Pre-op

Pronounced temporal activations, particularly in the ipsilateral temporal area

Limotai C et al.; J Clin Neurol 2018

Thank you